ONCOLOGY: ALGORITHMIC TESTING

OVERVIEW

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.

POLICY REFERENCE TABLE

Coverage 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 Index Prognostic (bioTheranostics)	81518		
Breast Cancer Prognostic Algorithmic Tests	EndoPredict (Myriad)	81522, S3854	C50.-C50.1, Z17.0, Z17.1	1
	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, 2, 3, 8
Breast DCIS Prognostic Algorithmic Tests	Oncotype DX Breast DCIS Score (Exact Sciences)	0045U	D05.1	1, 2, 3
Colorectal Cancer				
Colorectal Cancer Prognostic Algorithmic Tests	Oncotype DX Colon Recurrence Score (Exact Sciences)	81525	C18.0-C18.9	4
	miR-31now™ (GoPath Laboratories)	0069U		
Prostate Cancer				
Prostate Cancer Treatment and Prognostic Algorithmic Tests	Oncotype DX Genomic Prostate Score (MDxHealth)	0047U	C61	5, 22
	Decipher Prostate Biopsy Genomic Classified Classifier (GenomeDX Biosciences, Inc.)	81542		
	Decipher Prostate RP Genomic Classifier (GenomeDX Biosciences, Inc.)			
	Prolaris (Myriad Genetics)	81541		
Prostate Cancer Risk Assessment Algorithmic Tests	Kallikrein markers (e.g. 4Kscore Test, OPKO Lab)	81539	C61, Z12.5	6, 31
	Prostate Health Index (Beckman Coulter)	84153, 84154, 86316		

	SelectMDx for Prostate Cancer (MDx Health)	81599, 0339U		
	ExoDx Prostate Test (ExosomeDx)	0005U		
Prostate Cancer Diagnostic Algorithmic Tests	ConfirmMDx for Prostate Cancer (MDxHealth)	81551	C61, Z12.5	6, 7,
	MyProstateScore (MPS) (University of Michigan MLabs)	0113U		
Thyroid Cancer				
Thyroid Cancer Diagnostic Algorithmic Tests	ThyroSeq Genomic Classifier (CBLPath)	0026U	C73, D44.0, E04.1	9, 10, 11
	ThyGeNEXT (Interpace Diagnostics)	0245U		
	ThyraMIR (Interpace Diagnostics)	0018U		
	Afirma Genomic Sequencing Classifier (Veracyte)	81546		
	Afirma Xpression Atlas (Veracyte)	0204U		
Uveal Melanoma				
Uveal Melanoma Prognostic Algorithmic Tests	DecisionDX-UM (Castle Bioscience, Inc.)	81552	C69	12
	Uveal Melanoma Prognostic Test (LabCorp)	81599		
Cutaneous Melanoma				
Cutaneous Melanoma Prognostic Algorithmic Tests	DecisionDX-Melanoma (Castle Biosciences, Inc.)	81529	C43, D03.0-D03.9, Z12.83	13, 14
Cutaneous Melanoma Diagnostic Algorithmic Tests	myPath Melanoma (Castle Biosciences Inc)	0090U	D22-D22.9, D48.5, D49.2, Z12.83	13, 14, 30
Cutaneous Melanoma Risk Assessment Algorithmic Tests	Pigmented Lesion Assay (DermTech)	0089U	D22-D23, Z12.83	27

Ovarian Cancer				
Ovarian Cancer Diagnostic Algorithmic Tests	OVA1 (Aspira)	81503	D27.0-D27.9, D39.10-D39.12, D39.9, D49.59, D49.9	15
	Overa (Aspira)	0003U		
	Ovarian Malignancy Risk (ROMA)) (LabCorp)	81500		
Ovarian Cancer Treatment Algorithmic Tests	myChoice CDx (Myriad Genetics)	0172U	C56	15, 36
Gynecologic Cancer				
Gynecologic Cancer Treatment Algorithmic Tests	ChemoFx (Helomics Corporation)	81535	C51-C57	15, 20, 21, 23
	ChemoFx - Additional Drug (Helomics Corporation)	81536		
Lung Cancer				
Lung Cancer Treatment Algorithmic Tests	VeriStrat (Biodesix)	81538	C34, D38.1, D38.6	28
	DetermaRx (Oncocyte)	0288U		
Lung Cancer Diagnostic Algorithmic Tests	Nodify XL2 (Biodesix)	0080U	R91.1	29
	REVEAL Lung Nodule Characterization (MagArray)	0092U		
	Percepta Bronchial Genomic Classifier (Veracyte)	81599		
Bladder and Urinary Tract Cancer				
Bladder Cancer Diagnostic and Recurrence Algorithmic Tests	Cxbladder Triage (Pacific Edge)	81599	C67.0-C67.9, D09.0, D49.4, R31.9, Z85.51	16, 17
	Cxbladder Detect (Pacific Edge)	0012M		
	Cxbladder Monitor (Pacific Edge)	0013M		
Urinary Tract Cancer Recurrence Algorithmic Tests	Alere NMP22® (Alere)	86386	C67.0-C67.9, D09.0, D49.4, R31.9, Z85.51	
	Alere NMP22® BladderChek® (Alere)	86386		
Pancreatic Cancer				

Pancreatic Cyst Risk Assessment Algorithmic Tests	PancraGEN (Interpace Diagnostics)	81202, 81275, 81322, 81352, 81479	D49	25, 26
	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	19
Polygenic Risk Score Tests				
Breast Cancer Polygenic Risk Score Tests	riskScore (Myriad Genetics)	81599	Z13.71-Z13.79 Z80.3	18
	BrevaGen*plus* (Pathogen Sciences Laboratories)			
Multiple Myeloma Polygenic Risk Score Tests	Myeloma Prognostic Risk Signature (MyPRS) (Cleveland Clinic Laboratories)	81599	C90.00-C90.02	18
Oncology: Test-Specific Not Covered Algorithmic Tests				
Oncology: Test-Specific Not Covered Algorithmic Tests	Onco4D (Animated Dynamics, Inc.)	0083U		
	BBDRisk Dx (Silbiotech)	0067U		
	PreciseDx Breast Cancer Test (PreciseDx)	0220U		
	Lymph3Cx Lymphoma Molecular Subtyping Assay (Mayo Clinic Laboratories)	0120U		

OTHER RELATED POLICIES

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

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

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COVERAGE CRITERIA

BREAST CANCER

Breast Cancer Treatment and Prognostic Algorithmic Tests

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

   A. The member is female or male, **AND**
   B. The member has primary breast cancer that is ductal/NST, lobular, mixed or micropapillary, **AND**
   C. The member's tumor is hormone receptor-positive (estrogen receptor-positive or progesterone receptor-positive), **AND**

D. The member's tumor is human epidermal growth factor receptor 2 (HER2)-negative, **AND**
E. The member is considering treatment with adjuvant therapy (for example, tamoxifen, aromatase inhibitors, immunotherapy), **AND**
F. The member meets one of the following based on menopausal status:
    1. The member is premenopausal and meets one of the following:
        a) Tumor is greater than 0.5 cm and node negative (pN0), **OR**
        b) Lymph nodes are pN1mi (2mm or smaller axillary node metastases), **OR**
        c) Lymph nodes are pN1 (1-3 positive nodes), **OR**
    2. The member is postmenopausal and meets one of the following:
        a) Tumor is greater than 0.5 cm, **OR**
        b) Lymph nodes are pN1mi (2mm or smaller axillary node metastasis), **OR**
        c) Lymph nodes are pN1 (1-3 positive nodes), **OR**

II. The use of a breast cancer treatment and prognostic algorithmic test [specifically Breast Cancer Index (BCI)] (S3854, 81518) is considered **medically necessary** when:

A. The member is female, **AND**
B. The member has primary breast cancer that is ductal/NST, lobular, mixed or micropapillary, **AND**
C. The member's tumor is hormone receptor-positive (estrogen receptor-positive or progesterone receptor-positive), **AND**
D. The member's tumor is human epidermal growth factor receptor 2 (HER2)-negative, **AND**
E. The member is considering treatment with adjuvant therapy (for example, tamoxifen, aromatase inhibitors, immunotherapy), **AND**
F. The member meets one of the following based on menopausal status:
    1. The member is premenopausal and meets one of the following:
        a) Tumor is greater than 0.5 cm and node negative (pN0), **OR**
        b) Lymph nodes are pN1mi (2mm or smaller axillary node metastases), **OR**
        c) Lymph nodes are pN1 (1-3 positive nodes), **OR**

2. The member is postmenopausal and meets one of the following:
    a) Tumor is greater than 0.5 cm, **OR**
    b) Lymph nodes are pN1mi (2mm or smaller axillary node metastasis), **OR**
    c) Lymph nodes are pN1 (1-3 positive nodes)

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

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

Breast Cancer Prognostic Algorithmic Tests

I. The use of a hormone receptor positive breast cancer prognostic algorithmic test (examples: Endopredict, Prosigna, Mammaprint (S3854, 81520, 81521, 81522, 81523) is considered **medically necessary** when:

A. The member is female, **AND**
B. The member has primary breast cancer that is ductal/NST, lobular, mixed or micropapillary, **AND**
C. The member's tumor is hormone receptor-positive (estrogen receptor-positive or progesterone receptor-positive), **AND**
D. The member's tumor is human epidermal growth factor receptor 2 (HER2)-negative, **AND**
E. The member is considering treatment with adjuvant therapy (for example, tamoxifen, aromatase inhibitors, immunotherapy), **AND**
F. The member meets one of the following based on menopausal status:
    1. The member is premenopausal and meets one of the following:
        a) Tumor is greater than 0.5 cm and node negative (pN0), **OR**
        b) Lymph nodes are pN1mi (2mm or smaller axillary node metastases), **OR**
        c) Lymph nodes are pN1 (1-3 positive nodes), **OR**

2. The member is postmenopausal and meets one of the following:
    a) Tumor is greater than 0.5 cm, **OR**
    b) Lymph nodes are pN1mi (2mm or smaller axillary node metastasis), **OR**
    c) Lymph nodes are pN1 (1-3 positive nodes)

II. The use of a hormone receptor positive breast cancer prognostic algorithmic test (examples: Endopredict, Prosigna, Mammaprint) (S3854, 81520, 81521, 81522, 81523) in men with breast cancer is considered **investigational**.

III. The use of a hormone receptor positive breast cancer prognostic algorithmic test (i.e., Endopredict, Prosigna, Breast Cancer Index) (S3854, 81522, 81520, 81518) is considered **investigational** for all other indications.

Gene Expression Profiling Breast Cancer Subtyping Tests

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

Breast DCIS Prognostic Algorithmic Tests

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

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COLORECTAL CANCER

Colorectal Cancer Prognostic Algorithmic Tests

I. Colorectal cancer prognostic algorithmic tests (81525, 0069U) 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 Oncotype DX Prostate (0047U) is considered **medically necessary** when:

   A. The member meets all of the following:

      1. The member has low- or favorable intermediate-risk prostate cancer, **AND**

      2. The member has a life expectancy of 10 years or more, **OR**

II. The use of a prostate cancer treatment and prognostic algorithmic tests Decipher and Prolaris (81541, 81542) are considered **medically necessary** when:

   A. The member meets all of the following:

      1. The member has low-, favorable intermediate-, unfavorable intermediate- and high-risk prostate cancer **AND**

      2. The member has a life expectancy of 10 years or more

III. The use of the Decipher assay (81542) to inform adjuvant treatment and counseling for risk stratification is considered **medically necessary** when the member meets the following:

   A. Adverse features are found post-radical prostatectomy, including but not limited to PSA resistance/recurrence.

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

Prostate Cancer Risk Assessment Algorithmic Tests

I. Prostate cancer risk assessment algorithmic tests (81539, 84153, 84154, 86316, 81599, 0339U, 0005U) are considered **investigational**.

Prostate Cancer Diagnostic Algorithmic Tests

I. Prostate cancer diagnostic algorithmic tests (81551, 0113U) 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, 81599) is considered **medically necessary** when:

   A. The member has primary, localized uveal melanoma.

II. The use of a uveal melanoma prognostic algorithmic test (81552, 81599) 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**.

Cutaneous Melanoma Diagnostic Algorithmic Tests

I. Cutaneous melanoma diagnostic algorithmic tests (0090U) are considered **medically necessary** when:
   A. The member has a melanocytic neoplasm that is diagnostically uncertain or equivocal after histopathology

II. Cutaneous melanoma diagnostic algorithmic tests (0090U) are considered **investigational** when:
   A. A melanocytic neoplasm has pathology definitive for melanoma, desmoplastic melanoma, or sclerosing nevus.

III. Cutaneous melanoma diagnostic algorithmic tests (0090U) are considered **investigational** for all other indications.

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 (examples: OVA1, Overa, and ROMA) (0003U, 81500, 81503) are considered **investigational** for all indications, including but not limited to:

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

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Ovarian Cancer Treatment Algorithmic Tests

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

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

   B. The member 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.**

LUNG CANCER

Lung Cancer Treatment Algorithmic Tests

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

Lung Cancer Diagnostic Algorithmic Tests

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

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BLADDER AND URINARY TRACT CANCER

Bladder Cancer Diagnostic and Recurrence Algorithmic Tests

I. Bladder cancer diagnostic and recurrence algorithmic tests (0012M, 0013M, 81599), which are performed on urine are considered **investigational**.

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Urinary Tract Cancer Recurrence Algorithmic Tests

I. Urinary tract cancer recurrence algorithmic tests (86386) which are typically 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, 81202, 81275, 81322, 81352, 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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Multiple Myeloma Polygenic Risk Score Tests

I. The use of a multiple myeloma 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. Onco4D™ (0083U)
C. Lymph3Cx Lymphoma Molecular Subtyping Assay (0120U)
D. PreciseDxTM Breast Cancer Test (0220U)

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CLINICAL CONSIDERATIONS

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.

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DEFINITIONS

1. **Ductal/NST breast cancer** is ductal cancer that is no special type (NST), meaning the cancer cells have no features that class them as a special type of breast cancer when examined by microscope.
2. **Thyroid nodules with indeterminate findings** include Bethesda diagnostic category III (atypia/follicular lesion of undetermined significance) or Bethesda diagnostic category IV (follicular neoplasm/suspicion for a follicular neoplasm)
3. **Somatic** mutations can occur in any of the cells of the body except the germ cells (sperm and egg) and therefore are not passed on to children. These alterations can (but do not always) cause cancer or other diseases.
4. **Adjuvant** therapy refers to medication (such as chemotherapy or endocrine therapy) given after the surgical removal of a cancerous tumor.

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BACKGROUND AND RATIONALE

BREAST CANCER

National Comprehensive Cancer Network (NCCN)

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

Breast Cancer Treatment and Prognostic Algorithmic Tests

Oncotype DX

Oncotype DX for breast cancer is a 21-gene expression assay. NCCN guidelines for Breast Cancer (4.2022) strongly recommends consideration of the 21-gene expression assay for both prognosis and treatment decisions in the following patients:

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

Breast Cancer Index (BCI)

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

- Patients who are female (p. BINV-J 1 of 2)
- Evidence level 2A: Postmenopausal patients with a ductal/NST, lobular, mixed, or micropapillary tumor that is pT1–3, and 0.5cm or larger, with pN1mi (2 mm or smaller axillary node metastases) or pN1 (1–3 positive nodes). Tumor must be HR positive, HER2 negative. (p. BINV-6, BINV-N 1 of 5, BINV-N 4 of 5)
- Evidence level 2A: Premenopausal patients with a ductal/NST, lobular, mixed, or micropapillary tumor that is at least 0.5cm and pN0. Tumor must be HR positive, HER2 negative. (p. BINV-7, BINV-N 1 of 5, BINV-N 4 of 5)
- Evidence level 2A: Premenopausal patients with a ductal/NST, lobular, mixed, or micropapillary tumor that is at least 0.5cm and pN1mi (2 mm or smaller axillary node metastasis) or pN1 (1–3 positive nodes). Tumor must be HR positive, HER2 negative. (p. BINV-8, BINV-N 1 of 5, BINV-N 4 of 5)

Breast Cancer Prognostic Algorithmic Tests

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

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

COLORECTAL CANCER

Colorectal Cancer Prognostic Algorithmic Tests

National Comprehensive Cancer Network (NCCN)

Current NCCN guidelines for colon cancer (1.2022) 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

Prostate Cancer Treatment and Prognostic Algorithmic Tests

National Comprehensive Cancer Network (NCCN)

Current NCCN guidelines (.4.2022) 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.

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."

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. 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.

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.

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, 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.

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.” (page 21)

National Comprehensive Cancer Network (NCCN)

Current NCCN Guidelines for Thyroid Carcinoma (2.2022) state that clinicians can consider molecular diagnostics on fine needle aspirate (FNA) results of thyroid nodules

which are classified as Bethesda III or Bethesda IV if there is not high clinical and/or radiographic suspicion of malignancy. (page 8/THRY-1)

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

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

- *TERT* mutational analysis may improve the diagnostic sensitivity of molecular testing on cytologic samples.
- 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.

UVEAL MELANOMA

Uveal Melanoma Prognostic Algorithmic Tests

National Comprehensive Cancer Network (NCCN)

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

CUTANEOUS MELANOMA

Cutaneous Melanoma Prognostic Algorithmic Tests

National Comprehensive Cancer Network (NCCN)

NCCN guidelines for cutaneous melanoma (3.2022) recognize that the use of gene expression profiling as an emerging technology to differentiate melanomas at low versus

high risk for metastasis, to clarify indeterminate melanocytic neoplasms following histopathology, and to classify cutaneous melanoma into separate categories based on metastasis; however, currently there is insufficient data to recommend the use of gene expression profiling for cutaneous melanoma as the impact of these tests has not been established.

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.
- 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.

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.

Cutaneous Melanoma Diagnostic Algorithmic Tests

National Comprehensive Cancer Network (NCCN)

NCCN guidelines for cutaneous melanoma (3.2022) indicate that gene expression profiling is an acceptable test for diagnosing indeterminate melanocytic neoplasms by histopathology, along with immunohistochemistry (IHC), comparative genomic

hybridization (CGH), fluorescence in situ hybridization (FISH), single-nucleotide polymorphism (SNP) array, and next-generation sequencing (NGS). These tests may lead to a definitive diagnosis and guide therapy in cases that are diagnostically uncertain or controversial by histopathology. (p. ME-C 1 of 8).

American Academy of Dermatology

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

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

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.

OVARIAN CANCER

Ovarian Cancer Diagnostic Algorithmic Tests

National Comprehensive Cancer Network (NCCN)

NCCN guidelines for ovarian cancer (1.2022) 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 Algorithmic Tests

National Comprehensive Cancer Network (NCCN)

NCCN guidelines for ovarian cancer (1.2022) recommend genetic risk evaluation, and germline and somatic testing if not previously done, including BRCA1/2 to inform maintenance therapy for patients with ovarian, fallopian tube or primary peritoneal cancer. If a patient does not have a germline BRCA1/2 mutation, homologous recombination status may inform on the benefit of PARP inhibitor therapy.

The NCCN guideline for ovarian cancer (1.2022) 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).

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 PARP is in any setting are needed."

LUNG CANCER

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 Classifier, 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 Classifier, and Reveal Lung Nodule Characterization have not been adequately shown in peer-reviewed publications to effectively result in improved health outcomes compared to the current standard of care.

BLADDER AND URINARY TRACT CANCER

Bladder Cancer Diagnostic and Recurrence Algorithmic Tests

National Comprehensive Cancer Network (NCCN)

NCCN guidelines for bladder cancer (1.2022) support consideration for urinary urothelial tumor markers for high-risk patients with non-muscle-invasive bladder cancer. This suggestion is a weak recommendation from NCCN based on its recommendation category of 2B versus NCCN's typical recommendation category of 2A.

American Urological Association and Society of Urologic Oncology

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

- Urinary biomarker analysis should not replace cystoscopic evaluation in the surveillance of NMIBC.
- 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.

PANCREATIC CANCER

Pancreatic Cyst Risk Assessment

National Comprehensive Cancer Network (NCCN)

NCCN guidelines for pancreatic cancer (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.

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."

CANCER OF UNKNOWN PRIMARY

Cancer of Unknown Primary Gene Expression Profiling Tests

National Comprehensive Cancer Network (NCCN)

NCCN guidelines for occult primary (cancer of unknown primary) (2.2022) 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).

POLYGENIC RISK SCORE TESTS

Breast Cancer Polygenic Risk Score Tests

National Comprehensive Cancer Network (NCCN)

NCCN guidelines for genetic/familial high risk assessment: breast, ovarian, and pancreatic cancers (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.

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