Medical Coverage Policy | Circulating Tumor-Tissue-Modified Viral DNA Testing for Cancer Management

EFFECTIVE DATE: 03|01|2026
POLICY LAST REVIEWED: 04|01|2026

OVERVIEW
This policy addresses the use of circulating tumor-tissue-viral modified (TTMV) human papillomavirus (HPV) DNA testing for cancer management.

MEDICAL CRITERIA
Not applicable

PRIOR AUTHORIZATION
Not applicable

POLICY STATEMENT
Medicare Advantage Plans
Circulating tumor-tissue-modified viral (TTMV) human papillomavirus (HPV) DNA testing (e.g., NavDx) is not covered as the evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Commercial Products
Circulating tumor-tissue-modified viral (TTMV) human papillomavirus (HPV) DNA testing (e.g., NavDx) is not medically necessary as the evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

Note: Laboratories are not allowed to obtain clinical authorization or participate in the authorization process on behalf of the ordering physician. Only the ordering physician shall be involved in the authorization, appeal or other administrative processes related to prior authorization/medical necessity.

In no circumstance shall a laboratory or a physician/provider use a representative of a laboratory or anyone with a relationship to a laboratory and/or a third party to obtain authorization on behalf of the ordering physician, to facilitate any portion of the authorization process or any subsequent appeal of a claim where the authorization process was not followed and/or a denial for clinical appropriateness was issued, including any element of the preparation of necessary documentation of clinical appropriateness. If a laboratory or a third party is found to be supporting any portion of the authorization process, BCBSRI will deem the action a violation of this policy and severe action will be taken up to and including termination from the BCBSRI provider network. If a laboratory provides a laboratory service that has not been authorized, the service will be denied as the financial liability of the participating laboratory and may not be billed to the member.

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 ser-vices 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/contracts. Please refer to the Evidence of Coverage or Subscriber Agreement for applicable not medically necessary/not covered benefits/coverage.

BACKGROUND

Human Papillomavirus Related Cancers

Human papillomavirus (HPV) infections are the predominant cause of squamous cell carcinoma (SCC) of the oropharynx and constitute 50% of head and neck cancers. Additionally, HPV infections are highly associated with invasive anal carcinomas with over 85% of anal cancer being attributed to an HPV infection. Individuals with locally advanced HPV-related HNSCC as compared to HPV-unrelated individuals have improved response to treatment and survival (overall survival [OS] and progression-free survival [PFS]). Individuals with HPV-related anal carcinoma also demonstrate a favorable prognosis in regard to OS in comparison to HPV-unrelated tumors. Despite the favorable prognosis for HPV-related cancers, the treatment is highly similar to HPV-unrelated cancer as there is currently no evidence to support treatment algorithms that address the distinct biological differences between these malignancies. Decisions about neoadjuvant and adjuvant chemotherapy are currently based on clinicopathological risk factors.

Circulating Tumor Human Papillomavirus DNA

Normal and tumor cells release small fragments of DNA into the blood, which is referred to as cell-free DNA (cfDNA). Cell-free DNA from nonmalignant cells is released by apoptosis. Most cell-free tumor DNA is derived from apoptotic and/or necrotic tumor cells, either from the primary tumor, metastases, or circulating tumor cells.3, Circulating tumor DNA (ctDNA) is released by dying cancer cells and represents an accessible source for detecting tumor genetic biomarkers in many cancer types. Unlike apoptosis, necrosis is considered a pathologic process and generates larger DNA fragments due to incomplete and random digestion of genomic DNA. The length or integrity of the circulating DNA can potentially distinguish between apoptotic and necrotic origin. Circulating tumor DNA can be used for genomic characterization of the tumor. In human papillomavirus (HPV)-related cancer, HPV viral genomes are usually integrated into the tumor cell genome or episomal DNA and release circulating tumor HPV DNA (ctHPVDNA).

Circulating Tumor-Tissue-Modified Viral DNA

NavDx is a tumor-tissue-modified viral (TTMV) HPV DNA test for HPV-related cancers of the head and neck or anus. TTMV-HPV DNA is a unique cancer biomarker that tumor cells of cancers driven by human papillomavirus shed into the blood. The TTMV-HPV DNA biomarker is unique to HPV-related cancers such as head and neck squamous cell carcinoma (HNSCC) or anal squamous cell carcinoma (ASCC) and is specific to the implicated HPV-genotype. HPV-16 is the most common pathogenic genotype; however, other high-risk HPV genotypes include HPV-18, HPV-31, HPV-33, and HPV-35. These genotypes are distinguishable from noncancerous genotypes by using droplet digital polymerase chain reaction (ddPCR) and paired with an algorithmic analysis of fragmentation patterns used to generate a TTMV-HPV DNA score. This approach detects tumor-derived HPV DNA from the 5 high-risk HPV subtypes (16, 18, 31, 33, and 35). Results are reported as a TTMV-HPV DNA score, which reflects the normalized number of TTMV-HPV DNA fragments per milliliter of plasma. Scores are categorized as positive, indeterminate, or negative. Scores >7 (for HPV subtype 16) or >12 (for HPV subtypes 18, 31, 33, or 35) are considered positive, scores between 5 and 7 (HPV 16) or 5 and 12 (HPV 18, 31, 33, or 35) are considered indeterminate, while scores <5 are considered negative, regardless of HPV subtype.

In publicly available literature, ctHPVDNA and TTMV-HPV DNA are used synonymously as they both refer to circulating DNA derived from HPV-related tumors. However, TTMV-HPV DNA refers directly to DNA that is detected using the commercially available NavDx test.

Regulatory Status

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CILA). Laboratories that offer laboratory-developed tests must be licensed by the Clinical Laboratory Improvement Amendments for high-complexity testing.

NavDx® (Naveris) is the first commercially available tumor-tissue-modified (TTMV™) human papillomavirus (HPV) DNA blood test regulated under CLIA marketed for the detection of HPV-related cancer. The test has not been cleared or approved by the United States Food and Drug Administration.

For individuals who have HPV-related head and neck squamous cell carcinoma (HNSCC) who receive circulating tumor-tissue-modified viral (TTMV) HPV DNA testing with NavDx to guide treatment decisions and monitor for recurrence, the evidence includes systematic review/meta-analysis and nonrandomized observational studies. Relevant outcomes are overall survival, disease-specific survival, test validity, other test performance measures, change in disease status, morbid events, functional outcomes, health status measures, quality of life, and treatment-related mortality. The systematic review and observational studies have reported positive TTMV-HPV DNA scores measured at diagnosis, following surgery, during adjuvant therapy, and during surveillance after treatment that underscore the potential clinical utility of NavDx testing in determining recurrence at earlier stages with potential to make better treatment decisions. However, these studies are limited by an imperfect reference standard, imprecise estimates due to small sample sizes, clinical heterogeneity of study populations, variability in data recording, different conditions under which measurements occurred, and lack of a comparator that prohibit any concrete conclusions regarding clinical utility. One study reported management changes made in response to TTMV-HPV DNA test results and was terminated early, thus preventing any conclusions regarding the utility of TTMV-HPV DNA scores in management of individuals with HNSCC. There is no direct evidence that the use of the test improves health outcomes, and indirect evidence is not sufficient to draw conclusions about clinical utility given the lack of a bona fide reference standard. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have HPV-related anal squamous cell carcinoma (ASCC) who receive circulating tumor-tissue-modified viral (TTMV) HPV DNA testing with NavDx to monitor for reoccurrence, minimal residual disease, and guide treatment decisions, the evidence includes 1 nonrandomized clinical trial and 2 retrospective studies. Relevant outcomes are overall survival, disease-specific survival, test validity, other test performance measures, change in disease status, morbid events, functional outcomes, health status measures, quality of life, and treatment-related mortality. The retrospective and nonrandomized studies have reported an association between TTMV-HPV DNA positive scores measured at diagnosis, following surgery, during adjuvant therapy, and during surveillance after treatment and poor prognosis. Moreover, individuals whose TTMV-HPV DNA scores improved from baseline measurements were associated with clinical benefit as opposed to individuals whose TTMV-HPV DNA scores did not. However, these studies are limited by an imperfect reference standard, imprecise estimates due to small sample sizes, clinical heterogeneity of study populations, variability in data recording, different conditions under which measurements occurred, and lack of comparators. No study reported management changes made in response to TTMV-HPV DNA test results and current management algorithms do not substantially differ based on HPV-related pathology. There is no direct evidence that the use of the test improves health outcomes, and indirect evidence is not sufficient to draw conclusions about clinical utility given the lack of a bona fide reference standard. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

For individuals with cancer of the head and neck or anus that are suspected to be driven by the human papillomavirus (HPV) and receive circulating tumor-tissue-modified viral (TTMV) HPV DNA testing with NavDx to determine if their cancer is HPV-related, the evidence includes 3 observational studies (N = 300) have reported an association of circulating TTMV-HPV DNA with the diagnosis of HPV-related cancer. Relevant outcomes are test validity, overall survival, and disease-specific survival. Studies are limited by an imperfect reference standard, imprecise estimates due to small sample sizes, clinical heterogeneity of study populations, variability in data recording, different conditions under which measurements occurred, and lack of a comparator that prohibit any concrete conclusions regarding clinical utility. No study reported management changes made in response to TTMV-HPV DNA test results and current management algorithms do not substantially differ based on HPV-related pathology. There is no direct evidence that the use of the test improves health outcomes, and indirect evidence is not sufficient to draw conclusions about clinical utility given the lack of a bona fide reference standard. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

CODING

Medicare Advantage Plans and Commercial Products

The following code(s) are not covered for Medicare Advantage Plans and not medically necessary for Commercial Products:

0356U Oncology (oropharyngeal or anal), evaluation of 17 DNA biomarkers using droplet digital PCR (ddPCR), cell-free DNA, algorithm reported as a prognostic risk score for cancer recurrence

RELATED POLICIES

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

PUBLISHED

Provider Update, January/June 2026

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