BSC_CON_2.05	Oncology: Algorithmic (Genetic Expression) Testing		
Original Policy Date:	August 1, 2023	**Effective Date:**	November 1, 2023
Section:	2.0 Medicine	**Page:**	Page 1 of 35

Example Test Table

Below is a list of higher volume tests and the associated laboratories for each coverage criteria section. This list is not all inclusive.

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 Index Prognostic (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
Breast DCIS Prognostic Algorithmic Tests	Oncotype DX Breast DCIS Score (Exact Sciences)	0045U
Colorectal Cancer		
Colorectal Cancer Prognostic Algorithmic Tests	Oncotype DX Colon Recurrence Score (Exact Sciences)	81525
	miR-31now (GoPath Laboratories)	0069U
Prostate Cancer		
Prostate Cancer Treatment and Prognostic Algorithmic Tests	Oncotype DX Genomic Prostate Score (MDxHealth)	0047U
	Decipher Prostate Biopsy Genomic Classified Classifier (Veracyte)	81542
	Decipher Prostate RP Genomic Classifier (Veracyte)	
	Prolaris (Myriad Genetics)	81541
Prostate Cancer Risk Assessment Algorithmic Tests	4K Prostate Score (Serum) (BioReference Laboratories)	81539
	Prostate Health Index (ARUP Laboratories)	84153, 84154, 86316
	SelectMDx for Prostate Cancer (MDx Health)	0339U
	ExoDx Prostate Test (ExosomeDx)	0005U
	IsoPSA® (Cleveland Diagnostics, Inc)	0359U

Policy Statement Locations	Example Tests, Labs	Common CPT Codes
Prostate Cancer Diagnostic Algorithmic Tests	ConfirmMDx for Prostate Cancer (MDxHealth)	81551
	MyProstateScore (MPS) (University of Michigan MLabs)	0113U
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
Uveal Melanoma		
Uveal Melanoma Prognostic Algorithmic Tests	DecisionDX-UM (Castle Bioscience, Inc.)	81552
Cutaneous Melanoma		
Cutaneous Melanoma Prognostic Algorithmic Tests	DecisionDX-Melanoma (Castle Biosciences, Inc.)	81529
Cutaneous Melanoma Diagnostic Algorithmic Tests	myPath Melanoma (Castle Biosciences Inc)	0090U
Cutaneous Melanoma Risk Assessment Algorithmic Tests	Pigmented Lesion Assay (DermTech)	0089U
Ovarian Cancer		
Ovarian Cancer Diagnostic Algorithmic Tests	OVA1 (Aspira)	81503
	Overa (Aspira)	0003U
	Ovarian Malignancy Risk (ROMA) (LabCorp)	81500
Ovarian Cancer Treatment Algorithmic Tests	myChoice CDx (Myriad Genetics)	0172U
Other Cancer Treatment Algorithmic (Genetic Expression) Tests		
Other Cancer Treatment Algorithmic (Genetic Expression) Tests	ChemoFx (Helomics Corporation)	81535
	ChemoFx - Additional Drug (Helomics Corporation)	81536
Lung Cancer		
Lung Cancer Treatment Algorithmic Tests	VeriStrat (Biodesix)	81538
	DetermaRx (Oncocyte)	0288U
Lung Cancer Diagnostic Algorithmic Tests	Nodify XL2 (Biodesix)	0080U
	REVEAL Lung Nodule Characterization (MagArray)	0092U
	Percepta Bronchial Genomic Classifier (Veracyte)	81599

Policy Statement Locations	Example Tests, Labs	Common CPT Codes
Urinary Tract Cancer		
Urinary Tract Cancer Diagnostic or Recurrence Algorithmic Tests	Cxbladder Triage (Pacific Edge)	81599, 0363U
	Cxbladder Detect (Pacific Edge)	0012M
	Cxbladder Monitor (Pacific Edge)	0013M
	Alere NMP22® (Alere)	86386
	Alere NMP22® BladderChek® (Alere)	86386
Pancreatic Cancer		
Pancreatic Cyst Risk Assessment Algorithmic Tests	PancraGEN (Interpace Diagnostics)	81202, 81275, 81322, 81352, 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	BrevaGen*plus* (Pathogen Sciences Laboratories)	81599
Oncology: Miscellaneous Algorithmic Tests		
Oncology: Miscellaneous Algorithmic Tests	Onco4D (Animated Dynamics, Inc.)	0083U
	BBDRisk Dx (Silbiotech)	0067U
	PreciseDx Breast Cancer Test (PreciseDx)	0220U
	Lymph3Cx Lymphoma Molecular Subtyping Assay (Mayo Clinic Laboratories)	0120U

Policy Statement

BREAST CANCER

Breast Cancer Treatment and Prognostic Algorithmic (Genetic Expression) 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** when **all** of the following criteria are met:
   A. The member is female or male
   B. The member has invasive 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 tumor is greater than 0.5 cm with 0-3 positive lymph nodes (micrometastases of less than or equal to 2 millimeters (mm) in size are considered node-negative for this policy statement)

II. The use of the breast cancer treatment and prognostic algorithmic 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 is considering extended (beyond 5 years) treatment with adjuvant therapy (for example, tamoxifen, aromatase inhibitors, immunotherapy)
   F. The tumor is greater than 0.5 cm with 0-3 positive lymph nodes (micrometastases of less than or equal to 2 millimeters (mm) in size are considered node-negative for this policy statement)
   G. There are no distant metastases

III. The use of the hormone receptor positive breast cancer treatment and prognostic algorithmic test Breast Cancer Index (81518, S3854) in men with breast cancer is considered **investigational**.

IV. The use of a breast cancer treatment and prognostic algorithmic test (Oncotype DX Breast Recurrence Score or Breast Cancer Index) (81519, 81518, S3854) is considered **investigational** for all other indications.

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Breast Cancer Prognostic Algorithmic Tests

V. The use of a breast cancer prognostic algorithmic test (examples: 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 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 is considering treatment with adjuvant therapy (for example, tamoxifen, aromatase inhibitors, immunotherapy)
   F. The member meets **one** of the following based on menopausal status:
      1. The member is premenopausal and meets **one** of the following:
         a. Tumor is greater than 0.5 cm and node negative (pN0)
         b. Lymph nodes are pN1mi (2mm or smaller axillary node metastases)
         c. Lymph nodes are pN1 (1-3 positive nodes)
      2. The member is postmenopausal and meets **one** of the following:
         a. Tumor is greater than 0.5 cm
         b. Lymph nodes are pN1mi (2mm or smaller axillary node metastasis)
         c. Lymph nodes are pN1 (1-3 positive nodes)

VI. 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**.

VII. The use of a breast cancer prognostic algorithmic test (i.e., Endopredict, Prosigna, Breast Cancer Index) (S3854, 81520, 81521, 81522, 81523) is considered **investigational** for all other indications.

Gene Expression Profiling Breast Cancer Subtyping Tests

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

Breast DCIS Prognostic Algorithmic Tests

IX. Breast DCIS prognostic algorithmic tests (0045U) are considered **investigational**.

Colorectal Cancer

Colorectal Cancer Prognostic Algorithmic Tests

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

Prostate Cancer Treatment and Prognostic Algorithmic (Genetic Expression) Tests

XI. 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 the member has a life expectancy of 10 years or more, **AND** has **any** of the following (see Policy Guidelines):
   A. Low-risk prostate cancer
   B. Favorable intermediate prostate cancer
   C. Unfavorable intermediate prostate cancer
   D. High-risk prostate cancer

XII. The use of the prostate cancer treatment and prognostic algorithmic test Decipher assay (81542) may be considered **medically necessary** when:
   A. For initial risk stratification, the member meets the **both** of following:
      1. The member has a life expectancy of 10 years or more
      2. The member has **any** of the following (see Policy Guidelines):
         a. Low-risk prostate cancer
         b. Favorable intermediate prostate cancer
         c. Unfavorable intermediate prostate cancer
         d. High-risk prostate cancer
   B. For post-radical prostatectomy, the member meets the following:
      1. The member has a life expectancy of 5 years or more, **AND**
      2. The test is being used to inform adjuvant treatment and counseling for risk stratification as an alternative to PSADT, **AND/OR**
      3. Adverse features were found post-radical prostatectomy, including but not limited to PSA resistance/recurrence.

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

Prostate Cancer Risk Assessment Algorithmic (Genetic Expression)Tests

XIV. Prostate cancer risk assessment algorithmic tests (81539, 84153, 84154, 86316, 0339U, 0005U, 0359U) are considered **investigational**.

Prostate Cancer Diagnostic Algorithmic (Genetic Expression)Tests

XV. Prostate cancer diagnostic algorithmic tests (81551, 0113U) are considered **investigational**.

Thyroid Cancer Diagnostic Algorithmic (Genetic Expression) Tests

XVI. The use of a thyroid cancer diagnostic algorithmic test (0026U, 0018U, 0204U, 0245U, 81546) in fine needle aspirates of thyroid nodules may be considered **medically necessary** for **all** of the following:

A. Clinical and/or radiologic findings of the thyroid nodules are indeterminate of malignancy
B. The fine needle aspirate showed indeterminate cytologic findings
C. The result of the test would affect surgical decision making

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

Uveal Melanoma

Uveal Melanoma *Prognostic* Algorithmic (Genetic Expression) Tests

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

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

Cutaneous Melanoma *Prognostic* Algorithmic (Genetic Expression) Tests

XX. Cutaneous melanoma prognostic algorithmic tests (81529) are considered **investigational**.

Cutaneous Melanoma *Diagnostic* Algorithmic (Genetic Expression) Tests

XXI. Cutaneous melanoma diagnostic algorithmic tests (0090U) may be considered **medically necessary** when the member has a melanocytic neoplasm that is diagnostically uncertain or equivocal after histopathology.

XXII. Cutaneous melanoma diagnostic algorithmic tests (0090U) 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 (Genetic Expression) Tests

XXIII. Cutaneous melanoma risk assessment algorithmic tests (0089U) are considered **investigational**.

Ovarian Cancer Diagnostic Algorithmic (Genetic Expression) Tests

XXIV. Ovarian cancer diagnostic algorithmic tests (examples: OVA1, Ova1 Plus, Overa, and ROMA) (0003U, 81500, 81503) are considered **investigational** for all indications, including but not limited to:
A. Preoperative evaluation of adnexal masses to triage for malignancy
B. Screening for ovarian cancer
C. Selecting patients for surgery for an adnexal mass
D. Evaluation of patients with clinical or radiologic evidence of malignancy
E. Evaluation of patients with nonspecific signs or symptoms suggesting possible malignancy
F. Postoperative testing and monitoring to assess surgical outcome and/or to detect recurrent malignant disease following treatment

Ovarian Cancer Treatment Algorithmic (Genetic Expression) Tests

XXV. Ovarian cancer treatment algorithmic tests (0172U) may be considered **medically necessary** when the member has **both** of the following:
A. Has a diagnosis of ovarian cancer

B. Is being considered for PARP inhibitor therapy

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

Other Cancer Treatment Algorithmic (Genetic Expression) Tests

XXVII. In vitro chemoresistance cancer treatment algorithmic tests or assays (81535, 81536) in the assessment of gynecological cancers are considered **investigational.**

Lung Cancer Treatment Algorithmic (Genetic Expression) Tests

XXVIII. Lung cancer treatment algorithmic tests (81538, 0288U, 0360U) are considered **investigational**.

Lung Cancer Diagnostic Algorithmic (Genetic Expression) Tests

XXIX. Lung cancer diagnostic algorithmic tests (0080U, 0092U, 0360U 81599) are considered **investigational**, including for members with undiagnosed pulmonary nodules.

Urinary Tract Cancer Diagnostic or Recurrence Algorithmic (Genetic Expression) Tests

XXX. Urinary tract cancer (including bladder cancer) diagnostic or recurrence algorithmic tests (0012M, 0013M, 0363U, 81599, 86386) which are typically performed on urine are considered **investigational**.

Pancreatic Cyst Risk Assessment Algorithmic (Genetic Expression) Tests

XXXI. Pancreatic cyst risk assessment algorithmic tests (0313U, 81202, 81275, 81322, 81352, 81479) are considered **investigational**.

Cancer of Unknown Primary Gene Expression Profiling Tests

XXXII. The use of a cancer of unknown primary gene expression profiling test (81540) is considered **investigational** for **either** of the following:

A. To evaluate the site of origin of a tumor of unknown primary
B. To distinguish a primary from a metastatic tumor

Breast Cancer Polygenic Risk Score Tests

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

Oncology: Miscellaneous Algorithmic (Genetic Expression) Tests

XXXIV. The use of these specific oncology algorithmic tests are considered **investigational**:

A. BBDRisk Dx™ (0067U)
B. Onco4D™ (0083U)
C. Lymph3Cx Lymphoma Molecular Subtyping Assay (0120U)
D. PreciseDxTM Breast Cancer Test (0220U)

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

Policy Guidelines

These tests are indicated when the member is considering treatment with adjuvant endocrine therapy (e.g., tamoxifen, aromatase inhibitors, immunotherapy).

These tests (except BCI) should be ordered within 6 months after diagnosis (the value of the test for making decisions regarding delayed chemotherapy is unknown). Breast Cancer Index is indicated up to 6 years after initial diagnosis to determine if additional endocrine therapy is indicated.

The Oncotype DX, EndoPredict, the Breast Cancer Index, MammaPrint, and Prosigna assays should only be ordered on a tissue specimen obtained during surgical removal of the tumor and after subsequent pathology examination of the tumor has been completed and determined to meet the above criteria (i.e., the test should not be ordered on a preliminary core biopsy). The test should be ordered in the context of a physician-patient discussion regarding risk preferences when the test result will aid in making decisions regarding chemotherapy.

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

1. **Ductal/NST breast cancer** is ductal cancer that is 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. **Thyroid nodules with indeterminate 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. **Somatic** mutations can occur in any of the cells of the body except the germ cells (sperm and egg) and therefore are not passed on to children. These alterations can (but do not always) cause cancer or other diseases.
4. **Adjuvant** therapy refers to medication (such as chemotherapy or endocrine therapy) given after the surgical removal of a cancerous tumor.
5. **Ductal carcinoma in situ (DCIS)** is a condition in which abnormal cells are found in the lining of a breast duct. The abnormal cells have not spread outside the duct to other tissues in the breast.
6. **Adverse features post**-radical prostatectomy - i.e., positive margins, seminal vesicle invasion, extracapsular extension
7. **PSA**- Prostate-specific Antigen
8. **PSADT**- Prostate-specific antigen doubling time
9. **PSA persistence/recurrence after RP** is defined 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 >0.1 ng/mL.
10. **In vitro chemoresistance assays** measures (quantifies) the likely response the tumor will have to different chemotherapy treatments (sensitive or resistant) using live tumor cells. 81535 and 81536 are specific to gynecologic tumor testing.

Note: There are several types of assays available related to breast cancer prognosis and treatment. They share some common criteria but there are exceptions related to each test that are outlined below the main policy statement.

The types of tests include:
Most of these tests use multi-gene reverse transcriptase-polymerase chain reaction (RT-PCR) assays. These test the activity of certain genes by looking for the proteins they produce. The results are put into an algorithm that considers the results of several tests or patient characteristics to combine into a single score.

Hormone (estrogen/progesterone) receptor positive breast cancer prognostic algorithmic test (examples: Oncotype Dx, Endopredict, Prosigna, Breast Cancer Index) (81519, S3854, 81522, 81520, 81518). This means that unless the patient has hormone receptors present that can be blocked by

medications (e.g., Tamoxifen or Faslodex), they are not likely to get benefit. The hormones help cancer to grow, so blocking them helps to slow growth. Similarly, aromatase inhibitors block the effects of the enzyme aromatase that converts other hormones into estrogen.

Hormone receptor agnostic breast cancer prognostic algorithmic test (for example: Mammaprint) (S3854, 81521, 81523). It can be used for either hormone receptor positive or negative individuals.

Table PG1. National Comprehensive Cancer Network (NCCN) Risk Categories for Prostate Cancer (Version 1.2023)

Risk Group	Clinical/Pathologic Features		
Very low[a]	Has all of the following: • cT1c • Grade Group 1 • PSA <10 ng/mL • Fewer than 3 prostate biopsy fragments/cores positive, ≤50% cancer in each fragment/core[b] • PSA density <0.15 ng/mL/g		
Low[a]	Has all of the following but does not qualify for very low risk: • cT1–cT2a • Grade Group 1 • PSA <10 ng/mL		
Intermediate[a]	Has all of the following: • No high-risk group features • No very-high-risk group features • Has one or more intermediate risk factors (IRFs): o cT2b–cT2c o Grade Group 2 or 3 o PSA 10–20 ng/mL	Favorable intermediate	Has all of the following: • 1 IRF • Grade Group 1 or 2 • <50% biopsy cores positive (e.g., <6 of 12 cores)[b]
		Unfavorable intermediate	Has one or more of the following: • 2 or 3 IRFs • Grade Group 3 • ≥ 50% biopsy cores positive (e.g., ≥ 6 of 12 cores)[b]
High	Has no very-high-risk features and has exactly one high-risk feature: • cT3a OR • Grade Group 4 or Grade Group 5 OR • PSA >20 ng/mL		
Very high	Has at least one of the following: • cT3b–cT4 • Primary Gleason pattern 5 • 2 or 3 high-risk features • >4 cores with Grade Group 4 or 5		

[a] For asymptomatic patients in very-low-, low-, and intermediate-risk groups with life expectancy ≤5 years, no imaging or treatment is indicated until the patient becomes symptomatic, at which time imaging can be performed and androgen deprivation therapy (ADT) should be given

[b] An ultrasound- or MRI- or DRE-targeted lesion that is biopsied more than once and demonstrates cancer (regardless of percentage core involvement or number of cores involved) can be considered as a single positive core.

PSA: prostate-specific antigen; IRF: Intermediate risk factors

Description

Oncology prognostic and algorithmic tests are developed to aid in determining the likelihood that an individual has cancer, the prognosis for a patient diagnosed with cancer, and/or surveillance for recurrence. These tests may be used to guide clinical decision making for an individual diagnosed with cancer. The testing methodologies 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 chemotherapy.

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. ***(to be published)***
- ***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 Testing*** for coverage criteria related to algorithmic testing in oncology that is not specifically discussed in this or another non-general policy. ***(to be published)***

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

FDA:

Assays of Genetic Expression in Tumor Tissue as a Technique to Determine Prognosis in Patients with Breast Cancer

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments. Oncotype DX® and other tests listed herein are available under the auspices of the Clinical Laboratory Improvement Amendments. Laboratories that offer laboratory-developed tests must be licensed by the Clinical Laboratory Improvement Amendments for high-complexity testing. To date, the U.S. Food and Drug Administration (FDA) has chosen not to require any regulatory review of this test.

In 2007, MammaPrint® (Agendia) was cleared for marketing by the FDA through the 510(k) process for the prediction of breast cancer metastasis. In 2015, MammaPrint® was cleared for marketing by the FDA through the 510(k) process for use in fresh-frozen, paraffin-embedded breast cancer tissue.

In 2013, Prosigna® was cleared for marketing by the FDA through the 510(k) process. Moreover, the FDA determined that Prosigna® was substantially equivalent to MammaPrint®.

FDA product code: NYI.

Currently, the Breast Cancer Index℠ (Biotheranostics), EndoPredict® (distributed by Myriad), and Insight TNBCtype (Insight Genetics) are not FDA-approved.

Gene Expression Profiling and Protein Biomarkers for Prostate Cancer Management

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA). Prolaris® (Myriad Genetics), Oncotype DX® Prostate and Oncotype DX AR-V7 Nuclear Detect (Genomic Health), Decipher gene expression profiling test (Decipher Corp) , and the ProMark™ protein biomarker test (Metamark Genetics) are available under the auspices of the CLIA. Laboratories that offer laboratory-developed tests must be licensed by the CLIA for high-complexity testing. To date, the U.S. Food and Drug Administration (FDA) has chosen not to require any regulatory review of these tests.

In November 2015, the FDA's Office of Public Health Strategy and Analysis published a report suggesting FDA oversight of laboratory-developed tests. The FDA argued that many tests need more FDA oversight than the regulatory requirements of the CLIA. The CLIA standards relate to laboratory operations but do not address inaccuracies or unreliability of specific tests. Prolaris is among the 20 case studies in the document cited as needing FDA oversight. The report asserted that patients are potentially receiving inappropriate prostate cancer care because there is no evidence that results from the test meaningfully improve clinical outcomes.

Genetic and Protein Biomarkers for the Diagnosis and Cancer Risk Assessment of Prostate Cancer

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA). Laboratories that offer laboratory-developed tests

must be licensed under the CLIA for high-complexity testing. The following laboratories are certified under the CLIA : BioReference Laboratories and GenPath Diagnostics (subsidiaries of OPKO Health; 4Kscore®), ARUP Laboratories, Mayo Medical Laboratories, LabCorp, BioVantra, others (PCA3 assay), Clinical Research Laboratory (Prostate Core Mitomic Test™), MDx Health (SelectMDx, ConfirMDx), Innovative Diagnostics (phi™), and ExoDx® Prostate (Exosome Diagnostics). To date, the U.S. Food and Drug Administration (FDA) has chosen not to require any regulatory review of these tests.

In February 2012, the Progensa® PCA3 Assay (Gen-Probe; now Hologic) was approved by the FDA through the premarket approval process. The Progensa PCA3 Assay has been approved by the FDA to aid in the decision for repeat biopsy in men 50 years or older who have had 1 or more negative prostate biopsies and for whom a repeat biopsy would be recommended based on the current standard of care. The Progensa PCA3 Assay should not be used for men with atypical small acinar proliferation on their most recent biopsy. FDA product code: OYM.

In June 2012, proPSA, a blood test used to calculate the Prostate Health Index (phi; Beckman Coulter) was approved by the FDA through the premarket approval process. The phi test is indicated as an aid to distinguish prostate cancer from a benign prostatic condition in men ages 50 and older with prostate-specific antigen levels of 4 to 10 ng/mL and with digital rectal exam findings that are not suspicious. According to the manufacturer, the test reduces the number of prostate biopsies. FDA product code: OYA.

Multimarker Serum Testing Related to Ovarian Cancer

In July 2009, the OVA1® test (Aspira Labs [Austin, TX]) was cleared for marketing by the FDA through the 510(k) process. OVA1® was designed as a tool to further assess the likelihood that malignancy is present when the physician's independent clinical and radiologic evaluation does not indicate malignancy.

In September 2011, the Risk of Ovarian Malignancy Algorithm (ROMA™ test; Fujirebio Diagnostics [Sequin, TX]) was cleared for marketing by the FDA through the 510(k) process. The intended use of ROMA™ is as an aid, in conjunction with clinical assessment, in assessing whether a premenopausal or postmenopausal woman who presents with an ovarian adnexal mass is at a high or low likelihood of finding malignancy on surgery.

In March 2016, a second-generation test called Overa™ (also referred to as next-generation OVA1®), in which 2 of the 5 biomarkers in OVA1® are replaced with human epididymis secretory protein 4 and follicle-stimulating hormone, was cleared for marketing by the FDA through the 510(k) process. Similar to OVA1®, Overa™ generates a low- or high-risk of malignancy on a scale from 0 to 10.

Black Box Warning

In December 2011, the FDA amended its regulation for classifying ovarian adnexal mass assessment score test systems. The change required that off-label risks be highlighted using a black box warning. The warning is intended to mitigate the risk to health associated with off-label use as a screening test, stand-alone diagnostic test, or as a test to determine whether to proceed with surgery. Considering the history and currently unmet medical needs for ovarian cancer testing, the FDA concluded that there is a risk of off-label use of this device.[7] To address this risk, the FDA requires that manufacturers provide notice concerning the risks of off-label uses in the labeling, advertising, and promotional material of ovarian adnexal mass assessment score test systems. Manufacturers must address the following risks:

- Women without adnexal pelvic masses (i.e., for cancer "screening") are not part of the intended use population for the ovarian adnexal mass assessment score test systems. Public health risks associated with false-positive results for ovarian cancer screening tests are well described in the medical literature and include morbidity or mortality associated with unneeded testing and surgery. The risk from false-negative screening results also includes morbidity and mortality due to failure to detect and treat ovarian malignancy.

- Analogous risks, adjusted for prevalence and types of disease, arise if test results are used to determine the need for surgery in patients who are known to have ovarian adnexal masses.
- If used outside the "OR" rule that is described in this special control guidance, results from ovarian adnexal mass assessment score test systems pose a risk for morbidity and mortality due to nonreferral for oncologic evaluation and treatment.

Molecular Testing in the Management of Pulmonary Nodules
Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA). Xpresys Lung 2/Nodify XL2 (BDX-XL2; Integrated Diagnostics [Indi], purchased by Biodesix) and Percepta Bronchial Genomic Classifier (Veracyte) are available under the auspices of the CLIA. Laboratories that offer laboratory-developed tests must be licensed by the CLIA for high-complexity testing. To date, the U.S. Food and Drug Administration (FDA) has chosen not to require any regulatory review of this test.

Gene Expression-Based Assays for Cancers of Unknown Primary
In 2008, the PathWork® Tissue of Origin Test™ (Response Genetics; now Cancer Genetics, Cancer Genetics merged with StemoniX in 2020.) was cleared for marketing with limitations (see below) by the U.S. Food and Drug Administration (FDA) through the 510(k) process (FDA product code: OIW), with subsequent clearances for expanded applications in 2010 and minor modifications in 2012. FDA determined that the test was substantially equivalent to existing tests for use in measuring the degree of similarity between the RNA expression pattern in a patient's fresh-frozen tumor and the RNA expression patterns in a database of tumor samples (poorly differentiated, undifferentiated, metastatic cases) that were diagnosed according to current clinical and histopathologic practice.

Limitations to the clearance were as follows:

- The PathWork® Tissue of Origin Test is not intended to establish the origin of tumors that cannot be diagnosed according to current clinical and pathologic practice (e.g., a cancer of unknown primary).
- It is not intended to subclassify or modify the classification of tumors that can be diagnosed by current clinical and pathologic practice or to predict disease course, or survival or treatment efficacy, or to distinguish primary from metastatic tumor.
- Tumor types not in the PathWork® Tissue of Origin Test database may have RNA expression patterns similar to RNA expression patterns in tumor types in the database, leading to indeterminate results or misclassifications.

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests must meet the general regulatory standards of the Clinical Laboratory Improvement Amendments (CLIA). CancerTYPE ID® (Biotheranostics, San Diego, CA) is available under the auspices of the CLIA. Laboratories that offer laboratory-developed tests must be licensed by the CLIA for high-complexity testing. To date, the FDA has chosen not to require any regulatory review of this test.

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).

Rationale

BREAST CANCER

National Comprehensive Cancer Network (NCCN)

NCCN Guidelines 4.2022 for Breast Cancer makes recommendations for gene expression testing when considering adjuvant systemic therapy based on characteristics of the patient and the breast cancer. These characteristics include the patient's sex, menopause status, the TNM staging of the tumor, the expression of hormone receptors, HER2 status, and how the test will be used (such as for prognosis alone, or prognosis and treatment decisions).

Breast Cancer Treatment and Prognostic Algorithmic Tests

Oncotype DX

Oncotype DX for breast cancer is a 21-gene expression assay. NCCN guidelines for Breast Cancer (4.2022) 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 2A: 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 1: 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 Index (BCI)

The BCI is recommended by NCCN (Breast Cancer, 4.2022) for both indications of prognosis as well as predicting treatment for extended adjuvant endocrine therapy. Appropriate patients for this test are:

- Patients who are female (p. BINV-J 1 of 2)
- 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)

Breast Cancer Prognostic Algorithmic Tests

While Oncotype DX for Breast Recurrence Score is preferred by NCCN (Breast Cancer, 4.2022), other tests may be considered for prognosis/recurrence risk without treatment guidelines for patients who have hormone receptor-positive breast cancer. These tests include Endopredict and Prosignia (evidence level category 2A) and Mammaprint (evidence level category 1) for the following patients:

- Patients who are female (p. BINV-J 1 of 2)
- 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 3 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 3 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 3 of 5)

Gene Expression Profiling Breast Cancer Subtyping Tests
National Comprehensive Cancer Network (NCCN)
NCCN breast cancer guidelines (4.2022) do not reference gene expression profiling tests (example: Blueprint) for the purpose of subtyping breast cancer to provide information for clinical decision-making.

Breast DCIS Prognostic Algorithmic Tests
National Comprehensive Cancer Network (NCCN)
NCCN breast cancer guidelines (4.2022) do not reference DCIS prognostic algorithmic tests as part of the clinical work-up for DCIS.

COLORECTAL CANCER
Colorectal Cancer Prognostic Algorithmic Tests
National Comprehensive Cancer Network (NCCN)
NCCN guidelines for colon cancer (2.2022) state that there is currently insufficient data to recommend multigene panels to assist in making clinical decisions about adjuvant therapy (p. COL-3).

PROSTATE CANCER
Prostate Cancer Treatment and Prognostic Algorithmic Tests
National Comprehensive Cancer Network (NCCN)
Current NCCN guidelines (1.2023) support the consideration of gene expression profiling (specifically Decipher, Oncotype DX Prostate, and Prolaris) for prostate cancer prognosis and management in men with low, favorable intermediate, unfavorable intermediate, or high-risk disease and if the patient is expected to live 10 years or longer. (p. PROS-D 2 of 4)
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)

Prostate Cancer Risk Assessment Algorithm Tests
American Urological Association
The American Urological Association (Carter et al, 2013; confirmed 2018) published guidelines on the early detection of prostate cancer and concluded that the literature supporting the use of genetic and protein biomarkers for prostate cancer screening and risk assessment provides little evidence for routine use at this time (p. 5). However, the guidelines did recognize that multiple approaches subsequent to a PSA test (e.g., urinary and serum biomarkers, imaging, risk calculators) are available for identifying men more likely to harbor prostate cancer and/or one with an aggressive phenotype.

The use of such tools can be considered in men with a suspicious PSA level to inform prostate biopsy decisions (p. 17).

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 guidelines for prostate cancer early detection (1.2022) state that biomarkers meant to improve the specificity of detection of prostate cancer are not yet mandated as a first-line screening test in conjunction with serum prostate-specific antigen (PSA) (p. PROSD-3).

Prostate Cancer Diagnostic Algorithmic Tests

American Urological Association, American Society for Radiation Oncology, and Society of Urological Oncology
The American Urological Association, American Society for Radiation Oncology, and the Society of Urologic Oncology (Sanda et al, Part 1 2017, Part 2 2018) published joint guidelines on the management of clinically localized prostate cancer which state that among most low-risk localized prostate cancer patients, genomic biomarkers have not demonstrated a clear role in the selection of active surveillance (Part 1, p. 686) or in the follow-up of patients on active surveillance. (Part 2, p. 991)
National Comprehensive Cancer Network (NCCN)
NCCN guidelines for prostate cancer early detection (1.2022) state that biomarkers meant to improve the specificity of detection of prostate cancer are not yet mandated as a first-line screening test in conjunction with serum prostate-specific antigen (PSA) (page PROSD-3).

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)
Current NCCN Guidelines for Thyroid Carcinoma (3.2022) 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. THRY-1)

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 (2.2022) support gene expression profiling and chromosome analysis in all patients with uveal melanoma and further state that molecular testing for prognostication is preferred over cytology alone. (p. MS-6)

CUTANEOUS MELANOMA

Cutaneous Melanoma Prognostic Algorithmic Tests

National Comprehensive Cancer Network (NCCN)

NCCN guidelines for cutaneous melanoma (3.2022) recognize that the use of gene expression profiling as an emerging technology to differentiate melanomas at low versus high risk for metastasis, to clarify indeterminate melanocytic neoplasms following histopathology, and to classify cutaneous melanoma into separate categories based on metastasis; however, currently there is insufficient data to recommend the use of gene expression profiling for cutaneous melanoma as the impact of these tests has not been established. (p. ME-C 1 of 8)

American Academy of Dermatology

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

- There is insufficient evidence of benefit to recommend routine use of currently available prognostic molecular tests, including GEP, for prognosis of CM. (page 219)
- Routine molecular testing, including GEP, for prognostication is discouraged until better use criteria are defined. The application of molecular information for clinical management is not recommended. (p. 219)

Cutaneous Melanoma Diagnostic Algorithmic Tests

National Comprehensive Cancer Network (NCCN)

NCCN guidelines for cutaneous melanoma (3.2022) 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

Concert Genetics

This review focused on peer-reviewed, published evidence of the clinical utility of DermTech PLA through May, 2022. PubMed and ECRI Guidelines Trust searches were performed. Search terms included pigmented lesion assay, DermTech, 0089U, PRAME, LINC00518, cutaneous melanoma risk. References were also identified from the performing laboratory's website. A total of 110 abstracts from these sources were reviewed, and 30 full text publications were evaluated. At the present time, the DermTech Pigmented Lesion Assay has not been adequately shown in peer-reviewed publications to effectively result in improved health outcomes compared to the current standard of care.

OVARIAN CANCER

Ovarian Cancer Diagnostic Algorithmic Tests

National Comprehensive Cancer Network (NCCN)

NCCN guidelines for ovarian cancer, Fallopian tube, cancer, and primary peritoneal cancer (5.2022) recognize the use of biomarker analysis for risk assessment for ovarian cancer in women with a pelvic mass as an emerging technology; however, the NCCN panel of experts currently does not recommend these biomarker tests for clinical use. (p. MS-10 and p. MS-11)

Ovarian Cancer Treatment Algorithmic Tests

National Comprehensive Cancer Network (NCCN)

NCCN guidelines for ovarian cancer, Fallopian tube cancer, and primary peritoneal cancer (5.2022) 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 (5.2022) state that chemosensitivity or chemoresistance assays, or other biomarker assays, are being used at some institutions, but the current level of evidence is not sufficient to replace the current standard of care of chemotherapy (p. OV-C).

NCCN guidelines for cervical cancer (1.2022) do not mention chemosensitivity or chemoresistance assays as part of clinical care.
NCCN guidelines for uterine neoplasms (1.2022) do not mention chemosensitivity or chemoresistance assays as part of clinical care.

LUNG CANCER

Lung Cancer Treatment Algorithmic Tests

Concert Genetics

This review focused on peer-reviewed, published evidence of the clinical utility of VeriStrat® through June 2022. PubMed and ECRI Guidelines Trust searches were 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.

Lung Cancer Diagnostic Algorithmic Tests

Concert Genetics

This review focused on peer-reviewed, published evidence of the clinical utility of NodifyXL2, Percepta Bronchial Genomic Classifier, and Reveal Lung Nodule Characterization through June 2022. PubMed and ECRI Guidelines Trust searches were performed. Search terms included Nodify, Percepta, lung nodule, plasma-protein and multiplex. References were also identified from the performing laboratory's website. At the present time, NodifyXL2, Percepta Bronchial Genomic Classifier, and Reveal Lung Nodule Characterization have not been adequately shown in peer-reviewed publications to effectively result in improved health outcomes compared to the current standard of care.

BLADDER AND URINARY TRACT CANCER

Bladder Cancer Diagnostic and Recurrence Algorithmic Tests

National Comprehensive Cancer Network (NCCN)

NCCN guidelines for bladder cancer (2.2022) support consideration for urinary urothelial tumor markers for high-risk patients with non-muscle-invasive bladder cancer (category 2B recommendation) (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) 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:

- Urinary biomarker analysis should not replace cystoscopic evaluation in the surveillance of NMIBC [non-muscle invasive bladder cancer]. (Strong Recommendation; Evidence Strength: Grade B)
- Urinary biomarker analysis or cytology should not routinely be used during surveillance In a patient with a history of low-risk cancer and a normal cystoscopy (Expert Opinion) (p. 1024 and 1025)

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)

Urinary Tract Cancer Recurrence Algorithmic Tests

Current NCCN guidelines on bladder cancer (2.2022) does not include a recommendation for algorithmic-based screening for urinary tract cancer. .

Pancreatic Cancer

Pancreatic Cyst Risk Assessment Algorithmic Tests

National Comprehensive Cancer Network (NCCN)

NCCN guidelines for pancreatic cancer (1.2022 discuss the use of endoscopic ultrasound to follow patients with pancreatic cysts and after the removal, citing that the risk of malignancy in mucinous cystic neoplasms is less than 15%. (p. MS-6, MS-10) The guidelines do not include recommendation or discussion for the use of molecular analysis of pancreatic cysts to stratify risk of cancer.

American College of Gastroenterology

The American College of Gastroenterology (2018) published guidelines for the diagnosis and management of pancreatic cysts, which included the following:
"A number of DNA, RNA, protein, and metabolomic markers have been evaluated in cyst fluid. The majority of these are still early in development and not yet ready for translation into clinical practice. However, analysis of DNA mutations in cyst fluid has shown promise in identifying IPMNs [intraductal papillary mucinous neoplasms] and MCNs [mucinous cystic neoplasms]." (p. 471)

Cancer Of Unknown Primary

Cancer of Unknown Primary Gene Expression Profiling Tests

National Comprehensive Cancer Network (NCCN)

NCCN guidelines for occult primary (cancer of unknown primary) (2.2023) 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 (1.2023) 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).

Multiple Myeloma Polygenic Risk Score Tests

National Comprehensive Cancer Network (NCCN)

NCCN guidelines for multiple myeloma (2.2023) do not mention the use of polygenic risk score as part of clinical management for multiple myeloma.
NCCN guidelines for genetic/familial high-risk assessment for breast, ovarian, and pancreatic cancers (1.2023) speak broadly about the use of polygenic risk scores, stating that there are currently significant limitations to this type of testing, and it should not be used for clinical management at this time outside of the context of a clinical trial (p. EVAL-A).

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Documentation for Clinical Review

Please provide the following documentation:

- History and physical and/or consultation notes including:
  - Clinical findings (i.e., pertinent symptoms and duration)
  - Current diagnoses and status (i.e., type of cancer, stage)
  - Family history, if applicable
  - Reason for test when applicable
  - Pertinent past procedural and surgical history (i.e., biopsies, resections, etc.)
  - Pertinent past genetic or other laboratory tests as applicable

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

- Results/reports of tests performed
- Procedure report(s)
- Name of the test being requested or the Concert Genetics GTU identifier
  The Concert Genetics GTU can be found at https://app.concertgenetics.com

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
	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
	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)

Type	Code	Description
	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 ***(Code revision 7/1/2023)***
	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
	0220U	Oncology (breast cancer), image analysis with artificial intelligence assessment of 12 histologic and immunohistochemical features, reported as a recurrence score
	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
	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)
	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
	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
	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

Type	Code	Description
	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 ***(Code effective 7/1/2023)***
	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 ***(Code effective 7/1/2023)***
	0403U	Oncology (prostate), mRNA, gene expression profiling of 18 genes, first-catch post-digital rectal examination urine (or processed first-catch urine), algorithm reported as percentage of likelihood of detecting clinically significant prostate cancer ***(Code effective 10/1/2023)***
	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 ***(Code effective 10/1/2023)***
	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 ***(Code effective 10/1/2023)***
	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
	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

Type	Code	Description
	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
	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.

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	
BEFORE Red font: Verbiage removed	**AFTER**
Oncology: Algorithmic (Genetic Expression) Testing BSC_CON_2.05 **Policy Statement:** **Note**: 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). *(Moved to Regulatory Status section)* BREAST CANCER **Breast Cancer Treatment and Prognostic Algorithmic (Genetic Expression) 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** when **all** of the following criteria are met: A. The member is female or male B. The member has invasive 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 tumor is greater than 0.5 cm with 0-3 positive lymph nodes (micrometastases of less than or equal to 2 millimeters (mm) in size are considered node-negative for this policy statement) II. The use of the breast cancer treatment and prognostic algorithmic test Breast Cancer Index (BCI) (S3854, 81518) may be considered **medically necessary** when **all** of the following criteria are met:	**Oncology: Algorithmic (Genetic Expression) Testing BSC_CON_2.05** **Policy Statement:** BREAST CANCER **Breast Cancer Treatment and Prognostic Algorithmic (Genetic Expression) 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** when **all** of the following criteria are met: A. The member is female or male B. The member has invasive 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 tumor is greater than 0.5 cm with 0-3 positive lymph nodes (micrometastases of less than or equal to 2 millimeters (mm) in size are considered node-negative for this policy statement) II. The use of the breast cancer treatment and prognostic algorithmic test Breast Cancer Index (BCI) (S3854, 81518) may be considered **medically necessary** when **all** of the following criteria are met:

POLICY STATEMENT	
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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 is considering extended (beyond 5 years) treatment with adjuvant therapy (for example, tamoxifen, aromatase inhibitors, immunotherapy) F. The tumor is greater than 0.5 cm with 0-3 positive lymph nodes (micrometastases of less than or equal to 2 millimeters (mm) in size are considered node-negative for this policy statement) G. There are no distant metastases	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 is considering extended (beyond 5 years) treatment with adjuvant therapy (for example, tamoxifen, aromatase inhibitors, immunotherapy) F. The tumor is greater than 0.5 cm with 0-3 positive lymph nodes (micrometastases of less than or equal to 2 millimeters (mm) in size are considered node-negative for this policy statement) G. There are no distant metastases
III. The use of the hormone receptor positive breast cancer treatment and prognostic algorithmic test Breast Cancer Index (81518, S3854) in men with breast cancer is considered **investigational**.	III. The use of the hormone receptor positive breast cancer treatment and prognostic algorithmic test Breast Cancer Index (81518, S3854) in men with breast cancer is considered **investigational**.
IV. The use of a breast cancer treatment and prognostic algorithmic test (Oncotype DX Breast Recurrence Score or Breast Cancer Index) (81519, 81518, S3854) is considered **investigational** for all other indications. back to top	IV. The use of a breast cancer treatment and prognostic algorithmic test (Oncotype DX Breast Recurrence Score or Breast Cancer Index) (81519, 81518, S3854) is considered **investigational** for all other indications. back to top
Breast Cancer Prognostic Algorithmic Tests V. The use of a breast cancer prognostic algorithmic test (examples: 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 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)	**Breast Cancer Prognostic Algorithmic Tests** V. The use of a breast cancer prognostic algorithmic test (examples: 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 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)

POLICY STATEMENT	
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D. The member's tumor is human epidermal growth factor receptor 2 (HER2)-negative E. The member is considering treatment with adjuvant therapy (for example, tamoxifen, aromatase inhibitors, immunotherapy) F. The member meets **one** of the following based on menopausal status: 1. The member is premenopausal and meets **one** of the following: a. Tumor is greater than 0.5 cm and node negative (pN0) b. Lymph nodes are pN1mi (2mm or smaller axillary node metastases) c. Lymph nodes are pN1 (1-3 positive nodes) 2. The member is postmenopausal and meets **one** of the following: a. Tumor is greater than 0.5 cm b. Lymph nodes are pN1mi (2mm or smaller axillary node metastasis) c. Lymph nodes are pN1 (1-3 positive nodes)	D. The member's tumor is human epidermal growth factor receptor 2 (HER2)-negative E. The member is considering treatment with adjuvant therapy (for example, tamoxifen, aromatase inhibitors, immunotherapy) F. The member meets **one** of the following based on menopausal status: 1. The member is premenopausal and meets **one** of the following: a. Tumor is greater than 0.5 cm and node negative (pN0) b. Lymph nodes are pN1mi (2mm or smaller axillary node metastases) c. Lymph nodes are pN1 (1-3 positive nodes) 2. The member is postmenopausal and meets **one** of the following: a. Tumor is greater than 0.5 cm b. Lymph nodes are pN1mi (2mm or smaller axillary node metastasis) c. Lymph nodes are pN1 (1-3 positive nodes)
VI. 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**.	VI. 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**.
VII. The use of a breast cancer prognostic algorithmic test (i.e., Endopredict, Prosigna, Breast Cancer Index) (S3854, 81520, 81521, 81522, 81523) is considered **investigational** for all other indications. back to top	VII. The use of a breast cancer prognostic algorithmic test (i.e., Endopredict, Prosigna, Breast Cancer Index) (S3854, 81520, 81521, 81522, 81523) is considered **investigational** for all other indications. back to top
Gene Expression Profiling Breast Cancer Subtyping Tests VIII. Gene expression profiling breast cancer subtyping tests (e.g., BluePrint) (81599, S3854) are considered **investigational**. back to top	**Gene Expression Profiling Breast Cancer Subtyping Tests** VIII. Gene expression profiling breast cancer subtyping tests (e.g., BluePrint) (81599, S3854) are considered **investigational**. back to top
Breast DCIS Prognostic Algorithmic Tests IX. Breast DCIS prognostic algorithmic tests (0045U) are considered **investigational**.	**Breast DCIS Prognostic Algorithmic Tests** IX. Breast DCIS prognostic algorithmic tests (0045U) are considered **investigational**.

POLICY STATEMENT	
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Colorectal Cancer **Colorectal Cancer Prognostic Algorithmic Tests** X. Colorectal cancer prognostic algorithmic tests (81525, 0069U) are considered **investigational**.	**Colorectal Cancer** **Colorectal Cancer Prognostic Algorithmic Tests** X. Colorectal cancer prognostic algorithmic tests (81525, 0069U) are considered **investigational**.
Prostate Cancer Treatment and Prognostic Algorithmic (Genetic Expression) Tests XI. 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 the member has a life expectancy of 10 years or more, **AND** has **any** of the following (see Policy Guidelines): A. Low-risk prostate cancer B. Favorable intermediate prostate cancer C. Unfavorable intermediate prostate cancer D. High-risk prostate cancer	**Prostate Cancer Treatment and Prognostic Algorithmic (Genetic Expression) Tests** XI. 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 the member has a life expectancy of 10 years or more, **AND** has **any** of the following (see Policy Guidelines): A. Low-risk prostate cancer B. Favorable intermediate prostate cancer C. Unfavorable intermediate prostate cancer D. High-risk prostate cancer
XII. The use of the prostate cancer treatment and prognostic algorithmic test Decipher assay (81542) may be considered **medically necessary** when: A. For initial risk stratification, the member meets the **both** of following: 1. The member has a life expectancy of 10 years or more 2. The member has **any** of the following (see Policy Guidelines): a. Low-risk prostate cancer b. Favorable intermediate prostate cancer c. Unfavorable intermediate prostate cancer d. High-risk prostate cancer B. For post-radical prostatectomy, the member meets the following: 1. The member has a life expectancy of 5 years or more, **AND** 2. The test is being used to inform adjuvant treatment and counseling for risk stratification as an alternative to PSADT, **AND/OR**	XII. The use of the prostate cancer treatment and prognostic algorithmic test Decipher assay (81542) may be considered **medically necessary** when: A. For initial risk stratification, the member meets the **both** of following: 1. The member has a life expectancy of 10 years or more 2. The member has **any** of the following (see Policy Guidelines): a. Low-risk prostate cancer b. Favorable intermediate prostate cancer c. Unfavorable intermediate prostate cancer d. High-risk prostate cancer B. For post-radical prostatectomy, the member meets the following: 1. The member has a life expectancy of 5 years or more, **AND** 2. The test is being used to inform adjuvant treatment and counseling for risk stratification as an alternative to PSADT, **AND/OR**

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3. Adverse features were found post-radical prostatectomy, including but not limited to PSA resistance/recurrence.	3. Adverse features were found post-radical prostatectomy, including but not limited to PSA resistance/recurrence.
XIII. The use of a prostate cancer treatment and prognostic algorithmic test (0047U, 81541, 81542) is considered investigational for all other indications.	XIII. The use of a prostate cancer treatment and prognostic algorithmic test (0047U, 81541, 81542) is considered investigational for all other indications.
Prostate Cancer Risk Assessment Algorithmic (Genetic Expression)Tests	**Prostate Cancer Risk Assessment Algorithmic (Genetic Expression)Tests**
XIV. Prostate cancer risk assessment algorithmic tests (81539, 84153, 84154, 86316, 0339U, 0005U, 0359U) are considered **investigational**.	XIV. Prostate cancer risk assessment algorithmic tests (81539, 84153, 84154, 86316, 0339U, 0005U, 0359U) are considered **investigational**.
Prostate Cancer Diagnostic Algorithmic (Genetic Expression)Tests	**Prostate Cancer Diagnostic Algorithmic (Genetic Expression)Tests**
XV. Prostate cancer diagnostic algorithmic tests (81551, 0113U) are considered **investigational**.	XV. Prostate cancer diagnostic algorithmic tests (81551, 0113U) are considered **investigational**.
Thyroid Cancer Diagnostic Algorithmic (Genetic Expression) Tests	**Thyroid Cancer Diagnostic Algorithmic (Genetic Expression) Tests**
XVI. The use of a thyroid cancer diagnostic algorithmic test (0026U, 0018U, 0204U, 0245U, 81546) in fine needle aspirates of thyroid nodules may be considered **medically necessary** for **all** of the following: A. Clinical and/or radiologic findings of the thyroid nodules are indeterminate of malignancy B. The fine needle aspirate showed indeterminate cytologic findings C. The result of the test would affect surgical decision making	XVI. The use of a thyroid cancer diagnostic algorithmic test (0026U, 0018U, 0204U, 0245U, 81546) in fine needle aspirates of thyroid nodules may be considered **medically necessary** for **all** of the following: A. Clinical and/or radiologic findings of the thyroid nodules are indeterminate of malignancy B. The fine needle aspirate showed indeterminate cytologic findings C. The result of the test would affect surgical decision making
XVII. The use of a thyroid cancer diagnostic algorithmic test (0026U, 0018U, 0204U, 0245U, 81546) in fine needle aspirates of thyroid nodules is considered **investigational** for all other indications.	XVII. The use of a thyroid cancer diagnostic algorithmic test (0026U, 0018U, 0204U, 0245U, 81546) in fine needle aspirates of thyroid nodules is considered **investigational** for all other indications.
Uveal Melanoma **Uveal Melanoma *Prognostic* Algorithmic (Genetic Expression) Tests**	**Uveal Melanoma** **Uveal Melanoma *Prognostic* Algorithmic (Genetic Expression) Tests**
XVIII. The use of a uveal melanoma prognostic algorithmic test (81552) may be considered **medically necessary** when the member has primary, localized uveal melanoma.	XVIII. The use of a uveal melanoma prognostic algorithmic test (81552) may be considered **medically necessary** when the member has primary, localized uveal melanoma.

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XIX. The use of a uveal melanoma prognostic algorithmic test (81552) is considered **investigational** for all other indications.	XIX. The use of a uveal melanoma prognostic algorithmic test (81552) is considered **investigational** for all other indications.
Cutaneous Melanoma *Prognostic* Algorithmic (Genetic Expression) Tests XX. Cutaneous melanoma prognostic algorithmic tests (81529) are considered **investigational**.	**Cutaneous Melanoma *Prognostic* Algorithmic (Genetic Expression) Tests** XX. Cutaneous melanoma prognostic algorithmic tests (81529) are considered **investigational**.
Cutaneous Melanoma *Diagnostic* Algorithmic (Genetic Expression) Tests XXI. Cutaneous melanoma diagnostic algorithmic tests (0090U) may be considered **medically necessary** when the member has a melanocytic neoplasm that is diagnostically uncertain or equivocal after histopathology.	**Cutaneous Melanoma *Diagnostic* Algorithmic (Genetic Expression) Tests** XXI. Cutaneous melanoma diagnostic algorithmic tests (0090U) may be considered **medically necessary** when the member has a melanocytic neoplasm that is diagnostically uncertain or equivocal after histopathology.
XXII. Cutaneous melanoma diagnostic algorithmic tests (0090U) are considered **investigational** for all other indications, including: A. A melanocytic neoplasm that has pathology definitive for melanoma, desmoplastic melanoma, or sclerosing nevus.	XXII. Cutaneous melanoma diagnostic algorithmic tests (0090U) 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 (Genetic Expression) Tests XXIII. Cutaneous melanoma risk assessment algorithmic tests (0089U) are considered **investigational**.	**Cutaneous Melanoma *Risk Assessment* Algorithmic (Genetic Expression) Tests** XXIII. Cutaneous melanoma risk assessment algorithmic tests (0089U) are considered **investigational**.
Ovarian Cancer Diagnostic Algorithmic (Genetic Expression) Tests XXIV. Ovarian cancer diagnostic algorithmic tests (examples: OVA1, Ova1 Plus, Overa, and ROMA) (0003U, 81500, 81503) are considered **investigational** for all indications, including but not limited to: A. Preoperative evaluation of adnexal masses to triage for malignancy B. Screening for ovarian cancer C. Selecting patients for surgery for an adnexal mass D. Evaluation of patients with clinical or radiologic evidence of malignancy E. Evaluation of patients with nonspecific signs or symptoms suggesting possible malignancy	**Ovarian Cancer Diagnostic Algorithmic (Genetic Expression) Tests** XXIV. Ovarian cancer diagnostic algorithmic tests (examples: OVA1, Ova1 Plus, Overa, and ROMA) (0003U, 81500, 81503) are considered **investigational** for all indications, including but not limited to: A. Preoperative evaluation of adnexal masses to triage for malignancy B. Screening for ovarian cancer C. Selecting patients for surgery for an adnexal mass D. Evaluation of patients with clinical or radiologic evidence of malignancy E. Evaluation of patients with nonspecific signs or symptoms suggesting possible malignancy

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F. Postoperative testing and monitoring to assess surgical outcome and/or to detect recurrent malignant disease following treatment back to top	F. Postoperative testing and monitoring to assess surgical outcome and/or to detect recurrent malignant disease following treatment back to top
Ovarian Cancer Treatment Algorithmic (Genetic Expression) Tests XXV. Ovarian cancer treatment algorithmic tests (0172U) may be considered **medically necessary** when the member has **both** of the following: A. Has a diagnosis of ovarian cancer B. Is being considered for PARP inhibitor therapy	**Ovarian Cancer Treatment Algorithmic (Genetic Expression) Tests** XXV. Ovarian cancer treatment algorithmic tests (0172U) may be considered **medically necessary** when the member has **both** of the following: A. Has a diagnosis of ovarian cancer B. Is being considered for PARP inhibitor therapy
XXVI. Ovarian cancer treatment algorithmic tests (0172U) are considered **investigational** for all other indications.	XXVI. Ovarian cancer treatment algorithmic tests (0172U) are considered **investigational** for all other indications.
Other Cancer Treatment Algorithmic (Genetic Expression) Tests XXVII. In vitro chemoresistance cancer treatment algorithmic tests or assays (81535, 81536) in the assessment of gynecological cancers are considered **investigational.**	**Other Cancer Treatment Algorithmic (Genetic Expression) Tests** XXVII. In vitro chemoresistance cancer treatment algorithmic tests or assays (81535, 81536) in the assessment of gynecological cancers are considered **investigational.**
Lung Cancer Treatment Algorithmic (Genetic Expression) Tests XXVIII. Lung cancer treatment algorithmic tests (81538, 0288U, 0360U) are considered **investigational**.	**Lung Cancer Treatment Algorithmic (Genetic Expression) Tests** XXVIII. Lung cancer treatment algorithmic tests (81538, 0288U, 0360U) are considered **investigational**.
Lung Cancer Diagnostic Algorithmic (Genetic Expression) Tests XXIX. Lung cancer diagnostic algorithmic tests (0080U, 0092U, 0360U 81599) are considered **investigational**, including for members with undiagnosed pulmonary nodules.	**Lung Cancer Diagnostic Algorithmic (Genetic Expression) Tests** XXIX. Lung cancer diagnostic algorithmic tests (0080U, 0092U, 0360U 81599) are considered **investigational**, including for members with undiagnosed pulmonary nodules.
Urinary Tract Cancer Diagnostic or Recurrence Algorithmic (Genetic Expression) Tests XXX. Urinary tract cancer (including bladder cancer) diagnostic or recurrence algorithmic tests (0012M, 0013M, 0363U, 81599, 86386) which are typically performed on urine are considered **investigational**.	**Urinary Tract Cancer Diagnostic or Recurrence Algorithmic (Genetic Expression) Tests** XXX. Urinary tract cancer (including bladder cancer) diagnostic or recurrence algorithmic tests (0012M, 0013M, 0363U, 81599, 86386) which are typically performed on urine are considered **investigational**.

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Pancreatic Cyst Risk Assessment Algorithmic (Genetic Expression) Tests XXXI. Pancreatic cyst risk assessment algorithmic tests (0313U, 81202, 81275, 81322, 81352, 81479) are considered **investigational**.	**Pancreatic Cyst Risk Assessment Algorithmic (Genetic Expression) Tests** XXXI. Pancreatic cyst risk assessment algorithmic tests (0313U, 81202, 81275, 81322, 81352, 81479) are considered **investigational**.
Cancer of Unknown Primary Gene Expression Profiling Tests XXXII. The use of a cancer of unknown primary gene expression profiling test (81540) is considered **investigational** for **either** of the following: A. To evaluate the site of origin of a tumor of unknown primary B. To distinguish a primary from a metastatic tumor	**Cancer of Unknown Primary Gene Expression Profiling Tests** XXXII. The use of a cancer of unknown primary gene expression profiling test (81540) is considered **investigational** for **either** of the following: C. To evaluate the site of origin of a tumor of unknown primary D. To distinguish a primary from a metastatic tumor
Breast Cancer Polygenic Risk Score Tests XXXIII. The use of a breast cancer polygenic risk score test (81599) is considered **investigational**.	**Breast Cancer Polygenic Risk Score Tests** XXXIII. The use of a breast cancer polygenic risk score test (81599) is considered **investigational**.
Oncology: Miscellaneous Algorithmic (Genetic Expression) Tests XXXIV. The use of these specific oncology algorithmic tests are considered **investigational**: A. BBDRisk Dx™ (0067U) B. Onco4D™ (0083U) C. Lymph3Cx Lymphoma Molecular Subtyping Assay (0120U) D. PreciseDxTM Breast Cancer Test (0220U)	**Oncology: Miscellaneous Algorithmic (Genetic Expression) Tests** XXXIV. The use of these specific oncology algorithmic tests are considered **investigational**: A. BBDRisk Dx™ (0067U) B. Onco4D™ (0083U) C. Lymph3Cx Lymphoma Molecular Subtyping Assay (0120U) D. PreciseDxTM Breast Cancer Test (0220U)