Concert Genetics Genetic Testing: Hereditary Cancer Susceptibility

Reference Number: LA.CP.CG.22 Coding implications
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See Important Reminder at the end of this policy for important regulatory and legal information.

OVERVIEW

Genetic testing for hereditary cancer susceptibility is performed when an individual has risk factors that increase suspicion that they could develop an inherited form of cancer. These risk factors may include an individual's personal and/or medical histories, as well as their family medical history. When a genetic test is positive for hereditary cancer susceptibility, the individual is at an increased risk for cancer and this information may impact medical management, including screening, prevention, and treatment decisions.

Genetic testing for hereditary cancer susceptibility is a germline test and can be performed on individual genes (e.g., *BRCA1*) or on many genes simultaneously (i.e., multi-gene panels). Panels can range from a limited number of genes associated with hereditary susceptibility to one specific type of cancer (e.g., breast cancer panel), or a pan-cancer hereditary cancer susceptibility panel (i.e., a panel that tests for genes associated with several different hereditary cancer susceptibilities at the same time). The choice of gene panel should take into account factors such as patient preference, gene penetrance (high vs moderate penetrance breast cancer genes, for example, which may have different recommendations for management) and possibility of identifying a variant of uncertain significance, which increases with the number of genes on the panel.

Of note, the National Society of Genetic Counselors (NSGC) endorses the use of multi-gene panel tests when clinically warranted and appropriately applied. Specifically, the NSGC recommends thorough evaluation of the analytic and clinical validity of the test, as well as its clinical utility[3]. For this reason, several of the criteria in this policy require that panel tests do not include genes without known association with the disease in question.

~~Targeted mutation testing~~Targeted mutation testing is the process of analyzing one single pathogenic or likely pathogenic (P/LP) variant in one gene. Generally, this type of testing is recommended when there is a known P/LP variant in an individual's close relative. Importantly, an individual meeting criteria for broader testing (i.e. full gene or multi-gene panel testing) based on clinical history should have broader testing performed. Of note, if a variant of unknown significance (VUS) is detected in an individual, it is not recommended that family members also be tested for the VUS, unless the VUS is reclassified to a pathogenic or likely pathogenic variant.

Targeted germline genetic testing may also be recommended when there is a P/LP variant found on somatic tumor profiling. It should be noted that there is language in several National Comprehensive Cancer Network (NCCN) guidelines stating that somatic P/LP variants are

common in some genes and may not indicate the need for germline testing unless the clinical/family history is consistent with a P/LP variant in the germline. However, given these tests are targeted and have significant implications for a patient's medical management, it is clinically appropriate to allow for a path to coverage for this type of testing.

POLICY REFERENCE TABLE

Coding Implications

This clinical policy references Current Procedural Terminology (CPT®). CPT is a registered trademark of the American Medical Association. All CPT codes and descriptions are copyrighted 2023, American Medical Association. All rights reserved. CPT codes and CPT descriptions are from the current manuals and those included herein are not intended to be all-inclusive and are included for informational purposes only. Codes referenced in this clinical policy are for informational purposes only and may not support medical necessity. Inclusion or exclusion of any codes does not guarantee coverage. Providers should reference the most up-to-date sources of professional coding guidance prior to the submission of claims for reimbursement of covered services.

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

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

Criteria Sections	Example Tests (Labs)	Common CPT Codes	Common ICD10 Codes	Ref
Pan-Cancer Hereditary Cancer Susceptibility Panels	MyRisk (Myriad Genetics)	81432*, 81433*	C15-26, C50-58 Z17, Z80, Z85.0-Z85.9	1, 2, 3, 11
	Common Hereditary Cancers Panel (Invitae)			
	CancerNext (Ambry Genetics)			

	Tempus xG Hereditary Cancer Panel			
	+RNAinsight with CancerNext (Ambry Genetics)	0134U*		
	GeneticsNow Comprehensive Germline Panel (GoPath Diagnostics)	0474U*		
Hereditary Breast Cancer Susceptibility Panels	VistaSeq Breast Cancer Panel (Labcorp) Breast Cancer Panel (Invitae) Breast Cancer STAT NGS Panel (Sequencing & Deletion/Duplication) (Fulgent Genetics) Breast Cancer - High Risk Panel (PreventionGenetics, part of Exact Sciences) Breast Cancer High-Risk Panel plus PALB2 (GeneDx)	81162, 81163, 81164, 81165, 81166, 81167, 81216, 81307, 81321*, 81351, 81432*, 81433*	C50, Z80.3, Z83, Z84, Z85, Z86	1, 21
	BRCAplus (Ambry Genetics)	0129U*		
Hereditary GI/Colon Cancer Susceptibility Panels	Colorectal Cancer Panel (Invitae)	81435*, 81436*	C15-26, Z80, Z83, Z84, Z85, Z86	2
	ColoNext (Ambry Genetics)	0101U*		
	+RNAinsight for ColoNext (Ambry Genetics)	0130U*, 0162U*		
Hereditary Gastric Cancer Susceptibility Panels	Invitae Gastric Cancer Panel (Invitae)	81201, 81203, 81292, 81294, 81295, 81297, 81298, 81300, 81317, 81319, 81403*, 81404*, 81405*, 81406*, 81408*, 81479	C16, Z80, Z85, Z86	7
	Gastric Cancer Panel (PreventionGenetics, part of Exact Sciences)			
Hereditary Pancreatic Cancer Susceptibility Panels	Pancreatic Cancer Panel (Invitae)	81162, 81163, 81201, 81292, 81295, 81298, 81351, 81433* 81479	C25, Z80, Z84, Z85, Z86	1
	PancNext (Ambry Genetics)			
Hereditary Polyposis Susceptibility Panels	Hereditary Polyposis Panel (PreventionGenetics, part of Exact	81201, 81203, 81406*, 81479	D12, K63.5, Z80, Z84, Z85,	2

	Sciences)		Z86	
	~~COLARIS AP (Myriad Genetics)~~Adenomatous Polyposis Panel (Invitae)			
Hereditary Prostate Cancer Susceptibility Panels	Hereditary Prostate Cancer Panel~~ Primary Panel~~ (Invitae)	81162, 81292, 81295, 81351, 81479	C61, Z80, Z84, Z85, Z86	1~~, 19~~
	ProstateNext (Ambry Genetics)			
	+RNAinsight for ProstateNext (Ambry Genetics)	0133U*		
	ProstateNow Prostate Germline Panel (GoPath Diagnostics)	0475U		
Hereditary Neuroendocrine Cancer Susceptibility Panels	Hereditary Paraganglioma-Pheochromocytoma Panel (Invitae)	81437*, 81438*	C74, C75, C7A Z80, Z84, Z85, Z86	6
	PGLNext (Ambry Genetics)			
***BRCA1* and *BRCA2* Gene Testing**				
BRCA1 or BRCA2 Targeted Variant or Known Familial Variant Analysis	BRCA1 or BRCA2 Targeted Variant-Single Test (GeneDx)	81215, 81217	C50, C56, D05, Z17, Z80, Z83, Z84, Z85, Z86, C24.1	1
BRCA1 and/or *BRCA2* Targeted Variant Analysis - Ashkenazi Jewish Founder Variants	BRCA1/2 Ashkenazi Jewish 3-Site Mutation Panel (Ambry Genetics)	81212		
	MultiSite 3 BRCAnalysis (Myriad Genetics)			
BRCA1 and *BRCA2* Sequencing and/or Deletion/Duplication Analysis	Hereditary BRCA1/2 Panel (Invitae)	81162, 81163, 81164, 81165, 81166, 81167, 81216		1, 4, ~~2019~~, 21
	BRCA1/2 Seq and Del/Dup (Ambry Genetics)			
	+RNAinsight for BRCA1/2 (Ambry Genetics)	0138U*		
***PALB2* Gene Testing**				
PALB2 Targeted Variant Analysis	PALB2 Targeted Variant (GeneDx)	81308	C15-26, Z80, Z84, Z85, Z86	1
PALB2 Sequencing and/or Deletion/Duplication Analysis	PALB2 Sequencing PALB2 Deletion/Duplication (Quest)	81307, 81479		1, ~~2019~~
	PALB2 with +RNA insight (Ambry Genetics)	0137U*		

ATM and/or _CHEK2_ Gene Testing				
ATM or _CHEK2_ Targeted Variant Analysis	ATM Targeted Variant - Single Test (GeneDx)	81479	C50, D05, Z80, Z84, Z85, Z86	1
	CHEK2 Targeted Variant - Single Test (GeneDx)			
ATM or _CHEK2_ Sequencing and/or Deletion/Duplication Analysis	~~Ataxia-Telangiectasia Test~~ATM Full Gene Sequencing and Deletion/Duplication (Invitae)	81408*, 81479		
	Hereditary Breast Cancer via the CHEK2 Gene (PreventionGenetics, part of Exact Sciences)	81479		
	+RNAinsight for ATM (Ambry Genetics)	0136U*		
Lynch Syndrome / Hereditary Nonpolyposis Colorectal Cancer (HNPCC)				
MLH1, _MSH2_, _MSH6_, _PMS2_, or _EPCAM_ Targeted Variant Analysis	MSH6 Targeted Variant; PMS2 Targeted Variant; EPCAM Targeted Variant (GeneDx)	81299, 81318, 81479	C15-22, C24-6, C26 C53-57 Z80, Z84, Z85, Z86	2
	Hereditary Nonpolyposis Colorectal Cancer (HNPCC): MLH1 (Known Mutation) (Labcorp)	81293		
	Hereditary Nonpolyposis Colorectal Cancer (HNPCC): MSH2 (Known Mutation) (Labcorp)	81296		
MLH1, _MSH2_, _MSH6_ _PMS2_, and/or _EPCAM_ Sequencing and/or Deletion/Duplication Analysis	HNPCC Concurrent (Ambry Genetics)	81292, 81294, 81295, 81297, 81298, 81300, 81317, 81319, 81403*		
	Lynch Syndrome Panel (Invitae)			
	CustomNext + RNA: MLH1, MSH2, MSH6, and/or PMS2 (Ambry Genetics)	0158U*, 0159U*, 0160U*, 0161U*, 0162U*		
BAP1-Tumor Predisposition Syndrome				
BAP1 Targeted Variant Analysis	BAP1: Site Specific Analysis (familial) (Univ of Pennsylvania School of Medicine-Genetic Diagnostic Laboratory)	81403*	C22, C45, C64 C69, D22, D32, Z80, Z84, Z85, Z86	8
BAP1 Sequencing and/or Deletion/Duplication Analysis	BAP1 Full Gene Sequencing and Deletion/Duplication (Invitae)	81479		5, 8, 12, 13, 14

Birt-Hogg-Dube syndrome (BHDS)				
~~*FFLCNLCN*~~ Targeted Variant Analysis	FLCN Targeted Variant - Single Test (GeneDx)	81479	C65, D14.3, D23.9, Z84, Z85, Z86	8
FLCN Sequencing and/or Deletion/Duplication Analysis	Birt-Hogg-Dube Syndrome Test (Invitae)	81479		8, 10
Cowden Syndrome (CS)/PTEN Hamartoma Tumor Syndrome (PHTS)				
PTEN Targeted Variant Analysis	PTEN Targeted Variant - Single Test (GeneDx)	81322*	C15-21, C26, C50, C54, C55, C64, C73, D12, D13, D17, D23, D24, F78, F84.0, Q75.3, Q87.89, Z80, Z84, Z85, Z86	1
PTEN Sequencing and/or Deletion/Duplication Analysis	PTEN Gene Sequencing and Del/Dup (GeneDx)	81321*, 81323*		
Adenomatous Polyposis Conditions (Familial Adenomatous Polyposis Syndrome (FAP)/Attenuated FAP (AFAP) and *MUTYH*-Associated Polyposis Syndrome (MAP))				
APC ~~or~~ and/or *MUTYH* Targeted Variant Analysis	APC Targeted Variant - Single Test (GeneDx)	81202	C15-21, D12, Z80, Z84, Z85, Z86	2
	MUTYH Targeted Variant - Single Test (GeneDx)	81403*, 81401*		
APC and/or *MUTYH* Sequencing and/or Deletion/Duplication Analysis	APC Seq and Del/Dup (Ambry Genetics)	81201, 81203		
	Familial Adenomatous Polyposis Test (Invitae)			
	+RNAInsight for APC (Ambry Genetics)	0157U*		
	MUTYH Full Gene Sequencing and Deletion/Duplication (Invitae)	81406*, 81479		
Familial Atypical Multiple Mole Melanoma Syndrome (FAMMM)				
CDKN2A Targeted Variant Analysis	CDKN2A Targeted Variant - Single Test (GeneDx)	81479	C43, Z12.83, Z80, Z84, Z85, Z86	1
CDKN2A Sequencing and/or Deletion/Duplication Analysis	CDKN2A Full Gene Sequencing and Deletion/Duplication (Invitae)	81404*, 81479		1, 5, ~~21~~20

Hereditary Diffuse Gastric Cancer (aka, Signet Ring Cell Gastric Cancer)				
CDH1 Targeted Variant Analysis	CDH1 Targeted Variant - Single Test (GeneDx)	81479	C16, C50, Q35, Q36, Z80, Z84, Z85, Z86	1, 7
CDH1 Sequencing and/or Deletion/Duplication Analysis	~~Hereditary Diffuse Gastric Cancer Syndrome Test~~CDH1 Full Gene Sequencing and Deletion/Duplication (Invitae)	81406*, 81479		7
Juvenile Polyposis Syndrome (JPS)				
SMAD4 and/or *BMPR1A* Targeted Variant Analysis	Targeted Variant: SMAD4 (PreventionGenetics, part of Exact Sciences)	81403*	C15-C26, D12, Z80, Z84, Z85, Z86	2
	Targeted Variant: BMPR1A (PreventionGenetics, part of Exact Sciences)	81403*		
SMAD4 and/or *BMPR1A* Sequencing and/or Deletion/Duplication Analysis	Juvenile Polyposis Syndrome Panel (Invitae)	81405*, 81406*, 81479		
	BMPR1A, SMAD4 Gene Sequencing and Del/Dup (GeneDx)			
Hereditary Leiomyomatosis and Renal Cell Cancer (HLRCC)				
FH Targeted Variant Analysis	FH ~~Sequence Analysis (~~Known Familial Mutation~~Variant~~ Analysis~~)~~ ~~(Baylor Genetics)~~ (University Hospitals)	81403*	C44, C55, C64, D23, D25, Z84, Z85, Z86	8
FH Sequencing and/or Deletion/Duplication Analysis	Hereditary Leiomyomatosis and Renal Cell Carcinoma (Ambry Genetics)	81405*, 81479		8, 18
Li-Fraumeni Syndrome (LFS)				
TP53 Targeted Variant Analysis	TP53 Targeted Variant - Single Test (GeneDx)	81352	C30-41, C15-26, C45, C47-49, C50, C71, C95.9, Z80, Z84, Z85, Z86	1
TP53 Sequencing and/or Deletion/Duplication Analysis	TP53 Full Gene Sequencing and Deletion/Duplication (Invitae)	81351, 81479		
	Li-Fraumeni Syndrome, TP53 Sequencing and Deletion/Duplication (Quest Diagnostics)			
Multiple Endocrine Neoplasia - Type 1 (MEN1)				
MEN1 Targeted Variant Analysis	MEN1 Targeted Variant - Single Test (GeneDx)	81479	C25, C75.0, D35.2, E31.2, Z80, Z84, Z85, Z86	6
MEN1 Sequencing and/or	MEN1 Gene Sequencing and Del/Dup (GeneDx)	81404*, 81405*		

Deletion/Duplication Analysis	Multiple Endocrine Neoplasia Type 1 Test (Invitae)			
Multiple Endocrine Neoplasia Type 2 (MEN2)				
RET Targeted Variant Analysis	RET Targeted Variant - Single Test (GeneDx)	81404*	C73-75, C7A, D3A, Z80, Z84, Z85, Z86	6
RET Sequencing and/or Deletion/Duplication Analysis	RET Full Gene Sequencing and Deletion/Duplication (Invitae)	81406*, 81479, S3840*		6, 17
Nevoid Basal Cell Carcinoma Syndrome (NBCCS) (aka Gorlin syndrome)				
PTCH1 and/or *SUFU* Targeted Variant Analysis	Targeted Variant: PTCH1 or SUFU (GeneDx)	81479	C44, C71.6, G93, M27.4, Z84, Z85, Z86	15
PTCH1 and *SUFU* Sequencing and/or Deletion/Duplication Analysis	Basal Cell Nevus Syndrome Panel (Invitae)	81479		
Hereditary Paraganglioma/Pheochromocytoma Syndrome (PGL/PCC)				
MAX, SDHA, SDHAF2, SDHB, SDHC, SDHD, or *TMEM127* Targeted Variant Analysis	SDHB, SDHD, SDHC, MAX, SDHAF2, or TMEM127 Targeted Variant - Single Test (GeneDx) Targeted Variants: MAX, SDHAF2, TMEM127 (PreventionGenetics, part of Exact Sciences)	81479	C7A, C74.1, D35.00, D44.7, Z84, Z85, Z86	8
MAX, SDHA, SDHAF2, SDHB, SDHC, SDHD, and *TMEM127* Sequencing and/or Deletion/Duplication Analysis	SHDB Full Gene Sequencing and Deletion/Duplication (Invitae)	81405*, 81479		6, 16
	SDHA Full Gene Sequencing and Deletion/Duplication (Invitae)	81406*, 81479		
	SDHC Full Gene Sequencing and Deletion/Duplication (Invitae)	81404*, 81405*		
	SDHD Full Gene Sequencing and Deletion/Duplication (Invitae)	81404*, 81479		
	MAX Full Gene Sequencing and Deletion/Duplication (Invitae)	81479		
	SDHAF2 Full Gene Sequencing and Deletion/Duplication (Invitae)			
	TMEM127 Full Gene Sequencing and Deletion/Duplication (Invitae)			
Peutz-Jeghers Syndrome (PJS)				
STK11 Targeted Variant Analysis	STK11 Targeted Variant - Single Test (GeneDx)	81479	C50, Q85.8, Z80, Z84, Z85,	2

STK11 Sequencing and/or Deletion/Duplication Analysis	STK11 Gene Sequencing & Del/Dup (GeneDx)	81404*, 81405*	Z86	
Retinoblastoma				
RB1 Targeted Variant Analysis	Retinoblastoma: Site Specific Analysis (Familial) (Univ of Pennsylvania School of Medicine-Genetic Diagnostic Laboratory)	81403*	C69, C75.3, Z80, Z84, Z85, Z86	9
RB1 Sequencing and/or Deletion/Duplication Analysis	RB1 Full Gene Sequencing and Deletion/Duplication (Invitae)	81479, S3841*		
Von Hippel-Lindau Syndrome (VHL)				
VHL Targeted Variant Analysis	VHL ~~Sequence Analysis (Familial~~Known Mutation~~/Variant Analysis) (Baylor Genetics, LLC~~ (Children's Hospital of Philadelphia - Division of Genomic Diagnostics)	81403*	C64, C7A, D3A, D35.00, K86.2, N28, N50.3, Q85.8, Z80, Z84, Z85, Z86	8
VHL Sequencing and/or Deletion/Duplication Analysis	VHL Full Gene Sequencing and Deletion/Duplication (Invitae)	81403*, 81404*, S3842*		
	VHL Gene Sequencing and Del/Dup (GeneDx)			

OTHER RELATED POLICIES

This policy document provides criteria for genetic testing for hereditary cancer susceptibility. Please refer to:

- ***Genetic Testing: Multisystem Inherited Disorders, Intellectual Disability, and Developmental Delay*** for criteria related to diagnostic testing for Fanconi anemia.
- ***Oncology: Algorithmic Testing*** for criteria related to tests that give prognostic information for an individual with cancer, or any oncology related test that involved an algorithmic portion.
- ***Oncology: Molecular Analysis of Solid Tumors and Hematologic Malignancies*** for criteria related to somatic tumor testing, including Microsatellite Instability for colon cancer, and blood cancer testing
- ***Oncology: Cancer Screening*** for criteria related to tests that screen for the presence of cancer.

- ***Oncology: Circulating Tumor DNA and Circulating Tumor Cells (Liquid Biopsy)*** for criteria related to the testing of tumor DNA circulating in an individual's blood stream.
- ***Genetic Testing: General Approach to Genetic and Molecular Testing*** for criteria related to hereditary cancer susceptibility that is not specifically discussed in this or other non-general policies, including known familial variant testing not already addressed in this policy.

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CRITERIA

It is the policy of **Louisiana Healthcare Connections** that the specific genetic testing noted below is **medically necessary** when meeting the related criteria:

PAN-CANCER HEREDITARY CANCER SUSCEPTIBILITY PANELS

A pan-cancer hereditary cancer susceptibility panel includes genes that are associated with inherited susceptibility to several different types of cancer (e.g., breast cancer, colon cancer, stomach cancer, etc.).

I. Genetic testing using a pan-cancer hereditary cancer susceptibility panel (0474U, 81432, 81433) is considered **medically necessary** when:

   A. The member/enrollee is 18 years or older, **AND**

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

      1. The member/enrollee meets clinical criteria for *BRCA1* and *BRCA2* sequencing and/or deletion/duplication analysis, **OR**

      2. The member/enrollee meets clinical criteria for Lynch syndrome/HNPCC *MLH1, MSH2, MSH6, PMS2, or EPCAM* sequencing and/or deletion/duplication analysis, **AND**

   C. The panel includes, at a minimum, sequencing of the following genes: *BRCA1*, *BRCA2*, *EPCAM*, *MLH1*, *MSH2*, *MSH6*, *PMS2*~~, AND~~.

   ~~A. The panel does not include genes without a known association with cancer by ClinGen.~~

II. Genetic testing using a pan-cancer hereditary cancer susceptibility panel (0474U, 81432, 81433) is considered **investigational** for all other indications.

III. Hereditary cancer susceptibility panel targeted mRNA sequencing analysis for the interpretation of variants of unknown significance (0134U), when billed in addition, is considered **investigational** because it is typically either considered an existing component of the genetic testing process for quality assurance or follow up testing without proven utility.

NOTE: If a multigene cancer panel is performed, the appropriate panel code should be used.

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HEREDITARY BREAST CANCER SUSCEPTIBILITY PANELS

A hereditary breast cancer susceptibility panel includes genes that are associated with inherited susceptibility to breast cancer.

I. Genetic testing using a hereditary breast cancer susceptibility panel (81162, 81163, 81164, 81165, 81166, 81167, 81216, 81307, 81321, 81351, 81432, 81433, 0129U) is considered **medically necessary** when:

   A. The member/enrollee meets *BRCA1* and *BRCA2* Sequencing and Deletion/Duplication analysis, **AND**

   B. The panel includes, at a minimum, sequencing of the following genes: *BRCA1*, *BRCA2*~~, **AND**~~.

   ~~A. The panel does not include genes without known association with breast cancer by ClinGen.~~

II. Genetic testing using a STAT hereditary breast cancer panel (81162, 81163, 81164, 81165, 81166, 81167, 81216) is considered **medically necessary** when:

   A. The member/enrollee meets any of the above criteria, **AND**

   B. The member/enrollee requires a rapid turn-around-time for decision making related to surgical interventions and treatment.

III. Genetic testing using a hereditary breast cancer susceptibility panel (81162, 81163, 81164, 81165, 81166, 81167, 81216, 81307, 81321, 81351, 81432, 81433, 0129U) is considered **investigational** for all other indications.

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HEREDITARY GI/COLON CANCER SUSCEPTIBILITY PANELS

A hereditary colorectal cancer susceptibility panel includes genes that are associated with inherited susceptibility to colorectal cancer.

I. Genetic testing using a hereditary colorectal cancer susceptibility panel (81435, 81436, 0101U) is considered **medically necessary** when:

~~A. The member/enrollee is 18 years or older, **AND**~~

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

1. The member/enrollee has a personal history of, or at least one blood relative with any of the following:

a) At least 10 adenomatous polyps, **OR**

b) At least 2 hamartomatous polyps, **OR**

c) At least 5 serrated polyps/lesions proximal to the rectum, **OR**

~~1. The member/enrollee has a personal history of colorectal cancer under 50 years of age, **OR**~~

2. The member/enrollee meets clinical criteria for Lynch syndrome/HNPCC *MLH1*, *MSH2*, *MSH6*, *PMS2*, or *EPCAM* Sequencing and/or Deletion/Duplication Analysis, **AND**

B. The panel includes, at a minimum, sequencing of the following genes: *APC*, *MUTYH*, *MLH1*, *MSH2*, *MSH6*, *PMS2*, *EPCAM*, *BMPR1A*, *SMAD4*, *PTEN*, *STK11*, and *TP53*~~, **AND**~~.

~~B. The panel does not include genes without a known association with colorectal or gastrointestinal cancer by ClinGen.~~

II. Genetic testing using a hereditary colorectal cancer susceptibility panel (81435, 81436, 0101U) is considered **investigational** for all other indications.

III. Hereditary colorectal cancer susceptibility panel targeted mRNA sequencing analysis for the interpretation of variants of unknown significance (0130U, 0162U), when billed in addition, is considered **investigational** because it is typically either considered an existing component of the genetic testing process for quality assurance or follow up testing without proven utility.

NOTE: If a multigene cancer panel is performed, the appropriate panel code should be used.

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HEREDITARY GASTRIC CANCER SUSCEPTIBILITY PANELS

A hereditary gastric cancer panel includes genes that are associated with inherited susceptibility to gastric (stomach) cancer.

I. Genetic testing using a hereditary gastric susceptibility panel (81201, 81203, 81292, 81294, 81295, 81297, 81298, 81300, 81317, 81319, 81403, 81404, 81405, 81406, 81408, 81479) is considered **medically necessary** when:

   A. The member/enrollee is 18 years or older, **AND**

   B. The member/enrollee meets sequencing and/or deletion/duplication clinical criteria for at least one of the following:

      1. Lynch syndrome/Hereditary Nonpolyposis Colorectal Cancer, **OR**
      2. Hereditary Diffuse Gastric Cancer, **OR**
      3. Juvenile Polyposis Syndrome, **OR**
      4. Peutz-Jeghers Syndrome, **OR**
      5. Adenomatous Polyposis Syndromes**, AND**

   C. The panel includes, at a minimum, sequencing of the following genes: *APC, BMPR1A, CDH1, EPCAM, MLH1, MSH2, MSH6, PMS2, SMAD4, STK11*~~, AND~~.

   ~~A. The panel does not include genes without a known association with gastric (stomach) cancer by ClinGen.~~

II. Genetic testing using a hereditary gastric cancer susceptibility panel (81201, 81203, 81292, 81294, 81295, 81297, 81298, 81300, 81317, 81319, 81403, 81404, 81405, 81406, 81408, 81479) is considered **investigational** for all other indications.

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HEREDITARY PANCREATIC CANCER SUSCEPTIBILITY PANELS

A hereditary pancreatic cancer susceptibility panel includes genes that are associated with inherited susceptibility to pancreatic cancer.

I. Genetic testing using a hereditary pancreatic cancer susceptibility panel (81162, 81163, 81201, 81292, 81295, 81298, 81351, 81433, 81479) is considered **medically necessary** when:

A. The member/enrollee is 18 years or older, **AND**

B. The member/enrollee meets criteria for *BRCA1* and *BRCA2* sequencing and/or deletion/duplication analysis, **AND**

C. The panel includes, at a minimum, sequencing of the following genes: *ATM, BRCA1, BRCA2, CDKN2A, EPCAM, MLH1, MSH2, MSH6, PALB2, STK11, TP53*~~, **AND**~~.

~~A. The panel does not include genes without a known association with pancreatic cancer by ClinGen.~~

II. Genetic testing using a hereditary pancreatic cancer susceptibility panel (81162, 81163, 81201, 81292, 81295, 81298, 81351, 81433, 81479) is considered **investigational** for all other indications.

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HEREDITARY POLYPOSIS SUSCEPTIBILITY PANELS

A hereditary polyposis panel is one that includes genes that are associated with inherited susceptibility to colon polyposis.

I. Genetic testing using a hereditary polyposis panel (81201, 81203, 81406, 81479) is considered **medically necessary** when:

A. The member/enrollee meets criteria for sequencing and/or deletion/duplication analysis for Adenomatous Polyposis conditions (Familial Adenomatous Polyposis Syndrome (FAP)/Attenuated FAP (AFAP) and *MUTYH*-Associated Polyposis Syndrome (MAP), **AND**

B. The panel includes, at a minimum, sequencing of the following genes: *APC* and *MUTYH*~~, **AND**~~.

~~A. The panel does not include genes without a known association with colon polyposis by ClinGen.~~

II. Genetic testing using a hereditary polyposis panel (81201, 81203, 81406, 81479) is considered **investigational** for all other indications.

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HEREDITARY PROSTATE CANCER SUSCEPTIBILITY PANELS

A hereditary prostate cancer susceptibility panel is one that includes genes that are associated with inherited susceptibility to prostate cancer.

I. Genetic testing using a hereditary prostate cancer susceptibility panel (81162, 81292, 81295, 81351, 81479,) is considered **medically necessary** when:

A. The member/enrollee is 18 years or older, **AND**

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

1. Metastatic prostate cancer, **OR**

~~1. High- or very-high risk localized prostate cancer, **OR**~~

2. ~~Regional (node positive)~~High- or very-high risk localized prostate cancer, **OR**

~~2.~~3. Intermediate risk prostate cancer with intraductal/cribriform histology, **OR**

C. The member/enrollee has a personal history of prostate cancer and any of the following:

1. One or more close relatives with any of the following:

a) Breast cancer at or under age 50, **OR**

b) Triple-negative breast cancer at any age, **OR**

~~a) Colorectal or endometrial cancer at or under age 50, **OR**~~

c) Male ~~reproductive system~~ (sex assigned at birth) breast cancer at any age, **OR**

d) Ovarian cancer at any age, **OR**

e) Exocrine pancreatic cancer at any age, **OR**

f) Metastatic, ~~regional,~~ very-high-risk, or high-risk prostate cancer at any age, **OR**

~~2. One or more first-degree relatives with prostate cancer at or under age 60, **OR**~~

~~3. Two or more close relatives with either of the following:~~

~~a) Breast cancer at any age, **OR**~~

~~b) Prostate cancer at any age, **OR**~~

~~4. Three or more first- or second-degree relatives with a Lynch syndrome-related cancer, especially if diagnosed under age 50, **OR**~~

2. Three or more close relatives with prostate cancer (any grade) and/or breast cancer- on the same side of the family including the patient with prostate cancer, **OR**

3. Ashkenazi Jewish ancestry, **OR**

~~5. A personal history of breast cancer, **OR**~~

D. The member/enrollee has a first-degree ~~blood~~ relative meeting any of the criteria above, **OR**

~~D.~~E. The member/enrollee's probability of having a *BRCA1* or *BRCA2* pathogenic variant is greater than 2.5% based on prior probability models (examples: Tyrer-Cuzick, BRCApro, CanRisk), **AND**

~~E.~~F. The panel includes, at a minimum, sequencing of the following genes: *BRCA1, BRCA2*~~, **AND**~~.

~~B. The panel does not include genes without a known association with prostate cancer by ClinGen.~~

II. Genetic testing using a hereditary prostate cancer susceptibility panel (81162, 81292, 81295, 81351, 81479, is considered **investigational** for all other indications.

III. Hereditary prostate cancer susceptibility panel targeted mRNA sequencing analysis for the interpretation of variants of unknown significance (0133U), when billed in addition, is considered **investigational** because it is typically either considered an existing component of the genetic testing process for quality assurance, or follow up testing without proven utility.

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HEREDITARY NEUROENDOCRINE CANCER SUSCEPTIBILITY PANELS

A hereditary neuroendocrine cancer susceptibility panel is one that includes genes that are associated with inherited susceptibility to a neuroendocrine cancer.

I. Genetic testing using a hereditary neuroendocrine cancer susceptibility panel (81437, 81438) is considered **medically necessary** when:

A. The member/enrollee has a diagnosis of at least one of the following:

1. Adrenocortical carcinoma, **OR**
2. Paraganglioma/pheochromocytoma, **OR**
3. Parathyroid adenoma or primary hyperparathyroidism before age 30, **OR**
4. Multiple parathyroid adenomas, **OR**
5. Multigland hyperplasia without obvious secondary cause, **OR**
6. Recurrent primary hyperparathyroidism, **OR**
7. Gastrinoma, **OR**
8. Duodenal or pancreatic neuroendocrine tumor, **OR**
9. A first-degree relative meeting any of the above criteria, but is not available for testing, **OR**

B. The member/enrollee meets criteria for *MEN1* sequencing and/or deletion/duplication analysis, **OR**

C. The member/enrollee meets criteria for *RET* sequencing and/or deletion duplication analysis~~, AND~~.

~~A. The panel does not include genes without a known association with a neuroendocrine cancer by ClinGen.~~

II. Genetic testing using a hereditary neuroendocrine cancer susceptibility panel (81437, 81438) is considered **investigational** for all other indications.

NOTE: If a multigene cancer panel is performed, the appropriate panel code should be used~~.~~

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BRCA1 AND *BRCA2* GENE TESTING

BRCA1 or *BRCA2* Targeted Variant or Known Familial Variant Analysis

I. *BRCA1* (81215) or *BRCA2* (81217) targeted variant or known familial variant analysis for hereditary cancer susceptibility is considered **medically necessary** when:

A. The member/enrollee is 18 years or older, **AND**

B. One of the following:

1. The member/enrollee has a family history of a known *BRCA1* or *BRCA2* pathogenic or likely pathogenic variant, **OR**

2. A ~~*BRCA1* or *BRCA2*~~ pathogenic or likely pathogenic variant in *BRCA1* or *BRCA2* was identified by tumor profiling in the member/enrollee and germline analysis has not yet been performed.

II. *BRCA1* (81215) or *BRCA2* (81217) targeted variant analysis for hereditary cancer susceptibility is considered **investigational** for all other indications.

BRCA1 and/or *BRCA2* Targeted Variant Analysis - Ashkenazi Jewish Founder Variants

I. *BRCA1* and *BRCA2* (81212) targeted variant analysis for the 185delAG, 5385insC, 6174delT variants is considered **medically necessary** when:

A. The member/enrollee is 18 years or older, **AND**

B. The member/enrollee is of Ashkenazi Jewish ancestry (at least one grandparent of Ashkenazi Jewish ancestry).

II. *BRCA1* and *BRCA2* (81212) targeted variant analysis for the 185delAG, 5385insC, 6174delT variants is considered **investigational** for all other indications.

BRCA1 and *BRCA2* Sequencing and/or Deletion/Duplication Analysis

I. *BRCA1* and *BRCA2* (81162, 81163, 81164, 81165, 81166, 81167, 81216) sequencing and/or deletion/duplication analysis for hereditary breast and/or ovarian cancer susceptibility is considered **medically necessary** when**:**

A. The member/enrollee is 18 years or older, **AND**

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

1. Male ~~reproductive system~~ (sex assigned at birth) breast cancer, **OR**

2. Triple-negative breast cancer, **OR**

3. Breast cancer diagnosed at age ~~50~~65 or younger, **OR**

4. Epithelial ovarian cancer (including fallopian tube cancer or peritoneal cancer), **OR**

5. Exocrine pancreatic or ampullary cancer, **OR**

6. Metastatic prostate cancer, **OR**

7. High- or very-high-risk group prostate cancer, **OR**
8. Multiple primary ~~-~~breast cancers (diagnosed synchronously or metachronously), **OR**

C. The member/enrollee has a personal history of breast cancer **AND** any of the following:

1. Ashkenazi Jewish ancestry, **OR**
2. One or more close relatives with any of the following:
   a) Female ~~reproductive system~~ (sex assigned at birth) breast cancer diagnosed at age 50 years or younger, **OR**
   b) Male ~~reproductive system~~ (sex assigned at birth) breast cancer, **OR**
   c) Ovarian cancer, **OR**
   d) Pancreatic cancer, **OR**
   e) ~~Metastatic, or~~ Prostate cancer that is either metastatic, intermediate-risk with intraductal/cribriform histology, or high- or very-high-risk group ~~prostate cancer~~, **OR**
3. Three or more total diagnoses of breast cancer and/or prostate cancer (any grade) on the same side of the family including the member/enrollee with breast cancer, **OR**

D. The member/enrollee has a first- or second-degree relative meeting any of the above criteria, **OR**

E. The member/enrollee has metastatic breast cancer and is being considered for systemic treatment using PARP inhibitors, **OR**

F. The member/enrollee has high-risk, HER2-negative breast cancer and is being considered for adjuvant treatment with olaparib, **OR**

G. The member/enrollee's probability of having a *BRCA1* or *BRCA2* pathogenic variant is greater than 2.5% based on prior probability models (examples: Tyrer-Cuzick, BRCApro, CanRisk).

II. *BRCA1* and *BRCA2* (81162, 81163, 81164, 81165, 81166, 81167, 81216) sequencing and/or deletion/duplication analysis for hereditary breast and/or ovarian cancer susceptibility is considered **investigational** for all other indications.

III. *BRCA1/BRCA2* mRNA sequencing analysis for the interpretation of variants of unknown significance (0138U), when billed in addition, is considered **investigational** because it is

typically either considered an existing component of the genetic testing process for quality assurance or follow up testing without proven utility.

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PALB2 GENE TESTING

PALB2 Targeted Variant Analysis

I. *PALB2* targeted variant analysis (81308) for hereditary breast and/or ovarian cancer susceptibility is considered **medically necessary** when:

A. The member/enrollee is 18 years or older, **AND**

B. One of the following:

1. The member/enrollee has a family history of a known pathogenic or likely pathogenic variant in *PALB2*, **OR**

2. A pathogenic or likely pathogenic variant in *PALB2* was identified by tumor profiling in ~~*PALB2*~~the member/enrollee, and germline analysis has not yet been performed.

II. *PALB2* targeted variant analysis (81308) for hereditary breast and/or ovarian cancer susceptibility is considered **investigational** for all other indications.

PALB2 Sequencing and/or Deletion/Duplication Analysis

I. *PALB2* (81307, 81479) sequencing and/or deletion/duplication analysis for hereditary breast and/or ovarian cancer susceptibility is considered **medically necessary** when**:**

A. The member/enrollee is 18 years or older, **AND**

B. One of the following:

1. The member/enrollee has a personal history of any of the following:

a) Male ~~reproductive system~~ (sex assigned at birth) breast cancer, **OR**

b) Triple-negative breast cancer, **OR,**

c) Breast cancer diagnosed at age 50 or younger, **OR**

d) Epithelial ovarian cancer (including fallopian tube cancer or peritoneal cancer), **OR**

e) Exocrine pancreatic or ampullary cancer, **OR**

f) Multiple primary breast cancers (diagnosed synchronously or metachronously, **OR**

g) Metastatic prostate cancer, **OR**

2. The member/enrollee has a personal history of breast cancer **AND** any of the following:

   a) Ashkenazi Jewish ancestry, **OR**

   b) One or more close relatives with any of the following:

      (1) Female ~~reproductive system~~ (sex assigned at birth) breast cancer diagnosed at age 50 years or younger, **OR**

      (2) Male ~~reproductive system~~ (sex assigned at birth) breast cancer, **OR**

      (3) Ovarian cancer, **OR**

      (4) Exocrine pancreatic cancer, **OR**

   c) Three or more total diagnoses of breast cancer in the member/enrollee and/or close relatives, **OR**

3. The member/enrollee has a first- or second-degree relative meeting any of the above criteria, **OR**

4. The member/enrollee has metastatic breast cancer and is being considered for systemic treatment decisions using PARP inhibitors, **OR**

5. The member/enrollee has high-risk, HER2-negative breast cancer and is being considered for adjuvant treatment with olaparib, **OR**

6. The member/enrollee's probability of having a *BRCA1* or *BRCA2* pathogenic variant is greater than 2.5% based on prior probability models (examples: Tyrer-Curzick, BRCApro, CanRisk).

II. *PALB2* (81307) sequencing and/or deletion/duplication analysis for hereditary breast and/or ovarian cancer susceptibility is considered **investigational** for all other indications.

III. *PALB2* mRNA sequencing analysis for the interpretation of variants of unknown significance (0137U), when billed in addition, is considered **investigational** because it is typically either considered an existing component of the genetic testing process for quality assurance or follow up testing without proven utility.

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ATM AND/OR *CHEK2* GENE TESTING

ATM or *CHEK2* Targeted Variant Analysis

I. *ATM* (81479) or *CHEK2* (81479) targeted variant analysis for hereditary breast and/or ovarian cancer susceptibility is considered **medically necessary** when:

   A. The member/enrollee is 18 years or older, **AND**

   B. One of the following:

      1. The member/enrollee has a close relative with a known pathogenic or likely pathogenic variant in *ATM* or *CHEK2*, **OR**

      2. A pathogenic or likely pathogenic variant in *ATM* or *CHEK2* was identified by tumor profiling in ~~*ATM or CHEK2*~~the member/enrollee and germline analysis has not yet been performed.

II. *ATM* (81479) or *CHEK2* (81479) targeted variant analysis for hereditary breast and/or ovarian cancer susceptibility is considered **investigational** for all other indications.

ATM and/or *CHEK2* Sequencing and/or Deletion/Duplication Analysis

I. *ATM* (81408, 81479) and/or *CHEK2* (81479) sequencing and/or deletion/duplication analysis for hereditary breast and/or ovarian cancer susceptibility, as a stand alone test, is considered **investigational**.

II. *ATM* mRNA sequencing analysis for the interpretation of variants of unknown significance (0136U), when billed in addition, is considered **investigational** because it is typically either considered an existing component of the genetic testing process for quality assurance or follow up testing without proven utility.

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LYNCH SYNDROME / HEREDITARY NONPOLYPOSIS COLORECTAL CANCER (HNPCC) TESTING

MLH1, *MSH2*, *MSH6*, *PMS2*, or *EPCAM* Targeted Variant Analysis

I. *MLH1* (81293), *MSH2* (81296), *MSH6* (81299), *PMS2* (81318), or *EPCAM* (81479) targeted variant analysis for Lynch syndrome/HNPCC is considered **medically necessary** when:

A. The member/enrollee has a blood relative with a known pathogenic or likely pathogenic variant in *MLH1*, *MSH2*, *MSH6*, *PMS2*, or *EPCAM*, **OR**

B. A pathogenic or likely pathogenic variant in *MLH1*, *MSH2*, *MSH6*, *PMS2*, or *EPCAM* was identified by tumor profiling in ~~*MLH1, MSH2, MSH6, PMS2, or EPCAM*~~the member/enrollee and germline analysis has not yet been performed.

II. *MLH1* (81293), *MSH2* (81296), *MSH6* (81299), *PMS2* (81318), or *EPCAM* (81479) targeted variant analysis for Lynch syndrome/HNPCC is considered **investigational** for all other indications.

MLH1, MSH2, MSH6, PMS2, and/or *EPCAM* Sequencing and/or Deletion/Duplication Analysis

I. *MLH1* (81292, 81294), *MSH2* (81295, 81297), *MSH6* (81298, 81300), *PMS2* (81317, 81319), and/or *EPCAM* (81403) sequencing and/or duplication analysis for Lynch syndrome/HNPCC is considered **medically necessary** when:

A. The member/enrollee has a Lynch syndrome-related cancer **and** the tumor shows evidence of mismatch repair (MMR) deficiency (either by microsatellite instability (MSI) or loss of MMR protein expression), **OR**

B. The member/enrollee has a diagnosis of a Lynch syndrome-related cancer, **AND** any of the following:

1. Diagnosed before age 50, **OR**
2. Diagnosed at any age with an additional Lynch syndrome-related cancer, **OR**
3. Diagnosed at any age with one or more first- or second-degree relatives diagnosed before age 50 with a Lynch syndrome-related cancer, **OR**
4. Diagnosed at any age with two or more first- or second-degree relatives diagnosed at any age with a Lynch syndrome-related cancer, **OR**

C. The member/enrollee has a family history of **any** of the following:

1. One or more first-degree relatives diagnosed with colorectal or endometrial cancer before age 50, **OR**
2. One or more first-degree relatives diagnosed with colorectal or endometrial cancer and an additional Lynch syndrome-related cancer, **OR**
3. Two or more first- or second-degree relatives on the same side of the family diagnosed with a Lynch syndrome-related cancer, one of whom was diagnosed before age 50, **OR**

4. Three or more first- or second-degree relatives on the same side of the family diagnosed with a Lynch syndrome-related cancer, **OR**

D. The member/enrollee has a 5% or greater risk of having Lynch syndrome based on one of the following variant prediction models: MMRpro, PREMM5, MMRpredict, **OR**

E. The member/enrollee has a personal history of colorectal and/or endometrial cancer with a PREMM5 score of 2.5% or greater.

II. *MLH1* (81292, 81294), *MSH2* (81295, 81297), *MSH6* (81298, 81300), *PMS2* (81317, 81319), and/or *EPCAM* (81403) sequencing and/or duplication analysis for Lynch syndrome/HNPCC is considered **investigational** for all other indications.

III. *MLH1, MSH2, MSH6, PMS2* and *EPCAM* mRNA sequencing analysis for the interpretation of variants of unknown significance (0158U, 0159U, 0160U, 0161U, 0162U), when billed in addition, is considered **investigational** because it is typically either considered an existing component of the genetic testing process for quality assurance, or follow up testing without proven utility.

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BAP1-TUMOR PREDISPOSITION SYNDROME

BAP1 Targeted Variant Analysis

I. *BAP1* targeted variant analysis (81403) for *BAP1*-tumor predisposition syndrome is considered **medically necessary** when:

A. The member/enrollee has a close relative with a known pathogenic or likely pathogenic variant in *BAP1*, **OR**

B. A pathogenic or likely pathogenic variant in *BAP1* was identified by tumor profiling in the member/enrollee and germline analysis has not yet been performed.

II. *BAP1* targeted variant analysis (81403) for *BAP1*-tumor predisposition syndrome is considered **investigational** for all other indications.

BAP1 Sequencing and/or Deletion/Duplication Analysis

I. *BAP1* sequencing and/or deletion/duplication analysis (81479) for *BAP1*-tumor predisposition syndrome is considered **medically necessary** when:

A. The member/enrollee has a personal history of:

1. Two or more of the following:
    a) *BAP1*-inactivated melanocytic tumors (aka atypical spitz tumor), **OR**
    b) Uveal melanoma, **OR**
    c) Malignant mesothelioma, **OR**
    d) Renal cell carcinoma, **OR**
    e) Hepatocellular carcinoma, **OR**
    f) Cholangiocarcinoma, **OR**
    g) Meningioma, **OR**
2. One of the tumors/cancers listed in the criteria A.1., **AND**
    a) A cutaneous melanoma, **OR**
    b) A basal cell carcinoma, **OR**
3. One of the tumors/cancers listed in the criteria A.1., **AND**
    a) A first- or second-degree relative with any of the following tumors/cancers:
        (1) *BAP1*-inactivated melanocytic tumors (aka atypical spitz tumor), **OR**
        (2) Uveal melanoma, **OR**
        (3) Malignant mesothelioma, **OR**
        (4) Renal cell carcinoma, **OR**
        (5) Hepatocellular carcinoma, **OR**
        (6) Cholangiocarcinoma, **OR**
        (7) Meningioma, **OR**
        (8) Cutaneous melanoma, **OR**
        (9) Basal cell carcinoma, **OR**

4. ~~One or more~~Both of the following:
    ~~b)~~a) A diagnosis of:

(1) Cutaneous melanoma, **OR**

(2) Basal cell carcinoma, **AND**

~~c)~~b) A first- or second-degree relative with any of the following tumors/cancer:

(1) *BAP1*-inactivated melanocytic tumors (aka atypical spitz tumor), **OR**

(2) Uveal melanoma, **OR**

(3) Malignant mesothelioma, **OR**

(4) Renal cell carcinoma, **OR**

(5) Hepatocellular carcinoma, **OR**

(6) Cholangiocarcinoma, **OR**

(7) Meningioma.

II. *BAP1* sequencing and/or deletion/duplication analysis (81479) for *BAP1*-tumor predisposition syndrome is considered **investigational** for all other indications.

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BIRT-HOGG-DUBE SYNDROME (BHDS)

FLCN Targeted Variant Analysis

I. *FLCN* targeted variant analysis (81479) for Birt-Hogg-Dube syndrome (BHDS) is considered **medically necessary** when:

A. The member/enrollee has a first- or second-degree relative with a known pathogenic or likely pathogenic variant in *FLCN*, **OR**

B. A pathogenic or likely pathogenic variant in *FLCN* was identified by tumor profiling in the member/enrollee and germline analysis has not yet been performed.

II. *FLCN* targeted variant analysis (81479) for Birt-Hogg-Dube syndrome (BHDS) is considered **investigational** for all other indications.

FLCN Sequencing and/or Deletion/Duplication Analysis

I. *FLCN* sequencing and/or deletion/duplication analysis (81479) for Birt-Hogg-Dube syndrome (BHDS) is considered **medically necessary** when:

A. The member/enrollee has a personal history of any of the following:

1. 5 or more fibrofolliculomas/trichodiscomas with at least one confirmed histologically, **OR**
2. Multiple lung cysts with no apparent cause, ~~**OR**~~with or without pneumothorax, **OR**
3. Renal cancer diagnosed before 50 years of age, **OR**
4. Multifocal or bilateral renal cancer, **OR**
5. Renal cancer of mixed chromophobe and oncocytic, clear cell, or papillary histology, **OR**
6. Oncocytoma, **OR**
7. Angiomyolipoma, **OR**
8. A first-degree relative with BHDS who has not yet had genetic testing, or the results of genetic testing are unknown.

II. *FLCN* sequencing and/or deletion/duplication analysis (81479) for Birt-Hogg-Dube syndrome (BHDS) is considered **investigational** for all other indications.

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COWDEN SYNDROME (CS)/PTEN HAMARTOMA TUMOR SYNDROME (PHTS)

PTEN Targeted Variant Analysis

I. *PTEN* targeted variant analysis (81322) for Cowden syndrome (CS)/*PTEN* hamartoma tumor syndrome (PHTS) is considered **medically necessary** when:

A. The member/enrollee has a blood relative with a known pathogenic or likely pathogenic variant in *PTEN*, **OR**

B. A pathogenic or likely pathogenic variant in *PTEN* was identified by tumor profiling in the member/enrollee and germline analysis has not yet been performed.

II. *PTEN* targeted variant analysis (81322) for Cowden syndrome (CS)/*PTEN* hamartoma tumor syndrome (PHTS) is considered **investigational** for all other indications.

PTEN Sequencing and/or Deletion/Duplication Analysis

I. *PTEN* sequencing and/or deletion/duplication analysis (81321, 81323) for Cowden syndrome (CS)/*PTEN* hamartoma tumor syndrome (PHTS) is considered **medically necessary** when:

A. The member/enrollee has a personal history of any of the following:

1. Bannayan Riley-Ruvalcaba syndrome (BRRS), **OR**
2. Adult Lhermitte-Duclos disease (LDD) (defined as the presence of a cerebellar dysplastic gangliocytoma), **OR**
3. Autism-spectrum disorder and macrocephaly, **OR**
4. At least 2 biopsy-proven trichilemmomas, **OR**

B. The member/enrollee meets clinical criteria for CS/PHTS:

1. Macrocephaly (greater than or equal to 97 percentile), **OR**
2. Lhermitte-Duclos disease, **OR**
3. Gastrointestinal hamartomas or ganglioneuromas, **AND**
4. At least two of the following:

a) Breast Cancer, **OR**

b) Endometrial Cancer, **OR**

c) Thyroid Cancer (follicular), **OR**

d) Macular pigmentation of the glans penis, **OR**

e) Mucocutaneous lesions (One biopsy-proven trichilemmoma; multiple palmoplantar keratoses; multifocal or extensive oral mucosal papillomatosis; multiple cutaneous facial papules), **OR**

C. The member/enrollee has at least two of the following:

1. Breast Cancer, **OR**
2. Endometrial Cancer, **OR**
3. Thyroid Cancer (follicular), **OR**

4. Multiple gastrointestinal hamartomas or ganglioneuromas, **OR**
5. Macrocephaly (greater than or equal to 97 percentile), **OR**
6. Macular pigmentation of the glans penis, **OR**
7. Mucocutaneous lesions (One biopsy-proven trichilemmoma; multiple palmoplantar keratoses; multifocal or extensive oral mucosal papillomatosis; multiple cutaneous facial papules), **AND**
8. At least three of the following:
    a) Autism Spectrum Disorder, **OR**
    b) Colon Cancer, **OR**
    c) Esophageal glycogenic acanthosis (3 or more), **OR**
    d) Lipomas, **OR**
    e) Intellectual disability (i.e., IQ less than or equal to 75), **OR**
    f) Thyroid cancer (papillary or follicular variant of papillary thyroid cancer), **OR**
    g) Thyroid structural lesions (such as adenoma, multinodular goiter), **OR**
    h) Renal cell carcinoma, **OR**
    i) Single GI hamartoma or ganglioneuroma, **OR**
    j) Testicular lipomatosis, **OR**
    k) Vascular anomalies (including multiple intracranial developmental venous anomalies), **OR**

D. The member/enrollee has macrocephaly, **AND**

1. Breast Cancer, **OR**
2. Endometrial Cancer, **OR**
3. Thyroid Cancer (follicular), **OR**
4. Multiple gastrointestinal hamartomas or ganglioneuromas, **OR**
5. Macrocephaly (greater than or equal to 97 percentile), **OR**
6. Macular pigmentation of the glans penis, **OR**

7. Mucocutaneous lesions (One biopsy-proven trichilemmoma; multiple palmoplantar keratoses; multifocal or extensive oral mucosal papillomatosis; multiple cutaneous facial papules), **OR**

E. The member/enrollee has at least three of the following:

1. Breast Cancer, **OR**
2. Endometrial Cancer, **OR**
3. Thyroid Cancer (follicular), **OR**
4. Multiple gastrointestinal hamartomas or ganglioneuromas, **OR**
5. Macular pigmentation of the glans penis, **OR**
6. Mucocutaneous lesions (One biopsy-proven trichilemmoma; multiple palmoplantar keratoses; multifocal or extensive oral mucosal papillomatosis; multiple cutaneous facial papules), **OR**
7. The member/enrollee has a close relative with a clinical diagnosis of CS/PHTS or BRRS for whom testing has not been performed, **OR**

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

1. Breast Cancer, **OR**
2. Endometrial Cancer, **OR**
3. Thyroid Cancer (follicular), **OR**
4. Multiple gastrointestinal hamartomas or ganglioneuromas, **OR**
5. Macrocephaly (greater than or equal to 97 percentile), **OR**
6. Macular pigmentation of the glans penis, **OR**
7. Mucocutaneous lesions (One biopsy-proven trichilemmoma; multiple palmoplantar keratoses; multifocal or extensive oral mucosal papillomatosis; multiple cutaneous facial papules), **AND**
8. At least three of the following:
    a) Autism Spectrum Disorder, **OR**
    b) Colon Cancer, **OR**
    c) Esophageal glycogenic acanthosis (3 or more), **OR**
    d) Lipomas, **OR**

e) Intellectual disability (ie, IQ less than or equal to 75), **OR**

f) Thyroid cancer (papillary or follicular variant of papillary thyroid cancer), **OR**

g) Thyroid structural lesions (such as adenoma, multinodular goiter), **OR**

h) Renal cell carcinoma, **OR**

i) Single GI hamartoma or ganglioneuroma, **OR**

j) Testicular lipomatosis, **OR**

k) Vascular anomalies (including multiple intracranial developmental venous anomalies), **OR**

G. The member/enrollee has at least four of the following:

1. Autism Spectrum Disorder, **OR**
2. Colon Cancer, **OR**
3. Esophageal glycogenic acanthosis (3 or more), **OR**
4. Lipomas, **OR**
5. Intellectual disability (i.e., IQ less than or equal to 75), **OR**
6. Thyroid cancer (papillary or follicular variant of papillary thyroid cancer), **OR**
7. Thyroid structural lesions (such as adenoma, multinodular goiter), **OR**
8. Renal cell carcinoma, **OR**
9. Single GI hamartoma or ganglioneuroma, **OR**
10. Testicular lipomatosis, **OR**
11. Vascular anomalies (including multiple intracranial developmental venous anomalies), **OR**

H. The member/enrollee has a close relative with a clinical diagnosis of CS/PHTS or BRRS for whom testing has not been performed, **AND**

1. The member/enrollee has at least one of the following:

a) Breast Cancer, **OR**

b) Endometrial Cancer, **OR**

c) Thyroid Cancer (follicular), **OR**

d) Multiple gastrointestinal hamartomas or ganglioneuromas, **OR**

e) Macrocephaly (greater than or equal to 97 percentile), **OR**

f) Macular pigmentation of the glans penis, **OR**

g) Mucocutaneous lesions (One biopsy-proven trichilemmoma; multiple palmoplantar keratoses; multifocal or extensive oral mucosal papillomatosis; multiple cutaneous facial papules), **OR**

2. At least two of the following:

a) Autism Spectrum Disorder, **OR**

b) Colon Cancer, **OR**

c) Esophageal glycogenic acanthosis (3 or more), **OR**

d) Lipomas, **OR**

e) Intellectual disability (i.e., IQ less than or equal to 75), **OR**

f) Thyroid cancer (papillary or follicular variant of papillary thyroid cancer), **OR**

g) Thyroid structural lesions (such as adenoma, multinodular goiter), **OR**

h) Renal cell carcinoma, **OR**

i) Single GI hamartoma or ganglioneuroma, **OR**

j) Testicular lipomatosis, **OR**

k) Vascular anomalies (including multiple intracranial developmental venous anomalies).

II. *PTEN* sequencing and/or deletion/duplication analysis (81321, 81323,) for Cowden syndrome (CS)/*PTEN* hamartoma tumor syndrome (PHTS) is considered **investigational** for all other indications**.**

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ADENOMATOUS POLYPOSIS CONDITIONS (Familial Adenomatous Polyposis Syndrome (FAP)/Attenuated FAP (AFAP) ~~AND~~and/or *MUTYH*-Associated Polyposis Syndrome (MAP)

APC ~~*OR*~~and/or *MUTYH* Targeted Variant Analysis

I. *APC* (81202) and/or *MUTYH* targeted variant analysis (81401, 81403) for adenomatous polyposis testing is considered **medically necessary** when:

A. The member/enrollee has a family history of a known pathogenic or likely pathogenic variant in *APC* or *MUTYH*, **OR**

B. ~~An *APC* or *MUTYH* A~~ pathogenic or likely pathogenic variant in *APC* or *MUTYH* was identified by tumor profiling in the member/enrollee and germline analysis has not yet been performed.

II. *APC* (81202) and/or *MUTYH* (81401, 81403) targeted variant analysis for adenomatous polyposis conditions is considered **investigational** for all other indications.

APC and/or *MUTYH* Sequencing and/or Deletion/Duplication Analysis

I. *APC* sequencing and/or deletion/duplication analysis (81201, 81203) and/or *MUTYH* sequencing and/or deletion/duplication analysis (81406, 81479) for adenomatous polyposis conditions is considered **medically necessary** when:

A. The member/enrollee has a history of any of the following:

1. 10 or more cumulative adenomas, **OR**
2. Congenital hypertrophy of the retinal pigment epithelium (CHRPE), **OR**
3. Desmoid tumor, **OR**
4. Hepatoblastoma, **OR**
5. Cribriform-morular variant of papillary thyroid cancer, **OR**
6. A clinical diagnosis of serrated-polyposis syndrome, with at least some adenomas, based on one of the following:

a) 5 or more serrated polyps proximal to the rectum, all being 5mm or greater in size and at least 2 being 10mm or greater in size, **OR**

b) More than 20 serrated polyps of any size distributed throughout the large bowel, with at least 5 or more being proximal to the rectum, **OR**

7. Duodenal cancer, **OR**

8. Duodenal adenomas.

II. *APC* sequencing and/or deletion/duplication analysis (81201, 81203) and/or *MUTYH* sequencing and/or deletion/duplication analysis (81406, 81479) for adenomatous polyposis conditions is considered **investigational** for all other indications.

III. *APC* mRNA sequencing analysis for the interpretation of variants of unknown significance (0157U), when billed in addition, is considered **investigational** because it is typically either considered an existing component of the genetic testing process for quality assurance or follow up testing without proven utility.

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FAMILIAL ATYPICAL MULTIPLE MOLE MELANOMA (FAMMM) SYNDROME

CDKN2A Targeted Variant Analysis

I. *CDKN2A* targeted variant analysis (81479) for familial atypical multiple mole melanoma (FAMMM) syndrome, also known as melanoma-pancreatic cancer syndrome, is considered **medically necessary** when:

~~A. The member/enrollee is 18 years or older, **AND**~~

~~B. One of the following:~~

A. The member/enrollee has a close relative with a known pathogenic or likely pathogenic variant in *CDKN2A*, **OR**

B. A *CDKN2A* pathogenic or likely pathogenic variant was identified by tumor profiling in the member/enrollee and germline analysis has not yet been performed.

II. *CDKN2A* targeted variant analysis (81479) for familial ~~cutaneous malignant melanoma~~atypical multiple mole melanoma (FAMMM) syndrome, also known as melanoma-pancreatic cancer syndrome is considered **investigational** for all other indications.

CDKN2A Sequencing and/or Deletion/Duplication Analysis

I. *CDKN2A* sequencing and/or deletion/duplication analysis (81404, 81479) for familial atypical multiple mole melanoma (FAMMM) syndrome, also known as melanoma-pancreatic cancer syndrome, is considered **medically necessary** when:

A. The member/enrollee has had 3 or more invasive cutaneous melanomas, **OR**

B. The member/enrollee has had pancreatic adenocarcinoma, **OR**

C. The member/enrollee has had at least one cutaneous melanoma, **AND**

1. The member/enrollee has at least two close relatives with pancreatic cancer or cutaneous melanoma on the same side of the family.

II. *CDKN2A* sequencing and/or deletion/duplication analysis (81404, 81479) for familial atypical multiple mole melanoma (FAMMM) syndrome, also known as melanoma-pancreatic cancer syndrome, is considered **investigational** for all other indications.

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HEREDITARY DIFFUSE GASTRIC CANCER (AKA, SIGNET RING CELL GASTRIC CANCER~~):~~)

CDH1 Targeted Variant Analysis

I. *CDH1* targeted variant analysis (81479) for Hereditary Diffuse Gastric Cancer (aka, Signet Ring Cell Gastric Cancer) is considered **medically necessary** when:

A. The member/enrollee is 18 years or older, **AND**

B. One of the following:

1. The member/enrollee has a ~~blood relative~~close relative with a known pathogenic or likely pathogenic variant in *CDH1*, **OR**

2. A ~~*CDH1*~~ pathogenic or likely pathogenic variant in *CDH1* was identified by tumor profiling in the member/enrollee and germline analysis has not yet been performed.

II. *CDH1* targeted variant analysis (81479) for Hereditary Diffuse Gastric Cancer (aka, Signet Ring Cell Gastric Cancer) is considered **investigational** for all other indications.

CDH1 Sequencing and/or Deletion/Duplication Analysis

I. *CDH1* sequencing and/or deletion/duplication analysis for Hereditary Diffuse Gastric Cancer (aka, Signet Ring Cell Gastric Cancer) (81406, 81479) is considered **medically necessary** when:

A. The member/enrollee is 18 years or older, **AND**

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

1. Diffuse gastric cancer diagnosed before age 50 years, **OR**

2. Diffuse gastric cancer diagnosed at any age in a member/enrollee with Maori ancestry, **OR**
3. Diffuse gastric cancer diagnosed at any age in a member/enrollee with a personal or family history of cleft lip/cleft palate, **OR**
4. Bilateral lobular breast cancer diagnosed before age 70 years, **OR**
5. Personal or family history of diffuse gastric cancer and lobular breast cancer, one diagnosed before age 70 years, **OR**
6. Two cases of gastric cancer in the family, at least one of which is a confirmed case of diffuse gastric cancer, diagnosed at any age, **OR**
7. Two cases of lobular breast cancer in family members before 50 years of age**.**

II. *CDH1* sequencing and/or deletion/duplication analysis for Hereditary Diffuse Gastric Cancer (aka, Signet Ring Cell Gastric Cancer) (81406, 81479) is considered **investigational** for all other indications.

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JUVENILE POLYPOSIS SYNDROME (JPS)

SMAD4 or *BMPR1A* Targeted Variant Analysis

I. *SMAD4* and/or *BMPR1A* targeted variant analysis (81403) for juvenile polyposis syndrome (JPS) is considered **medically necessary** when:

A. The member/enrollee has a blood relative with a known pathogenic or likely pathogenic variant in *SMAD4* and/or *BMPR1A*, **OR**

B. ~~A *SMAD4* and/or *BMPR1A*~~ A pathogenic or likely pathogenic variant in *SMAD4* and/or *BMPR1A* was identified by tumor profiling in the member/enrollee and germline analysis has not yet been performed.

II. *SMAD4* and/or *BMPR1A* targeted variant analysis (81403) for juvenile polyposis syndrome (JPS) is considered **investigational** for all other indications.

SMAD4 and/or *BMPR1A* Sequencing and/or Deletion/Duplication Analysis

I. *SMAD4* and/or *BMPR1A* sequencing and/or deletion/duplication analysis (81405, 81406, 81479) for juvenile polyposis syndrome (JPS) is considered **medically necessary** when:

A. The member/enrollee has 5 or more juvenile polyps in the colon, **OR**

B. The member/enrollee has multiple juvenile polyps throughout the gastrointestinal tract, **OR**

C. The member/enrollee has ~~juvenile polyps (any number) and~~ a family history of JPS.

II. *SMAD4* and/or *BMPR1A* sequencing and/or deletion/duplication analysis (81405, 81406, 81479) for juvenile polyposis syndrome (JPS) is considered **investigational** for all other indications.

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HEREDITARY LEIOMYOMATOSIS AND RENAL CELL CANCER (HLRCC)

FH Targeted Variant Analysis

I. *FH* targeted variant analysis (81403) for hereditary leiomyomatosis and renal cell cancer (HLRCC) is considered **medically necessary** when:

~~A. The member/enrollee is 18 years or older, **AND**~~

~~B. One of the following:~~

A. The member/enrollee has a first- or second-degree relative with a known pathogenic or likely pathogenic variant in *FH*, **OR**

B. A ~~*FH*~~ pathogenic or likely pathogenic variant in *FH* was identified by tumor profiling in the member/enrollee and germline analysis has not yet been performed.

II. *FH* targeted variant analysis (81403) for hereditary leiomyomatosis and renal cell cancer (HLRCC) is considered **investigational** for all other indications.

FH Sequencing and/or Deletion/Duplication Analysis

I. *FH* sequencing and/or deletion/duplication analysis (81405, 81479) for hereditary leiomyomatosis and renal cell cancer (HLRCC) is considered **medically necessary** when:

A. The member/enrollee is 18 years or older, **AND**

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

1. Cutaneous leiomyomata, **OR**
2. Uterine leiomyomata (uterine fibroids), **OR**

3. Renal cell carcinoma.

II. *FH* sequencing and/or deletion/duplication analysis (81405, 81479) for hereditary leiomyomatosis and renal cell cancer (HLRCC) is considered **investigational** for all other indications.

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LI-FRAUMENI SYNDROME (LFS)

TP53 Targeted Variant Analysis

I. *TP53* targeted variant analysis (81352) for Li-Fraumeni syndrome (LFS) is considered **medically necessary** when:

A. The member/enrollee has a ~~blood relative~~close relative with a known pathogenic or likely pathogenic variant in *TP53*, **OR**

B. A ~~*TP53*~~ pathogenic or likely pathogenic variant in *TP53* was identified by tumor profiling in the member/enrollee and germline analysis has not yet been performed.

II. *TP53* targeted variant analysis (81352) for Li-Fraumeni syndrome (LFS) is considered **investigational** for all other indications.

TP53 Sequencing and/or Deletion/Duplication Analysis

I. *TP53* sequencing and/or deletion/duplication analysis (81351, 81479) for Li-Fraumeni syndrome (LFS) is considered **medically necessary** when:

A. The member/enrollee was diagnosed with breast cancer before 31 years of age, **OR**

B. The member/enrollee has a personal or family history of pediatric hypodiploid acute lymphoblastic leukemia, **OR**

C. The member/enrollee was diagnosed with a sarcoma before 45 years of age, **AND**

1. The member/enrollee has a first-degree relative diagnosed with any cancer before 45 years of age, **AND**

2. At least one of the following:

a) The member/enrollee has an additional first- or second-degree relative diagnosed with any cancer before 45 years of age, **OR**

b) The member/enrollee has an additional first- or second-degree relative diagnosed with sarcoma at any age, **OR**

D. The member/enrollee was diagnosed with any of the following at any age:

1. Adrenocortical carcinoma, **OR**
2. Choroid plexus carcinoma, **OR**
3. Rhabdomyosarcoma of embryonal anaplastic subtype, **OR**

E. The member/enrollee was diagnosed with any of the following tumors from the LFS tumor spectrum before 46 years of age:

1. Soft tissue sarcoma, **OR**
2. Osteosarcoma, **OR**
3. Central nervous system tumor, **OR**
4. Breast cancer, **OR**
5. Adrenocortical carcinoma, **AND**

a) The member/enrollee has had a second tumor from the LFS tumor spectrum (except breast cancer if the initial cancer was breast cancer), **OR**

b) The member/enrollee has a first- or second-degree relative with a tumor from the LFS tumor spectrum before 56 years of age (except breast cancer if the member~~/enrollee~~ had breast cancer), **OR**

c) The member/enrollee has a first- or second-degree relative with a history of multiple primary tumors from the LFS tumor spectrum at any age.

II. *TP53* sequencing and/or deletion/duplication analysis (81351, 81479) for Li-Fraumeni syndrome (LFS) is considered **investigational** for all other indications.

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MULTIPLE ENDOCRINE NEOPLASIA TYPE 1 (MEN1)

MEN1 Targeted Variant Analysis

I. *MEN1* targeted variant analysis (81479) for multiple endocrine neoplasia type 1 (MEN1) is considered **medically necessary** when:

A. The member/enrollee has a close relative with a known pathogenic or likely pathogenic variant in *MEN1*, **OR**

B. ~~An *MEN1*~~A pathogenic or likely pathogenic variant in *MEN1* was identified by tumor profiling in the member/enrollee and germline analysis has not yet been performed.

II. *MEN1* targeted variant analysis (81479) for multiple endocrine neoplasia type 1 (MEN1) is considered **investigational** for all other indications.

MEN1 Sequencing and/or Deletion/Duplication Analysis

I. *MEN1* sequencing and/or deletion/duplication analysis (81404, 81405) for multiple endocrine neoplasia type 1 (MEN1) is considered **medically necessary** when:

A. The member/enrollee has a personal history of at least two of the following:

1. Duodenal/pancreatic neuroendocrine tumor, **OR**
2. Primary hyperparathyroidism, **OR**
3. Pituitary adenoma, **OR**
4. Foregut (bronchial, thymic, or gastric) carcinoid, **OR**

B. The member/enrollee has a personal history of one of the above, **AND**

1. The member/enrollee has a close relative with at least one of the above.

II. *MEN1* sequencing and/or deletion/duplication analysis (81404, 81405) for multiple endocrine neoplasia type 1 (MEN1) is considered **investigational** for all other indications**.**

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MULTIPLE ENDOCRINE NEOPLASIA TYPE 2 (MEN2)

RET Targeted Variant Analysis

I. *RET* targeted variant analysis (81404) for multiple endocrine neoplasia type 2 (MEN2) is considered **medically necessary** when:

A. The member/~~enrolleee~~enrolleee has a close relative with a known pathogenic or likely pathogenic variant in *RET*, **OR**

B. A ~~*RET*~~ pathogenic or likely pathogenic variant in *RET* was identified by tumor profiling in the member/enrollee and germline analysis has not yet been performed.

II. *RET* targeted variant analysis (81404) for multiple endocrine neoplasia type 2 (MEN2) is considered **investigational** for all other indications.

RET Sequencing and/or Deletion/Duplication Analysis

I. *RET* sequencing and/or deletion/duplication analysis (81406, 81479, S3840) for multiple endocrine neoplasia type 2 (MEN2) is considered **medically necessary** when:

A. The member/enrollee has a diagnosis of ~~medullary thyroid cancer, **OR**~~ any of the following:

1. ~~The member/enrollee has an adrenal~~ Medullary thyroid cancer, **OR**

~~1.~~2. Adrenal pheochromocytoma, **OR**

~~2.~~3. ~~The member/enrollee has parathyroid~~ Parathyroid adenoma or hyperplasia, **OR**

B. The member/enrollee has a first-degree relative that meets at least one of the above criteria ~~and~~, **AND**

~~3.~~1. The relative has not previously undergone *RET* sequencing and/or deletion/duplication analysis.

II. *RET* sequencing and/or deletion/duplication analysis (81406, 81479, S3840) for multiple endocrine neoplasia type 2 (MEN2) is considered **investigational** for all other indications.

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NEVOID BASAL CELL CARCINOMA SYNDROME (NBCCS) (aka Gorlin syndrome)

PTCH1 or *SUFU* Targeted Variant Analysis

I. *PTCH1* or *SUFU* targeted variant analysis (81479) for nevoid basal cell carcinoma syndrome (NBCCS), also known as Gorlin syndrome, is considered **medically necessary** when:

A. The member/enrollee has a close relative with a known pathogenic or likely pathogenic variant in *PTCH1* or *SUFU*, **OR**

B. A ~~*PTCH1* or *SUFU*~~ pathogenic or likely pathogenic variant in *PTCH1* or *SUFU* was identified by tumor profiling in the member/enrollee and germline analysis has not yet been performed.

II. *PTCH1* or *SUFU* targeted variant analysis (81479) for nevoid basal cell carcinoma syndrome (NBCC), also known as Gorlin syndrome, is considered **investigational** for all other indications.

PTCH1 and *SUFU* Sequencing and/or Deletion/Duplication Analysis

I. *PTCH1* and *SUFU* sequencing and/or deletion duplication analysis (81479) for nevoid basal cell carcinoma syndrome (NBCCS), also known as Gorlin syndrome, is considered **medically necessary** when:

A. The member/enrollee has a personal history of:

1. At least two of the following:

a) Lamellar calcification of the falx, **OR**

b) Jaw keratocyst, **OR**

c) Palmar/plantar pits (2 or more), **OR**

d) Multiple basal cell carcinomas (more than 5 in lifetime) or a basal cell carcinoma diagnosed before 30 years of age, **OR**

e) A ~~first-degree relative~~first-degree relative with NBCCS, **AND**

2. At least one of the following:

a) Childhood medulloblastoma, **OR**

b) Lympho-mesenteric or pleural cysts, **OR**

c) Macrocephaly (OFC greater than 97th centile), **OR**

d) Cleft lip/palate, **OR**

e) Vertebral/rib anomalies (bifid/splayed/extra ribs; bifid vertebrae), **OR**

f) Pre- or post-axial polydactyly, **OR**

g) Ovarian fibromas, **OR**

h) Cardiac fibromas, **OR**

i) Ocular anomalies (examples: cataract, pigmentary changes of the retinal epithelium, developmental defects), **OR**

B. The member/enrollee has a personal history of:

1. At least one of the following:

a) Lamellar calcification of the falx, **OR**

b) Jaw keratocyst, **OR**

c) Palmar/plantar pits (2 or more), **OR**

d) Multiple basal cell carcinomas (more than 5 in lifetime) or a basal cell carcinoma diagnosed before 30 years of age, **OR**

e) A first-degree relative with NBCCS, **AND**

2. At least three of the following:

a) Childhood medulloblastoma, **OR**

b) Lympho-mesenteric or pleural cysts, **OR**

c) Macrocephaly (OFC greater than 97th centile), **OR**

d) Cleft lip/palate, **OR**

e) Vertebral/rib anomalies (bifid/splayed/extra ribs; bifid vertebrae), **OR**

f) Pre- or post-axial polydactyly, **OR**

g) Ovarian fibromas, **OR**

h) Cardiac fibromas, **OR**

i) Ocular anomalies (examples: cataract, pigmentary changes of the retinal epithelium, developmental defects).

II. *PTCH1* and *SUFU* sequencing and/or deletion/duplication analysis (81479) is considered **investigational** for all other indications.

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HEREDITARY PARAGANGLIOMA/PHEOCHROMOCYTOMA SYNDROME (PGL/PCC)

MAX, SDHA, SDHAF2, SDHB, SDHC, SDHD, or *TMEM127* Targeted Variant Analysis

I. *MAX*, *SDHA*, *SDHAF2*, *SDHB*, *SDHC*, *SDHD*, or *TMEM127* targeted variant analysis (81403) for hereditary paraganglioma/pheochromocytoma syndrome (PGL/PCC) is considered **medically necessary** when:

A. The member/enrollee has a close relative with a known pathogenic or likely pathogenic variant in *MAX*, *SDHA*, *SDHAF2*, *SDHB*, *SDHC*, *SDHD*, or *TMEM127*, **OR**

B. ~~A~~A pathogenic or likely pathogenic variant in *MAX*, *SDHA*, *SDHAF2*, *SDHB*, *SDHC*, *SDHD*, or *TMEM127* ~~pathogenic or likely pathogenic variant~~ was identified by tumor profiling in the member/enrollee and germline analysis has not yet been performed.

II. *MAX*, *SDHA*, *SDHAF2*, *SDHB*, *SDHC*, *SDHD*, or *TMEM127* targeted variant analysis (81403) for hereditary paraganglioma/pheochromocytoma syndrome (PGL/PCC) is considered **investigational** for all other indications.

MAX, SDHA, SDHAF2, SDHB, SDHC, SDHD, and *TMEM127* Sequencing and/or Deletion/Duplication Analysis

I. *MAX*, *SDHA*, *SDHAF2*, *SDHB*, *SDHC*, *SDHD*, and *TMEM127* sequencing and/or deletion/duplication analysis (81404, 81405, 81406, 81479) for hereditary paraganglioma/pheochromocytoma syndrome (PGL/PCC) is considered **medically necessary** when:

A. The member/enrollee has a diagnosis of one or more of the following:

1. Pheochromocytoma, **OR**
2. Paraganglioma, **OR**
3. Clear cell renal cell cancer, **OR**
4. Gastrointestinal stromal tumor (GIST), **OR**

~~1. Pulmonary chondromas, **OR**~~

B. The member/enrollee has a close relative with paraganglioma or pheochromocytoma.

II. *MAX*, *SDHA*, *SDHAF2*, *SDHB*, *SDHC*, *SDHD*, and *TMEM127* sequencing and/or deletion/duplication (81404, 81405, 81406, 81479) for hereditary paraganglioma/pheochromocytoma syndrome (PGL/PCC) is considered **investigational** for all other indications.

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PEUTZ-JEGHERS SYNDROME (PJS)

STK11 Targeted Variant Analysis

I. *STK11* targeted variant analysis (81479) for Peutz-Jeghers syndrome is considered **medically necessary** when:

A. The member/enrollee has a blood relative with a known pathogenic or likely pathogenic variant in *STK11,* **OR**

B. ~~An *STK11*~~A pathogenic or likely pathogenic variant in *STK11* was identified by tumor profiling in the member/enrollee and germline analysis has not yet been performed.

II. *STK11* targeted variant analysis (81479) for Peutz-Jeghers syndrome is considered **investigational** for all other indications.

STK11 Sequencing and/or Deletion/Duplication Analysis

I. *STK11* sequencing and/or deletion/duplication analysis (81404, 81405) for Peutz-Jeghers syndrome (PJS) is considered **medically necessary** when:

~~A.~~ The member/enrollee has ~~a clinical diagnosis of Peutz-Jeghers syndrome based on the presence of any two of the following:~~

A. ~~A~~at least two histologically confirmed Peutz-Jeghers-type hamartomatous polyps of the GI tract, **OR**

B. ~~Mucocutaneous~~The member/enrollee has mucocutaneous pigmentation of the mouth, lips, nose, eyes, genitalia, or fingers, **OR**

~~1. A close relative with PJS.~~

C. The member/enrollee has a family history of PJS.

II. *STK11* sequencing and/or deletion/duplication analysis (81404, 81405) for Peutz-Jeghers syndrome is considered **investigational** for all other indications.

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RETINOBLASTOMA

RB1 Targeted Variant Analysis

I. *RB1* targeted variant analysis (81403) for retinoblastoma is considered **medically necessary** when:

A. The member/enrollee has a close relative with a known pathogenic or likely pathogenic variant in *RB1*, **OR**

B. ~~An *RB1*~~A pathogenic or likely pathogenic variant in *RB1* was identified by tumor profiling in the member/enrollee and germline analysis has not yet been performed.

II. *RB1* targeted variant analysis (81403) for retinoblastoma is considered **investigational** for all other indications.

RB1 Sequencing and/or Deletion/Duplication Analysis

I. *RB1* sequencing and/or deletion/duplication analysis (81479, S3841) for retinoblastoma is considered **medically necessary** when:

A. The member/enrollee has a diagnosis of retinoblastoma in one or both eyes, **OR**

B. The member/enrollee has a close relative with retinoblastoma in one or both eyes.

II. *RB1* sequencing and/or deletion/duplication analysis (81479, S3841) for retinoblastoma is considered **investigational** for all other indications.

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VON HIPPEL-LINDAU SYNDROME (VHL)

VHL Targeted Variant Analysis

I. *VHL* targeted variant analysis (81403) for Von Hippel-Lindau syndrome is considered **medically necessary** when:

A. The member/enrollee has a first- or second-degree relative with a known pathogenic or likely pathogenic variant in *VHL*, **OR**

B. A ~~*VHL*~~ pathogenic or likely pathogenic variant in *VHL* was identified by tumor profiling in the member/enrollee and germline analysis has not yet been performed.

II. *VHL* targeted variant analysis (81403) for Von Hippel-Lindau syndrome is considered **investigational** for all other indications.

VHL Sequencing and/or Deletion/Duplication Analysis

I. *VHL* sequencing and/or deletion/duplication analysis (81403, 81404, S3842) for Von Hippel-Lindau syndrome is considered **medically necessary** when:

A. The member/enrollee has a diagnosis of one or more of the following:

1. Hemangioblastoma of the retina, spine, or brain, **OR**
2. ~~Clear cell renal~~Renal cell carcinoma diagnosed before age 40 years, **OR**
3. Multiple and/or bilateral ~~clear cell~~ renal cell carcinoma diagnosed at any age, **OR**
4. Pheochromocytoma or paraganglioma (in abdomen, thorax, or neck), **OR**
5. Retinal angiomas, **OR**
6. Endolymphatic sac tumor, **OR**
7. Epididymal or adnexal papillary cystadenoma, **OR**
8. Pancreatic serous cystadenoma, **OR**
9. Pancreatic neuroendocrine tumors, **OR**
10. Multiple renal, pancreatic or hepatic cysts.

II. *VHL* sequencing and/or deletion/duplication analysis (81403, 81404, S3842) for Von Hippel-Lindau syndrome is considered **investigational** for all other indications**.**

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DEFINITIONS

1. **Close relatives** include first, second, and third degree blood relatives on the same side of the family:

a. **First-degree relatives** are parents, siblings, and children

b. **Second-degree relatives** are grandparents, aunts, uncles, nieces, nephews, grandchildren, and half siblings

c. **Third-degree relatives** are great grandparents, great aunts, great uncles, great grandchildren, and first cousins

2. **Breast cancer**: Term that applies to patients with invasive cancer or ductal carcinoma in situ (DCIS).

3. **High-risk breast cancer** ~~**for olaparib therapy:** Defined~~is defined by NCCN as "those with ≥4

~~a. Triple negative breast cancer treated with either:~~

~~i. Adjuvant chemotherapy with axillary node~~ positive ~~disease or an invasive primary tumor greater than or equal to 2 cm on pathology analysis, **OR**~~

~~ii. Neoadjuvant chemotherapy with residual invasive breast cancer in the breast or resected~~ lymph nodes~~, **OR**~~

~~b. Hormone receptor positive disease treated with either:~~

~~i. Adjuvant chemotherapy with four or more positive pathologically~~ (confirmed preoperatively and/or at surgery), or 1–3 positive lymph nodes~~, OR~~

~~Neoadjuvant chemotherapy which did not have a complete pathologic response, with a CPS+CG score [pre-treatment clinical (CS) and post-treatment pathological stage (PS), estrogen-receptor status (E) and~~ with either grade 3 disease or tumor size ≥5 cm (on pre-operative imaging and/ or at surgery)". (p. ~~(G)] of 3 or higher~~BINV-K)

4. **Juvenile polyps:** Polyps associated with Juvenile Polyposis Syndrome. These polyps are exophytic and eroded. They typically contain the following: marked edema and inflammation within the lamina propria, cystic glands filled with thick mucin, and some degree of smooth muscle proliferation.

~~2. **ClinGen**: National Institutes of Health (NIH)-funded resource dedicated to building a central resource that defines the clinical relevance of genes and variants for use in precision medicine and research.~~

5. **Maori ancestry:** Describes individuals who are of indigenous New Zealand ethnic background

6. **High-risk prostate cancer:** Defined by NCCN as an individual who has no very-high-risk features but has exactly one of the following high-risk features:
   a. cT3a, OR
   b. Grade Group 4 or Grade Group 5, **OR**
   c. PSA > 20ng/ml

7. **Very-high-risk prostate cancer:** Defined by NCCN as an individual who has at least one of the following:
    a. CT3b-cT4
    b. Primary Gleason pattern 5
    c. 2 or 3 high-risk features
    d. >4 cores with Grade Group 4 or 5

8. **Adenomatous polyposis:** Conditions that cause multiple adenomas (i.e., benign polyps) in the gastrointestinal tract.

9. **Lynch syndrome-related cancer**: Defined as any of the following cancer types: colorectal, endometrial, gastric, ovarian, pancreatic, ureter and renal pelvic, brain (usually glioblastoma), biliary tract, small intestinal, sebaceous adenoma, sebaceous carcinoma, or keratoacanthoma.

BACKGROUND AND RATIONALE

Pan-Cancer Hereditary Susceptibility Panels

National Comprehensive Cancer Network (NCCN)

NCCN Breast, Ovarian, and/or Pancreatic Cancer Genetic Assessment guidelines (2.3.2024) recognizedefine multi-gene testing as analysis of a set of genes that next-generation sequencing technology has rapidly altered the clinical approach to testing at-risk patients and their families for hereditary forms of are associated with one or more cancer and that whenphenotypes in a family. It is possible for a personal or family history of cancer to be due to more than one gene hereditary cancer syndrome. This testing approach can explain an inherited cancer syndrome, tailored multi-gene testing is often be more efficient and/or cost effective than single-gene testing and is also available for individuals who have previously tested negative for a single syndrome but have a history concerning for a hereditary predisposition or for individuals who are positive for a cancer predisposition gene but may carry a second variant. However, there is the chance of finding a variant of uncertain significance in a well established gene, or finding a pathogenic variant in a gene with uncertain clinical management. These types of findings increase as additional genes are included in the multi-gene panel. It is recommended that multi-gene panel testing be offered by a professional genetic expert that provides detailed pre- and post-test counseling. (p. EVAL-A 1-3 of 10).)

These guidelines also state that RNA studies (when appropriate) may be arecommend consideration of RNA studies, to further define functional impactthe meaning of variants, and a referral to research of unknown significance. Research studies that aimdesigned to defineexplore the functional impact of variants, such as variant reclassification programs through clinical labs or registries should be considered. (p. EVAL-A, 9 of 10).)

NCCN Guidelines for Genetic/Familial High-Risk Assessment Colorectal (2.2023) state that

~~when more than one gene can explain an inherited cancer syndrome,~~recommend germline multigene ~~testing is more efficient than single-gene testing, or sequential single syndrome testing. There is also a role for multigene~~panel testing in individuals with a personal history of colorectal cancer who ~~have tested negative (indeterminate) for~~are under age 50 at diagnosis and in some other clinical scenarios (p. HRS-3). Test selection should include at a ~~single syndrome,~~minimum selected genes associated with colorectal cancer risk but ~~whose~~additional genes can be included based on a patient's personal ~~or~~and family history of cancer. (p. ~~remains strongly suggestive of an inherited susceptibility.~~HRS-A, 2 of 2) ~~(p. GENE-1)~~

National Society of Genetic Counselors (NSGC)

The National Society of Genetic Counselors released a position statement (2017) endorsing the use of multi-gene panels when clinically warranted and appropriately applied, stating the following:

> "These tests can provide a comprehensive and efficient route to identifying the genetic causes of disease. Before ordering a multi-gene panel test, providers should thoroughly evaluate the analytic and clinical validity of the test, as well as its clinical utility. Additional factors to consider include, but are not limited to: clinical and family history information, gene content of the panel, limitations of the sequencing and informatics technologies, and variant interpretation and reporting practices.
>
> Panels magnify the complexities of genetic testing and underscore the value of experts, such as genetic counselors, who can educate stakeholders about appropriate utilization of the technology to mitigate risks of patient harm and unnecessary costs to the healthcare system. NSGC supports straightforward and transparent pricing so that patients, providers, laboratories, and health plans can easily weigh the value of genetic testing in light of its cost."

American College of Obstetricians and Gynecologists

ACOG published Committee Opinion Number 793 (2019) regarding hereditary cancer syndromes and risk assessment that included the following recommendations:

- A hereditary cancer risk assessment is the key to identifying patients and families who may be at increased risk of developing certain types of cancer. Assessments should be performed by obstetrician–gynecologists or other obstetric–gynecologic care providers and should be updated regularly.
- If a hereditary cancer risk assessment suggests an increased risk of a hereditary cancer syndrome, referral to a specialist in cancer genetics or a health care provider with expertise in genetics is recommended for expanded gathering of family history information, risk assessment, education, and counseling, which may lead to genetic testing and tailored cancer screening or risk reduction measures, or both.
- Genetic testing may be performed using a panel of multiple genes through next-generation sequencing technology. This multigene testing process increases the likelihood of finding variants of unknown significance, and it also allows for testing for

pathogenic and likely pathogenic variants in multiple genes that may be associated with a specific cancer syndrome or family cancer phenotype (or multiple phenotypes). (p. e143)

Hereditary Breast Cancer Susceptibility Panels

National Comprehensive Cancer Network (NCCN)

The NCCN guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic Cancers (~~2~~3.2024) outline clinical criteria for germline genetic testing of high-penetrance breast cancer genes. These guidelines include:

1.) Personal history of breast cancer at 50 years of age or younger.

2.) Personal history of breast cancer at any age with specific features:

- Treatment indications
  - To aid in systemic treatment decisions using PARP inhibitors for metastatic breast cancer ~~in the metastatic setting~~
  - To aid in adjuvant treatment decisions with olaparib for high-risk, HER2-negative breast cancer, including triple-negative breast cancer
- Pathology/histology
  - Triple-negative breast cancer
  - Multiple primary breast cancers (synchronous or metachronous)
  - ~~Breast cancer in those with a male reproductive system~~
  - Male breast cancer
- Ashkenazi Jewish ancestry
- Family history of at least 1 close blood relative with:
  - Breast cancer at age 50 years or younger
  - ~~Breast cancer in those with a male reproductive system~~
  - Male breast cancer
  - Ovarian cancer
  - Pancreatic cancer
  - Prostate cancer with metastatic, or high- or very-high-risk group
  - 3 or more total diagnoses of breast cancer and/or prostate cancer in patient and/or close blood relatives on the same side of the family

3.) Family history-based criteria: ~~An affected individual (~~A person with breast cancer who does not ~~meeting~~meet the testing criteria listed above~~),~~ or unaffected individual ~~with~~who has a first- or second-degree blood relative meeting any of the criteria listed above (except unaffected individuals whose relatives meet criteria only for systemic therapy decision-making). If the affected relative has pancreatic cancer or prostate cancer, then only first-degree relatives should be offered testing unless indicated based on additional family history.

4.) An affected or unaffected individual who otherwise does not meet the criteria above but has a

probability of greater than 5% of a *BRCA1/2* pathogenic variant based on prior probability models (eg, Tyrer-Cuzick, BRCAPro, CanRisk). (p. CRIT-2)

These guidelines also recommend consideration of testing for patients with a personal history of breast cancer diagnosed at any age with ≥1 close blood relative with intermediate-risk prostate cancer with intraductal/cribriform histology, and for patients affected or unaffected with breast cancer who otherwise do not meet any of the above criteria but with a 2.5%–5% probability of BRCA1/2 P/LP variant based on prior probability models (eg, Tyrer-Cuzick, BRCAPro, CanRisk). (p, CRIT-3).

American Society of Clinical Oncology/Society of Surgical Oncology

New guidelines published by ASCO/SSO (2024) recommend BRCA1/2 testing to all newly diagnosed patients who are 65 years of age or younger at diagnosis (Type: Formal Consensus; Agreement 87.50%). (p. 590)

Hereditary GI/Colon Cancer Susceptibility Panel Tests

National Comprehensive Cancer Network (NCCN)

NCCN guidelines for Genetic/Familial High-Risk Assessment: Colorectal (2.2023) outline criteria for assessment for hereditary colorectal syndromes as follows:

- Polyposis: Patient with a personal history of, or a single family member with, at least 10 adenomatous polyps, at least 2 hamartomatous polyps, or at least 5 serrated polyps/lesions proximal to the rectum (p. HRS-1)
- Personal history of colorectal cancer: Patient ~~is under 50 years at age of diagnosis, or~~ meets Lynch syndrome criteria (p. HRS-1, HRS-3, LS-1) (see *MLH1, MSH2, MSH6, PMS2, EPCAM* Sequencing and/or Deletion/Duplication Analysis)
- Personal ~~of~~or family history of Lynch syndrome-related cancer that meets Lynch syndrome criteria (p. HRS-3, LS-1) (see *MLH1, MSH2, MSH6, PMS2, EPCAM* Sequencing and/or Deletion/Duplication Analysis).

NCCN also states that the ~~minimum number of~~ CRC-risk associated genes to include in germline multi-gene panel testing are as follows: *APC, MUTYH, MLH1, MSH2, MSH6, PMS2, EPCAM, BMPR1A, SMAD4, PTEN, STK11,* and *TP53.* (p. HRS-A 2 of 2). ~~Many~~

Some individuals will have variants of uncertain significance (VUS); post test counseling should include considering referral to research studies ~~that aim to define~~for the purpose of learning the functional impact of VUSs such as variant reclassification programs through clinical labs or registries. (p. HRS-A, 1 of 2 and HRS-B, 1 of 9)

Hereditary Gastric Cancer Susceptibility Panels

National Comprehensive Cancer Network (NCCN)

NCCN Gastric Cancer guidelines (~~3.2023~~2.2024) outline criteria for further genetic risk assessment for high-risk syndromes associated with gastric cancer, including: hereditary diffuse gastric cancer, Lynch syndrome, Juvenile Polyposis Syndrome, Peutz-Jeghers syndrome, and Familial Adenomatous Polyposis. (p. GAST-D 3 of 8 and p. GAST-D 4 of 8)

Hereditary Pancreatic Cancer Susceptibility Panels

National Comprehensive Cancer Network (NCCN)

NCCN Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic guidelines (~~2~~3.2024) recommend genetic counseling and germline testing for all individuals diagnosed with exocrine pancreatic cancer, as well as individuals with a first-degree relative diagnosed with exocrine pancreatic cancer. These guidelines list the following genes as those that are typically tested for pancreatic cancer risks: *ATM, BRCA1, BRCA2, CDKN2A, MLH1, MSH2, MSH6, EPCAM, PALB2, STK11, TP53*. (p. CRIT-5)

Hereditary Polyposis Susceptibility Panels

National Comprehensive Cancer Network (NCCN)

The NCCN Genetic/Familial High-Risk Assessment: Colorectal guidelines (2.2023) outline recommendations for evaluating individuals with adenomatous polyposis (defined as 10 or more adenomas) (p. HRS-2). Germline multigene testing for all polyposis and colorectal cancer genes is recommended. (p. POLYP-1)~~for germline mutations in *APC* and *MUTYH*. (p. HRS-2)~~

Hereditary Prostate Cancer Susceptibility Panels

National Comprehensive Cancer Network (NCCN)

~~NCCN Prostate Cancer guidelines (4.2023) state that germline testing is recommended in patients with a personal history of prostate cancer in the following scenarios:~~

- ~~By prostate cancer stage or risk group (diagnosed at any age)~~
  - ~~Metastatic, regional (node positive), very high-risk localized, or high-risk localized prostate cancer~~
- ~~By family history and/or ancestry:~~
  - ~~1 or more first-, second-, or third-degree relative with:~~
    - ~~breast cancer at age <50 y~~
    - ~~colorectal or endometrial cancer at age <50 y~~
    - ~~male reproductive system (sex assigned at birth) breast cancer at any age~~

- ovarian cancer at any age
- exocrine pancreatic cancer at any age
- metastatic, regional, very-high-risk, or high-risk prostate cancer at any age
- 1 or more first-degree relative (parent or sibling) with:
  - prostate cancer at age <60 y
- 2 or more first-, second-, or third-degree relatives with:
  - breast cancer at any age
  - prostate cancer at any age
- 3 or more first- or second-degree relatives with:
  - Lynch syndrome-related cancers, especially if diagnosed <50 y: colorectal, endometrial, gastric, ovarian, exocrine pancreas, upper tract urothelial, glioblastoma, biliary tract, and small intestinal cancer

- A known family history of familial cancer risk mutation (pathogenic/likely pathogenic variants), especially in: *BRCA1*, *BRCA2*, *ATM*, *PALB2*, *CHEK2*, *MLH1*, *MSH2*, *MSH6*, *PMS2*, and *EPCAM*
- Ashkenazi Jewish ancestry
- Personal history of breast cancer

These guidelines also state that post-test genetic counseling is recommended if only germline variants of unknown significance (VUS) are identified. This is to ensure accurate understanding of family implications and review indications for additional testing and/or follow-up (including clinical trials of reclassification). (p. PROS-C 1 of 3 and PROS-C 2 of 3)

NCCN Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic guidelines (23.2024) recommend the following testing criteria for prostate cancer susceptibility genes:

Personal history of prostate cancer with specific clinical features: metastatic disease, specific histology (intraductal/ cribriform, high- or very-high risk group), or with 1 or more close relatives with:

- Breast cancer at age 50 years or younger
- Triple-negative breast cancer at any age
- BreastMale breast cancer in those with a male reproductive system at any age
- Ovarian cancer any age
- Pancreatic cancer any age
- Metastatic, intraductal/ cribriform histology, or high- or very-high risk group at any age
- 3 or more close blood relatives with either breast or prostate cancer (any grade) on the same side of the family including the patient with prostate cancer;
- Ashkenazi Jewish ancestry
- Another fulfilling criterion is an individual with or without prostate cancer affected (not meeting testing criteria listed above) with a first-degree blood relative meeting any of the criteria listed above (except unaffected individuals whose relatives meet criteria only for systemic therapy decision-making). (p. CRIT-6)

These guidelines also recommend consideration of testing for:

- An individual with a 2.5%–5% probability of BRCA1/2 P/LP variant based on prior probability models (eg, Tyrer-Cuzick, BRCAPro, CanRisk) (p. CRIT-3)
- Patients with intermediate risk prostate cancer with intraductal/cribriform histology. (p. CRIT-6)

These guidelines also recommend consideration of RNA studies to further define the meaning of variants of unknown significance. Research studies designed to explore the functional impact of variants, such as variant reclassification programs through clinical labs or registries should be considered. (p. EVAL-A, 9 of 10).

Hereditary Neuroendocrine Cancer Susceptibility Panels

National Comprehensive Cancer Network (NCCN)

~~**Hereditary Neuroendocrine Cancer Susceptibility Panels**~~

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

The NCCN Neuroendocrine and Adrenal Tumors Guideline (~~1.2023~~2.2024) states that multigene panel testing may be a more efficient and cost-effective solution for evaluating a patient for a hereditary endocrine cancer syndrome, as there is clinical overlap between several genetic conditions that predispose to endocrine neoplasms. (p. NE-E 2 of 8)

The guidelines state that genetic testing for hereditary endocrine neoplasia syndromes is recommended for patients with:

- Adrenocortical carcinoma
- Paraganglioma/pheochromocytoma
- Parathyroid adenoma or primary hyperparathyroidism before age 30
- Multiple parathyroid adenomas
- Multigland hyperplasia without obvious secondary cause
- Recurrent primary hyperparathyroidism
- Clinical suspicion for MEN2
- Clinical suspicion for MEN1 ~~(p.~~

NCCN also recommends consideration of testing for patients with:

- Gastrinoma
- Duodenal/pancreatic neuroendocrine tumor. (p. NE-E, 3 of 8)

***BRCA1* AND *BRCA2* GENE TESTING**

BRCA1/BRCA2 Targeted Variant or Known Familial Variant Analysis

National Comprehensive Cancer Network (NCCN)

The NCCN Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic guidelines (~~2~~3.2024) states that testing for hereditary cancer susceptibility should be performed in the following situations:

1) Individuals with any blood relative with a known pathogenic/likely pathogenic variant in a cancer susceptibility gene

2) Individuals with a pathogenic/likely pathogenic (P/LP) variant identified on tumor genomic testing that ~~has clinical implications~~would impact cancer risk if ~~also identified in the~~confirmed to be a germline variant. (p.CRIT-1)

BRCA1/BRCA2 Targeted Variant Analysis - Ashkenazi Jewish Founder Variants

National Comprehensive Cancer Network (NCCN)

The NCCN Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic guidelines (~~2~~3.2024) ~~states that~~recommends consideration of testing for the three known Ashkenazi Jewish founder *BRCA1/2* mutations ~~is appropriate~~ for individuals who are age 18 years or older and have at least one grandparent who is of Ashkenazi Jewish ancestry. (p. CRIT-1 and p. CRIT-1A)

BRCA1 and *BRCA2* Sequencing and/or Deletion/Duplication Analysis

National Comprehensive Cancer Network (NCCN)

The NCCN guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic ~~guidelines (2~~(3.2024) outline clinical criteria for germline genetic testing of high-penetrance breast cancer genes, including *BRCA1* and *BRCA2*. These guidelines include:

Personal history of breast cancer with specific features:

- Diagnosed 50 years of age or younger
- Diagnosed at any age: To aid in systemic treatment decisions using PARP inhibitors for breast cancer in the metastatic setting; to aid in adjuvant treatment decisions with olaparib for high-risk, HER2-negative breast cancer; triple-negative breast cancer; multiple primary breast cancers (synchronous or metachronous); ~~Breast cancer in those with a male reproductive system~~Male breast cancer; Ashkenazi Jewish ancestry; at least 1 close blood relative with: breast cancer at age 50 years or younger, ~~Breast cancer in those with a male reproductive system~~male breast cancer, ovarian cancer, pancreatic cancer, prostate cancer with metastatic, or high- or very-high-risk group, 3 or more total diagnoses of breast or prostate cancer in patient and/or close blood relatives~~.~~ on the same

side of the family~~Family history-based criteria: An affected individual (not meeting testing criteria listed above) or unaffected individual with a first- or second degree blood relative meeting any of the criteria listed above (except unaffected individuals whose relatives meet criteria only for systemic therapy decision-making). If the affected relative has pancreatic cancer or prostate cancer only first-degree relatives should be offered testing unless indicated based on additional family history~~.

Family history-based criteria:

- An individual with breast cancer who does not meet testing criteria listed above, or an unaffected individual with a first- or second degree blood relative meeting any of the criteria listed above (except unaffected individuals whose relatives meet criteria only for systemic therapy decision-making). If the affected relative has pancreatic cancer or prostate cancer only first-degree relatives should be offered testing unless indicated based on additional family history.
- An affected or unaffected individual who otherwise does not meet the criteria above but has a probability of greater than 5% of a *BRCA1/2* pathogenic variant based on prior probability models (eg, Tyrer-Cuzick, BRCAPro, CanRisk) (p. CRIT-2)

NCCN recommends consideration of testing for the following clinical scenarios:

- An individual with breast cancer who was diagnosed at any age with at least one close blood relative with intermediate-risk prostate cancer with intraductal/ cribriform histology
- An individual with a 2.5%–5% probability of BRCA1/2 P/LP variant based on prior probability models (eg, Tyrer-Cuzick, BRCAPro, CanRisk) (p. CRIT-3)

These guidelines also ~~state that~~ recommend consideration of RNA studies ~~(when appropriate) may be a consideration~~ to further define ~~functional impact~~the meaning of variants~~, and a referral to research~~ of unknown significance. Research studies ~~that aim~~designed to ~~define~~explore the functional impact of variants, such as variant reclassification programs through clinical labs or registries should be considered. ~~(p. EVAL-A, 9 of 10).~~

(p. EVAL-A, 9 of 10)

The NCCN guidelines for Ampullary Adenocarcinoma (~~1~~2.2024) recommend consideration of genetic testing for inherited mutations for any patient with confirmed ampullary cancer. A comprehensive gene panel should be utilized. Genetic counseling is recommended for patients who test positive for a pathogenic mutation (*ATM*, *BRCA1*, *BRCA2*, *CDKN2A*, *MLH1*, *MSH2*, *MSH6*, *PALB2*, *PMS2*, *STK11*, and *TP53*~~) or for patients with a positive family history of cancer, especially pancreatic/ampullary cancer, regardless of mutation status.~~). (p. AMP-3)

US Preventive Services Task Force (USPSTF)

The USPSTF published a recommendation statement (2019) on risk assessment, genetic counseling, and genetic testing for *BRCA*-related cancer that included the following conclusion and recommendation:

"The USPSTF recommends that primary care clinicians assess women with a personal or family history of breast, ovarian, tubal, or peritoneal cancer or who have an ancestry associated with *BRCA1/2* gene mutations with an appropriate brief familial risk assessment tool. Women with a positive result on the risk assessment tool should receive genetic counseling and, if indicated after counseling, genetic testing. (B recommendation) The USPSTF recommends against routine risk assessment, genetic counseling, or genetic testing for women whose personal or family history or ancestry is not associated with potentially harmful *BRCA1/2* gene mutations. (D recommendation)". (p. 652)

American Society of Clinical Oncology/Society of Surgical Oncology

New guidelines published by ASCO/SSO (2024) recommend BRCA1/2 testing to all newly diagnosed patients who are 65 years of age or younger at diagnosis (Type: Formal Consensus; Agreement 87.50%). (p. 590)

PALB2 GENE TESTING

PALB2 Targeted Variant Analysis

National Comprehensive Cancer Network (NCCN)

The NCCN Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic guidelines (~~2~~3.2024) states that testing for hereditary cancer susceptibility should be performed in the following situations:

1) Individuals with any blood relative with a known pathogenic/likely pathogenic variant in a cancer susceptibility gene
2) Individuals with a pathogenic/likely pathogenic (P/LP) variant identified on tumor genomic testing that ~~has clinical implications~~would impact cancer risk if ~~also identified in the~~confirmed to be a germline variant. (p. CRIT-1)

PALB2 Sequencing and/or Deletion/Duplication Analysis

National Comprehensive Cancer Network (NCCN)

The NCCN guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic guidelines (~~2~~3.2024) outline clinical criteria for germline genetic testing of high-penetrance breast cancer genes, including *PALB2*. These guidelines include:

Personal history of breast cancer with specific features:

- Diagnosed 50 years of age or younger
- Diagnosed at any age: To aid in systemic treatment decisions using PARP inhibitors for breast cancer in the metastatic setting; to aid in adjuvant treatment decisions with

olaparib for high-risk, HER2-negative breast cancer, triple-negative breast cancer; multiple primary breast cancers (synchronous or metachronous); ~~Breast cancer in those with a male reproductive system~~Male breast cancer; Ashkenazi Jewish ancestry; at least 1 close blood relative with: breast cancer at age 50 years or younger, male breast cancer~~ in those with a male reproductive system~~, ovarian cancer, pancreatic cancer, prostate cancer with metastatic, or high- or very-high-risk group, 3 or more total diagnoses of breast cancer in patient and/or close blood relatives, 2 or more close blood relatives with either breast or prostate cancer (any grade),

Family history-based criteria:

- An affected individual (not meeting testing criteria listed above) or unaffected individual with a first- or second degree blood relative meeting any of the criteria listed above (except unaffected individuals whose relatives meet criteria only for systemic therapy decision-making). If the affected relative has pancreatic cancer or prostate cancer only first-degree relatives should be offered testing unless indicated based on additional family history.

An affected or unaffected individual who otherwise does not meet the criteria above but has a probability of greater than 5% of a *BRCA1/2* pathogenic variant based on prior probability models (eg, Tyrer-Cuzick, BRCAPro, CanRisk) (p. CRIT-2)

NCCN recommends consideration of testing for the following clinical scenarios:

- An individual with breast cancer who was diagnosed at any age with at least one close blood relative with intermediate-risk prostate cancer with intraductal/ cribriform histology
- An individual with a 2.5%–5% probability of BRCA1/2 P/LP variant based on prior probability models (eg, Tyrer-Cuzick, BRCAPro, CanRisk) (p. CRIT-3)

These guidelines also ~~state that~~recommend consideration of RNA studies ~~(when appropriate) may be a consideration to~~ further define ~~functional impact~~the meaning of variants~~, and a referral to research~~ of unknown significance. Research studies ~~that aim~~designed to ~~define~~explore the functional impact of variants such as variant reclassification programs through clinical labs or registries should be considered. (p. EVAL-A, 9 of 10).

The NCCN guidelines for Ampullary Adenocarcinoma (~~1~~2.2024) recommend genetic testing for inherited mutations for any patient with confirmed ampullary cancer. A comprehensive gene panel should be utilized. Genetic counseling is recommended for patients who test positive for a pathogenic mutation (*ATM, BRCA1, BRCA2, CDKN2A, MLH1, MSH2, MSH6, PALB2, PMS2, STK11,* and *TP53*~~) or for patients with a positive family history of cancer, especially pancreatic/ampullary cancer, regardless of mutation status.~~). (p. AMP-3)

ATM AND *CHEK2* GENE TESTING

ATM or *CHEK2* Targeted Variant Analysis

National Comprehensive Cancer Network (NCCN)

The NCCN Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic guidelines (~~2~~3.2024) state that testing for hereditary cancer susceptibility should be performed in the following situations:

- Individuals with any blood relative with a known pathogenic/likely pathogenic variant in a cancer susceptibility gene
- Individuals with a pathogenic/likely pathogenic (P/LP) variant identified on tumor genomic testing that ~~has clinical implications~~would impact cancer risk if ~~also identified in the~~confirmed to be a germline variant. (p. CRIT-1)

ATM or *CHEK2* Sequencing and/or Deletion/Duplication Analysis

National Comprehensive Cancer Network (NCCN)

While the NCCN Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic guidelines (~~2~~3.2024) do provide surveillance recommendations for individuals with germline *ATM* and *CHEK2* mutations (p. GENE-A 1 of 10 and p. GENE-A 4 of 10), these genes are not considered high-penetrance breast cancer susceptibility genes, and the guidelines do not include gene-specific clinical criteria for *ATM* and *CHEK2* as they do for the high-penetrance breast cancer susceptibility genes.

~~These guidelines also state that~~ In order to help further clarify variants of unknown significance, NCCN recommends consideration of RNA studies ~~(when appropriate) may be~~as well as a ~~consideration to further define functional impact of variants, and a~~clinical trials referral to ~~research studies that aim to~~help define the functional impact of variants ~~such as variant reclassification programs through clinical labs or registries should be considered.~~ (p. EVAL-A, 9 of 10~~).~~)

LYNCH SYNDROME/HEREDITARY NONPOLYPOSIS COLORECTAL CANCER (HNPCC) TESTING

MLH1, MSH2, MSH6, PMS2, or *EPCAM* Targeted Variant Analysis

National Comprehensive Cancer Network (NCCN)

NCCN Genetic/Familial High-Risk Assessment: Colorectal guidelines (2.2023) outline testing criteria for the evaluation of Lynch syndrome. ~~NCCN recommends analysis of *MLH1, MSH2, MSH6, PMS2* and/or *EPCAM* in individuals with a known pathogenic variant in the family.~~ If there is a known pathogenic variant in a Lynch syndrome gene (*MLH1, MSH2, MSH6, PMS2,* or *EPCAM*), genetic testing for the known variant is recommended. (p. LS-2) Additionally, it is

possible that pathogenic or likely pathogenic variants identified through tumor profiling could be of germline origin. Confirmatory germline testing is indicated for pathogenic/likely pathogenic variants identified via tumor profiling when there is a reasonable clinical suspicion of being of germline origin. (p. HRS-B 5 of 9~~(p. HRS-5)~~

~~Additionally, NCCN states that tumor testing can be complementary to germline testing and can assist in interpretation of results. Although germline origin can sometimes be inferred with a high degree of confidence, confirmatory germline testing is indicated for pathogenic/likely pathogenic variants with a reasonable clinical suspicion of being a germline origin (based on patient/family history or clinical characteristics, presence of founder mutation, and in some cases variant allele frequency). (p. HRS-A 4 of 7)~~

MLH1, MSH2, MSH6, PMS2, or EPCAM Sequencing and/or Deletion/Duplication Analysis

National Comprehensive Cancer Network (NCCN)

NCCN Genetic/Familial High-Risk Assessment: Colorectal guidelines (2.2023) outline testing criteria for the evaluation of Lynch syndrome. ~~NCCN recommends analysis of *MLH1*, *MSH2*, *MSH6*, *PMS2* and/or *EPCAM* in individuals with a personal and/or family history of Lynch syndrome-related cancers, such as colorectal, endometrial, gastric, ovarian, pancreatic, ureter and renal pelvic, brain (usually glioblastoma), biliary tract, small intestinal, sebaceous adenoma, sebaceous carcinoma, or keratoacanthoma. These criteria include:~~ These criteria include:

- An individual with a Lynch-syndrome (LS)-related cancer (colorectal, endometrial, gastric, ovarian, pancreatic, urothelial, brain (usually glioblastoma), biliary tract, and small intestine, as well as sebaceous adenomas, sebaceous carcinomas, and keratoacanthomas) and any of the following: Diagnosed younger than 50 years; a synchronous or metachronous LS -related cancer regardless of age; 1 first-degree or second-degree relative with an LS-related cancer diagnosed younger than 50 years; or 2 or more first-degree or second-degree relatives with an LS-related cancer regardless of age
- Family history of any of the following: at least 1 first-degree relative with a colorectal or endometrial cancer diagnosed younger than 50 years; at least 1 first-degree relative with a colorectal or endometrial cancer and a synchronous or metachronous LS-related cancer regardless of age; 2 or more first-degree or second-degree relatives with LS-related cancers, one of whom was diagnosed before age 50; 3 or more first-degree or second-degree relatives with LS-related cancers regardless of age
- An individual with a 5% risk or greater of having an MMR gene pathogenic variant based on predictive models (i.e., PREMM5, MMRpro, MMRpredict)
- An individual with a personal history of CRC and/or endometrial cancer with a PREMM5 score of 2.5% or greater ~~should be considered for multi-gene panel testing~~.

~~For~~Some individuals ~~without a personal history of CRC and/or endometrial cancer, some data~~will have ~~suggested using a PREMM5 score threshold of 2.5% or greater rather than 5% or~~

~~greater to select individuals for MMR genetic testing.~~ variants of uncertain significance (VUS); post test~~Based on these data, it is reasonable for testing to be done based on the 2.5% or greater score result and clinical judgment. (p. HRS-5)~~

~~Guidelines also state that genetic~~ counseling should include considering referral to research studies ~~that aim to define~~for the purpose of learning the functional impact of ~~variants of uncertain significance (VUS)~~VUSs such as variant reclassification programs through clinical labs or registries. (p. HRS-A, 1 of 2 and HRS-B, 1 of 9)

BAP1 TUMOR PREDISPOSITION SYNDROME

BAP1 Targeted Variant Analysis

National Comprehensive Cancer Network (NCCN)

NCCN guidelines for Kidney Cancer (~~2.2024~~1.2025) include *BAP1* tumor predisposition syndrome in their overview of hereditary renal cell carcinoma syndromes, and ~~state that this~~recommend testing ~~is indicated~~ for an individual with a close blood relative with a known pathogenic/likely pathogenic variant in a cancer susceptibility gene. (p. HERED-RCC-1 and HERED-RCC-2)

BAP1 Sequencing and/or Deletion/Duplication Analysis

National Comprehensive Cancer Network (NCCN)

NCCN guidelines for Cutaneous Melanoma (~~3.2023~~1.2024) state that ~~individuals with the presence of~~individual germline mutations in *CDKN2a*, *CDK4*, *MC1R*, *BRCA2*, *BAP1* and potentially other genes, are ~~predisposed~~at risk to develop single or multiple primary melanomas. (p. ME-A 1 of 2)

NCCN guidelines for Uveal Melanoma (1.~~2023~~2024) include germline *BAP1* mutations as a risk factor for developing uveal melanoma. (p. UM-A 1 of 2)

NCCN guidelines for Malignant Pleural Mesothelioma (1.2024) state that approximately 12-16% of patients with pleural or peritoneal mesothelioma have a germline mutation, including in *BAP1*. (p. ~~MPM~~PM-A 5 of 8)

NCCN guidelines for Kidney ~~cancer (2.2024~~Cancer (1.2025) include *BAP1* tumor predisposition syndrome in their overview of hereditary renal cell carcinoma syndromes. (p. HERED-RCC-2)

GeneReviews: BAP1 Tumor Predisposition Syndrome (BAP1-TPDS)

GeneReviews is an expert-authored review of current literature on a genetic disease, and goes through a rigorous editing and peer review process before being published online. The clinical description and testing indications for *BAP1* Tumor Predisposition syndrome are as follows:

BAP1-TPDS should be suspected in an individual who has EITHER of the following:

- Two or more confirmed BAP1-TPDS tumors*
- One BAP1-TPDS tumor and a first- or second-degree relative with a confirmed BAP1-TPDS tumor*

*Excluding two basal cell cancers and/or cutaneous melanomas, given their high frequency in the general population

In addition to *BAP1*-inactivated melanocytic tumors, uveal melanoma, malignant mesothelioma, cutaneous melanoma, renal cell carcinoma, and basal cell carcinoma, individuals with germline mutations in *BAP1* may have an increased risk for hepatocellular carcinoma, cholangiocarcinoma, and meningioma.

BIRT-HOGG DUBE SYNDROME (BHDS)

FLCN Targeted Variant Analysis

National Comprehensive Cancer Network (NCCN)

NCCN guidelines for Kidney Cancer (~~2.2024~~1.2025) includes Birt-Hogg-Dube syndrome in their overview of hereditary renal cell carcinoma syndromes, and ~~state that this~~recommend testing ~~is indicated~~ for an individual with a close blood relative with a known pathogenic/likely pathogenic variant in a cancer predisposition gene. (p. HERED-RCC-1 and HERED-RCC-2)

FLCN Sequencing and/or Deletion/Duplication Analysis

National Comprehensive Cancer Network (NCCN)

NCCN guidelines for Kidney Cancer (~~2.2024~~1.2025) include Birt-Hogg-Dube syndrome in their overview of hereditary renal cell carcinoma syndromes. ~~(p. HERED-RCC-2).~~ Commonly seen histologies include chromophobe, hybrid oncocytic tumors, clear cell, oncocytomas, angiomyolipomas, and papillary RCC. (p. HERED-RCC-2)

GeneReviews: Birt-Hogg-Dube Syndrome (BHDS)

GeneReviews is an expert-authored review of current literature on a genetic disease, and goes through a rigorous editing and peer review process before being published online. The clinical description and testing indications for Birt-Hogg-Dube syndrome (BHDS) are as follows:

BHDS should be suspected in individuals with any of the following major or minor criteria.

Major criteria

- Five or more fibrofolliculomas/trichodiscomas with at least one confirmed histologically
- Identification of a heterozygous pathogenic variant in *FLCN*

Minor criteria

- Multiple lung cysts. Bilateral basally located lung cysts with no other apparent cause, with or without spontaneous primary pneumothorax
- Early-onset renal cancer (age <50 years)
- Multifocal or bilateral renal cancer
- Renal cancer of mixed chromophobe and oncocytic histology
- First-degree relative with BHDS

The diagnosis of BHDS is established in a proband with:

- One major criteria (Note: Identification of a heterozygous pathogenic variant in FLCN is one of the major criteria); **OR**
- Two minor criteria

COWDEN SYNDROME (CS)/PTEN HAMARTOMA TUMOR SYNDROME (PHTS)

PTEN Targeted Variant Analysis

National Comprehensive Cancer Network (NCCN)

The NCCN Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic guidelines (~~2~~3.2024) states that testing should be performed in the following situations:

1) Individuals with any blood relative with a known pathogenic/likely pathogenic variant in a cancer susceptibility gene

2) Individuals with a pathogenic/likely pathogenic (P/LP) variant identified on tumor genomic testing that has clinical implications if also identified in the germline. (p. CRIT-1)

PTEN Sequencing and/or Deletion/Duplication Analysis

National Comprehensive Cancer Network (NCCN)

NCCN Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic guidelines (~~2~~3.2024) outline clinical criteria for the genetic testing for Cowden syndrome (CS)/*PTEN* hamartoma tumor syndrome (PHTS) These include:

- Individual from a family with a known *PTEN* pathogenic or likely pathogenic variant
- Individual with a personal history of Bannayan-Riley-Ruvalcaba syndrome (BRRS)
- Individual meeting clinical diagnostic criteria* for CS/PHTS [Cowden syndrome/PTEN hamartoma tumor syndrome]
- Individual not meeting clinical diagnostic criteria for CS/PHTS with a personal history of: Adult Lhermitte-Duclos disease (cerebellar tumors); Autism spectrum disorder and macrocephaly; Two or more biopsy-proven trichilemmomas; Two or more major criteria (one must be macrocephaly); Three major criteria, without macrocephaly; One major and 3 or more minor criteria; 4 or more minor criteria
- At-risk individual with a relative with a clinical diagnosis of CS/PHTS or BRRS for whom testing has not been performed. The at-risk individual must have the following: Any one major criterion or two minor criteria
- ~~*PTEN* pathogenic or likely pathogenic variant detected by tumor genomic testing on any tumor type in the absence of germline analysis.~~ (p. CRIT-8 and CRIT-8A)

*These NCCN guidelines also include Revised Clinical Diagnostic Criteria for PTEN Hamartoma Tumor Syndrome. This includes an operational diagnosis in an individual with either of the following:

1. Three or more major criteria, but one must include macrocephaly, Lhermitte-Duclos disease, or GI hamartomas; or
2. Two major and three minor criteria (~~CRIT-8A). (~~p. CRIT-8A)

ADENOMATOUS POLYPOSIS CONDITIONS (FAMILIAL ADENOMATOUS POLYPOSIS SYNDROME (FAP)/ATTENUATED FAP (AFAP) ~~AND~~and/or MUTYH-ASSOCIATED POLYPOSIS SYNDROME (MAP))

***APC* and/or *MUTYH* Targeted Variant Analysis**

National Comprehensive Cancer Network (NCCN)

NCCN Genetic/Familial High-Risk Assessment: Colorectal guidelines (2.2023) outline clinical criteria for the genetic testing, which includes a known pathogenic variant in an adenomatous polyposis gene in the family. (p. POLYP-1) and recommend targeted APC or MUTYH gene testing when the familial pathogenic variant is known (p. FAP-2, MAP-1). ~~POLYP-1)~~

~~Of note, NCCN recommends analysis of *MUTYH* in individuals when the familial pathogenic variant is known. Specifically, siblings of a patient with MAP are recommended to have site-specific testing for the familial pathogenic variants. (p. MAP-1 and MAP-3)~~

Additionally, ~~NCCN states~~it is possible that pathogenic or likely pathogenic variants identified through tumor ~~testing can~~profiling could be ~~complementary to germline testing and can assist in interpretation of results. Although~~ of germline origin ~~can sometimes be inferred with a high degree of confidence, confirmatory~~. Confirmatory germline testing is indicated for pathogenic/likely pathogenic variants ~~with~~identified via tumor profiling when there is a

reasonable clinical suspicion of being ~~a~~of germline origin (~~based on patient/family history or clinical characteristics, presence of founder mutation, and in some cases variant allele frequency). (p.~~ p. HRS-~~A 4~~B, 5 of ~~7~~9)

APC and/or *MUTYH* Sequencing and/or Deletion/Duplication Analysis

National Comprehensive Cancer Network (NCCN)

NCCN Genetic/Familial High-Risk Assessment: Colorectal guidelines (2.2023) outline Adenomatous Polyposis testing criteria. ~~-~~These include: Personal history of greater than or equal to 20 cumulative adenomas, ~~known pathogenic variant in adenomatous polyposis gene in family,~~ or multifocal/bilateral congenital hypertrophy of retinal pigment epithelium (CHRPE). ~~Other scenarios in which~~NCCN recommends consideration of testing ~~can be considered include having~~when there is a personal history of 10 or more cumulative adenomas, desmoid tumor, hepatoblastoma, ~~cribiform~~cribriform-morular variant of papillary thyroid cancer, and unilateral CHRPE. (p. POLYP-1). For *MUTYH*-Associated polyposis specifically, NCCN lists additional common features including duodenal cancer and duodenal adenomas. (p. MAP-1)

The guidelines also note that biallelic *MUTYH* mutations have also been implicated in rare cases of serrated polyposis syndrome (defined as 5 or more serrated polyps proximal to the rectum all being 5mm or larger with 2 or more being 10 or more mm in size, or more than 20 serrated polyps of any size distributed throughout the colon, with 5 or more being proximal to the rectum). (p. SPS-1)

~~The guidelines also acknowledge that many~~Some individuals will have variants of uncertain significance (VUS); post test counseling should include considering referral to research studies ~~that aim to define~~for the purpose of learning the functional impact of VUSs such as variant reclassification programs through clinical labs or registries. (p. HRS-A, 1 of 2 and HRS-B, 1 of 9)

FAMILIAL ATYPICAL MULTIPLE MOLE MELANOMA (FAMMM) SYNDROME

CDKN2A Targeted Variant Analysis

The NCCN Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic guidelines (~~2~~3.2024) state that testing for hereditary cancer susceptibility should be performed in the following situations:

- Individuals with any blood relative with a known pathogenic/likely pathogenic variant in a cancer susceptibility gene
- Individuals with a pathogenic/likely pathogenic (P/LP) variant identified on tumor genomic testing that ~~has clinical implications~~would impact cancer risk if ~~also identified in the~~ confirmed to be a germline variant (p.CRIT-1)

- ~~Comprehensive skin exam and additional evaluations by a dermatologist are recommended for individuals with a P/LP variant. (p. GENE-A, 4 of 11)~~

CDKN2A Sequencing and/or Deletion/Duplication Analysis

National Comprehensive Cancer Network (NCCN)

NCCN Cutaneous Melanoma guidelines (~~3.2023~~1.2024) recommend ~~considering~~consideration of a genetic counseling referral for *p16*/*CDKN2A* mutation testing (and possibly other genes) when a patient has 3 or more invasive cutaneous melanomas, or a personal or family history of ~~a mix of~~ invasive melanoma, pancreatic cancer, and/or astrocytoma diagnoses. (p. ME-~~11~~12)

NCCN Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic guidelines (~~2~~3.2024) recognize CDKN2A as a pancreatic cancer susceptibility gene; testing is ~~indicated~~recommended in an individual with exocrine pancreatic cancer or a first degree relative with exocrine pancreatic cancer. (p. CRIT-5).

American Academy of Dermatology

Guidelines published in 2018 by the American Academy of Dermatology (Swetter, et al) recommend genetic risk assessment for patients with cutaneous melanoma who have two or more relatives with cutaneous melanoma and/or pancreatic cancer, especially when a first degree relative is involved. (p. 237)

HEREDITARY DIFFUSE GASTRIC CANCER (aka, Signet Ring Cell Gastric Cancer~~):~~)

CDH1 Targeted Variant Analysis

National Comprehensive Cancer Network (NCCN)

NCCN Gastric Cancer guidelines (~~3.2023~~2.2024) outline ~~testing~~ criteria for ~~germline *CDH1* testing~~further risk assessment for high risk gastric cancer syndromes, which ~~states that~~recommend risk evaluation when there is a known mutation in a gastric cancer susceptibility gene in a close relative ~~is criteria for further risk evaluation.~~. (p. GAST-D 1 of 8)

The NCCN Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic guidelines (~~2~~3.2024) state that testing for hereditary cancer susceptibility should be performed in the following situations:

- Individuals with any blood relative with a known pathogenic/likely pathogenic variant in a cancer susceptibility gene
- Individuals with a pathogenic/likely pathogenic (P/LP) variant identified on tumor genomic testing that ~~has clinical implications~~would impact cancer risk if ~~also identified in the~~confirmed to be a germline variant. (p. CRIT-1)

CDH1 Sequencing and/or Deletion/Duplication Analysis

National Comprehensive Cancer Network (NCCN)

NCCN Gastric Cancer guidelines (~~3.2023~~2.2024) outline testing criteria for germline *CDH1* testing which incorporates both personal and family history of gastric cancer and lobular breast cancer. These include:

- Two gastric cancer cases in a family, one confirmed diffuse gastric cancer (DGC) regardless of age
- DGC diagnosed before age 50 years without a family history
- Personal or family history of DGC and lobular breast cancer, one diagnosed before age 70 years
- Two cases of lobular breast cancer in family members before 50 years of age
- DGC at any age in individuals of Māori ethnicity, or with a personal or family history of cleft lip/cleft palate
- Bilateral lobular breast cancer before age 70 years. (p. GAST-D 3 of 8)

JUVENILE POLYPOSIS SYNDROME (JPS)

SMAD4 and *BMPR1A* Targeted Variant Analysis

National Comprehensive Cancer Network (NCCN)

NCCN Genetic/Familial High-Risk Assessment: Colorectal guidelines (2.2023) outline clinical criteria for ~~the~~ genetic testing~~, which states that genetic testing should be performed~~ for ~~individuals with~~Juvenile Polyposis syndrome. Testing is recommended when there is a known *BMPR1*A or *SMAD4* pathogenic variant in ~~*BMPR1A* or *SMAD4*.~~the family. (p. JPS-1)

Additionally, ~~NCCN states that~~it is possible that pathogenic or likely pathogenic variants identified through tumor ~~testing can be complementary to germline testing and can assist in interpretation~~ profiling could be of ~~results. Although~~ germline origin~~ can sometimes be inferred with a high degree of confidence, confirmatory~~. Confirmatory germline testing is indicated for pathogenic/likely pathogenic variants ~~with~~identified via tumor profiling when there is a reasonable clinical suspicion of being ~~a~~of germline origin~~ (based on patient/family history or clinical characteristics, presence of founder mutation, and in some cases variant allele frequency).~~. (p. HRS-~~A-4~~B, 5 of ~~7)~~9)

SMAD4 and *BMPR1A* Sequencing and/or Deletion/Duplication Analysis

National Comprehensive Cancer Network (NCCN)

NCCN Genetic/Familial High-Risk Assessment: Colorectal guidelines (2.2023) outline clinical criteria for ~~the~~ genetic testing for juvenile polyposis syndrome (JPS) in individuals with a personal and/or family history suggestive of JPS~~, noting that clinical genetic~~. Genetic testing is recommended ~~as approximately 50%~~when criteria are met or when there is a family history of JPS ~~cases occurring due to pathogenic variants in *BMPR1A* and *SMAD4*.~~ .

These criteria include 5 or more colonic juvenile polyps, multiple juvenile polyps throughout the gastrointestinal tract, and any number of juvenile polyps in someone with a family history of JPS. (p. JPS-1)

HEREDITARY LEIOMYOMATOSIS AND RENAL CELL CANCER (HLRCC)

FH Targeted Variant Analysis

National Comprehensive Cancer Network (NCCN)

NCCN guidelines for Kidney Cancer (~~2.2024~~1.2025) include ~~Hereditary~~hereditary leiomyomatosis and renal cell carcinoma (HLRCC) in their overview of hereditary renal cell carcinoma syndromes, and state that ~~this~~ testing is indicated for an individual with a close blood relative with a known pathogenic/likely pathogenic variant in a cancer predisposition gene. (p. HERED-RCC-1 and HERED-RCC-2)

FH Sequencing and/or Deletion/Duplication Analysis

National Comprehensive Cancer Network (NCCN)

NCCN guidelines for Kidney Cancer (~~2.2024~~1.2025) outline criteria for further genetic risk evaluation for hereditary renal cell carcinoma syndromes, including HLRCC-associated renal cell carcinoma. Testing is recommended for an individual whose tumor is HLRCC-associated renal cell carcinoma, FH deficient renal cell carcinoma, or has other histologic features of HLRCC. (p. HERED-RCC-1~~(p. HERED-RCC-2~~)

GeneReviews: FH Tumor Predisposition Syndrome

GeneReviews is an expert-authored review of current literature on a genetic disease, and goes through a rigorous editing and peer review process before being published online. The recommended testing for FH tumor predisposition syndrome (HLRCC) is as follows:

FH tumor predisposition syndrome should be suspected in individuals with the following features:

Cutaneous leiomyomata (~50%):

- Skin-colored to light brown/reddish papules or nodules distributed over the trunk, extremities, and occasionally on the face and neck
- May be single, grouped/clustered, segmental, or disseminated
- Histopathology shows bundles of smooth muscle fibers with central, long blunt-edged nuclei

Uterine leiomyomata (uterine fibroids) (~90% of ~~those with a female reproductive system~~females):

- Fibroids tend to be numerous and large.
- Fibroids often demonstrate loss of FH staining and positive cytoplasmic staining for S-(2-succino) cysteine

Renal tumors (~15%) are usually solitary, highly aggressive renal cell carcinoma (RCC) that metastasizes early.

The spectrum of renal tumors includes type 2 papillary, undefined papillary, unclassified, tubulocystic, and collecting-duct carcinoma.

LI-FRAUMENI SYNDROME (LFS)

TP53 Targeted Variant Analysis

National Comprehensive Cancer Network (NCCN)

The NCCN Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic guidelines (~~2~~3.2024) states that testing for hereditary cancer susceptibility should be performed in the following situations:

- ~~1)~~ Individuals with any blood relative with a known pathogenic/likely pathogenic variant in a cancer susceptibility gene
- ~~2)~~ Individuals with a pathogenic/likely pathogenic (P/LP) variant identified on tumor genomic testing that ~~has clinical implications~~would impact cancer risk if ~~also identified in the~~confirmed to be a germline variant. (p. CRIT-1)

TP53 Sequencing and/or Deletion/Duplication Analysis

National Comprehensive Cancer Network (NCCN)

NCCN Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic guidelines (~~2~~3.2024) outline clinical testing criteria for the genetic testing for Li-Fraumeni syndrome. This Includes classic Li-Fraumeni syndrome criteria and Chompret criteria and considerations for family history:

Classic Li-Fraumeni syndrome (LFS) criteria:

- Combination of an individual diagnosed at age younger than 45 years with a sarcoma **AND**
- A first-degree relative diagnosed at age younger than 45 years with cancer **AND**
- An additional first- or second-degree relative in the same lineage with cancer diagnosed at age younger than 45 years, or a sarcoma at any age

Chompret criteria:

- Individual with a tumor from LFS tumor spectrum (e.g., soft tissue sarcoma, osteosarcoma, CNS tumor, breast cancer, adrenocortical carcinoma), before 46 years of age, **AND**
    - At least one first- or second-degree relative with any of the aforementioned cancers (other than breast cancer if the proband has breast cancer) before the age of 56 years or with multiple primaries at any age, **OR**
- Individual with multiple tumors (except multiple breast tumors), two of which belong to LFS tumor spectrum with the initial cancer occurring before the age of 46 years, **OR**
- Individual with adrenocortical carcinoma, or choroid plexus carcinoma or rhabdomyosarcoma of embryonal anaplastic subtype, at any age of onset, regardless of family history, **OR**
- Breast cancer before 31 years of age

Personal/Family history criteria:

- Personal or family history of pediatric hypodiploid acute lymphoblastic leukemia.

MULTIPLE ENDOCRINE NEOPLASIA TYPE 1 (MEN1)

MEN1 Targeted Variant Analysis

National Comprehensive Cancer Network (NCCN)

NCCN Neuroendocrine and Adrenal Tumors guidelines (~~1.2023~~2.2024) recommend that targeted genetic testing for *MEN1* be performed for individuals with a close blood relative with a known pathogenic variant/likely pathogenic variant in a cancer susceptibility gene. (p. NE-E 3 of 8)

Additionally, NCCN recommends genetic risk evaluation and genetic testing for Hereditary Endocrine Neoplasia Syndromes when a mutation is identified on tumor genomic testing that has clinical implications if also identified in the germline. (p NE-E 3 of 8)

MEN1 Sequencing and/or Deletion/Duplication Analysis

National Comprehensive Cancer Network (NCCN)

NCCN Neuroendocrine and Adrenal Tumors guidelines (1.2023) recommend that patients with two or more of the following, or ~~1~~one AND a family history of ~~1~~one or more of the following, be evaluated for *MEN1* germline mutations:

- Foregut carcinoid (bronchial, thymic, or gastric)
- Pituitary adenoma
- Duodenal or pancreatic neuroendocrine tumor
- Primary ~~hyperpararthyroidism.~~hyperparathyroidism. (p. NE-E 3 of 8)

MULTIPLE ENDOCRINE NEOPLASIA TYPE 2 (MEN2)

RET Targeted Variant Analysis

National Comprehensive Cancer Network (NCCN)

NCCN Neuroendocrine and Adrenal Tumors guidelines (~~1.2023~~2.2024) recommend that targeted genetic testing for MEN2 be performed for individuals with a close blood relative with a known pathogenic variant/likely pathogenic variant in a cancer susceptibility gene. (p. NE-E 3 of 8)

Additionally, NCCN states that testing is recommended when a mutation is identified on tumor genomic testing that has clinical implications if also identified in the germline. (p NE-E 3 of 8)

RET Sequencing and/or Deletion/Duplication Analysis

GeneReviews: Multiple Endocrine Neoplasia Type 2

GeneReviews is an expert-authored review of current literature on a genetic disease, and goes through a rigorous editing and peer review process before being published online. The clinical description and testing indications for multiple endocrine neoplasia type 2 are as follows:

Multiple endocrine neoplasia type 2A (MEN2A) should be suspected in any individual with medullary thyroid carcinoma, pheochromocytoma (usually adrenal) or parathyroid adenoma/hyperplasia. Familial Medullary Thyroid Carcinoma should be suspected in families with more than one individual diagnosed with MTC in the absence of pheochromocytoma or parathyroid adenoma/hyperplasia. Multiple endocrine neoplasia type 2B (MEN2B) should be suspected in individuals with distinctive facies including lip mucosal neuromas resulting in thick vermilion of the upper and lower lip, mucosal neuromas of the lips and tongue, medullated corneal nerve fibers, marfanoid habitus, and MTC.

National Comprehensive Cancer Network (NCCN)

NCCN Neuroendocrine and Adrenal Tumors guidelines (~~1.2023~~2.2024) also recommends MEN2 testing when there is clinical suspicion of MEN2 due to the presence of medullary thyroid cancer or other combination of MEN2-related features. Genetic testing is ~~indicated~~recommended for a

first degree relative meeting this criteria, where the relative is not available for testing. (p. NE-E 3 of 8)

NEVOID BASAL CELL CARCINOMA SYNDROME (aka Gorlin syndrome)

***PTCH1* and/or *SUFU* Targeted Variant Analysis**

GeneReviews: Nevoid Basal Cell Carcinoma Syndrome

GeneReviews is an expert-authored review of current literature on a genetic disease, and goes through a rigorous editing and peer review process before being published online.

GeneReviews states that it is appropriate to evaluate apparently asymptomatic older and younger at-risk relatives (including children) of an affected individual in order to identify as early as possible those who would benefit from surveillance for complications of NBCCS (most notably medulloblastoma in children and jaw cysts and BCCs in adults) and avoidance of x-rays and sun exposure. Evaluations can include molecular genetic testing if the pathogenic variant in the family is known.

***PTCH1* and/or *SUFU* Sequencing and/or Deletion/Duplication Analysis**

GeneReviews: Nevoid Basal Cell Carcinoma Syndrome

GeneReviews is an expert-authored review of current literature on a genetic disease, and goes through a rigorous editing and peer review process before being published online.

Nevoid basal cell carcinoma syndrome (NBCCS) should be suspected in individuals with the following findings, which constitute major or minor diagnostic criteria. The diagnosis of NBCCS is established in a proband with either:

- Two major diagnostic criteria and one minor diagnostic criterion, **OR**
- One major and three minor diagnostic criteria

Major criteria

- Lamellar (sheet-like) calcification of the falx or clear evidence of calcification in an individual younger than age 20 years. Falx calcification is nearly always present and is visible on anteroposterior (AP) x-rays of the skull after age 20 years (see Notes regarding radiographs).
- Jaw keratocyst. Odontogenic keratocyst histologically; seen on ~~orthopantogram~~orthopantomogram as an area of translucency
- Palmar/plantar pits (at least 2); particularly useful in diagnosis and more pronounced when the hands and feet are soaked in warm water for up to ten minutes. Pits may appear as white "punched-out" or pink "pin-prick" lesions.

- Multiple basal cell carcinomas (BCCs) (more than 5 in a lifetime) or a BCC before age 30 years. Provision needs to be made for decreased risk of BCC in individuals with dark skin and increased risk in those with light skin living in hot sunny climates, particularly those with type 1 Celtic skin and red hair, and of this group, particularly those with the common *MC1R* variant (rs1805007), which can modify age of onset for NBCCS.
- First-degree relative with NBCCS

Minor criteria

- Childhood medulloblastoma (also called primitive neuroectodermal tumor)
- Lympho-mesenteric or pleural cysts
- Macrocephaly (OFC greater than 97th centile)
- Cleft lip/palate
- Vertebral/rib anomalies observed on chest x-ray and/or spinal x-ray: bifid/splayed/extra ribs; bifid vertebrae
- Preaxial or postaxial polydactyly
- Ovarian/cardiac fibromas
- Ocular anomalies (e.g., cataract, developmental defects, and pigmentary changes of the retinal epithelium).

HEREDITARY PARAGANGLIOMA/PHEOCHROMOCYTOMA SYNDROME (PGL/PCC)

MAX, SDHA, SDHAF2, SDHB, SDHC, SDHD, or *TMEM127* Targeted Variant Analysis

National Comprehensive Cancer Network (NCCN)

NCCN guidelines for Kidney Cancer (~~2.2024~~1.2025) include Hereditary paraganglioma/pheochromocytoma (PGL/PCC) syndrome in their overview of hereditary renal cell carcinoma syndromes~~, and state that this~~. Genetic testing is ~~indicated~~recommended for an individual with a close blood relative with a known pathogenic/likely pathogenic variant in a cancer susceptibility gene. (p. HERED-RCC-1 and HERED-RCC-2)

MAX, SDHA, SDHAF2, SDHB, SDHC, SDHD, or *TMEM127* Sequencing and/or Deletion/Duplication Analysis

National Comprehensive Cancer Network (NCCN)

NCCN guidelines for Neuroendocrine and Adrenal Tumors (2.2024) recommend genetic testing for hereditary endocrine neoplasia syndromes such as Hereditary Paraganglioma/Pheochromocytoma Syndrome for patients with either a paraganglioma or pheochromocytoma or with a first degree relative with either of these tumors who is unavailable for testing (p. NE-E, 3 of 8). Other manifestations of this syndrome include gastrointestinal

stromal tumor and renal cell cancer (p. NE-E, 4 of 8).

GeneReviews: Hereditary Paraganglioma-Pheochromocytoma Syndromes

GeneReviews is an expert-authored review of current literature on a genetic disease, and goes through a rigorous editing and peer review process before being published online. The clinical description and testing indications for hereditary paraganglioma-pheochromocytoma syndromes are as follows:

Hereditary paraganglioma-pheochromocytoma (PGL/PCC) syndromes should be suspected in any individual with a paraganglioma or pheochromocytoma. Other tumors associated with these conditions are gastrointestinal stromal tumors (GIST~~), pulmonary chondromas,~~) and renal clear cell carcinoma. In addition, individuals with a family history of paraganglioma or pheochromocytoma should also be suspected to have hereditary paraganglioma-pheochromocytoma syndromes.

The diagnosis of hereditary PGL/PCC should be strongly suspected in an individual with multiple, multifocal, recurrent, or early-onset paraganglioma or pheochromocytoma and/or a family history of paraganglioma or pheochromocytoma.

PEUTZ-JEGHERS SYNDROME (PJS)

***STK11* Targeted Variant Analysis**

National Comprehensive Cancer Network (NCCN)

NCCN Genetic/Familial High-Risk Assessment: Colorectal guidelines (2.2023) outline testing criteria for the evaluation of Peutz-Jeghers Syndrome (PJS) and recommend clinical genetic testing when there is a family history of confirmed PJS. NCCN states that pathogenic mutations in ~~-~~*STK11* cause the majority of PJS cases. (p. PJS-1)

Additionally, ~~NCCN states~~it is possible that pathogenic or likely pathogenic variants identified through tumor ~~testing can~~profiling could be ~~complementary to germline testing and can assist in interpretation~~ of ~~results. Although~~ germline origin ~~can sometimes be inferred with a high degree of confidence, confirmatory~~. Confirmatory germline testing is indicated for pathogenic/likely pathogenic variants ~~with~~identified via tumor profiling when there is a reasonable clinical suspicion of being ~~a~~of germline origin (~~based on patient/family history or clinical characteristics, presence of founder mutation, and in some cases variant allele frequency). (~~p. HRS-~~A 4~~B, 5 of ~~7~~9)

***STK11* Sequencing and/or Deletion/Duplication Analysis**

National Comprehensive Cancer Network (NCCN)

NCCN Genetic/Familial High-Risk Assessment: Colorectal guidelines (2.2023) outline clinical criteria for PJS genetic testing in individuals with a personal and/or family history suggestive of PJS, as a majority of cases occur due to pathogenic variants in the *STK11* (*LKB1*) gene. These criteria include: two or more PJS-type hamartomas in the GI tract, hyperpigmentation in mucocutaneous membranes (such as the mouth, lips, nose, eyes, genitals, or fingers) and a family history of PJS. (p. PJS-1)

RETINOBLASTOMA

RB1 Targeted Variant Analysis

American Association of Ophthalmic Oncologists and Pathologists (AAOOP)

The AAOOP with support of the American Association for Pediatric Ophthalmology and Strabismus and the American Academy of Pediatrics (AAP) developed expert consensus guidelines for children at risk for development of retinoblastoma (2018). These guidelines indicate that identification of a germline mutation in RB1 in a patient with retinoblastoma should lead to testing relatives for the familial mutation to determine whether ophthalmic screening is required. In addition, identification of RB1 mutation in the tumor, followed by blood testing for the mutation, allows for recommendations for screening and genetic testing for family members. (p. 455)

RB1 Sequencing and/or Deletion/Duplication Analysis

American Association of Ophthalmic Oncologists and Pathologists (AAOOP)

The AAOOP with support of the American Association for Pediatric Ophthalmology and Strabismus and the American Academy of Pediatrics (AAP) developed expert consensus guidelines for children at risk for development of retinoblastoma (2018). The guidelines included the following recommendations:

Genetic counseling and testing clarify the risk for retinoblastoma in children with a family history of the disease and improve outcomes at reduced cost, justifying making testing available to all patients with a personal or family history of retinoblastoma. Genetic evaluation should be initiated whether the affected relative demonstrated unilateral or bilateral disease because both have a substantial risk of being heritable (grade C). (p. 456)

VON HIPPEL-LINDAU SYNDROME (VHL)

VHL Targeted Variant Analysis

National Comprehensive Cancer Network (NCCN)

NCCN guidelines for Kidney Cancer (~~2.2024~~1.2025) include von Hippel-Lindau (VHL)

syndrome in their overview of hereditary renal cell carcinoma syndromes, and state that this testing is indicated for an individual with a close blood relative with a known pathogenic/likely pathogenic variant~~.~~ in a cancer susceptibility gene. (p. HERED-RCC-1 and HERED-RCC-2)

VHL Sequencing and/or Deletion/Duplication Analysis

National Comprehensive Cancer Network (NCCN)

NCCN Kidney Cancer guidelines (~~2.2024~~1.2025) outline clinical features seen in Von Hippel-Lindau syndrome including: hemangioblastomas (in the retina, spine, or brain), clear cell RCC (diagnosed before age 40 years or multiple/bilateral RCC diagnosed at any age), pheochromocytomas, paragangliomas (in the abdomen, thorax, or neck), retinal angiomas, endolymphatic sac tumors, epididymal or broad ligament papillary cystadenomas, multiple pancreatic serous cystadenomas, pancreatic neuroendocrine tumors, or multiple cysts in the pancreas. While these clinical features are categorized within the categories "major" and "minor," the NCCN guidelines do not provide a scoring system required for patients to meet testing criteria. (p. HERED-RCC-A)

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Converted corporate to local policy.	10/23		

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Semi-annual review. Updated title to reflect V1.2024 version. Overview, coding, reference-table, background and references updated. Throughout policy: replaced "coverage criteria" with "criteria. For Overview: added "Of note, the National Society of Genetic Counselors…". For Policy Reference Table; under Pre-Cancer Hereditary Cancer Susceptibility Panels: removed "Breast and GYN Cancers Panel (Invitae)"; under Hereditary Breast Cancer Susceptibility Panels: added "VistaSeg" and "Fulgent Genetics" and "part of Exact Sciences" and "plus PALB2" and "81307, 81321, 81351"; under Hereditary GI/Colon Cancer Panel Tests: added "0162U"; under Hereditary Pancreatic Cancer Susceptibility Panels: removed "Primary Panel"; under Herrditary Polyposis Panels: added "part of Exact Sciences"; under BRCA1 and BRCA2 Sequencing and/or Deletion/Duplication Analysis: removed "Breast and Ovarian Cancer Panel" and replaced with "BRCA1/2 Panel"; under PALB2 Targeted Variant Analysis: removed "Mutation Tests…" and replaced with "Variant (GeneDx)"; under PALB2 Sequencing and/or Deletion/Duplication Analysis: added "(Quest)'; under ATM or CHEK2 Targeted Variant Analysis: removed "Targeted Variants" and replaced with "Targeted Variant- Single Test" and removed "PreventionGenetics" and replaced with "(GeneDx)"; under ATM or CHEK2 Sequencing…added "part of Exact Sciences"; under MLH1, MSH2…replaced "Mutation Tests" with "Variant"; removed "Mutation Analysis" and replaced with "Variant (GeneDx)"; removed "81403" and replaced with "81479"; for FLCN Targeted Variant Analysis: removed "Targeted Variant" and added "Targeted Variant-Single Test (GeneDx)" removed "(Prevention Genetics); under PTEN Targeted Variant Analysis: removed "Targeted Variant" and replaced with "Targeted Variant- Single Test (GeneDx)"; under PTEN Sequencing and/or Deletion/Duplication Analysis: removed "Genomic Unity PTEN Analysis (Variantx Inc) and removed "0235U"; under Familial Adenomatous Polyposis…added "Adenomatous Polyposis Conditions" and "and MUTYH-Associated Polyposis Syndrome (MAP)"; under APC Sequencing and/or Deletion/Duplication Analysis: added "+RNAInsight…" and added "0157U"; under MUTYH Sequencing…added "MUTYH Full Gene…" and added "81406, 81479"; under CDKN2A Targeted Variant Analysis: removed "Targeted Variant" and replaced with "Targeted Variant-Single Test (GeneDX)" and removed "81403" and replaced with "81479"; under CDH1 Targeted Variant Analysis: removed "Targeted Variant" and replaced with "Targeted Variant-Single Test (GeneDX)" and removed "81403" and replaced with "81479"; under SMAD4 and/or BMPR1A Targeted Variant Analysis: added "part of Exact Sciences"; under FH Targeted Variant Analysis: removed "Miraca", added "LLC" and removed "Laboratories"; under FH Sequencing and/or Deletion/Duplication Analysis: removed "FH Sequencint Tests…"; under TP53 Targeted Variant Analysis: removed "Targeted Variant" and replaced with "Targeted Variant-Single Test (GeneDX)"; under TP53 Sequcnging and/or Duplication/Deletion Analysis: added "TP53 Full Gene Sequencing and Deletion/Duplication" and temoved "Li Fraumeni Syndrome Test"; under MEN1 Targeted Variant Analysis: removed "Targeted Variant: MEN1 (Prevention Genetics)"" and replaced with "Targeted Variant-Single Test (GeneDX)" and removed "81403" and replaced with "81479"; for RET Targeted Variant Analysis: removed "Targeted Variant: RET (Prevention Genetics)" and replaced with "Targeted Variant-Single Test (GeneDX)" and	2/24	4/26/24	

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removed “81405”; removed MUTYH-associated Polyposis (MAP)…”; under MAX, SDHA…: added “SDHB, SDHD…”; and replaced “81403” with “81479”; under STK11 Targeted Variant Analysis: added “-Single Test (GeneDx) PreventionGenetics”; under VHL Targeted Variant Analysis: removed “Miraca”, added “, LLC” and removed “Laboratories”. For Hereditary Breast Cancer Susceptibility Panels: under I. added “81307, 81321, 81351” and removed “0102U”; under I.A.1. removed “has a personal history…”; under I.B. removed “The member/enrollee has a probability…” and added “meets sequencing and/or…”; under II.A. replaced “all” with “any”; under II.B. removed “decisions”; under III. Added “81307, 81321, 81351” and removed “0102U”; removed “IV. Hereditary breast cancer…”. For Hereditary GI/Colon Cancer Panel Tests: under I. removed “0130U”; under I.2.a. removed “The member/enrollee’s tumor has deficient…”; under I.C. added “ant TP53,”; under II. removed “0130U”; under III. Added “0162U”. For Hereditary Gastric Cancer Panels: under I. and II. added “81201, 81203, 81404, 81405, 81406, 81408”. For Hereditary Pancreatic Cancer Susceptibility Panels: under I. added “81201” and “81351, 81433”; under II. added “81201,” and “81351, 81433”. For Hereditary Polyposis Panels: under I.A. removed “at least one of the following:”; under I.A.1. added “Adenomatous Polyposis Conditions”. For Hereditary Prostate Cancer Susceptibility Panels: under I. removed “0133U”; under I.B. added “The patient has a personal history…”; added I.C. “A personal history of prostate…”; under II. removed “0133U”. For BRCA1 and BRCA2 Sequencing and/or Deletion/Duplication Analysis: under I. removed “0138U”; added I.A.g. “Multiple primary breast cancers…”; under I.A.2.c. removed “Multiple primary breast cancers…”; under I.A.3. removed “meet any of the above criteria” and added “have a personal history of…”; under I.A.4. removed “decisions”; under I.A.6. removed “member/enrollee has a probability of greater than 5%... and added “member/enrollee’s probability of having” and added “is greater than 5%”; under II. removed “0138U”. For PALB2 Sequencing and/or Deletion/Duplication Analysis: under I. removed “0137U”; under I.A.1. removed breast cancer AND”; under I.A.1.a. replaced “Female” with “Male” and removed “diagnosed at age 50 years…”; under I.A.1.b. removed “male” and added “Triple-negative”; under I.A.1.c. removed “Ashkenazi Jewish…”; under I.A.1.c. removed “Triple negative breast” and added “Epithelial ovarian cancer…” under I.A.1.d. added “Pancreatic”; removed I.A.1.f. “Epithelial ovarian cancer…” removed I.A.1.g. “Pancreatic cancer…”; under I.A.2. removed “At least one close relative” and added “The member/enrollee has a personal history…”; under I.A.2.c. added “One or more close relatives”; under I.A.3. removed “meet the above criteria” and added “have a personal history of…”; under I.A.5. removed “member/enrollee has a probability of greater…” and added “member/enrollee’s probability of having” and added “is greater than 5%”. For ATM AND/OR CHEK2 Gene Testing: replaced “81403” with “81479” throughout. For Lynch Syndrome/Hereditary Nonpolyposis Colorectal Cancer (HNPCC) Testing: : replaced “81403” with “81479” throughout. For MLH1, MSH2, MSH6, PMS2, or EPCAM Sequencing and/or Deletion/Duplication Analysis: under I.A. removed “(i.e., colorectal, endometrial…”; under I.B. removed “colorectal cancer…” and added “Lynch syndrome…”; under I.B.2. removed (i.e., colorectal, endometrial…”removed I.B.3. “Diagnosed at any age…” removed I.B.4. “Diagnosed at any age…”;			

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removed I.C. “The member/enrollee has a family history…”; added I.C.3. “Diagnosed at any age…”; added I.C.4. “Diagnosed at any age…”. For FLCN Sequencing and/or Deletion/Duplication Analysis: under I.A. added “any of the following…”; removed I.A.2. “Two of more of the following”; under I.A.5. removed “histology” and added “clear cell…”; added I.A.6. “Onocytoma, OR”; added I.A.7. “Angiomyolipoma”. For PTEN Sequencing and/or Deletion/Duplication Analysis: under I. removed “0235U”; removed “I.A.2. “Meets clinical criteria…”; and added I.A.2. “Autism-spectrum disorder…”. For Adenomatous Polyposis Conditions…: removed “Familial” from the title; under I. added “APC (81202)…”; added “81401, 81403”, removed “familial…” and added “adenomatous polyposis”, removed “(FAP)”; added “testing”; under I.A. and I.B. added “or MUTYH”; under APC and/or MUTYH Sequencing…: under I. removed “for familial” and added “and/or MUTYH sequencing…”; under I.A.1. replaced “20” with “10”; under I.A.2. removed “Multifocal/bilateral…” and added “congenital”; under I.A.3. added “Desmoid tumor…”; added II. APC sequencing…”; added III. “APC mRNA sequencing analysis…”. For Familial Atypical Multiple Mole Melanoma (FAMMM) Syndrome: under I. and II. replaced “81403” with “81479”. For Hereditary Diffuse Gastric Cancer: under I. and II. replaced “81403” with “81479”. For CDH1 Sequencing and/or Deletion/Duplication Analysis: under I.B.7. removed “The member/enrollee has a personal history…” and added “Two cases of lobular…”. For TP53 Sequencing and/or Deletion/Duplication Analysis: under I.D.3.b. removed “A member/enrollee has a diagnosis…”. For Multiple Endocrine Neoplasia Type 1 (MEN1): under I. and II. replaced “81403” with “81479”. For MEN1 Sequencing and/or Deletion/Duplication Analysis: under I.B. removed “diagnosis of cancer with a pathogenic…” and added “personal history of at least one…”. For Multiple Endocrine Neoplasia Type 2 (MEN2): under I. and II. replaced “81405” with “81404”. For Nevoid Basal Cell Carcinoma Syndrome (NBCCS) (aka Gorlin syndrome): under I. removed “MUTYH” and added “PTCH1 or SUFU”; removed “81403, 81404…” and added “81479…”; under I.A. replaced “blood relatve” with “close relative” and removed “MUTYH” and added “PTCH1 or SUFU”; under I.B. removed “MUTYH” and added “PTCH1 or SUFU”; for II. removed “MUTYH” and added “PTCH1 or SUFU” and removed “81403, 81404…” and added “81479…”. For PTCH1 and SUFU Sequencing and/or Deletion/Duplication Analysis: under I. removed removed “MUTYH” and added “PTCH1 or SUFU”;removed “81406”; removed “MYH associated polyposis…”. Removed Nevoid Basal Cell Carcinoma Syndrome (NBCCS) (aka Gorlin syndrome). For Peutz-Jeghers Syndrome (PJS): under I. and II. replaced “81403” with “81479”. For Retinoblastoma; RB1 Sequencing and/or Deletion/Duplication Analysis: under I.B. removed “and has not previously undergone RB1 sequencing…”. For Notes and Definitions: added “11. Adenomatous polyposis…”; added “12. Lynch Syndrome related cancer…”. For Background and Rationale: removed “NCCN guidelines…”; removed “or a pathogenic variant with uncertain clinical management…”; added “in a well established gene…”; added “NCCN Guidelines…”; for Hereditary GI/Colon Cancer Panel Tests: removed “multigene panel testing…” and added “assessment for hereditary…”; added “history of”; removed “cancer has a known…”; removed “HRS” and added “LS-1”; removed “Lynch syndrome related…”; added “NCCN also states that the minimum…”; for Hereditary			

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Pancreatic Cancer Panels: replaced "2.2022" with "1.2023"; for Hereditary Prostate Cancer Susceptibility Panels: added "NCCN Prostate Cancer guidelines…" and added ", triple-negative breast cancer…"; for BRCA1 and BRCA2 Sequencing and/or Deletion/Duplication Analysis: removed "American Society of Clinical Oncology (ASCO)"; for MLH1, MSH2, MSH6, PMS2, or EPCAM Sequencing and/or Deletion//Duplication Analysis: replaced "colorectal or endometrial" with "Lynch Syndrome…"; removed "including greater than…" and added "one of whom was diagnosed…"; added "An individual with a personal history of CRC…"; added "NCCN states that the minimum…"; for BAP1 Sequencing and/or Deletion/Duplication Analysis: removed "In addition to BAP1…"; added "BAP1-TBDS…"; added "*Excluding"; added "In addition to BAP1…"; for FLCN Sequencing and/or Deletion/Duplication Analysis: added "Commonly seen histologies…"; added "Identification of a heterozygous…"; for PTEN Sequencing and/or Deletion/Duplication Analysis: removed "or" multiple times throughout; added "*Revised Clinical Diagnostic Criteria…"; for Adennomatous Polyposis Conditions…": added "Of note, NCCN recommends…"; for APC and/or MUTYH Sequencing and/or Deletion/Duplication Analysis: removed "clinical criteria for the genetic testing…"; added "Adenomatous Polyposis testing criteria"; added "The guidelines also note…"; for Multiple Endocrine Neoplasia Type 1 (MEN1): removed "states that testing is recommended…" and added "recommends genetic risk evaluation…"; for MEN1 Sequencing and/or Deletion/Duplication Analysis: removed "be evaluated…" and added " or 1 AND a family history…"; removed "and parahyperthyroidism"; added "Primary hyperparathyroidism"; removed MUTYH-Associated Polyposis (MAP)…; for PTCH1 and SUFU Sequencing and/or Deletion/Duplication Analysis: added "The diagnosis of NBCCS…"; removed "The diagnosis of NBCCS…"; for MAX, SDHA, SDHAF2, SDHB, SDHC, SDHD, or TMEM127 Sequencing and/or Deletion/Duplication Analysis: added "The diagnosis of hereditary…". ~~Added note " "~~			
Semi-annual review. In *CDKN2A* Updated title to reflect V1.2025 version. ATM or CHEK2 Sequencing and/or Deletion/Duplication Analysis criteria, now ***COVERED*** to align with guidelines, which recommend genetic risk assessment for specific clinical indications. In Hereditary Breast Cancer Susceptibility Panels criteria, removed *PALB2* testing criteria and *PALB2* gene from the minimum gene list to reduce redundancy, given these criteria overlap with the *BRCA1/BRCA2* testing criteria. In Hereditary Breast Cancer Susceptibility Panels criteria, removed criteria point ("The member is 18 years or older") to reduce redundancy, given this criteria point overlaps with the *BRCA1/BRCA2* testing criteria. In Hereditary Prostate Cancer Susceptibility Panels criteria, clarified criteria to better align with existing guidelines and allow for coverage of genetic testing for additional clinical indications. Further clarified and simplified criteria based on client feedback (wording clarification). In Hereditary Neuroendocrine Cancer Susceptibility Panels criteria, clarified and simplified criteria to better align with existing guidelines. Removed minimum gene list; at	06/24	8/19/24	9/19/24

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present there is limited rationale for inclusion. In *BRCA1* and *BRCA2* Sequencing and Deletion/Duplication Analysis criteria, minor expansion to criteria to be consistent with guidelines and allow for coverage of genetic testing for additional clinical indications (added ampullary adenocarcinoma as an indication). Clarified and simplified criterion based on client feedback (wording clarification). In *PALB2* Sequencing and/or Deletion/Duplication Analysis criteria, minor expansion to criteria to be consistent with guidelines and allow for coverage of genetic testing for additional clinical indications (added ampullary adenocarcinoma as an indication). Clarified and simplified criteria based on client feedback (wording clarification). In *MLH1*, *MSH2*, *MSH6*, *PMS2*, or *EPCAM* Targeted Variant Analysis criteria, criteria set name changed (former name: *MLH1*, *MSH2*, *MSH6*, *PMS2*, or *EPCAM* Targeted Mutation Analysis). In *MLH1*, *MSH2*, *MSH6*, *PMS2*, or *EPCAM* Sequencing and/or Deletion/Duplication Analysis criteria, clarified criteria to better align with guidelines. In *RB1* Sequencing and/or Deletion/Duplication Analysis criteria, clarified family history criterion to streamline format. In *RET* Sequencing and/or Deletion/Duplication Analysis criteria, removed "diagnosis of primary C cell hyperplasia" from criteria for testing to align with updated guidelines. In *TP53* Sequencing and/or Deletion/Duplication Analysis criteria, Added "family history of pediatric hypodiploid ALL" as a criterion for testing to align with updated guidelines. Clarified criteria based on client feedback (wording clarification). In *FLCN* Sequencing and/or Deletion/Duplication Analysis criteria, clarified first degree relative criteria to be consistent with this category of testing. In *SMAD4* and/or *BMPR1A* Sequencing and/or Deletion/Duplication Analysis criteria, removed criterion point D (pathogenic or likely pathogenic mutation detected on tumor profiling) as this criterion is covered in another section of this policy. Minor rewording for clarity throughout. Coding, reference-table, background and references updated.			
Semi-annual review. ~~In *CDKN2A* Updated title to reflect V1.2025 version. ATM or CHEK2~~ Sequencing and/or Deletion/Duplication Analysis~~ criteria, now ***COVERED*** to align with~~ : Updated test in Policy Reference Table, updated NCCN version in Background and Rationale and references. VHL Targeted Variant Analysis: Updated the wording in criterion B from: "A VHL pathogenic or likely pathogenic variant was identified by tumor profiling and germline analysis has not yet been performed" to "A pathogenic or likely pathogenic variant in VHL was identified by tumor profiling in the member and germline analysis has not yet been performed"; Updated test name in Policy Reference Table Updated NCCN guidelines~~, which recommend genetic risk assessment for specific~~ for Kidney Cancer with new version number (previously 2.2024; now 3.2024). RET Targeted Variant Analysis: Updated the wording in criterion B from "A RET pathogenic or likely pathogenic variant was identified by tumor profiling and germline analysis has not yet been performed." to "A pathogenic or likely pathogenic variant in RET was identified by tumor profiling in the member and germline analysis has not yet been performed."; Streamlined	~~06/24~~1/25	~~8/19/24~~	~~9/19/24~~

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portions of Background and Rationale section for brevity. CDH1 Sequencing and/or Deletion/Duplication Analysis: Updated the test name in Policy Reference Table Updated NCCN Gastric Cancer guideline version in the Background and Rationale (from 3.2023 to 1.2024); Updated NCCN guideline version in the References (from 3.2023 to 1.2024). SMAD4 and/or BMPR1A Targeted Variant Analysis: Updating the wording in criteria B from "A SMAD4 and/or BMPR1A pathogenic or likely pathogenic variant was identified by tumor profiling and germline analysis has not yet been performed" to "A pathogenic or likely pathogenic variant in SMAD4 and/or BMPR1A was identified by tumor profiling in the member and germline analysis has not yet been performed"; Updated the Background and Rationale to include additional justification for criteria from NCCN Genetic/Familial High-Risk Assessment: Colorectal guidelines (2.2023). MLH1, MSH2, MSH6 PMS2, EPCAM Sequencing and/or Deletion/Duplication Analysis: Corrected the criteria name in the Policy Reference Table (added "and/"); Updated the Background and Rationale with additional supporting information. MAX, SDHA, SDHAF2, SDHB, SDHC, SDHD, or TMEM127 Targeted Variant Analysis: Updated the wording in criteria B from "A MAX, SDHA, SDHAF2, SDHB, SDHC, SDHD, or TMEM127 pathogenic or likely pathogenic variant was identified by tumor profiling and germline analysis has not yet been performed." to "A pathogenic or likely pathogenic variant in MAX, SDHA, SDHAF2, SDHB, SDHC, SDHD, or TMEM127 was identified by tumor profiling in the member and germline analysis has not yet been performed."; Updates to the NCCN guidelines for Kidney Cancer from version 2.2024 to version 3.2024. Hereditary Gastric Cancer Susceptibility Panels: Removed for ease of use for reviewers/clients; "The panel does not include genes without a known association with gastric (stomach) cancer by ClinGen."; Minor expansions to the STK11 Sequencing and/or Deletion/Duplication Analysis criteria: 1. Changed "The member has a close relative with PJS." to "The member has family history of PJS".; 2. Removed "The member has a clinical ~~indications. In~~diagnosis of Peutz-Jeghers syndrome based on the presence of any two of the following".; Minor expansion to the SMAD4 and/or BMPR1A Sequencing and/or Deletion/Duplication Analysis criteria to increase alignment with NCCN guidelines; The criteria previously said "The member has juvenile polyps (any number) and a family history of JPS". The criteria now says "The member has a family history of JPS".; Updated NCCN Gastric Cancer guidelines from 3.2023 to 1.2024. SMAD4 and/or BMPR1A Sequencing and/or Deletion/Duplication Analysis: Minor expansion in criteria to increase alignment with NCCN guidelines; The criteria previously said "The member has juvenile polyps (any number) and a family history of JPS". The criteria now says "The member has a family history of JPS".; Updates to Background and Rationale to include additional information from NCCN guidelines for criteria changes. Hereditary Breast Cancer Susceptibility Panels ~~criteria,~~; In the BRCA1 and BRCA2 Sequencing and/or Deletion/Duplication Analysis criteria, changed "Breast cancer diagnosed at age 50 or younger" to "Breast cancer diagnosed at age 65 or younger", based on updated ASCO guidelines for Germline Testing in Patients With Breast Cancer; Removed this statement for ease of use for reviewers/clients: "The panel does not include genes without a known association with gastric (stomach) cancer by ClinGen."; Minor			

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expansions to the BRCA1 and BRCA2 Sequencing and/or Deletion/Duplication Analysis criteria based on updates to NCCN guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic; 1. Added intermediate-risk prostate cancer with intraductal/cribriform histology to the list of criteria; 2. Changed criteria from "The member's probability of having a BRCA1 or BRCA2 pathogenic variant is greater than 5% based on prior probability models (examples: Tyrer-Curzick, BRCApro, CanRisk)." to "The member's probability of having a BRCA1 or BRCA2 pathogenic variant is greater than 2.5% based on prior probability models (examples: Tyrer-Curzick, BRCApro, CanRisk).", in order to better align with NCCN guidelines; Updated NCCN guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic Cancers from version 2.2024 to 3.2024; Added a new statement to the Background and Rationale from the NCCN guidelines: "These guidelines also recommend consideration of testing for patients with a personal history of breast cancer diagnosed at any age with ≥1 close blood relative with intermediate-risk prostate cancer with intraductal/cribriform histology, and for patients affected or unaffected with breast cancer who otherwise do not meet any of the above criteria but with a 2.5%–5% probability of BRCA1/2 P/LP variant based on prior probability models (eg, Tyrer-Cuzick, BRCAPro, CanRisk). (p, CRIT-3); Added a new statement to the Background and Rationale: "New guidelines published by ASCO/SSO (2024) recommend BRCA1/2 testing to all newly diagnosed patients who are 65 years of age or younger at diagnosis (Type: Formal Consensus; Agreement 87.50%). (p. 590)."; Added new reference: Bedrosian I, Somerfield MR, Achatz MI, et al. Germline Testing in Patients With Breast Cancer: ASCO-Society of Surgical Oncology Guideline. J Clin Oncol. 2024;42(5):584-604. doi:10.1200/JCO.23.02225; Streamlined portions of Background and Rationale section for brevity. PTCH1 and SUFU Sequencing and/or Deletion/Duplication Analysis: Updated GeneReviews copyright dates in Reference list. RET Sequencing and/or Deletion/Duplication Analysis: Updated wording in the Background and Rationale for the NCCN Neuroendocrine and Adrenal Tumors guideline (specifically, changed "indicated" to "recommended"), in order to be more consistent throughout the Concert policies. APC and/or MUTYH Sequencing and/or Deletion/Duplication Analysis: Added the phrase "and/or" to criteria set title for clarity; Updated Background and Rationale for the NCCN Genetic/Familial High-Risk Assessment: Colorectal guidelines to include additional rationale for criteria, and changed wording to be more consistent throughout the Concert policies. PTEN Targeted Variant Analysis: Updated the wording in criteria B from "A pathogenic or likely pathogenic variant in PTEN was identified by tumor profiling and germline analysis has not yet been performed." to "A pathogenic or likely pathogenic variant in PTEN was identified by tumor profiling in the member and germline analysis has not yet been performed." TP53 Sequencing and/or Deletion/Duplication Analysis: Streamlined portions of Background and Rationale section for brevity; Updated NCCN Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic version (from 2.2024 to 3.2024). BRCA1 and BRCA2 Sequencing and/or Deletion/Duplication Analysis: Changed criterion "Breast cancer diagnosed at age 50 or younger' to "Breast cancer diagnosed at age 65 or younger", based on updated ASCO guidelines for Germline Testing in Patients With Breast			

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Cancer; Minor expansions based on addition of criteria on page CRIT-3 of NCCN guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic: 1. Added intermediate-risk prostate cancer with intraductal/cribriform histology to the list of criteria; 2. Changed criteria from "The member's probability of having a BRCA1 or BRCA2 pathogenic variant is greater than 5% based on prior probability models (examples: Tyrer-Curzick, BRCApro, CanRisk)." to "The member's probability of having a BRCA1 or BRCA2 pathogenic variant is greater than 2.5% based on prior probability models (examples: Tyrer-Curzick, BRCApro, CanRisk).", in order to better align with NCCN guidelines; Added new reference: Bedrosian I, Somerfield MR, Achatz MI, et al. Germline Testing in Patients With Breast Cancer: ASCO-Society of Surgical Oncology Guideline. J Clin Oncol. 2024;42(5):584-604. doi:10.1200/JCO.23.02225; Updated NCCN guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic guidelines from version 2.2024 to 3.2024; Added information from NCCN guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic guidelines to Background and Rationale to support our coverage stance on standalone RNA studies: "These guidelines also recommend consideration of RNA studies to further define the meaning of variants of unknown significance; Research studies designed to explore the functional impact of variants, such as variant reclassification programs through clinical labs or registries should be considered. (p. EVAL-A, 9 of 10)."; Added supportive information for inclusion of additional criteria points from NCCN: "NCCN recommends consideration of testing for the following clinical scenarios: 1. An individual with breast cancer who was diagnosed at any age with at least one close blood relative with intermediate-risk prostate cancer with intraductal/ cribriform histology; 2. An individual with a 2.5%–5% probability of BRCA1/2 P/LP variant based on prior probability models (eg, Tyrer-Cuzick, BRCAPro, CanRisk) (CRIT3) in the Background and Rationale, Removed "or for patients with a positive family history of cancer, especially pancreatic/ampullary cancer, regardless of mutation status." the Background and Rational based on NCCN Ampullary Adenocarcinoma section. CDH1 Targeted Variant Analysis: Updated the wording in criterion B from "A CDH1 pathogenic or likely pathogenic variant was identified by tumor profiling and germline analysis has not yet been performed." to "A pathogenic or likely pathogenic variant in CDH1 was identified by tumor profiling in the member and germline analysis has not yet been performed."; Updated NCCN Gastric Cancer guidelines from version 3.2023 to version 1.2024. ATM or CHEK2 Targeted Variant Analysis: Updated the wording in criterion B from "A pathogenic or likely pathogenic variant was identified by tumor profiling in ATM or CHEK2 and germline analysis has not yet been performed" to "A pathogenic or likely pathogenic variant in ATM or CHEK2 was identified by tumor profiling in the member and germline analysis has not yet been performed". Updated NCCN Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic guidelines from version 2.2024 to 3.2024. Streamlined portions of Background and Rationale section for brevity. FH Sequencing and/or Deletion/Duplication Analysis: Updated NCCN guidelines for Kidney Cancer from version 2.2024 to 3.2024; Added the following information from NCCN to the Background and Rationale; "Testing is recommended for an individual			

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whose tumor is HLRCC-associated renal cell carcinoma, FH deficient renal cell carcinoma, or has other histologic features of HLRCC. (p. HERED-RCC-1)". CDKN2A Targeted Variant Analysis: Changed title to replace "familial cutaneous malignant melanoma syndrome" to "familial atypical multiple mole melanoma, aka melanoma-pancreatic cancer syndrome"; Minor expansion - removed ~~*PALB2* testing criteria and *PALB2* gene from the minimum gene list to reduce redundancy, given these criteria overlap with the *BRCA1/BRCA2* testing criteria. In Hereditary Breast Cancer Susceptibility Panels criteria, removed criteria point (“"~~The member is 18 years or older~~”) to reduce redundancy, given this criteria point overlaps with the *BRCA1/BRCA2* testing criteria. In~~" from the criteria, given there are sources that cite dermatology exam in children with Familiam Atypical Multiple Mole Melanoma (FAMMM) syndrome. Updated the wording in criterion B from "A CDKN2A pathogenic or likely pathogenic variant was identified by tumor profiling and germline analysis has not yet been performed" to "A CDKN2A pathogenic or likely pathogenic variant was identified by tumor profiling in the member and germline analysis has not yet been performed"; Updated NCCN Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic guidelines from version 2.2024 to 3.2024; Streamlined portions of Background and Rationale section for brevity. BRCA1/BRCA2 Targeted Variant or Known Familial Variant Analysis: Updated the wording in criterion B from "A BRCA1 or BRCA2 pathogenic or likely pathogenic variant was identified by tumor profiling and germline analysis has not yet been performed" to "A pathogenic or likely pathogenic variant in BRCA1 or BRCA2 was identified by tumor profiling in the member and germline analysis has not yet been performed"; Updated NCCN Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic guidelines from version 2.2024 to 3.2024; Streamlined portions of Background and Rationale section for brevity. PALB2 Sequencing and/or Deletion/Duplication Analysis: Minor expansion based on addition of criteria on pages CRIT-3 and CRIT-3 of NCCN guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic; 1. Added metastatic prostate cancer to the criteria given PARP inhibitors are FDA approved for men with mCRPC and a PALB2 mutation; 2. Changed criteria from "The member’s probability of having a BRCA1 or BRCA2 pathogenic variant is greater than 5% based on prior probability models (examples; Tyrer-Curzick, BRCApro, CanRisk)" to "The member’s probability of having a BRCA1 or BRCA2 pathogenic variant is greater than 2.5% based on prior probability models (examples: Tyrer-Curzick, BRCApro, CanRisk)", in order to better align with NCCN guidelines; Updated NCCN Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic version (from 2.2024 to 3.2024); Removed the following information in the Background and Rationale from the NCCN Ampullary Adenocarcinoma guidelines; "or for patients with a positive family history of cancer, especially pancreatic/ampullary cancer, regardless of mutation status."; Added the following background information - "NCCN recommends consideration of testing for the following clinical scenarios; 1. An individual with breast cancer who was diagnosed at any age with at least one close blood relative with intermediate-risk prostate cancer with intraductal/cribriform histology; 2. An individual with a 2.5%–5% probability of BRCA1/2 P/LP variant based on prior probability models (eg, Tyrer-Cuzick, BRCAPro, CanRisk)". PTEN			

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Sequencing and/or Deletion/Duplication Analysis: Removed from the Background and Rationale; "PTEN pathogenic or likely pathogenic variant detected by tumor genomic testing on any tumor type in the absence of germline analysis."; Updated NCCN Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic guidelines from version 2.2024 to 3.2024. Hereditary GI/Colon Cancer Susceptibility Panels: Removed the following criterion: "The member is 18 years or older", given a lack of rationale for age requirement; Removed this statement for ease of use for reviewers/clients; "The panel does not include genes without a known association with gastric (stomach) cancer by ClinGen."; Removed "The member has a personal history of colorectal cancer under 50 years of age", given this is included in the Lynch syndrome criteria; Streamlined portions of Background and Rationale section for brevity. BAP1 Sequencing and/or Deletion/Duplication Analysis: Updated criteria formatting / structure (see redline for formatting updates OR see Change Summary document); Updated NCCN guidelines for Cutaneous Melanoma from version 3.2023 to 1.2024; Updated NCCN guidelines for Kidney cancer from version 2.2024 to 3.2024; Streamlined portions of Background and Rationale section for brevity. MEN1 Targeted Variant Analysis: Updated the wording in criteria B from "An MEN1 pathogenic or likely pathogenic variant was identified by tumor profiling and germline analysis has not yet been performed" to "A pathogenic or likely pathogenic variant in MEN1 was identified by tumor profiling in the member and germline analysis has not yet been performed". MLH1, MSH2, MSH6, PMS2, and EPCAM Targeted Variant Analysis: Updated the wording in criteria B from "A pathogenic or likely pathogenic variant was identified by tumor profiling in MLH1, MSH2, MSH6, PMS2, or EPCAM and germline analysis has not yet been performed" to “A pathogenic or likely pathogenic variant in MLH1, MSH2, MSH6, PMS2, or EPCAM was identified by tumor profiling in the member and germline analysis has not yet been performed"; Removed from the Background and Rationale; "For individuals without a personal history of CRC and/or endometrial cancer, some data have suggested using a PREMM5 score threshold of 2.5% or greater rather than 5% or greater to select individuals for MMR genetic testing. Based on these data, it is reasonable for testing to be done based on the 2.5% or greater score result and clinical judgment. (p. HRS-5) Guidelines also state that genetic counseling should include considering referral to research studies that aim to define the functional impact of variants of uncertain significance (VUS) such as variant reclassification programs through clinical labs or registries. (p. HRS-B, 1 of 9)"; Added to Background and Rationale; "Some individuals will have variants of uncertain significance (VUS); post test counseling should include considering referral to research studies for the purpose of learning the functional impact of VUSs such as variant reclassification programs through clinical labs or registries. (p. HRS-A, 1 of 2 and HRS-B, 1 of 9)"; Streamlined portions of Background and Rationale section for brevity. STK11 Sequencing and/or Deletion/Duplication Analysis: Minor expansion; Changed "The member has a close relative with PJS." to "The member has family history of PJS"; Removed "The member has a clinical diagnosis of Peutz-Jeghers syndrome based on the presence of any two of the following"; Updated formatting/structure of the criteria for easier readability (see Redline document for changes). RB1 Targeted Variant Analysis: Updated wording in criteria B			

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from "An RB1 pathogenic or likely pathogenic variant was identified by tumor profiling and germline analysis has not yet been performed." to "A pathogenic or likely pathogenic variant in RB1 was identified by tumor profiling in the member and germline analysis has not yet been performed." Hereditary Neuroendocrine Cancer Susceptibility Panels: Added the following criteria based on NCCN guidelines; 1. Gastrinoma; 2. Duodenal or pancreatic neuroendocrine tumor; 3. A first degree relative meeting any of the above criteria but not available for testing; Added additional information to the Background and Rationale: "NCCN also recommends consideration of testing for patients with; Gastrinoma [or] Duodenal/pancreatic neuroendocrine tumor. (p. NE-E, 3 of 8). "TP53 Targeted Variant Analysis: Updated wording in criteria B from "A TP53 pathogenic or likely pathogenic variant was identified by tumor profiling and germline analysis has not yet been performed." to "A pathogenic or likely pathogenic variant in TP53 was identified by tumor profiling in the member and germline analysis has not yet been performed."; Updated NCCN Genetic/Familial High-Risk Assessment; Breast, Ovarian, and Pancreatic guidelines from version 2.2024 to 3.2024; Streamlined portions of Background and Rationale section for brevity. VHL Sequencing and/or Deletion/Duplication Analysis: Removed "clear cell" from renal cell carcinoma based on previous client feedback; Updated NCCN Kidney Cancer guidelines from version 2.2024 to 3.2024. FLCN Targeted Variant Analysis: Updated wording in criteria B from "A pathogenic or likely pathogenic variant in FLCN was identified by tumor profiling and germline analysis has not yet been performed." to "A pathogenic or likely pathogenic variant in FLCN was identified by tumor profiling in the member and germline analysis has not yet been performed."; Updated NCCN guidelines for Kidney Cancer from version 2.2024 to version 3.2024; Streamlined portions of Background and Rationale section for brevity. Pan-Cancer Hereditary Cancer Susceptibility Panels: In the BRCA1 and BRCA2 Sequencing and/or Deletion/Duplication Analysis criteria, changed "Breast cancer diagnosed at age 50 or younger" to "Breast cancer diagnosed at age 65 or younger", based on updated ASCO guidelines for Germline Testing in Patients With Breast Cancer; Removed this statement for ease of use for reviewers/clients; "The panel does not include genes without a known association with cancer by ClinGen"; In the BRCA1 and BRCA2 Sequencing and/or Deletion/Duplication Analysis criteria, minor expansions based on addition of criteria on page CRIT-3 of NCCN guidelines for Genetic/Familial High-Risk Assessment; Breast, Ovarian, and Pancreatic; 1. Added intermediate-risk prostate cancer with intraductal/cribriform histology to the list of criteria; 2. Changed criteria from "The member's probability of having a BRCA1 or BRCA2 pathogenic variant is greater than 5% based on prior probability models (examples: Tyrer-Curzick, BRCApro, CanRisk)." to "The member's probability of having a BRCA1 or BRCA2 pathogenic variant is greater than 2.5% based on prior probability models (examples: Tyrer-Curzick, BRCApro, CanRisk).", in order to better align with NCCN guidelines; Added the GeneticsNow Comprehensive Germline Panel (GoPath Diagnostics - 0474U) to the Policy Reference Table; Updated NCCN Breast, Ovarian, and/or Pancreatic Cancer Genetic Assessment guidelines from version 2.2024 to 3.2024; Added a new test to the policy reference table; GeneticsNow Comprehensive Germline Panel (CPT 0474U); Streamlined portions of Background and Rationale section for brevity. Hereditary Polyposis			

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Susceptibility Panels: Removed this statement for ease of use for reviewers/clients; "The panel does not include genes without a known association with gastric (stomach) cancer by ClinGen."; Removed test "COLARIS AP (Myriad Genetics)" from the Policy Reference Table and added test "Adenomatous Polyposis Panel (Invitae)"; Added to the Background and Rationale; "Germline multigene testing for all polyposis and colorectal cancer genes is recommended (p. POLYP-1)."; CDKN2A Sequencing and/or Deletion/Duplication Analysis: Updated NCCN Cutaneous Melanoma guidelines from 3.2023 to 1.2024; Streamlined portions of Background and Rationale section for brevity, as well as updated page numbers in NCCN guidelines. CDKN2A Sequencing and/or Deletion/Duplication Analysis: Added "with or without pneumothorax" to criteria I.A.2.; Updated NCCN guidelines for Kidney Cancer from 2.2024 to 3.2024. MAX, SDHA, SDHAF2, SDHB, SDHC, SDHD, and TMEM127 Sequencing and/or Deletion/Duplication Analysis: Removed "Pulmonary chondromas" from the criteria, given it is not included in NCCN guidelines for Neuroendocrine and Adrenal Tumors as an associated tumor; Updated to current NCCN guideline version in Background, References; Added NCCN guideline for Neuroendocrine and Adrenal Tumors version 1.2023 as a reference; Added the following information to the Background and Rationale; "NCCN guidelines for Neuroendocrine and Adrenal Tumors (1.2023) recommend genetic testing for hereditary endocrine neoplasia syndromes such as Hereditary Paraganglioma/Pheochromocytoma Syndrome for patients with either a paraganglioma or pheochromocytoma or with a first degree relative with either of these tumors who is unavailable for testing (p. NE-E, 3 of 8); Other manifestations of this syndrome include gastrointestinal stromal tumor and renal cell cancer (p. NE-E, 4 of 8)." APC or MUTYH Targeted Variant Analysis: Updated wording in criteria B from "An APC or MUTYH pathogenic or likely pathogenic variant was identified by tumor profiling and germline analysis has not yet been performed." to "A pathogenic or likely pathogenic variant in APC or MUTYH was identified by tumor profiling in the member and germline analysis has not yet been performed."; Add the following to the Background and Rationale for additional supporting information: "...and recommend targeted APC or MUTYH gene testing when the familial pathogenic variant is known (p. FAP-2, MAP-1). Additionally, it is possible that pathogenic or likely pathogenic variants identified through tumor profiling could be of germline origin. Confirmatory germline testing is indicated for pathogenic/likely pathogenic variants identified via tumor profiling when there is a reasonable clinical suspicion of being of germline origin (p. HRS-B, 5 of 9)". PTCH1 or SUFU Targeted Variant Analysis: Updated wording in criteria B from "A PTCH1 or SUFU pathogenic or likely pathogenic variant in was identified by tumor profiling and germline analysis has not yet been performed." to "A pathogenic or likely pathogenic variant in PTCH1 or SUFU was identified by tumor profiling in the member and germline analysis has not yet been performed."; Updated GeneReviews reference from "Updated 2018 Mar 29" to "Updated 2024 Feb 22". BAP1 Targeted Variant Analysis: Updated wording in criteria B from "A pathogenic or likely pathogenic variant in BAP1 was identified by tumor profiling and germline analysis has not yet been performed." to "A pathogenic or likely pathogenic variant in BAP1 was identified by tumor profiling in the member			

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and germline analysis has not yet been performed."; Updated NCCN guidelines for Kidney Cancer from version 2.2024 to 3.2024; Streamlined portions of Background and Rationale section for brevity. STK11 Targeted Variant Analysis: Updated wording in criteria B from "An STK11 pathogenic or likely pathogenic variant was identified by tumor profiling and germline analysis has not yet been performed" to "A pathogenic or likely pathogenic variant in STK11 was identified by tumor profiling in the member and germline analysis has not yet been performed"; Added the following information from NCCN Genetic/Familial High-Risk Assessment: Colorectal guidelines: "Additionally, it is possible that pathogenic or likely pathogenic variants identified through tumor profiling could be of germline origin. Confirmatory germline testing is indicated for pathogenic/likely pathogenic variants identified via tumor profiling when there is a reasonable clinical suspicion of being of germline origin (p. HRS-B, 5 of 9)". PALB2 Targeted Variant Analysis: Updated wording in criteria B.2 from "A pathogenic or likely pathogenic variant was identified by tumor profiling in PALB2, and germline analysis has not yet been performed." to "A pathogenic or likely pathogenic variant in PALB2 was identified by tumor profiling in the member, and germline analysis has not yet been performed."; Updated NCCN Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic guidelines from version 2.2024 to version 3.2024; Streamlined portions of Background and Rationale section for brevity. FH Targeted Variant Analysis: Minor expansion - removed "The member is 18 years or older" from the criteria, given there are surveillance guidelines for HLRCC that begin under age 18; Removed "FH Sequence Analysis (Familial Mutation/Variant Analysis) (Baylor Genetics)" from the policy reference table and replaced it with "FH Known Familial Mutation Analysis (University Hospitals)"; Updated criteria B.2 from "A FH pathogenic or likely pathogenic variant was identified by tumor profiling and germline analysis has not yet been performed." to "A pathogenic or likely pathogenic variant in FH was identified by tumor profiling in the member and germline analysis has not yet been performed." Hereditary Prostate Cancer Susceptibility Panels ~~criteria, clarified criteria to better align with existing guidelines and allow for coverage of genetic testing for additional clinical indications. Further clarified and simplified criteria based on client feedback (wording clarification). In Hereditary~~: Removed this statement for ease of use for reviewers/clients; "The panel does not include genes without a known association with prostate cancer by ClinGen."; Removed all criteria points from the NCCN Prostate Cancer guidelines to align with guidelines; Added "The member's probability of having a BRCA1 or BRCA2 pathogenic variant is greater than 2.5% based on prior probability models (examples: Tyrer-Cuzick, BRCApro, CanRisk)" to the criteria to avoid unnecessary coverage restrictions based on criteria points that were removed because of the changes in NCCN Prostate Cancer guidelines; Removed NCCN Prostate Cancer guidelines (4.2023) reference and all information from Background and Rationale; Updated NCCN Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic guidelines from version 2.2024 to 3.2024 and added the following: "These guidelines also recommend consideration of testing for patients with intermediate risk prostate cancer with intraductal/cribiform histology. (p. CRIT-6); These guidelines also recommend consideration of RNA studies to further define the meaning of variants of unknown significance; Research studies designed to explore the			

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functional impact of variants, such as variant reclassification programs through clinical labs or registries should be considered. (p. EVAL-A, 9 of 10)."; Changed test name from Prostate Cancer Panel-Primary Panel to Hereditary Prostate Cancer Panel in the policy reference table; Added new test to the Policy Reference Table - ProstateNow Prostate Germline Panel (GoPath Diagnostics) - 0475U; Added the following to the Background and Rationale section: "An individual with a 2.5%–5% probability of BRCA1/2 P/LP variant based on prior probability models (eg, Tyrer-Cuzick, BRCAPro, CanRisk) (CRIT-3)"; Streamlined portions of Background and Rationale section for brevity. BRCA1/BRCA2 Targeted Variant Analysis - Ashkenazi Jewish Founder Variants: Updated NCCN Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic guidelines from version 2.2024 to 3.2024; Updated wording in the Background and Rationale, including changing "states that testing" to "recommends consideration of testing". Hereditary Pancreatic Cancer Susceptibility Panels: Removed this statement for ease of use for reviewers/clients: The panel does not include genes without a known association with pancreatic cancer by ClinGen; Updated NCCN Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic guidelines from version 2.2024 to 3.2024. ~~Neuroendocrine Cancer Susceptibility Panels criteria, clarified and simplified criteria to better align with existing guidelines. Removed minimum gene list; at present there is limited rationale for inclusion. In *BRCA1* and *BRCA2* Sequencing and Deletion/Duplication Analysis criteria, minor expansion to criteria to be consistent with guidelines and allow for coverage of genetic testing for additional clinical indications (added ampullary adenocarcinoma as an indication). Clarified and simplified criterion based on client feedback (wording clarification). In *PALB2* Sequencing and/or Deletion/Duplication Analysis criteria, minor expansion to criteria to be consistent with guidelines and allow for coverage of genetic testing for additional clinical indications (added ampullary adenocarcinoma as an indication). Clarified and simplified criteria based on client feedback (wording clarification). In *MLH1*, *MSH2*, *MSH6*, *PMS2*, or *EPCAM* Targeted Variant Analysis criteria, criteria set name changed (former name: *MLH1*, *MSH2*, *MSH6*, *PMS2*, or *EPCAM* Targeted Mutation Analysis). In *MLH1*, *MSH2*, *MSH6*, *PMS2*, or *EPCAM* Sequencing and/or Deletion/Duplication Analysis criteria, clarified criteria to better align with guidelines. In *RB1* Sequencing and/or Deletion/Duplication Analysis criteria, clarified family history criterion to streamline format. In *RET* Sequencing and/or Deletion/Duplication Analysis criteria, removed "diagnosis of primary C cell hyperplasia" from criteria for testing to align with updated guidelines. In *TP53* Sequencing and/or Deletion/Duplication Analysis criteria, Added "family history of pediatric hypodiploid ALL" as a criterion for testing to align with updated guidelines. Clarified criteria based on client feedback (wording clarification). In *FLCN* Sequencing and/or Deletion/Duplication Analysis criteria, clarified first degree relative criteria to be consistent with this category of testing. In *SMAD4* and/or *BMPR1A* Sequencing~~			

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~~and/or Deletion/Duplication Analysis criteria, removed criterion point D (pathogenic or likely pathogenic mutation detected on tumor profiling) as this criterion is covered in another section of this policy. Minor rewording for clarity throughout. Coding, reference table, background and references updated.~~			

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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.

This clinical policy is the property of LHCC. Unauthorized copying, use, and distribution of this clinical policy or any information contained herein are strictly prohibited. Providers,

member/enrollees, and their representatives are bound to the terms and conditions expressed herein through the terms of their contracts. Where no such contract exists, providers, member/enrollees and their representatives agree to be bound by such terms and conditions by providing services to member/enrollees and/or submitting claims for payment for such services.

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