Revision log

CONCERT GENETICS ONCOLOGY: ALGORITHMIC TESTING

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

OVERVIEW

Oncology prognostic and algorithmic tests are tests that combine biomarkers and/or clinical data into an algorithm to generate a disease risk assessment, prognostic result, or clinical recommendation for treatment. Testing methodologies commonly include Gene Expression Profiling (GEP), which analyzes messenger RNA (mRNA) typically of multiple genes simultaneously, multimarker serum analysis, single-nucleotide variant testing, plasma-based proteomic analysis, and incorporation of other clinical data into test outputs.

In addition to the tests previously mentioned, proteogenomic testing is an emerging area. Proteogenomic testing combines the analysis of DNA with RNA and/or protein analysis. The current focus of proteogenomics is primarily on diagnostic and prognostic analyses in various cancers. Results also seek to provide potential treatment options, and to which treatments the cancer may be resistant.

Polygenic Risk Score (PRS) tests are another emerging area. These tests combine information from population SNP analysis with clinical and family history and aim to give additional insight into an individual's lifetime risk to develop a specific cancer.

Results of prognostic and algorithmic tests are often reported as a recurrence score, probability of distant disease recurrence, malignant potential, probable site of origin, or cancer risk score. Additionally, the output of these prognostic and algorithmic tests may be useful to assist in surgical and management decision-making and to identify individuals who may benefit from adjuvant therapy.

POLICY REFERENCE TABLE

Coding Implications

This clinical policy references Current Procedural Terminology (CPT®). CPT® is a registered trademark of the American Medical Association. All CPT codes and descriptions are copyrighted 2022, 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.

Please see the Concert Genetics Platform for a comprehensive list of registered tests.

Criteria Sections	Example Tests, Labs	Common CPT Codes	Common ICD Codes	Ref
Breast Cancer				
Breast Cancer Treatment and Prognostic Algorithmic Tests	Oncotype Dx Breast Recurrence Score (Exact Sciences)	81519, S3854	C50.011-C50.92, Z17.0	1
Breast Cancer Extended Endocrine Therapy Algorithmic Tests	Breast Cancer Index (bioTheranostics)	81518, S3854	C50.011-C50.92, Z17.0	1, 29
Breast Cancer Prognostic Algorithmic Tests	EndoPredict (Myriad)	81522, S3854	C50, Z17.0, Z17.1	1, 29
	MammaPrint (Agendia, Inc.)	81521, 81523 S3854		
	Prosigna Assay (NeoGenomics)	81520		
Gene Expression Profiling Breast Cancer Subtyping Tests	BluePrint (Agendia, Inc.)	81599, S3854	C50-C50.929	1
	Insight TNBCtype (Insight Molecular Labs)	0153U		
Breast DCIS Prognostic Algorithmic Tests	Oncotype DX Breast DCIS Score (Exact Sciences)	0045U	D05.1	1
	DCISion RT (PreludeDx)	0295U		

Colorectal Cancer				
Colorectal Cancer Prognostic Algorithmic Tests	Oncotype DX Colon Recurrence Score (Exact Sciences)	81525	C18.0-C18.9	2
	miR-31now (GoPath Laboratories)	0069U		
	Immunoscore (HalioDx)	0261U		
Prostate Cancer				
Prostate Cancer Treatment and Prognostic Algorithmic Tests	Oncotype DX Genomic Prostate Score (MDxHealth)	0047U	C61	3, 19
	Decipher Prostate Biopsy Genomic 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	C61, Z12.5	4, 27, 28
	Prostate Health Index (ARUP Laboratories)	84153, 84154, 86316		
	SelectMDx for Prostate Cancer (MDxHealth)	0339U		
	ExoDx Prostate Test (ExosomeDx)	0005U		
	IsoPSA (Cleveland Diagnostics, Inc)	0359U		
	MyProstateScore (Lynx DX)	0113U		
Prostate Cancer Diagnostic Algorithmic Tests	ConfirmMDx for Prostate Cancer (MDxHealth)	81551	C61, Z12.5	5, 28
	PanGIA (Genetics Institute of America)	0228U		
	Progensa (Avero Diagnostics)	81313		

Thyroid Cancer				
Thyroid Cancer Diagnostic Algorithmic Tests	ThyroSeq Genomic Classifier (CBLPath)	0026U	C73, D44.0, E04.1	6, 7, 8
	ThyGeNEXT (Interpace Diagnostics)	0245U		
	ThyraMIR (Interpace Diagnostics)	0018U		
	Afirma Genomic Sequencing Classifier (Veracyte)	81546		
	Afirma Xpression Atlas (Veracyte)	0204U		
	ThyroSeq CRC (UPMC)	0287U		
Uveal Melanoma				
Uveal Melanoma Prognostic Algorithmic Tests	DecisionDx-UM (Castle Bioscience, Inc.)	81552	C69	9
Cutaneous Melanoma				
Cutaneous Melanoma Prognostic Algorithmic Tests	DecisionDx-Melanoma (Castle Biosciences, Inc.)	81529	C43, D03.0-D03.9, Z12.83	10, 11
	AMBLor (AMLo Biosciences)	0387U		
Cutaneous Melanoma Diagnostic Algorithmic Tests	myPath Melanoma (Castle Biosciences, Inc.)	0090U	D22.0-D22.9, D48.5, D49.2, Z12.83	10, 11, 26
	DecisionDx-DiffDx-Melanoma (Castle Biosciences, Inc.)	0314U		
Cutaneous Melanoma Risk Assessment Algorithmic Tests	Pigmented Lesion Assay (DermTech)	0089U	D22-D23, Z12.83	23
Ovarian Cancer				

Ovarian Cancer Diagnostic Algorithmic Tests	OVA1 (Aspira Women's Health)	81503	D27.0, D27.1, D27.9, D39.10-D39.12, D39.9, D49.59, D49.9	12
	Overa (Aspira Women's Health)	0003U		
	Risk of Ovarian Malignancy (ROMA) (Labcorp)	81500		
	OvaWatch (Aspira Women's Health)	0375U		
Ovarian Cancer Treatment Algorithmic Tests	myChoice CDx (Myriad Genetics)	0172U	C48, C56, C57.0	12, 20
Gynecologic Cancer				
Gynecologic Cancer Treatment Algorithmic Tests	ChemoFx (Helomics Corporation)	81535	C51-C57	12, 17, 18
	ChemoFx - Additional Drug (Helomics Corporation)	81536		
Lung Cancer				
Lung Cancer Diagnostic Algorithmic Tests	Nodify XL2 (Biodesix)	0080U	R91.1	25
	REVEAL Lung Nodule Characterization (MagArray)	0092U		
	Percepta Bronchial Genomic Classifier (Veracyte)	81479		
	OncobiotaLUNG (Micronoma)	0395U		
Lung Cancer Treatment Algorithmic Tests	VeriStrat (Biodesix)	81538	C34, D38.1, D38.6	24
	DetermaRx (Oncocyte)	0288U		
Bladder and Urinary Tract Cancer				
Bladder/Urinary TractCancer Diagnostic, Treatment and Recurrence Algorithmic Tests	Cxbladder Triage (Pacific Edge)	0363U	C67, D09.0, D49.4, R31.9, Z85.51	13, 14
	Cxbladder Detect (Pacific Edge)	0012M		
	Cxbladder Monitor (Pacific Edge)	0013M		
	Oncuria Detect (DiaCarta	0365U		

	Clinical Lab)			
	Oncuria Monitor (DiaCarta Clinical Lab)	0366U		
	Oncuria Predict (DiaCarta Clinical Lab)	0367U		
	Decipher Bladder (Veracyte)	0016M		
Pancreatic Cancer				
Pancreatic Cyst Risk Assessment Algorithmic Tests	PancraGEN (Interpace Diagnostics)	81479	D49, K86.2	21, 22
	Pancreatic Cyst Fluid NGS Analysis-PancreaSeq (Univ of Pittsburgh Medical Center)	0313U		
Cancer of Unknown Primary				
Cancer of Unknown Primary Gene Expression Profiling Tests	CancerTYPE ID (Biotheranostics)	81540	C79.9, C80.0, C80.1	16
Polygenic Risk Score Tests				
Breast Cancer Polygenic Risk Score Tests	BrevaGen*plus* (Pathogen Sciences Laboratories)	81599	Z13.71, Z13.79 Z80.3	15
Oncology: Test-Specific Not Covered Algorithmic Tests				
Oncology: Test-Specific Not Covered Algorithmic Tests	BBDRisk Dx (Silbiotech)	0067U		
		0120U		

	Lymph3Cx Lymphoma Molecular Subtyping Assay (Mayo Clinic Laboratories)			

OTHER RELATED POLICIES

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

- ***Oncology: Molecular Analysis of Solid Tumors and Hematologic Malignancies*** for criteria related to DNA testing of a solid tumor or a blood cancer.
- ***Genetic Testing: Hereditary Cancer Susceptibility Syndromes*** for criteria related to genetic testing to determine if an individual has an inherited cancer susceptibility syndrome.
- ***Oncology: Cancer Screening*** for criteria related to the use of non-invasive fecal, urine or blood tests for screening for cancer.
- **Oncology:** ***Circulating Tumor DNA and Circulating Tumor Cells (Liquid Biopsy)*** for criteria related to circulating tumor DNA (ctDNA) or circulating tumor cell testing performed on peripheral blood for cancer diagnosis, management and surveillance.
- ***Genetic Testing: General Approach to Genetic and Molecular Testing*** for criteria related to algorithmic testing in oncology that is not specifically discussed in this or another non-general policy.

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CRITERIA

It is the policy of health plans affiliated with Centene Corporation® that the specific genetic testing noted below is **medically necessary** when meeting the related criteria:

BREAST CANCER

Breast Cancer Treatment and Prognostic Algorithmic Tests

I. The use of the breast cancer treatment and prognostic algorithmic test Oncotype DX Breast Recurrence Score (81519, S3854) is considered **medically necessary** in all patients, regardless of gender, when:

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

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

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

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

   E. The member/enrollee meets one of the following (regardless of menopausal status):

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

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

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

II. The use of a breast cancer treatment and prognostic algorithmic test (i.e., Oncotype DX Breast Recurrence Score (81519, S3854) is considered **investigational** for all other indications.

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Breast Cancer Extended Endocrine Therapy Algorithmic Tests

I. The use of the breast cancer extended endocrine therapy test Breast Cancer Index (BCI) (S3854, 81518) is considered **medically necessary** when:

   A. The member/enrollee is female, **AND**

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

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

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

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

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

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

   H. The member/enrollee meets one of the following (regardless of menopausal status):

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

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

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

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

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

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Breast Cancer Prognostic Algorithmic Tests

I. The use of a breast cancer prognostic algorithmic test (i.e., EndoPredict, Prosigna, MammaPrint) (S3854, 81520, 81521, 81522, 81523) is considered **medically necessary** when:

   A. The member/enrollee is female, **AND**

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

      1. Postmenopausal status, **OR**

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

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

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

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

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

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

      1. Node negative, **OR**

      2. 1-3 positive nodes*.

II. The use of a breast cancer prognostic algorithmic test (i.e., EndoPredict, Prosigna, MammaPrint) (S3854, 81520, 81521, 81522, 81523) in individuals with 4 or more positive nodes is considered **investigational**.

III. The use of the breast cancer prognostic algorithmic test Prosigna (81520) in individuals with node-negative breast cancer is considered **investigational.**

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

V. The use of a breast cancer prognostic algorithmic test (i.e., EndoPredict, Prosigna, MammaPrint) (S3854, 81520, 81521, 81522, 81523) is considered **investigational** for all other indications.

*Prosigna is indicated for node negative disease, but **not** for disease with 1-3 positive nodes. EndoPredict and Mammaprint are indicated for node negative disease and for disease with 1-3 positive nodes.

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Gene Expression Profiling Breast Cancer Subtyping Tests

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

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Breast DCIS Prognostic Algorithmic Tests

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

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COLORECTAL CANCER

Colorectal Cancer Prognostic Algorithmic Tests

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

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PROSTATE CANCER

Prostate Cancer Treatment and Prognostic Algorithmic Tests

I. The use of a prostate cancer treatment and prognostic algorithmic test (i.e., Oncotype DX Prostate (0047U), Prolaris (81541) is considered **medically necessary** when:

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

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

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

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

   A. For initial risk stratification, the member/enrollee meets the following:

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

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

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

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

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

   B. The member/enrollee meets the following:

      1. The member/enrollee has a life expectancy of more than 5 years, **AND**

2. The test is being used to inform adjuvant treatment and counseling for risk stratification, as an alternative to PSADT, **OR**

3. Adverse features were found post-radical prostatectomy, including but not limited to PSA persistence/recurrence.

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

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Prostate Cancer Risk Assessment Algorithmic Tests

I. Prostate cancer risk assessment algorithmic tests (81539, 84153, 84154, 86316, 0113U, 0339U, 0005U, 0359U) are considered **investigational**.

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Prostate Cancer Diagnostic Algorithmic Tests

I. Prostate cancer diagnostic algorithmic tests (81551, 81313, 0228U) are considered **investigational**.

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THYROID CANCER

Thyroid Cancer Diagnostic Algorithmic Tests

I. The use of a thyroid cancer diagnostic algorithmic test (0026U, 0018U, 0204U, 0245U, 81546) in fine needle aspirates of thyroid nodules is considered **medically necessary** when:

A. The fine needle aspirate showed indeterminate cytologic findings, **AND**

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

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

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

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UVEAL MELANOMA

Uveal Melanoma Prognostic Algorithmic Tests

I. The use of a uveal melanoma prognostic algorithmic test (81552) is considered **medically necessary** when:

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

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

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CUTANEOUS MELANOMA

Cutaneous Melanoma Prognostic Algorithmic Tests

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

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Cutaneous Melanoma Diagnostic Algorithmic Tests

I. Cutaneous melanoma diagnostic algorithmic tests (0090U, 0314U) are considered **medically necessary** when:

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

II. Cutaneous melanoma diagnostic algorithmic tests (0090U, 0314U) are considered **investigational** for all other indications, including:

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

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Cutaneous Melanoma Risk Assessment Algorithmic Tests

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

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OVARIAN CANCER

Ovarian Cancer Diagnostic Algorithmic Tests

I. Ovarian cancer diagnostic algorithmic tests (i.e., OVA1, Overa, ROMA, and OvaWatch) (0003U, 81500, 81503, 0375U) are considered **investigational** for all indications, including but not limited to:

   A. Preoperative evaluation of adnexal masses to triage for malignancy

   B. Screening for ovarian cancer

   C. Selecting patients for surgery for an adnexal mass

D. Evaluation of patients with clinical or radiologic evidence of malignancy
E. Evaluation of patients with nonspecific signs or symptoms suggesting possible malignancy
F. Postoperative testing and monitoring to assess surgical outcome and/or to detect recurrent malignant disease following treatment

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Ovarian Cancer Treatment Algorithmic Tests

I. Ovarian cancer treatment algorithmic tests (0172U) are considered **medically necessary** when:

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

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

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

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GYNECOLOGIC CANCER

Gynecologic Cancer Treatment Algorithmic Tests

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

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LUNG CANCER

Lung Cancer Diagnostic Algorithmic Tests

I. Lung cancer diagnostic algorithmic tests (0080U, 0092U, 81599) are considered **investigational**, including for member/enrollees with undiagnosed pulmonary nodules.

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Lung Cancer Treatment Algorithmic Tests

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

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BLADDER AND URINARY TRACT CANCER

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

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

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PANCREATIC CANCER

Pancreatic Cyst Risk Assessment Algorithmic Tests

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

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CANCER OF UNKNOWN PRIMARY

Cancer of Unknown Primary Gene Expression Profiling Tests

I. The use of a cancer of unknown primary gene expression profiling test (81540) to evaluate the site of origin of a tumor of unknown primary, or to distinguish a primary from a metastatic tumor is considered **investigational**.

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POLYGENIC RISK SCORE TESTS

Breast Cancer Polygenic Risk Score Tests

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

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ONCOLOGY: TEST-SPECIFIC NOT COVERED ALGORITHMIC TESTS

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

A. BBDRisk Dx (0067U)

B. Lymph3Cx Lymphoma Molecular Subtyping Assay (0120U)

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CLINICAL CONSIDERATIONS

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

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

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NOTES AND 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. **Prostate cancer pathology risk stratification** is described in detail in the NCCN Prostate Cancer 1.2023 guidelines (p. PROS-2).

6. **PSA persistence/recurrence** is defined in the NCCN Prostate Cancer guidelines (1.2023) as failure of PSA to fall to undetectable levels (PSA persistence) or undetectable PSA after RP with a subsequent detectable PSA that increases on 2 or more determinations (PSA recurrence) or that increases to PSA greater than 0.1 ng/mL (p. PROS-10)

7. **Adverse pathologic features** are discussed in the NCCN Prostate Cancer guidelines (1.2023), and examples of this included positive margins, seminal vesicle invasion, and extracapsular extension. (p. MS-38)

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BACKGROUND AND RATIONALE

BREAST CANCER

Breast Cancer Treatment and Prognostic Algorithmic Tests

National Comprehensive Cancer Network (NCCN)

Oncotype DX for breast cancer is a 21-gene expression assay. NCCN guidelines for Breast Cancer (4.2023) strongly recommends consideration of the 21-gene expression assay for both prognosis and treatment decisions in the following patients:

- Patients of either sex (p. BINV-J 1 of 2)
- Evidence level 1: Postmenopausal patients with a ductal/NST, lobular, mixed, or micropapillary tumor that is pT1–3, and at least 0.5cm, with pN1mi (2 mm or smaller axillary node metastases) or pN1 (1–3 positive nodes). Tumor must be HR positive, HER2 negative. (p. BINV-6, BINV-N 1 of 5, BINV-N 2 of 5)
- Evidence level 1: Premenopausal patient with a ductal/NST, lobular, mixed, or micropapillary tumor that is at least 0.5cm and pN0. Tumor must be HR positive, HER2 negative. (p. BINV-7, BINV-N 1 of 5, BINV-N 2 of 5)
- Evidence level 2A: Premenopausal patient with a ductal/NST, lobular, mixed, or micropapillary tumor that is at least 0.5cm and pN1mi (2 mm or smaller axillary node metastasis) or pN1 (1–3 positive nodes). Tumor must be HR positive, HER2 negative. (p. BINV-8, BINV-N 1 of 5, BINV-N 2 of 5)

Breast Cancer Extended Endocrine Therapy Tests

National Comprehensive Cancer Network (NCCN)

The BCI is recommended by NCCN Breast Cancer criteria (4.2023) for both indications of prognosis as well as predicting treatment for extended adjuvant endocrine therapy. Appropriate patients for this test are:

- Evidence level 2A: Postmenopausal patients with a ductal/NST, lobular, mixed, or micropapillary tumor that is pT1–3, and 0.5cm or larger, with pN1mi (2 mm or smaller axillary node metastases) or pN1 (1–3 positive nodes). Tumor must be HR positive, HER2 negative. (p. BINV-6, BINV-N 1 of 5, BINV-N 4 of 5)
- Evidence level 2A: Premenopausal patients with a ductal/NST, lobular, mixed, or micropapillary tumor that is at least 0.5cm and pN0. Tumor must be HR positive, HER2 negative. (p. BINV-7, BINV-N 1 of 5, BINV-N 4 of 5)
- Evidence level 2A: Premenopausal patients with a ductal/NST, lobular, mixed, or micropapillary tumor that is at least 0.5cm and pN1mi (2 mm or smaller axillary node metastasis) or pN1 (1–3 positive nodes). Tumor must be HR positive, HER2 negative. (p. BINV-8, BINV-N 1 of 5, BINV-N 4 of 5)
- Data are limited regarding the use of molecular assays to assess prognosis and to predict benefit from chemotherapy in males with breast cancer. Available data suggest the 21-gene assay recurrence score provides prognostic information in males with breast cancer Patients who are female (p. BINV-J 1 of 2)

American Society of Clinical Oncology (ASCO)

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

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

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

Breast Cancer Prognostic Algorithmic Tests

American Society of Clinical Oncology (ASCO)

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

National Comprehensive Cancer Network (NCCN)

The NCCN Invasive Breast Cancer guidelines (4.2023) provide guidance for prognostic gene expression assays in patients with ductal/NST, lobular, mixed, or micropapillary breast cancer who are postmenopausal and have hormone-receptor positive/HER2 negative disease. (p. BINV-6)

Gene Expression Profiling Breast Cancer Subtyping Tests

National Comprehensive Cancer Network (NCCN)

NCCN Breast Cancer guidelines (4.2023) do not reference gene expression profiling tests (i.e., 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 (4.2023) 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 (2.2023) state that there is currently insufficient data to recommend multigene panels to assist in making clinical decisions about adjuvant therapy (p. COL-4).

PROSTATE CANCER

Prostate Cancer Treatment and Prognostic Algorithmic Tests

National Comprehensive Cancer Network (NCCN)

NCCN guidelines for Prostate Cancer (3.2023) support the consideration of gene expression profiling (specifically Decipher, Oncotype DX Prostate, and Prolaris) for 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)

These guidelines for Prostate Cancer (3.2023) also recommend that, in individuals who have PSA recurrence/persistence after radical prostatectomy (RP) and are expected to live more than 5 years, molecular assay such as Decipher can be considered as an alternative to PSADT (PSA doubling time) to inform counseling. (p. PROS-10) Additionally, individuals with adverse feature(s) found post-RP and no lymph node metastases could consider Decipher molecular assay if not previously performed to inform adjuvant treatment. (p. PROS 8 and PROS 9)

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 (1.2023) 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 (1.2023) 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). Extent of validation of these tests across diverse populations is variable. It is not yet known how such tests could be applied in optimal combination with MRI. (p. 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)

NCCN Guidelines for Thyroid Carcinoma (3.2023) state that clinicians can consider molecular diagnostics on fine needle aspirate (FNA) results of thyroid nodules which are classified as Bethesda III or Bethesda IV if there is not high clinical and/or radiographic suspicion of malignancy. (p. THYR-1 and THYR-2)

American Association of Clinical Endocrinologists, American College of Endocrinology, and Associazone Medici Endocrinologi

The American Association of Clinical Endocrinologists, American College of Endocrinology, and Associazone Medici Endocrinologi (2016) updated their joint guidelines on molecular testing for cytologically indeterminate thyroid nodules and endorsed the following:

- *TERT* mutational analysis may improve the diagnostic sensitivity of molecular testing on cytologic samples. (p. 32)
- There is insufficient evidence to recommend either in favor of or against the use of gene expression classifiers for cytologically indeterminate nodules. (p. 10)
- With the exception of mutations such as BRAF V600E, there is insufficient evidence to recommend in favor of or against the use of mutation testing to determine the extent of surgery. (p. 10)

UVEAL MELANOMA

Uveal Melanoma Prognostic Algorithmic Tests

National Comprehensive Cancer Network (NCCN)

NCCN guidelines for Uveal Melanoma (1.2023) 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 (2.2023) recognize 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 clinical utility 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 (2.2023) indicate that gene expression profiling is an acceptable test for diagnosing indeterminate melanocytic neoplasms by histopathology, along with immunohistochemistry (IHC), comparative genomic hybridization (CGH), fluorescence in situ hybridization (FISH), single-nucleotide polymorphism (SNP) array, and next-generation sequencing (NGS). These tests may lead to a definitive diagnosis and guide therapy in cases that are diagnostically uncertain or controversial by histopathology. (p. ME-C 1 of 8).

American Academy of Dermatology

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

- Diagnostic molecular techniques are still largely investigative and may be appropriate as ancillary tests in equivocal melanocytic neoplasms, but they are not recommended for routine diagnostic use in CM. These include comparative genomic hybridization (CGH), fluorescence in situ hybridization (FISH), gene expression profiling (GEP), and (potentially) next-generation sequencing. (page 219)
- Ancillary diagnostic molecular techniques (e.g., CGH, FISH, GEP) may be used for equivocal melanocytic neoplasms. (p. 219)

American Society of Dermatopathology

The American Academy of Dermatopathology (AUC Committee Members, 2022) published conditions where a 23 gene qRT-PCR test (MyPath Melanoma) was determined by a review of published evidence to be "majority usually appropriate." These include the differential diagnosis of nevus versus melanoma in fully sampled histopathologically ambiguous tumors, partially sampled nevus versus melanoma in adults, nevus versus nevoid melanoma, and nevus versus melanoma in cosmetically sensitive sites and special sites in pediatric patients. These recommendations specifically exclude scenarios where pathology is definitive for melanoma or for distinction between incompletely sampled sclerosing (desmoplastic) nevus versus desmoplastic melanoma. (p. 237-8)

Cutaneous Melanoma Risk Assessment Algorithmic Tests

Concert Genetics

This review focused on peer-reviewed, published evidence of the clinical utility of DermTech PLA through August 2023. A PubMed search was performed. Search terms included pigmented lesion assay, DermTech, 0089U, PRAME, LINC00518, cutaneous melanoma risk. References were also identified from the performing laboratory's website. In the initial review of this topic (performed in May 2022), a total of 110 abstracts were reviewed, and 30 full text publications were evaluated. Updated review, performed in August 2023, included 26 additional abstracts and full review of 7 full text publications. 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 (2.2023) 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 (2.2023) recommend genetic risk evaluation, and germline and somatic testing if not previously done, including *BRCA1/2* to inform maintenance therapy for patients with ovarian, fallopian tube, or primary peritoneal cancer. If a patient does not have a germline *BRCA1/2* mutation, homologous recombination status may inform on the benefit of PARP inhibitor therapy. (p. OV-1)

American Society of Clinical Oncology (ASCO)

ASCO (2020) issued a guideline for the use of PARP inhibitors in the management of ovarian cancer, which included the following summary of recommendations:

> "The guideline pertains to patients who are PARPi naïve. All patients with newly diagnosed, stage III-IV EOC (epithelial ovarian, tubal, or primary peritoneal cancer), whose disease is in complete or partial response to first-line, platinum-based chemotherapy with high-grade serous or endometrioid EOC should be offered PARPi maintenance therapy with niraparib. For patients with germline or somatic pathogenic or likely pathogenic variants in *BRCA1* (g/sBRCA1) or *BRCA2* (g/sBRCA2) genes, should be treated with olaparib. The addition of olaparib to bevacizumab may be offered to patients with stage III-IV EOC with g/s*BRCA1/2* and/or genomic instability and a partial or complete response to chemotherapy plus bevacizumab combination. Maintenance therapy (second line or more) with single-agent PARPi may be offered for patients with EOC who have not received a PARPi and have responded to platinum-based therapy regardless of *BRCA* mutation status. Treatment with a PARPi should be offered to

patients with recurrent EOC that has not recurred within 6 months of platinum-based therapy, who have not received a PARPi and have a g/s*BRCA1/2*, or whose tumor demonstrates genomic instability. PARPis are not recommended for use in combination with chemotherapy, other targeted agents, or immune-oncology agents in the recurrent setting outside the context of a clinical trial. Recommendations for managing specific adverse events are presented. Data to support reuse of PARPis in any setting are needed." (p. 3)

GYNECOLOGIC CANCER

Gynecologic Cancer Treatment Algorithmic Tests

National Comprehensive Cancer Network (NCCN)

NCCN guidelines for Ovarian Cancer, Fallopian Tube Cancer, and Primary Peritoneal Cancer (2.2023) 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 (1.2023) do not mention chemosensitivity or chemoresistance assays as part of clinical care.

NCCN guidelines for Uterine Neoplasms (2.2023) 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 2023. A PubMed search was performed. Search terms included VeriStrat, proteomic non-small cell lung cancer, prognosis, and survival. References were also identified from the performing laboratory's website. At the present time, the VeriStrat test has not been

adequately shown in peer-reviewed publications to effectively result in improved health outcomes compared to the current standard of care.

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 2023. A PubMed search was 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/Urinary Tract Cancer Diagnostic, Treatment and Recurrence Algorithmic Tests

National Comprehensive Cancer Network (NCCN)

NCCN guidelines for Bladder Cancer (3.2023) support consideration for urinary urothelial tumor markers for high-risk patients with non-muscle-invasive bladder cancer (category 2B recommendation, which is based on lower-level evidence with NCCN consensus that the intervention is appropriate) (p. BL-E 2 of 6). Further discussion in these guidelines acknowledge that it is unclear if this type of testing offers information that is clinically useful for detecting or managing these tumors, hence the weaker recommendation of 2B by the panel (p. MS-13)

American Urological Association and Society of Urologic Oncology

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

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

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

PANCREATIC CANCER

Pancreatic Cyst Risk Assessment Algorithmic Tests

National Comprehensive Cancer Network (NCCN)

NCCN guidelines for Pancreatic Adenocarcinoma (2.2023) 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) (3.2023) 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 (3.2023) 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).

Reviews, Revisions, and Approvals	Revision Date	Approval Date
Policy developed.	03/23	03/23
Semi-annual review. Updated title to reflect V1.2024 version. Overview, coding, reference-table, background and references updated. Throughout policy: replaced “coverage criteria” with “criteria. For Overview: removed “developed to aid in determining…”; added “tests that combine biomarkers…”. For Policy Reference Table: added Breast Cancer Extended Endocrine Therapy Algorithmic Tests and related content; under Breast DCIS Prognostic Algorithmic Tests: added “DCISion RT (PrecludeDx)”; added “0295U”; under Colorectal Cancer Prognostic Algorithmic Tests: added “Immunoscore (HalioDx)”; added “0261U”: under Prostate Cancer Risk	10/23	10/23

Reviews, Revisions, and Approvals	Revision Date	Approval Date
Assessment Algorithmic Tests: added "MyProstateScore (Lynx Dx)"; added "0113U"; under Prostate Cancer Diagnostic Algorithmic Tests: removed "MyProstateScore…"; removed "0113U"; added "PanGIA…"; added "0228U"; added "Progensa…"; added "81313"; under Thyroid Cancer Diagnostic Algorithmic Tests: added "ThyroSeq…"; added "0287U"; under Cutaneous Melanoma Prognostic Algorithmic Tests: added "AMBL or…"; added "0387U"; replaced "81599" with "81479"; added "DecisionDx…"; added "0314U"; under Lung Cancer Diagnostic Algorithmic Tests: added "Oncobiotal…"; added "0395U"; removed Urinary Tract Cancer Recurrence Algorithmic Tests and related content; removed Multiple Myeloma Polygenic Risk Score Tests and related content; under Oncology: Test-Specific Not Covered Algorithmic Tests: removed "Onco1D…"; removed "0083U"; removed "PreciseDx…"; removed "0220U"; removed "LC MS/MS Targeted…"; removed "0174U". For Other Related Policies: added "and Molecular". For Criteria; under Breast Cancer Treatment and Prognostic Algorithmic Tests: II. added "test (i.e.,…)"; added Breast Cancer Extended Endocrine Therapy Algorithmic Tests: for I. added "The use of the breast cancer…"; I.D. removed "human epidermal…"; added "HER2-negative…"; I.F. added "The member/enrollee has completed…"; I.G. added "extended"; I.G.1. removed "based on menopausal status"; I.H. removed "The member/enrollee is premenopausal…"; added "regardless of menopausal status"; I.H.2.b. removed "The member/enrollee is postmenopausal…"; I.H.3. removed "Lymph nodes are…"; II. and III. removed "treatment and prognostic…"; added "extended endocrine therapy"; for Breast Cancer Prognostic Algorithmic Tests: I.B. added "meets at least…"; I.B.1. added "Postmenopausal…"; I.B.2. added "Greater than 50…"; I.C. added "The member/enrollee"; I.D. removed "hormone receptor-positive…"; added "estrogen receptor-positive"; I.F. removed "meets on of…"; I.G. removed "Lymph nodes are…"; added "has the following…"; II. added "The use of breast cancer…"; III. Added "The use of breast cancer…"; added "*Prosigna is indicated…"; for Breast DCIS Prognostic Algorithmic Tests : added "0295U"; for Colorectal Cancer: added "0261U"; for Prostate Cancer Treatment and Prognostic Algorithmic Tests: II. removed "The"; added "For initial risk…"; II.B.1. added "member/enrollee has a life expectancy…"; I.B.2. added "The"; removed "AND"; added "as an alternative…"; I.B.3. added "persistence"; for Prostate Cancer Risk Assessment Algorithmic Tests: added "0113U"; for Prostate Cancer Diagnostic Algorithmic Tests: removed "0113U"; added "81313, 0228U"; for Cutaneous Melanoma Diagnostic Algorithmic Tests: added "0314U" throughout; for Bladder/Urinary Tract Cancer Diagnostic, Treatment and Recurrence Algorithmic Tests: I. removed "cancer diagnostic"; added "/urinary tract cancer…"; removed "0375U, 0376U, 0377U"; added "0365U, 0366U, 0367U"; removed Urinary Tract Cancer Recurrence Algorithmic Tests and related content; removed Multiple Myeloma Polygenic Risk Score Tests and related content; for Oncology: Test-Specific		

Reviews, Revisions, and Approvals	Revision Date	Approval Date
Not Covered Algorithmic Tests: I.B. removed “Onco4D…”; removed I.D-I.E. For Notes and Definitions: added “6. PSA persistence/recurrence…”; added “7. Adverse pathologic features…”. For Background and Rationale: removed “OncoType DX”; added “National Comprehensive…”; removed “Index BCI”; added “Extended Endocrine…”; added “National Comprehensive…”; removed “Patients who are female…”; added “Data are limited regarding…”; added “American Society of Clinical Oncology (ASCO)…”; added “Breast Cancer Prognostic Algorithmic Tests…”; under Prostate Cancer Treatment and Prognostic Algorithmic Tests: added “The guidelines for Prostate…”; for Prostate Cancer Diagnostic Algorithmic Tests: added “Extent of validation…”; for Cutaneous Melanoma Prognostic Algorithmic Tests: removed “that”; removed “impact”; added “clinical utility”; for Cutaneous Melanoma Risk Assessment Algorithmic Tests: removed “May, 2022…”; added “August 2023…”; removed “A total of 110…”; added “In the initial review…”; for Lung Cancer Treatment Algorithmic Tests and Lung Cancer Diagnostic Algorithmic Tests: removed "PubMed and ECRI..."; added "PubMed search was"; for Bladder/Urinary Tract Cancer Diagnostic, Treatment and Recurrence Algorithmic Tests: added “which is based on lower-level…”; removed “Urinary biomarker analysis…”; added “In surveillance of NMIBC…”; added “In a patient with a history…”; added “In a patient with NMIBC…”; removed Urinary Tract Cancer Recurrence Algorithmic Tests and related content; removed Multiple Myeloma Polygenic Risk Score Tests and related content.		

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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 members/enrollees. This clinical policy is not intended to recommend treatment for members/enrollees. Members/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.

This clinical policy is the property of the Health Plan. Unauthorized copying, use, and distribution of this clinical policy or any information contained herein are strictly prohibited. Providers, members/enrollees and their representatives are bound to the terms and conditions expressed herein through the terms of their contracts. Where no such contract exists, providers, members/enrollees and their representatives agree to be bound by such terms and conditions by providing services to members/enrollees and/or submitting claims for payment for such services.

Note: For Medicaid members/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 members/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.

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