

CONCERT GENETIC TESTING: HEREDITARY CANCER SUSCEPTIBILITY

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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 more 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 many genes associated with hereditary cancer susceptibility at the same time).

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

Below is a list of higher volume tests and the associated laboratories for each coverage criteria section. This list is not all inclusive.

Coding Implications

This clinical policy references Current Procedural Terminology (CPT®). CPT® is a registered trademark of the American Medical Association. All CPT codes and descriptions are copyrighted 2022, American Medical Association. All rights reserved. CPT codes and CPT descriptions are from the current manuals and those included herein are not intended to be all-inclusive and are included for informational purposes only. Codes referenced in this clinical policy are for informational purposes only 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.

Coverage Criteria Sections	Example Tests (Labs)	Common CPT Codes	Common ICD10 Codes	Ref
Pan-Cancer Hereditary Cancer Susceptibility Panels	MyRisk (Myriad Genetics)	81432*, 81433*	C15 through 26, C50 through 58 Z17, Z80, Z85.0 through Z85.9	1, 3, 13
	Common Hereditary Cancers Panel (Invitae)			
	Breast and Gyn Cancers Panel (Invitae)			
	CancerNext (Ambry Genetics)			
	Tempus xG Hereditary Cancer Panel			
	+RNAinsight for CancerNext (Ambry Genetics)	0134U*		

Hereditary Breast Cancer Susceptibility Panels	Breast Cancer Panel (LabCorp) Breast Cancer Panel (Invitae) Breast Cancer STAT NGS Panel (Sequencing & Deletion/Duplication) (Invitae) Breast Cancer - Comprehensive Risk Panel (PreventionGenetics) Breast Cancer High-Risk Panel (GeneDx)	81162, 81163, 81164, 81165, 81166, 81167, 81216, 81432*, 81433*	C50, Z80.3, Z83, Z84, Z85, Z86	1
	BRCPlus (Ambry Genetics)	0129U*		
Hereditary GI/Colon Cancer Panel Tests	Colorectal Cancer Panel-Primary Genes (Invitae)	81435*, 81436*	C15 through 26, Z80, Z83, Z84, Z85, Z86	2
	ColoNext (Ambry Genetics)	0101U*		
	+RNAinsight for ColoNext (Ambry Genetics)	0130U*		
Hereditary Gastric Cancer Panels	Invitae Gastric Cancer Panel (Invitae)	81292, 81294, 81295, 81297, 81298, 81300, 81317, 81319, 81403*, 81406*, 81479	C16, Z80, Z85, Z86	8
	Gastric Cancer Panel (PreventionGenetics)			
Hereditary Pancreatic Cancer Susceptibility Panels	Pancreatic Cancer Panel-Primary Panel (Invitae)	81162, 81163, 81292, 81295, 81298, 81479	C25, Z80, Z84, Z85, Z86	1
	PancNext (Ambry Genetics)			
Hereditary Polyposis Panels	Hereditary Polyposis Panel (PreventionGenetics)	81201, 81203, 81406*, 81479	D12, K63.5, Z80, Z84, Z85, Z86	2
	COLARIS AP (Myriad Genetics)			
Hereditary Prostate Cancer Susceptibility Panels	Prostate Cancer Panel-Primary Panel (Invitae)	81162, 81292, 81295, 81351, 81479	C61, Z80, Z84, Z85, Z86	1
	ProstateNext (Ambry Genetics)			
	+RNAinsight for ProstateNext (Ambry Genetics)	0133U*		
Hereditary Neuroendocrine Cancer Susceptibility Panels	Hereditary Paraganglioma-Pheochromocytoma Panel (Invitae)	81437*, 81438*	C74, C75, C7A Z80, Z84, Z85, Z86	7
	PGLNext (Ambry Genetics)			
BRCA1 and BRCA2 Gene Testing				

<u>BRCA1 or BRCA2 Targeted Variant or Known Familial Variant Analysis</u>	BRCA1 or BRCA2 Targeted Variant-Single Test (GeneDx)	81215, 81217	C50, C56, D05, Z17, Z80, Z83, Z84, Z85, Z86	1, 4, 5, 12
<u>BRCA1 and/or BRCA2 Targeted Variant Analysis - Ashkenazi Jewish Founder Variants</u>	BRCA1/2 Ashkenazi Jewish 3-Site Mutation Panel (Ambry Genetics)	81212		
	MultiSite 3 BRCA Analysis (Myriad Genetics)			
<u>BRCA1 and BRCA2 Sequencing and/or Deletion/Duplication Analysis</u>	Hereditary Breast and Ovarian Cancer Panel (Invitae)	81162, 81163, 81164, 81165,		
	BRCA1/2 Seq and Del/Dup (Ambry Genetics)	81166, 81167, 81216		
	+RNAinsight for BRCA1/2 (Ambry Genetics)	0138U*		
<u>PALB2 Gene Testing</u>				
<u>PALB2 Targeted Variant Analysis</u>	PALB2 Targeted Mutation Tests PALB2 specific site analysis	81308	C15 through 26, Z80, Z84, Z85, Z86	1
<u>PALB2 Sequencing and/or Deletion/Duplication Analysis</u>	PALB2 Sequencing PALB2 Deletion/Duplication	81307, 81479		
	PALB2 with +RNA insight (Ambry Genetics)	0137*		
<u>ATM and/or CHEK2 Gene Testing</u>				
<u>ATM or CHEK2 Targeted Variant Analysis</u>	Targeted Variants-ATM (PreventionGenetics)	81403*	C50, D05, Z80, Z84, Z85, Z86	1
	Targeted Variants-CHEK2 (PreventionGenetics)			
<u>ATM or CHEK2 Sequencing and/or Deletion/Duplication Analysis</u>	Ataxia-Telangiectasia Test (Invitae)	81408*, 81479		
	Hereditary Breast Cancer via the CHEK2 Gene (PreventionGenetics)	81479		
	+RNAinsight for ATM (Ambry Genetics)	0136U*		
<u>Lynch Syndrome / Hereditary Nonpolyposis Colorectal Cancer (HNPCC)</u>				
<u>MLH1, MSH2, MSH6, PMS2, or EPCAM Targeted Mutation Analysis</u>	MSH6 Targeted Variant Analysis PMS2 Targeted Mutation Tests EPCAM Targeted Mutation Analysis	81299, 81318, 81403*	C15 through 22, C24 through 6, C26 C53 through 57	2
	Hereditary Nonpolyposis Colorectal Cancer (HNPCC): MLH1 (Known Mutation) (Labcorp)	81293	Z80, Z84, Z85, Z86	

	Hereditary Nonpolyposis Colorectal Cancer (HNPCC): MSH2 (Known Mutation) (Labcorp)	81296		
MLH1, MSH2, MSH6, PMS2, or EPCAM Sequencing and/or Deletion/Duplication Analysis	HNPCC Concurrent (Ambry Genetics)	81292, 81294, 81295, 81297,		
	Lynch Syndrome Panel (Invitae)	81298, 81300, 81317, 81319, 81403*		
	Genomic Unity Lynch Syndrome Analysis (Variantyx Inc)	0238U*		
<u>BAP1-Tumor Predisposition Syndrome</u>				
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	6, 9, 14, 15, 16
BAP1 Sequencing and/or Deletion/Duplication Analysis	BAP1 Full Gene Sequencing and Deletion/Duplication (Invitae)	81479		
<u>Birt-Hogg-Dube syndrome (BHDS)</u>				
FLCN Targeted Variant Analysis	Targeted Variant: FLCN (PreventionGenetics)	81479	C65, D14.3, D23.9, Z84, Z85, Z86	9, 12
FLCN Sequencing and/or Deletion/Duplication Analysis	Birt-Hogg-Dube Syndrome Test (Invitae)	81479		
<u>Cowden Syndrome (CS)/PTEN Hamartoma Tumor Syndrome (PHTS)</u>				
PTEN Targeted Variant Analysis	Targeted Variant: PTEN (PreventionGenetics)	81322*	C15 through 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*		
	Genomic Unity® PTEN Analysis (Variantyx Inc)	0235U*		
<u>Familial Adenomatous Polyposis (FAP)/Attenuated FAP (AFAP)</u>				
APC Targeted Variant Analysis	Targeted Variant: APC (PreventionGenetics)	81202	C15 through 21, D12, Z80, Z84, Z85, Z86	2
APC Sequencing and/or Deletion/Duplication Analysis	APC Seq and Del/Dup (Ambry Genetics)	81201, 81203		
	Familial Adenomatous Polyposis Test (Invitae)			

<u>Familial Atypical Multiple Mole Melanoma Syndrome (FAMMM)</u>				
<u>CDKN2A Targeted Variant Analysis</u>	Targeted Variant CDKN2A (PreventionGenetics)	81403*	C43, Z12.83, Z80, Z84, Z85, Z86	6, 21
<u>CDKN2A Sequencing and/or Deletion/Duplication Analysis</u>	CDKN2A Full Gene Sequencing and Deletion/Duplication (Invitae)	81404*, 81479		
<u>Hereditary Diffuse Gastric Cancer</u> (aka, Signet Ring Cell Gastric Cancer)				
<u>CDHI Targeted Variant Analysis</u>	Targeted Variant: CDH1 (PreventionGenetics)	81403*	C16, C50, Q35, Q36, Z80, Z84, Z85, Z86	1, 8
<u>CDHI Sequencing and/or Deletion/Duplication Analysis</u>	Hereditary Diffuse Gastric Cancer Syndrome Test (Invitae)	81406*, 81479		
<u>Juvenile Polyposis Syndrome (JPS)</u>				
<u>SMAD4 and/or BMPR1A Targeted Variant Analysis</u>	Targeted Variant: SMAD4 (PreventionGenetics)	81403*	C15 through C26, D12, Z80, Z84, Z85, Z86	2
	Targeted Variant: BMPR1A (PreventionGenetics)	81403*		
<u>SMAD4 and/or BMPR1A Sequencing and/or Deletion/Duplication Analysis</u>	Juvenile Polyposis Syndrome Panel (Invitae)	81405*, 81406*, 81479		
	BMPR1A, SMAD4 Gene Sequencing and Del/Dup (GeneDx)			
<u>Hereditary Leiomyomatosis and Renal Cell Cancer (HLRCC)</u>				
<u>FH Targeted Variant Analysis</u>	FH Sequence Analysis (Familial Mutation/Variant Analysis) (Baylor Miraca Genetics Laboratories)	81403*	C44, C55, C64, D23, D25, Z84, Z85, Z86	9, 20
<u>FH Sequencing and/or Deletion/Duplication Analysis</u>	FH Sequencing Tests FH Deletion/Duplication Tests Hereditary Leiomyomatosis and Renal Cell Carcinoma (Ambry Genetics)	81405*, 81479		
<u>Li-Fraumeni Syndrome (LFS)</u>				
<u>TP53 Targeted Variant Analysis</u>	Targeted Variant: TP53 (PreventionGenetics)	81352	C30 through 41, C15 through 26, C45, C47 through 49, C50, C71, C95.9, Z80, Z84, Z85, Z86	1
<u>TP53 Sequencing and/or Deletion/Duplication Analysis</u>	Li-Fraumeni Syndrome Test (Invitae)	81351, 81479		
	Li-Fraumeni Syndrome, TP53 Sequencing and Deletion/Duplication (Quest)			

	Diagnostics)			
<u>Multiple Endocrine Neoplasia - Type 1 (MEN1)</u>				
<u>MEN1 Targeted Variant Analysis</u>	Targeted Variant: MEN1 (PreventionGenetics)	81403*	C25, C75.0, D35.2, E31.2,	7
<u>MEN1 Sequencing and/or Deletion/Duplication Analysis</u>	MEN1 Gene Sequencing and Del/Dup (GeneDx) Multiple Endocrine Neoplasia Type 1 Test (Invitae)	81404*, 81405*	Z80, Z84, Z85, Z86	
<u>Multiple Endocrine Neoplasia Type 2 (MEN2)</u>				
<u>RET Targeted Variant Analysis</u>	Targeted Variant: RET (PreventionGenetics)	81404*, 81405*	C73 through 75, C7A, D3A,	7, 19
<u>RET Sequencing and/or Deletion/Duplication Analysis</u>	RET Full Gene Sequencing and Deletion/Duplication (Invitae)	81406*, 81479, S3840*	Z80, Z84, Z85, Z86	
<u>MUTYH-associated Polyposis (MAP)</u>				
<u>MUTYH Targeted Variant Analysis</u>	Targeted Variant: MUTYH (PreventionGenetics)	81403*, 81401*	C15 through 21, D12.6, Z80,	2
<u>MUTYH Sequencing and/or Deletion/Duplication Analysis</u>	MUTYH Full Gene Sequencing and Deletion/Duplication (Invitae)	81406*, 81479	Z84, Z85, Z86	
<u>Nevoid Basal Cell Carcinoma Syndrome (NBCCS) (aka Gorlin syndrome)</u>				
<u>PTCH1 and/or SUFU Targeted Variant Analysis</u>	Targeted Variant: PTCH1 or SUFU	81403*	C44, C71.6, G93, M27.4, Z84, Z85, Z86	19
<u>PTCH1 and SUFU Sequencing and/or Deletion/Duplication Analysis</u>	Basal Cell Nevus Syndrome Panel (Invitae)	81479		
<u>Hereditary Paraganglioma/Pheochromocytoma Syndrome (PGL/PCC)</u>				
<u>MAX, SDHA, SDHAF2, SDHB, SDHC, SDHD, or TMEM127 Targeted Variant Analysis</u>	Targeted Variants: SDHB, SDHD, SDHC (PreventionGenetics)	81403*	C7A, C74.1, D35.00, D44.7, Z84, Z85, Z86	9, 18
	Targeted Variants: MAX, SDHAF2, TMEM127 (PreventionGenetics)	81479		
<u>MAX, SDHA, SDHAF2, SDHB, SDHC, SDHD, and/or TMEM127 Sequencing and/or</u>	SHDB Full Gene Sequencing and Deletion/Duplication (Invitae)	81405*, 81479		
	SDHA Full Gene Sequencing and Deletion/Duplication (Invitae)	81406*, 81479		

Deletion/Duplication Analysis	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 (PreventionGenetics)	81403*	C50, Q85.8, Z80, Z84, Z85, Z86	2
STK11 Sequencing and/or Deletion/Duplication Analysis	STK11 Gene Sequencing & Del/Dup (GeneDx)	81404*, 81405*		
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	10
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 Mutation/Variant Analysis) (Baylor Miraca Genetics Laboratories)	81403*	C64, C7A, D3A, D35.00, K86.2, N28, N50.3, Q85.8, Z80, Z84, Z85, Z86	9
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 coverage criteria for genetic testing for hereditary cancer susceptibility. Please refer to:

- ***Genetic Testing: Multisystem Inherited Disorders, Intellectual Disability, and Developmental Delay*** for coverage criteria related to diagnostic testing for Fanconi anemia.
- ***Oncology: Algorithmic Testing*** for coverage 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 coverage criteria related to somatic tumor testing, including Microsatellite Instability for colon cancer, and blood cancer testing
- ***Oncology: Cancer Screening*** for coverage criteria related to tests that screen for the presence of cancer.
- ***Oncology: Circulating Tumor DNA and Circulating Tumor Cells (Liquid Biopsy)*** for coverage criteria related to the testing of tumor DNA circulating in an individual's blood stream.
- ***Genetic Testing: General Approach to Genetic Testing*** for coverage criteria related to hereditary cancer susceptibility that is not specifically discussed in this or other non-general policies.

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.).

Genetic testing using a pan-cancer hereditary cancer susceptibility panel (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**
 - D. 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 (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, 81432*, 81433*, 0102U*, 0129U*) is considered **medically necessary** when:
 - A. The member/enrollee is 18 years or older, **AND**
 1. The member/enrollee has a personal history of breast cancer **AND** any of the following:
 - a) Breast cancer diagnosed at age 45 years or younger, **OR**
 - b) Male breast cancer, **OR**
 - c) Ashkenazi Jewish ancestry, **OR**
 - d) Triple-negative breast cancer, **OR**
 - e) Multiple primary breast cancers (diagnosed synchronously or metachronously), **OR**

- f) Diagnosed at age ≤ 60 years with triple negative (ER–, PR–, HER2) breast cancer; **OR**
 - g) Epithelial ovarian cancer (including fallopian tube cancer or peritoneal cancer) at any age; **OR**
 - h) Exocrine pancreatic cancer at any age; **OR**
 - i) Metastatic or intraductal prostate cancer at any age; **OR**
 - j) A mutation identified on tumor genomic testing that has clinical implications if also identified in the germline; **OR**
 - k) At least one [close relative](#) with any of the following:
 - (1) Breast cancer diagnosed at age 45 years or younger, **OR**
 - (2) Male breast cancer, **OR**
 - (3) Ovarian cancer, **OR**
 - (4) Pancreatic cancer, **OR**
 - (5) Metastatic, or [high- or very-high-risk group prostate cancer](#), **OR**
 - l) Three or more total diagnoses of breast cancer in the member/enrollee and/or [close relatives](#), **OR**
 - m) Two or more [close relatives](#) with either breast or prostate cancer (of any grade), **OR**
2. The member/enrollee does not meet the above criteria, but has a [first- or second-degree relative](#) meeting any of the above criteria, **OR**
 3. The member/enrollee has breast cancer and is being considered for systemic treatment decisions using PARP inhibitors for metastatic breast cancer, **OR**
 4. The member/enrollee has high-risk, HER2-negative breast cancer and is being considered for adjuvant treatment with olaparib, **OR**
 5. The member/enrollee has a probability of greater than 5% of a *BRCA1* or *BRCA2* pathogenic variant based on prior probability models (examples: Tyrer-Curzick, BRC Apro, CanRisk), **AND**
- B. The panel includes, at a minimum, sequencing of the following genes: *BRCA1*, *BRCA2*, **AND**

- C. 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 all of the above criteria, **AND**
 - B. The member/enrollee requires a rapid turn-around-time for decision making related to surgical interventions and treatment decisions.
- III. Genetic testing using a hereditary breast cancer susceptibility panel (81162, 81163, 81164, 81165, 81166, 81167, 81216, 81432*, 81433*, 0102U, 0129U*) is considered **investigational** for all other indications.
- IV. Hereditary breast cancer susceptibility panel targeted mRNA sequencing analysis for the interpretation of variants of unknown significance (0131U), 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 GI/COLON CANCER PANEL TESTS

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*, 0130U*) 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 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**
 - d) The member/enrollee has a personal history of colorectal cancer under 50 years of age, **OR**

- e) The member's/enrollee's tumor has deficient mismatch repair (dMMR), indicated by any of the following:
 - (1) Microsatellite instability-high (MSI-H) by polymerase chain reaction (PCR) or next generation sequencing (NGS), **OR**
 - (2) Abnormal/deficient MMR protein expression (dMMR) on immunochemistry (IHC) without concurrent *MLH1* promoter hypermethylation or *BRAF* V600E mutation, **OR**
- f) 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: *APC*, *MUTYH*, *MLH1*, *MSH2*, *MSH6*, *PMS2*, *EPCAM*, *BMPRIA*, *SMAD4*, *PTEN*, *STK11*, **AND**
- D. 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*, 0130U*) 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*), 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 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 (81292, 81294, 81295, 81297, 81298, 81300, 81317, 81319, 81403*, 81406*, 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. [Familial Adenomatous Polyposis](#), **AND**
 - C. The panel includes, at a minimum, sequencing of the following genes: *APC*, *BMPRIA*, *CDH1*, *EPCAM*, *MLH1*, *MSH2*, *MSH6*, *PMS2*, *SMAD4*, *STK11*, **AND**
 - D. 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 (81292, 81294, 81295, 81297, 81298, 81300, 81317, 81319, 81403*, 81406*, 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, 81292, 81295, 81298, 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**
 - D. 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, 81292, 81295, 81298, 81479) is considered **investigational** for all other indications.

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HEREDITARY POLYPOSIS 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 at least one of the following:
 - 1. Personal history of > 20 cumulative adenomas; **OR**
 - 2. Known deleterious APC mutation in first-degree family member.
 - B. The panel includes, at a minimum, sequencing of the following genes: *APC* and *MUTYH*, **AND**
 - C. 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, 0133U*) 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: *BRCA1*, *BRCA2*, **AND**
- D. 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, 0133U*) 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 meets criteria for sequencing and/or deletion/duplication analysis for at least one of the following (see specific coverage criteria sections below):
 - 1. [Von-Hippel Lindau syndrome \(VHL\)](#), **OR**
 - 2. [Hereditary Paraganglioma-Pheochromocytoma syndrome \(PGL/PCC\)](#), **OR**
 - 3. [Multiple Endocrine Neoplasia Type 1 \(MEN1\)](#), **OR**
 - 4. [Multiple Endocrine Neoplasia Type 2 \(MEN2\)](#), **AND**
 - B. The panel includes, at a minimum, sequencing of the following genes: *MAX*, *SDHB*, *SDHC*, *SDHD*, *TMEM127*, *SDHAF2*, *SDHA*, *VHL*, *MEN1*, *RET*, **AND**
 - C. 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 was detected by tumor profiling 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, 0138U*) 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**
 1. The member/enrollee has a personal history of any of the following:

- a) Male breast cancer, **OR**
 - b) Triple-negative breast cancer, **OR**
 - c) Epithelial ovarian cancer (including fallopian tube cancer or peritoneal cancer), **OR**
 - d) Pancreatic cancer, **OR**
 - e) Metastatic prostate cancer, **OR**
 - f) [High- or very-high-risk group prostate cancer](#), **OR**
2. The member/enrollee has a personal history of breast cancer **AND** any of the following:
- a) Female breast cancer diagnosed at age 45 years or younger, **OR**
 - b) Ashkenazi Jewish ancestry, **OR**
 - c) Multiple primary breast cancers (diagnosed synchronously or metachronously), **OR**
 - d) One or more [close relatives](#) with any of the following:
 - (1) Female breast cancer diagnosed at age 45 years or younger, **OR**
 - (2) Male breast cancer, **OR**
 - (3) Ovarian cancer, **OR**
 - (4) Pancreatic cancer, **OR**
 - (5) Metastatic, or [high- or very-high-risk group prostate cancer](#), **OR**
 - e) Three or more total diagnoses of breast cancer in the member/enrollee and/or [close relatives](#), **OR**
 - f) Two or more [close relatives](#) with either breast or prostate cancer (of any grade), **OR**
3. The member/enrollee does not meet any of the above criteria, but 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 has a probability of greater than 5% of a *BRCA1* or *BRCA2* pathogenic variant based on prior probability models (examples: Tyrer-Curzick, BRC Apro, CanRisk).
- II. *BRCA1* and *BRCA2* (81162, 81163, 81164, 81165, 81166, 81167, 81216, 0138U*) 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 was detected by tumor profiling in *PALB2* 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, 0137*) 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**

1. The member/enrollee has a personal history of breast cancer **AND** any of the following:
 - a) Female breast cancer diagnosed at age 50 years or younger, **OR**
 - b) Male breast cancer, **OR**
 - c) Ashkenazi Jewish ancestry, **OR**
 - d) Triple-negative breast cancer, **OR**
 - e) Multiple primary breast cancers (diagnosed synchronously or metachronously), **OR**
 - f) Epithelial ovarian cancer (including fallopian tube cancer or peritoneal cancer), **OR**
 - g) Pancreatic cancer, **OR**
 - h) At least one close relative with any of the following:
 - (1) Female breast cancer diagnosed at age 50 years or younger, **OR**
 - (2) Male breast cancer, **OR**
 - (3) Ovarian cancer, **OR**
 - (4) Pancreatic cancer, **OR**
 - i) Three or more total diagnoses of breast cancer in the member/enrollee and/or close relatives, **OR**
2. The member/enrollee does not meet the above criteria, but has a first- or second-degree relative meeting any of the above criteria, **OR**
3. The member/enrollee has breast cancer and is being considered for systemic treatment decisions using PARP inhibitors for metastatic breast cancer, **OR**
4. The member/enrollee has high-risk, HER2-negative breast cancer and is being considered for adjuvant treatment with olaparib, **OR**
5. The member/enrollee has a probability of greater than 5% of a *BRCA1* or *BRCA2* pathogenic variant based on prior probability models (examples: Tyrer-Curzick, BRCAPro, CanRisk).

- II. *PALB2* (81307, 0137*) 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 (0137*), 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* (81403*) or *CHEK2* (81403*) 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 was detected by tumor profiling in *ATM* or *CHEK2* and germline analysis has not yet been performed.
- II. *ATM* (81403*) or *CHEK2* (81403*) 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* (81403*) 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 was detected by tumor profiling in *MLH1*, *MSH2*, *MSH6*, *PMS2*, or *EPCAM* and germline analysis has not yet been performed.
- II. *MLH1* (81293), *MSH2* (81296), *MSH6* (81299), *PMS2* (81318), or *EPCAM* (81403*) targeted variant analysis for Lynch syndrome/HNPCC is considered **investigational** for all other indications.

MLH1, MSH2, MSH6, PMS2, 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 (i.e., colorectal, endometrial, gastric, ovarian, pancreatic, ureter and renal pelvic, brain (usually glioblastoma), biliary tract, small intestinal, sebaceous adenoma, sebaceous carcinoma, or keratoacanthoma) **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 colorectal cancer or endometrial cancer **AND** any of the following:
 1. Diagnosed before age 50, **OR**
 2. Diagnosed at any age with an additional Lynch syndrome-related cancer (i.e., colorectal, endometrial, gastric, ovarian, pancreatic, ureter and renal pelvic, brain (usually glioblastoma), biliary tract, small intestinal, sebaceous adenoma, sebaceous carcinoma, or keratoacanthoma), **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 (i.e., colorectal, endometrial, gastric, ovarian, pancreatic, ureter and renal

pelvic, brain (usually glioblastoma), biliary tract, small intestinal, sebaceous adenoma, sebaceous carcinoma, or keratoacanthoma), **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 (i.e., colorectal, endometrial, gastric, ovarian, pancreatic, ureter and renal pelvic, brain (usually glioblastoma), biliary tract, small intestinal, sebaceous adenoma, sebaceous carcinoma, or keratoacanthoma), **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 (i.e., colorectal, endometrial, gastric, ovarian, pancreatic, ureter and renal pelvic, brain (usually glioblastoma), biliary tract, small intestinal, sebaceous adenoma, sebaceous carcinoma, or keratoacanthoma), **OR**
3. Two or more [first- or second-degree relatives](#) diagnosed with a Lynch syndrome-related cancer (i.e., colorectal, endometrial, gastric, ovarian, pancreatic, ureter and renal pelvic, brain (usually glioblastoma), biliary tract, small intestinal, sebaceous adenoma, sebaceous carcinoma, or keratoacanthoma), one of whom was diagnosed before age 50, **OR**
4. Three or more [first- or second-degree relatives](#) diagnosed with a Lynch syndrome-related cancer (i.e., colorectal, endometrial, gastric, ovarian, pancreatic, ureter and renal pelvic, brain (usually glioblastoma), biliary tract, small intestinal, sebaceous adenoma, sebaceous carcinoma, or keratoacanthoma), **OR**

D. The member/enrollee has a 5% or greater risk of Lynch syndrome 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.

***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 on tumor profiling 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 or more of the above listed tumors/cancer, **AND**
 - a) A [first or second-degree relative](#) with any of the above listed tumors/cancers.

- 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 on tumor profiling 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:
 - 1. 5 or more fibrofolliculomas/trichodiscomas with at least one confirmed histologically, **OR**
 - 2. Two or more of the following:
 - a) Multiple lung cysts with no apparent cause, **OR**
 - b) Renal cancer diagnosed before 50 years of age, **OR**
 - c) Multifocal or bilateral renal cancer, **OR**
 - d) Renal cancer of mixed chromophobe and oncocytic histology, **OR**
 - e) A [first-degree relative](#) with BHDS.
- 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 on tumor profiling 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*, 0235U*) 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. Meets clinical criteria for CS/PHTS:
 - a) Three or more major criteria (see below), with at least one being macrocephaly, Lhermitte-Duclos disease, or gastrointestinal hamartomas, **OR**
 - b) Two major and three minor criteria (see below)
 3. Adult Lhermitte-Duclos disease (LDD) (defined as the presence of a cerebellar dysplastic gangliocytoma), **OR**
 4. Autism-spectrum disorder and macrocephaly, **OR**
 5. At least 2 biopsy-proven trichilemmomas, **OR**
 6. Macrocephaly and at least one other major criteria (see below), **OR**
 7. Three major criteria (see below) without macrocephaly, **OR**
 8. One major and at least three minor criteria (see below), **OR**

9. Four or more minor criteria (see below), **OR**
- B. 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 meets one major or two minor criteria (see below), **OR**
- C. *PTEN* pathogenic or likely pathogenic variant reported on tumor/somatic genetic testing

Major Criteria:	Minor Criteria:
<ul style="list-style-type: none"> ● Breast Cancer ● Endometrial Cancer ● Thyroid Cancer (follicular) ● Multiple gastrointestinal hamartomas or ganglioneuromas ● Macrocephaly (greater than or equal to 97 percentile) ● Macular pigmentation of the glans penis ● Mucocutaneous lesions: <ul style="list-style-type: none"> ○ One biopsy-proven trichilemmoma ○ Multiple palmoplantar keratoses ○ Multifocal or extensive oral mucosal papillomatosis ○ Multiple cutaneous facial papules (often verrucous) 	<ul style="list-style-type: none"> ● Autism Spectrum Disorder ● Colon Cancer ● Esophageal glycogenic acanthosis (3 or more) ● Lipomas ● Intellectual disability (ie, IQ less than or equal to 75) ● Thyroid cancer (papillary or follicular variant of papillary thyroid cancer) ● Thyroid structural lesions (such as adenoma, multinodular goiter) ● Renal cell carcinoma ● Single GI hamartoma or ganglioneuroma ● Testicular lipomatosis ● Vascular anomalies (including multiple intracranial developmental venous anomalies)

- II. *PTEN* sequencing and/or deletion/duplication analysis (81321*, 81323*, 0235U*) for Cowden syndrome (CS)/*PTEN* hamartoma tumor syndrome (PHTS) is considered **investigational** for all other indications.

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FAMILIAL ADENOMATOUS POLYPOSIS (FAP)/ATTENUATED FAP (AFAP)

APC Targeted Variant Analysis

- I. *APC* targeted variant analysis (81202) for familial adenomatous polyposis (FAP) is considered **medically necessary** when:
- A. The member/enrollee has a family history of a known pathogenic or likely pathogenic variant in *APC*, **OR**
- B. An *APC* pathogenic or likely pathogenic variant was detected by tumor profiling and germline analysis has not yet been performed.

- II. *APC* targeted variant analysis (81202) for familial adenomatous polyposis (FAP) is considered **investigational** for all other indications.

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

- I. *APC* sequencing and/or deletion/duplication analysis (81201, 81203) for familial adenomatous polyposis (FAP) is considered **medically necessary** when:
 - A. The member/enrollee has a history of any of the following:
 - 1. 20 or more cumulative adenomas, **OR**
 - 2. Multifocal/bilateral congenital hypertrophy of the retinal pigment epithelium (CHRPE).
- II. *APC* sequencing and/or deletion/duplication analysis (81201, 81203) for familial adenomatous polyposis (FAP) is considered **investigational** for all other indications.

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FAMILIAL ATYPICAL MULTIPLE MOLE MELANOMA (FAMMM) SYNDROME

***CDKN2A* Targeted Variant Analysis**

- I. *CDKN2A* targeted variant analysis (81403*) 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:
 - 1. The member/enrollee has a [close relative](#) with a known pathogenic or likely pathogenic variant in *CDKN2A*, **OR**
 - 2. A *CDKN2A* pathogenic or likely pathogenic variant was detected by tumor profiling and germline analysis has not yet been performed.
- II. *CDKN2A* targeted variant analysis (81403*) for familial cutaneous malignant melanoma 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, as a standalone test, is considered **investigational**.

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

***CDHI* Targeted Variant Analysis**

- I. *CDHI* targeted variant analysis (81403*) 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 with a known pathogenic or likely pathogenic variant in *CDHI*, **OR**
 2. A *CDHI* pathogenic or likely pathogenic variant was detected by tumor profiling and germline analysis has not yet been performed.
- II. *CDHI* targeted variant analysis (81403*) for Hereditary Diffuse Gastric Cancer (aka, Signet Ring Cell Gastric Cancer) is considered **investigational** for all other indications.

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

- I. *CDHI* 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 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, one of which is a confirmed case of diffuse gastric cancer, diagnosed at any age, **OR**
 7. The member/enrollee has a personal history of cancer and a *CDHI* pathogenic or likely pathogenic variant was detected by tumor profiling and germline analysis has not yet been performed.
- II. *CDHI* 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 *BMPRIA* Targeted Variant Analysis

- I. *SMAD4* and/or *BMPRIA* 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 *BMPRIA*, **OR**
 - B. A *SMAD4* and/or *BMPRIA* pathogenic or likely pathogenic variant was detected by tumor profiling and germline analysis has not yet been performed.
- II. *SMAD4* and/or *BMPRIA* targeted variant analysis (81403*) for juvenile polyposis syndrome (JPS) is considered **investigational** for all other indications.

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

- I. *SMAD4* and/or *BMPRIA* 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, **OR**
 - D. The member/enrollee has a personal history of cancer and a *SMAD4* or *BMPRIA* pathogenic or likely pathogenic variant was detected by tumor profiling and germline analysis has not yet been performed.

- II. *SMAD4* and/or *BMPRIA* 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:
 - 1. The member/enrollee has a [first- or second-degree relative](#) with a known pathogenic or likely pathogenic variant in *FH*, **OR**
 - 2. A *FH* pathogenic or likely pathogenic variant was detected by tumor profiling 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. 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 with a known pathogenic or likely pathogenic variant in *TP53*, **OR**
 - B. A *TP53* pathogenic or likely pathogenic variant was detected by tumor profiling 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 was diagnosed with pediatric hypodiploid acute lymphoblastic leukemia, **OR**
 - C. The member/enrollee meets **all** of the following Classic LFS criteria:
 1. The member/enrollee was diagnosed with a sarcoma before 45 years of age, **AND**
 2. The member/enrollee has a [first-degree relative](#) diagnosed with any cancer before 45 years of age, **AND**
 3. At least one of the following:
 - a) The member/enrollee has a [first- or second-degree relative](#) diagnosed with any cancer before 45 years of age, **OR**
 - b) The member/enrollee has a [first- or second-degree relative](#) diagnosed with sarcoma at any age, **OR**
 - D. The member meets **any** of the following Chompret clinical diagnostic criteria:

1. The member/enrollee has been diagnosed at any age with an adrenocortical carcinoma, choroid plexus carcinoma, or rhabdomyosarcoma of embryonal anaplastic subtype, **OR**
 2. The member/enrollee has a multiple tumors (except multiple breast tumors), two of which belong to the LFS tumor spectrum (soft tissue sarcoma, osteosarcoma, CNS tumor, breast cancer) with the initial cancer occurring before 46 years of age, **OR**
 3. The member/enrollee has a diagnosis of soft tissue sarcoma, osteosarcoma, CNS tumor, breast cancer diagnosed before 46 years of age, **AND**
 - a) A [first- or second-degree relative](#) diagnosed with any of the aforementioned cancers (other than breast cancer if the proband has breast cancer) before 56 years of age, **OR** multiple primaries at any age, **OR**
- E. A member/enrollee has a diagnosis of cancer with a pathogenic or likely pathogenic *TP53* variant identified in tumor/somatic genetic testing that may have implications if present in the germline.
- 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 (81403*) 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* pathogenic or likely pathogenic variant was detected by tumor profiling and germline analysis has not yet been performed.
- II. *MEN1* targeted variant analysis (81403*) 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 diagnosis of cancer with a pathogenic or likely pathogenic *MEN1* variant identified in tumor/somatic genetic testing that may have implications if present in the germline.
- 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*, 81405) for multiple endocrine neoplasia type 2 (MEN2) is considered **medically necessary** when:
 - A. The member/enrollee has a [close relative](#) with a known pathogenic or likely pathogenic variant in *RET*, **OR**
 - B. A *RET* pathogenic or likely pathogenic variant was detected by tumor profiling and germline analysis has not yet been performed.
- II. *RET* targeted variant analysis (81404*, 81405) 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**
 - B. The member/enrollee has a diagnosis of primary C-cell hyperplasia, **OR**
 - C. The member/enrollee has a personal history of an adrenal pheochromocytoma and parathyroid hyperplasia, **OR**

- D. The member/enrollee has a [first-degree relative](#) that meets at least one of the above criteria and 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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***MUTYH*-ASSOCIATED POLYPOSIS (MAP)**

***MUTYH* Targeted Variant Analysis**

- I. *MUTYH* targeted variant analysis (81403*, 81401) for MYH-associated polyposis (MAP) is considered **medically necessary** when:
 - A. The member/enrollee has a blood relative with a known pathogenic or likely pathogenic variant in *MUTYH*, **OR**
 - B. A *MUTYH* pathogenic or likely pathogenic variant was detected by tumor profiling and germline analysis has not yet been performed.
- II. *MUTYH* targeted variant analysis (81403*, 81401) for MYH-associated polyposis (MAP) is considered **investigational** for all other indications.

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

- I. *MUTYH* sequencing and/or deletion/duplication analysis (81406*, 81479) for MYH-associated polyposis (MAP) is considered **medically necessary** when:
 - A. The member/enrollee has 10 or more cumulative colorectal adenomas, **OR**
 - B. The member/enrollee has a history of colorectal adenomas, **AND**
 - 1. Duodenal adenomas or carcinoma, **OR**
 - 2. 5 or more serrated polyps proximal to the rectum with at least 2 greater than 10mm and all polyps at least 5mm, **OR**
 - 3. More than 20 serrated polyps of any size, distributed throughout the large bowel with at least 5 proximal to the rectum.
- II. *MUTYH* sequencing and/or deletion/duplication analysis (81406*, 81479) for MYH-associated polyposis (MAP) is considered **investigational** for all other indications.

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

PTCHI or *SUFU* Targeted Variant Analysis

- I. *PTCHI* 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 *PTCHI* or *SUFU*, **OR**
 - B. A *PTCHI* or *SUFU* pathogenic or likely pathogenic variant was detected by tumor profiling and germline analysis has not yet been performed.
- II. *PTCHI* 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.

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

- I. *PTCHI* and *SUFU* sequencing and/or deletion duplication analysis (81479) for nevoid basal cell carcinoma syndrome (NBCC), also known as Gorlin syndrome, is considered **medically necessary** when:
 - A. The member/enrollee has a personal history of any of the following:
 1. Two major and one minor criteria (see below), **OR**
 2. One major and three minor criteria (see below).

Major criteria:	Minor Criteria:
<ul style="list-style-type: none"> ● Lamellar calcification of the falx ● Jaw keratocyst ● Palmar/plantar pits (2 or more) ● Multiple basal cell carcinomas (more than 5 in lifetime) or a basal cell carcinoma diagnosed before 30 years of age ● A first-degree relative with NBCCS 	<ul style="list-style-type: none"> ● Childhood medulloblastoma ● Lympho-mesenteric or pleural cysts ● Macrocephaly (OFC greater than 97th centile) ● Cleft lip/palate ● Vertebral/rib anomalies: <ul style="list-style-type: none"> ○ Bifid/splayed/extra ribs ○ Bifid vertebrae ● Pre- or post-axial polydactyly ● Ovarian fibromas ● Cardiac fibromas ● Ocular anomalies (examples: cataract,

	pigmentary changes of the retinal epithelium, developmental defects)
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- 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 *MAX, SDHA, SDHAF2, SDHB, SDHC, SDHD, or TMEM127* pathogenic or likely pathogenic variant was detected by tumor profiling 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 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**
 5. Pulmonary chondromas, **OR**
- B. The member/enrollee has a family history of 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 (81403*) 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* pathogenic or likely pathogenic variant was detected by tumor profiling and germline analysis has not yet been performed.
- II. *STK11* targeted variant analysis (81403*) 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:
 1. At least two histologically confirmed Peutz-Jeghers-type hamartomatous polyps of the GI tract, **OR**
 2. Mucocutaneous pigmentation of the mouth, lips, nose, eyes, genitalia, or fingers, **OR**
 3. 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

***RBI* Targeted Variant Analysis**

- I. *RBI* 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 *RBI*, **OR**
 - B. An *RBI* pathogenic or likely pathogenic variant was detected by tumor profiling and germline analysis has not yet been performed.
- II. *RBI* targeted variant analysis (81403*) for retinoblastoma is considered **investigational** for all other indications.

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

- I. *RBI* 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 family history of retinoblastoma in one or both eyes and has not previously undergone *RBI* sequencing and/or deletion/duplication analysis.
- II. *RBI* 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 was detected by tumor profiling 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 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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NOTES AND 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. A **limited history** is defined as a member/enrollee who has fewer than two 1st- or 2nd-degree female relatives in the same lineage that lived to age 45. The "limited family history" can occur on either side of the family. A 3-generation pedigree is needed to assess whether family history is limited
 3. "**Breast cancer**" applies to patients with invasive cancer or ductal carcinoma in situ (DCIS).
 4. **High-risk** breast cancer for olaparib therapy is defined as
 - 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 lymph nodes, OR
 - ii. 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 grade (G)] of 3 or higher
 5. **Juvenile polyps** are 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.
 6. **ClinGen** is a 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.
 7. **Maori ancestry** describes individuals who are of indigenous New Zealand ethnic background
 8. **High-risk-prostate cancer** is 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
9. **Very-high-risk prostate cancer** is 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
10. **Targeted mutation testing** is the process of analyzing one specific pathogenic or likely pathogenic (P/LP) variant in one gene. This testing is typically performed when there is a known familial mutation, or in cases where a P/LP variant is identified on somatic tumor profiling.

BACKGROUND AND RATIONALE

Pan-Cancer Hereditary Susceptibility Panels

National Comprehensive Cancer Network (NCCN)

NCCN Breast, Ovarian, and/or Pancreatic Cancer Genetic Assessment guidelines (3.2023) recognize that next-generation sequencing technology has rapidly altered the clinical approach to testing at-risk patients and their families for hereditary forms of cancer and that when more than one gene can explain an inherited cancer syndrome, tailored multi-gene testing is often more efficient and/or cost effective than single-gene testing. NCCN guidelines recognize that there are pros and cons to multi-gene panel testing, one con being that there is a chance of finding a variant of uncertain significance or a pathogenic variant with uncertain clinical management increase as the number of genes included in the multi-gene panel increases. Because of these pros and cons, 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 3 of 10)

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 (3.2023, pages CRIT-2, CRIT-4, CRIT-5 and CRIT-6) 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 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
 - Pathology/histology

- Triple-negative breast cancer
- Multiple primary breast cancers (synchronous or metachronous)..Male breast cancer
- Ashkenazi Jewish ancestry
- Family history of at least 1 close blood relative with:
 - Breast cancer at age 50 years or younger
 - 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 in patient and/or close blood relatives
 - 2 or more close blood relatives with either breast or prostate cancer (any grade).

3.) Personal history of epithelial ovarian cancer (including fallopian tube cancer or peritoneal cancer) at any age

4.) Personal history of metastatic prostate cancer OR high- or very-high-risk group prostate cancer) 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.

6.) 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)

Hereditary GI/Colon Cancer Panel Tests

National Comprehensive Cancer Network (NCCN)

NCCN Guidelines for Genetic/Familial High-Risk Assessment - Colorectal (2.2022) outlines criteria for multigene panel testing for colorectal cancer as follows:

- Polyposis: Patient with a personal 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 old at age of diagnosis, cancer has a known MMR deficiency (p. HRS-3), or meets Lynch syndrome criteria (p. HRS-3, HRS-5,) (see [MLH1, MSH2, MSH6, PMS2, EPCAM Sequencing and/or Deletion/Duplication Analysis](#))
- Family history of Lynch syndrome-related cancer that meets Lynch syndrome criteria (p. HRS-3, HRS-5) see [MLH1, MSH2, MSH6, PMS2, EPCAM Sequencing and/or Deletion/Duplication Analysis](#)).

- Lynch syndrome-related cancers are described in p. HRS-1.
- Minimum gene list is in p. HRS-4A.

Hereditary Gastric Cancer Panels

National Comprehensive Cancer Network (NCCN)

NCCN Gastric Cancer guidelines (2.2022) 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 7 and p. GAST-D 4 of 7)

Hereditary Pancreatic Cancer Susceptibility Panels

National Comprehensive Cancer Network (NCCN)

NCCN Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic guidelines (3.2023) 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 Panels

National Comprehensive Cancer Network (NCCN)

The NCCN Genetic/Familial High-Risk Assessment: Colorectal guidelines (2.2022) outline recommendations for evaluating individuals with adenomatous polyposis (defined as 10 or more adenomas) for germline mutations in *APC* and *MUTYH*. (p. HRS-2)

Hereditary Prostate Cancer Susceptibility Panels

National Comprehensive Cancer Network (NCCN)

NCCN Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic guidelines (3.2023) 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 specific family history/ancestry features: 1 or more close blood relative with breast cancer at age 50 years or

younger, ovarian cancer any age, pancreatic cancer any age, metastatic, intraductal/ cribriform histology, or high- or very-high risk group at any age, 2 or more close blood relatives with either breast or prostate cancer (any grade) at any age, and 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)

Hereditary Neuroendocrine Cancer Susceptibility Panels

National Comprehensive Cancer Network (NCCN)

The NCCN neuroendocrine and adrenal tumors guidelines (2.2022) state 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) These guidelines also outline common clinical and tumor manifestations of different hereditary endocrine neoplasia syndromes, including hereditary paraganglioma/pheochromocytoma syndrome, multiple endocrine neoplasia type 1 (MEN1), multiple endocrine neoplasia type 2 (MEN2), and von Hippel-Lindau syndrome. (p. NE through E 4 of 8 and p. NE through E 5 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 (3.2023) 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)

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 (31.2023) states that 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-6 and p. CRIT-6A)

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 (3.2023) 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)...Male breast cancer, Ashkenazi Jewish ancestry, at least 1 close blood relative with: breast cancer at age 50 years or younger, 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 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)

American Society of Clinical Oncology (ASCO)

ASCO (2020) published the following recommendations for somatic and germline genetic testing for women diagnosed with ovarian cancer:

- All women diagnosed with epithelial ovarian cancer should have germline genetic testing for *BRCA1/2* and other ovarian cancer susceptibility genes. In women who do not carry a germline pathogenic or likely pathogenic *BRCA1/2* variant, somatic tumor testing for *BRCA1/2* pathogenic or likely pathogenic variants should be performed. Women with identified germline or somatic pathogenic or likely pathogenic variants in *BRCA1/2* genes should be offered treatments that are US Food and Drug Administration (FDA) approved in the upfront and the recurrent setting.
- Women diagnosed with clear cell, endometrioid, or mucinous ovarian cancer should be offered somatic tumor testing for mismatch repair deficiency (dMMR). Women with identified dMMR should be offered FDA-approved treatment based on these results.

- Genetic evaluations should be conducted in conjunction with health care providers familiar with the diagnosis and management of hereditary cancer.
- First- or second-degree blood relatives of a patient with ovarian cancer with a known germline pathogenic cancer susceptibility gene variant should be offered individualized genetic risk evaluation, counseling, and genetic testing.
- Clinical decision making should not be made based on a variant of uncertain significance.
- Women with epithelial ovarian cancer should have testing at the time of diagnosis. (p. 1222 through 1223)

American Society of Breast Surgeons

Consensus guidelines (2019) on genetic testing for hereditary breast cancer from the American Society of Breast Surgeons concluded the following:

“Genetic testing should be made available to all patients with a personal history of breast cancer. Recent data are reviewed that support genetic testing being offered to each patient with breast cancer (newly diagnosed or with a personal history). If genetic testing is performed, such testing should include *BRCA1/BRCA2* and *PALB2*, with other genes as appropriate for the clinical scenario and family history. For patients with newly diagnosed breast cancer, identification of a mutation may impact local treatment recommendations. Patients who had genetic testing previously may benefit from updated testing. Genetic testing should be made available to patients without a history of breast cancer who meet National Comprehensive Cancer Network guidelines. Finally, variants of uncertain significance are not clinically actionable and these patients should be managed based on their individual risk factors”. (p. 3025)

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)

***PALB2* GENE TESTING**

***PALB2* Targeted Variant Analysis**

National Comprehensive Cancer Network (NCCN)

The NCCN Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic guidelines (3.2023) states that testing 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 if also identified in the germline. (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 (3.2023) 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)...Male breast cancer, Ashkenazi Jewish ancestry, at least 1 close blood relative with: breast cancer at age 50 years or younger, 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 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)

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 (3.2023) states that testing 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 if also identified in the germline. (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(3.2023) guidelines 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.

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 (2.2022) 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. (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 (2.2022) 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:

- An individual with colorectal or endometrial cancer and any of the following: Diagnosed younger than 50 y, a synchronous or metachronous LS [Lynch syndrome]-related cancer regardless of age, 1 first-degree or second-degree relative with an LS-related cancer diagnosed younger than 50 y, 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 y, 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, including greater than or equal to 1 diagnosed younger than 50 y, 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 (ie, PREMM5 , MMRpro, MMRpredict)

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)

***BAP1* TUMOR PREDISPOSITION SYNDROME**

***BAP1* Targeted Variant Analysis**

National Comprehensive Cancer Network (NCCN)

NCCN guidelines for Kidney Cancer (4.2023) include *BAP1* tumor predisposition 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. (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 (1.2023) state that individuals with the presence of germline mutations in *CDKN2a*, *CDK4*, *MC1R*, *BRCA2*, *BAP1* and potentially other genes, are predisposed to develop single or multiple primary melanomas. (p. ME-A 1 of 2)

NCCN guidelines for Uveal Melanoma (2.2022) include germline *BAP1* mutations as a risk factor for developing uveal melanoma. (p. UM-A 1 of 2)

NCCN guidelines for Malignant Pleural Mesothelioma (1.2023) state that approximately 12-16%

of patients with pleural or peritoneal mesothelioma have a germline mutation, including in *BAP1*. (p. MPM-A 5 of 8)

NCCN guidelines for Kidney cancer (4.2023) include *BAP1* tumor predisposition syndrome in their overview of hereditary renal cell carcinoma syndromes. (p. HERED-RCC-2)

GeneReviews: BAP1 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 clinical description and testing indications for *BAP1* Tumor Predisposition syndrome are as follows:

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.

BAP1 tumor predisposition syndrome should be suspected in an individual with two or more confirmed *BAP1* Tumor Predisposition Syndrome tumors, or one *BAP1*-associated tumor and a first- or second-degree relative with a confirmed *BAP1*-associated tumor (excluding two basal cell cancers and/or cutaneous melanomas given their relatively high frequency in the general population).

BIRT-HOGG DUBE SYNDROME (BHDS)

***FLCN* Targeted Variant Analysis**

National Comprehensive Cancer Network (NCCN)

NCCN guidelines for Kidney Cancer (4.2023) include Birt-Hogg-Dube 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. (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 (4.2023) include Birt-Hogg-Dube syndrome in their overview of hereditary renal cell carcinoma syndromes. (p. HERED-RCC-2)

GeneReviews: Birt-Hogg-Dube 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 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...

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 (3.2023) 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 (3.2023) outline clinical criteria for the genetic testing for Cowden syndrome (CS)/*PTEN* hamartoma tumor syndrome (PHTS) in individuals with a personal or family history of PHTS/CS. 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); or Autism spectrum disorder and macrocephaly; or Two or more biopsy-proven trichilemmomas; or Two or more major criteria (one must be macrocephaly); or Three major criteria, without macrocephaly; or One major and 3 or more minor criteria; or 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)

FAMILIAL ADENOMATOUS POLYPOSIS (FAP)/ATTENUATED FAP (AFAP)

APC Targeted Variant Analysis

National Comprehensive Cancer Network (NCCN)

NCCN Genetic/Familial High-Risk Assessment: Colorectal guidelines (2.2022) outline clinical criteria for the genetic testing, which includes a known pathogenic variant in an adenomatous polyposis gene in the family. (p. POLYP-1)

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)

APC Sequencing and/or Deletion/Duplication Analysis

National Comprehensive Cancer Network (NCCN)

NCCN Genetic/Familial High-Risk Assessment: Colorectal guidelines (2.2022) outline clinical criteria for the genetic testing for Classical FAP and Attenuated FAP in individuals with a personal and/or family history suggestive of FAP. These include: Personal history of greater than or equal to 20 cumulative adenomas, known pathogenic variant in adenomatous polyposis gene in family, multifocal/bilateral congenital hypertrophy of retinal pigment epithelium (CHRPE) (p. POLYP-1)

FAMILIAL ATYPICAL MULTIPLE MOLE MELANOMA (FAMMM) SYNDROME

CDKN2A Targeted Variant Analysis

Genetic Support Foundation

The Genetic Support Foundation's Genetics 101 information on inheritance patterns says the following about testing for familial pathogenic variants:

Genetic testing for someone who may be at risk for an inherited disease is always easier if we know the specific genetic cause. Oftentimes, the best way to find the genetic cause is to start by testing someone in the family who is known or strongly suspected to have the disease. If their testing is positive, then we can say that we have found the familial pathogenic (harmful) variant. We can use this as a marker to test other members of the family to see who is also at risk.

CDKN2A Sequencing and/or Deletion/Duplication Analysis

National Comprehensive Cancer Network (NCCN)

NCCN Cutaneous Melanoma guidelines (1.2023) recommend considering 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)

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

CDHI Targeted Variant Analysis

National Comprehensive Cancer Network (NCCN)

NCCN Gastric Cancer guidelines (2.2022) outline testing criteria for germline *CDHI* testing, which states that a known mutation in a gastric cancer susceptibility gene in a close relative is criteria for further risk evaluation. (p.GAST-D)

NCCN guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic Cancers (3.2023) address tumor genomic testing and state that somatic pathogenic and likely pathogenic variants may be of germline or somatic origin, and germline testing should be considered when clinically indicated. (p. EVAL-A 5 of 10)

CDHI Sequencing and/or Deletion/Duplication Analysis

National Comprehensive Cancer Network (NCCN)

NCCN Gastric Cancer guidelines (2.2022) outline testing criteria for germline *CDHI* 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 7)

JUVENILE POLYPOSIS SYNDROME (JPS)

***SMAD4* and *BMPRIA* Targeted Variant Analysis**

National Comprehensive Cancer Network (NCCN)

NCCN Genetic/Familial High-Risk Assessment: Colorectal guidelines (2.2022) outline clinical criteria for the genetic testing, which states that genetic testing should be performed for individuals with a family history of JPS. (p. JPS-1)

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)

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

National Comprehensive Cancer Network (NCCN)

NCCN Genetic/Familial High-Risk Assessment: Colorectal guidelines (2.2022) 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 testing is recommended as approximately 50% of JPS cases occurring due to pathogenic variants in *BMPRIA* 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) These guidelines also acknowledge that pathogenic or likely pathogenic variants report in tumor genetic analyses may be of germline or somatic origin, and confirmatory germline testing is indicated if applicable. (p. HRS-A 4 of 7).

HEREDITARY LEIOMYOMATOSIS AND RENAL CELL CANCER (HLRCC)

***FH* Targeted Variant Analysis**

National Comprehensive Cancer Network (NCCN)

NCCN guidelines for Kidney Cancer (4.2023) include 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. (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 (4.2023) outline criteria for further genetic risk evaluation for hereditary renal cell carcinoma syndromes, including HLRCC-associated renal cell carcinoma. (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 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%). 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 (3.2023) 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)

TP53 Sequencing and/or Deletion/Duplication Analysis

National Comprehensive Cancer Network (NCCN)

NCCN Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic guidelines (3.2023) outline clinical testing criteria for the genetic testing for Li-Fraumeni syndrome including classic Li-Fraumeni syndrome criteria and Chompret criteria and considerations for family history. These include:

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 (eg, 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
- Pediatric hypodiploid acute lymphoblastic leukemia
- Affected individual with pathogenic/likely pathogenic variant identified on tumor genomic testing that may have implications if also identified on germline testing (p. CRIT-7)

MULTIPLE ENDOCRINE NEOPLASIA TYPE 1 (MEN1)

MEN1 Targeted Variant Analysis

National Comprehensive Cancer Network (NCCN)

NCCN Neuroendocrine and Adrenal Tumors guidelines (2.2022) 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 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)

***MEN1* Sequencing and/or Deletion/Duplication Analysis**

National Comprehensive Cancer Network (NCCN)

NCCN Neuroendocrine and Adrenal Tumors guidelines (2.2022) recommend that patients with two or more of the following be evaluated for *MEN1* germline mutations: foregut carcinoid, pituitary adenoma, duodenal or pancreatic neuroendocrine tumor, and parathyroidism. (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 (2.2022) 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:

Germline testing for *RET* mutations is indicated for any individual with a diagnosis of primary C-cell hyperplasia or medullary thyroid cancer. Multiple endocrine neoplasia type 2 (MEN2) should be also suspected in any individual with pheochromocytoma or parathyroid adenoma/hyperplasia. GeneReviews also notes that pheochromocytomas in individuals with MEN2 are almost always adrenal.

National Comprehensive Cancer Network (NCCN)

NCCN Neuroendocrine and Adrenal Tumors guidelines (2.2022) 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. (p. NE-E 3 of 8)

MUTYH-ASSOCIATED POLYPOSIS (MAP)

MUTYH Targeted Variant Analysis

National Comprehensive Cancer Network (NCCN)

NCCN Genetic/Familial High-Risk Assessment: Colorectal guidelines (2.2022) outline testing criteria for the evaluation of Lynch syndrome. NCCN recommends analysis of *MUTYH* in individuals where the family 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)

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)

MUTYH Sequencing and/or Deletion/Duplication Analysis

National Comprehensive Cancer Network (NCCN)

NCCN Genetic/Familial High-Risk Assessment: Colorectal guidelines (2.2022) outline clinical criteria for the genetic testing for MAP in individuals with a personal and/or family history suggestive of MAP. These include: a history of 10 or more cumulative adenomas (p. HRS-2), duodenal adenomas or duodenal cancer (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)

NEVOID BASAL CELL CARCINOMA SYNDROME (aka Gorlin syndrome)

PTCHI 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. The clinical description and testing indications for nevoid basal cell carcinoma syndrome/Gorlin syndrome are as follows:

Nevoid basal cell carcinoma syndrome (NBCCS) should be suspected in individuals with the following findings, which constitute major or 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 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 (see Notes regarding radiographs): 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)

The diagnosis of NBCCS is established in a proband with the following findings:

- Two major diagnostic criteria and one minor diagnostic criterion or one major and three minor diagnostic criteria.

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 (4.2023) include Hereditary paraganglioma/pheochromocytoma (PGL/PCC) 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. (p. HERED-RCC-1 and HERED-RCC-2)

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

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.

PEUTZ-JEGHERS SYNDROME (PJS)

STK11 Targeted Variant Analysis

National Comprehensive Cancer Network (NCCN)

NCCN Genetic/Familial High-Risk Assessment: Colorectal guidelines (2.2022) outline testing criteria for the evaluation of Lynch syndrome. NCCN recommends analysis of *STK11* in individuals with a family history of PJS. (p. PJS-1)

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)

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

National Comprehensive Cancer Network (NCCN)

NCCN Genetic/Familial High-Risk Assessment: Colorectal guidelines (2.2022) outline clinical criteria for the genetic testing for PJS 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

***RBI* Targeted Variant Analysis**

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 that 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)

***RBI* 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 that 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 (4.2023) 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. (p. HERED-RCC-1 and HERED-RCC-2)

VHL Sequencing and/or Deletion/Duplication Analysis

National Comprehensive Cancer Network (NCCN)

NCCN Kidney Cancer guidelines (4.2023) 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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Reviews, Revisions, and Approvals	Revision Date	Approval Date
Converted corporate to local policy.	10/23	1/9/24

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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.

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