# Concert Genetics Oncology: Algorithmic Testing

Reference Number: LA.CP.CG.25 Coding implications
Date of Last Revision 01/25~~06/24~~
Revision Log

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

# OVERVIEW

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

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

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

Results of ~~prognostic and~~oncology 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~~adjuvant therapy.

In keeping with the language used in National Comprehensive Cancer Network (NCCN) guidelines, the terms “male” and “female” refer to sex assigned at birth.

# 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 2023, 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 and may not support medical necessity. 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.

**NOTE: Coverage is subject to each requested code's inclusion on the corresponding LDH fee schedule. Non-covered codes are denoted (*) and are reviewed for Medical Necessity for members under 21 years of age on a per case basis. The non-covered codes will only be denoted in the table below and not throughout the policy. Please only reference the policy reference table for covered and non-covered codes.**

The tests ~~and,~~ associated laboratories ~~and,~~ CPT codes, and ICD codes contained within this document serve only as examples to help users navigate claims and corresponding criteria; as such, they are not comprehensive and are not a guarantee of coverage or non-coverage. Please see the Concert ~~Genetics~~ Platform for a comprehensive list of registered tests.

| ~~Criteria Sections~~ Criteria Sections | Example Tests, Labs | Common CPT Codes | Common ICD Codes | ~~Ref~~Ref |
|---|---|---|---|---|
| **~~Breast Cancer~~ Breast Cancer** | | | | |
| ~~Breast Cancer Treatment and Prognostic Algorithmic Tests~~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 Extended Endocrine Therapy Algorithmic Tests | Breast Cancer Index (bioTheranostics) | 81518*, S3854* | C50.011-C50.92, Z17.0 | 1, ~~27~~23 |

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|---|---|---|---|---|
| ~~Breast Cancer Prognostic Algorithmic Tests~~Breast Cancer Prognostic Algorithmic Tests | EndoPredict (Myriad) | 81522*, S3854* | C50, Z17.0, Z17.1 | 1, ~~27~~23 |
| | MammaPrint (Agendia, Inc.) | 81521*, 81523* S3854* | | |
| | Prosigna Assay (NeoGenomics) | 81520* | | |
| ~~Gene Expression Profiling Breast Cancer Subtyping Tests~~Gene Expression Profiling Breast Cancer Subtyping Tests | BluePrint (Agendia, Inc.) | 81599*, S3854* | C50-C50.929 | 1, ~~27~~23 |
| | ~~Insight TNBCtype (Insight Molecular Labs)~~ | ~~0153U*~~ | | |
| ~~Breast DCIS Prognostic Algorithmic Tests~~Breast DCIS Prognostic Algorithmic Tests | Oncotype DX Breast DCIS Score (Exact Sciences) | 0045U* | D05.1 | ~~1, 28~~31 |
| | ~~DCISion RT (PreludeDx)~~ | ~~0295U*~~ | | |
| **~~Colorectal Cancer~~ Colorectal Cancer** | | | | |
| ~~Colorectal Cancer Prognostic Algorithmic Tests~~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~~Veracyte) | 0261U* | | |
| **~~Prostate Cancer~~ Prostate Cancer** | | | | |
| ~~Prostate Cancer Treatment and Prognostic Algorithmic Tests~~Prostate Cancer Treatment and Prognostic Algorithmic Tests | Oncotype DX Genomic Prostate Score (MDxHealth) | 0047U* | C61 | 3, 18 |
| | Decipher Prostate Biopsy Genomic Classifier (Veracyte) | 81542* | | |
| | Decipher Prostate RP Genomic Classifier (Veracyte) | | | |
| | Prolaris (Myriad Genetics) | 81541* | | |
| | ArteraAI Prostate Test (Artera) | 0376U* | | |
| ~~Evidence Based Prostate Cancer Risk Assessment~~ | 4K Prostate Score (Serum) (BioReference Laboratories) | 81539* | C61, Z12.5 | 4, ~~25, 26~~22 |

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|---|---|---|---|---|
| ~~and Diagnostic Algorithmic Tests~~Evidence-Based Prostate Cancer Risk Assessment and Diagnostic Algorithmic Tests | 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* | | |
| | ConfirmMDx for Prostate Cancer (MDxHealth) | 81551* | | |
| | Prostate Cancer Gene 3 (Integrated Regional Laboratories) | 81479 | | |
| ~~Emerging Evidence Prostate Cancer Risk Assessment and Diagnostic Algorithmic Tests~~ | ~~Apifiny (Armune Bioscience)~~ | ~~0021U*~~ | | ~~26~~ |

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|---|---|---|---|---|
| Emerging Evidence Prostate Cancer Risk Assessment and Diagnostic Algorithmic Tests | PanGIA Prostate (Genetics Institute of America) | 0228U* | C61, Z12.5 | 22 |
| | | | | |
| | MyProstateScore 2.0 (Lynx Dx) | 0403U* | | |
| | miR Sentinel Prostate Cancer Test (miR Scientific) | 0343U*, 0424U* | | |
| | EpiSwitch Prostate Screening Test (PSE) (Oxford BioDynamics) | 0433U* | | |
| | | | | |
| ~~**Thyroid Cancer**~~ | Stockholm3 (BioAgilytix Diagnostics) | 0495U* | | |

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|---|---|---|---|---|
| | OncoAssure Prostate (DiaCarta, Inc.) | 0497U* | | |
| | Tempus p-MSI (Tempus AI, Inc) | 0512U* | | |
| | Tempus p-Prostate (Tempus AI, Inc) | 0513U* | | |
| **Thyroid Cancer** | | | | |
| ~~Thyroid Cancer Diagnostic Algorithmic Tests~~ Thyroid Cancer Diagnostic Algorithmic Tests | ThyroSeq Genomic Classifier (CBLPath) | 0026U* | C73, D44.0, E04.1 | 5, 6, 7 |
| | 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** | | | | |
| ~~Uveal Melanoma Prognostic Algorithmic Tests~~Uveal Melanoma Prognostic Algorithmic Tests | DecisionDx-UM (Castle Bioscience, Inc.) | 81552* | C69 | 8 |
| **~~Cutaneous Melanoma~~ Cutaneous Melanoma** | | | | |
| ~~Evidence Based Cutaneous Melanoma Prognostic Algorithmic Tests~~Evidence-Based Cutaneous Melanoma Prognostic Algorithmic Tests | DecisionDx-Melanoma (Castle Biosciences, Inc.) | 81529* | C43, D03.0-D03.9, Z12.83 | ~~29,~~ ~~30~~24, 25 |
| | Merlin Melanoma (BioCartis) | 81479 | | |
| | MelaNodal | 81599* | | |

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|---|---|---|---|---|
| | (Quest) | | | |
| ~~Emerging Evidence Cutaneous Melanoma Prognostic Algorithmic Tests~~Emerging Evidence Cutaneous Melanoma Prognostic Algorithmic Tests | AMBLor (AMLo Biosciences) | 0387U* | C43, D03.0-D03.9, Z12.83 | ~~30~~25 |
| ~~Cutaneous Melanoma Diagnostic Algorithmic Tests~~Cutaneous Melanoma Diagnostic Algorithmic Tests | myPath Melanoma (Castle Biosciences, Inc.) | 0090U* | D22.0-D22.9, D48.5, D49.2, Z12.83 | 9, 10, ~~24~~21 |
| | DecisionDx-DiffDx-Melanoma (Castle Biosciences, Inc.) | 0314U* | | |
| ~~Cutaneous Melanoma Risk Assessment Algorithmic Tests~~Cutaneous Melanoma Risk Assessment Algorithmic Tests | Pigmented Lesion Assay (DermTech) | 0089U* | D22-D23, Z12.83 | 9, 10, ~~31, 32, 33~~26, 27, 28 |
| **~~Ovarian Cancer~~ Ovarian Cancer** | | | | |
| ~~Ovarian Cancer Diagnostic Algorithmic Tests~~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 | 11 |
| | Overa (Aspira Women's Health) | 0003U* | | |
| | Risk of Ovarian Malignancy (ROMA) (Labcorp) | 81500* | | |
| | OvaWatch (Aspira Women's Health) | 0375U* | | |
| | Avantect Ovarian Cancer Test (ClearNote Health)~~myChoice CDx (Myriad Genetics)~~ | 0507U*~~01 72U*~~ | | |
| **~~Gynecologic Cancer~~**Ovarian Cancer Treatment Algorithmic Tests | myChoice CDx (Myriad Genetics) | 0172U* | C48, C56, C57.0 | 11, 19 |

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|---|---|---|---|---|
| ~~Gynecologic Cancer Treatment Algorithmic Tests~~**Gynecologic Cancer** | ~~ChemoFx (Helomics Corporation)~~ | ~~81535*~~ | ~~C51-C57~~ | ~~11, 16, 17~~ |
| Gynecologic Cancer Treatment Algorithmic Tests | ChemoFx ~~- Additional Drug~~ (Helomics Corporation) | ~~81536~~81535* | C51-C57 | 11, 16, 17 |
| | ChemoFx - Additional Drug (Helomics Corporation) | 81536* | | |
| ~~Evidence Based Lung Cancer Diagnostic Algorithmic Tests~~**Lung Cancer** | ~~Nodify XL2 (Biodesix)~~ | ~~0080U*~~ | ~~R91.1~~ | ~~23~~ |
| ~~Emerging Evidence Lung Cancer Diagnostic Algorithmic Tests~~Evidence-Based Lung Cancer Diagnostic Algorithmic Tests | Nodify XL2 (Biodesix)~~REVEAL Lung Nodule Characterization (MagArray)~~ | 0080U~~0092U~~* | R91.1 | ~~23~~20 |
| Emerging Evidence Lung Cancer Diagnostic Algorithmic Tests | REVEAL Lung Nodule Characterization (MagArray)~~Percepta Bronchial Genomic Classifier (Veracyte)~~ | 0092U*~~81479~~ | R91.1 | 20 |
| | ~~LungLB (LungLife AI)~~Percepta Lung Cancer Diagnostics (Veracyte) | 81479 ~~0317U*~~ | | |
| | ~~Nodify CDT (Biodesix)~~LungLB Test (LungLife AI) | ~~0360U~~0317U* | | |
| | ~~OncobiotaLUNG (Micronoma)~~Nodify CDT (Biodesix) | 0360U*~~0395U*~~ | | |

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|---|---|---|---|---|
| | ~~CyPath Lung (bioAffinity Technologies)~~OncobiotaLUNGdetect (Micronoma) | 0395U*~~0406U~~ | | |
| | ~~VeriStrat (Biodesix)~~CyPath Lung (Precision Pathology Laboratory) | 0406U*~~81538*~~ | | |
| Evidence-Based Lung Cancer Treatment Algorithmic Tests | ~~DetermaRx (Oncocyte)~~Veristrat (Biodesix) | 81538*~~0288U*~~ | C34, D38.1, D38.6 | 29, 33 |
| | Razor14/Risk Reveal (RazorGenomics) ~~LungOI (Imagene)~~ | 81599~~0414U*~~ | | |
| | ~~PROphet NSCLC Test~~DetermaRx (Oncocyte Corporation) | 0288U*~~0436U*~~ | | |
| ~~**Bladder and Urinary Tract Cancer**~~ Emerging Evidence Lung Cancer Treatment Algorithmic Tests | LungOI (Imagene) | 0414U* | C34, D38.1, D38.6 | 29 |
| | PROphet NSCLC Test (OncoHost Inc)~~Cxbladder Triage (Pacific Edge)~~ | 0436U*~~0363U*~~ | ~~C67, D09.0, D49.4, , Z85.51~~ | |
| **Bladder and Urinary Tract Cancer** | ~~Cxbladder Detect (Pacific Edge)~~ | ~~0012M*~~ | | |
| Bladder/Urinary Tract Cancer Diagnostic Algorithmic Tests | ~~Cxbladder Monitor~~CxBladder Detect+ (Pacific Edge) | 0420U*~~0013M*~~ | R31.9 | 12, 13 |
| | ~~CxBladder~~Cxbladder Detect~~+~~ (Pacific Edge) | ~~0420U~~0012M* | | |

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|---|---|---|---|---|
| | Oncuria Detect (DiaCarta Clinical Lab) | 0365U* | | |
| Bladder Cancer Treatment and Recurrence Algorithmic Tests | ~~Oncuria~~Cxbladder Monitor (~~DiaCarta Clinical Lab)~~ Pacific Edge) | 0013M* | C67, C68 | 32 |
| | Decipher Bladder (Veracyte) | 0016M* | | |
| | Cxbladder Triage (Pacific Edge)~~Decipher Bladder (Veracyte)~~ | 0363U*~~00 16M*~~ | | |
| | Oncuria Monitor (DiaCarta Clinical Lab) | 0366U* | | |
| | Oncuria Predict (DiaCarta Clinical Lab) | 0367U* | | |
| **~~Pancreatic Cancer~~Pancreatic Cancer** | | | | |
| ~~Pancreatic Cyst Risk Assessment Algorithmic Tests~~ Evidence-Based Pancreatic Cyst Risk Assessment Algorithmic Tests | PancraGEN (Interpace Diagnostics) | 81479 | D49, K86.2 | ~~20,~~ ~~21~~30 |
| Emerging Evidence Pancreatic Cyst Risk Assessment Algorithmic Tests | ~~Pancreatic Cyst Fluid NGS Analysis~~ PancreaSeq Genomic Classifier (Univ of Pittsburgh Medical Center Molecular and Genomic Pathology Laboratory) | 0313U* | | |
| **~~Cancer of Unknown Primary~~Cancer of Unknown Primary** | | | | |
| ~~Cancer of Unknown Primary Gene Expression Profiling Tests~~Cancer of Unknown Primary Gene Expression | CancerTYPE ID (Biotheranostics) | 81540* | C79.9, C80.0, | 15 |

| | | | | |
|---|---|---|---|---|
| Profiling Tests | | | C80.1 | |
| **~~Polygenic Risk Score Tests~~Polygenic Risk Score Tests** | | | | |
| ~~Breast Cancer Polygenic Risk Score Tests~~Breast Cancer Polygenic Risk Score Tests | geneType for Breast Cancer (Genetic Technologies) | 81599** | Z13.71, Z13.79 Z80.3 | 14 |

# 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.

~~back to top~~

back to top

# CRITERIA

It is the policy of ~~Louisiana Healthcare Connections~~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~~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~~adjuvant therapy (e.g., tamoxifen, aromatase inhibitors, immunotherapy), **AND**

   E. The member/enrollee is status post tumor resection and surgical axillary nodal staging and 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~~the breast cancer treatment and prognostic algorithmic test ~~(i.e.,~~ Oncotype DX Breast Recurrence Score (81519, S3854) is considered **investigational** for all other indications.

~~back to top~~

back to top

# Breast Cancer Extended Endocrine Therapy Algorithmic Tests

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

A. The member/enrollee is ~~an individual with a~~ female ~~reproductive system,~~(sex assigned at birth), **AND**

B. The member/enrollee has primary breast cancer that is ~~ductal/NST~~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~~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 (sex assigned at birth) with breast cancer is considered **investigational**.

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

~~back to top~~

back to top

# 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, S3854) is considered **medically necessary** when:

A. The member/enrollee is ~~an individual with a~~ female ~~reproductive system,~~(sex assigned at birth), **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~~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~~adjuvant therapy (for example, tamoxifen, aromatase inhibitors, immunotherapy), **AND**

G. The member/enrollee has had axial nodal staging and has the following node status:

1. ~~Node~~pN0, nodes negative pathologically, **OR**

2. pN1mi or pN1 (1-3 nodes positive ~~nodes~~pathologically) **OR***.

II. The use of a breast cancer prognostic algorithmic test (i.e., EndoPredict, Prosigna, MammaPrint) (~~S3854,~~ 81520, 81521, 81522, 81523, S3854) 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 1-3 node positive 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, S3854) in men (sex assigned at birth) 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, S3854) 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.

~~back to top~~

back to top

## Gene Expression Profiling Breast Cancer Subtyping Tests

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

~~back to top~~

back to top

## Breast DCIS Prognostic Algorithmic Tests

I. Breast DCIS prognostic algorithmic tests (0045U~~, 0295U~~) are considered ~~**investigational.**~~**medically necessary** when:

~~back to top~~

A. The member/enrollee has ductal carcinoma in situ (DCIS), **AND**

B. The tumor specimen contains at least 0.5 mm of DCIS, **AND**

C. The result of testing would aid in treatment decision-making (i.e., pursuing additional surgery or radiation therapy), **AND**

D. The member/enrollee's DCIS was not removed via mastectomy (i.e., there is residual ipsilateral breast tissue).

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

back to top

# COLORECTAL CANCER

## Colorectal Cancer Prognostic Algorithmic Tests

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

~~back to top~~

back to top

# 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), Decipher (81542), ArteraAI (0376U)) 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~~does **not** have either of the following:

~~1. Low-risk prostate cancer, **OR**~~

~~2. Favorable intermediate prostate cancer, **OR**~~

1. ~~Unfavorable intermediate prostate cancer,~~Very low-risk prostate cancer, **OR**

2. Very high-risk prostate cancer.

~~3.~~a. ~~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:

~~B. 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, **AND**

3. The member/enrollee has not yet had treatment**, OR**

C. The member/enrollee meets the following:

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

B. The patient has had radical prostatectomy, **AND**

C. There are no lymph node metastases, **AND**

a) There is PSA persistence/recurrence, **OR**

D. Other adverse pathologic features were found. PSA persistence/recurrence.

III. The use of a prostate cancer treatment and prognostic algorithmic test (0047U, 0376U, 81541, 81542) is considered **investigational** for all other indications.

back to top

back to top

## Evidence--Based Prostate Cancer Risk Assessment and Diagnostic Algorithmic Tests

I. Prostate cancer risk assessment and diagnostic algorithmic tests (0005U, 0113U, 0339U, 0359U, 81539, 84153, 84154, 86316, 81479, 81551, 0113U, 0339U, 0005U, 0359U) with sufficient evidence of clinical validity and utility are considered **medically necessary** when:

A. The member/enrollee meets all of the following:

1. The member/enrollee has not had a prostate biopsy, **AND**

2. The member/enrollee has at least one of the following:
    a) Prostate specific antigen (PSA) of >3 ng/ml, **OR**
    b) A digital rectal exam (DRE) that is ~~very~~ suspicious for cancer, **AND**
3. The test is one of the following:
    a) Prostate Health Index (PHI), **OR**
    b) SelectMDx, **OR**
    c) 4Kscore, **OR**
    d) ExoDx Prostate Test, **OR**
    e) MyProstateScore (MPS), **OR**
    f) IsoPSA, **OR**

B. The member/enrollee meets all of the following:

~~4.~~1. The member/enrollee has had a prostate biopsy, **AND**

~~5.~~2. The result is one of the following:
    a) Atypia, suspicious for cancer, **OR**
    b) High-grade prostatic intraepithelial neoplasia (PIN)**, OR**
    c) Benign, **AND**

~~6.~~3. The test is one of the following:
    a) Prostate Health Index (PHI), **OR**
    b) 4Kscore, **OR**
    c) ExoDx Prostate Test, **OR**
    d) MyProstateScore (MPS), **OR**
    e) IsoPSA, **OR**
    f) ConfirmMDx, **OR**

g) PCA3.

II. The use of prostate cancer risk assessment and diagnostic algorithmic tests (0005U, 0113U, 0339U, 0359U, 81539, 84153, 84154, 86316, 81479, 81551~~, 0113U, 0339U, 0005U, 0359U~~) with sufficient evidence of clinical validity and utility are considered **investigational** for all other indications where clinical validity and utility have not been demonstrated.

~~back to top~~back to top

## Emerging Evidence Prostate Cancer Risk Assessment and Diagnostic Algorithmic Tests

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

~~back to top~~

back to top

# THYROID CANCER

## Thyroid Cancer Diagnostic Algorithmic Tests

I. The use of a thyroid cancer diagnostic algorithmic test (0018U, 0026U~~, 0018U~~, 0204U, 0245U, 0287U, 81546) in fine needle aspirates of thyroid nodules is considered **medically necessary** when:

A. The fine needle aspirate showed ~~indeterminate cytologic findings,~~indeterminate cytologic findings (i.e., Bethesda diagnostic category III or IV), **AND**

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

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

II. The use of a thyroid cancer diagnostic algorithmic test (0018U, 0026U~~, 0018U~~, 0204U, 0245U, 0287U, 81546) in fine needle aspirates of thyroid nodules is considered **investigational** for all other indications.

~~back to top~~

back to top

# 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.

~~back to top~~

back to top

# CUTANEOUS MELANOMA

## Evidence-~~-~~Based Cutaneous Melanoma Prognostic Algorithmic Tests

I. Cutaneous melanoma prognostic algorithmic tests (81479, 81529, 81599) with sufficient evidence of clinical validity and utility are considered **medically necessary** when:

A. The member/enrollee has either of the following:

1. Stage I melanoma (staging based on -AJCC American Joint Committee on Cancer), **OR**

2. Stage II melanoma (staging based on AJCC American Joint Committee on Cancer), **AND**

B. The member/enrollee does NOT have metastatic disease, **AND**

C. The results of testing will inform subsequent biopsy decisions, use of ~~adjuvant therapy(ies)~~adjuvant therapy(ies), or follow-up screening protocols.

II. Cutaneous melanoma prognostic algorithmic tests (81479, 81529, 81599) with sufficient evidence of clinical validity and utility are considered **investigational** for all other indications where clinical validity and utility have not been demonstrated.

~~back to top~~

back to top

## Emerging Evidence Cutaneous Melanoma Prognostic Algorithmic Tests

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

~~back to top~~back to top

## 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.

~~back to top~~

back to top

## Cutaneous Melanoma Risk Assessment Algorithmic Tests

I. Cutaneous melanoma risk assessment algorithmic tests (0089U) are considered **medically necessary** when:

A. The member/enrollee has a melanocytic neoplasm that shows at least one ~~ABCDE feature,~~ABCDE feature (**a**symmetry, **b**order irregularity, **c**olor variegation, **d**iameter >6 mm, and **e**volution), **AND**

B. A biopsy is being considered but has not yet been performed, **AND**

C. The use of the test ~~can only be used~~is limited to a maximum of 2 times per visit.

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

~~back to top~~

back to top

# OVARIAN CANCER

## Ovarian Cancer Diagnostic Algorithmic Tests

I. Ovarian cancer diagnostic algorithmic tests (i.e., OVA1, Overa, ROMA, and OvaWatch) (0003U, 0375U, 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.

~~back to top~~

back to top

## 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.

~~back to top~~

back to top

# GYNECOLOGIC CANCER

## Gynecologic Cancer Treatment Algorithmic Tests

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

~~back to top~~

back to top

# LUNG CANCER

## Evidence~~-~~-Based Lung Cancer Diagnostic Algorithmic Tests

I. Lung cancer diagnostic algorithmic tests (0080U) with sufficient evidence of clinical validity and utility are considered ~~**medical**~~**medically necessary** when:

   A. The member/enrollee is age 40 years or older, **AND**

   B. The member/enrollee has a single lung nodule between 8 and 30 mm in diameter, **AND**

C. The member/enrollee has a risk of cancer of 50% or less according to the Mayo risk prediction algorithm, **AND**

D. The member/enrollee does NOT have a diagnosis of cancer (except for nonmelanoma skin cancer) within 5 years of the lung nodule detection.

II. Lung cancer diagnostic algorithmic tests (0080U) with sufficient evidence of clinical validity and utility are considered **investigational** for all other indications where clinical validity and utility have not been demonstrated.

~~back to top~~

back to top

## Emerging Evidence Lung Cancer Diagnostic Algorithmic Tests

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

~~back to top~~

back to top

## Evidence-Based Lung Cancer Treatment Algorithmic Tests

I. Lung cancer treatment algorithmic tests (0288U, 81538, ~~0288U, 0414U)~~81599) with sufficient evidence of clinical validity and utility are considered **medically necessary** when:

A. The member/enrollee has a non-squamous non-small cell lung cancer (NSCLC), **AND**

B. The member/enrollee's tumor size less than 5 cm, **AND**

C. The member/enrollee has no positive lymph nodes (stages I and IIa), **AND**

D. The member/enrollee is considering adjuvant platinum-containing chemotherapy.

~~I.~~II. Lung cancer treatment algorithmic tests (0288U, 81538, 81599) with sufficient evidence of clinical validity and utility are considered **investigational** for all other indications where clinical validity and utility have not been demonstrated.

~~back to top~~

back to top

## Emerging Evidence Lung Cancer Treatment Algorithmic Tests

I. Lung cancer treatment algorithmic tests (0414U, 0436U) with insufficient evidence of clinical validity are considered **investigational.**

back to top

# BLADDER AND URINARY TRACT CANCER

## Bladder/Urinary Tract Cancer Diagnostic~~,~~ Algorithmic Tests

I. Bladder/urinary tract cancer diagnostic algorithmic tests (0012M, 0365U, 0420U) are considered **investigational** for all indications.

back to top

## Bladder Cancer Treatment and Recurrence Algorithmic Tests

I. ~~Bladder/urinary tract~~The use of bladder cancer ~~diagnostic,~~ treatment~~,~~ and recurrence algorithmic ~~tests (0012M,~~ test (0013M, 0016M, 0363U, ~~0365U,~~ 0366U, 0367U~~, 0420U),~~ ~~which are performed on urine, are~~) is considered ~~**investigational.**~~**medically necessary** when:

~~back to top~~

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

B. Results of algorithmic testing will affect management decisions for the member/enrollee's bladder cancer, **AND**

C. The member/enrollee has not previously undergone bladder cancer treatment and recurrence algorithmic testing for the current cancer diagnosis.

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

back to top

# PANCREATIC CANCER

## Evidence-Based Pancreatic Cyst Risk Assessment Algorithmic Tests

I. Pancreatic cyst risk assessment algorithmic tests (81479) with sufficient evidence of clinical validity and utility are considered **medically necessary** when:

A. The member/enrollee has a pancreatic cyst, **AND**

B. Initial testing (for example, CEA measurement, cytopathology and/or radiology) has been inconclusive for malignancy, **AND**

C. The results of the test will impact treatment decisions (e.g., surgery, more aggressive treatment).

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

back to top

## Emerging Evidence Pancreatic Cyst Risk Assessment Algorithmic Tests

I. Pancreatic cyst risk assessment algorithmic tests (0313U~~, 81479)~~) with insufficient evidence of clinical validity are considered **investigational**.

~~back to top~~

back to top

# 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**.

~~back to top~~

back to top

# 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**.

~~back to top~~

back to top

# DEFINITIONS

1. **Ductal/NST breast cancer:** Ductal cancer that is of no special type (NST), meaning the cancer cells have no features that class them as a special type of breast cancer when examined by microscope.
2. **Indeterminate cytologic findings:** In thyroid nodules, indeterminate cytologic findings include Bethesda diagnostic category III (atypia/follicular lesion of undetermined significance) or Bethesda diagnostic category IV (follicular neoplasm/suspicion for a follicular neoplasm)
3. **Adjuvant therapy:** Medication (such as chemotherapy or endocrine therapy) given after the surgical removal of a cancerous tumor.
4. **PSA persistence/recurrence:** Defined in the NCCN Prostate Cancer guidelines (4.~~2023~~2024) as failure of PSA to fall to undetectable levels (PSA persistence) or undetectable PSA after ~~RP~~a radical prostatectomy 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)

1. **Adverse pathologic features:** Discussed in the NCCN Prostate Cancer guidelines (4.2023), and examples of this included positive margins, seminal vesicle invasion, and extracapsular extension. (p. MS-38)

5. **ABCDE feature:** Feature outlined in ABCDE criteria, which is an acronym for examining patients with a lesion that is suspicious for melanoma: **a**symmetry, **b**order irregularity, **c**olor variegation, **d**iameter >6 mm, and **e**volution.

back to top

# 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.

back to top

6. **Very high-risk prostate cancer:** Defined by NCCN as an individual who has no very-high-risk features but has at least **one** of the following high-risk features:
    a. cT3b-cT4
    b. Primary Gleason pattern 5
    c. 2 or 3 high-risk features
    d. More than 4 cores with Grade Group 4 or 5
7. **Very low risk prostate cancer:** Defined by NCCN as all of the following:
    a. cT1c
    b. Grade Group 1
    c. PSA <10 mg/nl and density <0.15 ng/mL/g

d. Biopsy shows <3 positive cores/fragments and < or equal to 50% cancer in each core/fragment.

back to top

# 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 (~~1~~4.2024) ~~strongly recommends consideration of~~recommend 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 (Breast Cancer Index) is recommended by NCCN Breast Cancer ~~criteria (1~~guidelines (4.2024) for both indications of prognosis as well as predicting treatment for extended adjuvant endocrine therapy. Appropriate patients for this test are:

- Evidence level 2A: Postmenopausal patients with a ductal/NST, lobular, mixed, or micropapillary tumor that is pT1–3, and 0.5cm or larger, with pN1mi (2 mm or smaller

axillary node metastases) or pN1 (1–3 positive nodes). Tumor must be HR positive, HER2 negative. (p. BINV-6, BINV-N 1 of 5, BINV-N 4 of 5)

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

*American Society of Clinical Oncology (ASCO)*

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

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

**Breast Cancer Prognostic Algorithmic Tests**

*American Society of Clinical Oncology (ASCO)*

The 2022 ASCO guideline update for Biomarkers for Adjuvant Endocrine and Chemotherapy in Early-Stage Breast Cancer provides guidance for the diagnostic indications for several breast

cancer prognostic algorithmic tests, including EndoPredict, MammaPrint, and Prosigna (among others). Figure 1 summarizes the following: if a female patient ~~with a female reproductive system~~ is postmenopausal or older than age 50 years, has early-stage invasive breast cancer, node negative disease, and a HER2 negative, ER positive tumor, then EndoPredict, Prosnigna, or MammaPrint may be ordered. However, if the patient has 1 to 3 positive node disease, MammaPrint or EndoPredict may be ordered. (p. 1821)

*National Comprehensive Cancer Network (NCCN)*

~~Per the~~ NCCN Breast Cancer guidelines (~~1~~4.2024~~), clinicians should strongly consider performing a 21-gene RT-PCR assay if the patient is a candidate for chemotherapy (category 1) o for~~) recommend consideration of other prognostic gene expression assays to help assess risk of recurrence in ~~patients with ductal/NST, lobular, mixed, or micropapillary breast cancer who are~~ pre- and postmenopausal ~~and have hormone-receptor~~ patients with HR-positive~~/HER2-~~, Her2-negative ~~disease. Other prognostic gene expression assays may be considered to help assess risk of recurrence but~~pT1-3 and pN0 or pN+ tumors, but these other tests have not been validated to predict response to chemotherapy. (p. BINV- 6, BINV-7, BINV-8) Gene expression assays can provide prognostic and ~~therapy~~treatment-predictive information that ~~complements~~can be used with T,N,M and biomarker information. ~~The 21-gene assay (Oncotype Dx) is preferred by the NCCN Breast Cancer Panel for prognosis and prediction of chemotherapy benefit. Other~~These prognostic gene expression assays can provide prognostic information but the ability to predict chemotherapy benefit ~~is unknown.~~has not been shown. (p. BINV-N, 1 of 5, 3 of 5)

**Gene Expression Profiling Breast Cancer Subtyping Tests**

*National Comprehensive Cancer Network (NCCN)*

NCCN Breast Cancer guidelines (~~1~~4.2024) do not reference gene expression profiling tests (i.e., Blueprint) for the purpose of subtyping breast cancer to provide information for clinical decision-making.

*American Society of Clinical Oncology*

The ASCO Guideline Update on Biomarkers for Adjuvant Endocrine and Chemotherapy in Early Stage Breast Cancer (2022) does not include breast cancer subtyping tests (i.e., BluePrint) as recommended biomarker tests for guiding adjuvant therapy.

*Concert Note*

There is insufficient evidence to support the use of this test. No recommendations for or against this testing within standard professional society guidelines covering this area of testing were identified.

**Breast DCIS Prognostic Algorithmic Tests**

~~*National Comprehensive Cancer Network (NCCN)*~~

~~NCCN Breast Cancer guidelines (1.2024) do not reference DCIS prognostic algorithmic tests as part of the clinical work-up for DCIS.~~

~~*Collins et al, Up To Date, 2023*~~

~~"Gene expression analysis such as the Oncotype DX DCIS recurrence score and DCISionRT have been studied as a tool for identification of patients for whom post-lumpectomy RT may reasonably be omitted, but data regarding its utility are still limited. Further validation of these results is required before the multigene assay can become a standard part of clinical practice".~~

*Centers for Medicare and Medicaid Services*

The CMS local coverage determination (LCD) entitled "MolDX: Oncotype DX Breast Cancer for DCIS (Genomic Health)" includes the following criteria for OncotypeDX DCIS:

"The Oncotype DX DCIS assay is covered only when the following clinical conditions are met:

- Pathology (excisional or core biopsy) reveals ductal carcinoma in situ of the breast (no pathological evidence of invasive disease), and
- FFPE specimen with at least 0.5 mm of DCIS length, and
- Patient is a candidate for and is considering breast conserving surgery alone as well as breast conserving surgery combined with adjuvant radiation therapy, and
- Test result will be used to determine treatment choice between surgery alone vs. surgery with radiation therapy, and
- Patient has not received and is not planning on receiving a mastectomy."

**COLORECTAL CANCER**

**Colorectal Cancer Prognostic Algorithmic Tests**

*National Comprehensive Cancer Network (NCCN)*

NCCN guidelines for Colon Cancer (~~1~~4.2024) ~~state that there is currently insufficient data to~~does not recommend ~~routine~~ use of ~~circulating tumor DNA (ctDNA)~~multigene panel assays to assist in making clinical decisions about adjuvant therapy. (p. COL-4)

## PROSTATE CANCER

### Prostate Cancer Treatment and Prognostic Algorithmic Tests

*National Comprehensive Cancer Network (NCCN)*

NCCN guidelines for Prostate Cancer (4.~~2023~~2024) recommend advanced risk stratification tools (i.e., gene expression biomarkers, AI digital pathology) when there is the possibility of changing disease management in men with ~~low, favorable intermediate, unfavorable intermediate, or high-risk disease,~~localized prostate cancer and life expectancy of 10 yrs or more. (p. ~~if the patient is expected~~PROS-4,5,6) The most common reasons to ~~live 10 years~~use these tools is for deciding between active surveillance and radical treatment, or ~~longer.~~use of radiation alone vs radiation with androgen deprivation therapy (short or long term). These ~~tools are recommended to~~tests can also be useful post prostatectomy with recurrence, when choosing radiation with or without androgen deprivation therapy. (p. PROS-H, 1 of 8) These tests should not be used ~~when~~ for very low risk or very high risk disease as they ~~will~~ have not been validated in these populations. (p. ~~the potential ability to independently improve risk and change management.~~PROS-H, 1 and 4-6 of 8) The following tumor-based assays are called out for use: Decipher, ~~Oncotype DX~~Genomic Prostate~~,~~ Score, ArteraAI and Prolaris. (p. PROS-~~D 2~~H 3 of ~~4~~8)

~~These guidelines for Prostate Cancer (4.2023) also recommend that, in individuals who have PSA recurrence/persistence after radical prostatectomy (RP) and are expected to live more than 5 years, molecular assay such as Decipher can be considered as an alternative to PSADT (PSA doubling time) to inform counseling. (p. PROS-10) Additionally, individuals with adverse feature(s) found post-RP and no lymph node metastases could consider Decipher molecular assay if not previously performed to inform adjuvant treatment. (p. PROS-8 and PROS-8A)~~

*American Society of Clinical Oncology (ASCO)*

ASCO (2020) issued a guideline for the use of molecular biomarkers in localized prostate cancer that included the following summary of recommendations:

> "Tissue-based molecular biomarkers (evaluating the sample with the highest volume of the highest Gleason pattern) may improve risk stratification when added to standard clinical parameters, but the Expert Panel endorses their use only in situations in which the assay results, when considered as a whole with routine clinical factors, are likely to affect

a clinical decision. These assays are not recommended for routine use as they have not been prospectively tested or shown to improve long-term outcomes—for example, quality of life, need for treatment, or survival." (p. 1474)

**Evidence- Based Prostate Cancer Risk Assessment and Diagnostic Algorithmic Tests**

*American Urological Association/Society of Urologic Oncology*

The American Urological Association/Society of Urologic Oncology published guidelines on the early detection of prostate cancer (2023). They state that clinicians and patients may use adjunctive urine or serum markers to inform the shared decision making process regarding prostate biopsy (initial and/or repeat biopsy). It is imperative clinicians are familiar with biomarkers, understand what information or data each test provides, and consider whether additional information will impact management decisions before ordering a test. (conditional recommendation, evidence level C~~))~~). (p. 21-22, 24~~).~~) Of note, conditional recommendations are non-directive statements used when the evidence indicates that there is no apparent net benefit or harm, or when the balance between benefits and risks/burden is unclear. For evidence level C, the balance between benefits and risks is unclear but net benefit or net harm is comparable to other options.

~~*American Urological Association and Society of Abdominal Radiology*~~

~~The American Urological Association and the Society of Abdominal Radiology (Rosenkrantz et al, 2016) published joint guidelines on prostate magnetic resonance imaging and magnetic resonance imaging-targeted biopsy. The associations commented that there may be value in using genetic and protein biomarkers for prostate cancer risk in patients warranting repeat biopsy; however, further research is needed to fully assess the utility. (p. 2)~~

*National Comprehensive Cancer Network (NCCN)*

NCCN Prostate Cancer Early Detection guidelines (~~1~~2.2024) ~~indicate that~~recommends consideration of biomarkers that improve the specificity of screening ~~can be considered~~ in patients considering biopsy~~.~~ after abnormal PSA and/or DRE. Although ~~biomarkers that improve the specificity of detection~~these biomarker tests are not~~, as yet,~~ currently mandated as first-line screening tests in conjunction with serum PSA, there may be some patients who ~~meet~~could consider biopsy based on PSA standards ~~for consideration of prostate biopsy,~~ but ~~for whom the patient and/or the physician wish to~~are seeking further ~~define~~ risk clarification. The probability of high-grade cancer (Gleason score ≥3+4, Grade Group 2 or higher) may be further defined utilizing the Prostate Health Index (PHI), SelectMDx, 4Kscore, ExoDx Prostate Test, MyProstateScore (MPS), and IsoPSA. (p. PROSD-3) Tests that improve specificity when considering a repeat biopsy should be considered after negative biopsy in patients felt to be at

higher risk ~~even with negative biopsy~~ (p. PROSD-4). These tests include those listed above (except for SelectMDX) plus PCA3 and ConfirmMDX.

**Emerging Evidence Prostate Cancer Risk Assessment and Diagnostic Algorithmic Tests**

NCCN Prostate Cancer Early Detection guidelines (~~1~~2.2024) comment on the usefulness of biomarker testing to assist in biopsy decision making. The guidelines do not mention the following tests as part of recommended clinical care: EpiSwitch Prostate Screening Test (PSE), miR Sentinel Prostate Cancer Test, MyProstateScore 2.0, PanGIA Prostate, and Apifiny.

*Concert Note*

There is insufficient evidence to support the use of these tests. At this time, there are no known recommendations for or against this testing within standard professional society guidelines covering this area of testing~~.~~ as current evidence indicates neither benefit nor harm at this time.

**THYROID CANCER**

**Thyroid Cancer Diagnostic Algorithmic Tests**

*American Thyroid Association*

The American Thyroid Association (2016) updated its guidelines on the management of thyroid nodules and differentiated thyroid cancer in adults. These guidelines made the following statements on molecular diagnostics in thyroid nodules: “For nodules with AUS/FLUS [atypia of undetermined significance/follicular lesion of undetermined significance]... molecular testing may be used to supplement malignancy risk assessment in lieu or proceeding directly with either surveillance or diagnostic surgery.” (p. 21)

*National Comprehensive Cancer Network (NCCN)*

NCCN Guidelines for Thyroid Carcinoma (~~4.2023) state that clinicians can consider~~3.2024) recommends consideration of molecular diagnostics on fine needle aspirate (FNA) results of thyroid nodules which are classified as Bethesda III or Bethesda IV if there is not high clinical and/or radiographic suspicion of malignancy. (p. THYR-1 and THYR-2)

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

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

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

## UVEAL MELANOMA

### Uveal Melanoma Prognostic Algorithmic Tests

*National Comprehensive Cancer Network (NCCN)*

NCCN guidelines for Uveal Melanoma (1.~~2023) state that~~ 2024) recommends consideration of biopsy of the primary tumor ~~should be considered~~before radiation for prognostic analysis~~ and that molecular~~. Molecular testing for prognostication is ~~preferred~~recommended over cytology alone. (p. UM-2A) ~~Gene~~Tumor class defined by gene expression profiling ~~class had a stronger independent association~~ was more strongly associated with risk of metastasis than any other prognostic factor. (p. UM-4)

## CUTANEOUS MELANOMA

### Evidence-Based Cutaneous Melanoma Prognostic Algorithmic Tests

*ECRI Genetic Test Assessment*

A recent review completed by ECRI (2023) found evidence for the DecisionDx-Melanoma 31-gene profiling (31-GEP) test to be somewhat favorable based on the available data pertaining to clinical validity, and potential clinical utility of the test. Specifically, the available studies demonstrated that they may improve patient outcomes (e.g., overall survival, by informing decisions to escalate surveillance when the test is added to best available care (i.e., tumor staging, SLNB).

*Concert ~~Genetics~~ Evidence Review for Coverage Determination (Published 12/21/2023, Re-issued 7/1/2024 with minor updates to test names; no updates to literature)*

The current literature suggests that DecisionDx Melanoma (also referred to as 31-GEP in the literature) test exhibits high sensitivity (70-95%) and negative predictive value (>90%) in the prognosis of stage I and II cutaneous melanoma (CM) at multiple clinical endpoints including risk of recurrence, distant-site metastasis occurrence, and melanoma-specific death.

The literature demonstrates that the 31-GEP test has significant evidence of clinical validity and utility when incorporated as part of standard clinicopathologic features, both in predicting the potential prognosis of a cutaneous melanoma diagnosis as well as the prediction of SLNB positivity. Bailey et al (2023) showed that performing the 31-GEP test resulted in higher 3 year melanoma-specific survival (MSS) and overall survival (OS) in individuals with cutaneous melanoma, compared to patients not tested with the 31-GEP ($P < 0.001$). Additionally, the 31-GEP test was associated with a 29% lower MSS mortality and 17% lower overall mortality, allowing patients to be stratified by their risk. A study by Tassavor et al (2023) showed that the 31-GEP test outperformed the Memorial Sloan Kettering Cancer Center nomogram for predicting SLNB positivity in patients with cutaneous melanoma (T1-T2 tumors), thereby reducing the number of patients who need invasive procedures. Specifically, the study notes: "In patients with T1 tumors, for whom guidance on the clinical decision to perform SLNB is least clear, the i31-GEP for SLNB could have reduced the number of SLNBs by 43.7%, compared with standard NCCN SLNB guidance using AJCC staging, while maintaining a low false-negative rate." (p. 4514) Finally, in a prospective multicenter study, Yamamoto et al (2023) showed that overall 85.3% of decisions related to sentinel lymph node biopsy were influenced by 31-GEP test results in individuals with T1-T2 tumors. Concordance between performing an SLNB and 31-GEP influence was 78.5%.

Based upon retrospective cohort data, the Merlin assay shows relatively high clinical validity in individuals with primary cutaneous melanoma, with a NPV > 95% and elevated levels of sensitivity (80% in T1-T2 patients and 92.3% in T1-T3 patients) (Yousaf et al., 2021). Other research shows a potential for the Merlin assay to reduce SLNB complications by 50 - 69.1% by reducing the number of patients undergoing SLNB (Hieken et al., 2022). There is some evidence that suggests the CP-GEP assay can be used to further stratify the risk of recurrence, metastasis, and melanoma specific survival in patients (Eggermont et al., 2020).

MelaNodal Predict was added to this evidence review after determining that Melanodal uses the Merlin algorithm and is licensed by Quest. For this reason, we are assuming these tests are the same and therefore, the evidence review information above will apply to MelaNodal Predict.

Following on a systematic review of available peer-reviewed evidence, cutaneous melanoma prognostic algorithmic tests such as DecisionDx-Melanoma and Merlin / MelaNodal Predict, have **SUFFICIENT EVIDENCE** for clinical validity to effectively identify patients with a

poorer prognosis and for clinical utility in direct more aggressive treatment to promote increased patient survival.

**Emerging Evidence Cutaneous Melanoma Prognostic Algorithmic Tests**

*Concert ~~Genetics~~ Evidence Review for Coverage Determination (Published 12/21/2023)*

There were no available peer-reviewed studies concerning the AMBlor assay that met inclusion criteria for a systematic review. At this time, there is **INSUFFICIENT EVIDENCE** to support the clinical validity of this test in identifying early stage melanoma patients with poorer prognoses. No recommendations for or against this testing within standard professional society guidelines covering this area of testing were identified.

**Cutaneous Melanoma Diagnostic Algorithmic Tests**

*National Comprehensive Cancer Network (NCCN)*

NCCN guidelines for Cutaneous Melanoma (~~3.2023~~2.2024) indicate that gene expression profiling is an ~~acceptable~~available 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~~treatment selection in cases that are diagnostically ~~uncertain~~equivocal or controversial by histopathology and NCCN recommends consideration of these tests in conjunction with clinical and pathology evaluation. (p. ME-C 1 of 8).

*American Academy of Dermatology*

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

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

- Ancillary diagnostic molecular techniques (e.g., CGH, FISH, GEP) may be used for equivocal melanocytic neoplasms. (p. 219)

*American Society of Dermatopathology*

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

**Cutaneous Melanoma Risk Assessment Algorithmic Tests**

*National Comprehensive Cancer Network (NCCN)*

NCCN Guidelines for Cutaneous Melanoma (~~3.2023) state that~~2.2024) recommends consideration of pre-diagnostic noninvasive patch testing ~~may be useful~~ to help ~~guide~~inform decisions regarding biopsy for patients with melanocytic neoplasms that are clinically/dermoscopically suspicious for melanoma. (p. ME-~~11~~12)

*ECRI Genetic Test Assessment*

A recent review completed by ECRI (2023) found evidence for the Pigmented Lesion Assay (PLA) to be somewhat favorable based on the available data demonstrating clinical ~~utility and clinical~~ validity and utility to improve patient outcomes when added to standard of care. (p. 1)

*American Academy of Dermatology ~~(2018)~~*

In their 2019 publication, the American Academy of Dermatology stated the following: Skin biopsy remains the first step to establish a definitive diagnosis of CM, although various molecular and imaging techniques have been studied as adjuncts to histopathologic assessment of melanocytic neoplasms. (p. 211)

Newer noninvasive techniques (eg, reflectance confocal microscopy [RCM], as well as electrical impedance spectroscopy, gene expression analysis, optical coherence tomography, and others can also be considered as these become more readily available. (p. 211)

*UpToDate Melanoma: Clinical Features and diagnosis*

~~It is generally accepted that patients~~Patients with a pigmented lesion that is changing and has additional ABCDE (**a**symmetry, **b**order irregularity, **c**olor variegation, **d**iameter >6 mm, **e**volution) criteria ~~or features of the revised seven-point checklist~~ should be strongly considered for dermatology referral ~~to an expert in skin cancer~~.

~~*MolDX: Pigmented Lesion Assay LCD*~~

*Centers for Medicare & Medicaid Services*

Per MolDX: Pigmented Lesion Assay LCD (L38051), "Only 1 test may be used per patient per clinical encounter, in most cases. In roughly 10% of patients, a second test may be indicated for the same clinical encounter. For rare cases where more than 2 tests are indicated in a single clinical encounter, an appeal with supporting documentation may be submitted for additional tests."

## OVARIAN CANCER

### Ovarian Cancer Diagnostic Algorithmic Tests

*National Comprehensive Cancer Network (NCCN)*

NCCN guidelines for Ovarian Cancer, Fallopian Tube Cancer, and Primary Peritoneal Cancer (~~1~~3.2024) recognize that a number of specific biomarkers and algorithms using multiple biomarker test results have been proposed for preoperatively distinguishing benign from malignant tumors in patients who have an undiagnosed adnexal/pelvic mass. ~~Although the American Congress of Obstetricians and Gynecologists (ACOG) has suggested that ROMA and OVA1 may be useful for deciding which patients to refer to a gynecologic oncologist, other professional organizations have been non-committal.~~ Currently, the NCCN Panel does not recommend the use of these biomarker tests for ~~determining the status~~evaluation of an undiagnosed adnexal/pelvic mass. (p. ~~MS10-MS11).~~ MS-10, MS-11)

### Ovarian Cancer Treatment Algorithmic Tests

*National Comprehensive Cancer Network (NCCN)*

NCCN guidelines for Ovarian Cancer, Fallopian Tube Cancer, and Primary Peritoneal Cancer (~~1~~3.2024) recommend genetic risk evaluation, and germline and somatic testing if not previously done, including *BRCA1/2* to ~~inform~~guide 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~~help determine 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~~3.2024) state that chemosensitivity/resistance ~~and/or other biomarker~~ assays have been proposed for informing decisions related to future chemotherapy ~~in situations where~~if there are multiple equivalent chemotherapy options available~~, but the current~~. This has a category 3 level of evidence which indicates that there is ~~not sufficient to supplant standard-of-care chemotherapy (category 3).~~major NCCN disagreement that the intervention is appropriate. (p. ~~MS-26)~~OV-C, 1 of 12)

NCCN guidelines for Cervical Cancer (~~1~~3.2024) do not mention chemosensitivity or chemoresistance assays as part of clinical care.

NCCN guidelines for Uterine Neoplasms (~~1~~2.2024) do not mention chemosensitivity or chemoresistance assays as part of clinical care.

## LUNG CANCER

### Evidence-Based Lung Cancer Diagnostic Algorithmic Tests

*Concert ~~Genetics~~ Evidence Review for Coverage Determination (Published 12/21/23)*

This body of literature includes validation studies for NodifyXL2. These studies were each published with authors from the company that developed or currently offer the test, with the exception of the 2023 study published by Kheir et al examining NodifyXL2. In this case, the authors disclosed no conflicts of interest except for the lead author who received honoraria from Biodesix and Veracyte for educational events.

Multiple studies have been published on NodifyXL2 and the clinical validity of this test as it pertains to identifying the risk of cancer in patients with lung nodules. Two studies published in 2023 (Pritchett et al and Kheir et al) examined NodifyXL2 and demonstrated adequate clinical utility. Kheir et al published a retrospective study examining patients with lung nodules who were evaluated using the integrated proteomic classifier NodifyXL2 compared to standard clinical care during the same period of time, with a follow-up time of 1 year. In the study group of 102 patients, fewer invasive procedures were performed compared to the non-integrated classifier group of 129 patients (26.5% vs 79.1%; P<0.001). Pritchett et al also examined biopsy rates in patients in matched cohorts (197 patients in each group). Patients in the study group (tested with NodifyXL2) were 74% less likely to undergo an invasive procedure compared to the control group (absolute difference 14%; P<0.001), and for every 7 patients tested, one unnecessary invasive procedure was avoided. Both of these studies had similar inclusion criteria for patients: age 40 years or older, with a risk for cancer of 50% or less according to the Mayo Solitary Pulmonary Nodule calculator, a lung nodule between 8 and 30 mm in diameter, and no history of cancer (except non-melanomatous skin cancer) within 5 years of the discovery of the lung nodule.

### Emerging Evidence Lung Cancer Diagnostic Algorithmic Tests

*Concert ~~Genetics~~ Evidence Review for Coverage Determination (Published 12/21/23)*

Multiple studies have been published on Percepta Bronchial Genomic Classifier and REVEAL Lung Nodule Characterization and their ability to identify risk of cancer in patients with lung nodules. This body of literature includes studies meant to assess clinical validity for each test. Overall, these studies inadequately demonstrate the clinical validity of these tests for distinguishing high risk nodules from low risk nodules.

Percepta originally had a cost-effectiveness study published in 2017. A new validation study for this test was published in 2021 and it is not clear if the new test would also be cost-effective.

There are a few studies that include some characterization of clinical utility for the Percepta and REVEAL Lung Nodule Characterization and their ability to identify risk of cancer in patients with lung nodules. But these studies have significant flaws, including small population sizes, and potential bias due to authors with conflict of interest. These studies were each published with authors from the company that developed or currently offers the test. Additionally, the costs of these tests compared to costs of under- and over-diagnosis of lung cancer in patients with lung nodules needs to be completed. To our knowledge, there are currently no randomized controlled trials enrolling for Percept or REVEAL.

Tests that have limited established clinical utility or validity as defined in the Concert policy for General Approach to Genetic and Molecular testing do not meet the threshold for coverage. Evidence for validity may include a Technology Assessment conducted by an independent third party (e.g.MolDx Tech, ECRI, Optum Genomic) and/or evidence-based guidelines published by professional societies. Such evidence was not identified for the tests referenced by this policy.

**Evidence-Based Lung Cancer Treatment Algorithmic Tests**

~~*Concert Genetics*~~*Centers for Medicare and Medicaid Services*

The CMS local coverage determination (LCD) entitled "MolDX: Predictive Classifiers for Early Stage Non-Small Cell Lung Cancer" includes the following criteria for lung cancer treatment algorithmic tests:

- "The patient has a non-squamous NSCLC with a tumor size < 5cm, and there are no positive lymph nodes (i.e. American Joint Committee on Cancer (AJCC) Eighth Edition Stages I and IIa)
- The patient is sufficiently healthy to tolerate chemotherapy
- Adjuvant platinum-containing chemotherapy is being considered for the patient

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

From the Billing and Coding article:

DetermaRx (PLA code 0288U) is a covered test.

**Emerging Evidence** ~~*Review for Coverage Determination*~~ **Lung Cancer Treatment Algorithmic Tests**

~~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.~~

Tests that have limited established clinical utility or validity as defined in the Concert policy for General Approach to Genetic and Molecular testing do not meet the threshold for coverage. Evidence for validity may include a Technology Assessment conducted by an independent third party (e.g. MolDx Tech, ECRI, Optum Genomic) and/or evidence-based guidelines published by professional societies. Such evidence was not identified for the tests referenced by this policy.

**BLADDER AND URINARY TRACT CANCER**

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

There is insufficient evidence to support the use of this test. No recommendations for or against this testing within standard professional society guidelines covering this area of testing were identified. Sources reviewed: National Comprehensive Cancer Network ~~*(NCCN)*~~

~~NCCN guidelines for~~ Bladder Cancer ~~(1.2024) support consideration for urinary urothelial tumor markers for high-risk patients with non-muscle-invasive bladder cancer (category 2B recommendation, which is based on lower-level evidence with NCCN consensus that the intervention is appropriate). (p. BL-E 2 of 6) Further discussion in these~~ guidelines ~~acknowledge that it is unclear if this type of testing offers information that is clinically useful for detecting or managing these tumors, hence the weaker recommendation of 2B by the panel~~(4.2024), ~~. (p. MS-13)~~

~~*American Urological Association and Society of Urologic Oncology*~~

The American Urological Association and Society of Urologic Oncology (~~Chang~~Hozbeierlein et al~~, 2016; amended 2020) addressed the diagnosis and treatment of non-muscle-invasive bladder cancer, based on a systematic review and includes the following statements on the use of urine markers after the diagnosis of bladder cancer:~~).

## Bladder Cancer Treatment and Recurrence Algorithmic Tests

*Centers for Medicare and Medicaid Services*

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

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

1. The beneficiary is being actively managed for bladder cancer.
2. The beneficiary is within the population and has the indication for which the test was developed and is covered. The laboratory will make available the appropriate indications of the test to the treating/ordering physician.
3. At least 1 of the 2 criteria are met:
    a. The patient is a candidate for multiple potential treatments, which could be considered to have varied or increasing levels of intensity based on a consensus guideline, and the physician and patient must decide among these treatments. OR

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

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

b. The patient is a candidate for multiple therapies, and the test has shown that it predicts response to a specific therapy among accepted therapy options based on nationally recognized society consensus guidelines (i.e., National Comprehensive Cancer Network [NCCN], American Society of Clinical Oncology [ASCO], Society of Urologic Oncology [SUO], or American Urological Association [AUA]).

4. The test demonstrates analytical validity including both analytical and clinical validations. If the test relies on an algorithm (which may range in complexity from a threshold determination of a single numeric value to a complex mathematical or computational function), the algorithm must be validated in a cohort that is not a development cohort for the algorithm.
5. The test has demonstrated clinical validity and utility, establishing a clear and significant biological/molecular basis for stratifying patients and subsequently selecting (either positively or negatively) a clinical management decision (in 4. above) in a clearly defined population.
6. The test successfully completes a Molecular Diagnostic Services Program (MolDX®) technical assessment that ensures the test is reasonable and necessary as described above.
7. Only 1 test may be performed prior to the initiation of therapy UNLESS a second test that interrogates different genomic content AND meets all the criteria established herein, is reasonable and necessary.
8. The genomic content interrogated by the test must be relevant to the therapy under consideration."

## PANCREATIC CANCER

### Evidence-Based Pancreatic Cyst Risk Assessment Algorithmic Tests

~~*National Comprehensive Cancer Network (NCCN)*~~

~~NCCN guidelines for Pancreatic Adenocarcinoma (1.2024) discuss the use of endoscopic ultrasound to follow patients with pancreatic cysts and after the removal, citing that the risk of malignancy in mucinous cystic neoplasms is less than 15%. (p. MS-6, MS-10) The guidelines do not include recommendation or discussion for the use of molecular analysis of pancreatic cysts to stratify risk of cancer.~~

~~*American College of Gastroenterology*~~

~~The American College of Gastroenterology (2018) published guidelines for the diagnosis and management of pancreatic cysts, which included the following:~~

~~"A number of DNA, RNA, protein, and metabolomic markers have been evaluated in cyst fluid. The majority of these are still early in development and not yet ready for translation into clinical practice. However, analysis of DNA mutations in cyst fluid has shown promise in identifying IPMNs [intraductal papillary mucinous neoplasms] and MCNs [mucinous cystic neoplasms]."~~*Centers for Medicare and Medicaid Services*

The CMS local coverage determination (LCD) entitled "Loss-of-Heterozygosity Based Topographic Genotyping with PathfinderTG" includes the following criteria for PathfinderTG (currently known as PancraGen):

"PathfinderTG will be considered medically reasonable and necessary when selectively used as an occasional second-line diagnostic supplement:

- Only where there remains clinical uncertainty as to either the current malignancy or the possible malignant potential of the pancreatic cyst based upon a comprehensive first-line evaluation; AND
- A decision regarding treatment (e.g. surgery) has NOT already been made based on existing information.

The specific requirements for medical necessity involve:

- Highly-concise affirmation, documented in the medical record, that a decision regarding treatment has not already been made and that the results of the molecular evaluation will assist in determining if more aggressive treatment than what is being considered is necessary.

- Previous first-line diagnostics, such as, but not restricted to, the following have demonstrated:
    - A pancreatic cyst fluid carcinoembryonic antigen (CEA), which is greater than or equal to 200 ng/ml, suggesting a mucinous cyst, but is not diagnostic.
    - Cyst cytopathologic or radiographic findings, which raise the index of malignancy suspicion, but where second-line molecular diagnostics is expected to be more compelling in the context of a surgical vs. non-surgical care plan.

Specific criteria of Non-coverage to include either:

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

- Cytology not showing malignancy but meets AGA guidelines to reach a definitive diagnosis of benign disease. Lesions must be:
    - Under 1 cm;

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

**Emerging Evidence Pancreatic Cyst Risk Assessment Algorithmic Tests**

Tests that have limited established clinical utility or validity as defined in the Concert policy for General Approach to Genetic and Molecular testing do not meet the threshold for coverage. Evidence for validity may include a Technology Assessment conducted by an independent third party (e.g. MolDx Tech, ECRI, Optum Genomic) and/or evidence-based guidelines published by professional societies. Such evidence was not identified for the tests referenced by this policy.

~~(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) (1.~~2024~~2025) state that gene sequencing to predict tissue of origin is not recommended. (p. OCC-1) There has been no clinical benefit from gene expression profiling to identify tissue of origin. (p. MS-~~).~~4)

## POLYGENIC RISK SCORE TESTS

### Breast Cancer Polygenic Risk Score Tests

*National Comprehensive Cancer Network (NCCN)*

NCCN guidelines for Genetic/Familial High-Risk Assessment for Breast, Ovarian, and Pancreatic cancers (~~2~~3.2024) speak broadly about the use of polygenic risk scores, stating that there are currently significant limitations to this type of testing, and ~~it should~~their use is not ~~be used~~recommended for clinical management at this time outside of the context of a clinical trial (p. EVAL-A, 3 of 10).

~~back to top~~

| Reviews, Revisions, and Approvals | Revision Date | Approval Date | Effective Date |
|---|---|---|---|
| Converted Corporate to local policy. | 12/23 | 2/27/24 | |
| Semi-annual review. In Evidence Based Cutaneous Melanoma Prognostic Algorithmic Tests, now COVERED for specific cutaneous melanoma prognostic algorithmic tests, based on Concert Evidence Review demonstrating clinical validity and utility. In Evidence Based Lung Cancer Diagnostic Algorithmic Tests, now COVERED for specific lung cancer diagnostic algorithmic tests, based on Concert Evidence Review demonstrating clinical validity and utility. In Cutaneous Melanoma Risk Assessment Algorithmic Tests, now COVERED for specific cutaneous melanoma risk assessment algorithmic tests, based on review of guidelines and current literature, which demonstrated clinical validity and utility. In Evidence Based Prostate Cancer Risk Assessment and Diagnostic Algorithmic Tests, now COVERED for specific prostate cancer risk assessment and diagnostic algorithmic tests based on guidelines. In Prostate Cancer Diagnostic Algorithmic Tests, consolidated criteria into the Evidence Based Prostate Cancer Risk Assessment and Diagnostics Algorithmic Tests coverage criteria. In Emerging Evidence Prostate Cancer Diagnostic and Algorithmic Tests, NEW - Created separate criteria to distinguish between tests with varying levels of evidence for validity and guideline support. In Emerging Evidence Cutaneous Melanoma Prognostic Algorithmic Tests, NEW - Created separate criteria sets to distinguish between tests with varying levels of evidence for validity and guideline support. In Emerging Evidence Lung Cancer Diagnostic Algorithmic Tests, NEW - Created separate criteria sets to distinguish between tests with varying levels of evidence for validity and guideline support. In Oncology Test Specific Not Covered Algorithmic Tests, moved criteria to policy "Genetic Testing: General Approach to Genetic and Molecular Testing" to consolidate general coverage criteria for new algorithmic tests. Minor rewording for clarity throughout. Coding, reference-table, background and references updated. | 06/24 | 9/4/24 | 10/4/24 |
| ~~Semi-annual review. In Evidence Based Cutaneous Melanoma Prognostic Algorithmic Tests, now COVERED for specific cutaneous melanoma prognostic algorithmic tests, based on Concert Evidence Review demonstrating clinical validity and utility. In Evidence Based Lung Cancer Diagnostic Algorithmic Tests, now COVERED for specific lung cancer diagnostic algorithmic tests, based on Concert Evidence Review demonstrating clinical validity and utility. In Cutaneous Melanoma Risk Assessment Algorithmic Tests, now COVERED for specific cutaneous melanoma risk assessment algorithmic tests, based on review of guidelines and current literature, which demonstrated clinical validity and utility. In Evidence Based Prostate Cancer Risk Assessment and Diagnostic Algorithmic Tests, now COVERED for specific prostate cancer risk assessment and diagnostic algorithmic tests based on guidelines. In Prostate Cancer Diagnostic Algorithmic Tests, consolidated criteria into the~~ | ~~06/24~~1/25 | ~~9/4/24~~ | ~~10/4/24~~ |

| Reviews, Revisions, and Approvals | Revision Date | Approval Date | Effective Date |
|---|---|---|---|
| ~~Evidence Based Prostate Cancer Risk Assessment and Diagnostics Algorithmic Tests coverage criteria. In Emerging Evidence Prostate Cancer Diagnostic and Algorithmic Tests, NEW - Created separate criteria to distinguish between tests with varying levels of evidence for validity and guideline support. In Emerging Evidence Cutaneous Melanoma Prognostic Algorithmic Tests, NEW - Created separate criteria sets to distinguish between tests with varying levels of evidence for validity and guideline support. In Emerging Evidence Lung Cancer Diagnostic Algorithmic Tests, NEW - Created separate criteria sets to distinguish between tests with varying levels of evidence for validity and guideline support. In Oncology Test Specific Not Covered Algorithmic Tests, moved criteria to policy "Genetic Testing: General Approach to Genetic and Molecular Testing" to consolidate general coverage criteria for new algorithmic tests. Minor rewording for clarity throughout. Coding, reference table, background and references updated.~~Semi-annual review. Updated title to reflect V1.2025 version. Gene Expression Profiling Breast Cancer Subtyping Tests: Removed test "Insight TNBCtype (Insight Molecular Labs - 0153U" from the Policy Reference Table, given this test is unavailable online; Updated NCCN Breast Cancer guidelines from version 1.2024 to 2.2024. Breast DCIS Prognostic Algorithmic Tests: Coverage status changed from non-covered to covered based on LCD guidelines; Added radiation therapy as an additional example of a treatment for which this criteria may be appropriate; Updated NCCN Breast Cancer treatment guidelines version to 4.2024 in references; Updated Policy Reference Table; Streamlined portions of Background and Rationale section for brevity; Updated References. Colorectal Cancer Prognostic Algorithmic Tests: updated test in Policy Reference Table. Emerging Evidence Prostate Cancer Risk Assessment and Diagnostic Algorithmic Tests: Removed Apifiny (Armune Bioscience) and associated PLA 0021U due to non-orderability of this test; Added the following tests and their PLA codes; Stockholm3 (BioAgilytix Diagnostics) - 0495U, Oncriteria setssure Prostate (DiaCarta, Inc.) - 0497U, Tempus p-MSI - 0512U, Tempus p-Prostate - 0513U; Updated NCCN Prostate Cancer Early Detection guidelines to version 3.2024; Updated NCCN Prostate Cancer Early Detection guidelines from version 1.2024 to 2.2024; In the Background and Rationale, added the following; "as current evidence indicates neither benefit nor harm at this time." Ovarian Cancer Diagnostic Algorithmic Tests: Updated NCCN guidelines for Ovarian Cancer, Fallopian Tube Cancer, and Primary Peritoneal Cancer from version 1.2024 to 2.2024; Removed the following from the Background and Rationale; " Although the American Congress of Obstetricians and Gynecologists (ACOG) has suggested that ROMA and OVA1 may be useful for deciding which patients to refer to a gynecologic oncologist, other professional organizations have been non-committal."; Streamlined portions of Background and Rationale section for brevity. Gynecologic Cancer Treatment Algorithmic Tests: Updated NCCN | | | |

| Reviews, Revisions, and Approvals | Revision Date | Approval Date | Effective Date |
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| Ovarian Cancer treatment guidelines to version 3.2024; Updated "NCCN guidelines for Ovarian Cancer, Fallopian Tube Cancer, and Primary Peritoneal Cancer" section of the Background and Rationale; 1. Added "This has a category 3 level of evidence which indicates that there is major NCCN disagreement that the intervention is appropriate. (p. OV-C, 1 of 12)"; 2. Removed "but the current level of evidence is not sufficient to supplant standard-of-care chemotherapy (category 3). (p. MS-26)"; Updated NCCN guidelines for Uterine Neoplasms from version 1.2024 to 2.2024; Updated the NCCN guidelines for Cervical Cancer from 1.2024 to 3.2024. Lung Cancer Treatment Algorithmic Tests: RETIRED criteria and developed two criteria sets based on LCD guidelines. Emerging Evidence Lung Cancer Diagnostic Algorithmic Tests: NEW Criteria set created for lung cancer diagnostic algorithmic tests for which clinical validity has not been established; Evidence review update (see separate PDF). Bladder/Urinary Tract Cancer Diagnostic, Treatment and Recurrence Algorithmic Tests: RETIRED criteria and developed two criteria sets based on LCD guidelines; Updated Holzerbeierlin et al (AUA/ASCO/SUO) guideline to current amended version. Pancreatic Cyst Risk Assessment Algorithmic Tests: RETIRED criteria and developed two criteria sets based on LCD guidelines. Breast Cancer Polygenic Risk Score Tests: Updated NCCN Breast Cancer Treatment Guidelines version to 4.2024 in references; Updated NCCN guidelines for Genetic/Familial High-Risk Assessment for Breast, Ovarian, and Pancreatic cancers from version 2.2024 to 3.2024; Changed "it should not be used" to "their use is not recommended"; Updated page number for NCCN guideline. Evidence-Based Prostate Cancer Risk Assessment and Diagnostic Algorithmic Tests: Removed "very" from the phrase "very suspicious for cancer" in criteria I.B.2; Definition of high-risk prostate cancer was updated with criteria for very high-risk prostate cancer, including cT3b-cT4, primary Gleason pattern 5, or multiple high-risk features; The definition of very low-risk prostate cancer was expanded to specify ≤3 positive cores/fragments and ≤50% cancer in each core/fragment. Added "where clinical utility and validity have not been demonstrated." to section II of the criteria; Removed the following from the Background and Rationale: "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)"; Updated the NCCN Prostate Cancer Early Detection guidelines from version 1.2024 to 2.2024, and updating wording in this section of the Background and Rationale. Ovarian Cancer Treatment Algorithmic Tests: Added the following test and PLA Code to the Policy Reference Table; | | | |

| Reviews, Revisions, and Approvals | Revision Date | Approval Date | Effective Date |
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| Avantect Ovarian Cancer Test (ClearNote Health) - 0507U; Updated NCCN guidelines for Ovarian Cancer, Fallopian Tube Cancer, and Primary Peritoneal Cancer from version 1.2024 to 2.2024, and updated some of the wording in that section of the Background and Rationale; Evidence-Based Lung Cancer Diagnostic Algorithmic Tests: Added "where clinical utility and validity have not been demonstrated." to section II of the criteria. Thyroid Cancer Diagnostic Algorithmic Tests: Added "(i.e., Bethesda diagnostic category III or IV)" to exemplify potential indeterminate cytologic findings that may meet criteria; Removed the following criteria for coverage; "Clinical and/or radiologic findings of the thyroid nodules are indeterminate of malignancy" due to redundancy with another criteria; Updated NCCN Guidelines for Thyroid Carcinoma from version 4.2023 to 2.2024 and changed "state that clinicians can consider" to "recommends consideration of" in that section of the Background and Rationale. Breast Cancer Treatment and Prognostic Algorithmic Tests: Updated NCCN Breast Cancer Treatment Guidelines version to 4.2024 in references; Updated NCCN guidelines for Breast Cancer from version 1.2024 to 2.2024, and changed "strongly recommends" to "recommends consideration of" in that section of the Background and Rationale. Cutaneous Melanoma Diagnostic Algorithmic Tests: Updated NCCN guidelines for Cutaneous Melanoma from version 3.3023 to 2.2024; Updated wording in the NCCN guidelines for Cutaneous Melanoma section of the Background and Rationale and added this statement; "NCCN recommends consideration of these tests in conjunction with clinical and pathology evaluation". Breast Cancer Prognostic Algorithmic Tests: Refined nodal status criteria by specifying pathological nodal staging (pN0, pN1mi, pN1) to enhance clinical precision and clarity (formally, the terms "node negative" and "node positive" were used); Updated NCCN Breast Cancer Treatment Guidelines version to 4.2024 in references; Updated NCCN Breast Cancer guidelines from version 1.2024 to 2.2024; Streamlined portions of Background and Rationale section for brevity. Breast Cancer Extended Endocrine Therapy Algorithmic Tests: Updated NCCN Breast Cancer Treatment Guidelines version to 4.2024 in references; Updated NCCN Breast Cancer guidelines from version 1.2024 to 2.2024; Added "Breast Cancer Index" to the Background and Rationale for clarification of the BCI acronym. Uveal Melanoma Prognostic Algorithmic Tests: Streamlined portions of Background and Rationale section for brevity. Evidence-Based Cutaneous Melanoma Prognostic Algorithmic Tests: Added MelaNodal to the criteria. This test uses the same algorithm as the Merlin assay, for which we allow coverage based on this criteria set; Evidence review updated (see separate PDF); Updated Background and Rationale to add "MelaNodal Predict" where appropriate; Updated published date in the reference. Prostate Cancer Treatment and Prognostic Algorithmic Tests: Added Artera AI to the criteria for coverage; Multiple updates to the criteria based on NCCN guideline changes; Criteria | | | |

| Reviews, Revisions, and Approvals | Revision Date | Approval Date | Effective Date |
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| set was changed from " " to " "; Updated NCCN guidelines for Prostate Cancer from version 4.2023 to 3.2024; Added ArteraAI Prostate Test (Artera - CPT 0376U) to the policy reference table; Removed the following information, which is no longer included in NCCN guidelines; "These guidelines for Prostate Cancer (3.2023) also state that, in individuals who have PSA recurrence/persistence after radical prostatectomy (RP) and are expected to live more than 5 years, molecular assay such as Decipher can be considered as an alternative to PSADT (PSA doubling time) to inform counseling (p. PROS-10); Additionally, individuals with adverse feature(s) found post-RP and no lymph node metastases could consider Decipher molecular assay if not previously performed to inform adjuvant treatment (p. PROS 8 and PROS 8A)"; Added the following to the Background and Rationale: "when there is the possibility of changing disease management in men with localized prostate cancer and life expectancy of 10 yrs or more (p. PROS-4,5,6). The most common reasons to use these tools is for deciding between active surveillance and radical treatment, or use of radiation alone vs radiation with androgen deprivation therapy (short or long term). These tests can also be useful post prostatectomy with recurrence, when choosing radiation with or without androgen deprivation therapy. (p. PROS-H, 1 of 8). These tests should not be used for very low risk or very high risk disease as they have not been validated in these populations (p. PROS-H, 1 and 4-6 of 8)." Cutaneous Melanoma Risk Assessment Algorithmic Tests: Updated NCCN Guidelines for Cutaneous Melanoma from version 3.2023 to 2.2024; Changed "states that" to "recommends consideration of" in the NCCN Guidelines for Cutaneous Melanoma section of the Background and Rationale; Streamlined portions of Background and Rationale section for brevity. Emerging Evidence Pancreatic Cyst Risk Assessment Algorithmic Tests: NEW criteria set created for pancreatic cyst diagnostic algorithmic tests for which clinical validity has not been established. Evidence-Based Pancreatic Cyst Risk Assessment Algorithmic Tests: NEW criteria set developed based on LCD guideline. Emerging Evidence Lung Cancer Treatment Algorithmic Tests: NEW criteria set created for lung cancer treatment algorithmic tests for which clinical validity has not been established. Evidence-Based Lung Cancer Treatment Algorithmic Tests: NEW criteria set developed based on LCD guideline. Bladder Cancer Treatment and Recurrence Algorithmic Tests: Coverage status changed from non-covered to covered based on LCD guidelines; Criteria renamed (formerly "Bladder/Urinary Tract Cancer Diagnostic, Treatment, and Recurrence Algorithmic Tests").Semi-annual review. | | | |
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back to top

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back to top