2.04.160	Circulating Tumor-Tissue-Modified Viral DNA Testing for Cancer Management		
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Section:	2.0 Medicine	**Page:**	Page 1 of 32

Policy Statement

I. Circulating tumor-tissue-modified viral (TTMV) human papillomavirus (HPV) DNA testing (e.g., NavDx is considered **investigational.**

NOTE: Refer to Appendix A to see the policy statement changes (if any) from the previous version.

Policy Guidelines

Coding
See the Codes table for details.

Description

This evidence review addresses the use of circulating tumor-tissue-viral modified (TTMV) human papillomavirus (HPV) DNA testing for cancer management. The purpose of tumor-informed TTMV-HPV DNA testing in individuals with HPV-related cancer is to predict disease outcomes to inform treatment decisions and to monitor for recurrence following treatment.

Summary of Evidence
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.

Additional Information
Not applicable.

Related Policies

- Circulating Tumor DNA and Circulating Tumor Cells for Cancer Management (Liquid Biopsy)
- Tumor-Informed Circulating Tumor DNA Testing for Cancer Management

Benefit Application

Benefit determinations should be based in all cases on the applicable member health services contract language. To the extent there are conflicts between this Medical Policy and the member health services contract language, the contract language will control. 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.

Some state or federal law may prohibit health plans from denying FDA-approved Healthcare Services as investigational or experimental. In these instances, Blue Shield of California may be obligated to determine if these FDA-approved Healthcare Services are Medically Necessary.

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.

Rationale

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.[1,2,]

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 recent years, the development of genetic sequencing technology that can detect tumor-specific HPV DNA test in serum samples has sparked an increase in clinical studies to evaluate the validity and utility of this technology for HPV-associated cancers. Several studies have examined the relationship between circulating TTMV-HPV DNA levels and clinical disease characteristics, providing biological rationale for the potential utility of this biomarker in HPV-driven cancers. In a retrospective cohort of 94 patients with HPV-associated oropharyngeal squamous cell carcinoma, Lee et al. (2025) found that pretreatment TTMV-HPV DNA levels were significantly associated with cervical lymph node disease burden, including largest metastatic lymph node dimension on CT (p<.001) and surgical pathology (p=.01), number of metastatic nodes (p=.01), radiographic evidence of extranodal extension (p=.04), and lymph node SUV-max on positron emission tomography/computed tomography ([PET/CT]; p<.001). [4,] Similarly, Kuhs et al. (2025) reported in a single-institution cohort study (N=203) that patients with higher clinical T stage and N stage had increased odds of higher pretreatment TTMV-HPV DNA levels, and that total primary tumor plus nodal volume on PET-CT was independently associated with TTMV-HPV DNA levels. [5,] Notably, neither study found significant associations between pretreatment TTMV-HPV DNA levels and primary tumor size or adverse histopathologic features such as lymphovascular invasion, perineural invasion, or extranodal extension on surgical pathology, suggesting that circulating TTMV-HPV DNA may reflect nodal disease burden more closely than primary tumor characteristics.

Yin et al. (2025) extended the understanding of TTMV-HPV DNA behavior into the immediate postoperative period in a prospective cohort of 57 patients with HPV-associated OPSCC undergoing transoral robotic surgery with concurrent neck dissection. [6,] Among patients with detectable pretreatment TTMV-HPV DNA, undetectable levels on postoperative days 1 to 2 had a negative predictive value of 0.95 (95% CI: 0.74–1.00) for remaining undetectable at postoperative week 2, whereas a detectable level on postoperative days 1 to 2 had a positive predictive value of only 0.19 for persistence at week 2, indicating that early postoperative detectability is often transient and may not reliably predict residual disease. Beyond pretreatment correlations, Tang et al. (2025) examined TTMV-HPV DNA clearance kinetics during induction chemotherapy in 28 individuals with locally advanced HPV-positive oropharyngeal cancer and found that rapid clearance of TTMV-HPV DNA after the first cycle of induction therapy was significantly associated with remaining disease-free during surveillance (p=.046), whereas all six recurrences in the cohort occurred among patients with delayed clearance. [7,] Rapid responders also had significantly lower baseline TTMV-HPV DNA levels than slow responders (median 156 vs. 3017 fragments/mL, p=.049). Collectively, these studies demonstrate that circulating TTMV-HPV DNA levels correlate with measurable disease burden at diagnosis and that the kinetics of TTMV-HPV DNA clearance during treatment are prognostically informative, supporting the biological plausibility of this biomarker for monitoring disease status in HPV-driven cancers. However, much remains to be studied regarding the quantitative importance of a positive pre-treatment result and correlations with disease burden.

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.

Literature Review

Evidence reviews assess whether a medical test is clinically useful. A useful test provides information to make a clinical management decision that improves the net health outcome. That is, the balance of benefits and harms is better when the test is used to manage the condition than when another test or no test is used to manage the condition.

The first step in assessing a medical test is to formulate the clinical context and purpose of the test. The test must be technically reliable, clinically valid, and clinically useful for that purpose. Evidence reviews assess the evidence on whether a test is clinically valid and clinically useful. Technical reliability is outside the scope of these reviews, and credible information on technical reliability is available from other sources.

Circulating Tumor-Tissue-Modified Viral DNA Testing with NavDx in Individuals with Human Papillomavirus-related Head and Neck Cancer

Clinical Context and Test Purpose

The purpose of NavDx testing in patients who have human papillomavirus (HPV)-related head and neck cancer is to inform treatment decisions and to monitor for recurrence following treatment.

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest are individuals with HPV-related head and neck squamous cell carcinoma.

Interventions

The test being considered is circulating tumor-tissue-modified viral (TTMV) HPV DNA testing with NavDx:

- After treatment to inform decisions about adjuvant treatment, or
- During disease surveillance after treatment, to identify metastatic relapse at an early timepoint, and aid in the selection of individuals who may benefit from early/adjuvant treatment.

Comparators

The following practice is currently being used: standard clinical management without NavDx testing. In individuals with HPV-related head and neck cancer, surveillance and follow-up decisions are guided by the individual's tumor staging and other clinicopathological factors.

Individuals with HPV-related head and neck squamous cell carcinoma (HNSCC) lack the traditional risk factors present in HPV-unrelated HNSCC and have been shown to have better prognosis with limited incidences of developing a secondary primary malignancy. Individuals with HPV-related cancer have a longer median time to recurrence than individuals with HPV-unrelated cancer. The median time to recurrence for individuals with HNSCC is approximately 2 years. Surveillance can be challenging because of altered anatomy and/or fibrosis from surgery, radiation, and/or chemotherapy. Surveillance frequency and duration of follow up for HPV-related HNSCC is not well defined and varies amongst physicians in clinical practice. There are no consensus guidelines on the frequency and modality of routine post-treatment imaging in the asymptomatic patient. However, the National Comprehensive Cancer Network (NCCN) guidelines for disease surveillance following head and neck cancer treatment recommend clinical assessments at 4-8 week and regular history and physical exams (including mirror and fiberoptic examination) every 1 to 3 months during year 1, every 2 to 6 months in year 2, every 4 to 8 months in year 3 to 5, and every 12 months thereafter.[2,]

Outcomes

The general outcomes of interest are disease-specific survival, test accuracy and validity, and change in disease status. Specific outcomes of interest are recurrence risk, recurrence-free survival (RFS), progression-free survival (PFS), and overall survival (OS) at follow-up.

The treatment for HPV-related head and neck squamous cell carcinoma (HNSCC) is highly similar to HPV-unrelated HNSCC as there is currently no evidence to support treatment algorithms that address the distinct biological differences between these cancers. Decisions about neoadjuvant and

adjuvant chemotherapy are based on clinicopathological risk factors.[2,] If used for risk stratification to rule-out individuals for neoadjuvant chemotherapy at diagnosis or adjuvant treatment following surgery, the performance characteristics of most interest are negative predictive value and sensitivity. If used for risk stratification to rule-in individuals for neoadjuvant chemotherapy at diagnosis or adjuvant treatment following surgery, the performance characteristics of most interest are positive predictive value and specificity.

If used for disease surveillance following primary treatment, beneficial outcomes of a true positive test would be earlier detection of metastasis and initiation of appropriate treatment. Harmful outcomes of a false positive test would be undergoing unnecessary or incorrect treatment and experiencing adverse effects of such treatment. For individuals who are being monitored for relapse following treatment for HPV-related HNSCC, the timepoint of interest to assess recurrence should be between 2 - 5 years following treatment.

Study Selection Criteria

For the evaluation of clinical validity of the NavDx test, studies that meet the following eligibility criteria were considered:

- Reported on the accuracy of the marketed version of the technology (including any algorithms used to calculate scores)
- Included a suitable reference standard
- Patient/sample clinical characteristics were described
- Patient/sample selection criteria were described.

Clinically Valid

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Systematic Reviews

Campo et al (2024) published a systematic review of 12 studies (N=1311) investigating the use of circulating tumor human papillomavirus DNA (ctHPVDNA) and tumor-tissue-modified viral (TTMV) HPV DNA as a biomarker for recurrence in patients with HPV-related oropharynx squamous cell carcinoma (OPSCC) post-treatment; only 3 of the included studies used the NavDx TTMV-HPV DNA assay. [8,; 9,;10,] The results of this analysis demonstrate that TTMV-HPV DNA testing has high accuracy (Diagnostic Odds Ration [DOR] = 589), sensitivity (89.7% [95% CI 72.2 to 96.7]; p>.05), and specificity (96.4% [95% CI 91.1 to 98.6]; p>.05) for the diagnosis of recurrence in patient with HPV-related OPSCC.

Nonrandomized Studies

Ten nonrandomized studies examined the association of NavDx testing to diagnosis of recurrence, prognosis, or response rates in individuals with head and neck squamous cell carcinoma (HNSCC) (Table 1). They differed in their study designs, populations (e.g., stage of disease), frequency and timing of standard care, outcome measures, and timing of follow up. Four observational studies evaluated the association between positive TTMV-HPV DNA results and diagnosis of recurrence in HNSCC (Table 2). [11,8,9,10,] A fifth retrospective study, set out to determine if TTMV-HPV DNA testing had clinical utility in resolving indeterminate disease status for individuals with HPV-related oropharyngeal cancer and found that TTMV-HPV DNA testing was able to observe faster clinically confirmed recurrence rates with initial clinically indeterminate findings during surveillance. [12,] Three studies monitored the relationship between TTMV-HPV DNA levels and responses to select therapies in patients with recurrent/metastatic HNSCC.[13,14,15,] These studies did not provide comparisons of TTMV-HPV DNA testing to standard methods of risk stratification for therapy selection, monitoring response to therapy, or early relapse detection. There are no RCTs, and no studies in which NavDx testing was used to guide treatment decisions.

Reyes et al (2025) conducted a single-institution retrospective analysis of 88 individuals with HPV-positive oropharyngeal squamous cell carcinoma treated at the City of Hope National Medical Center between 2016 and 2024 who had both baseline-positive and post-treatment TTMV-HPV DNA testing using the NavDx assay. [16,] Individuals were classified as MRD-positive (detectable TTMV-HPV DNA after definitive treatment, N=11) or MRD-negative (undetectable after treatment, N=77). MRD-positive patients had significantly worse overall survival (OS) at 1 and 2 years (63.5% and 50.8%, respectively) compared to MRD-negative patients (100% and 96.4%), with a univariate hazard ratio of 14.76 (95% CI: 3.39 to 64.15, p<.001) for OS and 9.05 (95% CI: 3.75 to 21.83, p<.001) for progression-free survival (PFS). In a sensitivity analysis, MRD-negative status at 3 months after treatment completion was also associated with improved 2-year progression-free survival (88.9% vs. 55.5%, p=.0016) and overall survival (97.3% vs. 81.7%, p=.043) compared to individuals who were MRD-positive or had not yet cleared at that timepoint. On multivariate analysis adjusting for age, PD-L1 status, HPV subtype, treatment type, and stage, MRD positivity remained significantly associated with worse PFS (HR 4.43, 95% CI: 1.30 to 15.09, p=.017), though the association with OS did not reach significance (HR: 2.01, 95% CI: 0.20 to 20.54, p=.557). No other clinical factors were significantly associated with survival on multivariate analysis. Limitations include the retrospective single-center design, small number of MRD-positive individuals (N=11) resulting in wide confidence intervals, exclusion of 82 individuals who lacked paired pre- and post-treatment testing, non-uniform timing of post-treatment testing, a higher proportion of advanced-stage disease in the MRD-positive group that may confound unadjusted comparisons, and the absence of standard clinical validity metrics such as sensitivity, specificity, and predictive values for recurrence detection.

Chen et al (2026) conducted the first prospective pilot trial (NCT05307939) using NavDx TTMV-HPV DNA testing as an integral biomarker to guide omission of adjuvant radiation therapy in surgically managed HPV-positive oropharyngeal carcinoma at Memorial Sloan Kettering Cancer Center and affiliated sites. [17,] From the 55 individuals screened, 12 were enrolled after meeting stringent eligibility criteria (HPV-16 genotype, preoperative TTMV-HPV DNA score of 50 or greater, two negative postoperative TTMV-HPV DNA results, no evidence of disease on postoperative MRI, at least one pathologic risk factor warranting adjuvant radiation, and no extranodal extension or positive margins). Enrolled individuals underwent active surveillance with TTMV-HPV DNA testing, imaging, and physical exams every 3 months rather than receiving standard adjuvant radiation. At a median follow-up of 26.6 months, 8 of 12 individuals (67%) remained on active surveillance without recurrence. However, 3 of the 12 (25%) developed radiographic recurrence at 6 months after surgery, and 1 (8%) developed detectable TTMV-HPV DNA without radiographic disease and received delayed adjuvant radiation per protocol. Critically, TTMV-HPV DNA did not precede radiographic recurrence in any of the 3 patients with gross disease, but it was detected, synchronously, in 2 individuals and remained falsely negative in 1 individual despite a high pretreatment score of 1608. The postoperative assay sensitivity for gross disease was 67%, specificity was 100%, the false-negative rate for gross disease was 33%, and the false-negative rate for microscopic disease was 75%. Additionally, during screening, 27% of confirmed HPV-positive individuals with oropharyngeal carcinoma had negative or indeterminate baseline TTMV-HPV DNA scores, and 45% overall were excluded due to baseline TTMV-HPV DNA requirements. The study closed early due to a prespecified stopping rule triggered by the high recurrence rate. The authors concluded that the sensitivity of NavDx for minimal residual disease in the postoperative setting is not sufficient for omission of standard adjuvant radiation therapy and that such approaches should be reserved for clinical trial settings. Limitations include the very small sample size (N=12 enrolled), non-randomized single-arm design, restriction to HPV-16 genotype and individuals who underwent surgery without extranodal extension or positive margins (limiting generalizability), and the possibility that the high TTMV-HPV DNA eligibility threshold of 50 or greater may have excluded individuals with lower tumor shedding who could have different recurrence profiles.

Chung et al (2022) conducted multi-institutional phase II clinical trial to evaluate overall survival in patients with recurrent and/or metastatic (R/M) HNSCC who have received combination therapy of cetuximab and nivolumab.[14,] Analysis of the exploratory endpoints determined that patients with

TTMV-HPV DNA levels less than the median at baseline achieved longer median PFS (3.1 months) and OS (8.6 months) compared to those with higher than median levels of TTMV-HPV DNA (p =.02 and p =.05, respectively).

Jhawar et al (2024) evaluated the relationship of TTMV-HPV DNA clearance and its impact on progression-free survival (PFS) in a prospective biomarker study (N = 80) that included patients with non-metastatic HPV-related OPSCC who received definitive radiotherapy (RT)/chemoradiation therapy (CRT).[15,] PFS was significantly worse in patients who had persistent TTMV-HPV DNA levels at the end of treatment compared to patients who cleared TTMV-HPV DNA at 2 years (91.7% vs. 71.7%; log rank; p =.042). Moreover, this study included PET/CT surveillance at 3 months post-treatment to determine evidence of disease and found that among patients with complete TTMV-HPV DNA clearance at 3 months but had either a negative, equivocal, or incomplete PET/CT result had a 2-year PFS of 94.3%, 77.8%, and 59.3%, respectively (p =.029).

Hanna et al (2024) assessed the prognostic and surveillance value of TTMV-HPV DNA testing in R/M HPV-related OPSCC in a retrospective fashion. [13,] Patients with detectable TTMV-HPV DNA scores at last follow-up had significantly worse survival compared with those who were undetectable (p <.01).

Rettig et al (2024) enrolled 182 individuals with HPV-related oropharynx cancer in a prospective study to determine if TTMV-HPV DNA testing detects recurrence earlier than standard-of-care imaging techniques. [11,] Individuals with detectable TTMV-HPV DNA during surveillance were significantly associated with a worse RFS (HR = 75, 95% CI = 21 to 273; p <.001). Of note, these estimates were imprecise with wide confidence intervals. TTMV-HPV DNA testing was able to detect many recurrences at earlier intervals than stand-of-care treatment, especially in HPV16 serotypes. However, false-negatives and false-positives were reported in this study and highlight the variability of circulating TTMV-HPV DNA levels in HPV-related cancers. Additionally, due to the small sample size of individuals and the small number of recurrences no definitive conclusions can be drawn on the clinical utility and validity.

Study limitations are shown in Tables 3 and 4. Major limitations include a lack of comparison to tests used for the same purpose, imprecise estimates due to small sample sizes, and clinical heterogeneity of study populations.

Table 1. Nonrandomized Studies of NavDx Testing in HPV-related Head and Neck Cancer - Study Characteristics

Study*	Test Purpose	Study Population	Setting	Reference Standard	Timing of Reference and Index Test
Chen et al (2026) [17,]	1. Minimal residual disease detection 2. Guide administration of adjuvant therapy	12 individuals HPV-related OPSCC (both p16 and HPV mRNA in situ hybridization positive)	US, single cite, prospective	Imaging (MRI, CT with or without contrast, PET/CT) and clinical exams including fiberoptic endoscopic scope.	TTMV-HPV DNA was assessed every 3 months in year 1 and every 6 months in year 2. Timing was the same for the reference tests.
Reyes et al (2025) [16,]	1. Risk stratification 2. Early recurrence detection	88 individuals HPV-related OPSCC from 2016 to 2024	US, single cite, retrospective	Physical examinations and	TTMV and reference testing were performed for

Study*	Test Purpose	Study Population	Setting	Reference Standard	Timing of Reference and Index Test
				restaging imaging	individuals at clinicians' discretion
Berger et al (2022)[8],	1. Early recurrence detection	1076 individuals HPV-related OPSCC from February 6, 2020, to June 29, 2021	US, multicenter, retrospective	Physical examinations and restaging imaging	TTMV testing was obtained at least 3 months posttreatment Reference testing was collected at clinicians' discretion during management of the disease
Hanna et al (2023)[10],	1. Early recurrence detection	543 individuals with HPV-related OPSCC treated with curative intent between February 2020 and January 2022	US, multicenter, retrospective	Physical examinations and restaging imaging	TTMV testing was obtained at least 3 months posttreatment Reference testing was collected at clinicians' discretion during management of disease
Ferrandino et al (2023)[9],	1. Diagnosis of HPV-related cancer 2. Early recurrence detection	399 individuals OPSCC who had undergone TTMV-HPV DNA testing between Aprill 2020 and September 2022.	US, single center, retrospective	1.Tissue biopsy with IHC p16+ testing 2.Physical examinations and restaging imaging	TTMV-HPV DNA levels were obtained prospectively prior to treatment, at the end of treatment, or at least 3 months post-treatment in all patients. Reference testing was collected at clinicians' discretion during management of disease
Rettig et al (2024)[11],	1. Early recurrence detection	182 individuals with HPV-related oropharynx cancer who	US, single center, prospective	Physical examinations and	TTMV testing was performed for individuals at

Study*	Test Purpose	Study Population	Setting	Reference Standard	Timing of Reference and Index Test
		underwent curative-intent treatment between November 2020, to April 2023.		restaging imaging	prespecified intervals posttreatment during surveillance, generally corresponding to surveillance follow-up visits, including: 2 to 3 weeks after surgery for patients treated with surgery alone or 6 weeks after radiation completion; 3 months after treatment; every 3 months up to 2 years after treatment; and every 6 months up to 3 years after treatment Standard surveillance strategy at 3 months and at clinicians' discretion.
Hanna et al (2024)[13,]	1. Risk stratification 2. Early recurrence detection	80 individuals with biopsy-proven or radiologically identified R/M HPV-related OPSCC that had 1 or more TTMV-HPV DNA test during their course of the disease from February 2020 through June 2023	US, multicenter, retrospective	Physical examinations and restaging imaging	TTMV and reference testing were performed for individuals at clinicians' discretion
Jhawar et al (2024)[15,]	1. Risk stratification 2. Early recurrence detection	80 individuals with non-metastatic, HPV-related OPSCC	NA, prospective	PET/CT imaging	TTMV-HPV DNA levels were obtained prospectively

Study*	Test Purpose	Study Population	Setting	Reference Standard	Timing of Reference and Index Test
		who were treated with definitive radiation with or without concurrent chemotherapy between 16 June2021 and 9 February 2023			prior to treatment, at the end of treatment, and at least 3 months post-treatment in all patients. PET/CT scans were taken at 3months posttreatment
Chung et al (2022)[14],	1. Risk stratification 2. Monitoring response to adjuvant immunotherapy	95 individuals with histologically or cytologically confirmed SCC of oral cavity, oropharynx, paranasal sinuses, nasal cavity, hypopharynx, or larynx; p16-positive SCC of unknown primary in a cervical lymph node; or incurable R/M HNSCC by a local therapy (surgery or radiotherapy with or without chemotherapy)	US, multicenter phase 2 clinical trial	CT or MRI imaging	Whole blood was collected at 5 time points: (i) pretreatment, (ii) after cetuximab lead-in or 2 weeks after Cycle 1Day 1, (iii) Cycle 4 Day 1, (iv) end of treatment, and (v) end of 2-year follow-up or at the time of disease progression, whichever was earlier CT or MRI imaging studies were obtained every 6 weeks for cycles 1 to 4, every 2 cycles during cycles 5 to 6, and then every 3 cycles during cycles 7 to 24 while on study drugs

CT = computed tomography; HPV = human papillomavirus; IHC= immunohistochemistry; MRI = Magnetic resonance imaging; NA = not accessible; OPSCC = oropharyngeal squamous cell carcinoma; PET = positron emission tomography; R/M HNSCC = recurrent and/or metastatic head and neck squamous cell carcinoma; SCC = squamous cell carcinoma; TTMV = tumor-tissue-modified viral; *Positive, negative, and indeterminate scores were determined according to the manufacturer's instructions described in the background section of this medical policy.

Table 2. Observational Studies for Diagnosis of Recurrence in HPV-related Head and Neck Cancer

Study	Sensitivity % (95% CI)	Specificity % (95% CI)	PPV % (95% CI)	NPV % (95% CI)
Chen et al (2026) [17,]	67%	100%	NR	NR
Berger et al (2022)[8,]	99.4 (90.5 to 100)[a]	10.0 (0.6 to 67.4)[a]	95	95
Hanna et al (2023)[10,]	87.3 (79.1 to 95.5)	99.4 (98.7 to 100)	94.8 (89.1 to 100)	98.4 (97.3 to 99.5)
Ferrandino et al (2023)[9,]	81.8 (59.7 to 94.8)	100 (98.6 to 100)	100 (81.5 to 100)	98.5 (96.3 to 99.6)
Rettig et al (2024)[11,]	73 (45 to 92)	98 (94 to 100)	79 (49 to 95)	97 (93 to 99)

NA: not reported; NPV: negative predictive value; PPV: positive predictive value;
[a] Data was taken from the Campo et al (2024) systematic review as it was not accessible from the original source.

Table 3. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-Up[e]
Chen et al (2026) [17,]				1. Survival outcomes not assessed	
Reyes et al (2025) [16,]			3. No comparator		
Berger et al (2022)[8,]			3. No comparator	1. Survival outcomes not assessed	1. Follow up for recurrence was under 2 years (median 9 months)
Hanna et al (2023)[10,]			3. No comparator	1. Survival outcomes not assessed	1. Follow up for recurrence was under 2 years (median 13.8 months)
Ferrandino et al (2023)[9,]			3. No comparator	1. Survival outcomes not assessed	
Rettig et al (2024)[11,]			3. No comparator	1. Survival outcomes not assessed	1. Follow up for recurrence was under 2 years (median 23 months)
Hanna et al (2024)[13,]			3. No comparator	2. No decision model regarding survival outcomes	1. No median follow up was reported
Jhawar et al (2024)[15,]			3. No comparator	2. No decision model regarding survival outcomes	1. Follow up for recurrence was under 2 years (median 14.7 months)
Chung et al (2022)[14,]			3. No comparator	2. No decision model regarding survival outcomes	1. Follow up for recurrence was under 2 years (median 15.9 months)

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.

[b] Intervention key: 1. Classification thresholds not defined; 2. Version used unclear; 3. Not intervention of interest.
[c] Comparator key: 1. Classification thresholds not defined; 2. Not compared to credible reference standard; 3. Not compared to other tests in use for same purpose.
[d] Outcomes key: 1. Study does not directly assess a key health outcome; 2. Evidence chain or decision model not explicated; 3. Key clinical validity outcomes not reported (sensitivity, specificity and predictive values); 4. Reclassification of diagnostic or risk categories not reported; 5. Adverse events of the test not described (excluding minor discomforts and inconvenience of venipuncture or noninvasive tests).
[e] Follow-Up key: 1. Follow-up duration not sufficient with respect to natural history of disease (true positives, true negatives, false positives, false negatives cannot be determined).

Table 4. Study Design and Conduct Limitations

Study	Selection[a]	Blinding[b]	Delivery of Test[c]	Selective Reporting[d]	Data Completeness[e]	Statistical[f]
Chen et al (2026) [17,]		1.No blinding				2. Comparison to other tests not reported
Reyes et al (2025) [16,]	2. Retrospective analysis	1.No blinding	2. Timing of delivery of NavDx test was not the same			2. Comparison to other tests not reported
Berger et al (2022)[8,]	2. Retrospective analysis	1.No blinding	2. Timing of delivery of NavDx test was not the same			2. Comparison to other tests not reported
Hanna et al (2023)[10,]	2. Retrospective analysis	1.No blinding	2. Timing of delivery of NavDx test was not the same			2. Comparison to other tests not reported
Ferrandino et al (2023)[9,]	2. Retrospective analysis	1.No blinding	2. Timing of delivery of NavDx test was not the same			2. Comparison to other tests not reported
Rettig et al (2024)[11,]	2. Prospective analysis	1.No blinding	2. Timing of delivery of NavDx test was not the same			2. Comparison to other tests not reported
Hanna et al (2024)[13,]	2. Prospective analysis	1.No blinding	2. Timing of delivery of NavDx test was not the same			2. Comparison to other tests not reported
Jhawar et al (2024)[15,]	2. Prospective analysis	1.No blinding	2. Timing of delivery of NavDx test and PET/CT imaging was not the same			2. Comparison to other tests not reported
Chung et al (2022)[14,]		1.No blinding	2. Timing of delivery of NavDx test			2. Comparison to other tests not reported

Study	Selection[a]	Blinding[b]	Delivery of Test[c]	Selective Reporting[d]	Data Completeness[e]	Statistical[f]
			and CT or MRI imaging was not the same			

CT = computed tomography; MRI = Magnetic resonance imaging; PET = positron emission tomography
The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Selection key: 1. Selection not described; 2. Selection not random or consecutive (i.e., convenience).
[b] Blinding key: 1. Not blinded to results of reference or other comparator tests.
[c] Test Delivery key: 1. Timing of delivery of index or reference test not described; 2. Timing of index and comparator tests not same; 3. Procedure for interpreting tests not described; 4. Expertise of evaluators not described.
[d] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
[e] Data Completeness key: 1. Inadequate description of indeterminate and missing samples; 2. High number of samples excluded; 3. High loss to follow-up or missing data.
[f] Statistical key: 1. Confidence intervals and/or p values not reported; 2. Comparison to other tests not reported.

Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials. No studies have directly assessed health outcomes in individuals prospectively managed with and without TTMV-HPV DNA testing.

Chain of Evidence

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

Section Summary: Circulating Tumor-Tissue-Modified Viral DNA Testing for Human Papillomavirus-related Head and Neck Cancer

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.

Circulating Tumor-Tissue-Modified Viral DNA Testing for Human Papillomavirus-related Anal Cancer

Clinical Context and Test Purpose

The purpose of NavDx testing in patients who have human papillomavirus (HPV)-related anal cancer is to predict disease course (e.g., aggressiveness, risk of recurrence, death) and inform treatment decisions, and to monitor for recurrence following treatment.

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest are individuals with HPV-related anal squamous cell carcinoma (ASCC).

Interventions

The test being considered is circulating tumor-tissue-modified viral (TTMV) HPV DNA testing with NavDx:

- After treatment to inform decisions about adjuvant treatment, or
- During disease surveillance after treatment, to identify metastatic relapse at an early timepoint, and aid in the selection of individuals who may benefit from early/adjuvant treatment.

Comparators

The following practice is currently being used: standard clinical management without NavDx testing. In individuals with HPV-related anal cancer, surveillance and follow-up decisions are guided by the individual's tumor staging and other clinicopathological factors.

Individuals with HPV-related anal squamous cell carcinoma (ASCC) lack the traditional risk factors present in HPV-unrelated ASCC and have been shown to have better prognosis with limited incidences of developing a secondary primary malignancy. However, studies have shown that approximately 30% of individuals with ASCC will experience recurrence after receiving chemoradiation therapy.[18,] Individuals with HPV-related cancer have a longer median time to recurrence than individuals with HPV-unrelated cancer with the median time to recurrence of 2 years. Surveillance according to the National Comprehensive Cancer Netowrk (NCCN) guidelines includes re-evaluation using digital anorectal examination (DRE/DARE) between 8 and 12 weeks after completion of chemoradiation therapy. Based on the clinicopathological factors, patients are classified into 3 groups, complete remission of disease, persistent disease, or progressive disease and will undergo follow-up accordingly.[2,]

Outcomes

The general outcomes of interest are disease-specific survival, test accuracy and validity, and change in disease status. Specific outcomes of interest are recurrence risk, recurrence-free survival (RFS), progression-free survival (PFS), and overall survival (OS) at follow-up.

The treatment for HPV-related ASCC is highly similar to HPV-unrelated ASCC as there is currently no evidence to support treatment algorithms that address the distinct biological differences between these cancers. Decisions about neoadjuvant and adjuvant chemotherapy are based on clinicopathological risk factors.[2,] If used for risk stratification to rule-out individuals for neoadjuvant chemotherapy at diagnosis or adjuvant treatment following surgery, the performance characteristics of most interest are negative predictive value and sensitivity. If used for risk stratification to rule-in individuals for neoadjuvant chemotherapy at diagnosis or adjuvant treatment following surgery, the performance characteristics of most interest are positive predictive value and specificity.

If used for disease surveillance following primary treatment, beneficial outcomes of a true positive test would be earlier detection of metastasis and initiation of treatment. Harmful outcomes of a false positive test would be undergoing unnecessary or incorrect treatment and experiencing adverse effects of such treatment. For individuals who are being monitored for relapse following treatment for HPV-related ASCC, the timepoint of interest to assess recurrence should be between 2 - 5 years following treatment.

Study Selection Criteria

For the evaluation of clinical validity of the NavDx test, studies that meet the following eligibility criteria were considered:

- Reported on the accuracy of the marketed version of the technology (including any algorithms used to calculate scores)
- Included a suitable reference standard
- Patient/sample clinical characteristics were described
- Patient/sample selection criteria were described.

Clinically Valid

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Nonrandomized Studies

Two noncomparative studies and one cohort study reported the results of NavDx testing in anal squamous cell carcinoma (ASCC) (Table 5).

Kabarriti et al (2025) expanded on their previous work (see below) to assess the use of NavDx in resolving clinically indeterminate findings (CIFs) from clinical examination, anoscopy, and imaging during post-treatment surveillance for anal squamous cell carcinoma (ASCC) in a multi-center, retrospective cohort study (N=233). [19,] Out of the 233 individuals, only 90 (42%) had ≥1 post-treatment CIF(s) with a total of 214 instances observed, with 46% (98/214) arising from clinical examination and 54% (116/214) from imaging, but when normalized to the total number of assessments, CIFs occurred in 17% (116/677) of imaging studies and 7% (98/1379) of exams juxtaposed to 1.3% (8/603) for NavDx tests. Fifty-two CIFs were paired with TTMV-HPV DNA tests (NavDx) obtained within a 3-month window after the CIF and each TTMV-HPV DNA test result was compared with subsequent clinical follow-up and classified as correctly or incorrectly predicting recurrence or the absence of recurrence in the 3 months following the test. Eleven (21%) CIFs had a positive TTMV-HPV DNA test result and were concordant with clinically confirmed recurrence (100% concordance) thus demonstrating the tests' potential utility in resolving CIFs during post-treatment surveillance for ASCC. Eight of the eleven (73%) positive tests results were the first indication of recurrence with a median lead-time of 29 days highlighting the potential usefulness of this test to initiate salvage therapy sooner. Negative TTMV-HPV DNA results occurred in 79% (41/52) of evaluable pairs and of these, 90% (37/41) were concordant with the absence of recurrence within the prespecified follow-up window.

Kabarriti et al (2025) evaluated NavDx for disease surveillance in 117 individuals who had HPV-related ASCC and received at least one TTMV-HPV DNA test during the course of the disease. [20,] TTMV-HPV DNA testing with NavDx demonstrated high diagnostic accuracy, sensitivity, and specificity that result in meaningful positive and negative predictive values. Individuals with at least one positive NavDx score post-treatment had significantly worse recurrence-free survival and those whose test scores resolved to a negative score had significantly better recurrence-free survival (Table 6).

Huffman et al (2024) evaluated TTMV-HPV DNA levels as an exploratory endpoint in patients with advanced ASCC who have received pembrolizumab during a multi-institutional phase II clinical trial.[21,] Analysis of the exploratory endpoint determined that patients with lower baseline TTMV-HPV DNA scores were associated with clinical benefit (CR, PR, or SD ≥ 6 months; p =.003). Moreover, patients received an associated benefit in cycle 2 and cycle 3 when their TTMV-HPV DNA scores

improved from baseline at these time intervals in response to pembrolizumab (p =.008 and p =.01, respectively). Patients whose TTMV-HPV DNA scores increased from baseline had significantly worse PFS compared to those whose TTMV-HPV DNA scores decreased from baseline in response to pembrolizumab at cycle 3 (HR: 0.37; 95%CI: 0.14 to 0.99, log-rank p=.04).

Study limitations are shown in Tables 7 and 8. Major limitations of the studies include a lack of blinding , the retrospective design, inconsistent timing of delivery of reference and index tests, and heterogeneity in the study populations.

Table 5. Nonrandomized Studies of NavDx Testing in Anal Cancer - Study Characteristics

Study*	Test Purpose	Study Population	Study Design and Setting	Reference Standard	Timing of Reference and Index Tests	Blinding of Assessors
Kabarriti et al (2025) [19,]	1. Early recurrence detection	215 biopsy-confirmed HPV-associated ASCC with at least one TTMV-HPV DNA test during routine clinical care between January 2020 and February 2025	Retrospective Cohort, multicenter, US	Any exam, imaging study, or biopsy showing active disease	Plasma samples were collected before, during, and after treatment for the NavDx Testing. Reference testing was conduct throughout routine clinical care	No
Kabarriti et al (2025)[20,]	1. Risk stratification 2. Early recurrence detection	117 individuals with HPV-related ASCC with at least one TTMV-HPV DNA test obtained between March 2020 and June 2024	Retrospective Cohort, multicenter, US	Physical exam, imaging study, or biopsy showing active disease, or the initiation of salvage treatment	Plasma samples were collected before, during, and after treatment for the NavDx Testing. Reference testing was conduct throughout routine clinical care	No
Huffman et al (2024)[21,]	1. Risk stratification 2. Monitoring response to adjuvant immunotherapy	32 individuals who had incurable locally advanced or metastatic ASCC with measurable disease by RECIST V.1.1	Multicenter, open label, single arm phase II clinical trial	PET/CT or MRI imaging	Plasma samples were collected for NavDx testing before treatment and every cycle for the first 3 cycles and then every other cycle thereafter until disease progression or treatment discontinuation	No

Study*	Test Purpose	Study Population	Study Design and Setting	Reference Standard	Timing of Reference and Index Tests	Blinding of Assessors
					Imaging scans were taken every 9 weeks (3 cycles) until cycle 7. After cycle 12, restaging scans were performed every 3–4 cycles at the discretion of the treating investigator	

ASCC = anal squamous cell carcinoma; CT = computed tomography; HPV = human papillomavirus; MRI = Magnetic resonance imaging; PET = positron emission tomography; RECIST V.1.1 = response evaluation criteria in solid tumors version 1.1; TTMV = tumor-tissue-modified viral; *Positive, negative, and indeterminate scores were determined according to the manufacturer's instructions described in the background section of this medical policy.

Table 6. Nonrandomized Studies of NavDx Testing in Anal Cancer - Study Results

Study	Initial N	Final N	Excluded Samples	Recurrence Rate (%)	Median Time to Recurrence, months (range)	Clinical Validity			
						Sensitivity	Specificity	PPV	NPV
Kabarriti et al (2025) [19,]	233	90	125	11/11 (100)	within 6 months after testing	NR	NR	NR	NR
Kabarriti et al (2025)[20,]	104	22	82	18/49 (36.7)	8.9 (0.5 to 24.0)	82 (69.0 to 96.5)	98.4 (95.3 to 100)	96.0 (88.3 to 100)	92.5 (86.2 to 98.8)
HR (95% CI) for RFS (posttreatment sample)	13.6 (4.7 to 39.8), p<.0001								
HR (95% CI) for RFS (Baseline positive result resolved to a negative result	4.6 (0.94 to 22.8), p<.0099								

CI = confidence interval; RFS = recurrence-free survival; HR = hazard ratio; PPV = positive predictive value; NPV = negative predictive value

Table 7. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-Up[e]
Kabarriti et al (2025) [19,]	4. Race/ethnicity distribution (75% White) and the female predominance (74%)			1. No health outcomes were assessed	
Kabarriti et al (2025)[20,]					

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-Up[e]
Huffman et al (2024)[21],	2. Study population included a mix of individuals with HPV-related and HPV-unrelated cancers				

HPV = human papillomavirus
The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Population key: 1. Intended use population unclear; 2. Study population is unclear; 3. Study population not representative of intended use; 4, Enrolled populations do not reflect relevant diversity; 5. Other.
[b] Intervention key: 1. Classification thresholds not defined; 2. Version used unclear; 3. Not intervention of interest.
[c] Comparator key: 1. Classification thresholds not defined; 2. Not compared to credible reference standard; 3. Not compared to other tests in use for same purpose.
[d] Outcomes key: 1. Study does not directly assess a key health outcome; 2. Evidence chain or decision model not explicated; 3. Key clinical validity outcomes not reported (sensitivity, specificity and predictive values); 4. Reclassification of diagnostic or risk categories not reported; 5. Adverse events of the test not described (excluding minor discomforts and inconvenience of venipuncture or noninvasive tests).
[e] Follow-Up key: 1. Follow-up duration not sufficient with respect to natural history of disease (true positives, true negatives, false positives, false negatives cannot be determined).

Table 8. Study Design and Conduct Limitations

Study	Selection[a]	Blinding[b]	Delivery of Test[c]	Selective Reporting[d]	Data Completeness[e]	Statistical[f]
Kabarriti et al (2025) [19],	2. Retrospective analysis	1. No blinding	1. Timing of TTMV-HPV DNA and reference tests were not the same		2. Only 30% of CIFs paired with evaluable TTMV-HPV DNA tests	
Kabarriti et al (2025)[20],	2. Retrospective analysis	1. No blinding	1. Timing of TTMV-HPV DNA and reference tests were not the same			2. Comparison to other tests not reported
Huffman et al (2024)[21],	2. Prospective analysis	1. No blinding	1. Timing of TTMV-HPV DNA and imaging tests were not the same		1. Inadequate description of sample results included in data analysis	2. Comparison to other tests not reported

HPV = human papillomavirus; TTMV = tumor-tissue-modified viral
The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Selection key: 1. Selection not described; 2. Selection not random or consecutive (ie, convenience).
[b] Blinding key: 1. Not blinded to results of reference or other comparator tests.
[c] Test Delivery key: 1. Timing of delivery of index or reference test not described; 2. Timing of index and comparator tests not same; 3. Procedure for interpreting tests not described; 4. Expertise of evaluators not described.
[d] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
[e] Data Completeness key: 1. Inadequate description of indeterminate and missing samples; 2. High number of samples excluded; 3. High loss to follow-up or missing data.
[f] Statistical key: 1. Confidence intervals and/or p values not reported; 2. Comparison to other tests not reported.

Clinically Useful
A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct Evidence
Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials. There are no randomized controlled studies (RCTs), and no studies in which NavDx testing was used to prospectively guide treatment decisions.

Chain of Evidence
Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

Section Summary: Circulating Tumor-Tissue-Modified Viral DNA Testing for Human Papillomavirus-related Anal Cancer
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.

Circulating Tumor-Tissue-Modified Viral DNA Testing for Diagnosis of Human Papillomavirus-related Cancer of the Head and Neck or Anus

Clinical Context and Test Purpose
The purpose of NavDx testing in patients who have suspected human papillomavirus (HPV)-related cancer of the head and neck or anus is to diagnosis and confirm their HPV status.

The following PICO was used to select literature to inform this review.

Populations
The relevant population of interest are individuals with suspected HPV-related cancer of the head and neck or anus.

Interventions
The test being considered is circulating tumor-tissue-modified viral (TTMV) HPV DNA testing with NavDx for the diagnosis of HPV-related cancer of the head and neck or anus.

Comparators
There are currently no diagnostic tests with regulatory approval for HPV status. However, the National Comprehensive Cancer Network (NCCN) recommends that head and neck cancers undergo surrogate evaluation of tumor HPV status via p16 immunohistochemistry for all patients diagnosed with an oropharyngeal cancer. Furthermore, confirmatory HPV testing is recommended for clinical trials of HPV-targeted therapeutics or designed test deintensification strategies, which include polymerase chain reaction (PCR) and RNA and DNA *in situ* hybridization (ISH).[2,]

Outcomes
The general outcomes of interest are test validity and accuracy, more specifically, the association between test results and the diagnosis of HPV-related cancer of the head and neck or anus.

Study Selection Criteria
For the evaluation of clinical validity of the NavDx test, studies that meet the following eligibility criteria were considered:

- Reported on the accuracy of the marketed version of the technology (including any algorithms used to calculate scores)
- Included a suitable reference standard
- Patient/sample clinical characteristics were described
- Patient/sample selection criteria were described.

One study was excluded from the evaluation of the clinical validity of the NavDx test because they did not have a sufficient sample size to report on the accuracy of test due to the limited data collected. [22,]

Clinically Valid
A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Nonrandomized Studies
Three nonrandomized studies reported the association of a positive NavDx test and the diagnosis of HPV-related cancer of the head and neck (Table 9). Relevant outcomes such as test validity, accuracy, and other test performance measures are reported in Table 10.

Rettig et al (2022) conducted a retrospective matched case-control study in 12 individuals with head and neck squamous cell carcinoma (HNSCC [case]) that had plasma samples collected at least 6 months prior to their diagnosis and were matched to individuals without HNSCC (control) that had similar patient characteristics (age, calendar year at time of plasma collection, race, and sex).[23,] 10 out of the 12 patients with HNSCC were confirmed to have HPV-related cancer using archival tumor samples and of those 10 patients, tumor-tissue-modified viral (TTMV) HPV DNA testing with NavDx was able to confirm HPV status in 30 percent of patients (3/10, 95% CI = 7 to 65%) prior to their diagnosis with a median time of 30.5 months.

Ferrandino et al (2023) evaluated NavDx testing for diagnosis and disease surveillance in 399 individuals with oropharyngeal squamous cell carcinoma (OPSCC) who had at least one TTMV-HPV DNA test and stratified individuals into 2 cohorts: diagnostic cohort (n = 163) and surveillance cohort (n = 290).[9,] Out of the 163 individuals within the diagnostic cohort, 152 were confirmed to have HPV-related OPSCC with 139 of patients being detected via NavDx testing. The per-test sensitivity and specificity for diagnosis of HPV-related OPSCC was reported as 91.5% (95% CI, 85.8% to 95.4% [139 of 152 tests]) and 100% (95% CI, 71.5% to 100% [11 of 11 tests]), respectively.

Ferrandino et al (2024) enrolled 138 individuals into a prospective diagnostic study in which they were evaluated for a lateral neck mass suspected of malignancy. Individuals were only evaluated if they were able to obtain a definitive TTMV-HPV DNA test result and a tissue biopsy of the mass.[24,] The

study included an analysis of the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of NavDx testing in comparison with a tissue biopsy, but not to current methods to identify HPV status, such as p16 ICH, PCR, and ISH. The results demonstrated improved diagnostic accuracy with high sensitivity (95.7% [95% CI, 85.5% to 99.5%]) and specificity (97.8% [95% CI, 92.3% to 99.7%]) with favorable predictive values, but ultimately there was no significant difference.

Study limitations are shown in Tables 11 and 12. Major limitations of both studies include a lack of comparison to standard methods of monitoring, and heterogeneity in the study populations.

Table 9. Nonrandomized Studies of NavDx Testing for Diagnosis of HPV-related Cancer - Study Characteristics

Study*	Test Purpose	Study Population	Setting	Reference Standard	Timing of Reference and Index Test
Rettig et al (2022)[23,]	1. Diagnosis of HPV status		US, multicenter, retrospective	Physical examinations and restaging imaging	TTMV testing was obtained at least 3 months posttreatment Reference testing was collected at clinicians' discretion during management of the disease
Ferrandino et al (2023)[9,]	1. Diagnosis of HPV status 2. Early recurrence detection		US, multicenter, retrospective	Physical examinations and restaging imaging	TTMV testing was obtained at least 3 months posttreatment Reference testing was collected at clinicians' discretion during management of disease
Ferrandino et al (2024)[24,]	1. Diagnosis of HPV status				

HPV = human papillomavirus; TTMV = tumor-tissue-modified viral; *Positive, negative, and indeterminate scores were determined according to the manufacturer's instructions described in the background section of this medical policy.

Table 10. Observational Studies for Diagnosis of HPV-related Cancer

Study	Sensitivity (95% CI)	Specificity (95% CI)	PPV	NPV
Rettig et al (2022)[23,]	NA	NA	NA	NA
Ferrandino et al (2023)[9,]	91.5 (85.8 to 95.4)	100 (71.5 to 100)	NA	NA
Ferrandino et al (2024)[24,]	95.7 (85.5 to 99.5)	97.8 (92.3 to 99.7)	95.7 (85.5 to 99.5)	97.8 (92.3 to 99.7)

NA = not assessed; NPV = negative predictive value; PPV = positive predictive value

Table 11. Study Relevance Limitations

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-Up[e]
Rettig et al (2022)[23,]			3. No comparator	1. No health outcomes were assessed	
Ferrandino et al (2023)[9,]			3. No comparator	1. No health outcomes were assessed	
Ferrandino et al (2024)[24,]				1. No health outcomes were assessed	

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Population key: 1. Intended use population unclear; 2. Study population is unclear; 3. Study population not representative of intended use; 4, Enrolled populations do not reflect relevant diversity; 5. Other.
[b] Intervention key: 1. Classification thresholds not defined; 2. Version used unclear; 3. Not intervention of interest.
[c] Comparator key: 1. Classification thresholds not defined; 2. Not compared to credible reference standard; 3. Not compared to other tests in use for same purpose.
[d] Outcomes key: 1. Study does not directly assess a key health outcome; 2. Evidence chain or decision model not explicated; 3. Key clinical validity outcomes not reported (sensitivity, specificity and predictive values); 4. Reclassification of diagnostic or risk categories not reported; 5. Adverse events of the test not described (excluding minor discomforts and inconvenience of venipuncture or noninvasive tests).
[e] Follow-Up key: 1. Follow-up duration not sufficient with respect to natural history of disease (true positives, true negatives, false positives, false negatives cannot be determined).

Table 12. Study Design and Conduct Limitations

Study	Selection[a]	Blinding[b]	Delivery of Test[c]	Selective Reporting[d]	Data Completeness[e]	Statistical[f]
Rettig et al (2022)[23,]	2. Retrospective analysis	1. No blinding	1. Timing of TTMV-HPV DNA and reference tests were not the same			2. Comparison to other tests not reported
Ferrandino et al (2023)[9,]	2. Retrospective analysis	1. No blinding	1. Timing of TTMV-HPV DNA and reference tests were not the same			2. Comparison to other tests not reported
Ferrandino et al (2024)[24,]	2. Prospective analysis	1. No blinding	1. Timing of reference tests were not described			

HPV = human papillomavirus; TTMV = tumor-tissue-modified viral
The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Selection key: 1. Selection not described; 2. Selection not random or consecutive (i.e., convenience).
[b] Blinding key: 1. Not blinded to results of reference or other comparator tests.
[c] Test Delivery key: 1. Timing of delivery of index or reference test not described; 2. Timing of index and comparator tests not same; 3. Procedure for interpreting tests not described; 4. Expertise of evaluators not described.
[d] Selective Reporting key: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
[e] Data Completeness key: 1. Inadequate description of indeterminate and missing samples; 2. High number of samples excluded; 3. High loss to follow-up or missing data.
[f] Statistical key: 1. Confidence intervals and/or p values not reported; 2. Comparison to other tests not reported.

Clinically Useful
A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, or more effective therapy, or avoid unnecessary therapy, or avoid unnecessary testing.

Direct Evidence
Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from randomized controlled trials. There are no RCTs, and no studies in which NavDx testing was used to guide treatment decisions, including potential therapy de-escalation. Current treatment algorithms for HPV-related cancers do not substantially differ from HPV-unrelated cancers, underscoring uncertain clinical utility for testing.

Chain of Evidence
Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

Section Summary: Circulating Tumor-Tissue-Modified Viral DNA Testing for Diagnosis of Human Papillomavirus-related Cancer
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. The nonrandomized studies have reported positive TTMV-HPV DNA scores measured at diagnosis that underscore the potential clinical utility of NavDx testing in determining HPV status at earlier stages with the 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. 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.

Supplemental Information
The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

Practice Guidelines and Position Statements
Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

American Society of Clinical Oncology
In 2022, the American Society of Clinical Oncology (ASCO) published a provisional clinical opinion on somatic genetic testing in individuals with metastatic or advanced cancer. [25,] The opinion addressed circulating tumor DNA (ctDNA) testing under additional topics but did not include a specific statement with a strength of recommendation rating. The panel noted, "There is a growing body of evidence on the clinical utility of genomic testing on cell-free DNA (cfDNA) in the plasma," citing the

systematic review conducted by Merker et al (2018).[26,] The panel also noted that ASCO will update that systematic review over the next few years.

The discussion also included the following points:

- "In patients without tissue-based genomic test results, treatment may be based on actionable alterations identified in cfDNA."
- "Testing is most helpful when genomic testing is indicated, archival tissue is unavailable, and new tumor biopsies are not feasible."
- "cfDNA levels themselves may be prognostic and early cfDNA dynamics may serve as an early predictor of therapy response or resistance."
- "Ongoing studies are expected to better delineate the clinical utility of serial liquid biopsies.

Of note, neither of these reviews explicitly address circulating tumor-tissue-modified viral (TTMV) DNA.

California Head and Neck Consortium

The California Head and Neck Consortium (CHNC) convened a multidisciplinary expert panel to garner a consensus on the use of circulating TTMV-HPV DNA through a hybrid Delphi approach involving 33 multidisciplinary experts from 15 institutions within the California Head and Neck Consortium. [27,] The panel reached strong consensus (>80% agreement) that circulating TTMV-HPV DNA assays exhibit higher sensitivity and specificity than conventional surveillance tools, are clinically useful for identifying recurrence after treatment, and should supplement rather than replace standard surveillance modalities. Notably, the panel also reached strong consensus that circulating TTMV-HPV DNA has not yet demonstrated improvement in clinical outcomes and that large-scale prospective randomized controlled trials are necessary to validate its role. The panel rejected the use of circulating TTMV-HPV DNA for population screening, for adapting therapeutic intensity during definitive treatment, and for guiding decisions to stop maintenance systemic therapy. No consensus was reached on whether circulating TTMV-HPV DNA should be used to guide treatment intensification or de-intensification decisions.

Table 13. Consensus Statements for Circulating Tumor-tissue-modified Viral Human Papillomavirus DNA

Domain	Consensus Statement	Strength
General	ctHPVDNA assays collectively exhibit higher specificity and sensitivity than conventional surveillance tools	Strong Consensus
General	ctHPVDNA has yet to demonstrate improvement in clinical outcomes	Strong Consensus
General	Large-scale, prospective RCTs are necessary to validate ctHPVDNA's role	Strong Consensus
General	ctHPVDNA should be incorporated into clinical trials evaluating treatment response and outcome	Strong Consensus
Screening	ctHPVDNA should not be used to screen the general population	Strong Consensus
Screening	ctHPVDNA will artificially inflate outcomes through lead-time bias	Strong Consensus
Screening	Detectable ctHPVDNA without clinical or radiographic evidence of disease often increases patient distress	Strong Consensus
Pretreatment	ctHPVDNA can confirm an HPV+ etiology in cases with indeterminate biopsies or occult primary cancers	Strong Consensus
Pretreatment	Obtaining baseline/pretreatment ctHPVDNA levels is important for post-treatment surveillance	Strong Consensus
Surveillance	ctHPVDNA improves time to detection of recurrence compared to conventional tools	Strong Consensus
Surveillance	ctHPVDNA should supplement conventional surveillance tools, not reduce or replace them	Strong Consensus

Domain	Consensus Statement	Strength
Surveillance	Longitudinal, serial ctHPVDNA testing should be performed rather than a single post-treatment test	Strong Consensus
Surveillance	A single positive ctHPVDNA test should lead to immediate clinical exam and imaging	Strong Consensus
Surveillance	Best time to repeat ctHPVDNA after a single positive post-treatment test is 1 month	Strong Consensus
Surveillance	ctHPVDNA levels are clinically useful to identify recurrence after treatment	Strong Consensus
Surveillance	Recommended cadence: q3mo (years 1–2), q6mo (years 3–5), matching routine surveillance visits	Strong Consensus
Surveillance	In patients with persistent ctHPVDNA after treatment, more intense imaging surveillance should be undertaken	Strong Consensus
Surveillance	Earlier ctHPVDNA identification of locoregional recurrence should improve outcomes (given surgical salvage survival benefit)	Strong Consensus
Surveillance	Earlier ctHPVDNA identification of distant metastasis should improve outcomes (given oligometastatic ablation potential)	Strong Consensus
Treatment Response	First post-treatment ctHPVDNA should be checked at 3 months	Strong Consensus
Treatment Response	In the M1 setting, ctHPVDNA during therapy offers earlier response assessment, enabling faster pivots to alternative regimens	Strong Consensus

Source: Adapted from Ho et al. (2025) [27]. Table includes only items that reached strong consensus (>80% agreement). Items that reached consensus (66–80%), no consensus (20–66%), or were rejected (<20%) are not shown. Refer to the full publication for the complete set of 33 consensus items and voting results.

ctHPVDNA: circulating tumor HPV DNA; HPV: human papillomavirus; MRD: molecular residual disease; RCT: randomized controlled trial; SBRT: stereotactic body radiation therapy

National Comprehensive Cancer Network

There is no general National Comprehensive Cancer Network (NCCN) guideline on the use of circulating tumor-tissue-modified viral DNA. However, the NCCN guidelines for head and neck cancer (v.1.2026) state there is currently no diagnostic test with regulatory approval for HPV status and recommends that head and neck cancers undergo evaluation of tumor HPV status by use of a surrogate of p16 immunohistochemistry for all patients diagnosed with an oropharyngeal cancer. [1] Furthermore, confirmatory HPV testing is recommended for clinical trials of HPV-targeted therapeutics or designed test deintensification strategies, which include polymerase chain reaction (PCR) and RNA and DNA *in situ* hybridization (ISH). Lastly, the guideline notes: "At this time, persistent cell-free oncogenic HPV DNA detection in plasma (among those positive and quantifiable at diagnosis) may identify patients at increased risk for progression after completion of curative intent therapy. However, without concurrent clinical, radiographic or pathological correlates represents an outcome without actionable therapeutic implications outside of clinical trials."

Despite publishing unique staging criteria for head and neck cancer that is HPV-related and noting that it is biologically distinct from head and neck cancer that is HPV-unrelated, the treatment algorithms for both are highly similar. Further research is needed to explore the precise nature of HPV-related pathology that can be exploited by therapeutic intervention. Refer to treatment recommendations by cancer type for specific recommendations.

NCCN guidelines for anal cancer (v.1.2026) note that the optimal approach to screening for high-grade anal intraepithelial neoplasia (AIN) "remains an area of uncertainty, but it is likely that future approaches will include additional tests such as HPV."[2] Current NCCN treatment algorithms for anal cancer do not stratify by HPV status.

U.S. Preventive Services Task Force Recommendations
Not applicable

Medicare National Coverage
There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

Ongoing and Unpublished Clinical Trials
Some currently unpublished trials that might influence this review are listed in Table 14.

Table 14. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT05307939	A Study on Using Cell-Free Tumor DNA (ctDNA) Testing to Decide When to StartRoutine Treatment in People With Human Papilloma Virus (HPV)- Associated Oropharynx Cancer (OPC)	30	Mar 2027
NCT06373380[a]	A Study of HB-202/HB-201 in People With Human Papilloma Virus 16-Positive Head and Neck Squamous Cell Cancer (HPV 16+ HNSCC)	7 (actual)	Apr 2027 (active, not recruiting)
NCT05541016	De-Escalated Adjuvant and Definitive Radiation Therapy Informed by DART 2.0 ctHPV-DNA	455	Aug 2029
NCT05814549	A Study Using Human Papillomavirus (HPV) DNA Testing to Detect HPV-Related Oropharyngeal Cancer (OPC)	9 (actual)	Mar 2031 (active, not recruiting)
NCT04900623[a]	Risk-adapted Therapy in HPV+ Oropharyngeal Cancer Using Circulating Tumor (ct)HPV DNA Profile - The ReACT Study	145	Jun 2032
NCT05268614[a]	Risk Adapted De-Intensification of Radio-Chemotherapy for Oropharyngeal Squamous Cell Carcinoma	250	Jun 2032
NCT03215719	Adaptive De-escalation of Radiation Therapy Dose in HPV-Positive Oropharyngeal Carcinoma (ART) Demonstrating Favorable Mid-Treatment Response	120	Dec 2028
NCT05419089	The Sinai Robotic Surgery Trial in HPV-related Oropharyngeal Squamous Cell Carcinoma (SIRS 2.0 Trial)	83	Jun 2027
NCT05962242	Circulating Tumor Modified HPV DNA-Guided Radiotherapy De-intensification of the Elective Neck (RaDEN) in Squamous Cell Carcinoma of the Head and Neck	90	Nov 2029
NCT06088381	A Single Arm Phase II Trial Evaluating Selective Adjuvant Therapy for HPV-mediated Oropharynx SCCs Based on Residual Circulating Tumor DNA Levels (SAVAL)	61	Dec 2030
NCT06323460	A Pilot Study of Adaptive De-Intensified Radiotherapy Using Circulating Tumor DNA in HPV- Associated Oropharyngeal Cancer	45	Dec 2025 (recruiting)
NCT06445114	ULTRA-HPV Using Circulating Tumor DNA to Risk Adapt Post-operative Therapy for HPV Associated Oropharyngeal Cancer	50	Jun 2032
NCT06915038	Circulating TumorHPV DNA Driven Adjuvant Treatment Deintensification After Transoral Surgery for HPV-Positive Squamous Cell Carcinoma of the Oropharynx	120	Dec 2028
NCT05606133[a]	Circulating Human Papilloma Virus (HPV) DNA for the Screening and Surveillance of Gynecologic Cancers	100	Aug 2026
Unpublished			

NCT No.	Trial Name	Planned Enrollment	Completion Date
NCT05536843	Clinical, Translational and Biomarker-Based Female Genital HPV Induced Dysplasia and Cancer Screening Study Using Cf-HPV-DNA Blood Tests (TTMV HPV DNA)	500	Dec 2023 (unknown status)

NCT: national clinical trial.
[a] Denotes industry-sponsored or cosponsored trial.

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Documentation for Clinical Review

- No records required

Coding

The list of codes in this Medical Policy is intended as a general reference and may not cover all codes. Inclusion or exclusion of a code(s) does not constitute or imply member coverage or provider reimbursement policy.

Type	Code	Description
CPT®	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 INCLUDES: NavDx®, Naveris, Inc, Naveris, Inc
HCPCS	None	

Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

Effective Date	Action
08/01/2026	New policy.

Feedback

Blue Shield of California is interested in receiving feedback relative to developing, adopting, and reviewing criteria for medical policy. Any licensed practitioner who is contracted with Blue Shield of California or Blue Shield of California Promise Health Plan is welcome to provide comments, suggestions, or concerns. Our internal policy committees will receive and take your comments into consideration. Our medical policies are available to view or download at www.blueshieldca.com/provider.

For medical policy feedback, please send comments to: MedPolicy@blueshieldca.com

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department at (800) 541-6652, or the Transplant Case Management Department at (800) 637-2066 ext. 3507708 or visit the provider portal at www.blueshieldca.com/provider.

Disclaimer: Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as member health services contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member health services contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.

Appendix A

POLICY STATEMENT	
BEFORE	**AFTER** Blue font: Verbiage Changes/Additions
New policy **Policy Statement:** N/A	**Circulating Tumor-Tissue-Modified Viral DNA Testing for Cancer Management 2.04.160** **Policy Statement:** I. Circulating tumor-tissue-modified viral (TTMV) human papillomavirus (HPV) DNA testing (e.g., NavDx is considered **investigational.**