**DRAFT Medical Coverage Policy |** Prognostic and Predictive Molecular Classifiers for Bladder Cancer

**EFFECTIVE DATE:** 01|01|2024
**POLICY LAST UPDATED:** 10|02|2023

## OVERVIEW

Molecular subtyping has emerged as a potential diagnostic aid in bladder cancer both to help identify the type of bladder cancer and to more accurately assess the risk and benefit profile of various treatment approaches and to aid in the diagnosis of bladder cancer subtype and risk.

The following test is addressed in this policy:

- Decipher Bladder TURBT, Decipher Biosciences (CPT 0016M)

## MEDICAL CRITERIA

**Medicare Advantage Plans and Commercial Products**

The following tests may be medically necessary when all of the medical criteria below are met:

- Decipher Bladder TURBT, Decipher Biosciences (CPT 0016M)

1. The beneficiary is being actively managed for bladder cancer.
2. The beneficiary is within the population and has the indication for which the test was developed and is covered. The laboratory will make available the appropriate indications of the test to the treating/ordering physician.
3. At least 1 of the 2 criteria are met:
   a. The patient is a candidate for multiple potential treatments, which could be considered to have varied or increasing levels of intensity based on a consensus guideline, and the physician and patient must decide among these treatments.
   OR
   b. The patient is a candidate for multiple therapies, and the test has shown that it predicts response to a specific therapy among accepted therapy options based on nationally recognized society consensus guidelines (i.e., National Comprehensive Cancer Network [NCCN], American Society of Clinical Oncology [ASCO], Society of Urologic Oncology[SUO], or American Urological Association [AUA]).
4. If Next-Generation Sequencing (NGS) methodology is used in testing, the conditions set by NCD 90.2 are fulfilled (summarized: the patient has advanced cancer; plans on being treated for said cancer, and has not been previously tested with the same test for the same genetic content). See requirements below related to NCD 90.2.
5. The test demonstrates analytical validity including both analytical and clinical validations. If the test relies on an algorithm (which may range in complexity from a threshold determination of a single numeric value to a complex mathematical or computational function), the algorithm must be validated in a cohort that is not a development cohort for the algorithm.
6. The test has demonstrated clinical validity and utility, establishing a clear and significant biological/molecular basis for stratifying patients and subsequently selecting (either positively or negatively) a clinical management decision (in 4. above) in a clearly defined population.
7. Only 1 test may be performed prior to the initiation of therapy UNLESS a second test that interrogates different genomic content AND meets all the criteria established herein, is reasonable and necessary.
   - The genomic content interrogated by the test must be relevant to the therapy under consideration.

**NCD 90.2**

Somatic (Acquired) Cancer:

1. Patient has:
   A. either recurrent, relapsed, refractory, metastatic, or advanced stage III or IV cancer; and
   B. not been previously tested with the same test using NGS for the same cancer genetic content, and
   C. decided to seek further cancer treatment (e.g., therapeutic chemotherapy).

AND

2. The diagnostic laboratory test using next generation sequencing (NGS) must have:
   A. Food & Drug Administration (FDA) approval or clearance as a companion in vitro diagnostic; and,
   B. an FDA-approved or -cleared indication for use in that patient's cancer; and,
   C. results provided to the treating physician for management of the patient using a report template to specify treatment options.

**OR**

Germline (Inherited) Cancer:

1. Patient has:
   A. ovarian or breast cancer; and,
   B. a clinical indication for germline (inherited) testing for hereditary breast or ovarian cancer; and,
   C. a risk factor for germline (inherited) breast or ovarian cancer; and
   D. not been previously tested with the same germline test using NGS for the same germline genetic content.

AND

2. The diagnostic laboratory test using NGS must have all of the following:
   A. FDA-approval or clearance; and,
   B. results provided to the treating physician for management of the patient using a report template to specify treatment options.

## PRIOR AUTHORIZATION

**Medicare Advantage Plans and Commercial Products**

Prior authorization is required for Medicare Advantage Plans and recommended for Commercial Products for the following test:

- Decipher Bladder TURBT, Decipher Biosciences (CPT 0016M)

Prior authorization is required for Medicare Advantage Plans and recommended for Commercial Products and is obtained via the online tool for participating providers. See the Related Policies section.

## POLICY STATEMENT

**Medicare Advantage Plans and Commercial Products**

The following test may be considered medically necessary when the medical criteria above are met:

- Decipher Bladder TURBT, Decipher Biosciences (CPT 0016M)

**Commercial Products**

Some genetic testing services are not covered and a contract exclusion for any self-funded group that has excluded the expanded coverage of biomarker testing related to the state mandate, R.I.G.L. **§27-19-81** described in the Biomarker Testing Mandate policy. For these groups, a list of which genetic testing services are covered with prior authorization, are not medically necessary or are not covered because they are a contract exclusion can be found in the Coding section of the Genetic Testing Services or Proprietary Laboratory Analyses policies. Please refer to the appropriate Benefit Booklet to determine whether the member's plan has customized benefit coverage. Please refer to the list of Related Policies for more information

## COVERAGE

Benefits may vary between groups and contracts. Please refer to the appropriate Benefit Booklet, Evidence of Coverage or Subscriber Agreement for applicable laboratory and not medically necessary benefits/coverage.

## BACKGROUND

In the United States, the annual incidence of new bladder cancer is 83,730 patients with approximately 17,200 annual deaths. The majority of bladder cancers originate from the urothelium, with the most important initial risk stratification decision made for these cancers based on whether it is invasive or non-invasive, and how deeply it is has invaded if invasive. Variant histology, common at higher grades, may represent risk of progression or different genetic derivation which may determine whether a more aggressive treatment approach should be considered. In patients who do not have evidence of metastasis at the time of diagnosis, guidelines recommend considering a number of possible treatment approaches of varying intensity and invasiveness, often with recommended follow-up and potential escalation of therapy when there is persistent evidence of cancer. For clinical non-invasive papillary urothelial carcinoma potential treatment approaches include intravesical Bacillus Calmette-Guerin (BCG), intravesical chemotherapy, or even observation. For clinical T1 tumors, potential treatment options include either transurethral resection of the bladder tumor (TURBT) or cystectomy. In patients with stage II or stage IIIa disease, potential treatment options include chemotherapy, radiation, chemoradiation, and surgery accompanied possibly by neoadjuvant and/or adjuvant chemotherapy. While guidelines base recommendations for treatment of localized urothelial cancers heavily on risk stratification, within individual risk groups, the guidelines recommend consideration of multiple treatment strategies of varying levels in intensity and known significant side effects within individual strata. Risk stratification for treatment decisions in patients who are not having or have not yet had a cystectomy are based on clinical staging information; evidence has shown that changes in staging based on pathologic information following cystectomy are common, altering disease risk.

Among the non-urothelial bladder cancers, squamous cell carcinoma, adenocarcinoma, and neuroendocrine (NE) tumors have been recognized as important for implications concerning treatment. Current recommendations do not suggest chemotherapy for pure squamous or adenocarcinoma of the bladder, with radiotherapy and/or surgical resection being the mainstays of treatment.NE and NE-like tumors and those tumors with small cell features have been recognized to be a poor prognostic subtype for which aggressive treatment (including chemotherapy and possibly cystectomy and radiotherapy) is recommended regardless of stage. The diagnosis of NE and NE-like tumors in the bladder may be challenging, particularly on histology alone, and therefore often requires use of additional diagnostic information, such as special stains to look for NE features.

With current standards of care, patients diagnosed with bladder cancer have 5-year relative survival rates (compared to peers without bladder cancer) of 95.8% in cases of in-situ carcinoma and 69.5% in cases of localized cancer with absolute survival rates of 51% and 34% for in-situ and local disease respectively.

Seiler and colleagues developed and validated an algorithm that predicts outcomes in urothelial carcinoma based on molecular subtyping using an algorithm based on gene expression data. The algorithm classified bladder cancer into 1 of 4 subtypes: Claudin-low, basal, luminal-infiltrated, and luminal. They found that the algorithm also predicted response to neoadjuvant chemotherapy. Luminal tumors (non-infiltrated) demonstrated a comparatively good prognosis that appeared minimally affected by differences between patients who did and did not receive neoadjuvant therapy. Basal tumors demonstrated a poor prognosis without neoadjuvant therapy. The prognosis was significantly improved with neoadjuvant therapy to be similar to luminal tumors. The same subtyping algorithm was evaluated in bladder cancers pre-cystectomy as a predictor of pathologic upstaging.

Consistent with Seiler's work showing better prognoses for luminal tumors, it was found that luminal tumors were less likely to be upstaged. Gene expression data has also been found to identify NE-like bladder cancers that histologically appear like urothelial carcinomas. This discernment helps to inform the most appropriate treatment, as noted above.

Ross and colleagues looked at a comprehensive genomic profile (CGP) of 295 cases of advanced urothelial carcinoma and were able to demonstrate that over 90% had at least 1 clinically relevant genetic alteration. The most common clinically relevant genetic alterations were cyclin dependent kinase inhibitor 2A (CDKN2A),

fibroblast growth factor receptor 3 (FGFR3), phosphatidylinositol 3 kinase catalytic subunit alpha (PIK3CA), and erythroblastic oncogene B2 (ERBB2). 14Importantly, some of these are targetable mutations for therapies. For example, in advanced bladder cancer, FGFR3 and fibroblast growth factor receptor 2 (FGFR2) mutations have been found to be associated with response to erdafitinib, which has been Food and Drug Administration (FDA) approved for use in bladder cancer with FGFR3 and FGFR2 mutations.

Currently, erdafitinib, a tyrosine kinase pan-FGFR inhibitor, has been FDA approved as a targeted therapy for patients with prespecified FGFR alterations who had either previously received chemotherapy or were cisplatin-ineligible and chemotherapy-naïve. In a study of 99 patients with locally advanced and unresectable or metastatic urothelial carcinoma, Loriot et al demonstrated that after a median of five cycles of erdafitinib the rate of confirmed response to erdafitinib therapy was 40% (3%with a complete response and 37% with a partial response). Among the 22 patients who had undergone previous immunotherapy, the confirmed response rate was 59%. The median duration of progression-free survival was 5.5 months, and the median duration of overall survival was 13.8 months. Treatment-related adverse events of grade 3 or higher, which were managed mainly by dose adjustments, were reported in 46% of the patients; 13% of the patients discontinued treatment because of adverse events. There were no treatment-related deaths.
Other molecular classifiers and tests will be considered when there is evidence of clinical validity and utility or if nationally recognized treatment guidelines call for their inclusion in the treatment regimen of the defined population in which they are to be used.

The practical value of a diagnostic test can only be assessed by taking into account subsequent health outcomes. When a proven, well established association or pathway is available, intermediate health outcomes may also be considered. For example, if a particular diagnostic test result can be shown to change patient management and other evidence has demonstrated that those patient management changes improve health outcomes, then those separate sources of evidence may be sufficient to demonstrate positive health outcomes from the diagnostic test.

For patients with bladder cancer, an array of treatment possibilities exists at all stages of disease. Clinicians must consider not only the potential treatment options but must also make an individualized risk-to-benefit assessment to determine how to treat a specific patient. Diagnostic tests that aid in this assessment are expected to change physician management in a way that improves patient outcomes. In this regard, the NCCN Bladder Cancer Panel recommends that molecular/genomic testing be conducted for Stages IVA and IVB and may be considered for IIIB bladder cancer. The NCCN Bladder Cancer Panel recommends that molecular testing be conducted early, ideally at diagnosis, to facilitate treatment decision-making, prevent delays in administrating therapy, and to screen for clinical trial eligibility.

## CODING

The following CPT code may be considered medically necessary for Medicare Advantage Plans and Commercial Products when the medical criteria above are met:

This code can be used for Decipher Bladder TURBT:

**0016M** Oncology (bladder), mRNA, microarray gene expression profiling of 219 genes, utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as molecular subtype (luminal, luminal infiltrated, basal, basal claudin-low, neuroendocrine-like)

## RELATED POLICIES

Biomarker Testing Mandate
Proprietary Laboratory Analysis (PLA) and Multianalyte Assays with Algorithmic Analyses (MAAA)

## PUBLISHED

Provider Update, November 2023

## REFERENCES

1. Centers for Medicare and Medicaid Services. Local Coverage Determination (LCD) MolDX: Prognostic and Predictive Molecular Classifiers for Bladder Cancer (L38647)
2. Centers for Medicare and Medicaid Services. Local Coverage Article Billing and Coding: MolDX: Prognostic and Predictive Molecular Classifiers for Bladder Cancer (A58181)
3. Centers for Medicare and Medicaid Services. National Coverage Determination (NCD) Next Generation Sequencing (NGS) 90.2