Concert Genetics Oncology: Algorithmic Testing

Reference Number: LA.CP.CG.25 Coding implications
Date of Last Revision ~~01/25~~03/26
Revision Log

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

OVERVIEW

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

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

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

- ~~Results of 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 algorithmic tests may be useful to assist in surgical and management decision-making and to identify individuals who may benefit from 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.

For additional information see the Rationale section.

POLICY REFERENCE TABLE

Coding Implications

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

~~Criteria Sections~~CRITERIA SECTIONS	~~Example Tests, Labs~~EXAMPLE TESTS (LABS)		~~Common CPT Codes~~COMMON BILLING CODES	~~Common ICD Codes~~ REF	~~Ref~~
~~Breast Cancer~~ Breast Cancer					
Breast Cancer Treatment and Prognostic Algorithmic Tests	Oncotype Dx Breast Recurrence Score - 81519 (Exact Sciences)	~~81519, S3854*~~	81519*, S3854*, C50.01 1-C50.92, Z17.0	1	

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~~Criteria Sections~~CRITERIA SECTIONS	~~Example Tests, Labs~~EXAMPLE TESTS (LABS)		~~Common CPT Codes~~COMMON BILLING CODES	~~Common ICD Codes~~ REF	~~Ref~~
~~Breast Cancer Extended Endocrine Therapy Algorithmic Tests~~	~~Breast Cancer Index (bioTheranostics)~~		~~81518*, S3854*~~	~~C50.011 - C50.92, Z17.0~~	~~1, 23~~
Breast Cancer Extended Endocrine Therapy Algorithmic Tests	~~EndoPredict (Myriad)~~Breast Cancer Index - 81518 (bioTheranostics)	~~81522*, S3854*~~	81518*, S3854*, C50.011-C50.92, Z17.0~~,~~ ~~Z17.1~~	1, ~~23~~21	
Breast Cancer Prognostic Algorithmic Tests	~~MammaPrint (Agendia, Inc.)~~ End oPredict - 81522 (Myriad)		81520*, 81521*, 81522*, 81523~~**~~*, S3854~~**~~*, C50, Z17.0, Z17.1		
	~~Prosigna Assay (NeoGenomics)~~MammaPrint - 81521, 81523 (Agendia, Inc.)				
~~Gene Expression Profiling Breast Cancer Subtyping Tests~~	Prosigna Assay - 81520 (NeoGenomics)~~BluePrint (Agendia, Inc.)~~			~~C50-C50.929~~	~~1, 23~~
Gene Expression Profiling Breast Cancer Subtyping Tests~~Breast DCIS Prognostic Algorithmic Tests~~	BluePrint (Agendia, Inc.)~~Oncotype DX Breast DCIS Score (Exact Sciences)~~		~~0045U*~~ 81599*, S3854*, 0153U*	~~D05.~~ 1, 23	~~31~~

~~Criteria Sections~~CRITERIA SECTIONS	~~Example Tests, Labs~~EXAMPLE TESTS (LABS)		~~Common CPT Codes~~COMMON BILLING CODES	~~Common ICD Codes~~ REF	~~Ref~~
	Insight TNBCtype - 0153U (Insight Molecular Labs)		, C50-C50.929		
~~Colorectal Cancer Prognostic Algorithmic Tests~~Breast DCIS Prognostic Algorithmic Tests	Oncotype DX ~~Colon Recurrence~~Breast DCIS Score - 0045U (Exact Sciences)		~~81525*~~ 0045U*, D05.1	~~C18.0 - C18.9~~ 28	~~2~~
Colorectal Cancer	~~miR-31now (GoPath Laboratories)~~	~~0069U*~~			
Colorectal Cancer Prognostic Algorithmic Tests	~~Immunoscore (Veracyte)~~Oncotype DX Colon Recurrence Score - 81525 (Exact Sciences) miR-31now - 0069U* (GoPath Laboratories)		81525*, 0069U*, 0261U**, C18.0-C18.9	2	
	~~Oncotype DX Genomic Prostate Score (MDxHealth)~~Immunoscore - 0261U (Veracyte)			~~C61~~	~~3, 18~~
Prostate Cancer	~~Decipher Prostate Biopsy Genomic Classifier (Veracyte)~~	~~81542*~~			

~~Criteria Sections~~CRITERIA SECTIONS	~~Example Tests, Labs~~EXAMPLE TESTS (LABS)	~~Common CPT Codes~~COMMON BILLING CODES	~~Common ICD Codes~~ REF	~~Ref~~
Prostate Cancer Treatment and Prognostic Algorithmic Tests	~~Decipher~~ArteraAI Prostate ~~RP Genomic Classifier (Veracyte~~Test - 0376U (Artera)	81541*, 81542*, 0047U*, 0376U*, C61	3, 16	
	~~Prolaris (Myriad Genetics)~~ Oncotype DX Genomic Prostate Score - 0047U (MDxHealth)			
	~~ArteraAI~~Decipher Prostate ~~Test (Artera~~RP Genomic Classifier - 81542 (Veracyte)			
	~~4K Prostate Score (Serum) (BioReference Laboratories)~~Prolaris - 81541 (Myriad Genetics)		~~C61, Z12.5~~	~~4, 22~~
	Decipher Prostate ~~Health Index (ARUP Laboratories~~Biopsy Genomic Classifier - 81542 (Veracyte)			
Evidence-Based Prostate Cancer Risk Assessment and Diagnostic Algorithmic Tests	~~SelectMDx for~~4K Prostate ~~Cancer (MDxHealth~~Score (Serum) - 81539 (BioReference Laboratories)	~~0339U*~~ 81479, 81539*, 84153*, 84154*,	4, 20	

~~Criteria Sections~~CRITERIA SECTIONS	~~Example Tests, Labs~~EXAMPLE TESTS (LABS)	~~Common CPT Codes~~COMMON BILLING CODES	~~Common ICD Codes~~ REF	~~Ref~~
	~~ExoDx~~ Prostate ~~Test (ExosomeDx~~Health Index (ARUP Laboratories)	81551*, 86316*, 0005U*, 0339U*, 0359U*, 0403U*, C61, Z12.5		
	~~IsoPSA (Cleveland Diagnostics, Inc)~~SelectMDx for Prostate Cancer - 0339U (MDxHealth)			
	~~MyProstateScore (Lynx DX)~~ ExoDx Prostate Test - 0005U (ExosomeDx)			
	~~ConfirmMDx for Prostate Cancer (MDxHealth)~~IsoPSA - 0359U* (Cleveland Diagnostics, Inc)			
	~~Prostate Cancer Gene 3 (Integrated Regional Laboratories)~~MyProstateScore 2.0 - 0403U (LynxDX)			
~~Emerging Evidence Prostate Cancer Risk Assessment and Diagnostic Algorithmic Tests~~	~~PanGIA~~ConfirmMDx for Prostate ~~(Genetics Institute of America~~Cancer – 81551* (MDxHealth)		~~C~~	~~22~~
	Prostate Cancer Gene 3 (Integrated Regional			

~~Criteria Sections~~CRITERIA SECTIONS	~~Example Tests, Labs~~EXAMPLE TESTS (LABS)	~~Common CPT Codes~~COMMON BILLING CODES	~~Common ICD Codes~~ REF	~~Ref~~
	Laboratories)			
Emerging Evidence Prostate Cancer Risk Assessment and Diagnostic Algorithmic Tests	~~MyProstateScore 2.0 (Lynx Dx)~~Apifiny - 0021U* (Armune Bioscience) ~~miR Sentinel~~PanGIA Prostate ~~Cancer Test (miR Scientific~~- 0228U (Genetics Institute of America)	~~0403U*~~ 0021U*, 0228U*, 0343U*, 0424U*, 0433U*, 0495U*, 0497U*, 0512U*, 0513U*, C61, Z12.5	20	
	~~EpiSwitch~~miR Sentinel Prostate ~~Screening~~Cancer Test ~~(PSE) (Oxford BioDynamics~~- 0343U or 0424U (UmiR Scientific)			
	EpiSwitch Prostate Screening Test (PSE) - 0433U (Oxford BioDynamics)			
	Stockholm3 - 0495U (BioAgilytix Diagnostics)	~~0495U*~~		

~~Criteria Sections~~CRITERIA SECTIONS	~~Example Tests, Labs~~EXAMPLE TESTS (LABS)		~~Common CPT Codes~~COMMON BILLING CODES	~~Common ICD Codes~~ REF	~~Ref~~
	OncoAssure Prostate - 0497U (DiaCarta, Inc.)				
	Tempus p-MSI - 0512U* (Tempus AI, Inc)				
	Tempus p-Prostate - 0513U* (Tempus AI, Inc)				
~~Thyroid Cancer~~ Thyroid Cancer					
Thyroid Cancer Diagnostic Algorithmic Tests	ThyroSeq Genomic Classifier - 0026U (CBLPath)	~~0026U*~~	81546*, 0018U*, 0026U*, 0204U*, 0245U*, 0287U*, C73, D44.0, E04.1	5, 6~~, 7~~	
	ThyGeNEXT ~~(~~- 0245U*~~(~~Interpace Diagnostics)		~~0245U*~~		
	ThyraMIR - 0018U* (Interpace Diagnostics)				

~~Criteria Sections~~CRITERIA SECTIONS	~~Example Tests, Labs~~EXAMPLE TESTS (LABS)	~~Common CPT Codes~~COMMON BILLING CODES	~~Common ICD Codes~~ REF	~~Ref~~
	Afirma Genomic Sequencing Classifier – 81546* (Veracyte)			
	Afirma Xpression Atlas - 0204U* (Veracyte)			
	ThyroSeq CRC - 0287U* (UPMC)			
~~Uveal Melanoma~~ Uveal Melanoma				
Uveal Melanoma Prognostic Algorithmic Tests	DecisionDx-UM – 81552* (Castle Bioscience, Inc.)	81552~~*~~*, C69	~~C69~~7	~~8~~
~~Cutaneous Melanoma~~ Cutaneous Melanoma				
~~Evidence-Based Cutaneous Melanoma Prognostic Algorithmic Tests~~Cutaneous Melanoma Prognostic Algorithmic Tests	DecisionDx-Melanoma – 81529* (Castle Biosciences, Inc.) ~~81529*~~	81479, 81529*, 81599*, 0387U*, C43, D03.0-D03.9, Z12.83	~~24, 25~~22, 34	
	Merlin Melanoma (BioCartis)	~~81479~~		
	MelaNodal (Quest)			
~~Emerging Evidence Cutaneous Melanoma Prognostic Algorithmic Tests~~Emerging Evidence	AMBLor - 0387U* (AMLo ~~0387U*~~	81479, 81529	25	

~~Criteria Sections~~CRITERIA SECTIONS	~~Example Tests, Labs~~EXAMPLE TESTS (LABS)		~~Common CPT Codes~~COMMON BILLING CODES	~~Common ICD Codes~~ REF	~~Ref~~
Cutaneous Melanoma Prognostic Algorithmic Tests	Biosciences)		*, 81599*, 0387U*, C43, D03.0-D03.9, Z12.83		
Cutaneous Melanoma Diagnostic Algorithmic Tests	myPath Melanoma - 0090U* (Castle Biosciences, Inc.)	~~0090U*~~	0090U*, 0314U*, D22.0-D22.9, D48.5, D49.2, Z12.83	8, 9, ~~10, 21~~19	
	DecisionDx- DiffDx-Melanoma - 0314U* (Castle Biosciences, Inc.)				
Cutaneous Melanoma Risk Assessment Algorithmic Tests	Pigmented Lesion Assay - 0089U* (DermTech)		~~0314U*~~ 0089U*, D22-D23, Z12.83	8, 9, 23, 24, 25	
Ovarian Cancer	~~Pigmented Lesion Assay (DermTech)~~	~~0089U*~~	~~D22-D23, Z12.83~~		~~9, 10, 26, 27, 28~~

~~Criteria Sections~~CRITERIA SECTIONS	~~Example Tests, Labs~~EXAMPLE TESTS (LABS)	~~Common CPT Codes~~COMMON BILLING CODES	~~Common ICD Codes~~ REF	~~Ref~~
Ovarian Cancer Diagnostic Algorithmic Tests~~Ovarian Cancer~~	OVA1 – 81503* (Aspira Women's Health)	81500*, 81503*, 0003U*, 0375U*, 0507U*, D27.0, D27.1, D27.9, D39.10-D39.12, D39.9, D49.59, D49.9	10	
	~~OVA1~~Overa - 0003U* (Aspira Women's Health)	~~81503*~~	~~D27.0, D27.1, D27.9, D39.10-D39.12, D39.9, D49.59, D49.~~	~~11~~

~~Criteria Sections~~CRITERIA SECTIONS	~~Example Tests, Labs~~EXAMPLE TESTS (LABS)	~~Common CPT Codes~~COMMON BILLING CODES	~~Common ICD Codes~~ REF	~~Ref~~
			~~9~~	
Ovarian Cancer Treatment Algorithmic Tests	~~Overa (Aspira Women's Health)~~Risk of Ovarian Malignancy (ROMA) – 81500* (Labcorp)	~~0003U*~~0172U*, C48, C56, C57.0	11, 19	
	~~Risk of Ovarian Malignancy (ROMA) (Labcorp)~~OvaWatch - 0375U* (Aspira Women's Health)			
	~~OvaWatch (Aspira Women's~~Avantect Ovarian Cancer Test - 0507U* (ClearNote Health)			
Ovarian Cancer Treatment Algorithmic Tests	~~Avantect Ovarian Cancer Test (ClearNote Health)~~myChoice CDx - 0172U* (Myriad Genetics)	~~0507U*~~ 0172U*, C48, C56, C57.0	10, 17	
Gynecologic Cancer	~~myChoice CDx (Myriad Genetics)~~ ~~0172U*~~	~~C48, C56, C57.0~~		~~11, 19~~
Gynecologic Cancer Treatment Algorithmic Tests~~Gynecologic Cancer~~	ChemoFx – 81535* (Helomics Corporation)	81535*, 81536*, C51-C57	10, 14, 15	

~~Criteria Sections~~CRITERIA SECTIONS	~~Example Tests, Labs~~EXAMPLE TESTS (LABS)	~~Common CPT Codes~~COMMON BILLING CODES	~~Common ICD Codes~~ REF	~~Ref~~
	ChemoFx - Additional Drug – 81536* (Helomics Corporation)	~~81535 *~~	~~C51-C57~~	~~11, 16, 17~~
Lung Cancer	~~ChemoFx - Additional Drug (Helomics Corporation) 81536*~~			
~~Lung Cancer~~ Evidence-Based Lung Cancer Risk Assessment Algorithmic Tests	Nodify XL2 - 0080U *(Biodesix)	0080U*, R91.1	31, 35, 36	
~~Evidence-Based Lung Cancer Diagnostic Algorithmic Tests~~Emerging Evidence Lung Cancer Diagnostic Algorithmic Tests	~~Nodify XL2 (Biodesix)~~REVEAL Lung Nodule Characterization - 0092U* (MagArray) ~~0080U*~~	~~R91.18~~ 1479, 0092U*, 0317U*, 0360U*, 0395U*, 0406U*, R91.1	~~2018~~	
	~~REVEAL~~Percepta Lung ~~Nodule Characterization (MagArray~~Cancer Diagnostics (Veracyte)			~~20~~
	~~Percepta Lung Cancer Diagnostics (Veracyte)~~LungLB Test - 0317U* (LungLife AI)			
	~~LungLB Test (LungLife AI)~~Nodify CDT - 0360U* (Biodesix)			

~~Criteria Sections~~CRITERIA SECTIONS	~~Example Tests, Labs~~EXAMPLE TESTS (LABS)	~~Common CPT Codes~~COMMON BILLING CODES	~~Common ICD Codes~~ REF	~~Ref~~
	~~Nodify CDT (Biodesix)~~OncobiotaLUNGdetect - 0395U* (Micronoma)			
	~~OncobiotaLUNGdetect (Micronoma)~~CyPath Lung - 0406U* (Precision Pathology Laboratory)			
Evidence-Based Lung Cancer Treatment Algorithmic Tests	~~CyPath Lung (Precision Pathology Laboratory)~~Veristrat – 81538* (Biodesix)	~~0406U*~~ 81538*, 81599*, 0288U*, C34, D38.1, D38.6	26, 30	~~29, 33~~
	~~Veristrat (Biodesix)~~Razor14/Risk Reveal (RazorGenomics)			
	~~Razor14/Risk Reveal (RazorGenomics)~~DetermaRx - 0288U* (Oncocyte Corporation)			
Emerging Evidence Lung Cancer Treatment Algorithmic Tests	~~DetermaRx (Oncocyte Corporation)~~LungOI - 0414U* (Imagene)	~~0288U*~~ 0414U*, 0436U*, C34, D38.1, D38.6		~~29~~
	~~LungOI (Imagene)~~PROphet NSCLC Test - 0436U (OncoHost Inc)			

~~Criteria Sections~~CRITERIA SECTIONS	~~Example Tests, Labs~~EXAMPLE TESTS (LABS)	~~Common CPT Codes~~COMMON BILLING CODES	~~Common ICD Codes~~ REF	~~Ref~~
Bladder and Urinary Tract Cancer	~~PROphet NSCLC Test (OncoHost Inc)~~ ~~0436U*~~			
~~**Bladder and Urinary Tract Cancer**~~ Bladder/Urinary Tract Cancer Diagnostic Algorithmic Tests	CxBladder Detect+ - 0420U* (Pacific Edge)	0012M*, 0365U*, 0420U*, R31.9	11, 12	
	~~Cx~~Bladder~~Cx~~bladder Detect~~+~~ - 0012M* (Pacific Edge)	~~0420U*~~	~~R31.9~~	~~12, 13~~
	~~Cxbladder~~Oncuria Detect ~~(Pacific Edge-~~ 0365U* (DiaCarta Clinical Lab)			
Bladder Cancer Treatment and Recurrence Algorithmic Tests	~~Oncuria Detect (DiaCarta Clinical Lab)~~Cxbladder Monitor - 0013M* (Pacific Edge)	~~0365U~~0013M*, 0016M*, 0363U*, 0366U*, 0367U*, C67, C68	29	~~32~~
	~~Cxbladder Monitor (Pacific Edge)~~Decipher Bladder Genomic Test - 0016M* (Veracyte)			
	~~Decipher Bladder (Veracyte)~~Cxbladder Triage - 0363U* (Pacific Edge)			

~~Criteria Sections~~CRITERIA SECTIONS	~~Example Tests, Labs~~EXAMPLE TESTS (LABS)	~~Common CPT Codes~~COMMON BILLING CODES	~~Common ICD Codes~~ REF	~~Ref~~
Evidence-Based Pancreatic Cyst Risk Assessment Algorithmic Tests	~~Cxbladder Triage (Pacific Edge)~~Oncuria Monitor - 0366U* (DiaCarta Clinical Lab)	~~0363U*~~81479, D49, K86.2	30	
Emerging Evidence Pancreatic Cyst Risk Assessment Algorithmic Tests	Oncuria ~~Monitor~~Predict - 0367U* (DiaCarta Clinical Lab)	~~0366U*~~0313U*, D49, K86.2	30	
Pancreatic Cancer	~~Oncuria Predict (DiaCarta Clinical Lab)~~ ~~0367U*~~			
Evidence-Based Pancreatic Cyst Risk Assessment Algorithmic Tests~~Pancreatic Cancer~~	PancraGEN (Interpace Diagnostics)	81479, D49, K86.2	27	
Emerging Evidence Pancreatic Cyst Risk Assessment Algorithmic Tests~~Evidence-Based Pancreatic Cyst Risk Assessment Algorithmic Tests~~	PancreaSeq Genomic Classifier - 0313U (Univ of Pittsburgh Medical Center Molecular and Genomic Pathology Laboratory)~~PancraGEN (Interpace~~ ~~81479~~	031	~~30~~	

~~Criteria Sections~~CRITERIA SECTIONS	~~Example Tests, Labs~~EXAMPLE TESTS (LABS)		~~Common CPT Codes~~COMMON BILLING CODES	~~Common ICD Codes~~ REF	~~Ref~~
	~~Diagnostics)~~				
~~Emerging Evidence Pancreatic Cyst Risk Assessment Algorithmic Tests~~**Cancer of Unknown Primary**	~~PancreaSeq Genomic Classifier (Univ of Pittsburgh Medical Center Molecular and Genomic Pathology Laboratory)~~	~~0313U*~~			
Cancer of Unknown Primary Gene Expression Profiling Tests~~**Cancer of Unknown Primary**~~	CancerTYPE ID – 81540* (Biotheranostics)		81540*, C79.9, C80.0, C80.1	13	
Esophageal Cancer~~Cancer of Unknown Primary Gene Expression Profiling Tests~~	~~CancerTYPE ID (Biotheranostics)~~	~~81540*~~	~~C79.9, C80.0, C80.1~~		~~15~~
~~**Polygenic Risk Score Tests**~~Barrett's Esophagus Risk Assessment Algorithmic Tests	TissueCypher - 0108U* (Cernostics Lab)		0108U*, 0114U*, 0398U*, 0506U*	32, 33	
	~~geneType for Breast Cancer (Genetic Technologies)~~EsoGuard -		~~81599*~~	~~Z~~	~~14~~

~~Criteria Sections~~CRITERIA SECTIONS	~~Example Tests, Labs~~EXAMPLE TESTS (LABS)	~~Common CPT Codes~~COMMON BILLING CODES	~~Common ICD Codes~~ REF	~~Ref~~
	0114U* (Lucid Diagnostics)		~~Z80.3~~	
	ESOPREDICT Barrett's Esophagus Risk Classifier Assay - 0398U* (Capsulomics Inc. d/b/a Previse)			
	EndoSign Barrett's Esophagus Test - 0506U* (Cyted Health)			

~~OTHER~~ RELATED POLICIES

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

- ***Oncology~~:~~ Testing: Solid Tumor Molecular ~~Analysis of Solid Tumors and~~ Diagnostics*** for criteria related to molecular profiling of a known or suspected cancer (e.g. broad molecular profiling, including Minimal Residual Disease (MRD) Testing, Tumor Mutational Burden (TMB), and cytogenetic / fusion testing).

- ***Oncology Testing:*** ***Hematologic*** ***~~Malignancies~~Malignancy Molecular Diagnostics*** for criteria related to ~~DNA testing~~molecular profiling of a ~~solid tumor~~known or ~~a~~suspected blood cancer~~.~~ (e.g. broad molecular profiling, including Minimal Residual Disease (MRD) Testing, Tumor Mutational Burden (TMB), and cytogenetic / fusion testing).

- ***~~Genetic~~Oncology Testing: Hereditary Cancer ~~Susceptibility Syndromes~~*** for criteria related to genetic testing ~~to determine if an individual has an inherited cancer susceptibility syndrome~~for hereditary cancer predisposition syndromes.

- ***Oncology Testing: 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)~~and Surveillance*** for criteria related to ~~circulating tumor DNA (ctDNA) or circulating tumor cell testing performed on peripheral blood for~~screening and biomarker cancer ~~diagnosis, management and surveillance~~tests.

- ***~~Genetic Testing:~~ General Approach to ~~Genetic and Molecular~~ Laboratory Testing*** for criteria related to ~~algorithmic~~oncology, including known familial variant testing ~~in oncology,~~ that is not specifically discussed in this or another non-general policy.

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CRITERIA

It is the policy of ~~health plans affiliated with Centene Corporation~~Louisiana Healthcare Connections® 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~~members/enrollees, 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):~~, **AND**

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

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

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

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

II. ~~The~~Current evidence does not support the use of the breast cancer treatment and prognostic algorithmic test Oncotype DX Breast Recurrence Score ~~(81519, S3854) is considered **investigational** ~~for all other indications.

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Breast Cancer Extended Endocrine Therapy Algorithmic Tests

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

A. The member/enrollee is female (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 human epidermal growth factor receptor 2 (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).

~~I. 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**.~~

II. ~~The~~Current evidence does not support the use of the breast cancer extended endocrine therapy test Breast Cancer Index (BCI) ~~(81518, S3854) is considered **investigational** in men (sex assigned at birth) with breast cancer.~~

~~II.~~III. Current evidence does not support the use of the breast cancer extended endocrine therapy test Breast Cancer Index (BCI) for all other indications.

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Breast Cancer Prognostic Algorithmic Tests

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

A. The member/enrollee is female (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 (for example~~adjuvant therapy (e.g, tamoxifen, aromatase inhibitors, immunotherapy), **AND**

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

1. pN0~~,~~ (nodes negative pathologically~~),~~ **OR**
2. pN1mi or pN1 (1-3 nodes positive pathologically) ~~**OR***~~.[1].

II. ~~The~~Current evidence does not support the use of a breast cancer prognostic algorithmic test (i.e., EndoPredict, Prosigna, MammaPrint) ~~(81520, 81521, 81522, 81523, S3854)~~ in individuals with 4 or more positive nodes ~~is considered **investigational**~~.

III. ~~The~~Current evidence does not support 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~~Current evidence does not support the use of a breast cancer prognostic algorithmic test (i.e., EndoPredict, Prosigna, MammaPrint) ~~(81520, 81521, 81522, 81523, S3854)~~ in men (sex assigned at birth) with breast cancer ~~is considered **investigational**~~.

V. ~~The~~Current evidence does not support the use of a breast cancer prognostic algorithmic test (i.e., EndoPredict, Prosigna, MammaPrint ~~) (81520, 81521, 81522, 81523, S3854) is considered **investigational**~~) for all other indications.

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

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Gene Expression Profiling Breast Cancer Subtyping Tests

I. ~~Gene~~Current evidence does not support gene expression profiling breast cancer subtyping tests (e.g., BluePrint~~) (81599, S3854) are considered **investigational**~~, Insight TNBCtype) for all indications.

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Breast DCIS Prognostic Algorithmic Tests

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

   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~~Current evidence does not support breast DCIS prognostic algorithmic tests ~~(0045U) are considered **investigational** for all other indications.

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COLORECTAL CANCER

Colorectal Cancer Prognostic Algorithmic Tests

I. ~~Colorectal~~Current evidence does not support colorectal cancer prognostic algorithmic ~~tests (0069U, 0261U, 81525) are considered **investigational**~~for all indications.

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PROSTATE CANCER

Prostate Cancer Treatment and Prognostic Algorithmic Tests

I. The use of a prostate cancer treatment and prognostic algorithmic test (i.e., Oncotype DXGenomic Prostate (0047U),Score Test, 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 does **not** have either of the following:

1. Very low-risk prostate cancer, **OR**
2. Very high-risk prostate cancer.

1. The use Very low-risk prostate cancer, as defined by all of the following characteristics:

a) cT1c

b) Grade Group 1

c) PSA less than 10 mg/nl and density less than 0.15 ng/mL/g

d) Biopsy shows less than 3 positive cores/fragments and less than or equal to 50% cancer in each core/fragment, **OR**

1.2.Very high-risk prostate cancer treatment and prognostic algorithmic test Decipher assay (81542) is considered **medically necessary** when, as defined by all of the following characteristics:

B. The member/enrollee has a life expectancy of more than 5 years, **AND**
C. The patient has had radical prostatectomy, **AND**
D. There are no lymph node metastases, **AND**
E. There is PSA persistence/recurrence.

a) ThecT3-cT4

b) PSA greater than 40 ng/mL

c) Grade Group 4 or 5.

II. Current evidence does not support the use of a prostate cancer treatment and prognostic algorithmic test ~~(0047U, 0376U, 81541, 81542) is considered **investigational**~~ for all other indications.

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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)~~ 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 >~~greater than 3 ng/ml, **OR**
    b) A digital rectal exam (DRE) that is 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~~2.0 (MPS2), **OR**
    f) IsoPSA, **OR**

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

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

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**
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~~2.0 (MPS2), **OR**
    e) IsoPSA, **OR**
    f) ConfirmMDx, **OR**
    g) PCA3.

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

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Emerging Evidence Prostate Cancer Risk Assessment and Diagnostic Algorithmic Tests

I. ~~Prostate~~Current evidence does not support prostate cancer risk assessment and diagnostic algorithmic tests ~~(0228U, 0343U, 0403U, 0424U, 0433U)~~ with insufficient guidance for use ~~are considered **investigational**.~~ for all indications.

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THYROID CANCER

Thyroid Cancer Diagnostic Algorithmic Tests

I. The use of a thyroid cancer diagnostic algorithmic test ~~(0018U, 0026U, 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**

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

II. ~~The~~Current evidence does not support the use of a thyroid cancer diagnostic algorithmic test ~~(0018U, 0026U, 0204U, 0245U, 0287U, 81546)~~ in fine needle aspirates of thyroid nodules ~~is considered **investigational**~~ for all other indications.

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UVEAL MELANOMA

Uveal Melanoma Prognostic Algorithmic Tests

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

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

II. ~~The~~Current evidence does not support the use of a uveal melanoma prognostic algorithmic test ~~(81552) is considered **investigational**~~ for all other indications.

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CUTANEOUS MELANOMA

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

I. ~~Cutaneous~~Current evidence does not support 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), 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.~~

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~~Emerging Evidence Cutaneous Melanoma Prognostic Algorithmic Tests~~

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

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Cutaneous Melanoma Diagnostic Algorithmic Tests

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

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

II. ~~Cutaneous~~Current evidence does not support cutaneous melanoma diagnostic algorithmic

tests ~~(0090U, 0314U) are considered **investigational**~~ for all other indications, including:

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

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Cutaneous Melanoma Risk Assessment Algorithmic Tests

I. Cutaneous melanoma risk assessment algorithmic tests ~~(0089U)~~ are considered **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 ~~>~~greater than 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 is limited to a maximum of 2 times per visit.

II. ~~Cutaneous~~Current evidence does not support cutaneous melanoma risk assessment algorithmic tests ~~(0089U) are considered **investigational**~~ for all other indications.

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OVARIAN CANCER

Ovarian Cancer Diagnostic Algorithmic Tests

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

A. Preoperative evaluation of adnexal masses to triage for malignancy

B. Screening for ovarian cancer

C. Selecting ~~patients~~members/enrollees for surgery for an adnexal mass

D. Evaluation of ~~patients~~members/enrollees with clinical or radiologic evidence of malignancy

E. Evaluation of ~~patients~~members/enrollees with nonspecific signs or symptoms suggesting possible malignancy

F. Postoperative testing and monitoring to assess surgical outcome and/or to detect recurrent malignant disease following treatment.

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Ovarian Cancer Treatment Algorithmic Tests

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

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

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

II. ~~Ovarian~~Current evidence does not support ovarian cancer treatment algorithmic tests ~~(0172U) are considered **investigational**~~ for all other indications.

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GYNECOLOGIC CANCER

Gynecologic Cancer Treatment Algorithmic Tests

I. ~~Gynecologic~~Current evidence does not support gynecologic cancer treatment algorithmic tests ~~(81535, 81536)~~ in the assessment of gynecological cancers ~~are considered **investigational**~~for all indications**.**

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LUNG CANCER

Evidence-Based Lung Cancer ~~Diagnostic~~Risk Assessment Algorithmic Tests

I. Lung cancer ~~diagnostic~~risk assessment algorithmic tests ~~(0080U)~~ with sufficient evidence of clinical validity and utility are considered **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~~Current evidence does not support lung cancer ~~diagnostic~~risk assessment 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.

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Emerging Evidence Lung Cancer Diagnostic Algorithmic Tests

I. ~~Lung~~Current evidence does not support lung cancer diagnostic algorithmic tests ~~(0092U, 0317U, 0360U, 0395U, 0406U, 81479)~~ with insufficient evidence of clinical validity ~~are considered **investigational**~~for all indications.

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Evidence-Based Lung Cancer Treatment Algorithmic Tests

I. Lung cancer treatment algorithmic tests ~~(0288U, 81538, 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 is 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.

II. ~~Lung~~Current evidence does not support 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.

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Emerging Evidence Lung Cancer Treatment Algorithmic Tests

I. ~~Lung~~Current evidence does not support lung cancer treatment algorithmic tests ~~(0414U, 0436U)~~ with insufficient evidence of clinical validity ~~are considered **investigational.**~~for all indications.

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BLADDER AND URINARY TRACT CANCER

Bladder/Urinary Tract Cancer Diagnostic Algorithmic Tests

I. ~~Bladder~~Current evidence does not support bladder/urinary tract cancer diagnostic algorithmic tests ~~(0012M, 0365U, 0420U) are considered **investigational** for all indications.~~

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Bladder Cancer Treatment and Recurrence Algorithmic Tests

I. The use of bladder cancer treatment and recurrence algorithmic ~~test (0013M, 0016M, 0363U, 0366U, 0367U)~~tests is considered **medically necessary** when:

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

   B. ~~Results~~The 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~~Current evidence does not support the use of bladder cancer treatment and recurrence algorithmic test ~~(0013M, 0016M, 0363U, 0366U, 0367U) is considered **investigational**~~ for all other indications.

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PANCREATIC CANCER

Evidence-Based Pancreatic Cyst Risk Assessment Algorithmic Tests

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~~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,~~e.g., 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~~Current evidence does not support 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.

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Emerging Evidence Pancreatic Cyst Risk Assessment Algorithmic Tests

I. ~~Pancreatic~~Current evidence does not support pancreatic cyst risk assessment algorithmic tests ~~(0313U)~~ with insufficient evidence of clinical validity ~~are considered investigational~~for all indications.

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CANCER OF UNKNOWN PRIMARY

Cancer of Unknown Primary Gene Expression Profiling Tests

I. ~~The~~Current evidence does not support 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**~~for all indications.

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~~POLYGENIC RISK SCORE TESTS~~

~~Breast Cancer Polygenic~~view rationale

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ESOPHAGEAL CANCER

Barrett's Esophagus Risk ~~Score~~Assessment and Diagnostic Algorithmic Tests

~~I.~~ ~~The use of a breast cancer polygenic~~Current evidence does not support Barrett's esophagus risk ~~score test (81599) is considered **investigational**.~~

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~~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~~ assessment and diagnostic ~~category III (atypia/follicular lesion of undetermined significance) or Bethesda diagnostic category IV (follicular neoplasm/suspicion~~algorithmic tests 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 (4.2024) as failure of PSA to fall to undetectable levels (PSA persistence) or undetectable PSA after 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)

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.

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

I. **Very low risk prostate cancer:** Defined by NCCN as all of the following:indications.
    e.a) cT1c
    f.a) Grade Group 1
    g. PSA <10 mg/nl and density <0.15 ng/mL/g
    h. Biopsy shows <3 positive cores/fragments and < or equal to 50% cancer in each core/fragment.

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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. and is one of many gene expression assays used to aid in determining adjuvant systemic therapy. NCCN

guidelines for Breast Cancer (46.2024) 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, BINV-N 1 of 5). Per NCCN, the breast tumor must be either ductal/NST, lobular, mixed, or micropapillary, and it also must be hormone receptor positive (either Estrogen receptor or Progesterone receptor), and HER2 negative (p. BINV-6, BINV-7, BINV-8).

Females (sex assigned at birth) with postmenopausal breast tumors must be considering chemotherapy and have one of the following:

- A tumor that is pT1–3, and at least 0.5cm, with 5 cm or larger (p. BINV-6)
- A tumor that is pN1mi (2 mm or smaller axillary node metastases) or (p. BINV-6)
- A tumor that is 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)) (p. BINV-6).

Evidence level 1: Premenopausal patientFemales (sex assigned at birth) with a ductal/NST, lobular, mixed, or micropapillarypremenopausal breast tumors must be a candidate for chemotherapy and have one of the following:

- A tumor that is at least 0.5cm5 cm or larger 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 A tumor that is pN1mi (2 mm or smaller axillary node metastasis) or(p. BINV-7)
- A tumor that is 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) (p. BINV-7)

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Breast Cancer Extended Endocrine Therapy Algorithmic Tests

National Comprehensive Cancer Network (NCCN)

The BCI (Breast Cancer Index) is recommended by NCCN Breast Cancer guidelines (46.2024) for both indications of prognosis as well as predicting treatment for extended adjuvant endocrine therapy. (p. BINV-N 1 of 5). Appropriate patients for this test are: include pre and postmenopausal women with HR positive, HER2 negative breast cancer (either ductal/NST, lobular, mixed, or micropapillary) (BINV-6, BINV-7, BINV-8).

Evidence level 2A: Postmenopausal patients with a ductal/NST, lobular, mixed, or micropapillary tumor that is pT1–3, and breast tumors must be one of the following:

- 0.~~5cm~~5 cm 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~~ tumors must be one of the following:

- 0.~~5cm~~5 cm or larger 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~~(BINV-8)
- ~~Data are~~ pN1 (1–3 positive nodes) (BINV-8).

NCCN guidelines also state that there is limited data regarding the use of ~~molecular assays to assess prognosis and to predict benefit from chemotherapy in males with breast cancer. Available data suggest the 21-gene assay recurrence score provides prognostic information~~these tests in males with breast cancer ~~(p.~~ who are being considered for chemotherapy (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:~~They recommend consideration of the Breast Cancer Index (BCI) test for either node-negative cancer or cancer with 1-3 positive nodes, which has been treated with primary endocrine therapy for 5 years with no evidence of recurrence (Recommendation 1.24., p. 1819).

- ~~Recommendation 1.24: If~~The guideline cites 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~~lack of sufficient evidence ~~of recurrence, the clinician may offer~~for 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~~ in individuals with 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~~following 5 years of endocrine therapy (Recommendation 1.25, p. 1819).

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Breast Cancer Prognostic Algorithmic Tests

American Society of Clinical Oncology (ASCO)

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

Figure 1 (p. 1821) includes an algorithm that acts as a guide for prognostic test choice in women with early-stage invasive breast cancer. In summary, a female patient must have the following in order to recommend EndoPredict, Prosigna, or MammaPrint testing:

- Postmenopausal **OR** older than age 50 years
- Early-stage invasive breast cancer
- Node negative disease,
- HER2 negative tumor
- ER positive tumor

Of note, per the guide, if the patient has 1 to 3 positive node disease then only MammaPrint or EndoPredict may be ordered. The algorithm also shows that there is "Insufficient evidence to recommend a biomarker for use" in women with 4 or more positive nodes (p. 1821).

National Comprehensive Cancer Network (NCCN)

NCCN Breast Cancer guidelines (~~4~~6.2024) recommend consideration of other prognostic gene expression assays to help assess risk of recurrence in pre- and postmenopausal patients with either ductal/NST, lobular, mixed, or micropapillary breast cancer that is HR-positive, Her2-negative, pT1-3 and pN0 or pN~~+ tumors, but~~+. However, these other tests have not been validated to predict response to chemotherapy~~.~~ (p. BINV- 6, BINV-7, BINV-8~~)~~).

A footnote on page BINV-N 3 of 5 states: "Gene expression assays can provide prognostic and treatment-predictive information that can be used with T,N,M and biomarker information~~.~~". These prognostic gene expression assays can provide prognostic information but ~~the ability to predict~~ there is limited evidence for prediction of chemotherapy benefit ~~has not been shown.~~ (p. BINV-N~~, 1 of 5,~~ 3 of 5~~)~~).

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Gene Expression Profiling Breast Cancer Subtyping Tests

National Comprehensive Cancer Network (NCCN)

NCCN Breast Cancer guidelines (~~4~~6.2024) 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.

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Breast DCIS Prognostic Algorithmic Tests

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~~

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Colorectal Cancer Prognostic Algorithmic Tests

National Comprehensive Cancer Network (NCCN)

NCCN guidelines for Colon Cancer (~~4~~6.2024) does not recommend use of multigene panel assays to assist in making clinical decisions about adjuvant therapy~~.~~ (p. COL-4~~)~~).

~~PROSTATE CANCER~~

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Prostate Cancer Treatment and Prognostic Algorithmic Tests

National Comprehensive Cancer Network (NCCN)

NCCN guidelines for Prostate Cancer (~~4.2024) recommend~~1.2025) recommends use of advanced risk stratification tools (i.e., gene expression biomarkers, AI digital pathology) ~~when there is the possibility of changing~~for disease management ~~in~~, most commonly for men with localized prostate cancer and life expectancy of 10 yrs or more~~.~~ (p. PROS-4,5,6~~)~~, PROS-H 1 of 8). The most common reasons to use these tools ~~is~~are 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) ~~) (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~~.~~ and there are no current treatment implications based on the results (p. PROS-H~~,~~ 1 ~~and 4-6 ~~of 8~~)~~ and PROS-H 4, 5,6, of 8). The following tumor-based assays are called out for use: Decipher, Genomic Prostate Score~~,~~ (GPS), ArteraAI Prostate and Prolaris~~.~~ (p. PROS-H 3 of 8~~)~~).

American Society of Clinical Oncology (ASCO)

~~*American Society of Clinical Oncology (ASCO)*~~

ASCO (2020) issued a guideline ~~for the use of molecular biomarkers~~called "Molecular Biomarkers in ~~localized prostate cancer~~Localized Prostate Cancer: ASCO Guideline". The guideline overall states that ~~included the following summary of recommendations:~~

~~"Tissue~~tissue-based ~~molecular biomarkers (evaluating the sample with the highest volume of the highest Gleason pattern) ~~biomarker testing "~~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 should be interpreted in combination with other routine clinical factors, (p. 1474) and in situations where the results 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)medical management (p. 1475).

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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.

National Comprehensive Cancer Network (NCCN)

NCCN Prostate Cancer Early Detection guidelines (2.2024) recommends consideration of biomarkers that improve the specificity of screening in patients considering biopsy after abnormal PSA and/or DRE. Although these biomarker tests are not currently mandated as first-line screening tests in conjunction with serum PSA, there may be some patients who could consider biopsy based on PSA standards but are seeking further risk clarification. The probability of high-grade cancer (Gleason score ≥3+4, Grade Group 2 or higher) may be further defined utilizing theSpecifically, on page PROSD-2, NCCN recommends further evaluation for individuals with PSA "greater than 3 ng/ml and/or a very suspicious DRE". Biomarker testing is mentioned on page PROSD-3 as part of this additional evaluation, and NCCN specifies the following tests as options for risk stratification: 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 (p. PROSD-4). These tests include those listed above (except for SelectMDX) plus PCA3 and ConfirmMDX.".

On page PROSD-4, NCCN also recommends consideration of biomarker tests to improve specificity when considering a repeat biopsy for biopsy results showing the following: atypia, suspicious for cancer; high-grade prostatic intraepithelial neoplasia (PIN); benign. These tests include those listed above (except for SelectMDX) plus PCA3 and ConfirmMDX.

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Emerging Evidence Prostate Cancer Risk Assessment and Diagnostic Algorithmic Tests

National Comprehensive Cancer Network (NCCN)

NCCN Prostate Cancer Early Detection guidelines (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~~Stockholm3, OncoAssure Prostate, Tempus p-MSI, or Tempus p-Prostate.

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~~demonstrates neither benefit nor harm ~~at this time~~.

~~THYROID CANCER~~

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Thyroid Cancer Diagnostic Algorithmic Tests

American Thyroid Association

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

National Comprehensive Cancer Network (NCCN)

NCCN Guidelines for Thyroid Carcinoma (~~3~~5.2024) 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**~~

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Uveal Melanoma Prognostic Algorithmic Tests

National Comprehensive Cancer Network (NCCN)

NCCN guidelines for Uveal Melanoma (1.2024) recommends consideration of biopsy of the primary tumor before radiation for prognostic analysis. Molecular testing for prognostication is recommended over cytology alone~~.~~ (p. UM-2A~~)~~). Tumor class defined by gene expression profiling ~~-~~was more strongly associated with risk of ~~-~~metastasis than any other prognostic factor~~.~~ (p. UM-4~~)~~).

~~**CUTANEOUS MELANOMA**~~

~~**Evidence-Based**~~ back to top

Cutaneous Melanoma Prognostic Algorithmic Tests

Society of Surgical Oncology

The Society of Surgical Oncology (SSO), in its 2024 consensus statement, "Assessing the Evidence for and Utility of Gene Expression Profiling of Primary Cutaneous Melanoma", does not recommend the use of gene expression profiling (GEP) in adults with pT1a-pT4b primary cutaneous melanoma for predicting sentinel lymph node (SLN) status, guiding surveillance or follow-up approaches, or informing the use of adjuvant therapy due to insufficient high-level evidence (p. 2). These conclusions were reached through a rigorous process involving 20 experts, who used the PICOT framework to refine clinical questions and systematically reviewed 50 studies selected from over 130 articles. The recommendations were developed through the Modified Delphi process, achieving consensus with at least 80% agreement among a diverse panel of specialists (p. 4-6).

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). The review determined that current research does not provide sufficient evidence to conclude whether DecisionDx-Melanoma allows patients to safely skip sentinel lymph node biopsy (SLNB). Additional longitudinal studies are necessary to assess long-term health outcomes, such as recurrence, in patients who opt out of the biopsy.

~~*Concert 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 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.

Concert Note

Cutaneous melanoma prognostic testing is addressed by the Local Coverage Determination (LCD), MolDX: Melanoma Risk Stratification Molecular Testing - L38016, which provides a path to coverage for the DecisionDx-Melanoma and Merlin test assays. However, these recommendations were established prior to the release of the Society of Surgical Oncology (SSO) guidelines, which represent the latest expert consensus in the field. Given the rapidly evolving landscape of precision medicine and the methodological rigor applied in developing these guidelines, we place greater weight on the SSO's recommendations as a more current and comprehensive standard for clinical practice.

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Cutaneous Melanoma Diagnostic Algorithmic Tests

National Comprehensive Cancer Network (NCCN)

NCCN guidelines for Cutaneous Melanoma (~~2.2024) indicate that~~1.2025) recommends gene expression profiling ~~is~~as an 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 treatment selection in cases that are diagnostically 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).~~several other ancillary tests (p. ME-C 1 of 8). NCCN does not recommend incorporation of GEP testing into the initial workup of a stage 0 in situ, T1a, or T1b melanoma (p. ME-2 and ME-2A).

American Academy of Dermatology

The American Academy of Dermatology (Swetter, 2019) published ~~guidelines~~an article titled "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~~do not ~~recommended for routine diagnostic use in CM. These include comparative genomic hybridization (CGH), fluorescence in situ hybridization (FISH),~~recommend gene expression profiling (GEP~~), and (potentially) next-generation sequencing. (page 219)~~

~~Ancillary~~) as a routine diagnostic ~~molecular techniques (e.g., CGH, FISH, GEP) may be used~~test for ~~equivocal melanocytic neoplasms.~~individuals with cutaneous melanoma (p. ~~219)~~291).

American Society of Dermatopathology

The American Academy of Dermatopathology (AUC Committee Members, 2022) published ~~conditions~~clinical scenarios 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)~~The guideline also found that qRT-PCR testing for individuals with confirmed melanoma or nevus and adults with sclerosing (desmoplastic) nevus and desmoplastic melanoma were classified as "rarely inappropriate" (p. 238) clinical scenarios.

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Cutaneous Melanoma Risk Assessment Algorithmic Tests

National Comprehensive Cancer Network (NCCN)

NCCN Guidelines for Cutaneous Melanoma (~~2~~3.2024) recommends consideration of ~~pre-diagnostic~~"prediagnostic noninvasive patch testing" to help inform~~-~~ decisions regarding biopsy for patients with melanocytic neoplasms that are clinically/dermoscopically suspicious for melanoma~~.~~ (p. ME-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 validity and utility to improve patient outcomes when added to standard of care~~.~~ (p. 1~~)~~).

American Academy of Dermatology

In their 2019 publication, the American Academy of Dermatology ~~stated the following: Skin~~states that skin biopsy ~~remains~~should be the ~~first~~initial step ~~to establish~~in establishing a ~~definitive~~ diagnosis of ~~CM, although various molecular and imaging~~cutaneous melanoma. The article mentions consideration of newer noninvasive techniques ~~have been studied as adjuncts to histopathologic assessment of melanocytic neoplasms.~~, including gene expression analysis (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

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 should be strongly considered for dermatology referral.

Centers for Medicare & Medicaid Services

Per MolDX: Pigmented Lesion Assay LCD (L38051), this test is used to determine whether a biopsy should be performed. The LCD lists characteristics for the skin lesion that are appropriate for testing, which includes having at least 1 ABCDE criteria.

The LCD also states that "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**~~

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Ovarian Cancer Diagnostic Algorithmic Tests

National Comprehensive Cancer Network (NCCN)

NCCN guidelines for Ovarian Cancer~~,~~ including Fallopian Tube Cancer, and Primary Peritoneal Cancer (3.2024) recognize ~~that a number of specific biomarkers~~several biomarker tests and algorithms using multiple biomarker test results that have been proposed for preoperatively distinguishing benign from malignant tumors in patients who have an undiagnosed adnexal/pelvic mass~~. Currently, the NCCN Panel does not recommend the use of these biomarker tests for evaluation of an undiagnosed adnexal/pelvic mass. (p. MS-10, MS-11)~~ (p. MS-7).

In the NCCN Panel discussion section regarding Biomarker Tests, there is a comment stating "the NCCN panel does not recommend the use of these biomarker tests for determining the status of an undiagnosed adnexal/pelvic mass" (p. MS-10, 11). The discussion section includes OVA1 and ROMA as test examples.

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Ovarian Cancer Treatment Algorithmic Tests

National Comprehensive Cancer Network (NCCN)

The NCCN guidelines for Ovarian Cancer~~,~~ including Fallopian Tube Cancer, and Primary Peritoneal Cancer (3.2024) recommend "~~"~~genetic risk evaluation, and germline and somatic testing if not previously done, ~~including *BRCA1/2* to 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~~ Testing should include *BRCA1/2* status ~~may help determine the benefit of PARP inhibitor therapy.~~, which will aid in treatment decision-making (p. OV-1~~)~~).

~~*American Society of Clinical Oncology (ASCO)*~~

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~~a recommendation for PARPi ~~naïve. All~~maintenance therapy (niraparib) for "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)~~" (p. 3879).

~~**GYNECOLOGIC CANCER**~~

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Gynecologic Cancer Treatment Algorithmic Tests

National Comprehensive Cancer Network (NCCN)

NCCN guidelines for Ovarian Cancer~~,~~ including Fallopian Tube Cancer, and Primary Peritoneal Cancer (3.2024) state that chemosensitivity/resistance assays have been proposed for informing

decisions related to future chemotherapy if there are multiple ~~equivalent chemotherapy~~similar treatment options ~~available. This has a category 3 level of~~being considered. However, there is insufficient evidence ~~which indicates that there is major NCCN disagreement that the intervention is appropriate.~~to recommend these tests at this time (p. OV-C, 1 of 12~~)~~).

NCCN guidelines for Cervical Cancer (~~3.2024~~1.2025) do not mention chemosensitivity or chemoresistance assays as part of clinical care.

NCCN guidelines for Uterine Neoplasms (~~2.2024~~1.2025) do not mention chemosensitivity or chemoresistance assays as part of clinical care.

~~**LUNG CANCER**~~

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Evidence-Based Lung Cancer ~~**Diagnostic**~~**Risk Assessment** Algorithmic Tests

~~*Concert 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.~~

Centers for Medicare and Medicaid Services

The CMS local coverage determination (LCD) entitled BDX-XL2 (L37031) includes the following criteria for the NodifyXL2 test for the management of a lung nodule:

- Nodule must be between 8 and 30mm in diameter
- Patients must be 40 years or older
- Patients must have a pre-test cancer risk (as assessed by the Mayo Clinic Model for Solitary Pulmonary Nodules) of 50% or less.

"The intended use of the test is to assist physicians in the management of lung nodules by identifying those lung nodules with a high probability of being benign. These lung nodules would then be candidates for non-invasive computed tomography (CT) surveillance instead of invasive procedures."

Pritchett, et al

A 2023 study titled: "Assessing a biomarker's ability to reduce invasive procedures in patients with benign lung nodules: Results from the ORACLE study" aimed to assess the clinical impact of proteomic integrated classifier (IC) tests (specifically, NodifyXL2), following confirmation of clinical validity (PANOPTIC trial) in 2018. The study included a matched cohort and ultimately found that "[p]atients with a benign nodule in the IC group underwent fewer invasive procedures (n = 8, 5%) compared to patients in the untested control group (n = 30, 19%), yielding…[a] relative reduction of 74%" (p. 6).

Kheir, et al

A 2023 retrospective study titled: "Impact of an integrated classifier using biomarkers, clinical and imaging factors on clinical decisions making for lung nodules" compared individuals with lung nodules who were evaluated with the integrated classifier (IC) test (NodifyXL2) versus individuals receiving standard of care. The findings showed that invasive procedures were decreased by 57.5% in individuals with indeterminate lung nodules "without missing a malignant diagnosis at 1-year follow-up)", when compared to the control arm (p. 3563).

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Emerging Evidence Lung Cancer Diagnostic Algorithmic Tests

Concert Evidence Review for Coverage Determination (Published ~~12/21/23~~1/1/2025)

- ~~Multiple studies have been published on~~At the present time, lung cancer diagnostic algorithmic tests, specifically Nodify CDT, Percepta ~~Bronchial Genomic Classifier and~~ Lung Cancer Diagnostics, REVEAL Lung Nodule Characterization~~ and their ability~~, and CyPathLung, have **INSUFFICIENT EVIDENCE** in peer-reviewed publications to

identify risk effectively result in improved health outcomes compared to the current standard of cancer in patients with lung nodules. This body of care. The current literature includes studies meant to assess does not demonstrate strong evidence for clinical validity for each test. Overall, these studies inadequately demonstrate the clinical validitydue to a lack of robust evidence that these tests accurately help to classify malignancy risk 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 withan individual's 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 nodule and 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 REVEALresults are used to determine if biopsy is performed.

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.

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Evidence-Based Lung Cancer Treatment Algorithmic Tests

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 listed as a covered test.

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Emerging Evidence Lung Cancer Treatment 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.

~~BLADDER AND URINARY TRACT CANCER~~

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Bladder/Urinary Tract Cancer Diagnostic Algorithmic Tests

National Comprehensive Cancer Network (NCCN)

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~~ the NCCN Bladder Cancer guidelines (~~4~~6.2024~~),~~) were identified.

The American Urological Association ~~and~~ *(AUA) / American Society of Clinical Oncology (ASCO) /* *Society of Urologic Oncology (*~~Hozbeierlein et al).~~ *SUO)*

The updated AUA/SCO/SUO guideline highlights several key areas for which further evidence is needed. Included in this section is a statement regarding the need to identify and validate both prognostic and predictive markers to improve clinical outcomes, including therapeutic decision-making.

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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.
~~1. 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.~~
2. 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
    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]).~~

~~2. 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.~~
~~3. 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.~~
3. The test successfully completes a Molecular Diagnostic Services Program (MolDX®) technical assessment that ensures the test is reasonable and necessary as described above.
4. 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.
5. The genomic content interrogated by the test must be relevant to the therapy under consideration."

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Evidence-Based Pancreatic Cyst Risk Assessment Algorithmic Tests

~~PANCREATIC CANCER~~

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

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".~~

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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.

~~CANCER OF UNKNOWN PRIMARY~~

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Cancer of Unknown Primary Gene Expression Profiling Tests

National Comprehensive Cancer Network (NCCN)

NCCN guidelines for Occult Primary (Cancer of Unknown Primary) (~~1~~2.2025) state that ~~gene sequencing~~testing 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)~~5).

~~POLYGENIC RISK SCORE TESTS~~

~~**Breast Cancer Polygenic**~~back to top

Barrett's Esophagus Risk ~~**Score Tests**~~

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

~~NCCN guidelines for Genetic/Familial High-Risk~~ Assessment ~~for Breast, Ovarian,~~ and ~~Pancreatic cancers (3.2024) speak broadly about the use of polygenic risk scores, stating~~Diagnostic Algorithmic Tests

Centers for Medicare and Medicaid Services

The CMS local coverage determination (LCD) entitled "MolDX: Molecular Testing for Detection of Upper Gastrointestinal Metaplasia, Dysplasia, and Neoplasia" states that ~~there~~molecular diagnostic tests that identify individuals with upper gastrointestinal metaplasia, dysplasia, and neoplasia are ~~currently significant limitations to this type of testing, and~~ not covered.

American College of Gastroenterology

In their ~~use is not recommended~~2022 guidelines for ~~clinical~~diagnosis and management ~~at this time outside~~ of Barrett's esophagus, the ACG suggests that a swallowable, nonendoscopic capsule sponge device combined with biomarker testing is an acceptable alternative to endoscopy for screening for BE in those with risk factors, including chronic reflux. However, the ~~context~~strength of ~~a clinical trial~~the recommendation is categorized as "conditional," and the quality of evidence is categorized as "very low" (p. ~~EVAL-A, 3 of~~ 10).

The ACG also states they are unable to make a recommendation about the TissueCypher and WATS-3D tests based on either current evidence showing low sensitivity and specificity, or lack of data, respectively (p. 18-21).

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DEFINITIONS

1. **ABCDE feature** is an acronym for examining patients with a lesion that is suspicious for melanoma: **a**symmetry, **b**order irregularity, **c**olor variegation, **d**iameter greater than 6 mm, and **e**volution.
2. **Adjuvant** therapy is a medication (such as chemotherapy or endocrine therapy) given after the surgical removal of a cancerous tumor.
3. **Ductal/NST** is a ductal breast cancer of no special type (NST), meaning the cancer cells have no features that classify them as a specific type of breast cancer when examined by microscope.

4. **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)

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. 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	1/25	3/31/25	5/1/25

Reviews, Revisions, and Approvals	Revision Date	Approval Date	Effective Date
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 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			

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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; 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			

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(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 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			

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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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Annual review. Minor rewording without clinical significance. Removed common codes from criteria sections. For Prostate Cancer Treatment and Prognostic Algorithmic Tests: removed criterion II (specific Decipher coverage for men with greater than five but less than 10 years life expectancy) and added detail to define very low and high risk prostate cancer (formerly in "Definitions"). Condensed two prior criteria sets (Evidence-Based Cutaneous Melanoma Prognostic Algorithmic Tests and Emerging Evidence Cutaneous Melanoma Prognostic Algorithmic Tests) and changed name to "Cutaneous Melanoma Prognostic Algorithmic Tests" and changed criteria to note that current evidence does not support these tests. Name of "Emerging Evidence Cutaneous Melanoma Risk Assessment Algorithmic Tests" criteria changed to "Cutaneous Melanoma Risk Assessment Algorithmic Tests." Name of "Evidence-Based Lung Cancer Diagnostic Algorithmic Tests" criteria changed to "Evidence-Based Lung Cancer Risk Assessment Algorithmic Tests." Removed criteria for Breast Cancer Polygenic Risk Score Tests. Added criteria for Barrett's Esophagus Risk Assessment Algorithmic Tests. "Investigational" policy statements changed to note that "current evidence does not support…" Updated table of commonly billed codes, rationale, background, and references.	03/26		

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Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. LHCC makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved.

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

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

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

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

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