

# Medical Policy

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## Description/Scope

This document addresses gene expression profiling to diagnose bladder cancer, predict response to therapy in individuals with bladder cancer, and monitor individuals with a history of bladder cancer. There are commercially available gene expression tests for the diagnosis and monitoring of bladder cancer (Cxbladder™) and for the selection of treatment in individuals with bladder cancer (Decipher Bladder TURBT®).

## Position Statement

### Investigational and Not Medically Necessary:

Gene expression profiling for diagnosing, managing and monitoring bladder cancer is considered investigational and not medically necessary.

## Rationale

### Diagnosis of Bladder Cancer

Several studies have evaluated detection of bladder cancer using a Cxbladder test. In 2012, O’Sullivan and colleagues prospectively studied 485 individuals with no history of urothelial carcinoma (UC) who presented with macroscopic hematuria and underwent cystoscopy. Bladder cancer was diagnosed based on cystoscopic findings and histopathological analysis. In addition to cystoscopy, investigators analyzed urine samples using an early version of the Cxbladder test, as well as using urinary cytology and the biomarker tests NWMP22 and BladderChek. A total of 66 of the 485 individuals (13.6%) were diagnosed with UC. Cxbladder detected 54 of the 66 cases (sensitivity of 82%) at a prespecified specificity of 85%. The sensitivity of Cxbladder was

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## Gene Expression Profiling for Bladder Cancer

**higher than cytology (56.1%) and the NMP22 BladderChek test (37.9%) but the specificity was lower. The specificity of cytology was 94.5% and of NMP22 BladderChek was 96.4%.**

**Breen and colleagues (2015) evaluated five datasets owned by the manufacturer of Cxbladder. The datasets included a total of 939 individuals, including 476 from the O’Sullivan (2012) study, described above. In the initial dataset, the sensitivity of CxBladder Detect was 79.5%, which was higher than the other included tests, cytology (sensitivity of 45.5%), NMP22 (sensitivity of 44.9%) and FISH testing (sensitivity of 40.0%). The specificity of CxBladder Detect was 82.2%, which was lower than the other tests, which had specificities of 96.3%, 89.0% and 87.3%, respectively.**

**Another analysis of the O’Sullivan (2012) data was published by Kavalieris and colleagues (2015). This study addressed the development and validation of a model to “triage out” individuals presenting with hematuria who have a low probability of UC (test now known as Cxbladder Triage). The dataset was supplemented with additional cohorts with hematuria. The final dataset included 587 samples from individuals, 72 UC-positive and 515 UC-negative. Logistic regression analysis found that four clinical characteristics: age 60 or higher, male gender, history of smoking, and high frequency of macrohematuria, were significantly associated with an increased risk of UC. The investigators then tested the gene profile plus an index created from the clinical characteristic variables. Their testing generated models with negative predictive values (NPV) of at least 97%. This is a preliminary modeling study and did not prospectively evaluate diagnostic accuracy in a clinical sample or evaluate the clinical utility of Cxbladder Triage.**

**A systematic review and meta-analysis by independent investigators (Sathianathen, 2018) evaluated the diagnostic accuracy of various urinary biomarkers. The review included studies that compared the accuracy of biomarkers compared with cystoscopy in individuals presenting with primary hematuria. A total of 14 studies met the review’s inclusion criteria. Pooled estimates were calculated for each biomarker that had more than 1 study. Sensitivities were 67% for BTA, 78% for NMP22 Quantitative, 79% for NMP22 Qualitative, 82% for Cxbladder and 82% for UCyt. Specificities were 69% for BTA, 82% for NMP22 Quantitative, 84% for NMP22 Qualitative, 85% for Cxbladder and 87% for UCyt. In comparison cytology, findings from the same studies had specificities ranging from 92% to 98%. The authors concluded that the diagnostic performance of the biomarkers was inadequate to replace cystoscopy for individuals with primary hematuria.**

**A manufacturer-sponsored study examined the potential impact of Cxbladder test results on clinical decision-making (Darling, 2017; Lough, 2017). They recruited 12 urologists and presented each of them with**  
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## Medical Policy

### Gene Expression Profiling for Bladder Cancer

information on 33 individuals with hematuria. The urologists were first presented with clinical information only and were asked to provide a ‘yes’ or ‘no’ response regarding whether they thought that urological evaluation was needed. The urologists were then provided results on the Cxbladder test and asked to whether or not their initial recommendation changed. Cases were selected from a database of individuals enrolled in previous Cxbladder studies and were selected to represent a cross-section of demographic groups. Out of a total of 396 urologist/subject decisions, urologists initially recommended at least one invasive diagnostic test in 259 (65.4%) of cases. They recommended a total of 689 diagnostic procedures, of which 425 were considered invasive. After reviewing Cxbladder test results, the total number of invasive procedures recommended was 397, an 11% reduction. This study is a simulation of clinical practice, not data from actual practice. In addition, participating urologists were not provided with results from any other tests, knew the study was sponsored by the manufacturer of Cxbladder, and were provided honoraria. Moreover, it is not known whether any changes in management recommendations would have improved clinical outcomes.

The American Urological Association (AUA) 2020 Microhematuria guideline, developed in conjunction with the Society of Urodynamics, Female Pelvic Medicine & Urogenital Reconstruction (SUFU) stated, “Clinicians should not use urine cytology or urine-based tumor markers in the initial evaluation of patients with microhematuria. (Strong Recommendation; Evidence Level: Grade C).”

#### Surveillance of Individuals with a History of Bladder Cancer

Kavalieris and colleagues (2017) reported on the development and validation of the Cxbladder Monitor test, proposed for the surveillance of individuals with a history of urothelial cancer. The prospective study evaluated 763 individuals with a history of UC undergoing surveillance, including cystoscopy, for possible recurrent disease. Study participants were followed for up to 6 months, which included three scheduled clinical visits per person. In a training set of data from 339 individuals, the investigators identified three clinical variables that were strongly associated with UC: previous tumor type (primary or recurrent), number of years since the previous tumor, and gene expression data. The latter factor was a statistically modified version of the results of the Cxbladder test. In a validation set of samples from 424 individuals, the test (gene expression profiling plus clinical variables) had a sensitivity of 92% and a negative predictive value (NPV) of 96% (specificity was not reported). A total of 14 of 156 individuals (9%) with recurrent UC identified by cystoscopy tested negative with the Cxbladder Monitor test.

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## Medical Policy

### Gene Expression Profiling for Bladder Cancer

Koya and colleagues (2020) reported on findings from New Zealand’s healthcare system. The study was a retrospective audit of three public health providers who incorporated the Cxbladder Monitor test into their routine clinical surveillance of individuals with a history of bladder cancer. In the surveillance protocol, Cxbladder Monitor-negative individuals were considered to be at low risk of recurrence and did not undergo cystoscopy at that visit, but at their next scheduled visit 12 months later. Thus, annual surveillance visits alternated between Cxbladder Monitor tests (when negative) and cystoscopy. Individuals with a positive Cxbladder Monitor test and those considered to be high-risk individuals underwent cystoscopy. (Details of definitions of low risk and high risk were not available). During the 35-month study period, 305 individuals participated in the surveillance protocol, 257 (83.2%) low-risk and 52 (16.8%) high-risk. A total of 196 of 253 (77.5%) low-risk individuals had a negative Cxbladder result. Confirmed recurrence occurred in 3 of these 196 individuals over 35 months. In addition, 3 of 57 Cxbladder Monitor-positive low-risk individuals had confirmed recurrences. Among evaluable high-risk individuals, 4 of 49 had confirmed recurrences during the study; all 4 had positive Cxbladder Monitor results. Overall, 57 of 305 (19%) individuals were considered low risk and had negative Cxbladder findings and could thus potentially be managed with fewer cystoscopies. This study was conducted in New Zealand; it is not clear how many bladder cancer survivors or physicians in the United States would chose to follow this protocol. For low-risk individuals with a history of bladder cancer, the National Comprehensive Cancer Network (NCCN) recommends cystoscopy at 3 and 12 months and annually thereafter.

The AUA and SUFU do not recommend use of urinary biomarkers for surveillance of individuals with bladder cancer. In their 2016 guideline, amended in 2020, entitled Diagnosis and Treatment of Non-Muscle Invasive Bladder Cancer (NMIBC), they included the following relevant recommendations:

In surveillance of NMIBC, a clinician should not use urinary biomarkers in place of cystoscopic evaluation. (Strong Recommendation; Evidence Strength: Grade B)

In a patient with a history of low-risk cancer and a normal cystoscopy, a clinician should not routinely use a urinary biomarker or cytology during surveillance. (Expert Opinion)

The NCCN’s guideline on bladder cancer (V6.2020) discusses management of individuals with bladder cancer. For intermediate-risk individuals with non-muscle-invasive bladder cancer, the NCCN recommends follow-up with cystoscopy, imaging and urine cytology. For individuals with high-risk non-muscle-invasive bladder cancer, the NCCN recommends cystoscopy, upper tract imaging, abdominal pelvic imaging and urine cytology. All of the above are category 2A recommendations. In addition the guideline states, “consider urinary urothelial tumor markers” (category 2B recommendation). The document notes, “it remains unclear

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Gene Expression Profiling for Bladder Cancer

**whether these tests offer additional information that is useful for detection and management of non-muscle-invasive bladder tumors. Therefore, the panel considers this to be a category 2B recommendation.”**

Management of Bladder Cancer

**A gene expression profiling test, Decipher Bladder, is proposed to aid in treatment decisions in individuals with locally advanced muscle-invasive bladder cancer. Seiler and colleagues (2017) published preliminary research that served as the basis for development of the test. They analyzed bladder tumor samples, prior to neoadjuvant chemotherapy, and determined that classification of tumors into four molecular sub-types would be optimal for predicting clinical outcomes. They then trained a genomic subtyping classifier to predict the four molecular subtypes: claudin-low, basal, luminal-infiltrated, and luminal. In the discovery cohort (n=233), the overall accuracy of the classifier was 76%, and in the validation cohort (n=82), the accuracy was 73%. The authors also conducted an analysis of clinical outcomes by molecular sub-type, using an independent non-neo-adjuvant chemotherapy dataset. Their findings suggested that individuals with basal tumors might benefit the most from neoadjuvant chemotherapies. Individuals with basal tumors, as determined by the classifier, had a 3-year overall survival (OS) rate of 49.2% in the cohort without neo-adjuvant chemotherapy compared with 77.8% in the neo-adjuvant chemotherapy cohort.**

**Batista da Costa (2019) explored the ability of the gene expression classifier (the Decipher test) to identify neuroendocrine (NE)-like tumors when histologic features of NE carcinoma were missing. The training cohort consisted of Decipher test results in 175 individuals with muscle-invasive bladder cancer and the radical cystectomy cohort included 225 individuals who underwent cystectomy without receiving neoadjuvant therapy. The classifier identified 8 (4.2%) samples in the training cohort as having NE-like tumors and 4 (1.8%) individuals in the radical cystectomy cohort. In the radical cystectomy cohort, individuals with NE-like tumors had a lower 1-year progression-free survival (PFS) rate compared with the rest of the cohort (65% vs 82%, p=0.046). Grivas and colleagues (2020) also focused on NE-like tumors. They used the Decipher test to identify NE-like tumors in a retrospective study of individuals with bladder cancer who underwent cisplatin-based neoadjuvant chemotherapy followed by radical cystectomy. Ten (4.3%) of 234 individuals were classified as having the NE-like subtype. In the primary analysis of 211 individuals with complete information, individuals with NE-like tumors had worse outcomes than those with non-NE-like tumors, including having all 5 cancer-specific deaths.**

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**No prospective studies were available that compared outcomes in individuals with muscle-invasive bladder cancer who did and did not undergo testing with Decipher Bladder to aid in the decision regarding neo-adjuvant chemotherapy.**

**The NCCN Bladder Cancer guideline (V.6. 2020) does not recommend different approaches to chemotherapy treatment of muscle invasive bladder cancer according to molecular sub-type.**

#### **Background/Overview**

**Bladder cancer is the sixth most common type of cancer in the United States. The American Cancer Society (2020) estimates that, in 2020, there will be an estimated 81,400 new cases of bladder cancer and 17,980 deaths. Risk factors for bladder cancer include age, family history, tobacco use and environmental exposure to carcinogens. (NCI, 2020). About 90% of bladder cancer cases are urothelial, also known as transitional cancer, originating in the cells that line the urinary tract. Moreover, most bladder cancer diagnosed in the United States is non-muscle-invasive; that means, it has not spread into the detrusor muscle of the bladder. About 70-80% of bladder cancers present as non-muscle-invasive tumors; the remaining 20-30% are muscle-invasive tumors (DeGeorge, 2017).**

**Painless hematuria is the most common presenting sign of bladder cancer. Approximately 1.3% of individuals with microscopic hematuria and no obvious cause, and 20% of individuals with gross hematuria, will have bladder cancer (DeGeorge, 2017). Individuals with bladder cancer may also present with symptoms such as urinary frequency, nocturia and dysuria (NCI, 2020).**

**For individuals with incidentally discovered microscopic hematuria on urinalysis, clinical assessment is recommended, along with repeat urinalysis after treatment of any benign causes that were identified. If repeat urinalysis is also positive, individuals should be evaluated for medical renal disease and, if negative, should undergo cystoscopy and imaging of the upper urinary tract. Cystoscopy is recommended for all individuals presenting with gross hematuria and in individuals with microscopic hematuria who are at least 35 years old (DeGeorge, 2017).**

**Bladder cancer frequently recurs and therefore regular surveillance of the urinary tract is recommended after bladder cancer. The NCCN Bladder Cancer Guideline (V.6. 2020) has various recommended follow-up surveillance protocols depending on the type of cancer with which the individual was initially diagnosed. For**

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## Medical Policy

### Gene Expression Profiling for Bladder Cancer

**Individuals with low-risk non-muscle-invasive bladder cancer, follow-up with cystoscopy is recommended and, for individuals with intermediate- or high-risk non-muscle-invasive bladder cancer, recommended protocols involve a combination of cystoscopy, upper tract imaging with or without abdominal pelvic imaging and urine tests at intervals that vary over time.**

**Several gene expression profiling tests are commercially available for the diagnosis or management of bladder cancer. None of these tests have been cleared or approved by the U.S. Food and Drug Administration (FDA). As laboratory-developed tests, FDA approval is not required.**

**The Cxbladder group of tests involve processing urine samples to extract mRNA and using reverse transcription quantitative polymerase chain reaction (RT-qPCR) to amplify and measure the expression of 5 genes. Findings are combined with clinical characteristics and, using a proprietary algorithm, a risk score is calculated. Cxbladder Detect, the original test, is intended for the diagnosis of bladder cancer in high-risk individuals who present with gross hematuria. Cxbladder Triage, which also incorporates factors such as age, sex, smoking status and hematuria history, is intended to evaluate the likelihood of bladder cancer in low-risk individuals who present with hematuria. Cxbladder Monitor is intended to be used in the surveillance of individuals with a history of bladder cancer to rule out disease recurrence. The tests are intended to reduce the need for additional clinical evaluation, in the case of Cxbladder Triage, or invasive testing such as cystoscopy in the case of Cxbladder Detect and Cxbladder Monitor.**

**The Decipher Bladder TURBT test (Decipher Biosciences, Vancouver, BC) is used in the management of bladder cancer, specifically to aid in the decision of individuals with locally advanced muscle-invasive bladder cancer who are considering neoadjuvant chemotherapy (NAC) prior to radical cystectomy. The test uses gene expression analysis to classify the molecular subtype (luminal, luminal infiltrated, basal, basal claudin-low, neuroendocrine-like) of tumor specimens.**

**Determining treatment decisions according to the molecular subtype of bladder tumors is not recommended by the NCCN. The NCCN Bladder Cancer guideline, V.6. 2020, recommends neoadjuvant cisplatin-based combination chemotherapy prior to cystectomy for individuals with Stage II muscle-invasive bladder cancer. For individuals who are not eligible for cisplatin-based chemotherapy, the guideline recommends cystectomy alone. As noted above, the NCCN guideline does not recommend different approaches to chemotherapy treatment of muscle invasive bladder cancer according to molecular subtype.**

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**Definitions**

**Gene expression profiling: A laboratory test that measures the activity of multiple genes at once for diagnostic or prognostic purposes. The test result is often reported as a proprietary summary score.**

**Hematuria: The presence of blood in urine.**

**Neoadjuvant therapy: Therapy given prior to the main treatment.**

**Urothelial: Cells that line the urinary tract, which includes that bladder, urethra, ureters and renal pelvis. Also called transitional cells. Bladder cancer that begins here is called urothelial cancer or transitional cancer.**

**Coding**

**The following codes for treatments and procedures applicable to this document are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement policy. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.**

**When services are Investigational and Not Medically Necessary:**

**For the following procedure codes; or when the code describes a procedure indicated in the Position Statement section as investigational and not medically necessary.**

**CPT**

**0012M**

**Oncology (urothelial), mRNA, gene expression profiling by real-time quantitative PCR of five genes (MDK, HOXA13, CDC2 [CDK1], IGFBP5, and CXCR2), utilizing urine, algorithm reported as a risk score for having urothelial carcinoma Cxbladder™ Detect, Pacific Edge Diagnostics USA, Ltd.**

**0013M**

**Oncology (urothelial), mRNA, gene expression profiling by real-time quantitative PCR of five genes (MDK, HOXA13, CDC2 [CDK1], IGFBP5, and CXCR2), utilizing urine, algorithm reported as a risk score for having recurrent urothelial carcinoma Cxbladder™ Monitor, Pacific Edge Diagnostics USA, Ltd**

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**Medical Policy****Gene Expression Profiling for Bladder Cancer****0016M**

**Oncology (bladder), mRNA, microarray gene expression profiling of 209 genes, utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as molecular subtype (luminal, luminal infiltrated, basal, basal claudin-low, neuroendocrine-like) Decipher Bladder TURBT®, Decipher Biosciences, Inc**

**ICD-10 Diagnosis****All diagnoses****References****Peer Reviewed Publications:**

1. **Batista da Costa J, Gibb EA, Bivalacqua TJ et al. Molecular Characterization of Neuroendocrine-like Bladder Cancer. Clin Cancer Res. 2019; 25(13):3908-3920.**
2. **Breen V, Kasabov N, Kamat AM et al. A holistic comparative analysis of diagnostic tests for urothelial carcinoma: a study of Cxbladder Detect, UroVysion® FISH, NMP22® and cytology based on imputation of multiple datasets. BMC Med Res Methodol. 2015; 15:45.**
3. **Darling D, Luxmanan C, O'Sullivan P et al. Clinical utility of Cxbladder for the diagnosis of urothelial carcinoma. Adv Ther. 2017; 34(5):1087-1096.**
4. **DeGeorge KC, Holt HR, Hodges SC. Bladder cancer: Diagnosis and treatment. Am Fam Physician. 2017; 96(8):507-514.**
5. **Grivas P, Bismar TA, Alva AS et al. Validation of a neuroendocrine-like classifier confirms poor outcomes in patients with bladder cancer treated with cisplatin-based neoadjuvant chemotherapy. Urol Oncol. 2020; 38(4):262-268.**
6. **Kavalieris L, O'Sullivan P, Frampton C et al. Performance characteristics of a multigene urine biomarker test for monitoring for recurrent urothelial carcinoma in a multicenter study. J Urol. 2017; 197(6):1419-1426.**
7. **Kavalieris L, O'Sullivan PJ, Suttie JM et al. A segregation index combining phenotypic (clinical characteristics) and genotypic (gene expression) biomarkers from a urine sample to triage out patients presenting with hematuria who have a low probability of urothelial carcinoma. BMC Urol. 2015; 15:23.**
8. **Koya M, Osborne S, Chemaslé C et al. An evaluation of the real world use and clinical utility of the Cxbladder Monitor assay in the follow-up of patients previously treated for bladder cancer. BMC Urol. 2020; 20(1):12.**

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9. Lough T, Luo Q, Luxmanan C et al. Clinical utility of a non-invasive urine test for risk assessing patients with no obvious benign cause of hematuria: a physician-patient real world data analysis. BMC Urol. 2018; 18(1):18.
10. O'Sullivan P, Sharples K, Dalphin M et al. A multigene urine test for the detection and stratification of bladder cancer in patients presenting with hematuria. J Urol. 2012; 188(3):741-747.
11. Sathianathan NJ, Butaney M, Weight CJ et al. Urinary biomarkers in the evaluation of primary hematuria: a systematic review and meta-analysis. Bladder Cancer. 2018; 4(4):353-363.
12. Seiler R, Ashab HAD, Erho N et al. Impact of molecular subtypes in muscle-invasive bladder cancer on predicting response and survival after neoadjuvant chemotherapy. Eur Urol. 2017; 72(4):544-554.

#### Government Agency, Medical Society, and Other Authoritative Publications:

1. American Urological Association (AUA)/ Society of Urodynamics, Female Pelvic Medicine & Urogenital Reconstruction (SUFU). Diagnosis and Treatment of Non-Muscle Invasive Bladder Cancer Guideline, 2016, amended 2020. Available at: <https://www.auanet.org/guidelines/bladder-cancer-non-muscle-invasive-guideline> Accessed on January 12, 2021.
2. American Urological Association (AUA)/ Society of Urodynamics, Female Pelvic Medicine & Urogenital Reconstruction (SUFU). Microhematuria Guideline. 2020. Available at: <https://www.auanet.org/guidelines/microhematuria>. Accessed on January 12, 2021.
3. NCCN Clinical Practice Guidelines in Oncology®. © 2020 National Comprehensive Cancer Network, Inc. For additional information visit the NCCN website: <http://www.nccn.org/index.asp>. Accessed on December 1, 2020.
  - Bladder Cancer (V6.2020). Revised July 16, 2020.
4. National Cancer Institute. Bladder Cancer- Health Professional Version. Available at: <https://www.cancer.gov/types/bladder/hp>. Accessed on January 12, 2021.

#### Websites for Additional Information

1. American Cancer Society (ACS). Bladder cancer. 2020. Available at: <https://www.cancer.org/cancer/bladder-cancer.html>. Accessed January 12, 2021.
2. National Cancer Institute. Bladder Cancer- Patient Version. Available at: <https://www.cancer.gov/types/bladder>. Accessed on December 9, 2020.

#### Index

This Medical Policy provides assistance in understanding Healthy Blue's standard Medicaid benefit plan. When evaluating coverage for a specific member benefit, reference to federal and state law, as well as contractual requirements may be necessary, since these may differ from our standard benefit plan. In the event of a conflict with standard plan benefits, federal, state and/or contractual requirements will govern. Before using this policy, please check all federal, state and/or contractual requirements applicable to the specific benefit plan coverage. Healthy Blue reserves the right to modify its Policies and Guidelines as necessary and in accordance with legal and contractual requirements. This Medical Policy is provided for informational purposes. It does not constitute medical advice. Healthy Blue may also use tools and criteria developed by third parties, to assist us in administering health benefits. Healthy Blue's Policies and Guidelines are intended to be used in accordance with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.

Federal and State law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over Medical Policy and must be considered first in determining eligibility for coverage. The member's contract benefits in effect on the date that services are rendered must be used. Medical Policy, which addresses medical efficacy, should be considered before utilizing medical opinion in adjudication. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

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# Medical Policy

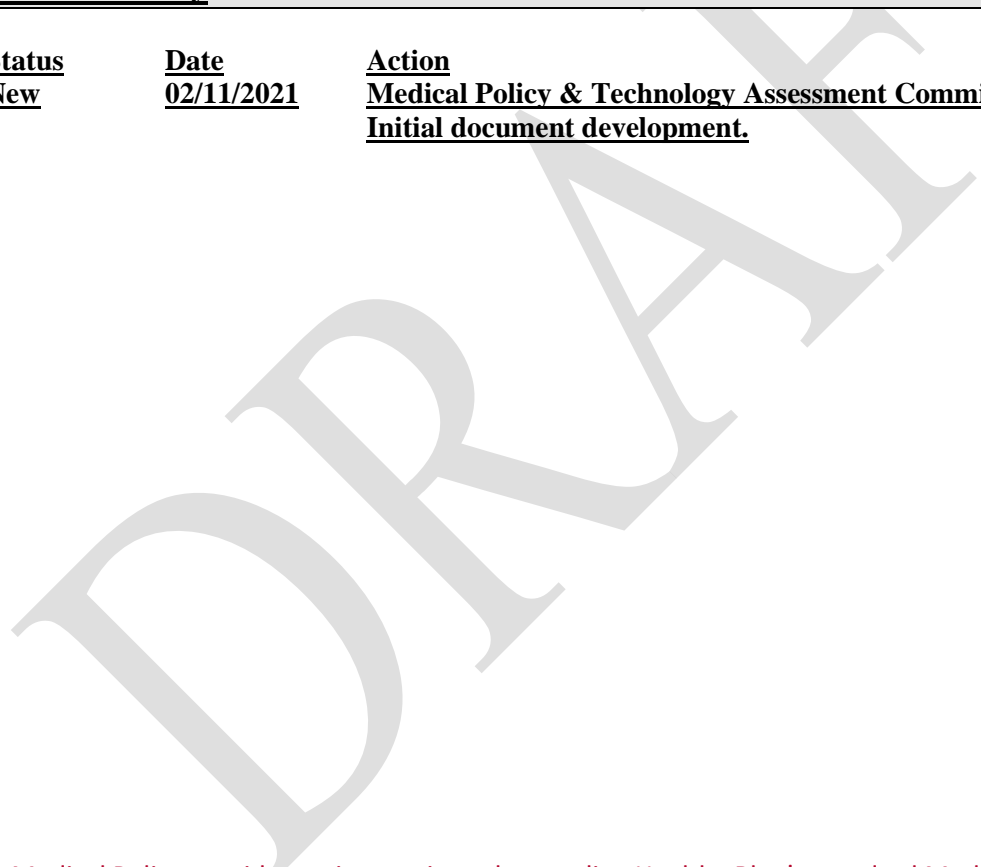
## Gene Expression Profiling for Bladder Cancer

Cxbladder™ Detect  
Cxbladder™ Monitor  
Decipher Bladder TURBT®

**The use of specific product names is illustrative only. It is not intended to be a recommendation of one product over another, and is not intended to represent a complete listing of all products available.**

### Document History

<u>Status</u>	<u>Date</u>	<u>Action</u>
<u>New</u>	<u>02/11/2021</u>	<u>Medical Policy &amp; Technology Assessment Committee (MPTAC) review. Initial document development.</u>



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