Revision log
Coding Implications

CONCERT GENETIC TESTING ONCOLOGY: ALGORITHMIC TESTING

See Important Reminder at the end of this policy for important regulatory and legal information.

OVERVIEW

Oncology diagnostic, prognostic and algorithmic tests combine biomarkers and/or clinical data into an algorithm to generate a disease risk assessment, prognostic result, or clinical recommendation for treatment. Testing methodologies commonly include Gene Expression Profiling (GEP), which analyzes messenger RNA (mRNA) typically of multiple genes simultaneously, multimarker serum analysis, single-nucleotide variant testing, plasma-based proteomic analysis, and incorporation of other clinical data into test outputs.

In addition to the tests previously mentioned, proteogenomic testing is an emerging area. Proteogenomic testing combines the analysis of DNA with RNA and/or protein analysis. The current focus of proteogenomics is primarily on diagnostic and prognostic analyses in various cancers. Results also seek to provide potential treatment options, and to which treatments the cancer may be resistant.

Polygenic Risk Score (PRS) tests are another emerging area. These tests combine information from population SNP analysis with clinical and family history and aim to give additional insight into an individual's lifetime risk to develop a specific cancer.

Results of oncology algorithmic tests are often reported as a recurrence score, probability of distant disease recurrence, malignant potential, probable site of origin, or cancer risk score. Additionally, the output of these algorithmic tests may be useful to assist in surgical and management decision-making and to identify individuals who may benefit from adjuvant therapy.

In keeping with the language used in National Comprehensive Cancer Network (NCCN) guidelines, the terms “male” and “female” refer to sex assigned at birth.

POLICY REFERENCE TABLE

Coding Implications

This clinical policy references Current Procedural Terminology (CPT®). CPT is a registered trademark of the American Medical Association. All CPT codes and descriptions are copyrighted 2023, American Medical Association. All rights reserved. CPT codes and CPT descriptions are from the current manuals and those included herein are not intended to be all-inclusive and are included for informational purposes only. Codes referenced in this clinical policy are for informational purposes only. Inclusion or exclusion of any codes does not guarantee coverage. Providers should reference the most up-to-date sources of professional coding guidance prior to the submission of claims for reimbursement of covered services.

The tests, associated laboratories, CPT codes, and ICD codes contained within this document serve only as examples to help users navigate claims and corresponding criteria; as such, they are not comprehensive and are not a guarantee of coverage or non-coverage. Please see the Concert Platform for a comprehensive list of registered tests.

Criteria Sections	Example Tests, Labs	Common CPT Codes	Common ICD Codes	Ref
Breast Cancer				
Breast Cancer Treatment and Prognostic Algorithmic Tests	Oncotype Dx Breast Recurrence Score (Exact Sciences)	81519, S3854	C50.011-C50.92, Z17.0	1
Breast Cancer Extended Endocrine Therapy Algorithmic Tests	Breast Cancer Index (bioTheranostics)	81518, S3854	C50.011-C50.92, Z17.0	1, 23
Breast Cancer Prognostic Algorithmic Tests	EndoPredict (Myriad)	81522, S3854	C50, Z17.0, Z17.1	1, 23
	MammaPrint (Agendia, Inc.)	81521, 81523 S3854		
	Prosigna Assay (NeoGenomics)	81520		
Gene Expression Profiling Breast Cancer Subtyping Tests	BluePrint (Agendia, Inc.)	81599, S3854	C50-C50.929	1, 23
Breast DCIS Prognostic Algorithmic Tests	Oncotype DX Breast DCIS Score (Exact Sciences)	0045U	D05.1	31
Colorectal Cancer				
Colorectal Cancer Prognostic Algorithmic Tests	Oncotype DX Colon Recurrence Score (Exact Sciences)	81525	C18.0-C18.9	2
	miR-31now (GoPath Laboratories)	0069U		

	Immunoscore (Veracyte)	0261U		
Prostate Cancer				
Prostate Cancer Treatment and Prognostic Algorithmic Tests	Oncotype DX Genomic Prostate Score (MDxHealth)	0047U	C61	3, 18
	Decipher Prostate Biopsy Genomic Classifier (Veracyte)	81542		
	Decipher Prostate RP Genomic Classifier (Veracyte)			
	Prolaris (Myriad Genetics)	81541		
	ArteraAI Prostate Test (Artera)	0376U		
Evidence-Based Prostate Cancer Risk Assessment and Diagnostic Algorithmic Tests	4K Prostate Score (Serum) (BioReference Laboratories)	81539	C61, Z12.5	4, 22
	Prostate Health Index (ARUP Laboratories)	84153, 84154, 86316		
	SelectMDx for Prostate Cancer (MDxHealth)	0339U		
	ExoDx Prostate Test (ExosomeDx)	0005U		
	IsoPSA (Cleveland Diagnostics, Inc)	0359U		
	MyProstateScore (Lynx DX)	0113U		
	ConfirmMDx for Prostate Cancer (MDxHealth)	81551		
	Prostate Cancer Gene 3 (Integrated Regional Laboratories)	81479		
Emerging Evidence Prostate Cancer Risk Assessment and Diagnostic Algorithmic Tests	PanGIA Prostate (Genetics Institute of America)	0228U	C61, Z12.5	22
	MyProstateScore 2.0 (Lynx Dx)	0403U		
	miR Sentinel Prostate Cancer Test (miR Scientific)	0343U, 0424U		
	EpiSwitch Prostate Screening Test (PSE) (Oxford BioDynamics)	0433U		
	Stockholm3 (BioAgilytix Diagnostics)	0495U		

	OncoAssure Prostate (DiaCarta, Inc.)	0497U		
	Tempus p-MSI (Tempus AI, Inc)	0512U		
	Tempus p-Prostate (Tempus AI, Inc)	0513U		
Thyroid Cancer				
Thyroid Cancer Diagnostic Algorithmic Tests	ThyroSeq Genomic Classifier (CBLPath)	0026U	C73, D44.0, E04.1	5, 6, 7
	ThyGeNEXT (Interpace Diagnostics)	0245U		
	ThyraMIR (Interpace Diagnostics)	0018U		
	Afirma Genomic Sequencing Classifier (Veracyte)	81546		
	Afirma Xpression Atlas (Veracyte)	0204U		
	ThyroSeq CRC (UPMC)	0287U		
Uveal Melanoma				
Uveal Melanoma Prognostic Algorithmic Tests	DecisionDx-UM (Castle Bioscience, Inc.)	81552	C69	8
Cutaneous Melanoma				
Evidence-Based Cutaneous Melanoma Prognostic Algorithmic Tests	DecisionDx-Melanoma (Castle Biosciences, Inc.)	81529	C43, D03.0-D03.9, Z12.83	24, 25
	Merlin Melanoma (BioCartis)	81479		
	MelaNodal (Quest)	81599		
Emerging Evidence Cutaneous Melanoma Prognostic Algorithmic Tests	AMBLor (AMLo Biosciences)	0387U	C43, D03.0-D03.9, Z12.83	25
Cutaneous Melanoma Diagnostic Algorithmic Tests	myPath Melanoma (Castle Biosciences, Inc.)	0090U	D22.0-D22.9, D48.5, D49.2, Z12.83	9, 10, 21
	DecisionDx-DiffDx-Melanoma (Castle Biosciences, Inc.)	0314U		
Cutaneous Melanoma	Pigmented Lesion Assay	0089U	D22-D23, Z12.83	9, 10,

Risk Assessment Algorithmic Tests	(DermTech)			26, 27, 28
Ovarian Cancer				
Ovarian Cancer Diagnostic Algorithmic Tests	OVA1 (Aspira Women's Health)	81503	D27.0, D27.1, D27.9, D39.10-D39.12, D39.9, D49.59, D49.9	11
	Overa (Aspira Women's Health)	0003U		
	Risk of Ovarian Malignancy (ROMA) (Labcorp)	81500		
	OvaWatch (Aspira Women's Health)	0375U		
	Avantect Ovarian Cancer Test (ClearNote Health)	0507U		
Ovarian Cancer Treatment Algorithmic Tests	myChoice CDx (Myriad Genetics)	0172U	C48, C56, C57.0	11, 19
Gynecologic Cancer				
Gynecologic Cancer Treatment Algorithmic Tests	ChemoFx (Helomics Corporation)	81535	C51-C57	11, 16, 17
	ChemoFx - Additional Drug (Helomics Corporation)	81536		
Lung Cancer				
Evidence-Based Lung Cancer Diagnostic Algorithmic Tests	Nodify XL2 (Biodesix)	0080U	R91.1	20
Emerging Evidence Lung Cancer Diagnostic Algorithmic Tests	REVEAL Lung Nodule Characterization (MagArray)	0092U	R91.1	20
	Percepta Lung Cancer Diagnostics (Veracyte)	81479		
	LungLB Test (LungLife AI)	0317U		
	Nodify CDT (Biodesix)	0360U		
	OncobiotaLUNGdetect (Micronoma)	0395U		
	CyPath Lung (Precision Pathology Laboratory)	0406U		
Evidence-Based Lung Cancer Treatment Algorithmic Tests	Veristrat (Biodesix)	81538	C34, D38.1, D38.6	29, 33
	Razor14/Risk Reveal (RazorGenomics)	81599		
	DetermaRx (Oncocyte	0288U		

	Corporation)			
Emerging Evidence Lung Cancer Treatment Algorithmic Tests	LungOI (Imagene)	0414U	C34, D38.1, D38.6	29
	PROphet NSCLC Test (OncoHost Inc)	0436U		
Bladder and Urinary Tract Cancer				
Bladder/Urinary Tract Cancer Diagnostic Algorithmic Tests	CxBladder Detect+ (Pacific Edge)	0420U	R31.9	12, 13
	Cxbladder Detect (Pacific Edge)	0012M		
	Oncuria Detect (DiaCarta Clinical Lab)	0365U		
Bladder Cancer Treatment and Recurrence Algorithmic Tests	Cxbladder Monitor (Pacific Edge)	0013M	C67, C68	32
	Decipher Bladder (Veracyte)	0016M		
	Cxbladder Triage (Pacific Edge)	0363U		
	Oncuria Monitor (DiaCarta Clinical Lab)	0366U		
	Oncuria Predict (DiaCarta Clinical Lab)	0367U		
Pancreatic Cancer				
Evidence-Based Pancreatic Cyst Risk Assessment Algorithmic Tests	PancraGEN (Interpace Diagnostics)	81479	D49, K86.2	30
Emerging Evidence Pancreatic Cyst Risk Assessment Algorithmic Tests	PancreaSeq Genomic Classifier (Univ of Pittsburgh Medical Center Molecular and Genomic Pathology Laboratory)	0313U		
Cancer of Unknown Primary				
Cancer of Unknown Primary Gene Expression Profiling Tests	CancerTYPE ID (Biotheranostics)	81540	C79.9, C80.0, C80.1	15
Polygenic Risk Score Tests				
Breast Cancer Polygenic Risk Score Tests	geneType for Breast Cancer (Genetic Technologies)	81599	Z13.71, Z13.79 Z80.3	14

OTHER RELATED POLICIES

This policy document provides criteria for tests that determine the risk for or the prognosis for cancer. For other oncology related testing, please refer to:

- ***Oncology: Molecular Analysis of Solid Tumors and Hematologic Malignancies*** for criteria related to DNA testing of a solid tumor or a blood cancer.
- ***Genetic Testing: Hereditary Cancer Susceptibility Syndromes*** for criteria related to genetic testing to determine if an individual has an inherited cancer susceptibility syndrome.
- ***Oncology: Cancer Screening*** for criteria related to the use of non-invasive fecal, urine or blood tests for screening for cancer.
- **Oncology:** ***Circulating Tumor DNA and Circulating Tumor Cells (Liquid Biopsy)*** for criteria related to circulating tumor DNA (ctDNA) or circulating tumor cell testing performed on peripheral blood for cancer diagnosis, management and surveillance.
- ***Genetic Testing: General Approach to Genetic and Molecular Testing*** for criteria related to algorithmic testing in oncology that is not specifically discussed in this or another non-general policy.

back to top

CRITERIA

It is the policy of Coordinated Care of Washington, Inc.that the specific genetic testing noted below is **medically necessary** when meeting the related criteria. Criteria for breast cancer, prostate cancer, multiple myeloma, and colon cancer are in accordance with the Washington State Health Care Authority's Health Technology Assessment "Gene Expression Profile Testing of Cancer Tissue".

BREAST CANCER

Breast Cancer Treatment and Prognostic Algorithmic Tests

I. The use of the breast cancer treatment and prognostic algorithmic test Oncotype DX Breast Recurrence Score (81519, S3854) is considered **medically necessary** at a rate of one test per twelve months per index cancer, when test results will impact treatment decisions and when:

   A. The member/enrollee has stage 1 or 2 breast cancer, **AND**

B. The member/enrollee's tumor is hormone receptor-positive (estrogen receptor-positive, **AND**

C. The member/enrollee's tumor is human epidermal growth factor receptor 2 (HER2)-negative, **AND**

D. The member/enrollee is considering treatment with adjuvant therapy (e.g., tamoxifen, aromatase inhibitors, immunotherapy), **AND**

1. The member/enrollee meets one of the following (regardless of menopausal status):Tumor is node negative (pN0), **OR**

2. Lymph nodes are pN1 (1-3 positive nodes).

II. The use of the breast cancer treatment and prognostic algorithmic test Oncotype DX Breast Recurrence Score (81519, S3854) is considered **investigational** for all other indications.

Breast Cancer Immunohistochemistry Prognostic Algorithmic Test

I. The use of the immunohistochemistry prognostic test Mammostrat (81599) is considered **medically necessary** only when the member has stage 1 or 2 cancer and is deciding about hormone therapy.

II. The use of immunohistochemistry prognostic test Mammostrat (81599) is considered **investigational** for all other indications.

back to top

Breast Cancer Extended Endocrine Therapy Algorithmic Tests

I. The use of the breast cancer extended endocrine therapy test Breast Cancer Index (BCI) (81518, S3854) is considered **medically necessary** only when the member has stage 1 or 2 cancer, distant recurrence free and is deciding about hormone or endocrine therapy.

A. The member/enrollee's tumor is hormone receptor-positive (estrogen receptor-positive or progesterone receptor-positive), **AND**

B. The member/enrollee meets one of the following (regardless of menopausal status):

1. Tumor is greater than 0.5 cm and node negative (pN0), **OR**

2. Lymph nodes are pN1 (1-3 positive nodes).

II. The use of the breast cancer extended endocrine therapy test Breast Cancer Index (BCI) (81518, S3854) in men (sex assigned at birth) with breast cancer is considered **investigational**.

III. The use of the breast cancer extended endocrine therapy test Breast Cancer Index (BCI) (81518, S3854) is considered **investigational** for all other indications.

back to top

Breast Cancer Prognostic Algorithmic Tests

I. The use of a breast cancer prognostic algorithmic test (i.e., EndoPredict, Prosigna, MammaPrint) (81520, 81521, 81522, 81523, S3854) is considered **medically necessary** when:

   A. The member/enrollee has stage 1 or 2 breast cancer, **AND**

   B. The member/enrollee's tumor is estrogen receptor-positive, **AND**

   C. The member/enrollee's tumor is human epidermal growth factor receptor 2 (HER2)-negative, **AND**

   D. The member/enrollee is considering treatment with adjuvant therapy (for example, tamoxifen, aromatase inhibitors, immunotherapy), **AND**

   E. The member/enrollee has had axial nodal staging and has the following node status:

      1. pN0, nodes negative pathologically, **OR**

      2. pN1mi or pN1 (1-3 nodes positive pathologically) *.

II. The use of a breast cancer prognostic algorithmic test (i.e., EndoPredict, Prosigna, MammaPrint) (81520, 81521, 81522, 81523, S3854) in individuals with 4 or more positive nodes is considered **investigational**.

III. The use of the breast cancer prognostic algorithmic test Prosigna (81520) in individuals with 1-3 node positive breast cancer is considered **investigational.**

IV. The use of a breast cancer prognostic algorithmic test (i.e., EndoPredict, Prosigna, MammaPrint) (81520, 81521, 81522, 81523, S3854) in men (sex assigned at birth) with breast cancer is considered **investigational**.

V. The use of a breast cancer prognostic algorithmic test (i.e., EndoPredict, Prosigna, MammaPrint) (81520, 81521, 81522, 81523, S3854) is considered **investigational** for all other indications.

*Prosigna is indicated for node negative disease, but **not** for disease with 1-3 positive nodes. EndoPredict and Mammaprint are indicated for node negative disease and for disease with 1-3 positive nodes.

back to top

Gene Expression Profiling Breast Cancer Subtyping Tests

I. Gene expression profiling breast cancer subtyping tests (e.g., BluePrint) (81599, S3854) are considered **investigational**.

back to top

Breast DCIS Prognostic Algorithmic Tests

I. Breast DCIS prognostic algorithmic tests (0045U) are considered **medically necessary** when:

   A. The member/enrollee has ductal carcinoma in situ (DCIS), **AND**

   B. The tumor specimen contains at least 0.5 mm of DCIS, **AND**

   C. The result of testing would aid in treatment decision-making (i.e., pursuing additional surgery or radiation therapy), **AND**

   D. The member/enrollee's DCIS was not removed via mastectomy (i.e., there is residual ipsilateral breast tissue).

II. Breast DCIS prognostic algorithmic tests (0045U) are considered **investigational** for all other indications.

back to top

COLORECTAL CANCER

Colorectal Cancer Prognostic Algorithmic Tests

I. Colorectal cancer prognostic algorithmic tests (0069U, 0261U, 81525) are considered **investigational**.

back to top

MULTIPLE MYELOMA

Multiple Myeloma Prognostic Algorithmic Tests

I. Multiple Myeloma prognostic algorithmic tests are considered **not medically necessary.**.

back to top

PROSTATE CANCER

Prostate Cancer Treatment and Prognostic Algorithmic Tests

I. The use of a prostate cancer treatment and prognostic algorithmic test (i.e., Oncotype DX Prostate (0047U), Prolaris (81541), ArteraAI (0376U)) is considered **medically necessary** when:

   A. The member/enrollee does **not** have any of the following:

      1. Very low-risk prostate cancer, **OR**
      2. High-risk prostate cancer**, OR**
      3. Very high-risk prostate cancer.

II. The use of the prostate cancer treatment and prognostic algorithmic test Decipher assay (81542) is considered **medically necessary** when:

III. The member/enrollee is deciding between active surveillance and adjuvant radiotherapy after radical prostatectomy. The use of a prostate cancer treatment and prognostic algorithmic test (0047U, 0376U, 81541, 81542) is considered **investigational** for all other indications.

back to top

Evidence-Based Prostate Cancer Risk Assessment and Diagnostic Algorithmic Tests

I. Prostate cancer risk assessment and diagnostic algorithmic tests (0005U, 0113U, 0339U, 0359U, 81539, 84153, 84154, 86316, 81479, 81551) with sufficient evidence of clinical validity and utility are considered **medically necessary** when:

   A. The member/enrollee meets all of the following:

      1. The member/enrollee has not had a prostate biopsy, **AND**

2. The member/enrollee has at least one of the following:
    a) Prostate specific antigen (PSA) of >3 ng/ml, **OR**
    b) A digital rectal exam (DRE) that is suspicious for cancer, **AND**
3. The test is one of the following:
    a) Prostate Health Index (PHI), **OR**
    b) SelectMDx, **OR**
    c) 4Kscore, **OR**
    d) ExoDx Prostate Test, **OR**
    e) MyProstateScore (MPS), **OR**
    f) IsoPSA, **OR**

B. The member/enrollee meets all of the following:
1. The member/enrollee has had a prostate biopsy, **AND**
2. The result is one of the following:
    a) Atypia, suspicious for cancer, **OR**
    b) High-grade prostatic intraepithelial neoplasia (PIN)**, OR**
    c) Benign, **AND**
3. The test is one of the following:
    a) Prostate Health Index (PHI), **OR**
    b) 4Kscore, **OR**
    c) ExoDx Prostate Test, **OR**
    d) MyProstateScore (MPS), **OR**
    e) IsoPSA, **OR**
    f) ConfirmMDx, **OR**
    g) PCA3.

II. The use of prostate cancer risk assessment and diagnostic algorithmic tests (0005U, 0113U, 0339U, 0359U, 81539, 84153, 84154, 86316, 81479, 81551) with sufficient evidence of clinical validity and utility are considered **investigational** for all other

indications where clinical validity and utility have not been demonstrated.

back to top

Emerging Evidence Prostate Cancer Risk Assessment and Diagnostic Algorithmic Tests

I. Prostate cancer risk assessment and diagnostic algorithmic tests (0228U, 0343U, 0403U, 0424U, 0433U) with insufficient guidance for use are considered **investigational**.

back to top

THYROID CANCER

Thyroid Cancer Diagnostic Algorithmic Tests

I. The use of a thyroid cancer diagnostic algorithmic test (0018U, 0026U, 0204U, 0245U, 0287U, 81546) in fine needle aspirates of thyroid nodules is considered **medically necessary** when:

   A. The fine needle aspirate showed indeterminate cytologic findings (i.e., Bethesda diagnostic category III or IV), **AND**

   B. The result of the test would affect surgical decision making.

II. The use of a thyroid cancer diagnostic algorithmic test (0018U, 0026U, 0204U, 0245U, 0287U, 81546) in fine needle aspirates of thyroid nodules is considered **investigational** for all other indications.

back to top

UVEAL MELANOMA

Uveal Melanoma Prognostic Algorithmic Tests

I. The use of a uveal melanoma prognostic algorithmic test (81552) is considered **medically necessary** when:

   A. The member/enrollee has primary, localized uveal melanoma.

II. The use of a uveal melanoma prognostic algorithmic test (81552) is considered **investigational** for all other indications.

back to top

CUTANEOUS MELANOMA

Evidence-Based Cutaneous Melanoma Prognostic Algorithmic Tests

I. Cutaneous melanoma prognostic algorithmic tests (81479, 81529, 81599) with sufficient evidence of clinical validity and utility are considered **medically necessary** when:

   A. The member/enrollee has either of the following:

      1. Stage I melanoma (staging based on AJCC American Joint Committee on Cancer), **OR**

      2. Stage II melanoma (staging based on AJCC American Joint Committee on Cancer), **AND**

   B. The member/enrollee does NOT have metastatic disease, **AND**

   C. The results of testing will inform subsequent biopsy decisions, use of adjuvant therapy(ies), or follow-up screening protocols.

II. Cutaneous melanoma prognostic algorithmic tests (81479, 81529, 81599) with sufficient evidence of clinical validity and utility are considered **investigational** for all other indications where clinical validity and utility have not been demonstrated.

back to top

Emerging Evidence Cutaneous Melanoma Prognostic Algorithmic Tests

I. Cutaneous melanoma prognostic algorithmic tests (0387U) with insufficient evidence of clinical validity are considered **investigational**.

back to top

Cutaneous Melanoma Diagnostic Algorithmic Tests

I. Cutaneous melanoma diagnostic algorithmic tests (0090U, 0314U) are considered **medically necessary** when:

   A. The member/enrollee has a melanocytic neoplasm that is diagnostically uncertain or equivocal after histopathology.

II. Cutaneous melanoma diagnostic algorithmic tests (0090U, 0314U) are considered **investigational** for all other indications, including:

A. A melanocytic neoplasm that has pathology definitive for melanoma, desmoplastic melanoma, or sclerosing nevus.

back to top

Cutaneous Melanoma Risk Assessment Algorithmic Tests

I. Cutaneous melanoma risk assessment algorithmic tests (0089U) are considered **medically necessary** when:

A. The member/enrollee has a melanocytic neoplasm that shows at least one ABCDE feature (**a**symmetry, **b**order irregularity, **c**olor variegation, **d**iameter >6 mm, and **e**volution), **AND**

B. A biopsy is being considered but has not yet been performed, **AND**

C. The use of the test is limited to a maximum of 2 times per visit.

II. Cutaneous melanoma risk assessment algorithmic tests (0089U) are considered **investigational** for all other indications.

back to top

OVARIAN CANCER

Ovarian Cancer Diagnostic Algorithmic Tests

I. Ovarian cancer diagnostic algorithmic tests (i.e., OVA1, Overa, ROMA, and OvaWatch) (0003U, 0375U, 81500, 81503) are considered **investigational** for all indications, including but not limited to:

A. Preoperative evaluation of adnexal masses to triage for malignancy
B. Screening for ovarian cancer
C. Selecting patients for surgery for an adnexal mass
D. Evaluation of patients with clinical or radiologic evidence of malignancy
E. Evaluation of patients with nonspecific signs or symptoms suggesting possible malignancy
F. Postoperative testing and monitoring to assess surgical outcome and/or to detect recurrent malignant disease following treatment.

back to top

Ovarian Cancer Treatment Algorithmic Tests

I. Ovarian cancer treatment algorithmic tests (0172U) are considered **medically necessary** when:

   A. The member/enrollee has a diagnosis of ovarian cancer, **AND**

   B. The member/enrollee is being considered for PARP inhibitor therapy.

II. Ovarian cancer treatment algorithmic tests (0172U) are considered **investigational** for all other indications.

back to top

GYNECOLOGIC CANCER

Gynecologic Cancer Treatment Algorithmic Tests

I. Gynecologic cancer treatment algorithmic tests (81535, 81536) in the assessment of gynecological cancers are considered **investigational.**

back to top

LUNG CANCER

Evidence-Based Lung Cancer Diagnostic Algorithmic Tests

I. Lung cancer diagnostic algorithmic tests (0080U) with sufficient evidence of clinical validity and utility are considered **medically necessary** when:

   A. The member/enrollee is age 40 years or older, **AND**

   B. The member/enrollee has a single lung nodule between 8 and 30 mm in diameter, **AND**

   C. The member/enrollee has a risk of cancer of 50% or less according to the Mayo risk prediction algorithm, **AND**

   D. The member/enrollee does NOT have a diagnosis of cancer (except for nonmelanoma skin cancer) within 5 years of the lung nodule detection.

II. Lung cancer diagnostic algorithmic tests (0080U) with sufficient evidence of clinical validity and utility are considered **investigational** for all other indications where clinical validity and utility have not been demonstrated.

back to top

Emerging Evidence Lung Cancer Diagnostic Algorithmic Tests

I. Lung cancer diagnostic algorithmic tests (0092U, 0317U, 0360U, 0395U, 0406U, 81479) with insufficient evidence of clinical validity are considered **investigational**.

back to top

Evidence-Based Lung Cancer Treatment Algorithmic Tests

I. Lung cancer treatment algorithmic tests (0288U, 81538, 81599) with sufficient evidence of clinical validity and utility are considered **medically necessary** when:

   A. The member/enrollee has a non-squamous non-small cell lung cancer (NSCLC), **AND**

   B. The member/enrollee's tumor size less than 5 cm, **AND**

   C. The member/enrollee has no positive lymph nodes (stages I and IIa), **AND**

   D. The member/enrollee is considering adjuvant platinum-containing chemotherapy.

II. Lung cancer treatment algorithmic tests (0288U, 81538, 81599) with sufficient evidence of clinical validity and utility are considered **investigational** for all other indications where clinical validity and utility have not been demonstrated.

back to top

Emerging Evidence Lung Cancer Treatment Algorithmic Tests

I. Lung cancer treatment algorithmic tests (0414U, 0436U) with insufficient evidence of clinical validity are considered **investigational.**

back to top

BLADDER AND URINARY TRACT CANCER

Bladder/Urinary Tract Cancer Diagnostic Algorithmic Tests

I. Bladder/urinary tract cancer diagnostic algorithmic tests (0012M, 0365U, 0420U) are considered **investigational** for all indications.

back to top

Bladder Cancer Treatment and Recurrence Algorithmic Tests

I. The use of bladder cancer treatment and recurrence algorithmic test (0013M, 0016M, 0363U, 0366U, 0367U) is considered **medically necessary** when:

   A. The member/enrollee has a diagnosis of bladder cancer, **AND**

   B. Results of algorithmic testing will affect management decisions for the member/enrollee's bladder cancer, **AND**

   C. The member/enrollee has not previously undergone bladder cancer treatment and recurrence algorithmic testing for the current cancer diagnosis.

II. The use of bladder cancer treatment and recurrence algorithmic test (0013M, 0016M, 0363U, 0366U, 0367U) is considered **investigational** for all other indications.

back to top

PANCREATIC CANCER

Evidence-Based Pancreatic Cyst Risk Assessment Algorithmic Tests

I. Pancreatic cyst risk assessment algorithmic tests (81479) with sufficient evidence of clinical validity and utility are considered **medically necessary** when:

   A. The member/enrollee has a pancreatic cyst, **AND**

   B. Initial testing (for example, CEA measurement, cytopathology and/or radiology) has been inconclusive for malignancy, **AND**

   C. The results of the test will impact treatment decisions (e.g., surgery, more aggressive treatment).

II. Pancreatic cyst risk assessment algorithmic tests (81479) with sufficient evidence of clinical validity and utility are considered **investigational** for all other indications where clinical validity and utility have not been demonstrated.

back to top

Emerging Evidence Pancreatic Cyst Risk Assessment Algorithmic Tests

I. Pancreatic cyst risk assessment algorithmic tests (0313U) with insufficient evidence of clinical validity are considered **investigational**.

back to top

CANCER OF UNKNOWN PRIMARY

Cancer of Unknown Primary Gene Expression Profiling Tests

I. The use of a cancer of unknown primary gene expression profiling test (81540) to evaluate the site of origin of a tumor of unknown primary, or to distinguish a primary from a metastatic tumor is considered **investigational**.

back to top

POLYGENIC RISK SCORE TESTS

Breast Cancer Polygenic Risk Score Tests

I. The use of a breast cancer polygenic risk score test (81599) is considered **investigational**.

back to top

DEFINITIONS

1. **Ductal/NST breast cancer:** Ductal cancer that is of no special type (NST), meaning the cancer cells have no features that class them as a special type of breast cancer when examined by microscope.
2. **Indeterminate cytologic findings:** In thyroid nodules, indeterminate cytologic findings include Bethesda diagnostic category III (atypia/follicular lesion of undetermined

significance) or Bethesda diagnostic category IV (follicular neoplasm/suspicion for a follicular neoplasm)

3. **Adjuvant therapy:** Medication (such as chemotherapy or endocrine therapy) given after the surgical removal of a cancerous tumor.

4. **PSA persistence/recurrence:** Defined in the NCCN Prostate Cancer guidelines (4.2024) as failure of PSA to fall to undetectable levels (PSA persistence) or undetectable PSA after a radical prostatectomy with a subsequent detectable PSA that increases on 2 or more determinations (PSA recurrence) or that increases to PSA greater than 0.1 ng/mL (p. PROS-10)

5. **ABCDE feature:** Feature outlined in ABCDE criteria, which is an acronym for examining patients with a lesion that is suspicious for melanoma: **a**symmetry, **b**order irregularity, **c**olor variegation, **d**iameter >6 mm, and **e**volution.

6. **Very high-risk prostate cancer:** Defined by NCCN as an individual who has at least **one** of the following high-risk features:
    a. cT3b-cT4
    b. Primary Gleason pattern 5
    c. 2 or 3 high-risk features
    d. More than 4 cores with Grade Group 4 or 5

7. **High-risk prostate cancer:** Defined by NCCN as an individual who has no very-high-risk features but has at least one of the following high-risk features:
    a. cT3a
    b. Grade Group 4 or 5 (Gleason score 8 to 10).
    c. PSA >20 mg/nl

8. **Very low risk prostate cancer:** Defined by NCCN as all of the following:
    a. cT1c
    b. Grade Group 1
    c. PSA <10 mg/nl and density <0.15 ng/mL/g
    d. Biopsy shows <3 positive cores/fragments and < or equal to 50% cancer in each core/fragment.

back to top

BACKGROUND AND RATIONALE

BREAST CANCER

Breast Cancer Treatment and Prognostic Algorithmic Tests

National Comprehensive Cancer Network (NCCN)

Oncotype DX for breast cancer is a 21-gene expression assay. NCCN guidelines for Breast Cancer (4.2024) recommend the 21-gene expression assay for both prognosis and treatment decisions in the following patients:

- Patients of either sex (p. BINV-J 1 of 2)
- Evidence level 1: Postmenopausal patients with a ductal/NST, lobular, mixed, or micropapillary tumor that is pT1–3, and at least 0.5cm, with pN1mi (2 mm or smaller axillary node metastases) or pN1 (1–3 positive nodes). Tumor must be HR positive, HER2 negative. (p. BINV-6, BINV-N 1 of 5, BINV-N 2 of 5)
- Evidence level 1: Premenopausal patient with a ductal/NST, lobular, mixed, or micropapillary tumor that is at least 0.5cm and pN0. Tumor must be HR positive, HER2 negative. (p. BINV-7, BINV-N 1 of 5, BINV-N 2 of 5)
- Evidence level 2A: Premenopausal patient with a ductal/NST, lobular, mixed, or micropapillary tumor that is at least 0.5cm and pN1mi (2 mm or smaller axillary node metastasis) or pN1 (1–3 positive nodes). Tumor must be HR positive, HER2 negative. (p. BINV-8, BINV-N 1 of 5, BINV-N 2 of 5)

Breast Cancer Extended Endocrine Therapy Tests

National Comprehensive Cancer Network (NCCN)

The BCI (Breast Cancer Index) is recommended by NCCN Breast Cancer guidelines (4.2024) for both indications of prognosis as well as predicting treatment for extended adjuvant endocrine therapy. Appropriate patients for this test are:

- Evidence level 2A: Postmenopausal patients with a ductal/NST, lobular, mixed, or micropapillary tumor that is pT1–3, and 0.5cm or larger, with pN1mi (2 mm or smaller axillary node metastases) or pN1 (1–3 positive nodes). Tumor must be HR positive, HER2 negative. (p. BINV-6, BINV-N 1 of 5, BINV-N 4 of 5)
- Evidence level 2A: Premenopausal patients with a ductal/NST, lobular, mixed, or micropapillary tumor that is at least 0.5cm and pN0. Tumor must be HR positive, HER2 negative. (p. BINV-7, BINV-N 1 of 5, BINV-N 4 of 5)
- Evidence level 2A: Premenopausal patients with a ductal/NST, lobular, mixed, or micropapillary tumor that is at least 0.5cm and pN1mi (2 mm or smaller axillary node metastasis) or pN1 (1–3 positive nodes). Tumor must be HR positive, HER2 negative. (p. BINV-8, BINV-N 1 of 5, BINV-N 4 of 5)
- Data are limited regarding the use of molecular assays to assess prognosis and to predict benefit from chemotherapy in males with breast cancer. Available data suggest the 21-gene assay recurrence score provides prognostic information in males with breast cancer (p. BINV-J 1 of 2)

American Society of Clinical Oncology (ASCO)

In 2022, the American Society of Clinical Oncology (ASCO) issued a statement regarding the use of Breast Cancer Index testing for extended endocrine therapy for ER-positive HER2-negative breast cancer. Their recommendations are as follows:

- Recommendation 1.24: If a patient has node-negative or node-positive breast cancer with 1-3 positive nodes and has been treated with 5 years of primary endocrine therapy without evidence of recurrence, the clinician may offer the BCI test to guide decisions about extended endocrine therapy with either tamoxifen, an AI, or a sequence of tamoxifen followed by AI (Type: evidence-based; Evidence quality: intermediate; Strength of recommendation: moderate).
- Recommendation 1.25: If a patient has node-positive breast cancer with 4 or more positive nodes and has been treated with 5 years of primary endocrine therapy without evidence of recurrence, there is insufficient evidence to use the BCI test to guide decisions about extended endocrine therapy with either tamoxifen, an AI, or a sequence of tamoxifen followed by AI (Type: evidence-based; Evidence quality: intermediate; Strength of recommendation: strong).

Breast Cancer Prognostic Algorithmic Tests

American Society of Clinical Oncology (ASCO)

The 2022 ASCO guideline update for Biomarkers for Adjuvant Endocrine and Chemotherapy in Early-Stage Breast Cancer provides guidance for the diagnostic indications for several breast cancer prognostic algorithmic tests, including EndoPredict, MammaPrint, and Prosigna (among others). Figure 1 summarizes the following: if a female patient is postmenopausal or older than age 50 years, has early-stage invasive breast cancer, node negative disease, and a HER2 negative, ER positive tumor, then EndoPredict, Prosnigna, or MammaPrint may be ordered. However, if the patient has 1 to 3 positive node disease, MammaPrint or EndoPredict may be ordered. (p. 1821)

National Comprehensive Cancer Network (NCCN)

NCCN Breast Cancer guidelines (4.2024) recommend consideration of other prognostic gene expression assays to help assess risk of recurrence in pre- and postmenopausal patients with HR-positive, Her2-negative pT1-3 and pN0 or pN+ tumors, but these other tests have not been validated to predict response to chemotherapy. (p. BINV- 6, BINV-7, BINV-8) Gene expression assays can provide prognostic and treatment-predictive information that can be used with T,N,M and biomarker information. These prognostic gene expression assays can provide prognostic information but the ability to predict chemotherapy benefit has not been shown. (p. BINV-N, 1 of 5, 3 of 5)

Gene Expression Profiling Breast Cancer Subtyping Tests

National Comprehensive Cancer Network (NCCN)

NCCN Breast Cancer guidelines (4.2024) do not reference gene expression profiling tests (i.e., Blueprint) for the purpose of subtyping breast cancer to provide information for clinical decision-making.

American Society of Clinical Oncology

The ASCO Guideline Update on Biomarkers for Adjuvant Endocrine and Chemotherapy in Early Stage Breast Cancer (2022) does not include breast cancer subtyping tests (i.e., BluePrint) as recommended biomarker tests for guiding adjuvant therapy.

Concert Note
There is insufficient evidence to support the use of this test. No recommendations for or against this testing within standard professional society guidelines covering this area of testing were identified.

Breast DCIS Prognostic Algorithmic Tests

Centers for Medicare and Medicaid Services

The CMS local coverage determination (LCD) entitled "MolDX: Oncotype DX Breast Cancer for DCIS (Genomic Health)" includes the following criteria for OncotypeDX DCIS:

"The Oncotype DX DCIS assay is covered only when the following clinical conditions are met:

- Pathology (excisional or core biopsy) reveals ductal carcinoma in situ of the breast (no pathological evidence of invasive disease), and
- FFPE specimen with at least 0.5 mm of DCIS length, and
- Patient is a candidate for and is considering breast conserving surgery alone as well as breast conserving surgery combined with adjuvant radiation therapy, and
- Test result will be used to determine treatment choice between surgery alone vs. surgery with radiation therapy, and
- Patient has not received and is not planning on receiving a mastectomy."

COLORECTAL CANCER

Colorectal Cancer Prognostic Algorithmic Tests

National Comprehensive Cancer Network (NCCN)

NCCN guidelines for Colon Cancer (4.2024) does not recommend use of multigene panel assays to assist in making clinical decisions about adjuvant therapy. (p. COL-4)

PROSTATE CANCER

Prostate Cancer Treatment and Prognostic Algorithmic Tests

National Comprehensive Cancer Network (NCCN)

NCCN guidelines for Prostate Cancer (4.2024) recommend advanced risk stratification tools (i.e., gene expression biomarkers, AI digital pathology) when there is the possibility of changing disease management in men with localized prostate cancer and life expectancy of 10 yrs or more. (p. PROS-4,5,6) The most common reasons to use these tools is for deciding between active surveillance and radical treatment, or use of radiation alone vs radiation with androgen deprivation therapy (short or long term). These tests can also be useful post prostatectomy with recurrence, when choosing radiation with or without androgen deprivation therapy. (p. PROS-H, 1 of 8) These tests should not be used for very low risk or very high risk disease as they have not been validated in these populations. (p. PROS-H, 1 and 4-6 of 8) The following tumor-based assays are called out for use: Decipher, Genomic Prostate Score, ArteraAI and Prolaris. (p. PROS-H 3 of 8)

American Society of Clinical Oncology (ASCO)

ASCO (2020) issued a guideline for the use of molecular biomarkers in localized prostate cancer that included the following summary of recommendations:

> "Tissue-based molecular biomarkers (evaluating the sample with the highest volume of the highest Gleason pattern) may improve risk stratification when added to standard clinical parameters, but the Expert Panel endorses their use only in situations in which the assay results, when considered as a whole with routine clinical factors, are likely to affect a clinical decision. These assays are not recommended for routine use as they have not been prospectively tested or shown to improve long-term outcomes—for example, quality of life, need for treatment, or survival." (p. 1474)

Evidence-Based Prostate Cancer Risk Assessment and Diagnostic Algorithmic Tests

American Urological Association/Society of Urologic Oncology

The American Urological Association/Society of Urologic Oncology published guidelines on the early detection of prostate cancer (2023). They state that clinicians and patients may use adjunctive urine or serum markers to inform the shared decision making process regarding prostate biopsy (initial and/or repeat biopsy). It is imperative clinicians are familiar with biomarkers, understand what information or data each test provides, and consider whether additional information will impact management decisions before ordering a test. (conditional recommendation, evidence level C). (p. 21-22, 24) Of note, conditional recommendations are non-directive statements used when the evidence indicates that there is no apparent net benefit or

harm, or when the balance between benefits and risks/burden is unclear. For evidence level C, the balance between benefits and risks is unclear but net benefit or net harm is comparable to other options.

National Comprehensive Cancer Network (NCCN)

NCCN Prostate Cancer Early Detection guidelines (2.2024) recommends consideration of biomarkers that improve the specificity of screening in patients considering biopsy after abnormal PSA and/or DRE. Although these biomarker tests are not currently mandated as first-line screening tests in conjunction with serum PSA, there may be some patients who could consider biopsy based on PSA standards but are seeking further risk clarification. The probability of high-grade cancer (Gleason score ≥3+4, Grade Group 2 or higher) may be further defined utilizing the Prostate Health Index (PHI), SelectMDx, 4Kscore, ExoDx Prostate Test, MyProstateScore (MPS), and IsoPSA. (p. PROSD-3) Tests that improve specificity when considering a repeat biopsy should be considered after negative biopsy in patients felt to be at higher risk (p. PROSD-4). These tests include those listed above (except for SelectMDX) plus PCA3 and ConfirmMDX.

Emerging Evidence Prostate Cancer Risk Assessment and Diagnostic Algorithmic Tests

NCCN Prostate Cancer Early Detection guidelines (2.2024) comment on the usefulness of biomarker testing to assist in biopsy decision making. The guidelines do not mention the following tests as part of recommended clinical care: EpiSwitch Prostate Screening Test (PSE), miR Sentinel Prostate Cancer Test, MyProstateScore 2.0, PanGIA Prostate, and Apifiny.

Concert Note

There is insufficient evidence to support the use of these tests. At this time, there are no known recommendations for or against this testing within standard professional society guidelines covering this area of testing as current evidence indicates neither benefit nor harm at this time.

THYROID CANCER

Thyroid Cancer Diagnostic Algorithmic Tests

American Thyroid Association

The American Thyroid Association (2016) updated its guidelines on the management of thyroid nodules and differentiated thyroid cancer in adults. These guidelines made the following statements on molecular diagnostics in thyroid nodules: “For nodules with AUS/FLUS [atypia of undetermined significance/follicular lesion of undetermined significance]... molecular testing may be used to supplement malignancy risk assessment in lieu or proceeding directly with either surveillance or diagnostic surgery.” (p. 21)

National Comprehensive Cancer Network (NCCN)

NCCN Guidelines for Thyroid Carcinoma (3.2024) recommends consideration of molecular diagnostics on fine needle aspirate (FNA) results of thyroid nodules which are classified as Bethesda III or Bethesda IV if there is not high clinical and/or radiographic suspicion of malignancy. (p. THYR-1 and THYR-2)

American Association of Clinical Endocrinologists, American College of Endocrinology, and Associazone Medici Endocrinologi

The American Association of Clinical Endocrinologists, American College of Endocrinology, and Associazone Medici Endocrinologi (2016) updated their joint guidelines on molecular testing for cytologically indeterminate thyroid nodules and endorsed the following:

- *TERT* mutational analysis may improve the diagnostic sensitivity of molecular testing on cytologic samples. (p. 32)
- There is insufficient evidence to recommend either in favor of or against the use of gene expression classifiers for cytologically indeterminate nodules. (p. 10)
- With the exception of mutations such as *BRAF* V600E, there is insufficient evidence to recommend in favor of or against the use of mutation testing to determine the extent of surgery. (p. 10)

UVEAL MELANOMA

Uveal Melanoma Prognostic Algorithmic Tests

National Comprehensive Cancer Network (NCCN)

NCCN guidelines for Uveal Melanoma (1.2024) recommends consideration of biopsy of the primary tumor before radiation for prognostic analysis. Molecular testing for prognostication is recommended over cytology alone. (p. UM-2A) Tumor class defined by gene expression profiling was more strongly associated with risk of metastasis than any other prognostic factor. (p. UM-4)

CUTANEOUS MELANOMA

Evidence-Based Cutaneous Melanoma Prognostic Algorithmic Tests

ECRI Genetic Test Assessment

A recent review completed by ECRI (2023) found evidence for the DecisionDx-Melanoma 31-gene profiling (31-GEP) test to be somewhat favorable based on the available data pertaining to clinical validity, and potential clinical utility of the test. Specifically, the available studies demonstrated that they may improve patient outcomes (e.g., overall survival, by informing

decisions to escalate surveillance when the test is added to best available care (i.e., tumor staging, SLNB).

Concert Evidence Review for Coverage Determination (Published 12/21/2023, Re-issued 7/1/2024 with minor updates to test names; no updates to literature)

The current literature suggests that DecisionDx Melanoma (also referred to as 31-GEP in the literature) test exhibits high sensitivity (70-95%) and negative predictive value (>90%) in the prognosis of stage I and II cutaneous melanoma (CM) at multiple clinical endpoints including risk of recurrence, distant-site metastasis occurrence, and melanoma-specific death.

The literature demonstrates that the 31-GEP test has significant evidence of clinical validity and utility when incorporated as part of standard clinicopathologic features, both in predicting the potential prognosis of a cutaneous melanoma diagnosis as well as the prediction of SLNB positivity. Bailey et al (2023) showed that performing the 31-GEP test resulted in higher 3 year melanoma-specific survival (MSS) and overall survival (OS) in individuals with cutaneous melanoma, compared to patients not tested with the 31-GEP ($P < 0.001$). Additionally, the 31-GEP test was associated with a 29% lower MSS mortality and 17% lower overall mortality, allowing patients to be stratified by their risk. A study by Tassavor et al (2023) showed that the 31-GEP test outperformed the Memorial Sloan Kettering Cancer Center nomogram for predicting SLNB positivity in patients with cutaneous melanoma (T1-T2 tumors), thereby reducing the number of patients who need invasive procedures. Specifically, the study notes: "In patients with T1 tumors, for whom guidance on the clinical decision to perform SLNB is least clear, the i31-GEP for SLNB could have reduced the number of SLNBs by 43.7%, compared with standard NCCN SLNB guidance using AJCC staging, while maintaining a low false-negative rate." (p. 4514) Finally, in a prospective multicenter study, Yamamoto et al (2023) showed that overall 85.3% of decisions related to sentinel lymph node biopsy were influenced by 31-GEP test results in individuals with T1-T2 tumors. Concordance between performing an SLNB and 31-GEP influence was 78.5%.

Based upon retrospective cohort data, the Merlin assay shows relatively high clinical validity in individuals with primary cutaneous melanoma, with a NPV > 95% and elevated levels of sensitivity (80% in T1-T2 patients and 92.3% in T1-T3 patients) (Yousaf et al., 2021). Other research shows a potential for the Merlin assay to reduce SLNB complications by 50 - 69.1% by reducing the number of patients undergoing SLNB (Hieken et al., 2022). There is some evidence that suggests the CP-GEP assay can be used to further stratify the risk of recurrence, metastasis, and melanoma specific survival in patients (Eggermont et al., 2020).

MelaNodal Predict was added to this evidence review after determining that Melanodal uses the Merlin algorithm and is licensed by Quest. For this reason, we are assuming these tests are the same and therefore, the evidence review information above will apply to MelaNodal Predict.

Following on a systematic review of available peer-reviewed evidence, cutaneous melanoma prognostic algorithmic tests such as DecisionDx-Melanoma and Merlin / MelaNodal Predict,

have **SUFFICIENT EVIDENCE** for clinical validity to effectively identify patients with a poorer prognosis and for clinical utility in direct more aggressive treatment to promote increased patient survival.

Emerging Evidence Cutaneous Melanoma Prognostic Algorithmic Tests

Concert Evidence Review for Coverage Determination (Published 12/21/2023)

There were no available peer-reviewed studies concerning the AMBlor assay that met inclusion criteria for a systematic review. At this time, there is **INSUFFICIENT EVIDENCE** to support the clinical validity of this test in identifying early stage melanoma patients with poorer prognoses. No recommendations for or against this testing within standard professional society guidelines covering this area of testing were identified.

Cutaneous Melanoma Diagnostic Algorithmic Tests

National Comprehensive Cancer Network (NCCN)

NCCN guidelines for Cutaneous Melanoma (2.2024) indicate that gene expression profiling is an available test for diagnosing indeterminate melanocytic neoplasms by histopathology, along with immunohistochemistry (IHC), comparative genomic hybridization (CGH), fluorescence in situ hybridization (FISH), single-nucleotide polymorphism (SNP) array, and next-generation sequencing (NGS). These tests may lead to a definitive diagnosis and treatment selection in cases that are diagnostically equivocal or controversial by histopathology and NCCN recommends consideration of these tests in conjunction with clinical and pathology evaluation. (p. ME-C 1 of 8).

American Academy of Dermatology

The American Academy of Dermatology (Swetter, 2019) published guidelines of care for the management of primary cutaneous melanoma. The guidelines state the following regarding GEP tests:

- Diagnostic molecular techniques are still largely investigative and may be appropriate as ancillary tests in equivocal melanocytic neoplasms, but they are not recommended for routine diagnostic use in CM. These include comparative genomic hybridization (CGH), fluorescence in situ hybridization (FISH), gene expression profiling (GEP), and (potentially) next-generation sequencing. (page 219)
- Ancillary diagnostic molecular techniques (e.g., CGH, FISH, GEP) may be used for equivocal melanocytic neoplasms. (p. 219)

American Society of Dermatopathology

The American Academy of Dermatopathology (AUC Committee Members, 2022) published conditions where a 23 gene qRT-PCR test (MyPath Melanoma) was determined by a review of published evidence to be "majority usually appropriate." These include the differential diagnosis of nevus versus melanoma in fully sampled histopathologically ambiguous tumors, partially sampled nevus versus melanoma in adults, nevus versus nevoid melanoma, and nevus versus melanoma in cosmetically sensitive sites and special sites in pediatric patients. These recommendations specifically exclude scenarios where pathology is definitive for melanoma or for distinction between incompletely sampled sclerosing (desmoplastic) nevus versus desmoplastic melanoma. (p. 237-8)

Cutaneous Melanoma Risk Assessment Algorithmic Tests

National Comprehensive Cancer Network (NCCN)

NCCN Guidelines for Cutaneous Melanoma (2.2024) recommends consideration of pre-diagnostic noninvasive patch testing to help inform decisions regarding biopsy for patients with melanocytic neoplasms that are clinically/dermoscopically suspicious for melanoma. (p. ME-12)

ECRI Genetic Test Assessment

A recent review completed by ECRI (2023) found evidence for the Pigmented Lesion Assay (PLA) to be somewhat favorable based on the available data demonstrating clinical validity and utility to improve patient outcomes when added to standard of care. (p. 1)

American Academy of Dermatology

In their 2019 publication, the American Academy of Dermatology stated the following: Skin biopsy remains the first step to establish a definitive diagnosis of CM, although various molecular and imaging techniques have been studied as adjuncts to histopathologic assessment of melanocytic neoplasms. (p. 211)

Newer noninvasive techniques (eg, reflectance confocal microscopy [RCM], as well as electrical impedance spectroscopy, gene expression analysis, optical coherence tomography, and others can also be considered as these become more readily available. (p. 211)

UpToDate Melanoma: Clinical Features and diagnosis

Patients with a pigmented lesion that is changing and has additional ABCDE (**a**symmetry, **b**order irregularity, **c**olor variegation, **d**iameter >6 mm, **e**volution) criteria should be strongly considered for dermatology referral.

Centers for Medicare & Medicaid Services

Per MolDX: Pigmented Lesion Assay LCD (L38051), "Only 1 test may be used per patient per clinical encounter, in most cases. In roughly 10% of patients, a second test may be indicated for the same clinical encounter. For rare cases where more than 2 tests are indicated in a single

clinical encounter, an appeal with supporting documentation may be submitted for additional tests."

OVARIAN CANCER

Ovarian Cancer Diagnostic Algorithmic Tests

National Comprehensive Cancer Network (NCCN)

NCCN guidelines for Ovarian Cancer, Fallopian Tube Cancer, and Primary Peritoneal Cancer (3.2024) recognize that a number of specific biomarkers and algorithms using multiple biomarker test results have been proposed for preoperatively distinguishing benign from malignant tumors in patients who have an undiagnosed adnexal/pelvic mass. Currently, the NCCN Panel does not recommend the use of these biomarker tests for evaluation of an undiagnosed adnexal/pelvic mass. (p. MS-10, MS-11)

Ovarian Cancer Treatment Algorithmic Tests

National Comprehensive Cancer Network (NCCN)

NCCN guidelines for Ovarian Cancer, Fallopian Tube Cancer, and Primary Peritoneal Cancer (3.2024) recommend genetic risk evaluation, and germline and somatic testing if not previously done, including *BRCA1/2* to guide maintenance therapy for patients with ovarian, fallopian tube, or primary peritoneal cancer. If a patient does not have a germline *BRCA1/2* mutation, homologous recombination status may help determine the benefit of PARP inhibitor therapy. (p. OV-1)

American Society of Clinical Oncology (ASCO)

ASCO (2020) issued a guideline for the use of PARP inhibitors in the management of ovarian cancer, which included the following summary of recommendations:

> "The guideline pertains to patients who are PARPi naïve. All patients with newly diagnosed, stage III-IV EOC (epithelial ovarian, tubal, or primary peritoneal cancer), whose disease is in complete or partial response to first-line, platinum-based chemotherapy with high-grade serous or endometrioid EOC should be offered PARPi maintenance therapy with niraparib. For patients with germline or somatic pathogenic or likely pathogenic variants in *BRCA1* (g/sBRCA1) or *BRCA2* (g/sBRCA2) genes, should be treated with olaparib. The addition of olaparib to bevacizumab may be offered to patients with stage III-IV EOC with g/s*BRCA1/2* and/or genomic instability and a partial or complete response to chemotherapy plus bevacizumab combination. Maintenance therapy (second line or more) with single-agent PARPi may be offered for patients with EOC who have not received a PARPi and have responded to platinum-based therapy

regardless of *BRCA* mutation status. Treatment with a PARPi should be offered to patients with recurrent EOC that has not recurred within 6 months of platinum-based therapy, who have not received a PARPi and have a g/s*BRCA1/2*, or whose tumor demonstrates genomic instability. PARPis are not recommended for use in combination with chemotherapy, other targeted agents, or immune-oncology agents in the recurrent setting outside the context of a clinical trial. Recommendations for managing specific adverse events are presented. Data to support reuse of PARPis in any setting are needed." (p. 3)

GYNECOLOGIC CANCER

Gynecologic Cancer Treatment Algorithmic Tests

National Comprehensive Cancer Network (NCCN)

NCCN guidelines for Ovarian Cancer, Fallopian Tube Cancer, and Primary Peritoneal Cancer (3.2024) state that chemosensitivity/resistance assays have been proposed for informing decisions related to future chemotherapy if there are multiple equivalent chemotherapy options available. This has a category 3 level of evidence which indicates that there is major NCCN disagreement that the intervention is appropriate. (p. OV-C, 1 of 12)

NCCN guidelines for Cervical Cancer (3.2024) do not mention chemosensitivity or chemoresistance assays as part of clinical care.

NCCN guidelines for Uterine Neoplasms (2.2024) do not mention chemosensitivity or chemoresistance assays as part of clinical care.

LUNG CANCER

Evidence-Based Lung Cancer Diagnostic Algorithmic Tests

Concert Evidence Review for Coverage Determination (Published 12/21/23)

This body of literature includes validation studies for NodifyXL2. These studies were each published with authors from the company that developed or currently offer the test, with the exception of the 2023 study published by Kheir et al examining NodifyXL2. In this case, the authors disclosed no conflicts of interest except for the lead author who received honoraria from Biodesix and Veracyte for educational events.

Multiple studies have been published on NodifyXL2 and the clinical validity of this test as it pertains to identifying the risk of cancer in patients with lung nodules. Two studies published in 2023 (Pritchett et al and Kheir et al) examined NodifyXL2 and demonstrated adequate clinical utility. Kheir et al published a retrospective study examining patients with lung nodules who were evaluated using the integrated proteomic classifier NodifyXL2 compared to standard

clinical care during the same period of time, with a follow-up time of 1 year. In the study group of 102 patients, fewer invasive procedures were performed compared to the non-integrated classifier group of 129 patients (26.5% vs 79.1%; P<0.001). Pritchett et al also examined biopsy rates in patients in matched cohorts (197 patients in each group). Patients in the study group (tested with NodifyXL2) were 74% less likely to undergo an invasive procedure compared to the control group (absolute difference 14%; P<0.001), and for every 7 patients tested, one unnecessary invasive procedure was avoided. Both of these studies had similar inclusion criteria for patients: age 40 years or older, with a risk for cancer of 50% or less according to the Mayo Solitary Pulmonary Nodule calculator, a lung nodule between 8 and 30 mm in diameter, and no history of cancer (except non-melanomatous skin cancer) within 5 years of the discovery of the lung nodule.

Emerging Evidence Lung Cancer Diagnostic Algorithmic Tests

Concert Evidence Review for Coverage Determination (Published 12/21/23)

Multiple studies have been published on Percepta Bronchial Genomic Classifier and REVEAL Lung Nodule Characterization and their ability to identify risk of cancer in patients with lung nodules. This body of literature includes studies meant to assess clinical validity for each test. Overall, these studies inadequately demonstrate the clinical validity of these tests for distinguishing high risk nodules from low risk nodules.

Percepta originally had a cost-effectiveness study published in 2017. A new validation study for this test was published in 2021 and it is not clear if the new test would also be cost-effective.

There are a few studies that include some characterization of clinical utility for the Percepta and REVEAL Lung Nodule Characterization and their ability to identify risk of cancer in patients with lung nodules. But these studies have significant flaws, including small population sizes, and potential bias due to authors with conflict of interest. These studies were each published with authors from the company that developed or currently offers the test. Additionally, the costs of these tests compared to costs of under- and over-diagnosis of lung cancer in patients with lung nodules needs to be completed. To our knowledge, there are currently no randomized controlled trials enrolling for Percept or REVEAL.

Tests that have limited established clinical utility or validity as defined in the Concert policy for General Approach to Genetic and Molecular testing do not meet the threshold for coverage. Evidence for validity may include a Technology Assessment conducted by an independent third party (e.g.MolDx Tech, ECRI, Optum Genomic) and/or evidence-based guidelines published by professional societies. Such evidence was not identified for the tests referenced by this policy.

Evidence-Based Lung Cancer Treatment Algorithmic Tests

Centers for Medicare and Medicaid Services

The CMS local coverage determination (LCD) entitled "MolDX: Predictive Classifiers for Early Stage Non-Small Cell Lung Cancer" includes the following criteria for lung cancer treatment algorithmic tests:

- "The patient has a non-squamous NSCLC with a tumor size < 5cm, and there are no positive lymph nodes (i.e. American Joint Committee on Cancer (AJCC) Eighth Edition Stages I and IIa)
- The patient is sufficiently healthy to tolerate chemotherapy
- Adjuvant platinum-containing chemotherapy is being considered for the patient
- The test is ordered by a physician who is treating the patient for NSCLC (generally a medical oncologist, surgeon, or radiation oncologist) to help in the decision of whether or not to recommend adjuvant chemotherapy".

From the Billing and Coding article:

DetermaRx (PLA code 0288U) is a covered test.

Emerging Evidence Lung Cancer Treatment Algorithmic Tests

Tests that have limited established clinical utility or validity as defined in the Concert policy for General Approach to Genetic and Molecular testing do not meet the threshold for coverage. Evidence for validity may include a Technology Assessment conducted by an independent third party (e.g. MolDx Tech, ECRI, Optum Genomic) and/or evidence-based guidelines published by professional societies. Such evidence was not identified for the tests referenced by this policy.

BLADDER AND URINARY TRACT CANCER

Bladder/Urinary Tract Cancer Diagnostic Algorithmic Tests

There is insufficient evidence to support the use of this test. No recommendations for or against this testing within standard professional society guidelines covering this area of testing were identified. Sources reviewed: National Comprehensive Cancer Network Bladder Cancer guidelines (4.2024), The American Urological Association and Society of Urologic Oncology (Hozbeierlein et al).

Bladder Cancer Treatment and Recurrence Algorithmic Tests

Centers for Medicare and Medicaid Services

The CMS local coverage determination (LCD) entitled "MolDX: Prognostic and Predictive Molecular Classifiers for Bladder Cancer" states the following regarding bladder cancer molecular diagnostic tests, including algorithmic tests:

"This contractor will cover molecular diagnostic tests for use in a beneficiary with bladder cancer when all of the following conditions are met:

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

PANCREATIC CANCER

Evidence-Based Pancreatic Cyst Risk Assessment Algorithmic Tests

Centers for Medicare and Medicaid Services

The CMS local coverage determination (LCD) entitled "Loss-of-Heterozygosity Based Topographic Genotyping with PathfinderTG" includes the following criteria for PathfinderTG (currently known as PancraGen):

"PathfinderTG will be considered medically reasonable and necessary when selectively used as an occasional second-line diagnostic supplement:

- Only where there remains clinical uncertainty as to either the current malignancy or the possible malignant potential of the pancreatic cyst based upon a comprehensive first-line evaluation; AND
- A decision regarding treatment (e.g. surgery) has NOT already been made based on existing information.

The specific requirements for medical necessity involve:

- Highly-concise affirmation, documented in the medical record, that a decision regarding treatment has not already been made and that the results of the molecular evaluation will assist in determining if more aggressive treatment than what is being considered is necessary.

- Previous first-line diagnostics, such as, but not restricted to, the following have demonstrated:
    - A pancreatic cyst fluid carcinoembryonic antigen (CEA), which is greater than or equal to 200 ng/ml, suggesting a mucinous cyst, but is not diagnostic.
    - Cyst cytopathologic or radiographic findings, which raise the index of malignancy suspicion, but where second-line molecular diagnostics is expected to be more compelling in the context of a surgical vs. non-surgical care plan.

Specific criteria of Non-coverage to include either:

- Image guided needle aspiration of the pancreatic cyst or cystic component of a mass lesion or dilated duct demonstrate definitive diagnosis of malignancy by cytology; OR

- Cytology not showing malignancy but meets AGA guidelines to reach a definitive diagnosis of benign disease. Lesions must be:
    - Under 1 cm;
    - Lack a solid component;
    - Lack concerning cytology features;
    - Lack main pancreatic duct dilatation of > 1cm in diameter with absence of abrupt change in duct diameter;
    - Have fluid CEA level not exceeding 5 ng/ml".

Emerging Evidence Pancreatic Cyst Risk Assessment Algorithmic Tests

Tests that have limited established clinical utility or validity as defined in the Concert policy for General Approach to Genetic and Molecular testing do not meet the threshold for coverage. Evidence for validity may include a Technology Assessment conducted by an independent third party (e.g. MolDx Tech, ECRI, Optum Genomic) and/or evidence-based guidelines published by professional societies. Such evidence was not identified for the tests referenced by this policy.

CANCER OF UNKNOWN PRIMARY

Cancer of Unknown Primary Gene Expression Profiling Tests

National Comprehensive Cancer Network (NCCN)

NCCN guidelines for Occult Primary (Cancer of Unknown Primary) (1.2025) state that gene sequencing to predict tissue of origin is not recommended. (p. OCC-1) There has been no clinical benefit from gene expression profiling to identify tissue of origin. (p. MS-4)

POLYGENIC RISK SCORE TESTS

Breast Cancer Polygenic Risk Score Tests

National Comprehensive Cancer Network (NCCN)

NCCN guidelines for Genetic/Familial High-Risk Assessment for Breast, Ovarian, and Pancreatic cancers (3.2024) speak broadly about the use of polygenic risk scores, stating that there are currently significant limitations to this type of testing, and their use is not recommended for clinical management at this time outside of the context of a clinical trial (p. EVAL-A, 3 of 10).

Reviews, Revisions, and Approvals	Revision Date	Approval Date
Policy developed using Concert Genetic Testing Oncology Algorithmic Testing v1.2025 and Washington State Health Technology Assessment "Gene Expression Profile Testing of Cancer Tissue".	12/24	12/24

back to top

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Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. The Health Plan makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved. "Health Plan" means a health plan that has adopted this clinical policy and that is operated or administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan's affiliates, as applicable.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions, and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a

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Note: For Medicaid member/enrollees, when state Medicaid coverage provisions conflict with the coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.

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