Medica Central Coverage Policy

Policy Name:	**Genetic Testing – Oncology Testing: Algorithmic Assays MP9605**
Effective Date:	**July 01, 2025**

Important Information – Please Read Before Using This Policy

These services may or may not be covered by all Medica Central plans. Coverage is subject to requirements in applicable federal or state laws. Please refer to the member's plan document for other specific coverage information. If there is a difference between this general information and the member's plan document, the member's plan document will be used to determine coverage. With respect to Medicare, Medicaid, and other government programs, this policy will apply unless these programs require different coverage.

Members may contact Medica Customer Service at the phone number listed on their member identification card to discuss their benefits more specifically. Providers with questions may call the Provider Service Center. Please use the Quick Reference Guide on the Provider Communications page for the appropriate phone number. https://mo-central.medica.com/Providers/SSM-employee-health-plan-for-IL-MO-OK-providers

Medica Central coverage policies are not medical advice. Members should consult with appropriate health care providers to obtain needed medical advice, care, and treatment.

OVERVIEW

This policy addresses the use of tests that combine biomarkers and/or clinical data into an algorithm to generate a disease risk assessment, prognostic result, or clinical recommendation for treatment.

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

For additional information see the Rationale section.

The tests, CPT codes, and ICD codes referenced in this policy are not comprehensive, and their inclusion does not represent a guarantee of coverage or non-coverage.

POLICY REFERENCE TABLE

COVERAGE CRITERIA SECTIONS	EXAMPLE TESTS (LABS)	COMMON BILLING CODES	REF
Breast Cancer			
Breast Cancer Treatment and Prognostic Algorithmic Tests	Oncotype Dx Breast Recurrence Score - 81519 (Exact Sciences)	81519, S3854, C50.011-C50.92, Z17.0	1

COVERAGE CRITERIA SECTIONS	EXAMPLE TESTS (LABS)	COMMON BILLING CODES	REF
Breast Cancer Extended Endocrine Therapy Algorithmic Tests	Breast Cancer Index - 81518 (bioTheranostics)	81518, S3854, C50.011-C50.92, Z17.0	1, 21
Breast Cancer Prognostic Algorithmic Tests	End oPredict - 81522 (Myriad) MammaPrint - 81521, 81523 (Agendia, Inc.) Prosigna Assay - 81520 (NeoGenomics)	81520, 81521, 81522, 81523, S3854, C50, Z17.0, Z17.1	
Gene Expression Profiling Breast Cancer Subtyping Tests	BluePrint (Agendia, Inc.)	81599, S3854, 0153U, C50-C50.929	1, 23
	Insight TNBCtype - 0153U (Insight Molecular Labs)		
Breast DCIS Prognostic Algorithmic Tests	Oncotype DX Breast DCIS Score - 0045U (Exact Sciences)	0045U, D05.1	28
Colorectal Cancer			
Colorectal Cancer Prognostic Algorithmic Tests	Oncotype DX Colon Recurrence Score - 81525 (Exact Sciences) miR-31now - 0069U (GoPath Laboratories)	81525, 0069U, 0261U, C18.0-C18.9	2
	Immunoscore - 0261U (Veracyte)		
Prostate Cancer			
	ArteraAI Prostate Test - 0376U (Artera)	81541, 81542, 0047U, 0376U, C61	3, 16

COVERAGE CRITERIA SECTIONS	EXAMPLE TESTS (LABS)	COMMON BILLING CODES	REF
Prostate Cancer Treatment and Prognostic Algorithmic Tests	Oncotype DX Genomic Prostate Score - 0047U (MDxHealth)		
	Decipher Prostate RP Genomic Classifier - 81542 (Veracyte)		
	Prolaris - 81541 (Myriad Genetics)		
	Decipher Prostate Biopsy Genomic Classifier - 81542 (Veracyte)		
Evidence-Based Prostate Cancer Risk Assessment and Diagnostic Algorithmic Tests	4K Prostate Score (Serum) - 81539 (BioReference Laboratories) Prostate Health Index (ARUP Laboratories)	81479, 81539, 84153, 84154, 81551, 86316, 0005U, 0339U, 0359U, 0403U, C61, Z12.5	4, 20
	SelectMDx for Prostate Cancer - 0339U (MDxHealth)		
	ExoDx Prostate Test - 0005U (ExosomeDx)		
	IsoPSA - 0359U (Cleveland Diagnostics, Inc)		
	MyProstateScore 2.0 - 0403U (LynxDX)		
	ConfirmMDx for Prostate Cancer - 81551 (MDxHealth)		

COVERAGE CRITERIA SECTIONS	EXAMPLE TESTS (LABS)	COMMON BILLING CODES	REF
	Prostate Cancer Gene 3 (Integrated Regional Laboratories)		
Emerging Evidence Prostate Cancer Risk Assessment and Diagnostic Algorithmic Tests	Apifiny - 0021U (Armune Bioscience) PanGIA Prostate - 0228U (Genetics Institute of America) miR Sentinel Prostate Cancer Test - 0343U or 0424U (UmiR Scientific) EpiSwitch Prostate Screening Test (PSE) - 0433U (Oxford BioDynamics)	0021U, 0228U, 0343U, 0424U, 0433U, 0495U, 0497U, 0512U, 0513U, C61, Z12.5	20
	Stockholm3 - 0495U (BioAgilytix Diagnostics)		
	OncoAssure Prostate - 0497U (DiaCarta, Inc.) Tempus p-MSI - 0512U (Tempus AI, Inc) Tempus p-Prostate - 0513U (Tempus AI, Inc)		
Thyroid Cancer			
Thyroid Cancer Diagnostic Algorithmic Tests	ThyroSeq Genomic Classifier - 0026U (CBLPath)	81546, 0018U, 0026U, 0204U, 0245U, 0287U, C73, D44.0, E04.1	5, 6

COVERAGE CRITERIA SECTIONS	EXAMPLE TESTS (LABS)	COMMON BILLING CODES	REF
	ThyGeNEXT - 0245U (Interpace Diagnostics)		
	ThyraMIR - 0018U (Interpace Diagnostics)		
	Afirma Genomic Sequencing Classifier - 81546 (Veracyte) Afirma Xpression Atlas - 0204U (Veracyte) ThyroSeq CRC - 0287U (UPMC)		
Uveal Melanoma			
Uveal Melanoma Prognostic Algorithmic Tests	DecisionDx-UM - 81552 (Castle Bioscience, Inc.)	81552, C69	7
Cutaneous Melanoma			
Cutaneous Melanoma Prognostic Algorithmic Tests	DecisionDx-Melanoma - 81529 (Castle Biosciences, Inc.) Merlin Melanoma (BioCartis)	81479, 81529, 81599, 0387U, C43, D03.0-D03.9, Z12.83	22, 34
	MelaNodal (Quest)		
Emerging Evidence Cutaneous Melanoma Prognostic Algorithmic Tests	AMBLor - 0387U (AMLo Biosciences)	81479, 81529, 81599, 0387U, C43, D03.0-D03.9, Z12.83	25
	myPath Melanoma - 0090U (Castle Biosciences, Inc.)		8, 9, 19

COVERAGE CRITERIA SECTIONS	EXAMPLE TESTS (LABS)	COMMON BILLING CODES	REF
Cutaneous Melanoma Diagnostic Algorithmic Tests	DecisionDx DiffDx-Melanoma - 0314U (Castle Biosciences, Inc.)	0090U, 0314U, D22.0-D22.9, D48.5, D49.2, Z12.83	
Cutaneous Melanoma Risk Assessment Algorithmic Tests	Pigmented Lesion Assay - 0089U (DermTech)	0089U, D22-D23, Z12.83	8, 9, 23, 24, 25
Ovarian Cancer			
Ovarian Cancer Diagnostic Algorithmic Tests	OVA1 - 81503 (Aspira Women's Health) Overa - 0003U (Aspira Women's Health)	81500, 81503, 0003U, 0375U, 0507U, D27.0, D27.1, D27.9, D39.10-D39.12, D39.9, D49.59, D49.9	10
Ovarian Cancer Treatment Algorithmic Tests	Risk of Ovarian Malignancy (ROMA) - 81500 (Labcorp)	0172U, C48, C56, C57.0	11, 19
	OvaWatch - 0375U (Aspira Women's Health)		
	Avantect Ovarian Cancer Test - 0507U (ClearNote Health)		
Ovarian Cancer Treatment Algorithmic Tests	myChoice CDx - 0172U (Myriad Genetics)	0172U, C48, C56, C57.0	10, 17
Gynecologic Cancer			
Gynecologic Cancer Treatment Algorithmic Tests	ChemoFx - 81535 (Helomics Corporation)	81535, 81536, C51-C57	10, 14, 15
	ChemoFx - Additional Drug - 81536 (Helomics Corporation)		
Lung Cancer			

COVERAGE CRITERIA SECTIONS	EXAMPLE TESTS (LABS)	COMMON BILLING CODES	REF
Evidence-Based Lung Cancer Risk Assessment Algorithmic Tests	Nodify XL2 - 0080U (Biodesix)	0080U, R91.1	31, 35, 36
Emerging Evidence Lung Cancer Diagnostic Algorithmic Tests	REVEAL Lung Nodule Characterization - 0092U (MagArray)	81479, 0092U, 0317U, 0360U, 0395U, 0406U, R91.1	18
	Percepta Lung Cancer Diagnostics (Veracyte)		
	LungLB Test - 0317U (LungLife AI)		
	Nodify CDT - 0360U (Biodesix) OncobiotaLUNGdetect - 0395U (Micronoma) CyPath Lung - 0406U (Precision Pathology Laboratory)		
Evidence-Based Lung Cancer Treatment Algorithmic Tests	Veristrat - 81538 (Biodesix)	81538, 81599, 0288U, C34, D38.1, D38.6	26, 30
	Razor14/Risk Reveal (RazorGenomics)		
	DetermaRx - 0288U (Oncocyte Corporation)		
Emerging Evidence Lung Cancer Treatment Algorithmic Tests	LungOI - 0414U (Imagene) PROphet NSCLC Test - 0436U (OncoHost Inc)	0414U, 0436U, C34, D38.1, D38.6	
Bladder and Urinary Tract Cancer			

COVERAGE CRITERIA SECTIONS	EXAMPLE TESTS (LABS)	COMMON BILLING CODES	REF
Bladder/Urinary Tract Cancer Diagnostic Algorithmic Tests	CxBladder Detect+ - 0420U (Pacific Edge)	0012M, 0365U, 0420U, R31.9	11, 12
	Cxbladder Detect - 0012M (Pacific Edge)		
	Oncuria Detect - 0365U (DiaCarta Clinical Lab)		
Bladder Cancer Treatment and Recurrence Algorithmic Tests	Cxbladder Monitor - 0013M (Pacific Edge)	0013M, 0016M, 0363U, 0366U, 0367U, C67, C68	29
	Decipher Bladder Genomic Test - 0016M (Veracyte)		
	Cxbladder Triage - 0363U (Pacific Edge)		
Evidence-Based Pancreatic Cyst Risk Assessment Algorithmic Tests	Oncuria Monitor - 0366U (DiaCarta Clinical Lab)	81479, D49, K86.2	30
Emerging Evidence Pancreatic Cyst Risk Assessment Algorithmic Tests	Oncuria Predict - 0367U (DiaCarta Clinical Lab)	0313U, D49, K86.2	30
Pancreatic Cancer			
Evidence-Based Pancreatic Cyst Risk Assessment Algorithmic Tests	PancraGEN (Interpace Diagnostics)	81479, D49, K86.2	27
Emerging Evidence Pancreatic Cyst Risk Assessment Algorithmic Tests	PancreaSeq Genomic Classifier - 0313U (Univ of Pittsburgh Medical Center Molecular and Genomic Pathology Laboratory)	0313U, D49, K86.2	

COVERAGE CRITERIA SECTIONS	EXAMPLE TESTS (LABS)	COMMON BILLING CODES	REF
Cancer of Unknown Primary			
Cancer of Unknown Primary Gene Expression Profiling Tests	CancerTYPE ID - 81540 (Biotheranostics)	81540, C79.9, C80.0, C80.1	13
Esophageal Cancer			
Barrett's Esophagus Risk Assessment Algorithmic Tests	TissueCypher - 0108U (Cernostics Lab)	0108U, 0114U, 0398U, 0506U	32, 33
	EsoGuard - 0114U (Lucid Diagnostics)		
	ESOPREDICT Barrett's Esophagus Risk Classifier Assay - 0398U (Capsulomics Inc. d/b/a Previse) EndoSign Barrett's Esophagus Test - 0506U (Cyted Health)		

RELATED POLICIES

This policy document provides coverage criteria for testing related to diagnosis and prognosis for cancer. Please refer to:

- ***Oncology Testing: Solid Tumor Molecular Diagnostics*** for coverage criteria related to molecular profiling of a known or suspected cancer (e.g. broad molecular profiling, including Minimal Residual Disease (MRD) Testing, Tumor Mutational Burden (TMB), and cytogenetic / fusion testing).
- ***Oncology Testing: Hematologic Malignancy Molecular Diagnostics*** for coverage criteria related to molecular profiling of a known or suspected blood cancer (e.g. broad molecular profiling, including Minimal Residual Disease (MRD) Testing, Tumor Mutational Burden (TMB), and cytogenetic / fusion testing).
- ***Oncology Testing: Hereditary Cancer*** for coverage criteria related to genetic testing for hereditary cancer predisposition syndromes.

- ***Oncology Testing: Cancer Screening and Surveillance*** for coverage criteria related to screening and biomarker cancer tests.
- ***General Approach to Laboratory Testing*** for coverage criteria related to oncology, including known familial variant testing, that is not specifically discussed in this or another non-general policy.

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COVERAGE CRITERIA

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 is considered **medically necessary** in all members, regardless of gender, when:

A. The member has primary breast cancer that is ductal/NST, lobular, mixed or micropapillary, **AND**

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

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

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

E. The member is status post tumor resection and surgical axillary nodal staging, **AND**

1. The member meets one of the following (regardless of menopausal status):

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

b) Lymph nodes are pN1mi (2mm or smaller axillary node metastases), **OR**

c) 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 is considered **investigational** for all other indications.

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Breast Cancer Extended Endocrine Therapy Algorithmic Tests

I. The use of the breast cancer extended endocrine therapy test Breast Cancer Index (BCI) is considered **medically necessary** when:

A. The member is female (sex assigned at birth), **AND**

B. The member has primary breast cancer that is ductal/NST, lobular, mixed or micropapillary, **AND**

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

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

E. The member has no distant metastases, **AND**

F. The member has completed at least 4 years of endocrine therapy, **AND**

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

H. The member 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 pN1mi (2mm or smaller axillary node metastases), **OR**

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

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

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Breast Cancer Prognostic Algorithmic Tests

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

A. The member is female (sex assigned at birth), **AND**

B. The member meets at least one of the following:

1. Postmenopausal status, **OR**

2. Greater than 50 years of age, **AND**

C. The member has primary breast cancer that is ductal/NST, lobular, mixed or micropapillary, **AND**

D. The member's tumor is estrogen receptor-positive, **AND**

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

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

G. The member has had axillary nodal staging and has the following node status:

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

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

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

III. The use of the breast cancer prognostic algorithmic test Prosigna 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) 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) is considered **investigational** for all other indications.

[1] 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.

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Gene Expression Profiling Breast Cancer Subtyping Tests

I. Gene expression profiling breast cancer subtyping tests (e.g., BluePrint, Insight TNBCtype) are considered **investigational** for all indications.

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Breast DCIS Prognostic Algorithmic Tests

I. Breast DCIS prognostic algorithmic tests are considered **medically necessary** when:

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

II. Breast DCIS prognostic algorithmic tests are considered **investigational** for all other indications.

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COLORECTAL CANCER

Colorectal Cancer Prognostic Algorithmic Tests

I. Colorectal cancer prognostic algorithmic tests are considered **investigational** for all indications.

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PROSTATE CANCER

Prostate Cancer Treatment and Prognostic Algorithmic Tests

I. The use of a prostate cancer treatment and prognostic algorithmic test (i.e., Genomic Prostate Score Test, Prolaris, Decipher, ArteraAI) is considered **medically necessary** when:

A. The member has a life expectancy of 10 years or more, **AND**

B. The member does **not** have either of the following:

1. Very low-risk prostate cancer, as defined by all of the following characteristics:

a) cT1c

b) Grade Group 1

c) PSA less than 10 mg/nl and density less than 0.15 ng/mL/g

d) Biopsy shows less than 3 positive cores/fragments and less than or equal to 50% cancer in each core/fragment, **OR**

2. Very high-risk prostate cancer, as defined by all of the following characteristics:

a) cT3-cT4

b) PSA greater than 40 ng/mL

c) Grade Group 4 or 5.

II. The use of a prostate cancer treatment and prognostic algorithmic test is considered **investigational** for all other indications.

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Evidence-Based Prostate Cancer Risk Assessment and Diagnostic Algorithmic Tests

I. Prostate cancer risk assessment and diagnostic algorithmic tests with sufficient evidence of clinical validity and utility are considered **medically necessary** when:

A. The member meets all of the following:

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

2. The member has at least one of the following:

a) Prostate specific antigen (PSA) greater than 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 2.0 (MPS2), **OR**

f) IsoPSA, **OR**

B. The member meets all of the following:

1. The member 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 2.0 (MPS2), **OR**

e) IsoPSA, **OR**

f) ConfirmMDx, **OR**

g) PCA3.

II. The use of prostate cancer risk assessment and diagnostic algorithmic tests with sufficient evidence of clinical validity and utility are considered **investigational** for all other indications where clinical validity and utility have not been demonstrated.

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Emerging Evidence Prostate Cancer Risk Assessment and Diagnostic Algorithmic Tests

I. Prostate cancer risk assessment and diagnostic algorithmic tests with insufficient guidance for use are considered **investigational** for all indications.

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THYROID CANCER

Thyroid Cancer Diagnostic Algorithmic Tests

I. The use of a thyroid cancer diagnostic algorithmic test 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 in fine needle aspirates of thyroid nodules is considered **investigational** for all other indications.

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UVEAL MELANOMA

Uveal Melanoma Prognostic Algorithmic Tests

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

   A. The member has primary, localized uveal melanoma.

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

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CUTANEOUS MELANOMA

Cutaneous Melanoma Prognostic Algorithmic Tests

I. Cutaneous melanoma prognostic algorithmic tests with insufficient evidence of clinical validity are considered **investigational** for all indications.

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Cutaneous Melanoma Diagnostic Algorithmic Tests

I. Cutaneous melanoma diagnostic algorithmic tests are considered **medically necessary** when:

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

II. Cutaneous melanoma diagnostic algorithmic tests are considered **investigational** for all other indications, including:

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

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Cutaneous Melanoma Risk Assessment Algorithmic Tests

I. Cutaneous melanoma risk assessment algorithmic tests are considered **medically necessary** when:

   A. The member has a melanocytic neoplasm that shows at least one ABCDE feature (**a**symmetry, **b**order irregularity, **c**olor variegation, **d**iameter greater than 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 are considered **investigational** for all other indications.

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OVARIAN CANCER

Ovarian Cancer Diagnostic Algorithmic Tests

I. Ovarian cancer diagnostic algorithmic tests (i.e., OVA1, Overa, ROMA, and OvaWatch) 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 members for surgery for an adnexal mass

D. Evaluation of members with clinical or radiologic evidence of malignancy

E. Evaluation of members 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.

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Ovarian Cancer Treatment Algorithmic Tests

I. Ovarian cancer treatment algorithmic tests are considered **medically necessary** when:

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

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

II. Ovarian cancer treatment algorithmic tests are considered **investigational** for all other indications.

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GYNECOLOGIC CANCER

Gynecologic Cancer Treatment Algorithmic Tests

I. Gynecologic cancer treatment algorithmic tests in the assessment of gynecological cancers are considered **investigational** for all indications**.**

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LUNG CANCER

Evidence-Based Lung Cancer Risk Assessment Algorithmic Tests

I. Lung cancer risk assessment algorithmic tests with sufficient evidence of clinical validity and utility are considered **medically necessary** when:

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

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

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

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

II. Lung cancer risk assessment algorithmic tests with sufficient evidence of clinical validity and utility are considered **investigational** for all other indications where clinical validity and utility have not been demonstrated.

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Emerging Evidence Lung Cancer Diagnostic Algorithmic Tests

I. Lung cancer diagnostic algorithmic tests with insufficient evidence of clinical validity are considered **investigational** for all indications.

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Evidence-Based Lung Cancer Treatment Algorithmic Tests

I. Lung cancer treatment algorithmic tests with sufficient evidence of clinical validity and utility are considered **medically necessary** when:

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

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

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

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

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

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Emerging Evidence Lung Cancer Treatment Algorithmic Tests

I. Lung cancer treatment algorithmic tests with insufficient evidence of clinical validity are considered **investigational** for all indications**.**

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BLADDER AND URINARY TRACT CANCER

Bladder/Urinary Tract Cancer Diagnostic Algorithmic Tests

I. Bladder/urinary tract cancer diagnostic algorithmic tests are considered **investigational** for all indications.

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Bladder Cancer Treatment and Recurrence Algorithmic Tests

I. The use of bladder cancer treatment and recurrence algorithmic tests is considered **medically necessary** when:

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

B. The results of algorithmic testing will affect management decisions for the member's bladder cancer, **AND**

C. The member 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 is considered **investigational** for all other indications.

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PANCREATIC CANCER

Evidence-Based Pancreatic Cyst Risk Assessment Algorithmic Tests

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

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

   B. Initial testing (e.g., 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 with sufficient evidence of clinical validity and utility are considered **investigational** for all other indications where clinical validity and utility have not been demonstrated.

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Emerging Evidence Pancreatic Cyst Risk Assessment Algorithmic Tests

I. Pancreatic cyst risk assessment algorithmic tests with insufficient evidence of clinical validity are considered **investigational** for all indications.

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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 to evaluate the site of origin of a tumor of unknown primary, or to distinguish a primary from a metastatic tumor is considered **investigational** for all indications.

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ESOPHAGEAL CANCER

Barrett's Esophagus Risk Assessment and Diagnostic Algorithmic Tests

I. Barrett's esophagus risk assessment and diagnostic algorithmic tests are considered **investigational** for all indications.

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PRIOR AUTHORIZATION
Prior authorization is not required. However, services with specific coverage criteria may be reviewed retrospectively to determine if criteria are being met. Retrospective denial may result if criteria are not met.

RATIONALE

Breast Cancer Treatment and Prognostic Algorithmic Tests

National Comprehensive Cancer Network (NCCN)

Oncotype DX for breast cancer is a 21-gene expression assay and is one of many gene expression assays used to aid in determining adjuvant systemic therapy. NCCN guidelines for Breast Cancer (6.2024) recommend the 21-gene expression assay for both prognosis and treatment decisions in patients of either sex (p. BINV-J 1 of 2, BINV-N 1 of 5). Per NCCN, the breast tumor must be either ductal/NST, lobular, mixed, or micropapillary, and it also must be hormone receptor positive (either Estrogen receptor or Progesterone receptor), and HER2 negative (p. BINV-6, BINV-7, BINV-8).

Females (sex assigned at birth) with postmenopausal breast tumors must be considering chemotherapy and have one of the following:

- A tumor that is 0.5 cm or larger (p. BINV-6)
- A tumor that is pN1mi (2 mm or smaller axillary node metastases) (p. BINV-6)
- A tumor that is pN1 (1–3 positive nodes) (p. BINV-6).

Females (sex assigned at birth) with premenopausal breast tumors must be a candidate for chemotherapy and have one of the following:

- A tumor that is 0.5 cm or larger and pN0 (p. BINV-7)
- A tumor that is pN1mi (2 mm or smaller axillary node metastasis) (p. BINV-7)
- A tumor that is pN1 (1-3 positive nodes) (p. BINV-7)

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Breast Cancer Extended Endocrine Therapy Algorithmic Tests

National Comprehensive Cancer Network (NCCN)

The BCI (Breast Cancer Index) is recommended by NCCN Breast Cancer guidelines (6.2024) for both indications of prognosis as well as predicting treatment for extended adjuvant endocrine therapy (p. BINV-N 1 of 5). Appropriate patients for this test include pre and postmenopausal women with HR positive, HER2 negative breast cancer (either ductal/NST, lobular, mixed, or micropapillary) (BINV-6, BINV-7, BINV-8).

Postmenopausal breast tumors must be one of the following:

- 0.5 cm or larger

- pN1mi (2 mm or smaller axillary node metastases)
- pN1 (1–3 positive nodes) (p. BINV-6, BINV-N 1 of 5).

Premenopausal tumors must be one of the following:

- 0.5 cm or larger and pN0 (p. BINV-7)
- pN1mi (2 mm or smaller axillary node metastasis) (BINV-8)
- pN1 (1–3 positive nodes) (BINV-8).

NCCN guidelines also state that there is limited data regarding the use of these tests in males with breast cancer who are being considered for chemotherapy (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. They recommend consideration of the Breast Cancer Index (BCI) test for either node-negative cancer or cancer with 1-3 positive nodes, which has been treated with primary endocrine therapy for 5 years with no evidence of recurrence (Recommendation 1.24., p. 1819).

The guideline cites a lack of sufficient evidence for the BCI test to guide decisions about extended endocrine therapy in individuals with node-positive breast cancer with 4 or more positive nodes following 5 years of endocrine therapy (Recommendation 1.25, p. 1819).

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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 (p. 1821) includes an algorithm that acts as a guide for prognostic test choice in women with early-stage invasive breast cancer. In summary, a female patient must have the following in order to recommend EndoPredict, Prosigna, or MammaPrint testing:

- Postmenopausal **OR** older than age 50 years
- Early-stage invasive breast cancer
- Node negative disease,
- HER2 negative tumor
- ER positive tumor

Of note, per the guide, if the patient has 1 to 3 positive node disease then only MammaPrint or EndoPredict may be ordered. The algorithm also shows that there is "Insufficient evidence to recommend a biomarker for use" in women with 4 or more positive nodes (p. 1821).

National Comprehensive Cancer Network (NCCN)

NCCN Breast Cancer guidelines (6.2024) recommend consideration of other prognostic gene expression assays to help assess risk of recurrence in pre- and postmenopausal patients with either ductal/NST, lobular, mixed, or micropapillary breast cancer that is HR-positive, Her2-negative, pT1-3 and pN0 or pN+. However, these other tests have not been validated to predict response to chemotherapy (p. BINV- 6, BINV-7, BINV-8).

A footnote on page BINV-N 3 of 5 states: "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 there is limited evidence for prediction of chemotherapy benefit (p. BINV-N 3 of 5).

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Gene Expression Profiling Breast Cancer Subtyping Tests

National Comprehensive Cancer Network (NCCN)

NCCN Breast Cancer guidelines (6.2024) 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 professional society guidelines covering this area of testing were identified.

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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 coverage 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."

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Colorectal Cancer Prognostic Algorithmic Tests

National Comprehensive Cancer Network (NCCN)

NCCN guidelines for Colon Cancer (6.2024) does not recommend use of multigene panel assays to assist in making clinical decisions about adjuvant therapy (p. COL-4).

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Prostate Cancer Treatment and Prognostic Algorithmic Tests

National Comprehensive Cancer Network (NCCN)

NCCN guidelines for Prostate Cancer (1.2025) recommends use of advanced risk stratification tools (i.e., gene expression biomarkers, AI digital pathology) for disease management, most commonly for men with localized prostate cancer and life expectancy of 10 yrs or more (p. PROS-4,5,6, PROS-H 1 of 8). The most common reasons to use these tools are for deciding between active surveillance and radical treatment, or use of radiation alone vs radiation with androgen deprivation therapy (short or long term) (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 and there are no current treatment implications based on the results (p. PROS-H 1 of 8 and PROS-H 4, 5,6, of 8). The following tumor-based assays are called out for use: Decipher, Genomic Prostate Score (GPS), ArteraAI Prostate and Prolaris (p. PROS-H 3 of 8).

American Society of Clinical Oncology (ASCO)

ASCO (2020) issued a guideline called "Molecular Biomarkers in Localized Prostate Cancer: ASCO Guideline". The guideline overall states that tissue-based biomarker testing "may improve risk stratification", but results should be interpreted in combination with other routine clinical factors (p. 1474) and in situations where the results are likely to affect medical management (p. 1475).

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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. Specifically, on page PROSD-2, NCCN recommends further evaluation for individuals with PSA "greater than 3 ng/ml and/or a very suspicious DRE". Biomarker testing is mentioned on page PROSD-3 as part of this additional evaluation, and NCCN specifies the following tests as options for risk stratification: Prostate Health Index (PHI), SelectMDx, 4Kscore, ExoDx Prostate Test, MyProstateScore (MPS), and IsoPSA".

On page PROSD-4, NCCN also recommends consideration of biomarker tests to improve specificity when considering a repeat biopsy for biopsy results showing the following: atypia, suspicious for cancer; high-grade prostatic intraepithelial neoplasia (PIN); benign. These tests include those listed above (except for SelectMDX) plus PCA3 and ConfirmMDX.

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Emerging Evidence Prostate Cancer Risk Assessment and Diagnostic Algorithmic Tests

National Comprehensive Cancer Network (NCCN)

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, Stockholm3, OncoAssure Prostate, Tempus p-MSI, or Tempus p-Prostate.

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 professional society guidelines covering this area of testing, as current evidence demonstrates neither benefit nor harm.

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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 (5.2024) 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).

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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).

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Cutaneous Melanoma Prognostic Algorithmic Tests

Society of Surgical Oncology

The Society of Surgical Oncology (SSO), in its 2024 consensus statement, “Assessing the Evidence for and Utility of Gene Expression Profiling of Primary Cutaneous Melanoma”, does not recommend the use of gene expression profiling (GEP) in adults with pT1a-pT4b primary cutaneous melanoma for predicting sentinel lymph node (SLN) status, guiding surveillance or follow-up approaches, or informing the use of adjuvant therapy due to insufficient high-level evidence (p. 2). These conclusions were reached through a rigorous process involving 20 experts, who used the PICOT framework to refine clinical questions and systematically reviewed 50 studies selected from over 130 articles. The recommendations were developed through the Modified Delphi process, achieving consensus with at least 80% agreement among a diverse panel of specialists (p. 4-6).

ECRI Genetic Test Assessment

A 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). The review determined that current research does not provide sufficient evidence to conclude whether DecisionDx-Melanoma allows patients to safely skip sentinel lymph node biopsy (SLNB). Additional longitudinal studies are necessary to assess long-term health outcomes, such as recurrence, in patients who opt out of the biopsy.

Concert Note

Cutaneous melanoma prognostic testing is addressed by the Local Coverage Determination (LCD), MolDX: Melanoma Risk Stratification Molecular Testing - L38016, which provides a path to coverage for the DecisionDx-Melanoma and Merlin test assays. However, these recommendations were established prior to the release of the Society of Surgical Oncology (SSO) guidelines, which

represent the latest expert consensus in the field. Given the rapidly evolving landscape of precision medicine and the methodological rigor applied in developing these guidelines, we place greater weight on the SSO's recommendations as a more current and comprehensive standard for clinical practice.

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Cutaneous Melanoma Diagnostic Algorithmic Tests

National Comprehensive Cancer Network (NCCN)

NCCN guidelines for Cutaneous Melanoma (1.2025) recommends gene expression profiling as an available test for diagnosing indeterminate melanocytic neoplasms by histopathology, along with several other ancillary tests (p. ME-C 1 of 8). NCCN does not recommend incorporation of GEP testing into the initial workup of a stage 0 in situ, T1a, or T1b melanoma (p. ME-2 and ME-2A).

American Academy of Dermatology

The American Academy of Dermatology (Swetter, 2019) published an article titled “Guidelines of care for the management of primary cutaneous melanoma”. The guidelines do not recommend gene expression profiling (GEP) as a routine diagnostic test for individuals with cutaneous melanoma (p. 291).

American Society of Dermatopathology

The American Academy of Dermatopathology (AUC Committee Members, 2022) published clinical scenarios where a 23 gene qRT-PCR test (MyPath Melanoma) was determined by a review of published evidence to be “majority usually appropriate.” The guideline also found that qRT-PCR testing for individuals with confirmed melanoma or nevus and adults with sclerosing (desmoplastic) nevus and desmoplastic melanoma were classified as “rarely inappropriate” (p. 238) clinical scenarios.

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Cutaneous Melanoma Risk Assessment Algorithmic Tests

National Comprehensive Cancer Network (NCCN)

NCCN Guidelines for Cutaneous Melanoma (3.2024) recommends consideration of “prediagnostic 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 states that skin biopsy should be the initial step in establishing a diagnosis of cutaneous melanoma. The article mentions consideration of newer noninvasive techniques, including gene expression analysis (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), this test is used to determine whether a biopsy should be performed. The LCD lists characteristics for the skin lesion that are appropriate for testing, which includes having at least 1 ABCDE criteria.

The LCD also states that "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."

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Ovarian Cancer Diagnostic Algorithmic Tests

National Comprehensive Cancer Network (NCCN)

NCCN guidelines for Ovarian Cancer including Fallopian Tube Cancer, and Primary Peritoneal Cancer (3.2024) recognize several biomarker tests and algorithms using multiple biomarker test results that have been proposed for preoperatively distinguishing benign from malignant tumors in patients who have an undiagnosed adnexal/pelvic mass (p. MS-7).

In the NCCN Panel discussion section regarding Biomarker Tests, there is a comment stating "the NCCN panel does not recommend the use of these biomarker tests for determining the status of an undiagnosed adnexal/pelvic mass" (p. MS-10, 11). The discussion section includes OVA1 and ROMA as test examples.

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Ovarian Cancer Treatment Algorithmic Tests

National Comprehensive Cancer Network (NCCN)

The NCCN guidelines for Ovarian Cancer including Fallopian Tube Cancer, and Primary Peritoneal Cancer (3.2024) recommend "genetic risk evaluation, and germline and somatic testing if not previously done, for patients with ovarian, fallopian tube, or primary peritoneal cancer. Testing should include *BRCA1/2* status, which will aid in treatment decision-making (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 a recommendation for PARPi maintenance therapy (niraparib) for "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" (p. 3879).

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Gynecologic Cancer Treatment Algorithmic Tests

National Comprehensive Cancer Network (NCCN)

NCCN guidelines for Ovarian Cancer including 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 similar treatment options being considered. However, there is insufficient evidence to recommend these tests at this time (p. OV-C, 1 of 12).

NCCN guidelines for Cervical Cancer (1.2025) do not mention chemosensitivity or chemoresistance assays as part of clinical care.

NCCN guidelines for Uterine Neoplasms (1.2025) do not mention chemosensitivity or chemoresistance assays as part of clinical care.

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Evidence-Based Lung Cancer Risk Assessment Algorithmic Tests

Centers for Medicare and Medicaid Services

The CMS local coverage determination (LCD) entitled BDX-XL2 (L37031) includes the following coverage criteria for the NodifyXL2 test for the management of a lung nodule:

- Nodule must be between 8 and 30mm in diameter
- Patients must be 40 years or older
- Patients must have a pre-test cancer risk (as assessed by the Mayo Clinic Model for Solitary Pulmonary Nodules) of 50% or less.

“The intended use of the test is to assist physicians in the management of lung nodules by identifying those lung nodules with a high probability of being benign. These lung nodules would then be candidates for non-invasive computed tomography (CT) surveillance instead of invasive procedures.”

Pritchett, et al

A 2023 study titled: “Assessing a biomarker's ability to reduce invasive procedures in patients with benign lung nodules: Results from the ORACLE study” aimed to assess the clinical impact of proteomic integrated classifier (IC) tests (specifically, NodifyXL2), following confirmation of clinical validity (PANOPTIC trial) in 2018. The study included a matched cohort and ultimately found that “[p]atients with a benign nodule in the IC group underwent fewer invasive procedures (n = 8, 5%) compared to patients in the untested control group (n = 30, 19%), yielding…[a] relative reduction of 74%” (p. 6).

Kheir, et al

A 2023 retrospective study titled: “Impact of an integrated classifier using biomarkers, clinical and imaging factors on clinical decisions making for lung nodules” compared individuals with lung nodules who were evaluated with the integrated classifier (IC) test (NodifyXL2) versus individuals receiving standard of care. The findings showed that invasive procedures were decreased by

57.5% in individuals with indeterminate lung nodules “without missing a malignant diagnosis at 1-year follow-up)”, when compared to the control arm (p. 3563).

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Emerging Evidence Lung Cancer Diagnostic Algorithmic Tests

Concert Evidence Review for Coverage Determination (Published 1/1/2025)

At the present time, lung cancer diagnostic algorithmic tests, specifically Nodify CDT, Percepta Lung Cancer Diagnostics, REVEAL Lung Nodule Characterization, and CyPathLung, have **INSUFFICIENT EVIDENCE** in peer-reviewed publications to effectively result in improved health outcomes compared to the current standard of care. The current literature does not demonstrate strong evidence for clinical validity due to a lack of robust evidence that these tests accurately help to classify malignancy risk for an individual’s lung nodule and that results are used to determine if biopsy is performed.

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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 coverage 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”.

From the Billing and Coding article, DetermaRx (PLA code 0288U) is listed as a covered test.

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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.

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Bladder/Urinary Tract Cancer Diagnostic Algorithmic Tests

National Comprehensive Cancer Network (NCCN)

There is insufficient evidence to support the use of this test. No recommendations for or against this testing within the NCCN Bladder Cancer guidelines (6.2024) were identified.

The American Urological Association (AUA) / American Society of Clinical Oncology (ASCO) / Society of Urologic Oncology (SUO)

The updated AUA/SCO/SUO guideline highlights several key areas for which further evidence is needed. Included in this section is a statement regarding the need to identify and validate both prognostic and predictive markers to improve clinical outcomes, including therapeutic decision-making.

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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. 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
3. The test successfully completes a Molecular Diagnostic Services Program (MolDX®) technical assessment that ensures the test is reasonable and necessary as described above.
4. 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.
5. The genomic content interrogated by the test must be relevant to the therapy under consideration.”

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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 coverage 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.”

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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.

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Cancer of Unknown Primary Gene Expression Profiling Tests

National Comprehensive Cancer Network (NCCN)

NCCN guidelines for Occult Primary (Cancer of Unknown Primary) (2.2025) state that testing 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-5).

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Barrett’s Esophagus Risk Assessment and Diagnostic Algorithmic Tests

Centers for Medicare and Medicaid Services

The CMS local coverage determination (LCD) entitled “MolDX: Molecular Testing for Detection of Upper Gastrointestinal Metaplasia, Dysplasia, and Neoplasia” states that molecular diagnostic tests that identify individuals with upper gastrointestinal metaplasia, dysplasia, and neoplasia are not covered.

American College of Gastroenterology

In their 2022 guidelines for diagnosis and management of Barrett’s esophagus, the ACG suggests that a swallowable, nonendoscopic capsule sponge device combined with biomarker testing is an acceptable alternative to endoscopy for screening for BE in those with risk factors, including chronic reflux. However, the strength of the recommendation is categorized as “conditional,” and the quality of evidence is categorized as “very low” (p. 10).

The ACG also states they are unable to make a recommendation about the TissueCypher and WATS-3D tests based on either current evidence showing low sensitivity and specificity, or lack of data, respectively (p. 18-21).

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DEFINITIONS

1. **ABCDE feature** is an acronym for examining patients with a lesion that is suspicious for melanoma: **a**symmetry, **b**order irregularity, **c**olor variegation, **d**iameter greater than 6 mm, and **e**volution.
2. **Adjuvant** therapy is a medication (such as chemotherapy or endocrine therapy) given after the surgical removal of a cancerous tumor.
3. **Ductal/NST** is a ductal breast cancer of no special type (NST), meaning the cancer cells have no features that classify them as a specific type of breast cancer when examined by microscope.
4. **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)

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Note: The Health Plan uses the genetic testing clinical criteria developed by Concert Genetics, an industry-leader in genetic testing technology assessment and policy development.

	Committee/Source	Date(s)
Document Created:	Medical Policy Committee/Health Services Division	December 21, 2022
Revised:	Medical Policy Committee/Health Services Division	February 15, 2023
	Medical Policy Committee/Health Services Division	March 15, 2023
	Medical Policy Committee/Health Services Division	September 20, 2023
	Medical Policy Committee/Health Services Division	March 20, 2024
Reviewed:	Medical Policy Committee/Health Services Division	February 15, 2023
	Medical Policy Committee/Health Services Division	March 15, 2023
	Medical Policy Committee/Health Services Division	September 20, 2023
	Medical Policy Committee/Health Services Division	March 20, 2024

Original Effective Date:	01/01/2023
Re-Review Date(s):	12/19/2024- Concert Genetics Effective Date: January 01, 2025 (V.1.2025)
	06/18/2025 - Concert Genetics Effective Date: July 01, 2025 (V.2.2025)
Administrative Update:	