BSC_CON_2.05	Oncology: Algorithmic Testing		
Original Policy Date:	August 1, 2023	**Effective Date:**	November 1, 2024
Section:	2.0 Medicine	**Page:**	Page 1 of 44

Example Test Table

The tests and associated laboratories and CPT codes contained within this document serve only as examples to help users navigate claims and corresponding coverage 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.

Policy Statement Locations	Example Tests, Labs	Common CPT Codes
Breast Cancer		
Breast Cancer Treatment and Prognostic Algorithmic Tests	Oncotype Dx Breast Recurrence Score (Exact Sciences)	81519, S3854
Breast Cancer Extended Endocrine Therapy Algorithmic Tests	Breast Cancer Index (bioTheranostics)	81518, S3854
Breast Cancer Prognostic Algorithmic Tests	EndoPredict (Myriad)	81522, S3854
	MammaPrint (Agendia, Inc.)	81521, 81523 S3854
	Prosigna Assay (NeoGenomics)	81520
Gene Expression Profiling Breast Cancer Subtyping Tests	BluePrint (Agendia, Inc.)	81599, S3854
	Insight TNBCtype (Insight Molecular Labs)	0153U
Breast DCIS Prognostic Algorithmic Tests	Oncotype DX Breast DCIS Score (Exact Sciences)	0045U
	DCISion RT (PreludeDx)	0295U
Colorectal Cancer		
Colorectal Cancer Prognostic Algorithmic Tests	Oncotype DX Colon Recurrence Score (Exact Sciences)	81525
	miR-31now (GoPath Laboratories)	0069U
	Immunoscore (HalioDx)	0261U
Prostate Cancer		
Prostate Cancer Treatment and Prognostic Algorithmic Tests	Oncotype DX Genomic Prostate Score (MDxHealth)	0047U
	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
	Prostate Health Index (ARUP Laboratories)	84153, 84154, 86316
	SelectMDx for Prostate Cancer (MDxHealth)	0339U

Policy Statement Locations	Example Tests, Labs	Common CPT Codes
	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
	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
	Tempus p-MSI (Tempus AI, Inc)	0512U
	Tempus p-Prostate (Tempus AI, Inc)	0513U
Thyroid Cancer		
Thyroid Cancer Diagnostic Algorithmic Tests	ThyroSeq Genomic Classifier (CBLPath)	0026U
	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
Cutaneous Melanoma		
Evidence Based Cutaneous Melanoma Prognostic Algorithmic Tests	DecisionDx-Melanoma (Castle Biosciences, Inc.)	81529
	Merlin Melanoma	81479
Emerging Evidence Cutaneous Melanoma Prognostic Algorithmic Tests	AMBLor (AMLo Biosciences)	0387U

Policy Statement Locations	Example Tests, Labs	Common CPT Codes
Cutaneous Melanoma Diagnostic Algorithmic Tests	myPath Melanoma (Castle Biosciences, Inc.)	0090U
	DecisionDx-DiffDx-Melanoma (Castle Biosciences, Inc.)	0090U
		0314U
Cutaneous Melanoma Risk Assessment Algorithmic Tests	Pigmented Lesion Assay (DermTech)	0089U
Ovarian Cancer		
Ovarian Cancer Diagnostic Algorithmic Tests	OVA1 (Aspira Women's Health)	81503
	Overa (Aspira Women's Health)	0003U
	Risk of Ovarian Malignancy (ROMA) (Labcorp)	81500
	OvaWatch (Aspira Women's Health)	0375U
	Avantect Ovarian Cancer Test (ClearNote Health)	0507U
Ovarian Cancer Treatment Algorithmic Tests	myChoice CDx (Myriad Genetics)	0172U
Gynecologic Cancer		
Gynecologic Cancer Treatment Algorithmic Tests	ChemoFx (Helomics Corporation)	81535
	ChemoFx - Additional Drug (Helomics Corporation)	81536
Lung Cancer		
Evidence Based Lung Cancer Diagnostic Algorithmic Tests	Nodify XL2 (Biodesix)	0080U
Emerging Evidence Lung Cancer Diagnostic Algorithmic Tests	REVEAL Lung Nodule Characterization (MagArray)	0092U
	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
	DetermaRx (Oncocyte)	0288U
	LungOI (Imagene)	0414U
	PROphet NSCLC Test	0436U
Bladder and Urinary Tract Cancer		
	Cxbladder Triage (Pacific Edge)	0363U

Policy Statement Locations	Example Tests, Labs	Common CPT Codes
Bladder/Urinary TractCancer Diagnostic, Treatment and Recurrence Algorithmic Tests	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
	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
Polygenic Risk Score Tests		
Breast Cancer Polygenic Risk Score Tests	geneType for Breast Cancer (Genetic Technologies)	81599

Policy Statement

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) may be considered **medically necessary** in **all** patients, regardless of gender, when **all** of the following criteria are met:
   A. The member has primary breast cancer that is ductal/NST, lobular, mixed or micropapillary
   B. The member's tumor is hormone receptor-positive (estrogen receptor-positive or progesterone receptor-positive)
   C. The member's tumor is human epidermal growth factor receptor 2 (HER2)-negative
   D. The member is considering treatment with adjuvant therapy (e.g., tamoxifen, aromatase inhibitors, immunotherapy)
   E. The member meets **one** of the following (regardless of menopausal status):
      1. Tumor is greater than 0.5 cm and node negative (pN0)
      2. Lymph nodes are pN1mi (2mm or smaller axillary node metastases)
      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.

Breast Cancer Extended Endocrine Therapy Algorithmic Tests

III. The use of the breast cancer extended endocrine therapy test Breast Cancer Index (BCI) (S3854, 81518) may be considered **medically necessary** when **all** of the following criteria are met:
   A. The member is female
   B. The member has primary breast cancer that is ductal/NST, lobular, mixed or micropapillary
   C. The member's tumor is hormone receptor-positive (estrogen receptor-positive or progesterone receptor-positive)
   D. The member's tumor is human epidermal growth factor receptor 2 (HER2)-negative
   E. The member has no distant metastases
   F. The member has completed at least 4 years of endocrine therapy
   G. The member is considering extended treatment with adjuvant therapy (e.g., tamoxifen, aromatase inhibitors, immunotherapy)
   H. The member meets **one** of the following (regardless of menopausal status):
      1. Tumor is greater than 0.5 cm and node negative (pN0)
      2. Lymph nodes are pN1mi (2mm or smaller axillary node metastases)
      3. Lymph nodes are pN1 (1-3 positive nodes).

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

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

Breast Cancer Prognostic Algorithmic Tests

VI. The use of a breast cancer prognostic algorithmic test (i.e., EndoPredict, Prosigna, MammaPrint) (S3854, 81520, 81521, 81522, 81523) may be considered **medically necessary** when **all** of the following criteria are met:
   A. The member is female
   B. The member meets at least **one** of the following:
      1. Postmenopausal status
      2. Greater than 50 years of age
   C. The member has primary breast cancer that is ductal/NST, lobular, mixed or micropapillary
   D. The member's tumor is estrogen receptor-positive
   E. The member's tumor is human epidermal growth factor receptor 2 (HER2)-negative
   F. The member is considering treatment with adjuvant therapy (for example, tamoxifen, aromatase inhibitors, immunotherapy)
   G. The member has **any** of the following node status:
      1. Node negative
      2. 1-3 positive nodes*.

VII. 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**.

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

IX. 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**.

X. 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.

Gene Expression Profiling Breast Cancer Subtyping Tests

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

Breast DCIS Prognostic Algorithmic Tests

XII. Breast DCIS prognostic algorithmic tests (0045U) may be considered **medically necessary** when **all** of the following are met:
- A. The member has ductal carcinoma in situ (DCIS)
- B. The tumor specimen contains at least 0.5 mm of DCIS
- C. The result of testing would aid in treatment decision-making (i.e., pursuing additional surgery)
- D. The patient's DCIS was not removed via mastectomy (i.e. there is residual ipsilateral breast tissue).

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

Colorectal Cancer

Colorectal Cancer Prognostic Algorithmic Tests

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

Prostate Cancer

Prostate Cancer Treatment and Prognostic Algorithmic Tests

XV. The use of a prostate cancer treatment and prognostic algorithmic test (i.e., Oncotype DX Prostate (0047U), Prolaris (81541)) may be considered **medically necessary** when:
- A. The member has a life expectancy of 10 years or more, **AND**
- B. The member has **any** of the following:
  1. Low-risk prostate cancer
  2. Favorable intermediate prostate cancer
  3. Unfavorable intermediate prostate cancer
  4. High-risk prostate cancer.

XVI. The use of the prostate cancer treatment and prognostic algorithmic test Decipher assay (81542) may be considered **medically necessary** when:
- A. The member meets **all** of the following:
  1. The member has a life expectancy of 10 years or more
  2. The member has **any** of the following:
     a. Low-risk prostate cancer
     b. Favorable intermediate prostate cancer
     c. Unfavorable intermediate prostate cancer

d. High-risk prostate cancer
3. The member has not yet had treatment**, OR**

B. The member meets the following:
1. The member 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.

XVII. The use of a prostate cancer treatment and prognostic algorithmic test (0047U, 81541, 81542) is considered **investigational** for all other indications.

Evidence Based Prostate Cancer Risk Assessment and Diagnostic Algorithmic Tests

XVIII. 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 may be considered **medically necessary** when **all** of the following are met:

A. The member has not had a prostate biopsy
B. The member has at least **one** of the following:
1. Prostate specific antigen (PSA) of greater than 3 ng/ml
2. A digital rectal exam (DRE) that is very suspicious for cancer
C. The test is **one** of the following:
1. Prostate Health Index (PHI)
2. SelectMDx
3. 4Kscore
4. ExoDx Prostate Test
5. MyProstateScore (MPS)
6. IsoPSA
D. The member has had a prostate biopsy
E. The result is **one** of the following:
1. Atypia, suspicious for cancer
2. High-grade prostatic intraepithelial neoplasia (PIN)
3. Benign
F. The test is **one** of the following:
1. Prostate Health Index (PHI)
2. 4Kscore
3. ExoDx Prostate Test
4. MyProstateScore (MPS)
5. IsoPSA
6. ConfirmMDx
7. PCA3.

XIX. 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.

Emerging Evidence Prostate Cancer Risk Assessment and Diagnostic Algorithmic Tests

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

Thyroid Cancer

Thyroid Cancer Diagnostic Algorithmic Tests

XXI. The use of a thyroid cancer diagnostic algorithmic test (0026U, 0018U, 0204U, 0245U, 0287U, 81546) in fine needle aspirates of thyroid nodules may be considered **medically necessary** when **all** of the following are met:
- A. The fine needle aspirate showed indeterminate cytologic findings
- B. Clinical and/or radiologic findings of the thyroid nodules are indeterminate of malignancy
- C. The result of the test would affect surgical decision making.

XXII. 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.

Uveal Melanoma

Uveal Melanoma Prognostic Algorithmic Tests

XXIII. The use of a uveal melanoma prognostic algorithmic test (81552) may be considered **medically necessary** when:
- A. The member has primary, localized uveal melanoma.

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

Cutaneous Melanoma

Evidence Based Cutaneous Melanoma Prognostic Algorithmic Tests

XXV. Cutaneous melanoma prognostic algorithmic tests (81479, 81529) with sufficient evidence of clinical validity and utility may be considered **medically necessary** when **all** of the following are met:
- A. The member has **either** of the following:
  1. Stage I melanoma (staging based on AJCC American Joint Committee on Cancer)
  2. Stage II melanoma (staging based on AJCC American Joint Committee on Cancer)
- B. The member does NOT have metastatic disease
- C. The results of testing will inform subsequent biopsy decisions, use of adjuvant therapy(ies), or follow-up screening protocols.

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

Emerging Evidence Cutaneous Melanoma Prognostic Algorithmic Tests

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

Cutaneous Melanoma Diagnostic Algorithmic Tests

XXVIII. Cutaneous melanoma diagnostic algorithmic tests (0090U, 0314U) may be considered **medically necessary** when:
- A. The member has a melanocytic neoplasm that is diagnostically uncertain or equivocal after histopathology.

XXIX. 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.

Cutaneous Melanoma Risk Assessment Algorithmic Tests

XXX. Cutaneous melanoma risk assessment algorithmic tests (0089U) may be considered **medically necessary** when **all** of the following are met:
- A. The member has a melanocytic neoplasm that shows at least one ABCDE feature
- B. A biopsy is being considered but has not yet been performed
- C. The test can only be used a maximum of 2 times per visit.

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

Ovarian Cancer

Ovarian Cancer Diagnostic Algorithmic Tests

XXXII. 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.

Ovarian Cancer Treatment Algorithmic Tests

XXXIII. Ovarian cancer treatment algorithmic tests (0172U) may be considered **medically necessary** when **both** of the following are met:
- A. The member has a diagnosis of ovarian cancer
- B. The member is being considered for PARP inhibitor therapy.

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

Gynecologic Cancer

Gynecologic Cancer Treatment Algorithmic Tests

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

Lung Cancer

Evidence Based Lung Cancer Diagnostic Algorithmic Tests

XXXVI. Lung cancer diagnostic algorithmic tests (0080U) with sufficient evidence of clinical validity and utility may be considered **medical necessary** when **all** of the following are met:
- A. The member is age 40 years or older
- B. The member has a single lung nodule between 8 and 30 mm in diameter
- C. The member has a risk of cancer of 50% or less according to the Mayo risk prediction algorithm
- D. The member does NOT have a diagnosis of cancer (except for nonmelanoma skin cancer) within 5 years of the lung nodule detection.

XXXVII. Lung cancer diagnostic algorithmic tests (0080U) with sufficient evidence of clinical validity and utility are considered **investigational** for all other indications.

Emerging Evidence Lung Cancer Diagnostic Algorithmic Tests

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

Evidence-Based Lung Cancer Treatment Algorithmic Tests

XXXIX. Lung cancer treatment algorithmic tests (0288U, 81538, 81599) with sufficient evidence of clinical utility and validity may be considered **medically necessary** when **all** of the following are met:

A. The member has a non-squamous non-small cell lung cancer (NSCLC) with tumor size less than 5 cm
B. There are no positive lymph nodes (stages I and IIa)
C. The member is considering adjuvant platinum-containing chemotherapy.

XL. Lung cancer treatment algorithmic tests (CPT codes) with sufficient evidence of clinical utility and validity are considered investigational for all other indications where clinical utility and validity have not been demonstrated.

Bladder/Urinary Tract Cancer Treatment and Recurrence Algorithmic Tests

XLI. The use of bladder/urinary tract cancer treatment and recurrence algorithmic test (0013M, 0016M, 0363U, 0366U, 0367U) may be considered **medically necessary** when **all** of the following are met:

A. The member has a diagnosis of bladder cancer
B. Results of algorithmic testing will affect management decisions for the member's bladder cancer
C. The member has not previously undergone bladder/urinary tract cancer diagnostic, treatment, and recurrence algorithmic testing for the current cancer diagnosis.

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

Evidence-Based Pancreatic Cyst Risk Assessment Algorithmic Tests

XLIII. Pancreatic cyst risk assessment algorithmic tests (81479) with sufficient evidence of clinical utility and validity may be considered **medically necessary** when **all** of the following are met:

A. The member has a pancreatic cyst
B. Initial testing (for example, CEA measurement, cytopathology and/or radiology) has been inconclusive for malignancy
C. The results of the test will impact treatment decisions (e.g., surgery, more aggressive treatment).

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

Cancer Of Unknown Primary

Cancer of Unknown Primary Gene Expression Profiling Tests

XLV. 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**.

Polygenic Risk Score Tests

Breast Cancer Polygenic Risk Score Tests

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

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

Policy Guidelines

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.

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.

Coding

See the Codes table for details.

Description

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.

Related Policies

This policy document provides coverage 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 coverage criteria related to algorithmic testing in oncology that is not specifically discussed in this or another non-general policy.

Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

Regulatory Status

State:
Starting on July 1, 2022 (per CA law SB 535) for commercial plans regulated by the California Department of Managed Healthcare and California Department of Insurance (PPO and HMO), health care service plans and insurers shall not require prior authorization for biomarker testing, including biomarker testing for cancer progression and recurrence, if a member has stage 3 or 4

cancer. Health care service plans and insurers can still do a medical necessity review of a biomarker test and possibly deny coverage after biomarker testing has been completed and a claim is submitted (post service review).

SB 496 requires health plans licensed under the Knox-Keene Act ("Plans"), Medi-Cal managed care plans ("MCPS"), and health insurers ("Insurers") to cover biomarker testing for the diagnosis, treatment, appropriate management, or ongoing monitoring of an enrollee's disease or condition to guide treatment decisions, as prescribed. The bill does not require coverage of biomarker testing for screening purposes. Restricted or denied use of biomarker testing for these purposes is subject to state and federal grievance and appeal processes. Where biomarker testing is deemed medically necessary, Plans and Insurers must ensure that the testing is provided in a way that limits disruptions in care.

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 males with breast cancer. Available data suggest the 21-gene

assay recurrence score provides prognostic information in males with breast cancer (p. BINV-J 1 of 2)

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

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

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

National Comprehensive Cancer Network (NCCN)
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".

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."

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 (e.g., 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.

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
- The test is ordered by a physician who is treating the patient for NSCLC (generally a medical oncologist, surgeon, or radiation oncologist) to help in the decision of whether or not to recommend adjuvant chemotherapy".

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)

Centers for Medicare and Medicaid Services

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

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

1. The beneficiary is being actively managed for bladder cancer.
2. The beneficiary is within the population and has the indication for which the test was developed and is covered. The laboratory will make available the appropriate indications of the test to the treating/ordering physician.
3. At least 1 of the 2 criteria are met:
    a. The patient is a candidate for multiple potential treatments, which could be considered to have varied or increasing levels of intensity based on a consensus guideline, and the physician and patient must decide among these treatments. OR
    b. The patient is a candidate for multiple therapies, and the test has shown that it predicts response to a specific therapy among accepted therapy options based on nationally recognized society consensus guidelines (i.e., National Comprehensive Cancer Network [NCCN], American Society of Clinical Oncology [ASCO], Society of Urologic Oncology [SUO], or American Urological Association [AUA]).
4. The test demonstrates analytical validity including both analytical and clinical validations. If the test relies on an algorithm (which may range in complexity from a threshold determination of a single numeric value to a complex mathematical or computational function), the algorithm must be validated in a cohort that is not a development cohort for the algorithm.
5. The test has demonstrated clinical validity and utility, establishing a clear and significant biological/molecular basis for stratifying patients and subsequently selecting (either

positively or negatively) a clinical management decision (in 4. above) in a clearly defined population.
6. The test successfully completes a Molecular Diagnostic Services Program (MolDX®) technical assessment that ensures the test is reasonable and necessary as described above.
7. Only 1 test may be performed prior to the initiation of therapy UNLESS a second test that interrogates different genomic content AND meets all the criteria established herein, is reasonable and necessary.
8. The genomic content interrogated by the test must be relevant to the therapy under consideration."

PANCREATIC CANCER

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)

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.

The specific requirements for medical necessity involve:

- Highly-concise affirmation, documented in the medical record, that a decision regarding treatment has not already been made and that the results of the molecular evaluation will assist in determining if more aggressive treatment than what is being considered is necessary.
  Previous first-line diagnostics, such as, but not restricted to, the following have demonstrated:
  - A pancreatic cyst fluid carcinoembryonic antigen (CEA), which is greater than or equal to 200 ng/ml, suggesting a mucinous cyst, but is not diagnostic.
  - Cyst cytopathologic or radiographic findings, which raise the index of malignancy suspicion, but where second-line molecular diagnostics is expected to be more compelling in the context of a surgical vs. non-surgical care plan.

Specific criteria of Non-coverage to include either:

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

Cytology not showing malignancy but meets AGA guidelines to reach a definitive diagnosis of benign disease. Lesions must be:

- Under 1 cm;
- Lack a solid component;
- Lack concerning cytology features;
- Lack main pancreatic duct dilatation of > 1cm in diameter with absence of abrupt change in duct diameter;
- Have fluid CEA level not exceeding 5 ng/ml".

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).

References

1. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Breast Cancer. Version 4.2022. https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf
2. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Colon Cancer. Version 2.2022. https://www.nccn.org/professionals/physician_gls/pdf/colon.pdf
3. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Prostate Cancer. Version 1.2023. https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf
4. Carter HB, Albertsen PC, Barry MJ, et al. Early Detection of Prostate Cancer: AUA Guideline. J Urol. 2013;190(2):419.426. doi:10.1016/j.juro.2013.04.119.
5. Sanda MG, Cadeddu JA, Kirkby E, et al. Clinically Localized Prostate Cancer: AUA/ASTRO/SUO Guideline. Part I: Risk Stratification, Shared Decision Making, and Care Options. J Urol. 2018;199(3):683-690.doi:10.1016/j.juro.2017.11.095.
6. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Thyroid Cancer. Version 3.2022. https://www.nccn.org/professionals/physician_gls/pdf/thyroid.pdf
7. Gharib H, Papini E, Garber JR, et al. American Association of Clinical Endocrinologists, American College of Endocrinology, and Associazione Medici Endocrinologi Medical Guidelines for Clinical Practice for the Diagnosis and Management of Thyroid Nodules--2016 Update. Endocr Pract. 2016;22(5):622-639. doi:10.4158/EP161208.GL.
8. Haugen BR, Alexander EK, Bible KC, et al. American Thyroid Association management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer: The American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer. Thyroid. 2016;26(1):1-133. doi:10.1089/thy.2015.0020.

9. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Uveal Melanoma. Version 2.2022. https://www.nccn.org/professionals/physician_gls/pdf/uveal.pdf
10. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Cutaneous Melanoma. Version 3.2022. https://www.nccn.org/professionals/physician_gls/pdf/cutaneous_melanoma.pdf
11. Swetter, SS, Tsao, HH, Bichakjian, CC, et al. Guidelines of care for the management of primary cutaneous melanoma. J Am Acad Dermatol. 2019;80(1):208-250. doi:10.1016/j.jaad.2018.08.055.
12. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Ovarian Cancer including Fallopian Tube Cancer and Primary Peritoneal Cancer. Version 5.2022. https://www.nccn.org/professionals/physician_gls/pdf/ovarian.pdf
13. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Bladder Cancer. Version 2.2022. https://www.nccn.org/professionals/physician_gls/pdf/bladder.pdf
14. Chang SS, Boorjian SA, Chou R, et al. Diagnosis and treatment of non-muscle invasive bladder cancer: AUA/SUO Guideline. J Urol. 2016;196(4):1021-1029. doi:10.1016/j.juro.2016.06.049.
15. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Genetic/Familial High Risk Assessment: Breast, Ovarian and Pancreatic. Version 1.2023. https://www.nccn.org/professionals/physician_gls/pdf/genetics_bop.pdf
16. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Occult Primary (Cancer of Unknown Primary). Version 2.2023. https://www.nccn.org/professionals/physician_gls/pdf/occult.pdf
17. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Cervical Cancer. Version 1.2022. https://www.nccn.org/professionals/physician_gls/pdf/cervical.pdf
18. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Uterine Neoplasms. Version 1.2022. https://www.nccn.org/professionals/physician_gls/pdf/uterine.pdf
19. Eggener SE, Rumble RB, Armstrong AJ, et al. Molecular Biomarkers in Localized Prostate Cancer: ASCO Guideline. J Clin Oncol. 2020;38(13):1474-1494. doi:10.1200/JCO.19.02768
20. Tew WP, Lacchetti C, Ellis A, et al. PARP Inhibitors in the Management of Ovarian Cancer: ASCO Guideline. J Clin Oncol. 2020;38(30):3468-3493. doi:10.1200/JCO.20.01924
21. Elta GH, Enestvedt BK, Sauer BG, Lennon AM. ACG Clinical Guideline: Diagnosis and Management of Pancreatic Cysts. Am J Gastroenterol. 2018;113(4):464-479. doi:10.1038/ajg.2018.14
22. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Pancreatic Adenocarcinoma. Version 1.2022. https://www.nccn.org/professionals/physician_gls/pdf/pancreatic.pdf
23. Concert Genetics. Evidence Review for Coverage Determination for Cutaneous Melanoma Risk Assessment Algorithmic Tests. V1.2.2022
24. Concert Genetics. Evidence Review for Coverage Determination for Lung Cancer Treatment Algorithmic Tests. V1.2.2022
25. Concert Genetics. Evidence Review for Coverage Determination for Lung Cancer Diagnostic Algorithmic Tests. V1.2.2022
26. AUC Committee Members, Fung MA, Vidal CI, et al. Appropriate use criteria for ancillary diagnostic testing in dermatopathology: New recommendations for 11 tests and 220 clinical scenarios from the American Society of Dermatopathology Appropriate Use Criteria Committee. J Cutan Pathol. 2022;49(3):231-245. doi:10.1111/cup.14135
27. Rosenkrantz AB, Verma S, Choyke P, et al. Prostate Magnetic Resonance Imaging and Magnetic Resonance Imaging Targeted Biopsy in Patients with a Prior Negative Biopsy: A Consensus Statement by AUA and SAR. J Urol. 2016;196(6):1613-1618. doi:10.1016/j.juro.2016.06.079

28. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Multiple Myeloma. Version 2.2023. https://www.nccn.org/professionals/physician_gls/pdf/myeloma.pdf
29. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Prostate Cancer Early Detection. Version 1.2022. https://www.nccn.org/professionals/physician_gls/pdf/prostate_detection.pdf
30. National Cancer Institute. NCI Dictionary of Cancer Terms/DCIS. https://www.cancer.gov/publications/dictionaries/cancer-terms/def/dcis. Accessed July 13, 2023.
31. Centers for Medicare & Medicaid Services. Medicare Coverage Database: Local Coverage Local Coverage DeterminationMolDX: Oncotype DX Breast Cancer for DCIS (Genomic Health) (L36912). Available at: https://www.cms.gov/medicare-coverage-database/view/lcd.aspx?lcdid=36912
32. Centers for Medicare & Medicaid Services. Medicare Coverage Database: Local Coverage Determination. MolDX: Predictive Classifiers for Early Stage Non-Small Cell Lung Cancer (L38238). Available at: https://www.cms.gov/medicare-coverage-database/view/lcd.aspx?lcdid=38238
33. Centers for Medicare & Medicaid Services., Dep't of Health & Human Services ("CMS"), Medicare Local Coverage Determinations Manual ("LCD"), L38576. "MolDX: Prognostic and Predictive Molecular Classifiers for Bladder Cancer." Revision date: 08/06/2023. Revision History Number: R1. Available at: https://www.cms.gov/medicare-coverage-database/view/lcd.aspx?lcdid=38576
34. Centers for Medicare & Medicaid Services. Medicare Coverage Database: Local Coverage Determination. MolDX: Loss-of-Heterozygosity Based Topographic Genotyping with PathfinderTG ®. (L34864). Available at: https://www.cms.gov/medicare-coverage-database/view/lcd.aspx?lcdid=34864

Documentation for Clinical Review

Please provide the following documentation:

- Name of the test being requested or the Concert Genetics GTU identifier. The Concert Genetics GTU can be found at https://app.concertgenetics.com
- CPT codes to be billed for the particular genetic test (GTU required for unlisted codes)
- History and physical and/or consultation notes including:
  - Clinical findings:
    - Signs/symptoms leading to a suspicion of genetic condition
    - Family history if applicable
  - Prior evaluation/treatment:
    - Previous test results (i.e., imagining, lab work, etc.) related to reason for genetic testing
    - Family member's genetic test result, if applicable
  - Rationale
    - Reason for performing test
    - How test result will impact clinical decision making

Post Service (in addition to the above, please include the following):

- Results/reports of tests performed

Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy.

The following codes are included below for informational purposes. Inclusion or exclusion of a code(s) does not constitute or imply member coverage or provider reimbursement policy. Policy Statements are intended to provide member coverage information and may include the use of some codes for clarity. The Policy Guidelines section may also provide additional information for how to interpret the Policy Statements and to provide coding guidance in some cases.

Type	Code	Description
CPT®	0003U	Oncology (ovarian) biochemical assays of five proteins (apolipoprotein A-1, CA 125 II, follicle stimulating hormone, human epididymis protein 4, transferrin), utilizing serum, algorithm reported as a likelihood score
	0005U	Oncology (prostate) gene expression profile by real-time RT-PCR of 3 genes (ERG, PCA3, and SPDEF), urine, algorithm reported as risk score
	0012M	Oncology (urothelial), mRNA, gene expression profiling by real-time quantitative PCR of five genes (MDK, HOXA13, CDC2 [CDK1], IGFBP5, and CXCR2), utilizing urine, algorithm reported as a risk score for having urothelial carcinoma
	0013M	Oncology (urothelial), mRNA, gene expression profiling by real-time quantitative PCR of five genes (MDK, HOXA13, CDC2 [CDK1], IGFBP5, and CXCR2), utilizing urine, algorithm reported as a risk score for having recurrent urothelial carcinoma
	0018U	Oncology (thyroid), microRNA profiling by RT-PCR of 10 microRNA sequences, utilizing fine needle aspirate, algorithm reported as a positive or negative result for moderate to high risk of malignancy
	0021U	Oncology (prostate), detection of 8 autoantibodies (ARF 6, NKX3-1, 5'-UTR-BMI1, CEP 164, 3'-UTR-Ropporin, Desmocollin, AURKAIP-1, CSNK2A2), multiplexed immunoassay and flow cytometry serum, algorithm reported as risk score
	0026U	Oncology (thyroid), DNA and mRNA of 112 genes, next-generation sequencing, fine needle aspirate of thyroid nodule, algorithmic analysis reported as a categorical result ("Positive, high probability of malignancy" or "Negative, low probability of malignancy")
	0045U	Oncology (breast ductal carcinoma in situ), mRNA, gene expression profiling by real-time RT-PCR of 12 genes (7 content and 5 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as recurrence score
	0047U	Oncology (prostate), mRNA, gene expression profiling by real-time RT-PCR of 17 genes (12 content and 5 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as a risk score
	0067U	Oncology (breast), immunohistochemistry, protein expression profiling of 4 biomarkers (matrix metalloproteinase-1 [MMP-1], carcinoembryonic antigen-related cell adhesion molecule 6 [CEACAM6], hyaluronoglucosaminidase [HYAL1], highly expressed in cancer protein [HEC1]), formalin-fixed paraffin-embedded precancerous breast tissue, algorithm reported as carcinoma risk score
	0069U	Oncology (colorectal), microRNA, RT-PCR expression profiling of miR-31-3p, formalin-fixed paraffin-embedded tissue, algorithm reported as an expression score
	0080U	Oncology (lung), mass spectrometric analysis of galectin-3-binding protein and scavenger receptor cysteine-rich type 1 protein M130, with five clinical risk factors (age, smoking status, nodule diameter, nodule-spiculation status and nodule location), utilizing plasma, algorithm reported as a categorical probability of malignancy

Type	Code	Description
	0083U	Oncology, response to chemotherapy drugs using motility contrast tomography, fresh or frozen tissue, reported as likelihood of sensitivity or resistance to drugs or drug combinations
	0089U	Oncology (melanoma), gene expression profiling by RTqPCR, PRAME and LINC00518, superficial collection using adhesive patch(es)
	0090U	Oncology (cutaneous melanoma), mRNA gene expression profiling by RT-PCR of 23 genes (14 content and 9 housekeeping), utilizing formalin-fixed paraffin-embedded (FFPE) tissue, algorithm reported as a categorical result (i.e., benign, intermediate, malignant)
	0092U	Oncology (lung), three protein biomarkers, immunoassay using magnetic nanosensor technology, plasma, algorithm reported as risk score for likelihood of malignancy
	0113U	Oncology (prostate), measurement of PCA3 and TMPRSS2-ERG in urine and PSA in serum following prostatic massage, by RNA amplification and fluorescence-based detection, algorithm reported as risk score
	0120U	Oncology (B-cell lymphoma classification), mRNA, gene expression profiling by fluorescent probe hybridization of 58 genes (45 content and 13 housekeeping genes), formalin-fixed paraffin-embedded tissue, algorithm reported as likelihood for primary mediastinal B-cell lymphoma (PMBCL) and diffuse large B-cell lymphoma (DLBCL) with cell of origin subtyping in the latter
	0172U	Oncology (solid tumor as indicated by the label), somatic mutation analysis of BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) and analysis of homologous recombination deficiency pathways, DNA, formalin-fixed paraffin-embedded tissue, algorithm quantifying tumor genomic instability score
	0204U	Oncology (thyroid), mRNA, gene expression analysis of 593 genes (including BRAF, RAS, RET, PAX8, and NTRK) for sequence variants and rearrangements, utilizing fine needle aspirate, reported as detected or not detected ***(Deleted code effective 7/1/2024)***
	0220U	Oncology (breast cancer), image analysis with artificial intelligence assessment of 12 histologic and immunohistochemical features, reported as a recurrence score
	0228U	Oncology (prostate), multianalyte molecular profile by photometric detection of macromolecules adsorbed on nanosponge array slides with machine learning, utilizing first morning voided urine, algorithm reported as likelihood of prostate cancer
	0245U	Oncology (thyroid), mutation analysis of 10 genes and 37 RNA fusions and expression of 4 mRNA markers using next-generation sequencing, fine needle aspirate, report includes associated risk of malignancy expressed as a percentage
	0288U	Oncology (lung), mRNA, quantitative PCR analysis of 11 genes (BAG1, BRCA1, CDC6, CDK2AP1, ERBB3, FUT3, IL11, LCK, RND3, SH3BGR, WNT3A) and 3 reference genes (ESD, TBP, YAP1), formalin-fixed paraffin-embedded (FFPE) tumor tissue, algorithmic interpretation reported as a recurrence risk score
	0295U	Oncology (breast ductal carcinoma in situ), protein expression profiling by immunohistochemistry of 7 proteins (COX2, FOXA1, HER2, Ki-67, p16, PR, SIAH2), with 4 clinicopathologic factors (size, age, margin status, palpability), utilizing formalin-fixed paraffin-embedded (FFPE) tissue, algorithm reported as a recurrence risk score

Type	Code	Description
	0313U	Oncology (pancreas), DNA and mRNA next-generation sequencing analysis of 74 genes and analysis of CEA (CEACAM5) gene expression, pancreatic cyst fluid, algorithm reported as a categorical result (i.e., negative, low probability of neoplasia or positive, high probability of neoplasia)
	0317U	Oncology (lung cancer), four-probe FISH (3q29, 3p22.1, 10q22.3, 10cen) assay, whole blood, predictive algorithm-generated evaluation reported as decreased or increased risk for lung cancer
	0339U	Oncology (prostate), mRNA expression profiling of HOXC6 and DLX1, reverse transcription polymerase chain reaction (RT-PCR), first-void urine following digital rectal examination, algorithm reported as probability of high-grade cancer
	0343U	Oncology (prostate), exosome-based analysis of 442 small noncoding RNAs (sncRNAs) by quantitative reverse transcription polymerase chain reaction (RT-qPCR), urine, reported as molecular evidence of no-, low-, intermediate- or high-risk of prostate cancer
	0359U	Oncology (prostate cancer), analysis of all prostate-specific antigen (PSA) structural isoforms by phase separation and immunoassay, plasma, algorithm reports risk of cancer
	0360U	Oncology (lung), enzyme-linked immunosorbent assay (ELISA) of 7 autoantibodies (p53, NY-ESO-1, CAGE, GBU4-5, SOX2, MAGE A4, and HuD), plasma, algorithm reported as a categorical result for risk of malignancy
	0363U	Oncology (urothelial), mRNA, gene-expression profiling by real-time quantitative PCR of 5 genes (MDK, HOXA13, CDC2 [CDK1], IGFBP5, and CXCR2), utilizing urine, algorithm incorporates age, sex, smoking history, and macrohematuria frequency, reported as a risk score for having urothelial carcinoma
	0365U	Oncology (bladder), analysis of 10 protein biomarkers (A1AT, ANG, APOE, CA9, IL8, MMP9, MMP10, PAI1, SDC1 and VEGFA) by immunoassays, urine, algorithm reported as a probability of bladder cancer
	0375U	Oncology (ovarian), biochemical assays of 7 proteins (follicle stimulating hormone, human epididymis protein 4, apolipoprotein A-1, transferrin, beta-2 macroglobulin, prealbumin [i.e., transthyretin], and cancer antigen 125), algorithm reported as ovarian cancer risk score
	0376U	Oncology (prostate cancer), image analysis of at least 128 histologic features and clinical factors, prognostic algorithm determining the risk of distant metastases, and prostate cancer-specific mortality, includes predictive algorithm to androgen deprivation-therapy response, if appropriate
	0387U	Oncology (melanoma), autophagy and beclin 1 regulator 1 (AMBRA1) and loricrin (AMLo) by immunohistochemistry, formalinfixed paraffin-embedded (FFPE) tissue, report for risk of progression
	0395U	Oncology (lung), multi-omics (microbial DNA by shotgun next-generation sequencing and carcinoembryonic antigen and osteopontin by immunoassay), plasma, algorithm reported as malignancy risk for lung nodules in early-stage disease
	0403U	Oncology (prostate), mRNA, gene expression profiling of 18 genes, first-catch urine, algorithm reported as percentage of likelihood of detecting clinically significant prostate cancer ***(Code revision 10/1/2024)***

Type	Code	Description
	0406U	Oncology (lung), flow cytometry, sputum, 5 markers (meso-tetra [4-carboxyphenyl] porphyrin [TCPP], CD206, CD66b, CD3, CD19), algorithm reported as likelihood of lung cancer
	0414U	Oncology (lung), augmentative algorithmic analysis of digitized whole slide imaging for 8 genes (ALK, BRAF, EGFR, ERBB2, MET, NTRK1-3, RET, ROS1), and KRAS G12C and PD-L1, if performed, formalin-fixed paraffin-embedded (FFPE) tissue, reported as positive or negative for each biomarker
	0420U	Oncology (urothelial), mRNA expression profiling by real-time quantitative PCR of MDK, HOXA13, CDC2, IGFBP5, and CXCR2 in combination with droplet digital PCR (ddPCR) analysis of 6 single-nucleotide polymorphisms (SNPs) genes TERT and FGFR3, urine, algorithm reported as a risk score for urothelial carcinoma ***(Code effective 1/1/2024)***
	0424U	Oncology (prostate), exosome-based analysis of 53 small noncoding RNAs (sncRNAs) by quantitative reverse transcription polymerase chain reaction (RT-qPCR), urine, reported as no molecular evidence, low-, moderate- or elevated-risk of prostate cancer ***(Code effective 1/1/2024)***
	0433U	Oncology (prostate), 5 DNA regulatory markers by quantitative PCR, whole blood, algorithm, including prostate-specific antigen, reported as likelihood of cancer ***(Code effective 1/1/2024)***
	0465U	Oncology (urothelial carcinoma), DNA, quantitative methylation-specific PCR of 2 genes (ONECUT2, VIM), algorithmic analysis reported as positive or negative ***(Code effective 7/1/2024)***
	0507U	Oncology (ovarian), DNA, wholegenome sequencing with 5-hydroxymethylcytosine (5hmC) enrichment, using whole blood or plasma, algorithm reported as cancer detected or not detected ***(Code effective 10/1/2024)***
	0512U	Oncology (prostate), augmentative algorithmic analysis of digitized whole-slide imaging of histologic features for microsatellite instability (MSI) status, formalin-fixed paraffinembedded (FFPE) tissue, reported as increased or decreased probability of MSI-high (MSI-H) ***(Code effective 10/1/2024)***
	0513U	Oncology (prostate), augmentative algorithmic analysis of digitized whole-slide imaging of histologic features for microsatellite instability (MSI) and homologous recombination deficiency (HRD) status, formalinfixed paraffin-embedded (FFPE) tissue, reported as increased or decreased probability of each biomarker ***(Code effective 10/1/2024)***
	81202	APC (adenomatous polyposis coli) (e.g., familial adenomatosis polyposis [FAP], attenuated FAP) gene analysis; known familial variants
	81275	KRAS (Kirsten rat sarcoma viral oncogene homolog) (e.g., carcinoma) gene analysis; variants in exon 2 (e.g., codons 12 and 13)
	81322	PTEN (phosphatase and tensin homolog) (e.g., Cowden syndrome, PTEN hamartoma tumor syndrome) gene analysis; known familial variant
	81352	TP53 (tumor protein 53) (e.g., Li-Fraumeni syndrome) gene analysis; targeted sequence analysis (e.g., 4 oncology)
	81479	Unlisted molecular pathology procedure
	81500	Oncology (ovarian), biochemical assays of two proteins (CA-125 and HE4), utilizing serum, with menopausal status, algorithm reported as a risk score

Type	Code	Description
	81503	Oncology (ovarian), biochemical assays of five proteins (CA-125, apolipoprotein A1, beta-2 microglobulin, transferrin, and pre-albumin), utilizing serum, algorithm reported as a risk score
	81518	Oncology (breast), mRNA, gene expression profiling by real-time RT-PCR of 11 genes (7 content and 4 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithms reported as percentage risk for metastatic recurrence and likelihood of benefit from extended endocrine therapy
	81519	Oncology (breast), mRNA, gene expression profiling by real-time RT-PCR of 21 genes, utilizing formalin-fixed paraffin embedded tissue, algorithm reported as recurrence score
	81520	Oncology (breast), mRNA gene expression profiling by hybrid capture of 58 genes (50 content and 8 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as a recurrence risk score
	81521	Oncology (breast), mRNA, microarray gene expression profiling of 70 content genes and 465 housekeeping genes, utilizing fresh frozen or formalin-fixed paraffin-embedded tissue, algorithm reported as index related to risk of distant metastasis
	81522	Oncology (breast), mRNA, gene expression profiling by RT-PCR of 12 genes (8 content and 4 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as recurrence risk score
	81523	Oncology (breast), mRNA, next-generation sequencing gene expression profiling of 70 content genes and 31 housekeeping genes, utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as index related to risk to distant metastasis
	81525	Oncology (colon), mRNA, gene expression profiling by real-time RT-PCR of 12 genes (7 content and 5 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as a recurrence score
	81529	Oncology (cutaneous melanoma), mRNA, gene expression profiling by real-time RT-PCR of 31 genes (28 content and 3 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as recurrence risk, including likelihood of sentinel lymph node metastasis
	81535	Oncology (gynecologic), live tumor cell culture and chemotherapeutic response by DAPI stain and morphology, predictive algorithm reported as a drug response score; first single drug or drug combination
	81536	Oncology (gynecologic), live tumor cell culture and chemotherapeutic response by DAPI stain and morphology, predictive algorithm reported as a drug response score; each additional single drug or drug combination (List separately in addition to code for primary procedure)
	81538	Oncology (lung), mass spectrometric 8-protein signature, including amyloid A, utilizing serum, prognostic and predictive algorithm reported as good versus poor overall survival
	81539	Oncology (high-grade prostate cancer), biochemical assay of four proteins (Total PSA, Free PSA, Intact PSA, and human kallikrein-2 [hK2]), utilizing plasma or serum, prognostic algorithm reported as a probability score
	81540	Oncology (tumor of unknown origin), mRNA, gene expression profiling by real-time RT-PCR of 92 genes (87 content and 5 housekeeping) to classify tumor into main cancer type and subtype, utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as a probability of a predicted main cancer type and subtype

Type	Code	Description
	81541	Oncology (prostate), mRNA gene expression profiling by real-time RT-PCR of 46 genes (31 content and 15 housekeeping), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as a disease-specific mortality risk score
	81542	Oncology (prostate), mRNA, microarray gene expression profiling of 22 content genes, utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as metastasis risk score
	81546	Oncology (thyroid), mRNA, gene expression analysis of 10,196 genes, utilizing fine needle aspirate, algorithm reported as a categorical result (e.g., benign or suspicious)
	81551	Oncology (prostate), promoter methylation profiling by real-time PCR of 3 genes (GSTP1, APC, RASSF1), utilizing formalin-fixed paraffin-embedded tissue, algorithm reported as a likelihood of prostate cancer detection on repeat biopsy
	81552	Oncology (uveal melanoma), mRNA, gene expression profiling by real-time RT-PCR of 15 genes (12 content and 3 housekeeping), utilizing fine needle aspirate or formalin-fixed paraffin-embedded tissue, algorithm reported as risk of metastasis
	81599	Unlisted multianalyte assay with algorithmic analysis
	84153	Prostate specific antigen (PSA); total
	84154	Prostate specific antigen (PSA); free
	86316	Immunoassay for tumor antigen, other antigen, quantitative (e.g., CA 50, 72-4, 549), each
	86386	Nuclear Matrix Protein 22 (NMP22), qualitative
HCPCS	S3854	Gene expression profiling panel for use in the management of breast cancer treatment

Policy History

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

Effective Date	Action
08/01/2023	New policy (combined policies 2.04.36, 2.04.111, 2.04.33, 2.04.62, 2.04.142, 2.04.07 and 2.04.54).
11/01/2023	Coding Update.
03/01/2024	Coding Update.
07/01/2024	Annual review. Policy statement, guidelines and literature updated. Policy title changed from Oncology: Algorithmic (Genetic Expression) Testing to current one.
09/01/2024	Coding Update.
11/01/2024	Coding Update.

Definitions of Decision Determinations

Medically Necessary: Services that are Medically Necessary include only those which have been established as safe and effective, are furnished under generally accepted professional standards to treat illness, injury or medical condition, and which, as determined by Blue Shield, are: (a) consistent with Blue Shield medical policy; (b) consistent with the symptoms or diagnosis; (c) not furnished primarily for the convenience of the patient, the attending Physician or other provider; (d) furnished at the most appropriate level which can be provided safely and effectively to the patient; and (e) not

more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of the Member's illness, injury, or disease.

Investigational/Experimental: A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

Split Evaluation: Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

Prior Authorization Requirements and Feedback (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

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

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

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

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

Appendix A

POLICY STATEMENT (No changes)	
BEFORE	**AFTER**
Oncology: Algorithmic Testing BSC_CON_2.05 **Policy Statement:** **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) may be considered **medically necessary** in **all** patients, regardless of gender, when **all** of the following criteria are met: A. The member has primary breast cancer that is ductal/NST, lobular, mixed or micropapillary B. The member's tumor is hormone receptor-positive (estrogen receptor-positive or progesterone receptor-positive) C. The member's tumor is human epidermal growth factor receptor 2 (HER2)-negative D. The member is considering treatment with adjuvant therapy (e.g., tamoxifen, aromatase inhibitors, immunotherapy) E. The member meets **one** of the following (regardless of menopausal status): 1. Tumor is greater than 0.5 cm and node negative (pN0) 2. Lymph nodes are pN1mi (2mm or smaller axillary node metastases) 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. **Breast Cancer Extended Endocrine Therapy Algorithmic Tests** III. The use of the breast cancer extended endocrine therapy test Breast Cancer Index (BCI) (S3854, 81518) may be considered **medically necessary** when **all** of the following criteria are met: A. The member is female	**Oncology: Algorithmic Testing BSC_CON_2.05** **Policy Statement:** **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) may be considered **medically necessary** in **all** patients, regardless of gender, when **all** of the following criteria are met: A. The member has primary breast cancer that is ductal/NST, lobular, mixed or micropapillary B. The member's tumor is hormone receptor-positive (estrogen receptor-positive or progesterone receptor-positive) C. The member's tumor is human epidermal growth factor receptor 2 (HER2)-negative D. The member is considering treatment with adjuvant therapy (e.g., tamoxifen, aromatase inhibitors, immunotherapy) E. The member meets **one** of the following (regardless of menopausal status): 1. Tumor is greater than 0.5 cm and node negative (pN0) 2. Lymph nodes are pN1mi (2mm or smaller axillary node metastases) 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. **Breast Cancer Extended Endocrine Therapy Algorithmic Tests** III. The use of the breast cancer extended endocrine therapy test Breast Cancer Index (BCI) (S3854, 81518) may be considered **medically necessary** when **all** of the following criteria are met: A. The member is female

POLICY STATEMENT (No changes)	
BEFORE	**AFTER**
B. The member has primary breast cancer that is ductal/NST, lobular, mixed or micropapillary C. The member's tumor is hormone receptor-positive (estrogen receptor-positive or progesterone receptor-positive) D. The member's tumor is human epidermal growth factor receptor 2 (HER2)-negative E. The member has no distant metastases F. The member has completed at least 4 years of endocrine therapy G. The member is considering extended treatment with adjuvant therapy (e.g., tamoxifen, aromatase inhibitors, immunotherapy) H. The member meets **one** of the following (regardless of menopausal status): 1. Tumor is greater than 0.5 cm and node negative (pN0) 2. Lymph nodes are pN1mi (2mm or smaller axillary node metastases) 3. Lymph nodes are pN1 (1-3 positive nodes).	B. The member has primary breast cancer that is ductal/NST, lobular, mixed or micropapillary C. The member's tumor is hormone receptor-positive (estrogen receptor-positive or progesterone receptor-positive) D. The member's tumor is human epidermal growth factor receptor 2 (HER2)-negative E. The member has no distant metastases F. The member has completed at least 4 years of endocrine therapy G. The member is considering extended treatment with adjuvant therapy (e.g., tamoxifen, aromatase inhibitors, immunotherapy) H. The member meets **one** of the following (regardless of menopausal status): 1. Tumor is greater than 0.5 cm and node negative (pN0) 2. Lymph nodes are pN1mi (2mm or smaller axillary node metastases) 3. Lymph nodes are pN1 (1-3 positive nodes).
IV. The use of the breast cancer extended endocrine therapy test Breast Cancer Index (BCI) (81518, S3854) in men with breast cancer is considered **investigational**.	IV. The use of the breast cancer extended endocrine therapy test Breast Cancer Index (BCI) (81518, S3854) in men with breast cancer is considered **investigational**.
V. The use of a breast cancer extended endocrine therapy test Breast Cancer Index) (81518, S3854) is considered **investigational** for all other indications.	V. The use of a breast cancer extended endocrine therapy test Breast Cancer Index) (81518, S3854) is considered **investigational** for all other indications.
Breast Cancer Prognostic Algorithmic Tests VI. The use of a breast cancer prognostic algorithmic test (i.e., EndoPredict, Prosigna, MammaPrint) (S3854, 81520, 81521, 81522, 81523) may be considered **medically necessary** when **all** of the following criteria are met: A. The member is female B. The member meets at least **one** of the following: 1. Postmenopausal status 2. Greater than 50 years of age	**Breast Cancer Prognostic Algorithmic Tests** VI. The use of a breast cancer prognostic algorithmic test (i.e., EndoPredict, Prosigna, MammaPrint) (S3854, 81520, 81521, 81522, 81523) may be considered **medically necessary** when **all** of the following criteria are met: A. The member is female B. The member meets at least **one** of the following: 1. Postmenopausal status 2. Greater than 50 years of age

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C. The member has primary breast cancer that is ductal/NST, lobular, mixed or micropapillary D. The member's tumor is estrogen receptor-positive E. The member's tumor is human epidermal growth factor receptor 2 (HER2)-negative F. The member is considering treatment with adjuvant therapy (for example, tamoxifen, aromatase inhibitors, immunotherapy) G. The member has **any** of the following node status: 1. Node negative 2. 1-3 positive nodes*.	C. The member has primary breast cancer that is ductal/NST, lobular, mixed or micropapillary D. The member's tumor is estrogen receptor-positive E. The member's tumor is human epidermal growth factor receptor 2 (HER2)-negative F. The member is considering treatment with adjuvant therapy (for example, tamoxifen, aromatase inhibitors, immunotherapy) G. The member has **any** of the following node status: 1. Node negative 2. 1-3 positive nodes*.
VII. 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**.	VII. 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**.
VIII. The use of the breast cancer prognostic algorithmic test Prosigna (81520) in individuals with 1-3 node positive breast cancer is considered **investigational.**	VIII. The use of the breast cancer prognostic algorithmic test Prosigna (81520) in individuals with 1-3 node positive breast cancer is considered **investigational.**
IX. 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**.	IX. 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**.
X. 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.	X. 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.	*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.
Gene Expression Profiling Breast Cancer Subtyping Tests XI. Gene expression profiling breast cancer subtyping tests (e.g., BluePrint) (81599, S3854, 0153U) are considered **investigational**.	**Gene Expression Profiling Breast Cancer Subtyping Tests** XI. Gene expression profiling breast cancer subtyping tests (e.g., BluePrint) (81599, S3854, 0153U) are considered **investigational**.

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BEFORE	**AFTER**
Breast DCIS Prognostic Algorithmic Tests XII. Breast DCIS prognostic algorithmic tests (0045U) may be considered **medically necessary** when **all** of the following are met: A. The member has ductal carcinoma in situ (DCIS) B. The tumor specimen contains at least 0.5 mm of DCIS C. The result of testing would aid in treatment decision-making (i.e., pursuing additional surgery) D. The patient's DCIS was not removed via mastectomy (i.e. there is residual ipsilateral breast tissue). XIII. Breast DCIS prognostic algorithmic tests (0045U) are considered **investigational** for all other indications.	**Breast DCIS Prognostic Algorithmic Tests** XII. Breast DCIS prognostic algorithmic tests (0045U) may be considered **medically necessary** when **all** of the following are met: A. The member has ductal carcinoma in situ (DCIS) B. The tumor specimen contains at least 0.5 mm of DCIS C. The result of testing would aid in treatment decision-making (i.e., pursuing additional surgery) D. The patient's DCIS was not removed via mastectomy (i.e. there is residual ipsilateral breast tissue). XIII. Breast DCIS prognostic algorithmic tests (0045U) are considered **investigational** for all other indications.
Colorectal Cancer **Colorectal Cancer Prognostic Algorithmic Tests** XIV. Colorectal cancer prognostic algorithmic tests (81525, 0069U, 0261U) are considered **investigational**.	**Colorectal Cancer** **Colorectal Cancer Prognostic Algorithmic Tests** XIV. Colorectal cancer prognostic algorithmic tests (81525, 0069U, 0261U) are considered **investigational**.
Prostate Cancer **Prostate Cancer Treatment and Prognostic Algorithmic Tests** XV. The use of a prostate cancer treatment and prognostic algorithmic test (i.e., Oncotype DX Prostate (0047U), Prolaris (81541)) may be considered **medically necessary** when: A. The member has a life expectancy of 10 years or more, **AND** B. The member has **any** of the following: 1. Low-risk prostate cancer 2. Favorable intermediate prostate cancer 3. Unfavorable intermediate prostate cancer 4. High-risk prostate cancer. XVI. The use of the prostate cancer treatment and prognostic algorithmic test Decipher assay (81542) may be considered **medically necessary** when: A. The member meets **all** of the following: 1. The member has a life expectancy of 10 years or more	**Prostate Cancer** **Prostate Cancer Treatment and Prognostic Algorithmic Tests** XV. The use of a prostate cancer treatment and prognostic algorithmic test (i.e., Oncotype DX Prostate (0047U), Prolaris (81541)) may be considered **medically necessary** when: A. The member has a life expectancy of 10 years or more, **AND** B. The member has **any** of the following: 1. Low-risk prostate cancer 2. Favorable intermediate prostate cancer 3. Unfavorable intermediate prostate cancer 4. High-risk prostate cancer. XVI. The use of the prostate cancer treatment and prognostic algorithmic test Decipher assay (81542) may be considered **medically necessary** when: A. The member meets **all** of the following: 1. The member has a life expectancy of 10 years or more

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2. The member has **any** of the following: a. Low-risk prostate cancer b. Favorable intermediate prostate cancer c. Unfavorable intermediate prostate cancer d. High-risk prostate cancer 3. The member has not yet had treatment**, OR** B. The member meets the following: 1. The member 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.	2. The member has **any** of the following: a. Low-risk prostate cancer b. Favorable intermediate prostate cancer c. Unfavorable intermediate prostate cancer d. High-risk prostate cancer 3. The member has not yet had treatment**, OR** B. The member meets the following: 1. The member 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.
XVII. The use of a prostate cancer treatment and prognostic algorithmic test (0047U, 81541, 81542) is considered **investigational** for all other indications.	XVII. The use of a prostate cancer treatment and prognostic algorithmic test (0047U, 81541, 81542) is considered **investigational** for all other indications.
Evidence Based Prostate Cancer Risk Assessment and Diagnostic Algorithmic Tests	**Evidence Based Prostate Cancer Risk Assessment and Diagnostic Algorithmic Tests**
XVIII. 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 may be considered **medically necessary** when **all** of the following are met: A. The member has not had a prostate biopsy B. The member has at least **one** of the following: 1. Prostate specific antigen (PSA) of greater than 3 ng/ml 2. A digital rectal exam (DRE) that is very suspicious for cancer C. The test is **one** of the following: 1. Prostate Health Index (PHI) 2. SelectMDx 3. 4Kscore 4. ExoDx Prostate Test 5. MyProstateScore (MPS) 6. IsoPSA D. The member has had a prostate biopsy	XVIII. 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 may be considered **medically necessary** when **all** of the following are met: A. The member has not had a prostate biopsy B. The member has at least **one** of the following: 1. Prostate specific antigen (PSA) of greater than 3 ng/ml 2. A digital rectal exam (DRE) that is very suspicious for cancer C. The test is **one** of the following: 1. Prostate Health Index (PHI) 2. SelectMDx 3. 4Kscore 4. ExoDx Prostate Test 5. MyProstateScore (MPS) 6. IsoPSA D. The member has had a prostate biopsy

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E. The result is **one** of the following: 1. Atypia, suspicious for cancer 2. High-grade prostatic intraepithelial neoplasia (PIN) 3. Benign F. The test is **one** of the following: 1. Prostate Health Index (PHI) 2. 4Kscore 3. ExoDx Prostate Test 4. MyProstateScore (MPS) 5. IsoPSA 6. ConfirmMDx 7. PCA3.	E. The result is **one** of the following: 1. Atypia, suspicious for cancer 2. High-grade prostatic intraepithelial neoplasia (PIN) 3. Benign F. The test is **one** of the following: 1. Prostate Health Index (PHI) 2. 4Kscore 3. ExoDx Prostate Test 4. MyProstateScore (MPS) 5. IsoPSA 6. ConfirmMDx 7. PCA3.
XIX. 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.	XIX. 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.
Emerging Evidence Prostate Cancer Risk Assessment and Diagnostic Algorithmic Tests XX. Prostate cancer risk assessment and diagnostic algorithmic tests (0021U, 0228U, 0403U, 0343U, 0424U, 0433U) with insufficient guidance for use are considered **investigational**.	**Emerging Evidence Prostate Cancer Risk Assessment and Diagnostic Algorithmic Tests** XX. Prostate cancer risk assessment and diagnostic algorithmic tests (0021U, 0228U, 0403U, 0343U, 0424U, 0433U) with insufficient guidance for use are considered **investigational**.
Thyroid Cancer **Thyroid Cancer Diagnostic Algorithmic Tests** XXI. The use of a thyroid cancer diagnostic algorithmic test (0026U, 0018U, 0204U, 0245U, 0287U, 81546) in fine needle aspirates of thyroid nodules may be considered **medically necessary** when **all** of the following are met: A. The fine needle aspirate showed indeterminate cytologic findings B. Clinical and/or radiologic findings of the thyroid nodules are indeterminate of malignancy C. The result of the test would affect surgical decision making.	**Thyroid Cancer** **Thyroid Cancer Diagnostic Algorithmic Tests** XXI. The use of a thyroid cancer diagnostic algorithmic test (0026U, 0018U, 0204U, 0245U, 0287U, 81546) in fine needle aspirates of thyroid nodules may be considered **medically necessary** when **all** of the following are met: A. The fine needle aspirate showed indeterminate cytologic findings B. Clinical and/or radiologic findings of the thyroid nodules are indeterminate of malignancy C. The result of the test would affect surgical decision making.

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BEFORE	**AFTER**
XXII. 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.	XXII. 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.
Uveal Melanoma	**Uveal Melanoma**
Uveal Melanoma Prognostic Algorithmic Tests	**Uveal Melanoma Prognostic Algorithmic Tests**
XXIII. The use of a uveal melanoma prognostic algorithmic test (81552) may be considered **medically necessary** when: A. The member has primary, localized uveal melanoma.	XXIII. The use of a uveal melanoma prognostic algorithmic test (81552) may be considered **medically necessary** when: A. The member has primary, localized uveal melanoma.
XXIV. The use of a uveal melanoma prognostic algorithmic test (81552) is considered **investigational** for all other indications.	XXIV. The use of a uveal melanoma prognostic algorithmic test (81552) is considered **investigational** for all other indications.
Cutaneous Melanoma	**Cutaneous Melanoma**
Evidence Based Cutaneous Melanoma Prognostic Algorithmic Tests	**Evidence Based Cutaneous Melanoma Prognostic Algorithmic Tests**
XXV. Cutaneous melanoma prognostic algorithmic tests (81479, 81529) with sufficient evidence of clinical validity and utility may be considered **medically necessary** when **all** of the following are met: A. The member has **either** of the following: 1. Stage I melanoma (staging based on AJCC American Joint Committee on Cancer) 2. Stage II melanoma (staging based on AJCC American Joint Committee on Cancer) B. The member does NOT have metastatic disease C. The results of testing will inform subsequent biopsy decisions, use of adjuvant therapy(ies), or follow-up screening protocols.	XXV. Cutaneous melanoma prognostic algorithmic tests (81479, 81529) with sufficient evidence of clinical validity and utility may be considered **medically necessary** when **all** of the following are met: A. The member has **either** of the following: 1. Stage I melanoma (staging based on AJCC American Joint Committee on Cancer) 2. Stage II melanoma (staging based on AJCC American Joint Committee on Cancer) B. The member does NOT have metastatic disease C. The results of testing will inform subsequent biopsy decisions, use of adjuvant therapy(ies), or follow-up screening protocols.
XXVI. Cutaneous melanoma prognostic algorithmic tests (81479, 81529) with sufficient evidence of clinical validity and utility are considered **investigational** for all other indications.	XXVI. Cutaneous melanoma prognostic algorithmic tests (81479, 81529) with sufficient evidence of clinical validity and utility are considered **investigational** for all other indications.
Emerging Evidence Cutaneous Melanoma Prognostic Algorithmic Tests	**Emerging Evidence Cutaneous Melanoma Prognostic Algorithmic Tests**
XXVII. Cutaneous melanoma prognostic algorithmic tests (0387U) with insufficient evidence of clinical validity and clinical utility are considered **investigational**.	XXVII. Cutaneous melanoma prognostic algorithmic tests (0387U) with insufficient evidence of clinical validity and clinical utility are considered **investigational**.

POLICY STATEMENT (No changes)	
BEFORE	**AFTER**
Cutaneous Melanoma Diagnostic Algorithmic Tests XXVIII. Cutaneous melanoma diagnostic algorithmic tests (0090U, 0314U) may be considered **medically necessary** when: A. The member has a melanocytic neoplasm that is diagnostically uncertain or equivocal after histopathology. XXIX. 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. **Cutaneous Melanoma Risk Assessment Algorithmic Tests** XXX. Cutaneous melanoma risk assessment algorithmic tests (0089U) may be considered **medically necessary** when **all** of the following are met: A. The member has a melanocytic neoplasm that shows at least one ABCDE feature B. A biopsy is being considered but has not yet been performed C. The test can only be used a maximum of 2 times per visit. XXXI. Cutaneous melanoma risk assessment algorithmic tests (0089U) are considered **investigational** for all other indications. **Ovarian Cancer** **Ovarian Cancer Diagnostic Algorithmic Tests** XXXII. 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	**Cutaneous Melanoma Diagnostic Algorithmic Tests** XXVIII. Cutaneous melanoma diagnostic algorithmic tests (0090U, 0314U) may be considered **medically necessary** when: A. The member has a melanocytic neoplasm that is diagnostically uncertain or equivocal after histopathology. XXIX. 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. **Cutaneous Melanoma Risk Assessment Algorithmic Tests** XXX. Cutaneous melanoma risk assessment algorithmic tests (0089U) may be considered **medically necessary** when **all** of the following are met: A. The member has a melanocytic neoplasm that shows at least one ABCDE feature B. A biopsy is being considered but has not yet been performed C. The test can only be used a maximum of 2 times per visit. XXXI. Cutaneous melanoma risk assessment algorithmic tests (0089U) are considered **investigational** for all other indications. **Ovarian Cancer** **Ovarian Cancer Diagnostic Algorithmic Tests** XXXII. 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

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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. **Ovarian Cancer Treatment Algorithmic Tests** XXXIII. Ovarian cancer treatment algorithmic tests (0172U) may be considered **medically necessary** when **both** of the following are met: A. The member has a diagnosis of ovarian cancer B. The member is being considered for PARP inhibitor therapy. XXXIV. Ovarian cancer treatment algorithmic tests (0172U) are considered **investigational** for all other indications. **Gynecologic Cancer** **Gynecologic Cancer Treatment Algorithmic Tests** XXXV. Gynecologic cancer treatment algorithmic tests (81535, 81536) in the assessment of gynecological cancers are considered **investigational.** **Lung Cancer** **Evidence Based Lung Cancer Diagnostic Algorithmic Tests** XXXVI. Lung cancer diagnostic algorithmic tests (0080U) with sufficient evidence of clinical validity and utility may be considered **medical necessary** when **all** of the following are met: A. The member is age 40 years or older B. The member has a single lung nodule between 8 and 30 mm in diameter C. The member has a risk of cancer of 50% or less according to the Mayo risk prediction algorithm D. The member does NOT have a diagnosis of cancer (except for nonmelanoma skin cancer) within 5 years of the lung nodule detection.	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. **Ovarian Cancer Treatment Algorithmic Tests** XXXIII. Ovarian cancer treatment algorithmic tests (0172U) may be considered **medically necessary** when **both** of the following are met: A. The member has a diagnosis of ovarian cancer B. The member is being considered for PARP inhibitor therapy. XXXIV. Ovarian cancer treatment algorithmic tests (0172U) are considered **investigational** for all other indications. **Gynecologic Cancer** **Gynecologic Cancer Treatment Algorithmic Tests** XXXV. Gynecologic cancer treatment algorithmic tests (81535, 81536) in the assessment of gynecological cancers are considered **investigational.** **Lung Cancer** **Evidence Based Lung Cancer Diagnostic Algorithmic Tests** XXXVI. Lung cancer diagnostic algorithmic tests (0080U) with sufficient evidence of clinical validity and utility may be considered **medical necessary** when **all** of the following are met: A. The member is age 40 years or older B. The member has a single lung nodule between 8 and 30 mm in diameter C. The member has a risk of cancer of 50% or less according to the Mayo risk prediction algorithm D. The member does NOT have a diagnosis of cancer (except for nonmelanoma skin cancer) within 5 years of the lung nodule detection.

POLICY STATEMENT (No changes)	
BEFORE	**AFTER**
XXVII. Lung cancer diagnostic algorithmic tests (0080U) with sufficient evidence of clinical validity and utility are considered **investigational** for all other indications.	XXVII. Lung cancer diagnostic algorithmic tests (0080U) with sufficient evidence of clinical validity and utility are considered **investigational** for all other indications.
Emerging Evidence Lung Cancer Diagnostic Algorithmic Tests XXVIII. Lung cancer diagnostic algorithmic tests (0092U, 0317U, 0360U, 0395U, 81479, 0406U) with insufficient evidence of clinical validity and clinical utility are considered **investigational**.	**Emerging Evidence Lung Cancer Diagnostic Algorithmic Tests** XXVIII. Lung cancer diagnostic algorithmic tests (0092U, 0317U, 0360U, 0395U, 81479, 0406U) with insufficient evidence of clinical validity and clinical utility are considered **investigational**.
Evidence-Based Lung Cancer Treatment Algorithmic Tests XXXIX. Lung cancer treatment algorithmic tests (0288U, 81538, 81599) with sufficient evidence of clinical utility and validity may be considered **medically necessary** when **all** of the following are met: A. The member has a non-squamous non-small cell lung cancer (NSCLC) with tumor size less than 5 cm B. There are no positive lymph nodes (stages I and IIa) C. The member is considering adjuvant platinum-containing chemotherapy.	**Evidence-Based Lung Cancer Treatment Algorithmic Tests** XXXIX. Lung cancer treatment algorithmic tests (0288U, 81538, 81599) with sufficient evidence of clinical utility and validity may be considered **medically necessary** when **all** of the following are met: A. The member has a non-squamous non-small cell lung cancer (NSCLC) with tumor size less than 5 cm B. There are no positive lymph nodes (stages I and IIa) C. The member is considering adjuvant platinum-containing chemotherapy.
XL. Lung cancer treatment algorithmic tests (CPT codes) with sufficient evidence of clinical utility and validity are considered investigational for all other indications where clinical utility and validity have not been demonstrated.	XL. Lung cancer treatment algorithmic tests (CPT codes) with sufficient evidence of clinical utility and validity are considered investigational for all other indications where clinical utility and validity have not been demonstrated.
Bladder/Urinary Tract Cancer Treatment and Recurrence Algorithmic Tests XLI. The use of bladder/urinary tract cancer treatment and recurrence algorithmic test (0013M, 0016M, 0363U, 0366U, 0367U) may be considered **medically necessary** when **all** of the following are met: A. The member has a diagnosis of bladder cancer B. Results of algorithmic testing will affect management decisions for the member's bladder cancer C. The member has not previously undergone bladder/urinary tract cancer diagnostic, treatment, and recurrence algorithmic testing for the current cancer diagnosis.	**Bladder/Urinary Tract Cancer Treatment and Recurrence Algorithmic Tests** XLI. The use of bladder/urinary tract cancer treatment and recurrence algorithmic test (0013M, 0016M, 0363U, 0366U, 0367U) may be considered **medically necessary** when **all** of the following are met: A. The member has a diagnosis of bladder cancer B. Results of algorithmic testing will affect management decisions for the member's bladder cancer C. The member has not previously undergone bladder/urinary tract cancer diagnostic, treatment, and recurrence algorithmic testing for the current cancer diagnosis.

POLICY STATEMENT (No changes)	
BEFORE	**AFTER**
XLII. The use of bladder/urinary tract cancer treatment and recurrence algorithmic test (0013M, 0016M, 0363U, 0366U, 0367U) is considered investigational for all other indications.	XLII. The use of bladder/urinary tract cancer treatment and recurrence algorithmic test (0013M, 0016M, 0363U, 0366U, 0367U) is considered investigational for all other indications.
Evidence-Based Pancreatic Cyst Risk Assessment Algorithmic Tests XLIII. Pancreatic cyst risk assessment algorithmic tests (81479) with sufficient evidence of clinical utility and validity may be considered **medically necessary** when **all** of the following are met: A. The member has a pancreatic cyst B. Initial testing (for example, CEA measurement, cytopathology and/or radiology) has been inconclusive for malignancy C. The results of the test will impact treatment decisions (e.g., surgery, more aggressive treatment).	**Evidence-Based Pancreatic Cyst Risk Assessment Algorithmic Tests** XLIII. Pancreatic cyst risk assessment algorithmic tests (81479) with sufficient evidence of clinical utility and validity may be considered **medically necessary** when **all** of the following are met: A. The member has a pancreatic cyst B. Initial testing (for example, CEA measurement, cytopathology and/or radiology) has been inconclusive for malignancy C. The results of the test will impact treatment decisions (e.g., surgery, more aggressive treatment).
XLIV. Pancreatic cyst risk assessment algorithmic tests (81479) with sufficient evidence of clinical utility and validity are considered investigational for all other indications where clinical utility and validity have not been demonstrated.	XLIV. Pancreatic cyst risk assessment algorithmic tests (81479) with sufficient evidence of clinical utility and validity are considered investigational for all other indications where clinical utility and validity have not been demonstrated.
Cancer Of Unknown Primary **Cancer of Unknown Primary Gene Expression Profiling Tests** XLV. 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**.	**Cancer Of Unknown Primary** **Cancer of Unknown Primary Gene Expression Profiling Tests** XLV. 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**.
Polygenic Risk Score Tests **Breast Cancer Polygenic Risk Score Tests** XLVI. The use of a breast cancer polygenic risk score test (81599) is considered **investigational**.	**Polygenic Risk Score Tests** **Breast Cancer Polygenic Risk Score Tests** XLVI. The use of a breast cancer polygenic risk score test (81599) is considered **investigational**.