Medical Policy Manual Laboratory, Policy No. 82

Circulating Tumor-Tissue Modified Viral DNA Testing for Cancer Management

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Next Review: August 2026
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IMPORTANT REMINDER

Medical Policies are developed to provide guidance for members and providers regarding coverage in accordance with contract terms. Benefit determinations are based in all cases on the applicable contract language. To the extent there may be any conflict between the Medical Policy and contract language, the contract language takes precedence.

PLEASE NOTE: Contracts exclude from coverage, among other things, services or procedures that are considered investigational or cosmetic. Providers may bill members for services or procedures that are considered investigational or cosmetic. Providers are encouraged to inform members before rendering such services that the members are likely to be financially responsible for the cost of these services.

DESCRIPTION

Circulating tumor-tissue-viral modified (TTMV) human papillomavirus (HPV) DNA testing (e.g., NavDx®) refers to the analysis of biomarkers that are unique to HPV-related cancers. 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.

MEDICAL POLICY CRITERIA

Circulating tumor-tissue-modified viral (TTMV) human papillomavirus (HPV) DNA testing (e.g., NavDx®) is considered **investigational** for any indication, including but not limited to diagnosing, guiding treatment decisions, or monitoring for recurrence of HPV-related cancers.

CROSS REFERENCES

1. Genetic and Molecular Diagnostic Testing, Genetic Testing, Policy No. 20
2. Expanded Molecular Testing of Cancers to Select Targeted Therapies, Genetic Testing, Policy No. 83

3. Circulating Tumor DNA and Circulating Tumor Cells for Management (Liquid Biopsy) of Solid Tumor Cancers, Laboratory, Policy No. 46

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 head and neck SCC (HNSCC) as compared to people with HPV-unrelated cancer 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 five 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 five and seven (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.

EVIDENCE SUMMARY

CIRCULATING TTMV-HPV DNA TESTING FOR CANCER TREATMENT SELECTION AND RECURRENCE MONITORING

Head and Neck Cancer

Systematic Reviews

Campo (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 three of the included studies used the NavDx TTMV-HPV DNA assay. [4-6] 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>0.05), and specificity (96.4% [95% CI 91.1 to 98.6]; p>0.05) for the diagnosis of recurrence in patient with HPV-related OPSCC.

Nonrandomized Studies

Eight 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).[4-7] 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.[8] Three studies monitored the relationship between

TTMV-HPV DNA levels and responses to select therapies in patients with recurrent/metastatic HNSCC.[9-11] 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.

Chung (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.[10] 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 ($p = 0.02$ and $p = 0.05$, respectively).

Jhawar (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).[11] 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 two years (91.7% vs. 71.7%; log rank; $p =0.042$). Moreover, this study included PET/CT surveillance at three months post-treatment to determine evidence of disease and found that among patients with complete TTMV-HPV DNA clearance at three months but had either a negative, equivocal, or incomplete PET/CT result had a two-year PFS of 94.3%, 77.8%, and 59.3%, respectively ($p =0.029$).

Hanna (2024) assessed the prognostic and surveillance value of TTMV-HPV DNA testing in R/M HPV-related OPSCC in a retrospective fashion.[9] Patients with detectable TTMV-HPV DNA scores at last follow-up had significantly worse survival compared with those who were undetectable ($p <0.01$).

Rettig (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.[7] Individuals with detectable TTMV-HPV DNA during surveillance were significantly associated with a worse RFS (HR = 75, 95% CI = 21 to 273; $p <0.001$). 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
Berger (2022)[4]	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 (2023)[6]	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 (2023)[5]	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 (2024)[7]	1. Early recurrence detection	182 individuals with HPV-related oropharynx cancer who underwent curative-intent treatment between November 2020, to April 2023.	US, single center, prospective	Physical examinations and restaging imaging	TTMV testing was performed for individuals at 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

Study*	Test Purpose	Study Population	Setting	Reference Standard	Timing of Reference and Index Test
					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 (2024)[9]	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 (2024)[11]	1. Risk stratification 2. Early recurrence detection	80 individuals with non-metastatic, HPV-related OPSCC who were treated with definitive radiation with or without concurrent chemotherapy between 16 June2021 and 9 February 2023	NA, prospective	PET/CT imaging	TTMV-HPV DNA levels were obtained prospectively 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 (2022)[10]	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	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,

Study*	Test Purpose	Study Population	Setting	Reference Standard	Timing of Reference and Index Test
		HNSCC by a local therapy (surgery or radiotherapy with or without chemotherapy)			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	Specificity	PPV	NPV
Berger (2022)[4]	99.4 (90.5 to 100)[a]	10.0 (0.6 to 67.4)[a]	95	95
Hanna (2023)[6]	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 (2023)[5]	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 (2024)[7]	73 (45 to 92)	98 (94 to 100)	79 (49 to 95)	97 (93 to 99)

NA: not assessed; 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]
Berger (2022)[4]			3. No comparator	1. Survival outcomes not assessed	1. Follow up for recurrence was under 2 years (median 9 months)
Hanna (2023)[6]			3. No comparator	1. Survival outcomes not assessed	1. Follow up for recurrence was under 2 years (median 13.8 months)
Ferrandino (2023)[5]			3. No comparator	1. Survival outcomes not assessed	
Rettig (2024)[7]			3. No comparator	1. Survival outcomes not assessed	1. Follow up for recurrence was under 2 years (median 23 months)
Hanna (2024)[9]			3. No comparator	2. No decision model regarding survival outcomes	1. No median follow up was reported

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-Up[e]
Jhawar (2024)[11],			3. No comparator	2. No decision model regarding survival outcomes	1. Follow up for recurrence was under 2 years (median 14.7 months)
Chung (2022)[10]			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]
Berger (2022)[4]	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 (2023)[6]	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 (2023)[5]	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 (2024)[7]	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 (2024)[9]	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 (2024)[11],	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

Study	Selection[a]	Blinding[b]	Delivery of Test[c]	Selective Reporting[d]	Data Completeness[e]	Statistical[f]
Chung (2022)[10]		1.No blinding	2. Timing of delivery of NavDx test and CT or MRI imaging was not the same			2. Comparison to other tests not reported

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 (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.

Section Summary

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 one systematic review/meta-analysis, one nonrandomized clinical trial, four retrospective (N = 2,126) studies, and three prospective (N = 444) 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, nonrandomized, 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. 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.

Anal Cancer

Nonrandomized Studies

Two noncomparative studies reported the association of NavDx testing with survival outcomes in anal squamous cell carcinoma (ASCC) (Table 5).

Kabarriti (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.[12] 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 (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.14, 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 =0.003). Moreover, patients received an associated benefit in cycle two and cycle three when their TTMV-HPV DNA scores improved from baseline at these time intervals in response to pembrolizumab (p =0.008 and p =0.01, 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 three (HR: 0.37; 95%CI: 0.14 to 0.99, log-rank p=0.04).

Study limitations are shown in Tables 7 and 8. Major limitations of both studies include a lack of comparison to standard methods of monitoring, 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 (2025)[12]	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 (2024)[13]	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	No

Study*	Test Purpose	Study Population	Study Design and Setting	Reference Standard	Timing of Reference and Index Tests	Blinding of Assessors
					thereafter until disease progression or treatment discontinuation 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 (2025)[12]	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<0.0001								
HR (95% CI) for RFS (Baseline positive result resolved to a negative result	4.6 (0.94 to 22.8), p<0.0099								

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 (2025)[12],			3. No comparator	1. No health outcomes were assessed	
Huffman (2024)[13]	2. Study population included a mix of individuals with HPV-related and HPV-unrelated cancers		3. No comparator	1. No health outcomes were assessed	

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 (2025)[12]	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 (2024)[13]	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.

Section Summary

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 recurrence, minimal residual disease, and guide treatment decisions, the evidence includes one nonrandomized clinical trial and one retrospective (N = 117) study. 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 TTMV-HPV DNA TESTING FOR DIAGNOSIS OF HPV-RELATED CANCER

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 (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 six 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).[14] 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 (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 two cohorts: diagnostic cohort (n = 163) and surveillance cohort (n = 290).[5] 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 (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.[15] 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 (2022)[14]	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 (2023)[5]	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 (2024)[15]	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 (2022)[14]	NA	NA	NA	NA
Ferrandino (2023)[5]	91.5 (85.8 to 95.4)	100 (71.5 to 100)	NA	NA
Ferrandino (2024)[15]	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 (2022)[14]			3. No comparator	1. No health outcomes were assessed	
Ferrandino (2023)[5]			3. No comparator	1. No health outcomes were assessed	
Ferrandino (2024)[15]				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 (2022)[14]	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 (2023)[5]	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 (2024)[15]	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 (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.

Section Summary

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 three 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.

PRACTICE GUIDELINE SUMMARY

NATIONAL COMPREHENSIVE CANCER NETWORK

The NCCN guidelines for head and neck cancer (v.4.2025) 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."

The NCCN guidelines for anal cancer (v4.2025) do not address the use of circulating TTMV HPV DNA testing and do not stratify treatment by HPV status.[2]

SUMMARY

There is not enough research to show that circulating tumor-tissue-modified viral (TTMV) HPV DNA testing (e.g., NavDx) leads to improved diagnosis, changes to cancer treatment, or improved health outcomes for people with HPV-related cancer. There are no clinical practice guidelines that recommend this testing for people with HPV-related cancers including head and neck, or anal cancer. Therefore, circulating TTMV HPV DNA testing (e.g., NavDx®) is considered investigational for any indication, including but not limited to the diagnosis, treatment determination, or recurrence monitoring of HPV-related cancers.

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CODES

Codes	Number	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. NavDx® by Naveris Inc
	0470U	Oncology (oropharyngeal), detection of minimal residual disease by next-generation sequencing (NGS) based quantitative evaluation of 8 DNA targets, cell-free HPV 16 and 18 DNA from plasma
HCPCS	None	

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