CONCERT GENETICS ONCOLOGY: ALGORITHMIC TESTING

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Coding implications
Revision Log

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

OVERVIEW

Oncology 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 prognostic and 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 prognostic and algorithmic tests may be useful to assist in surgical and management decision-making and to identify individuals who may benefit from adjuvant therapy.

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 and may not support medical necessity. 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.

NOTE: Coverage is subject to each requested code's inclusion on the corresponding LDH fee schedule. Non-covered codes are denoted (*) and are reviewed for Medical Necessity for members under 21 years of age on a per case basis. The non-covered codes will only be denoted in the table below and not throughout the policy. Please only reference the policy reference table for covered and non-covered codes.

The tests and associated laboratories and CPT 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 Genetics 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, 27
Breast Cancer Prognostic Algorithmic Tests	EndoPredict (Myriad)	81522*, S3854*	C50, Z17.0, Z17.1	1, 27
	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, 27
	Insight TNBCtype (Insight Molecular Labs)	0153U*		
Breast DCIS Prognostic Algorithmic Tests	Oncotype DX Breast DCIS Score (Exact Sciences)	0045U*	D05.1	1, 28
	DCISion RT (PreludeDx)	0295U*		
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 (HalioDx)	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*		
Evidence Based Prostate Cancer Risk Assessment and Diagnostic Algorithmic Tests	4K Prostate Score (Serum) (BioReference Laboratories)	81539*	C61, Z12.5	4, 25, 26
	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	Apifiny (Armune Bioscience)	0021U*	C61, Z12.5	26
	PanGIA Prostate (Genetics Institute of America)	0228U*		
	MyProstateScore 2.0 (Lynx Dx)	0403U*		
	miR Sentinel Prostate Cancer Test (miR Scientific)	0343U*, 0424U*		
	EpiSwitch Prostate Screening Test (PSE) (Oxford BioDynamics)	0433U*		

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	29, 30
	Merlin Melanoma	81479		
Emerging Evidence Cutaneous Melanoma Prognostic Algorithmic Tests	AMBLor (AMLo Biosciences)	0387U*	C43, D03.0-D03.9, Z12.83	30
Cutaneous Melanoma Diagnostic Algorithmic Tests	myPath Melanoma (Castle Biosciences, Inc.)	0090U*	D22.0-D22.9, D48.5, D49.2, Z12.83	9, 10, 24
	DecisionDx-DiffDx-Melanoma (Castle Biosciences, Inc.)	0314U*		
Cutaneous Melanoma Risk Assessment Algorithmic Tests	Pigmented Lesion Assay (DermTech)	0089U*	D22-D23, Z12.83	9, 10, 31, 32, 33
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*		
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	23
Emerging Evidence Lung Cancer Diagnostic Algorithmic Tests	REVEAL Lung Nodule Characterization (MagArray)	0092U*	R91.1	23
	Percepta Bronchial Genomic Classifier (Veracyte)	81479		
	LungLB (LungLife AI)	0317U*		
	Nodify CDT (Biodesix)	0360U*		
	OncobiotaLUNG (Micronoma)	0395U*		
	CyPath Lung (bioAffinity Technologies)	0406U		
Lung Cancer Treatment Algorithmic Tests	VeriStrat (Biodesix)	81538*	C34, D38.1, D38.6	22
	DetermaRx (Oncocyte)	0288U*		
	LungOI (Imagene)	0414U*		
	PROphet NSCLC Test	0436U*		
Bladder and Urinary Tract Cancer				
Bladder/Urinary TractCancer Diagnostic, Treatment and Recurrence Algorithmic Tests	Cxbladder Triage (Pacific Edge)	0363U*	C67, D09.0, D49.4, R31.9, Z85.51	12, 13
	Cxbladder Detect (Pacific Edge)	0012M*		
	Cxbladder Monitor (Pacific Edge)	0013M*		
	CxBladder Detect+ (Pacific Edge)	0420U		
	Oncuria Detect (DiaCarta Clinical Lab)	0365U*		

	Oncuria Monitor (DiaCarta Clinical Lab)	0366U*		
	Oncuria Predict (DiaCarta Clinical Lab)	0367U*		
	Decipher Bladder (Veracyte)	0016M*		
Pancreatic Cancer				
Pancreatic Cyst Risk Assessment Algorithmic Tests	PancraGEN (Interpace Diagnostics)	81479	D49, K86.2	20, 21
	Pancreatic Cyst Fluid NGS Analysis-PancreaSeq (Univ of Pittsburgh Medical Center)	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.

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CRITERIA

It is the policy of Louisiana Healthcare Connections that the specific genetic testing noted below is **medically necessary** when meeting the related 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 (81519, S3854) is considered **medically necessary** in all patients, regardless of gender, when:

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

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

   E. 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 pN1mi (2mm or smaller axillary node metastases), **OR**
      3. Lymph nodes are pN1 (1-3 positive nodes).

II. The use of a breast cancer treatment and prognostic algorithmic test (i.e., Oncotype DX Breast Recurrence Score (81519, S3854) 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) (S3854, 81518) is considered **medically necessary** when:

   A. The member/enrollee is an individual with a female reproductive system, **AND**

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

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

   D. The member/enrollee's tumor is HER2-negative, **AND**

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

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

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

   H. 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 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) (81518, S3854) in men with breast cancer is considered **investigational**.

III. The use of a breast cancer extended endocrine therapy test Breast Cancer Index) (81518, S3854) 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) (S3854, 81520, 81521, 81522, 81523) is considered **medically necessary** when:

A. The member/enrollee is an individual with a female reproductive system, **AND**

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

1. Postmenopausal status, **OR**

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

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

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

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

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

G. The member/enrollee has the following node status:

1. Node negative, **OR**

2. 1-3 positive nodes*.

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

V. The use of a breast cancer prognostic algorithmic test (i.e., EndoPredict, Prosigna, MammaPrint) (S3854, 81520, 81521, 81522, 81523) 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.

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Gene Expression Profiling Breast Cancer Subtyping Tests

I. Gene expression profiling breast cancer subtyping tests (e.g., BluePrint) (81599, S3854, 0153U) are considered **investigational**.

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Breast DCIS Prognostic Algorithmic Tests

I. Breast DCIS prognostic algorithmic tests (0045U, 0295U) are considered **investigational**.

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COLORECTAL CANCER

Colorectal Cancer Prognostic Algorithmic Tests

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

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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., Oncotype DX Prostate (0047U), Prolaris (81541)) is considered **medically necessary** when:

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

   B. The member/enrollee has any of the following:

      1. Low-risk prostate cancer, **OR**
      2. Favorable intermediate prostate cancer, **OR**
      3. Unfavorable intermediate prostate cancer, **OR**
      4. High-risk prostate cancer.

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

   A. The member/enrollee meets the following:

      1. The member/enrollee has a life expectancy of 10 years or more, **AND**
      2. The member/enrollee has any of the following:

a) Low-risk prostate cancer, **OR**

b) Favorable intermediate prostate cancer, **OR**

c) Unfavorable intermediate prostate cancer, **OR**

d) High-risk prostate cancer, **AND**

3. The member/enrollee has not yet had treatment**, OR**

B. The member/enrollee meets the following:

1. The member/enrollee has a life expectancy of more than 5 years, **AND**
2. The patient has had radical prostatectomy, **AND**

a) There are no lymph node metastases, **AND**

b) There is PSA persistence/recurrence, **OR**

c) Other adverse pathologic features were found.

III. The use of a prostate cancer treatment and prognostic algorithmic test (0047U, 81541, 81542) 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 (81539, 84153, 84154, 86316, 81479, 81551, 0113U, 0339U, 0005U, 0359U) with sufficient evidence of clinical validity and utility are considered **medically necessary** when:

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

B. The member/enrollee has at least one of the following:

1. Prostate specific antigen (PSA) of >3 ng/ml, **OR**
2. A digital rectal exam (DRE) that is very suspicious for cancer, **AND**

C. The test is one of the following:

1. Prostate Health Index (PHI), **OR**
2. SelectMDx, **OR**
3. 4Kscore, **OR**

4. ExoDx Prostate Test, **OR**
5. MyProstateScore (MPS), **OR**
6. IsoPSA, **OR**

D. The member/enrollee has had a prostate biopsy, **AND**

E. The result is one of the following:

1. Atypia, suspicious for cancer, **OR**
2. High-grade prostatic intraepithelial neoplasia (PIN)**, OR**
3. Benign, **AND**

F. The test is one of the following:

1. Prostate Health Index (PHI), **OR**
2. 4Kscore, **OR**
3. ExoDx Prostate Test, **OR**
4. MyProstateScore (MPS), **OR**
5. IsoPSA, **OR**
6. ConfirmMDx, **OR**
7. PCA3.

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

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Emerging Evidence Prostate Cancer Risk Assessment and Diagnostic Algorithmic Tests

I. Prostate cancer risk assessment and diagnostic algorithmic tests (0021U, 0228U, 0403U, 0343U, 0424U, 0433U) with insufficient guidance for use are considered **investigational**.

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THYROID CANCER

Thyroid Cancer Diagnostic Algorithmic Tests

I. The use of a thyroid cancer diagnostic algorithmic test (0026U, 0018U, 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, **AND**

   B. Clinical and/or radiologic findings of the thyroid nodules are indeterminate of malignancy, **AND**

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

II. The use of a thyroid cancer diagnostic algorithmic test (0026U, 0018U, 0204U, 0245U, 0287U, 81546) 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 (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.

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CUTANEOUS MELANOMA

Evidence Based Cutaneous Melanoma Prognostic Algorithmic Tests

I. Cutaneous melanoma prognostic algorithmic tests (81479, 81529) 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) with sufficient evidence of clinical validity and utility are considered **investigational** for all other indications.

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Emerging Evidence Cutaneous Melanoma Prognostic Algorithmic Tests

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

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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.

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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, **AND**

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

   C. The test can only be used a maximum of 2 times per visit.

II. Cutaneous melanoma risk assessment algorithmic tests (0089U) 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) (0003U, 81500, 81503, 0375U) 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.

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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.

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GYNECOLOGIC CANCER

Gynecologic Cancer Treatment Algorithmic Tests

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

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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 **medical 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.

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Emerging Evidence Lung Cancer Diagnostic Algorithmic Tests

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

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Lung Cancer Treatment Algorithmic Tests

I. Lung cancer treatment algorithmic tests (81538, 0288U, 0414U) are considered **investigational**.

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BLADDER AND URINARY TRACT CANCER

Bladder/Urinary Tract Cancer Diagnostic, Treatment and Recurrence Algorithmic Tests

I. Bladder/urinary tract cancer diagnostic, treatment, and recurrence algorithmic tests (0012M, 0013M, 0016M, 0363U, 0365U, 0366U, 0367U, 0420U), which are performed on urine, are considered **investigational**.

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PANCREATIC CANCER

Pancreatic Cyst Risk Assessment Algorithmic Tests

I. Pancreatic cyst risk assessment algorithmic tests (0313U, 81479) are considered **investigational**.

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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 (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**.

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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**.

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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 (4.2023) as failure of PSA to fall to undetectable levels (PSA persistence) or undetectable PSA after RP 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. **Adverse pathologic features:** Discussed in the NCCN Prostate Cancer guidelines (4.2023), and examples of this included positive margins, seminal vesicle invasion, and extracapsular extension. (p. MS-38)
6. **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.

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CLINICAL CONSIDERATIONS

The Oncotype DX, EndoPredict, Breast Cancer Index, MammaPrint, and Prosigna assays should only be ordered on a tissue specimen obtained during surgical removal of the tumor and after subsequent pathology examination of the tumor has been completed and determined to meet the above criteria (i.e., the test should not be ordered on a preliminary core biopsy). The test should

be ordered in the context of a physician-patient discussion regarding risk preferences when the test result will aid in making decisions regarding chemotherapy.

For patients who otherwise meet the criteria for gene expression profiling for breast cancer but who have multiple ipsilateral primary tumors, a specimen from the tumor with the most aggressive histologic characteristics should be submitted for testing. It is not necessary to test each tumor; treatment is based on the most aggressive lesion.

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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 (1.2024) strongly recommends consideration of 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 is recommended by NCCN Breast Cancer criteria (1.2024) 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 those with a male reproductive system with breast cancer. Available data suggest the 21-gene assay recurrence score provides prognostic information in those with a male reproductive system 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 patient with a female reproductive system 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)

Per the NCCN Breast Cancer guidelines (1.2024), clinicians should strongly consider performing a 21-gene RT-PCR assay if the patient is a candidate for chemotherapy (category 1) o for prognostic gene expression assays in patients with ductal/NST, lobular, mixed, or micropapillary breast cancer who are postmenopausal and have hormone-receptor positive/HER2 negative disease. Other prognostic gene expression assays may be considered to help assess risk of recurrence but have not been validated to predict response to chemotherapy. (p. BINV- 6) Gene expression assays provide prognostic and therapy-predictive information that complements T,N,M and biomarker information. The 21-gene assay (Oncotype Dx) is preferred by the NCCN Breast Cancer Panel for prognosis and prediction of chemotherapy benefit. Other prognostic gene expression assays can provide prognostic information but the ability to predict chemotherapy benefit is unknown. (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 (1.2024) 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.

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

National Comprehensive Cancer Network (NCCN)

NCCN Breast Cancer guidelines (1.2024) do not reference DCIS prognostic algorithmic tests as part of the clinical work-up for DCIS.

Collins et al, Up To Date, 2023

"Gene expression analysis such as the Oncotype DX DCIS recurrence score and DCISionRT have been studied as a tool for identification of patients for whom post-lumpectomy RT may reasonably be omitted, but data regarding its utility are still limited. Further validation of these results is required before the multigene assay can become a standard part of clinical practice".

COLORECTAL CANCER

Colorectal Cancer Prognostic Algorithmic Tests

National Comprehensive Cancer Network (NCCN)

NCCN guidelines for Colon Cancer (1.2024) state that there is currently insufficient data to recommend routine use of circulating tumor DNA (ctDNA) 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 (4.2023) recommend advanced risk stratification tools (i.e., gene expression biomarkers, AI digital pathology) in men with low, favorable intermediate, unfavorable intermediate, or high-risk disease, and if the patient is expected to live 10 years or longer. These tools are recommended to be used when they will have the potential ability to independently improve risk and change management. The following tumor-based assays are called out for use: Decipher, Oncotype DX Prostate, and Prolaris. (p. PROS-D 2 of 4)

These guidelines for Prostate Cancer (4.2023) also recommend that, in individuals who have PSA recurrence/persistence after radical prostatectomy (RP) and are expected to live more than 5 years, molecular assay such as Decipher can be considered as an alternative to PSADT (PSA doubling time) to inform counseling. (p. PROS-10) Additionally, individuals with adverse feature(s) found post-RP and no lymph node metastases could consider Decipher molecular assay if not previously performed to inform adjuvant treatment. (p. PROS 8 and PROS 8A)

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.

American Urological Association and Society of Abdominal Radiology

The American Urological Association and the Society of Abdominal Radiology (Rosenkrantz et al, 2016) published joint guidelines on prostate magnetic resonance imaging and magnetic resonance imaging-targeted biopsy. The associations commented that there may be value in using genetic and protein biomarkers for prostate cancer risk in patients warranting repeat biopsy; however, further research is needed to fully assess the utility. (p. 2)

National Comprehensive Cancer Network (NCCN)

NCCN Prostate Cancer Early Detection guidelines (1.2024) indicate that biomarkers that improve the specificity of screening can be considered in patients considering biopsy. Although biomarkers that improve the specificity of detection are not, as yet, mandated as first-line screening tests in conjunction with serum PSA, there may be some patients who meet PSA standards for consideration of prostate biopsy, but for whom the patient and/or the physician wish to further define risk. 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 in patients felt to be at higher risk even with negative biopsy (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 (1.2024) 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.

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.

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 (4.2023) state that clinicians can consider 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 (1.2023) state that biopsy of the primary tumor should be considered for prognostic analysis and that molecular testing for prognostication is preferred over cytology alone. (p. UM-2A) Gene expression profiling class had a stronger independent association 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 Genetics Evidence Review for Coverage Determination

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).

Following on a systematic review of available peer-reviewed evidence, cutaneous melanoma prognostic algorithmic tests such as DecisionDx-Melanoma and Merlin, 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 Genetics Evidence Review for Coverage Determination

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 (3.2023) indicate that gene expression profiling is an acceptable 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 guide therapy in cases that are diagnostically uncertain or controversial by histopathology. (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 (3.2023) state that pre-diagnostic noninvasive patch testing may be useful to help guide decisions regarding biopsy for patients with melanocytic neoplasms that are clinically/dermoscopically suspicious for melanoma. (p. ME-11)

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 utility and clinical validity to improve patient outcomes when added to standard of care. (p. 1)

American Academy of Dermatology (2018)

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

It is generally accepted that 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 or features of the revised seven-point checklist should be strongly considered for referral to an expert in skin cancer.

MolDX: Pigmented Lesion Assay LCD

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 (1.2024) 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. Although the American Congress of Obstetricians and Gynecologists (ACOG) has suggested that ROMA and OVA1 may be useful for deciding which patients to refer to a gynecologic oncologist, other professional organizations have been non-committal. Currently, the NCCN Panel does not recommend the use of these biomarker tests for determining the status of an undiagnosed adnexal/pelvic mass (p. MS10-MS11).

Ovarian Cancer Treatment Algorithmic Tests

National Comprehensive Cancer Network (NCCN)

NCCN guidelines for Ovarian Cancer, Fallopian Tube Cancer, and Primary Peritoneal Cancer (1.2024) recommend genetic risk evaluation, and germline and somatic testing if not previously done, including *BRCA1/2* to inform 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 inform on 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 (2.2024) state that chemosensitivity/resistance and/or other biomarker assays have been proposed for informing decisions related to future chemotherapy in situations where there are multiple equivalent chemotherapy options available, but the current level of evidence is not sufficient to supplant standard-of-care chemotherapy (category 3). (p. MS-26)

NCCN guidelines for Cervical Cancer (1.2024) do not mention chemosensitivity or chemoresistance assays as part of clinical care.

NCCN guidelines for Uterine Neoplasms (1.2024) do not mention chemosensitivity or chemoresistance assays as part of clinical care.

LUNG CANCER

Evidence Based Lung Cancer Diagnostic Algorithmic Tests

Concert Genetics Evidence Review for Coverage Determination

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 Genetics Evidence Review for Coverage Determination

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.

Lung Cancer Treatment Algorithmic Tests

Concert Genetics Evidence Review for Coverage Determination

This review focused on peer-reviewed, published evidence of the clinical utility of VeriStrat through June 2023. A PubMed search was performed. Search terms included VeriStrat, proteomic non-small cell lung cancer, prognosis, and survival. References were also identified from the performing laboratory's website. At the present time, the VeriStrat test has not been adequately shown in peer-reviewed publications to effectively result in improved health outcomes compared to the current standard of care.

BLADDER AND URINARY TRACT CANCER

Bladder/Urinary Tract Cancer Diagnostic, Treatment and Recurrence Algorithmic Tests

National Comprehensive Cancer Network (NCCN)

NCCN guidelines for Bladder Cancer (1.2024) support consideration for urinary urothelial tumor markers for high-risk patients with non-muscle-invasive bladder cancer (category 2B recommendation, which is based on lower-level evidence with NCCN consensus that the intervention is appropriate). (p. BL-E 2 of 6) Further discussion in these guidelines acknowledge that it is unclear if this type of testing offers information that is clinically useful for detecting or managing these tumors, hence the weaker recommendation of 2B by the panel. (p. MS-13)

American Urological Association and Society of Urologic Oncology

The American Urological Association and Society of Urologic Oncology (Chang et al, 2016; amended 2020) addressed the diagnosis and treatment of non-muscle-invasive bladder cancer, based on a systematic review and includes the following statements on the use of urine markers after the diagnosis of bladder cancer:

- In surveillance of NMIBC, a clinician should ***not*** use urinary biomarkers in place of cystoscopic evaluation. (Strong Recommendation; Evidence Strength: Grade B)
- In a patient with a history of low-risk cancer and a normal cystoscopy, a clinician should ***not*** routinely use a urinary biomarker or cytology during surveillance. (Expert Opinion)
- In a patient with NMIBC, a clinician ***may*** use biomarkers to assess response to intravesical BCG (UroVysion® FISH) and adjudicate equivocal cytology (UroVysion® FISH and ImmunoCyt™). (Expert Opinion)

Note: "Evidence Strength B" describes a recommendation of moderate certainty. "Expert Opinion" is defined in this guideline as "A statement, achieved by consensus of the Panel, that is based on members' clinical training, experience, knowledge, and judgment for which there is no evidence." (p.1022)

PANCREATIC CANCER

Pancreatic Cyst Risk Assessment Algorithmic Tests

National Comprehensive Cancer Network (NCCN)

NCCN guidelines for Pancreatic Adenocarcinoma (1.2024) discuss the use of endoscopic ultrasound to follow patients with pancreatic cysts and after the removal, citing that the risk of malignancy in mucinous cystic neoplasms is less than 15%. (p. MS-6, MS-10) The guidelines do not include recommendation or discussion for the use of molecular analysis of pancreatic cysts to stratify risk of cancer.

American College of Gastroenterology

The American College of Gastroenterology (2018) published guidelines for the diagnosis and management of pancreatic cysts, which included the following:

“A number of DNA, RNA, protein, and metabolomic markers have been evaluated in cyst fluid. The majority of these are still early in development and not yet ready for translation into clinical practice. However, analysis of DNA mutations in cyst fluid has shown promise in identifying IPMNs [intraductal papillary mucinous neoplasms] and MCNs [mucinous cystic neoplasms].” (p. 471)

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) (1.2024) state that gene sequencing to predict tissue of origin is not recommended (p. OCC-1).

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 (2.2024) speak broadly about the use of polygenic risk scores, stating that there are currently significant limitations to this type of testing, and it should not be used for clinical management at this time outside of the context of a clinical trial (p. EVAL-A).

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Reviews, Revisions, and Approvals	Revision Date	Approval Date	Effective Date
Converted Corporate to local policy	12/23	2/27/24	
Semi-annual review. In Evidence Based Cutaneous Melanoma Prognostic Algorithmic Tests, now COVERED for specific cutaneous melanoma prognostic algorithmic tests, based on Concert Evidence Review demonstrating clinical validity and utility. In Evidence Based Lung Cancer Diagnostic Algorithmic Tests, now COVERED for specific lung cancer diagnostic algorithmic tests, based on Concert Evidence Review demonstrating clinical validity and utility. In Cutaneous Melanoma Risk Assessment Algorithmic Tests, now COVERED for specific cutaneous melanoma risk assessment algorithmic tests, based on review of guidelines and current literature, which demonstrated clinical validity and utility. In Evidence Based Prostate Cancer Risk Assessment and Diagnostic Algorithmic Tests, now COVERED for specific prostate cancer risk assessment and diagnostic algorithmic tests based on guidelines. In Prostate Cancer Diagnostic Algorithmic Tests, consolidated criteria into the Evidence Based Prostate Cancer Risk Assessment and Diagnostics Algorithmic Tests coverage criteria. In Emerging Evidence Prostate Cancer Diagnostic and Algorithmic Tests, NEW - Created separate criteria to distinguish between tests with varying levels of evidence for validity and guideline support. In Emerging Evidence Cutaneous Melanoma Prognostic Algorithmic Tests, NEW - Created separate criteria sets to distinguish between tests with varying levels of evidence for validity and guideline support. In Emerging Evidence Lung Cancer Diagnostic Algorithmic Tests, NEW - Created separate criteria sets to distinguish between tests with varying levels of evidence for validity and guideline support. In Oncology Test Specific Not Covered Algorithmic Tests, moved criteria to policy “Genetic Testing: General Approach to Genetic and Molecular Testing” to consolidate general coverage criteria for new algorithmic tests. Minor rewording for clarity throughout. Coding, reference-table, background and references updated.	06/24	9/4/24	10/4/24

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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. LHCC 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.

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