Clinical Policy: Oncology Algorithmic Testing

Reference Number: CP.MP.237

Coding Implications

Date of Last Revision: 02/22

Revision Log

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

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.

CPT® Codes	Example Tests (Labs)	Criteria Section	Common ICD Codes
81519	OncotypeDx Breast Recurrence Score (Genomic Health, Inc.)	Breast Cancer Treatment and Prognostic Algorithmic Tests	C50.011-C50.929, Z17.0
81522,S3854	EndoPredict, Sividon	Receptor Positive Breast Cancer Prognostic Algorithmic Tests	C50.011-C50.929, D05.00-D05.92, Z17.0
S3854	Diagnostics (Myriad)	Receptor Positive Breast Cancer Prognostic Algorithmic Tests	C50.011-C50.929, D05.00-D05.92, Z17.0
81518	Breast Cancer Index Prognostic (Biotheranostics)	Receptor Positive Breast Cancer Prognostic Algorithmic Tests	C50.011-C50.929, D05.00-D05.92, Z17.0

CPT® Codes	Example Tests (Labs)	Criteria Section	Common ICD Codes
81520,0008M	Prosigna (NanoString Technologies)	Receptor Positive Breast Cancer Prognostic Algorithmic Tests	C50.011-C50.929, D05.00-D05.92, Z17.0
81599, S3854	BluePrint (Agendia, Inc.)	Gene Expression Profiling Breast Cancer Subtyping Tests	N/A
0153U	Insight TNBCtype™ (Insight Molecular Labs)	Gene Expression Profiling Breast Cancer Subtyping Tests	N/A
0045U	OncotypeDX Breast DCIS (Genomic Health, Inc.)	Breast DCIS Prognostic Algorithmic Tests	D05.1, Z17.0
81525	Oncotype DX Colon Recurrence Score (Genomic Health, Inc.)	Colorectal Cancer Prognostic Algorithmic Tests	C18.0-C18.9
81599	GeneFx Colon, Helomics Therapeutics (aka CoIDx) (Almac Diagnostics)	Colorectal Cancer Prognostic Algorithmic Tests	C18.0-C18.9
0069U	miR-31now™ (GoPath Laboratories)	Colorectal Cancer Prognostic Algorithmic Tests	C18.0-C18.9
0047U	Oncotype DX Genomic Prostate (Genomic Health, Inc.)	Prostate Cancer Treatment and Prognostic Algorithmic Tests	C61
81542	Decipher Prostate Cancer Classifier (GenomeDX Biosciences, Inc.)	Prostate Cancer Treatment and Prognostic Algorithmic Tests	C61
81541	Prolaris (Myriad Genetics)	Prostate Cancer Treatment and Prognostic Algorithmic Tests	C61
81599	ProMark (Metamark Genetics)	Prostate Cancer Treatment and Prognostic Algorithmic Tests	C61
0053U	Prostate Cancer Risk Panel (Mayo Medical Laboratories	Prostate Cancer Treatment and Prognostic Algorithmic Tests	C61
81539	Kallikrein markers (e.g. 4Kscore Test, OPKO Lab)	Prostate Cancer Risk Assessment Algorithmic Tests	C61, Z12.5

CPT® Codes	Example Tests (Labs)	Criteria Section	Common ICD Codes
84153, 84154, 86316	Prostate Health Index (Beckman Coulter)	Prostate Cancer Risk Assessment Algorithmic Tests	C61, Z12.5
81599	SelectMDx (MDx Health	Prostate Cancer Risk Assessment Algorithmic Tests	C61, Z12.5
0005U	ExoDx Prostate Test (ExosomeDx)	Prostate Cancer Risk Assessment Algorithmic Tests	C61, Z12.5
81551	ConfirmMDX (MDxHealth)	Prostate Cancer Diagnostic Algorithmic Tests	C61, Z12.5
81313	PCA3 testing (e.g. Progensa PCA3 Assay)	Prostate Cancer Diagnostic Algorithmic Tests	C61, Z12.5
0113U	MiPS (Mi-Prostate), University of Michigan MLabs	Prostate Cancer Diagnostic Algorithmic Tests	C61, Z12.5
81479	Prostate Core Mitomics Test	Prostate Cancer Diagnostic Algorithmic Tests	C61, Z12.5
0026U	ThyroSeq Genomic Classifier (University of Pittsburgh Medical Center)	Thyroid Cancer Diagnostic Algorithmic Tests	C73, D44.0, E04.1
0245U	ThyGeNEXT (Interpace Diagnostics)	Thyroid Cancer Diagnostic Algorithmic Tests	C73, D44.0, E04.1
0018U	ThyraMIR (Interpace Diagnostics)	Thyroid Cancer Diagnostic Algorithmic Tests	C73, D44.0, E04.1
81546	Afirma Genomic Sequencing Classifier (Veracyte)	Thyroid Cancer Diagnostic Algorithmic Tests	C73, D44.0, E04.1
0204U	Afirma Xpression Atlas (Veracyte)	Thyroid Cancer Diagnostic Algorithmic Tests	C73, D44.0, E04.1
81552, 0081U	DecisionDX-UM (Castle Bioscience, Inc.)	Uveal Melanoma Prognostic Algorithmic Tests	C69.00-C69.92

CPT® Codes	Example Tests (Labs)	Criteria Section	Common ICD Codes
81599	Uveal Melanoma Prognostic Test (LabCorp)	Uveal Melanoma Prognostic Algorithmic Tests	C69.00-C69.92
81529	DecisionDX-Melanoma (Castle Biosciences, Inc.)	Cutaneous Melanoma Prognostic Algorithmic Tests	C43.0-C43.9, C44.0-C44.99, C4A.0-C4A.9, D03.0-D03.9, D04.0-D04.9, Z12.83
0090U	myPath Melanoma ((Castle Biosciences Inc)	Cutaneous Melanoma Prognostic Algorithmic Tests	D22-D23, Z12.83
0089U	Pigmented Lesion Assay (DermTech)	Cutaneous Melanoma Risk Assessment Algorithmic Tests	D22-D23, Z12.83
81503	OVA1 (Aspira)	Ovarian Cancer Diagnostic Algorithmic Tests	D27.0-D27.9, D39.10-D39.12, D39.9, D49.59, D49.9
0003U	Overa (Aspira)	Ovarian Cancer Diagnostic Algorithmic Tests	D27.0-D27.9, D39.10-D39.12, D39.9, D49.59, D49.9
81500	ROMA (Risk of Ovarian Malignancy Algorithm) (Roche Diagnostics)	Ovarian Cancer Diagnostic Algorithmic Tests	D27.0-D27.9, D39.10-D39.12, D39.9, D49.59, D49.9
81535	ChemoFx	Gynecologic Cancer Treatment Algorithmic Tests	C51-C57
81536	ChemoFx - Additional Drug	Gynecologic Cancer Treatment Algorithmic Tests	C51-C57
81538	VeriStrat (Biodesix)	Lung Cancer Treatment Algorithmic Tests	C34, D38.1, D38.6
81599	DetermaRx (Oncocyte)	Lung Cancer Treatment Algorithmic Tests	C34, D38.1, D38.6
0080U	Nodify XL2 (Biodesix)	Lung Cancer Treatment Algorithmic Tests	R91.1
0092U	REVEAL Lung Nodule Characterization (MagArray)	Lung Cancer Treatment Algorithmic Tests	R91.1

CPT® Codes	Example Tests (Labs)	Criteria Section	Common ICD Codes
81599	Percepta Bronchial Genomic Classifier (Veracyte)	Lung Cancer Treatment Algorithmic Tests	R91.1
81599	Cxbladder Triage (Pacific Edge)	Bladder Cancer Diagnostic and Recurrence Algorithmic Tests	C67.0-C67.9, D09.0, D49.4, R31.9, Z85.51
0012M	Cxbladder Detect (Pacific Edge)	Bladder Cancer Diagnostic and Recurrence Algorithmic Tests	C67.0-C67.9, D09.0, D49.4, R31.9, Z85.51
0013M	Cxbladder Monitor (Pacific Edge)	Bladder Cancer Diagnostic and Recurrence Algorithmic Tests	C67.0-C67.9, D09.0, D49.4, R31.9, Z85.51
81599	Xpert Bladder Cancer Monitor (Cepheid)	Bladder Cancer Diagnostic and Recurrence Algorithmic Tests	C67.0-C67.9, D09.0, D49.4, R31.9, Z85.51
86294	BTA *stat*® (Polymedco)	Bladder Cancer Diagnostic and Recurrence Algorithmic Tests	C67.0-C67.9, D09.0, D49.4, R31.9, Z85.51
86386	Alere NMP22® (Alere)	Urinary Tract Cancer Recurrence Algorithmic Tests	C67.0-C67.9, D09.0, D49.4, R31.9, Z85.51
86386	Alere NMP22® BladderChek® (Alere)	Urinary Tract Cancer Recurrence Algorithmic Tests	C67.0-C67.9, D09.0, D49.4, R31.9, Z85.51
81479	PancraGEN (Interpace Diagnostics)	Pancreatic Cyst Risk Assessment Algorithmic Tests	C25
81504	Tissue of Origin (Cancer Genetics Inc.)	Cancer of Unknown Primary Gene Expression Profiling Tests	C79.9, C80.0, C80.1
81540	CancerTYPE ID (Biotheranostics)	Cancer of Unknown Primary Gene Expression Profiling Tests	C79.9, C80.0, C80.1
81599	riskScore (Myriad Genetics)	Breast Cancer Polygenic Risk Score Tests	Z13.71-Z13.79 Z80.3
81599	AmbryScore-Breast (Ambry Genetics)	Breast Cancer Polygenic Risk Score Tests	Z13.71-Z13.79

CPT® Codes	Example Tests (Labs)	Criteria Section	Common ICD Codes
81599	BrevaGen (Pathogen Sciences Laboratories)	Breast Cancer Polygenic Risk Score Tests	Z80.3
81599	BrevaGen*plus* (Pathogen Sciences Laboratories)	Breast Cancer Polygenic Risk Score Tests	Z13.71-Z13.79
81599	AmbryScore-Prostate (Ambry Genetics)	Prostate Cancer Polygenic Risk Score Tests	C61, R97.2, Z19.1-Z19.2, Z80.42
81599	MyPRS (Signal Genetics)	Multiple Myeloma Polygenic Risk Score Tests	C90.00-C90.02
0083U	Onco4D (Animated Dynamics, Inc.)	Oncology: Test-Specific Algorithmic Tests	N/A
0174U	LC-MS/MS Targeted Proteomic Assay (OncoOmicDx laboratory)	Oncology: Test-Specific Algorithmic Tests	N/A
0067U	BBDRisk Dx (Silbiotech)	Oncology: Test-Specific Algorithmic Tests	N/A
0220U	PreciseDx Breast Cancer Test (PreciseDx)	Oncology: Test-Specific Algorithmic Tests	N/A
0120U	Lymph3Cx Lymphoma Molecular Subtyping Assay	Oncology: Test-Specific Algorithmic Tests	N/A

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

- ***CP.MP.237 Oncology: Molecular Analysis of Solid Tumors and Hematologic Malignancies*** for criteria related to DNA testing of a solid tumor or a blood cancer.

- ***CP.MP.225 Genetic Testing: Hereditary Cancer Susceptibility Syndromes*** for criteria related to genetic testing to determine if an individual has an inherited cancer susceptibility syndrome.

- ***CP.MP.238 Oncology: Cancer Screening*** for criteria related to the use of non-invasive fecal, urine or blood tests for screening for cancer.

- ***CP.MP.239 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.

- ***CP.MP.222 Genetic Testing: General Approach to Genetic Testing*** for criteria related to algorithmic testing in oncology that is not specifically discussed in this or another non-general policy.

Policy/Criteria

Breast Cancer

Breast Cancer Treatment and Prognostic Algorithmic Tests

I. It is the policy of health plans affiliated with Centene Corporation® that the use of a breast cancer treatment and prognostic algorithmic test (e.g., Oncotype DX Breast Recurrence Score) (81519, S3854) is considered **medically necessary** when meeting all of the following:

   A. The member/enrollee is a female with primary, invasive breast cancer,

   B. The tumor meets **all** of the following characteristics:

      1. Hormone receptor-positive (ie, estrogen receptor-positive or progesterone receptor-positive),

      2. Human epidermal growth factor receptor 2 (HER2)- negative,

      3. Anatomic stage I or II,

      4. Node-negative (lymph nodes with micrometastases [≤2 mm in size] are considered node-negative for this policy statement) or 1 - 3 lymph node positive,

   C. The member/enrollee is considering treatment with adjuvant endocrine therapy (eg, tamoxifen, aromatase inhibitors).

II. It is the policy of health plans affiliated with Centene Corporation® that current evidence does not support the use of a breast cancer treatment and prognostic algorithmic test (e.g., Oncotype DX Breast Recurrence Score) (81519, S3854) in men with breast cancer.

III. It is the policy of health plans affiliated with Centene Corporation® that current evidence does not support the use of a breast cancer treatment and prognostic algorithmic test (e.g., Oncotype DX Breast Recurrence Score) (81519, S3854) for all other indications.

Hormone Receptor Positive Breast Cancer Prognostic Algorithmic Tests

I. It is the policy of health plans affiliated with Centene Corporation® that the use of a hormone receptor positive breast cancer prognostic algorithmic test (e.g., Endopredict, Prosigna, Breast Cancer Index) (S3854, 81522, 81520, 81518, 0008M) is considered **medically necessary** when meeting both of the following:

   A. The member/enrollee is a female with primary, invasive breast cancer,

B. The tumor meets **all** of the following characteristics:

1. Hormone receptor-positive (ie, estrogen receptor-positive or progesterone receptor-positive);

2. Human epidermal growth factor receptor 2 (HER2)- negative;

3. Anatomic stage I or II;

4. Node negative or one to three positive nodes;

C. The member/enrollee is considering treatment with adjuvant endocrine therapy (eg, tamoxifen, aromatase inhibitors).

II. It is the policy of health plans affiliated with Centene Corporation® that current evidence does not support the use of a hormone receptor positive breast cancer prognostic algorithmic test (e.g., Endopredict, Prosigna, Breast Cancer Index) (S3854, 81522, 81520, 81518, 0008M) in men with breast cancer.

III. It is the policy of health plans affiliated with Centene Corporation® that current evidence does not support the use of a hormone receptor positive breast cancer prognostic algorithmic test (e.g., Endopredict, Prosigna, Breast Cancer Index) (S3854, 81522, 81520, 81518, 0008M) for all other indications.

Hormone Receptor Agnostic Breast Cancer Prognostic Algorithmic Tests

I. It is the policy of health plans affiliated with Centene Corporation® that the use of a hormone receptor agnostic breast cancer prognostic algorithmic test (e.g., Mammaprint) (S3854, 81521) is considered **medically necessary** when meeting all of the following:

A. The member/enrollee is a female with primary, invasive breast cancer,

B. The tumor meets **all** of the following characteristics:

1. Hormone receptor-positive (ie, estrogen receptor-positive or progesterone receptor-positive) or hormone receptor-negative;

2. Human epidermal growth factor receptor 2 (HER2)- negative;

3. Anatomic stage I or II;

4. Node-negative or one to three positive nodes;

C. The member/enrollee is considering treatment with adjuvant endocrine therapy (eg, tamoxifen, aromatase inhibitors).

II. It is the policy of health plans affiliated with Centene Corporation® that current evidence does not support the use of a hormone receptor agnostic breast cancer prognostic algorithmic test (e.g., Mammaprint) (81521) in men with breast cancer.

III.   It is the policy of health plans affiliated with Centene Corporation® that current evidence does not support the use of a hormone receptor agnostic breast cancer prognostic algorithmic test (e.g., Mammaprint) (81521) for all other indications.

Gene Expression Profiling Breast Cancer Subtyping Tests
   I.   It is the policy of health plans affiliated with Centene Corporation® that current evidence does not support gene expression profiling breast cancer subtyping tests (e.g., BluePrint, Insight TNBCtype) (0153U, 81599).

Breast DCIS Prognostic Algorithmic Tests
   I.   It is the policy of health plans affiliated with Centene Corporation® that current evidence does not support breast DCIS prognostic algorithmic tests (e.g., OncotypeDX Breast DCIS Score) (0045U).

Colorectal Cancer
Colorectal Cancer Prognostic Algorithmic Tests
   I.   It is the policy of health plans affiliated with Centene Corporation® that current evidence does not support colorectal cancer prognostic algorithmic tests (e.g. OncotypeDx Colon Recurrence Score, GeneFX Colon) (81525, 81599).

Prostate Cancer
Prostate Cancer Treatment and Prognostic Algorithmic Tests
   I.   It is the policy of health plans affiliated with Centene Corporation® that the use of a prostate cancer treatment and prognostic algorithmic test (i.e. Prolaris, Decipher Prostate Cancer Genomic Classifier, Oncotype DX Prostate) (81541, 81542, 0047U) is considered **medically necessary** when:
      A. The member/enrollee meets all of the following:
         1. The member/enrollee has low risk, favorable intermediate risk prostate cancer,
         2. The member/enrollee has a life expectancy of $\geq$ 10 years.

   II.   It is the policy of health plans affiliated with Centene Corporation® that the use of a prostate cancer treatment and prognostic algorithmic test (i.e. Prolaris, Decipher Prostate Cancer Genomic Classifer) (81541, 81542) is considered **medically necessary** when:
      A. The member/enrollee meets all of the following:
         1. The member/enrollee has unfavorable intermediate- and high-risk prostate cancer
         2. The member/enrollee has a life expectancy of $\geq$ 10 years.

   III.   It is the policy of health plans affiliated with Centene Corporation® that current evidence does not support the use of a prostate cancer treatment and prognostic

algorithmic test (e.g. Prolaris, Decipher Prostate Cancer Genomic Classifier) (81541, 81542) for all other indications.

Prostate Cancer Risk Assessment Algorithmic Tests
    I.   It is the policy of health plans affiliated with Centene Corporation® that current evidence does not support prostate cancer risk assessment algorithmic tests (e.g., 4Kscore (81539), Prostate Health Index (84153, 84154, 86316), SelectMDx (81599), ExoDx Prostate Test (0005U), Apfinity (0021U)).

Prostate Cancer Diagnostic Algorithmic Tests
    I.   It is the policy of health plans affiliated with Centene Corporation® that current evidence does not support prostate cancer diagnostic algorithmic tests (e.g. ConfirmMDx (81551), Progensa PCA3 Assay (81313), MiPS (0013U), Prostate Core Mitomics Test (81479)).

Thyroid Cancer
Thyroid Cancer Diagnostic Algorithmic Tests
    I.   It is the policy of health plans affiliated with Centene Corporation® that the use of a thyroid cancer diagnostic algorithmic test (e.g., ThyroSeq Genomic Classifier, ThyGeNEXT, ThyraMIR, Afirma Genomic Sequence Classifier, Afirma Gene Expression Classifier, Afirma MTC, Afirma Xpression Atlas) (0026U, 0018U, 0208U, 0204U, 0245U, 81546) in fine needle aspirates of thyroid nodules is considered **medically necessary** when meeting all of the following:

        A. The fine needle aspirates showed indeterminate or suspicious cytologic findings[1];

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

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

    II.   It is the policy of health plans affiliated with Centene Corporation® that current evidence does not support the use of a thyroid cancer diagnostic algorithmic test (e.g., ThyroSeq Genomic Classifier, ThyGeNEXT, ThyraMIR, Afirma Genomic Sequence Classifier, Afirma Gene Expression Classifier, Afirma MTC, Afirma Xpression Atlas) (0026U, 0018U, 0208U, 0204U, 0245U, 81546) in fine needle aspirates of thyroid nodules for all other indications.

Uveal Melanoma
Uveal Melanoma Prognostic Algorithmic Tests
    I.   It is the policy of health plans affiliated with Centene Corporation® that the use of a uveal melanoma prognostic algorithmic test (e.g., DecisionDX-UM or Uveal Melanoma Prognostic Test) (81552, 0081U, 81599) is considered **medically necessary** when:

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

    II.   It is the policy of health plans affiliated with Centene Corporation® that current evidence does not support the use of a uveal melanoma prognostic algorithmic test (e.g.,

DecisionDX-UM or Uveal Melanoma Prognostic Test) (81552, 0081U, 81599) for all other indications.

Cutaneous Melanoma
Cutaneous Melanoma Prognostic Algorithmic Tests
   I.   It is the policy of health plans affiliated with Centene Corporation® that current evidence does not support cutaneous melanoma prognostic algorithmic tests (e.g., Decision-DX Melanoma) (81529).

Cutaneous Melanoma Diagnostic Algorithmic Tests
   I.   It is the policy of health plans affiliated with Centene Corporation® that current evidence does not support cutaneous melanoma diagnostic algorithmic tests (e.g. myPath) (0090U).

Cutaneous Melanoma Risk Assessment Algorithmic Tests
   I.   It is the policy of health plans affiliated with Centene Corporation® that current evidence does not support cutaneous melanoma risk assessment algorithmic tests (e.g. Pigmented Lesion Assay) (0089U).

Ovarian Cancer
Ovarian Cancer Diagnostic Algorithmic Tests
   I.   It is the policy of health plans affiliated with Centene Corporation® that current evidence does not support ovarian cancer diagnostic algorithmic tests (e.g., OVA1, Overa, and ROMA) (0003U, 81500, 81503) for all indications, including but not limited to:

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

Ovarian Cancer Treatment Algorithmic Tests
   I.   It is the policy of health plans affiliated with Centene Corporation® that ovarian cancer treatment algorithmic tests (e.g., myChoice CDx) (0172U, 81479) are considered **medically necessary** when meeting all of the following:

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

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

        C. One of the following:

                1. The member/enrollee has had previous germline or somatic tumor genetic testing for *BRCA1* and *BRCA2* and the results were negative,

2. Testing is being done in lieu of germline *BRCA1* and *BRCA2* analysis.

II. It is the policy of health plans affiliated with Centene Corporation® that current evidence does not support ovarian cancer treatment algorithmic tests (e.g., myChoice CDx) (0172U, 81479) for all other indications.

Gynecologic Cancer
Gynecologic Cancer Treatment Algorithmic Tests
I. Gynecologic cancer treatment algorithmic tests (e.g. ChemoFX, ChemoFX - Additional Drug) (81535, 81536) in the assessment of gynecological cancers are considered **investigational.**

Lung Cancer
Lung Cancer Treatment Algorithmic Tests
I. It is the policy of health plans affiliated with Centene Corporation® that current evidence does not support lung cancer treatment algorithmic tests (e.g. Veristrat, DetermaRx) (81538, 81599).

Lung Cancer Diagnostic Algorithmic Tests
I. It is the policy of health plans affiliated with Centene Corporation® that current evidence does not support lung cancer diagnostic algorithmic test (e.g. NodifyXL2, Reveal Lung Nodule Characterization, Percepta Bronchial Genomic Classifier) (0080U, 0092U, 81599), including for member/enrollees with undiagnosed pulmonary nodules.

Bladder and Urinary Tract Cancer
Bladder Cancer Diagnostic and Recurrence Algorithmic Tests
I. It is the policy of health plans affiliated with Centene Corporation® that current evidence does not support bladder cancer diagnostic and recurrence algorithmic tests (e.g., Cxbladder Triage, Cxbladder Detect, Cxbladder Monitor, Xpert Bladder Cancer Monitor, BTAstat) (0012M, 0013M, 81599, 86294).

Urinary Tract Cancer Recurrence Algorithmic Tests
I. It is the policy of health plans affiliated with Centene Corporation® that current evidence does not support urinary tract cancer recurrence algorithmic tests (e.g., Alere NMP22, Alere NMP22 BladderCheck) (86386).

Pancreatic Cancer
Pancreatic Cyst Risk Assessment Algorithmic Tests
I. It is the policy of health plans affiliated with Centene Corporation® that current evidence does not support pancreatic cyst risk assessment algorithmic tests (e.g., PancraGEN) (81479).

Cancer Of Unknown Primary
Cancer of Unknown Primary Gene Expression Profiling Tests
I. It is the policy of health plans affiliated with Centene Corporation® that current evidence does not support the use of a cancer of unknown primary gene expression profiling test (81504, 81540) to evaluate the site of origin of a tumor of unknown primary, or to distinguish a primary from a metastatic tumor.

Polygenic Risk Score Tests
Breast Cancer Polygenic Risk Score Tests
I.   It is the policy of health plans affiliated with Centene Corporation® that current evidence does not support the use of a breast cancer polygenic risk score test (81599).

Prostate Cancer Polygenic Risk Score Tests
I.   It is the policy of health plans affiliated with Centene Corporation® that current evidence does not support the use of a prostate cancer polygenic risk score test (e.g. AmbryScore) (81599).

Multiple Myeloma Polygenic Risk Score Tests
I.   It is the policy of health plans affiliated with Centene Corporation® that current evidence does not support the use of a multiple myeloma polygenic risk score test (e.g., myPRS) (81599).

Oncology: Test-Specific Algorithmic Tests
I.   It is the policy of health plans affiliated with Centene Corporation® that current evidence does not support the use of these specific oncology algorithmic tests:

   A. BBDRisk Dx™ (0067U)
   B. Onco4D™ (0083U)
   C. Lymph3Cx Lymphoma Molecular Subtyping Assay (0120U)
   D. LC-MS/MS Targeted Proteomic Assay (0174U)
   E. PreciseDxTM Breast Cancer Test (0220U)

Notes and Definitions
1. 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)

2. **<u>Somatic</u>** 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.

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 (ie, 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.

Background

National Comprehensive Cancer Network (NCCN):

Adjuvant Chemotherapy for Node-Negative Breast Cancer
Current NCCN guidelines on the use of multigene assays for consideration of addition of adjuvant systemic chemotherapy to adjuvant endocrine therapy for breast cancer (v.8.2021) recognize that multigene assays provide prognostic and therapy-predictive information that compliments T,N,M biomarker information and based on higher level evidence there is uniform NCCN consensus that the intervention is appropriate (category 1) and support strong consideration 21-gene RT-PCR assay (specifically OncotypeDx) to help estimate the likelihood of recurrence and the benefit from chemotherapy and cites this as the preferred test. The panel also recognizes other multigene expression assays to help predict risk of recurrence including MammaPrint (category 1), Endopredict, Breast Cancer Index and Prosignia (category 2A) for node-negative, ER+, HER2- breast cancer with pT1, pT2, or pT3; and pN0 and tumor less than 0.5 cm. They further state that only one of these assays should be ordered for an individual patient and tumor.

Adjuvant Chemotherapy for Node-Positive Breast Cancer
Current NCCN guidelines on the use of multigene assays for consideration of addition of adjuvant systemic chemotherapy to adjuvant endocrine therapy for breast cancer (v.8.2021) recognize that multigene assays provide prognostic and therapy-predictive information that compliments T,N,M biomarker information and based on lower level evidence there is uniform NCCN consensus that the intervention is appropriate (category 2A) and support the consideration of multigene assay to assess prognosis and determine chemotherapy benefit for node-positive, ER+, HER2- breast cancer with pN1mi (≤2 mm axillary node metastasis) or N1 (<4 nodes).

Extended Endocrine Therapy for Breast Cancer
Current NCCN guidelines (v.8.2021) provides a flow chart on adjuvant endocrine therapy recommendations and considerations, based on menopausal status at diagnosis and after 5 years of therapy, and on prior therapy history.

Predicting Recurrence of Colon Cancer
Current NCCN guidelines (v.2.2021) recognize that the use of multigene assays to inform the risk of recurrence is an emerging technology to aid in determination of adjuvant therapy; however, there is currently insufficient data to recommend the use of multigene assays to determine adjuvant therapy for stage II or III colon cancer.

Prostate Cancer Prognosis and Management
Current NCCN guidelines (v.1.2022) support the consideration of gene expression profiling for prostate cancer prognosis and management in men with low or favorable intermediate clinically localized disease, at the time of initial risk stratification (i.e. before treatment). Additionally, a subset of these tests are recommended for consideration in men with unfavorable intermediate- and high-risk disease.

Prostate Cancer Risk Assessment and Early Detection
Current NCCN guidelines (v.1.2021) support the consideration of biomarkers that improve the specificity of screening in patients with a PSA level greater than 3 ng/mL who have not yet had a biopsy and in men who had a negative biopsy but are thought to be at higher risk.
Current NCCN guidelines (v.1.2021) recommend considering the use of tests that improve specificity post-biopsy, including percent-free PSA, 4kscore, PHI, PCA3 and ConfirmMDx.

Thyroid Cancer
Current NCCN guidelines (v.2.2021) support the use of molecular diagnostics for thyroid nodules evaluated with FNA when lesions are suspicious for follicular or Hurthle cell neoplasms, atypia of undetermined significance or follicular lesions of undetermined significance.

Uveal Melanoma
Current NCCN guidelines (v.2.2021) 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.

Cutaneous Melanoma
Current NCCN guidelines (v.2.2021) 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.
Current NCCN guidelines (v.2.2021) also recognize that there are emerging technologies aiming to differentiate benign from malignant melanocytic neoplasms (e.g., IHC, CGH, FISH, GEP, SNP arrays, and NGS). The guideline states that these tests may facilitate interpretation of cases that are diagnostically uncertain and that these tests should be used as adjuncts to clinical and expert dermatopathologic examination and interpreted within the context of those findings.

Ovarian Cancer Risk
Current NCCN guidelines (v.1.2021) recognize the use of biomarker analysis for risk assessment for ovarian cancer in women with a pelvic mass as an emerging technology; however, there is currently insufficient data to recommend the use of biomarker analysis for determining risk for ovarian cancer.

Ovarian Cancer Treatment
Current NCCN guidelines (v.3.2021) recommend in the absence of a BRCA1/2 mutation homologous recombination deficiency (HRD) status may provide information on the magnitude of benefit of PARP inhibitor therapy.
The NCCN guideline for ovarian cancer (v.3.2021) recognizes that chemosensitivity/resistance assays are used in some situations where multiple equivalent chemotherapy options are available, however the current level of evidence is not sufficient to take the place of standard-of-care chemotherapy (category 3 recommendation).

Urinary Biomarkers for Bladder Cancer

Current NCCN guidelines (v.2.2021) support consideration for urinary urothelial tumor markers for high-risk patients with non-muscle-invasive bladder cancer (category 2b recommendation).

Pancreatic Cyst Risk Assessment Algorithmic Tests
Current NCCN guidelines (v.2.2021) 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%. The guidelines do not include recommendation or discussion for the use of molecular analysis of pancreatic cysts to stratify risk of cancer.

Genetic/Familial High Risk Assessment: Breast, Ovarian and Pancreatic
Current NCCN guidelines (v.1.2022) recognize the use of polygenic risk scores as an emerging technology in the risk assessment of cancer; however, there are significant limitations in the interpretation of polygenic risk scores and therefore polygenic risk scores should not be used for clinical management at this time.

Cancers of Unknown Primary (Occult Primary)
Current NCCN guidelines (v.2.2021) recognize the use of gene expression profiling as a tool that may be beneficial for diagnosis, but not necessarily clinical benefit. Gene sequencing to predict tissue of origin is not recommended (category 3 recommendation).

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 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/sBRCA1/2 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/sBRCA1/2, 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."

ASCO (2019) 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."

ASCO (2017) updated its evidence-based guidelines on the use of biomarkers to guide decisions on adjuvant systemic therapy for women with early-stage invasive breast cancer and published a focused update of those guidelines in 2019. The recommendations state that gene expression profiling biomarkers have been found to demonstrate clinical utility to guide decisions on the need for adjuvant systemic therapy in women with early-stage invasive breast cancer and known estrogen and progesterone and *HER2* status and are as follows:

Node-Negative
- For patients older than 50 years and whose tumors have Onco*type* DX recurrence scores of less than 26 and for patients age 50 years or younger whose tumors have Onco*type* DX recurrence scores of less than 16, there is little to no benefit from chemotherapy. Clinicians may offer endocrine therapy alone.
- For patients 50 years of age or younger with Onco*type* DX recurrence scores of 16 to 25, clinicians may offer chemoendocrine therapy.
- Patients with Onco*type* DX recurrence scores of greater than 30 should be considered candidates for chemoendocrine therapy.
- Based on Expert Panel consensus, oncologists may offer chemoendocrine therapy to patients with Onco*type* DX scores of 26 to 30.
- Clinician may use the EndoPredict 12-gene risk score to guide decisions on adjuvant systemic chemotherapy
- Clinician may use the Breast Cancer Index to guide decisions on adjuvant systemic therapy
- Clinician may use the MammaPrint 70-gene assay to guide decisions on adjuvant systemic therapy in women with high clinical risk per MINDACT categorization
- Clinician should **not** use the MammaPrint 70-gene assay to guide decisions on adjuvant systemic therapy in women with low clinical risk per MINDACT categorization
- Clinician may use the Prosigna PAM50 risk of recurrence score, in conjunction with other clinicopathologic variables, to guide decisions on adjuvant systemic therapy

Node-Positive (1-3 nodes)
- Clinician may use the MammaPrint 70-gene assay to guide decisions on adjuvant systemic therapy in women with high clinical risk per MINDACT categorization

ASCO (2011) published a clinical practice guideline update on the use of chemotherapy sensitivity and resistance assays which included the following summary recommendation:
"The use of [chemotherapy sensitivity and resistance assays] CSRAs to select chemotherapeutic agents for individual patients is not recommended outside of the clinical trial setting. Oncologists should make chemotherapy treatment recommendations based on published reports of clinical trials and a patient's health status and treatment preferences. Because the in vitro analytic strategy has potential importance, participation in clinical trials evaluating these technologies remains a priority."

American Urological Association
Prostate Cancer Management
The American Urological Association, American Society for Radiation Oncology, and the Society of Urologic Oncology (2017, 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 or in the follow-up of patients on active surveillance.

Prostate Cancer Early Detection
The American Urological Association (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. 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.
The American Urological Association and the Society of Abdominal Radiology (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.

Urinary Biomarkers for Bladder Cancer
The American Urological Association and Society of Urologic Oncology (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.

- 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

- Urinary biomarker analysis may be used to assess response to intravesical BCG (UroVysion® FISH) and adjudicate equivocal cytology (UroVysion® FISH and ImmunoCyt™) in a patient with NMIBC.

American Association of Clinical Endocrinologists
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.

- There is insufficient evidence to recommend either in favor of or against the use of gene expression classifiers for cytologically indeterminate nodules.

- With the exception of mutations such as BRAFV600E, there is insufficient evidence to recommend in favor of or against the use of mutation testing to determine the extent of surgery.

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, molecular testing may be used to supplement malignancy risk assessment in lieu or proceeding directly with either surveillance or diagnostic surgery.

- Molecular testing may be used to supplement risk assessment in lieu of proceeding directly with surgery.

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:

- 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.

- Ancillary diagnostic molecular techniques (eg, CGH, FISH, GEP) may be used for equivocal melanocytic neoplasms.

- There is insufficient evidence of benefit to recommend routine use of currently available prognostic molecular tests, including GEP, for prognosis of CM.

- 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.

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 and MCNs."

Cutaneous Melanoma Prognostic Algorithmic Tests

Concert Genetics

This review focused on peer-reviewed, published evidence of the clinical utility of DermTech PLA through August, 2021. 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.

Lung Cancer Treatment Algorithmic Tests

Concert Genetics

This review focused on peer-reviewed, published evidence of the clinical utility of VeriStrat® through September 2021. 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. A total of 69 abstracts from these sources were reviewed, and 44 full text publications were evaluated. 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 Classifer, and Reveal Lung Nodule Characterization through October 2021. 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. A total of 53 abstracts from these sources were reviewed, and 15 full text publications were evaluated. At the present time, NodifyXL2, Percepta Bronchial Genomic Classifer, 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.

Coding Implications
This clinical policy references Current Procedural Terminology (CPT®). CPT® is a registered trademark of the American Medical Association. All CPT codes and descriptions are copyrighted 2021, American Medical Association. All rights reserved. CPT codes and CPT descriptions are from the current manuals and those included herein are not intended to be all-inclusive and are included for informational purposes only. Codes referenced in this clinical policy are for informational purposes only. Inclusion or exclusion of any codes does not guarantee coverage. Providers should reference the most up-to-date sources of professional coding guidance prior to the submission of claims for reimbursement of covered services.

Reviews, Revisions, and Approvals	Revision Date	Approval Date
Policy developed.	02/22	02/22

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Important Reminder

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

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

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and regulatory requirements relating to provider notification. If there is a discrepancy between the effective date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment or medical care. It is not intended to dictate to providers how to practice medicine. Providers are expected to exercise professional medical judgment in providing the most appropriate care, and are solely responsible for the medical advice and treatment of member/enrollees. This clinical policy is not intended to recommend treatment for member/enrollees. Member/enrollees should consult with their treating physician in connection with diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent judgment and over whom the Health Plan has no control or right of control. Providers are not agents or employees of the Health Plan.

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

Note: For Medicare member/enrollees, to ensure consistency with the Medicare National Coverage Determinations (NCD) and Local Coverage Determinations (LCD), all applicable NCDs, LCDs, and Medicare Coverage Articles should be reviewed prior to applying the criteria set forth in this clinical policy. Refer to the CMS website at http://www.cms.gov for additional information.