GENETIC TESTING: HEREDITARY CANCER SUSCEPTIBILITY

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).

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.

Coverage Criteria Sections	Example Tests (Labs)	Common CPT Codes	Common ICD10 Codes	Ref
Pan-Cancer Hereditary Cancer Susceptibility Panels	MyRisk (Myriad) VistaSeq (LabCorp) Comprehensive Common Cancer Panel (GeneDx) Common Hereditary Cancer	81432, 81433, 81435, 81436	C15-26, C50-58 Z17, Z80, Z83, Z84, Z85, Z86	1, 2, 3, 4, 9, 19, 20, 30

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	Panel (Invitae) Breast & Gyn Cancer Panel (Invitae) Tempus xG (Tempus) Tempus xG+ (Tempus)			
	CancerNext (Ambry Genetics)			
	OvaNext (Ambry Genetics)	0103U		
	RNAinsight for OvaNext (Ambry Genetics)	0132U		
	RNAinsight for CancerNext (Ambry Genetics)	0134U		
	RNAinsight for GYNPlus (Ambry Genetics)	0135U		
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, 3, 4, 7, 9, 19, 20, 30
	BreastNext (Ambry Genetics)	0102U		
	BRCAplus (Ambry Genetics)	0129U		
	RNAinsight for BreastNext (Ambry Genetics)	0131U		
Hereditary Colorectal Cancer Susceptibility Panels	Colorectal Cancer Panel (PreventionGenetics) VistaSeq Colorectal Cancer Panel (LabCorp) Colorectal Cancer Guidelines-based Panel (Invitae) Colaris (Myriad)	81435, 81436	C15-26, Z23, Z80, Z83, Z84, Z85, Z86	2, 3, 4, 5, 9, 19, 20, 30
	ColoNext (Ambry Genetics)	0101U		
	RNAinsight for ColoNext (Ambry Genetics)	0130U		

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Hereditary Gastric Cancer Susceptibility Panels	Invitae Gastric Cancer Panel (Invitae) Gastric Cancer Panel (Fulgent Genetics)	81292, 81294, 81295, 81297, 81298, 81300, 81317, 81319, 81403, 81406, 81479	C16, Z80, Z85, Z86	3, 4, 9, 13, 19, 20, 30
Hereditary Pancreatic Cancer Susceptibility Panels	Pancreatic Cancer Panel (GeneDx) Invitae Pancreatic Cancer Panel (Invitae) Pancreatic Cancer Panel (PreventionGenetics) PancNext (Ambry Genetics)	81162, 81163, 81164, 81165, 81166, 81167, 81216, 81292, 81294, 81295, 81297, 81298, 81300, 81307, 81317, 81319, 81404, 81405, 81479	C25, Z80, Z84, Z85, Z86	1, 3, 4, 9, 19, 20, 30
Hereditary Polyposis Panels	Hereditary Polyposis Panel (PreventionGenetics) Familial Adenomatous Polyposis Panel (ARUP)	81201, 81203, 81406, 81479, S3833	D12, K63.5, Z80, Z84, Z85, Z86	2, 3, 4, 9, 19, 20, 30
Hereditary Prostate Cancer Susceptibility Panels	Prostate Cancer Panel (PreventionGenetics) Invitae Prostate Cancer Panel (Invitae) Hereditary Prostate Cancer Panel (GeneDx) ProstateNext (Ambry Genetics)	81162, 81163, 81164, 81165, 81166, 81167, 81216, 81292, 81294, 81295, 81297, 81298, 81300, 81317, 81319	C61, Z80, Z84, Z85, Z86	1, 3, 4, 9, 19, 20, 30
	RNAinsight for ProstateNext (Ambry Genetics)	0133U		
Hereditary Neuroendocrine Cancer Susceptibility Panels	Hereditary Paraganglioma-Pheochromocytoma syndrome Panel (PreventionGenetics) Invitae Hereditary Paraganglioma-Pheochromocytoma syndrome Panel (Invitae) PGL/PCC (Paraganglioma/ Pheochromocytoma) Panel	81437, 81438	C74-75, C7A Z80, Z84, Z85, Z86	3, 8, 9, 11, 19, 20, 30

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	(GeneDx) PGLNext (Ambry Genetics)			
Simultaneous Germline and Tumor Molecular Profiling	CancerNext-*Expanded* (Ambry Genetics) with MI Profile (Caris Life Sciences)	81432, 81433, 81435, 81436, 81437, 81438, 81445, 81450, 81455	C00-D49, Z85	24
BRCA1 and BRCA2 Gene Testing				
BRCA1/BRCA2 Targeted Variant Analysis	BRCA1 Targeted Mutation Tests BRCA2 Targeted Mutation Tests	81215, 81217	C50-58, D05, Z17, Z80, Z83, Z84, Z85, Z86	1, 3, 6, 7, 9, 19, 20, 24, 30, 31
	BRCA Ashkenazi Jewish Panel (185delAG, 5385insC, and 6174delT)	81212		
BRCA1/BRCA2 Sequencing and/or Deletion Duplication Analysis	BRCA1 Sequencing BRCA2 Sequencing	81162, 81163, 81164, 81165, 81166, 81167, 81216		
	RNAinsight for BRCA1/2 (Ambry Genetics)	0138U		
PALB2 Gene Testing				
PALB2 Targeted Variant Analysis	PALB2 Targeted Mutation Tests	81308	C15-26, Z80, Z84, Z85, Z86	1, 7, 9, 19, 20, 30
PALB2 Sequencing and/or Deletion/Duplication Analysis	PALB2 Sequencing PALB2 Deletion/Duplication	81307, 81479		
	RNAinsight for PALB2 (Ambry Genetics)	0137U		
ATM and/or CHEK2 Gene Testing				
ATM or CHEK2 Targeted Variant Analysis	ATM Targeted Mutation Tests CHEK2 Targeted Mutation Tests	81403	C50, D05, Z80, Z84, Z85, Z86	1, 9, 19, 20, 30
ATM or CHEK2 Sequencing and/or Deletion/Duplication Analysis	ATM Sequencing Tests ATM Deletion/Duplication Tests CHEK2 Sequencing Tests CHEK2 Deletion/Duplication Tests	81408, 81479		
	RNAinsight for ATM (Ambry	0136U		

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	Genetics)			
	CustomNext + RNA: APC (Ambry Genetics)	0157U		
Lynch Syndrome / Hereditary Nonpolyposis Colorectal Cancer (HNPCC)				
MLH1, MSH2, MSH6, and PMS2 Targeted Variant Analysis	MLH1 Targeted Mutation Tests MSH2 Targeted Mutation Tests MSH6 Targeted Mutation Tests PMS2 Targeted Mutation Tests	81293, 81296, 81299, 81318	C15-26, C50-58 Z23, Z80, Z84, Z85, Z86	2, 3, 5, 9, 19, 20, 30
MLH1, MSH2, MSH6 PMS2, EPCAM Sequencing and/or Deletion/Duplication Analysis	Lynch Syndrome Panel (Quest Diagnostics) HNPCC Seq and del/dup (Ambry Genetics) Lynch Syndrome Panel (GeneDx) Lynch Syndrome (Invitae)	81292, 81294, 81295, 81297, 81298, 81300, 81317, 81319, 81403		
	Genomic Unity Lynch Syndrome Analysis (Variantyx Inc)	0238U		
BAP1-Tumor Predisposition Syndrome				
BAP1 Targeted Variant Analysis	BAP1 Targeted Mutation Tests	81403	C22, C45, C64 C69, D22, D32, Z80, Z84, Z85, Z86	9, 19, 29, 30
BAP1 Sequencing and/or Deletion/Duplication Analysis	BAP1 Sequencing Tests BAP1 Deletion/Duplication Tests	81479		
Birt-Hogg-Dube syndrome (BHDS)				
FLCN Targeted Variant Analysis	FLCN Targeted Mutation Tests	81403	C65, Z84, Z85, Z86	9, 19, 20, 27, 30
FLCN Sequencing and/or Deletion/Duplication Analysis	FLCN Sequencing Tests FLCN Deletion/Duplication Tests	81479		
Cowden Syndrome (CS)/PTEN Hamartoma Tumor Syndrome (PHTS)				
PTEN Targeted Variant Analysis	PTEN Targeted Mutation Tests	81322	C15-26, C50-58, C73-75, D10-36,	1, 9, 19, 20, 30
PTEN Sequencing and/or	PTEN Sequencing Tests PTEN Deletion/Duplication Tests	81321, 81323		

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Deletion/Duplication Analysis	Genomic Unity® PTEN Analysis (Variantyx Inc)	0235U	Q87.89, Z80, Z84, Z85, Z86	
Familial Adenomatous Polyposis (FAP)/Attenuated FAP (AFAP)				
APC Targeted Variant Analysis	APC Targeted Mutation Tests	81202, S3834	C15-26, Z80, Z84, Z85, Z86	2, 5, 9, 15, 19, 20, 30
APC Sequencing and/or Deletion/Duplication Analysis	APC Sequencing Tests APC Deletion/Duplication Tests	81201, 81203, S3833		
Familial Atypical Multiple Mole Melanoma Syndrome (FAMMM)				
CDKN2A Targeted Variant Analysis	CDKN2A Targeted Mutation Tests	81403	C43, Z12.83, Z80, Z84, Z85, Z86	9, 10, 19, 20, 30
CDKN2A Sequencing and/or Deletion/Duplication Analysis	CDKN2A Sequencing Tests CDKN2A Deletion/Duplication Tests	81404, 81479		
Hereditary Diffuse Gastric Cancer (aka, Signet Ring Cell Gastric Cancer)				
CDH1 Targeted Variant Analysis	CDH1 Targeted Mutation Tests	81403	C16, Z80, Z84, Z85, Z86	9, 13, 16, 19, 20, 26, 30
CDH1 Sequencing and/or Deletion/Duplication Analysis	CDH1 Sequencing Tests CDH1 Deletion/Duplication Tests	81406, 81479		
Juvenile Polyposis Syndrome (JPS)				
SMAD4 and/or BMPR1A Targeted Variant Analysis	SMAD4 Targeted Mutation Tests BMPR1A Targeted Mutation Tests	81403	C15-C26, Z80, Z84, Z85, Z86	2, 9, 19, 20, 30
SMAD4 and/or BMPR1A Sequencing and/or Deletion/Duplication Analysis	SMAD4 Sequencing Tests BMPR1A Sequencing Tests SMAD4 Deletion/Duplication Tests BMPR1A Deletion/Duplication Tests	81405, 81406		
Hereditary Leiomyomatosis and Renal Cell Cancer (HLRCC)				

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FH Targeted Variant Analysis	FH Targeted Mutation Tests	81403	C44, C55, C64, D23, D25, Z84, Z85, Z86	9, 14, 19, 20, 22, 23, 30
FH Sequencing and/or Deletion/Duplication Analysis	FH Sequencing Tests FH Deletion/Duplication Tests	81405, 81479		
Li-Fraumeni Syndrome (LFS)				
TP53 Targeted Variant Analysis	TP53 Targeted Mutation Tests	81404, 81352, 81353	C30-41, C15-26, C45-58, Z80, Z84, Z85, Z86	1, 9, 19, 30
TP53 Sequencing and/or Deletion/Duplication Analysis	TP53 Sequencing Tests TP53 Deletion/Duplication Tests	81351, 81405, 81479		
Multiple Endocrine Neoplasia - Type 1 (MEN1)				
MEN1 Targeted Variant Analysis	MEN1 Targeted Mutation Tests	81403	C73-75, E31.2, Z80, Z84, Z85, Z86	9, 11, 19, 20, 30
MEN1 Sequencing and/or Deletion/Duplication Analysis	MEN1 Sequencing Tests MEN1 Deletion/Duplication Tests	81404, 81405		
Multiple Endocrine Neoplasia Type 2 (MEN2)				
RET Targeted Variant Analysis	RET Targeted Mutation Tests	81404, 81405	C73-75, C7A, D3A, Z80, Z84, Z85, Z86	8, 9, 11, 19, 20, 30
RET Sequencing and/or Deletion/Duplication Analysis	RET Sequencing Tests RET Deletion/Duplication Tests	81406, 81479, S3840		
MUTYH-associated Polyposis (MAP)				
MUTYH Targeted Variant Analysis	MUTYH Targeted Mutation Tests	81401	C15-26, Z80, Z84, Z85, Z86	2, 5, 9, 19, 20, 30
MUTYH Sequencing and/or Deletion/Duplication Analysis	MUTYH Sequencing Tests MUTYH Deletion/Duplication Tests	81406, 81479		
Nevoid Basal Cell Carcinoma (NBCC) syndrome (aka Gorlin syndrome)				

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PTCH1 and/or SUFU Targeted Variant Analysis	PTCH1 Targeted Mutation Tests SUFU Targeted Mutation Tests	81403	C44, G93, M27, Z84, Z85, Z86	19, 20, 28, 30
PTCH1 and SUFU Sequencing and/or Deletion/Duplication Analysis	PTCH1 Sequencing Tests SUFU Sequencing Tests PTCH1 Deletion/Duplication Tests SUFU Deletion/Duplication Tests	81479		
Hereditary Paraganglioma-Pheochromocytoma Syndrome (PGL/PCC)				
MAX, SDHA, SDHAF2, SDHB, SDHC, SDHD, or TMEM127 Targeted Variant Analysis	SDHB Targeted Mutation Tests SDHD Targeted Mutation Tests MAX Targeted Mutation Tests SDHAF2 Targeted Mutation Tests SDHC Targeted Mutation Tests TMEM127 Targeted Mutation Tests	81403	C7A, C74.10, D35.00, Z84, Z85, Z86	3, 8, 9, 11, 12, 19, 20, 30
MAX, SDHA, SDHAF2, SDHB, SDHC, SDHD, and/or TMEM127 Sequencing and/or Deletion/Duplication Analysis	SDHB Sequencing Tests SDHD Sequencing Tests SDHB Deletion/Duplication Tests SDHD Deletion/Duplication Tests	81404, 81405, 81406, 81479		
Peutz-Jeghers Syndrome (PJS)				
STK11 Targeted Variant Analysis	STK11 Targeted Mutation Tests	81403	C50, Q85, Z80, Z84, Z85, Z86	2, 9, 19, 20, 30
STK11 Sequencing and/or Deletion/Duplication Analysis	STK11 Sequencing Tests STK11 Deletion/Duplication Tests	81404, 81405		
Retinoblastoma				
RB1 Targeted Variant Analysis	RB1 Targeted Mutation Tests	81403, S3841	C69, Z80, Z84, Z85, Z86	9, 18, 19, 20, 21
RB1 Sequencing and/or Deletion/Duplication Analysis	RB1 Sequencing Tests RB1 Deletion/Duplication Tests	81479, S3841		
Von Hippel-Lindau Syndrome (VHL)				

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VHL Targeted Variant Analysis	VHL Targeted Mutation Tests	81403, S3842	C64, Q85, Z80, Z84, Z85, Z86	8, 9, 14, 17, 19, 20, 30
VHL Sequencing and/or Deletion/Duplication Analysis	VHL Sequencing Tests VHL Deletion/Duplication Tests	81403, 81404, S3842		

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.

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COVERAGE CRITERIA

PAN-CANCER HEREDITARY CANCER SUSCEPTIBILITY PANELS

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

I. Genetic testing using a pan-cancer hereditary cancer susceptibility panel (including hereditary breast and gynecological panels) (81432, 81433, 81435, 81436, 0103U) is considered **medically necessary** when:

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

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

      1. The member meets at least one criteria for *BRCA1* and *BRCA2* sequencing and/or deletion/duplication gene testing (see *BRCA1* and *BRCA2* sequencing and/or deletion/duplication criteria below), **OR**

      2. The member meets at least one criteria for Lynch syndrome/HNPCC sequencing and/or deletion duplication gene testing (see Lynch syndrome/HNPCC sequencing and/or deletion/duplication gene testing criteria below), **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 (including hereditary breast and gynecological panels) (81432, 81433, 81435, 81436) is considered **investigational** for all other indications.

III. Hereditary cancer susceptibility panel targeted mRNA sequencing analysis for the interpretation of variants of unknown significance (0132U, 0134U, 0135U, 0138U), when billed in addition, is considered **investigational** because it is typically either

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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 is 18 years or older, **AND**

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

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

         a) Male breast cancer

         b) Bilateral breast cancer

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

      2. The member is a female who has a personal history of breast cancer, **AND**

         a) Diagnosed ≤45 years, **OR**

         b) Diagnosed 46-50 with **ANY**

            (1) Unknown or limited family history

            (2) Multiple primary breast cancers (synchronous or metachronous)

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(3) At least 1 close relative with breast, ovarian, pancreatic or prostate cancer at any age

c) Diagnosed >50 years, **AND**

(1) One or more close relatives with

(a) Breast cancer <50 years **OR**

(b) Male breast cancer at any age, **OR**

(c) Ovarian cancer at any age, OR

(d) Pancreatic cancer at any age, OR

(e) Metastatic, intraductal/cribriform histology, or high- or very-high risk group prostate cancer at any age, OR

(2) **Three or** more close relatives with breast cancer including patient at any age, **OR**

(3) Two or more close relatives with either breast or prostate cancer at any age, **OR**

(4) An unknown or limited family history, **OR**

d) Ashkenazi Jewish ancestry, **OR**

3. The member does not meet any of the above criteria, but has one or more first- or second-degree relatives meeting any of the above criteria, **OR**

4. The member is being considered for PARP inhibitor therapy and has a personal history of recurrent or metastatic breast cancer, **OR**

5. The member is being considered for olaparib therapy, and has a personal history of high-risk, HER-2 negative breast cancer, **AND**

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

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D. 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 meets one of the above criteria, **AND**

B. The member 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 COLORECTAL CANCER SUSCEPTIBILITY PANELS

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

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

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

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

1. The member meets criteria for Lynch syndrome/HNPCC sequencing and/or deletion duplication gene testing (see Lynch syndrome/HNPCC sequencing and/or deletion/duplication gene testing criteria below), **OR**

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2. The member meets criteria for sequencing and/or deletion/duplication analysis for at least two of the following (see specific coverage criteria sections below):

    a) Familial Adenomatous Polyposis (FAP)/Attenuated FAP (AFAP)

    b) Cowden Syndrome (CS)/PTEN Hamartoma Tumor Syndrome (PHTS)

    c) Hereditary Diffuse Gastric Cancer (aka, Signet Ring Cell Gastric Cancer),

    d) Juvenile Polyposis Syndrome (JPS)

    e) MUTYH-associated Polyposis (MAP)

    f) Peutz-Jeghers Syndrome (PJS), **AND**

C. The panel includes, at a minimum, sequencing of the following genes: *APC, EPCAM*, *MLH1, MSH2, MSH6, MUTYH, PMS2*, **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) 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 SUSCEPTIBILITY PANELS

A hereditary gastric cancer susceptibility 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 is 18 years or older, **AND**

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

      1. The member meets criteria for *EPCAM*, *MLH1*, *MSH2*, *MSH6*, and *PMS2* sequencing and/or deletion duplication analysis (see Lynch syndrome/hereditary non-polyposis colorectal cancer sequencing and/or deletion/duplication criteria below), **OR**

      2. The member meets criteria for *CDH1* sequencing and/or deletion/duplication analysis (see hereditary diffuse gastric cancer (aka Signet ring cell gastric cancer) criteria below), **AND**

   C. The panel includes, at a minimum, sequencing of the following genes: *CDH1, EPCAM, MLH1, MSH2, MSH6, PMS2*, **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.

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I. Genetic testing using a hereditary pancreatic cancer susceptibility panel (81162, 81163, 81164, 81165, 81166, 81167, 81216, 81292, 81294, 81295, 81297, 81298, 81300, 81307, 81317, 81319, 81404, 81405, 81479) is considered **medically necessary** when:

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

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

      1. The member has a personal history of exocrine pancreatic cancer, **OR**

      2. The member has a first-degree relative with a diagnosis of exocrine pancreatic cancer, **OR**

      3. The member meets criteria for *BRCA1* and *BRCA2* sequencing and/or deletion/duplication gene testing (see *BRCA1* and *BRCA2* sequencing and/or deletion/duplication criteria below), **AND**

   C. The panel includes, at a minimum, sequencing of the following genes: *BRCA1, BRCA2, CDKN2A, MLH1, MSH2, MSH6, PALB2, PMS2, STK11*, **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, 81164, 81165, 81166, 81167, 81216, 81292, 81294, 81295, 81297, 81298, 81300, 81307, 81317, 81319, 81404, 81405, 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, S3833) is considered **medically necessary** when:

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A. The member meets criteria for sequencing and/or deletion/duplication analysis for at least one of the following (see specific coverage criteria sections below):

1. Familial Adenomatous Polyposis (FAP)/Attenuated FAP, **OR**

2. MUTYH associated polyposis (MAP), **AND**

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, S3833) 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 (0133U, 81162, 81163, 81164, 81165, 81166, 81167, 81216, 81292, 81294, 81295, 81297, 81298, 81300, 81317, 81319) is considered **medically necessary** when:

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

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

1. The member has a personal history of metastatic prostate cancer, **OR**

2. The member's prostate cancer has intraductal, cribriform or ductal histology, **OR**

3. The member's prostate cancer has a high- or very high-risk classification, OR

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4. The member has family history that includes at least one relative with any the following

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

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

    c) Pancreatic cancer at any age, **OR**

    d) Prostate cancer with metastasis, intraductal/cribriform histology, or a high- or very high-risk classification, **OR**

5. The member meets criteria for *BRCA1* and *BRCA2* sequencing and/or deletion/duplication gene testing (see *BRCA1* and *BRCA2* sequencing and/or deletion/duplication criteria below), **AND**

C. The panel includes, at a minimum, sequencing of the following genes: *BRCA1, BRCA2, MLH1, MSH2, MSH6, PMS2, HOXB13*, **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 (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.

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

   A. The member 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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SIMULTANEOUS GERMLINE AND TUMOR MOLECULAR PROFILING

I. The use of **hereditary cancer susceptibility panels** (81432, 81433, 81435, 81436, 81437, 81438) simultaneously with **comprehensive tumor molecular profiling panels** (81445, 81450, 81455) is considered **investigational**, when the member does not independently meet criteria for the hereditary cancer susceptibility panel *(see specific panel coverage criteria above)*.

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BRCA1 AND BRCA2 GENE TESTING

BRCA1 or BRCA2 Targeted Variant Analysis - Known Familial Variant

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

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

   B. One of the following:

      1. The member has a close relativewith a known *BRCA1* or *BRCA2* pathogenic or likely pathogenic variant, **OR**

      2. The member is seeking confirmatory testing for a *BRCA1* or *BRCA2* variant detected by an Food and Drug Administration (FDA)-authorized direct-to-consumer (DTC) test report, **OR**

      3. 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 is 18 years or older, **AND**

   B. The member is 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.

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BRCA1 and BRCA2 Sequencing and/or Deletion/Duplication Analysis

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

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

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

1. Epithelial ovarian cancer
2. Fallopian tube cancer
3. Primary peritoneal cancer
4. Male breast cancer
5. Pancreatic cancer
6. Bilateral breast cancer
7. Triple-negative breast cancer
8. Metastatic prostate cancer, **OR**

C. The member is a female who has a personal history of breast cancer, **AND**

1. Diagnosed ≤50 years, **OR**

2. Diagnosed >50 years, **AND**

a) One or more close relative with ovarian, pancreatic, or metastatic prostate cancer at any age, **OR**

b) One or more close relatives with breast cancer <50 years, **OR**

c) Two or more close relatives with breast or prostate cancer at any age, **OR**

d) An unknown or limited family history, **OR**

D. Personal history of high-grade prostate cancer (Gleason score ≥7) at any age with:

1. One or more close relatives with ovarian, pancreatic, or metastatic prostate cancer at any age, **OR**

2. One or more close relatives with breast cancer <50 years, **OR**

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3. Two or more close relatives with breast or prostate cancer at any age, **OR**

E. The member does not meet any of the above criteria, but has one or more first- or second-degree relatives meeting any of the above criteria, **OR**

F. The member is being considered for PARP inhibitor therapy and has a personal history of recurrent or metastatic breast cancer, **OR**

G. The member has a probability >5% of a BRCA1 or BRCA2 pathogenic variant based on prior probability models (e.g., Tyrer-Cuzick, BRCAPro, PennII).

II. *BRCA1* and *BRCA2* sequencing and/or deletion/duplication analysis (81162, 81163, 81164, 81165, 81166, 81167, 81216, 0138U) for hereditary cancer susceptibility is considered **investigational** for all other indications.

III. *BRCA1* and *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 is 18 years or older, **AND**

B. One of the following:

1. The member has a close relative with a known pathogenic or likely pathogenic variant in *PALB2*, **OR**

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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, 0137U) sequencing and/or deletion/duplication analysis for hereditary breast and/or ovarian cancer susceptibility is considered **medically necessary** when:

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

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

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

a) Epithelial ovarian cancer

b) Fallopian tube cancer

c) Primary peritoneal cancer

d) Male breast cancer

e) Pancreatic cancer

f) Bilateral breast cancer

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

2. The member is a female who has a personal history of breast cancer, **AND**

a) Diagnosed ≤50 years, **OR**

b) Diagnosed >50 years, **AND**

(1) One or more close relative with ovarian or pancreatic cancer at any age, **OR**

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(2) One or more close relatives with breast cancer <50 years, **OR**

(3) Two or more close relatives with breast cancer at any age, **OR**

(4) An unknown or limited family history, **OR**

3. The member does not meet any of the above criteria, but has one or more first- or second-degree relatives meeting any of the above criteria, **OR**

4. The member is being considered for PARP inhibitor therapy and has a personal history of metastatic HER2-negative breast cancer, **AND**

C. The member has previously undergone BRCA1/2 gene testing and the results were negative.

II. *PALB2* (81307, 0137U) sequencing and/or deletion/duplication analysis for hereditary breast and/or ovarian cancer susceptibility is considered **investigational** for all other indications.

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

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ATM and/or CHEK2 Gene Testing

ATM or CHEK2 Targeted Variant Analysis

I. *ATM* (81403) or *CHEK2* (81403) targeted variant analysis for hereditary breast and/or ovarian cancer susceptibility is considered **medically necessary** when:

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

B. One of the following:

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1. The member 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, 0157U), when billed in addition, is considered **investigational** because it is typically either considered an existing component of the genetic testing process for quality assurance, or follow up testing without proven utility.

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LYNCH SYNDROME / HEREDITARY NONPOLYPOSIS COLORECTAL CANCER (HNPCC) TESTING

MLH1, MSH2, MSH6, PMS2 Targeted Variant Analysis

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

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

B. A pathogenic or likely pathogenic variant was detected by tumor profiling in *MLH1*, *MSH2*, *MSH6*, or *PMS2* and germline analysis has not yet been performed.

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II. *MLH1* (81293), *MSH2* (81296), *MSH6* (81299), or *PMS2* (81318) 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) (0238U) sequencing and/or duplication analysis for Lynch syndrome/HNPCC is considered **medically necessary** when:

A. The member 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 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,

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small intestinal, sebaceous adenoma, sebaceous carcinoma, or keratoacanthoma), **OR**

C. The member 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 which 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 has a 5% or greater risk of Lynch syndrome on one or the following variant prediction models: MMRpro, PREMM, MMRpredict.

II. *MLH1* (81292, 81294), *MSH2* (81295, 81297), *MSH6* (81298, 81300), *PMS2* (81317, 81319), and/or *EPCAM* (81403) (0238U) sequencing and/or duplication analysis for Lynch syndrome/HNPCC is considered **investigational** for all other indications.

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

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BAP1-TUMOR PREDISPOSITION SYNDROME

BAP1 Targeted Variant Analysis

I. *BAP1* targeted variant analysis (81479) for *BAP1*-tumor predisposition syndrome is considered **medically necessary** when:

   A. The member 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 (81479) 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 has a personal history of:

      1. Two or more of the following:

         a) *BAP1*-inactivated melanocytic tumors (aka atypical spitz tumor)

         b) Uveal melanoma

         c) Malignant mesothelioma

         d) Renal cell carcinoma

         e) Hepatocellular carcinoma

         f) Cholangiocarcinoma

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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 (81403) for Birt-Hogg-Dube syndrome (BHDS) is considered **medically necessary** when:

A. The member has a close 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 (81403) 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 has a personal history of:

1. ≥5 fibrofolliculomas/trichodiscomas with at least one confirmed histologically, **OR**

2. Two or more of the following:

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a) Multiple lung cysts with no apparent cause

b) Renal cancer before 50 years of age

c) Multifocal or bilateral renal cancer

d) Renal cancer of mixed chromophobe and oncocytic histology

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 has a close relative with a known pathogenic or likely pathogenic variant in *PTEN*.

II. *PTEN* targeted variant analysis 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 has a personal history of any of the following:

1. Bannayan Riley-Ruvalcaba syndrome (BRRS), **OR**

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2. Adult Lhermitte-Duclos disease (LDD) (defined as the presence of a cerebellar dysplastic gangliocytoma), **OR**
3. Autism-spectrum disorder and macrocephaly, **OR**
4. At least 2 biopsy-proven trichilemmomas, **OR**
5. Macrocephaly and at least one other major criteria (see below), **OR**
6. Three major criteria (see below) without macrocephaly, **OR**
7. One major and at least three minor criteria (see below), **OR**
8. Four or more minor criteria (see below), **OR**

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

1. The member meets one major or two minor criteria (see below).

Major Criteria:	Minor Criteria:

• Breast Cancer
• Endometrial Cancer (epithelial)
• Thyroid Cancer (follicular)
• Gastrointestinal hamartomas
• Macrocephaly (≥97 percentile)
• Macular pigmentation of the glans penis
• Multiple mucocutaneous lesions:
  ○ One biopsy-proven trichilemmoma
  ○ Multiple palmoplantar keratoses
  ○ Multifocal or extensive oral mucosal papillomatosis
  ○ Multiple cutaneous facial papules (often verrucous)
	• Autism Spectrum Disorder
	• Colon Cancer
	• Esophageal glycogenic acanthosis (≥3)
	• Lipomas (≥3)
	• Intellectual disability (ie, IQ ≤ 75)
	• Thyroid cancer (papillary or follicular)
	• Thyroid structural lesions (eg, 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, S3834) for familial adenomatous polyposis (FAP) is considered **medically necessary** when:

   A. The member has a close relative with 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, S3834) 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, S3833) for familial adenomatous polyposis (FAP) is considered **medically necessary** when:

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

      1. 10 or more cumulative colorectal adenomas, **OR**
      2. Hepatoblastoma, **OR**
      3. Congenital hypertrophy of the retinal pigment epithelium (CHRPE), **OR**
      4. A desmoid tumor, **OR**
      5. Gastric fundus gland polyps, **OR**

   B. The member has a history of colorectal adenomas, **AND**

      1. Duodenal or other small bowel adenomas, **OR**
      2. Papillary thyroid carcinoma, **OR**
      3. Medulloblastoma, **OR**

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C. The member has a first-degree relative that meets at least one of the above criteria and has not previously undergone *APC* sequencing and/or deletion duplication analysis.

II. *APC* sequencing and/or deletion/duplication analysis (81201, 81203, S3833) 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 is 18 years or older, **AND**

B. One of the following:

1. The member 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**.

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

CDH1 Targeted Variant Analysis

I. *CDH1* targeted variant analysis (81403) for Hereditary Diffuse Gastric Cancer (aka, Signet Ring Cell Gastric Cancer) is considered **medically necessary** when:

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

   B. One of the following:

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

      2. A *CDH1* pathogenic or likely pathogenic variant was detected by tumor profiling and germline analysis has not yet been performed.

II. *CDH1* targeted variant analysis (81403) for Hereditary Diffuse Gastric Cancer (aka, Signet Ring Cell Gastric Cancer) is considered **investigational** for all other indications.

CDH1 Sequencing and/or Deletion/Duplication Analysis

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

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

   B. One of the following:

      1. The member has diffuse gastric cancer diagnosed before 40 years of age, **OR**

      2. The member has a personal history of diffuse gastric cancer and lobular breast cancer, **OR**

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3. The member has diffuse gastric cancer and one or more first- or second-degree relatives diagnosed with gastric cancer, **OR**

4. The member has a close relative with diffuse gastric cancer **AND** a close relative with lobular breast cancer, **OR**

5. The member has a first-degree relative that meets at least one of the above criteria and has not previously undergone *CDH1* sequencing and/or deletion duplication analysis.

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

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JUVENILE POLYPOSIS SYNDROME (JPS)

SMAD4 or BMPR1A Targeted Variant Analysis

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

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

   B. A *SMAD4* and/or *BMPR1A* pathogenic or likely pathogenic variant was detected by tumor profiling and germline analysis has not yet been performed.

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

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

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

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

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

C. The member has a first-degree relative that meets at least one of the above criteria and has not previously undergone *SMAD4* and/or *BMPR1A* sequencing and/or deletion duplication analysis.

II. *SMAD4* and/or *BMPR1A* sequencing and/or deletion/duplication analysis (81405, 81406) 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 is 18 years or older, **AND**

B. One of the following:

1. The member has a close 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.

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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 is 18 years or older, **AND**

   B. One of the following:

      1. The member has one or more biopsy proven cutaneous leiomyoma(s), **OR**

      2. The member has cutaneous leiomyosarcoma, **OR**

      3. The member is a female with:

         a) Multiple or large uterine fibroids, **OR**

         b) Hysterectomy or myomectomy before 40 years of age due to large or numerous uterine fibroids, **OR**

         c) A single uterine fibroid with loss of FH staining on IHC analysis, **OR**

         d) Uterine leiomyosarcoma, **OR**

      4. The member has renal cell cancer diagnosed before 45 years of age.

II. *FH* sequencing and/or deletion/duplication analysis 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 (81404) for Li-Fraumeni syndrome (LFS) is considered **medically necessary** when:

   A. The member has a close relative with a known pathogenic or likely pathogenic variant in *TP53*.

II. *TP53* targeted variant analysis (81404) 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 (81405, 81479) for Li-Fraumeni syndrome (LFS) is considered **medically necessary** when:

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

   B. The member meets all of the following *Classic LFS* criteria:

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

      2. The member 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 has a first- or second-degree relative diagnosed with any cancer before 45 years of age

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

   C. The member meets any of the following Chompret clinical diagnostic criteria:

      1. The member has been diagnosed with an adrenocortical carcinoma, choroid plexus carcinoma, or rhabdomyosarcoma of embryonal anaplastic subtype, **OR**

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2. The member has three or more primary tumors, **OR**

3. The member has a diagnosis of at least two of the following:

    a) Soft tissue sarcoma
    b) Osteosarcoma
    c) Central nervous system tumor
    d) Breast cancer, **OR**

4. The member 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 soft tissue sarcoma, osteosarcoma, CNS tumor, breast cancer, adrenocortical carcinoma before 56 years of age.

II. *TP53* sequencing and/or deletion/duplication analysis (81405, 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 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.

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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 has a personal history of at least two of the following:

      1. Pancreatic neuroendocrine tumor (islet cell tumor)
      2. Multi-gland parathyroid hyperplasia
      3. Pituitary adenoma

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 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:

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A. The member has a diagnosis of medullary thyroid cancer, **OR**

B. The member has a diagnosis of primary C-cell hyperplasia, **OR**

C. The member has a personal history of an adrenal pheochromocytoma and parathyroid hyperplasia, **OR**

D. The member 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 (81401) for MYH-associated polyposis (MAP) is considered **medically necessary** when:

A. The member has a close 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 (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 has 10 or more cumulative colorectal adenomas, **OR**

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B. The member 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, **OR**
3. More than 20 serrated polyps of any size, distributed throughout the large bowel with at least 4 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 (aka Gorlin syndrome)

PTCH1 or SUFU Targeted Variant Analysis

I. *PTCH1* or *SUFU* targeted variant analysis (81403) for nevoid basal cell carcinoma syndrome (NBCC), also known was Gorlin syndrome, is considered **medically necessary** when:

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

B. A *PTCH1* or *SUFU* pathogenic or likely pathogenic variant was detected by tumor profiling and germline analysis has not yet been performed.

II. *PTCH1* or *SUFU* targeted variant analysis (81403) for nevoid basal cell carcinoma syndrome (NBCC), also known as Gorlin syndrome, is considered **investigational** for all other indications.

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PTCH1 and SUFU Sequencing and/or Deletion/Duplication Analysis

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

A. The member 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:

• Lamellar calcification of the falx
• Jaw keratocyst
• Palmar/plantar pits
• Multiple basal cell carcinomas (>5 in lifetime) or a basal cell carcinoma diagnosed before 30 years of age
• A first degree relative with NBCC
	• Childhood medulloblastoma
	• Lympho-mesenteric or pleural cysts
	• Macrocephaly (OFC >97th centile)
	• Cleft lip/palate
	• Vertebral/rib anomalies:
	  ○ Bifid/splayed/extra ribs
	  ○ Bifid vertebrae
	• Pre- or post-axial polydactyly
	• Ovarian fibromas
	• Cardiac fibromas
	• Ocular anomalies
	  ○ Cataract
	  ○ Pigmentary changes of the retinal epithelium
	  ○ Developmental defects

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

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HEREDITARY PARAGANGLIOMA/PHEOCHROMOCYTOMA SYNDROME (PGL/PCC)

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

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

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

      1. Pheochromocytoma, including bilateral adrenal pheochromocytoma
      2. Paraganglioma, including paravertebral, carotid body, vagal, and/or jugulotympanic
      3. Clear cell renal cell cancer
      4. Gastrointestinal stromal tumor (GIST)

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5. Pulmonary chondromas**, OR**

B. The member has a close relative who meets the above criteria.

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 has a close relative with a known pathogenic or likely pathogenic variant in *STK11*.

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 is considered **medically necessary** when:

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

1. Two or more histologically confirmed Peutz-Jeghers-type hamartomatous polyps of the GI tract

2. Mucocutaneous pigmentation of the mouth, lips, nose, eyes, genitalia, or fingers

3. Close relative with a clinical diagnosis of PJS.

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

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RETINOBLASTOMA

RB1 Targeted Variant Analysis

I. *RB1* targeted variant analysis (81403, S3841) for retinoblastoma is considered **medically necessary** when:

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

   B. An *RB1* pathogenic or likely pathogenic variant was detected by tumor profiling and germline analysis has not yet been performed.

II. *RB1* targeted variant analysis (81403, S3841) for retinoblastoma is considered **investigational** for all other indications.

RB1 Sequencing and/or Deletion/Duplication Analysis

I. *RB1* sequencing and/or deletion/duplication analysis (81403, S3841) for retinoblastoma is considered **medically necessary** when:

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

   B. The member has a close relative diagnosed with retinoblastoma in one or both eyes and has not previously undergone *RB1* sequencing and/or deletion duplication analysis.

II. *RB1* sequencing and/or deletion/duplication analysis (81403, 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, S3842) for Von Hippel-Lindau syndrome is considered **medically necessary** when:

   A. The member has a close 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, S3842) 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 has a diagnosis of one or more of the following:

      1. Hemangioblastoma of the retina, spine, or brain
      2. Clear cell renal cell carcinoma
      3. Pheochromocytoma or paraganglioma
      4. Endolymphatic sac tumor
      5. Epididymal or adnexal papillary cystadenoma
      6. Pancreatic serous cystadenoma
      7. Pancreatic neuroendocrine tumors
      8. Multiple renal, pancreatic or hepatic cysts**, OR**

   B. The member has a close relative diagnosed with VHL.

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ll. *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 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 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. Neoadjustant chemotherapy with residual invasive breast cancer in the breast or resected lymph nodes, OR
    b. Hormone receptor positive disease treated with either

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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.

CLINICAL CONSIDERATIONS

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.

BACKGROUND AND RATIONALE

Practice Guidelines and Position Statements

National Comprehensive Cancer Network (NCCN)

Multi-gene Panel Testing

NCCN guidelines (1.2022) 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

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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.

Germline Testing after Tumor Profiling

NCCN guidelines recommend confirmatory germline testing through an appropriately certified laboratory when a potential pathogenic/likely pathogenic variant is identified by commercial entities providing ancestry information, tumor profiling testing, and research. The recommendation recognizes that there are several genes (eg, *TP53*, *STK11*, *PTEN*) that are frequently identified in tumor testing that would have germline implications, however are rarely confirmed to be germline and therefore are rarely indicative of a need for germline testing unless clinical and/or family history are significant.

High-Penetrance Breast and Ovarian Cancer Susceptibility Genes Testing

NCCN guidelines (1.2022) outline testing criteria for high-penetrance breast and/or ovarian cancer susceptibility genes, specifically *BRCA1/2*, *CDH1*, *PALB2*, *PTEN*, and *TP53*. NCCN recommends this testing in individuals with a personal and/or family history of HBOC-related cancers, such as breast, ovarian, prostate, and pancreatic cancer.

Additionally, current guidelines (2.2022) recommend assessing for germline high-penetrance breast cancer susceptibility gene mutations (*BRCA1/2, CDH1, PALB2, PTEN, TP53)* in all patients with recurrent or metastatic breast cancer to identify candidates for PARP inhibitor therapy. Additionally, patients with high-risk HER-2 negative breast cancer should have high-penetrance breast cancer susceptibility gene mutation analysis (BRCA1/2, CDH1, PALB2, PTEN, TP53) if olaparib treatment is being considered.

Pancreatic Cancer Susceptibility Genes Testing

NCCN guidelines (2.2022) 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.

Lynch Syndrome/HNPCC

NCCN guidelines (1.2021) outline testing criteria for the evaluation of Lynch syndrome.

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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.

Cowden Syndrome (CS)/PTEN Hamartoma Tumor Syndrome (PHTS)

NCCN guidelines (1.2022) 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.

Familial Adenomatous Polyposis (FAP)/Attenuated (AFAP)

NCCN guidelines (1.2021) 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.

Familial Cutaneous Malignant Melanoma

NCCN guidelines (2.2021) 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.

NCCN guidelines (2.2021) also 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.

Hereditary Diffuse Gastric Cancer

NCCN guidelines (1.2021) outline criteria for further genetic risk assessment for high-risk syndromes associated with gastric cancer, including recommending criteria for which genetic testing for *CDH1* mutation should be considered.

Juvenile Polyposis Syndrome (JPS)

NCCN guidelines (1.2021) outline clinical criteria for the genetic testing for JPS in individuals with a personal and/or family history suggestive of JPS, noting that clinical genetic testing is recommended approximately 50% of JPS cases occurring due to pathogenic variants in *BMPR1A* and *SMAD4*.

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Hereditary Leiomyomatosis and Renal Cell Cancer (HLRCC)

NCCN guidelines (2.2022) outline criteria for further genetic risk evaluation for hereditary renal cell carcinoma syndromes, including HLRCC-associated renal cell carcinoma.

Li-Fraumeni Syndrome (LFS)

NCCN guidelines (1.2022) 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.

Multiple Endocrine Neoplasia Syndrome Type 1

NCCN guidelines (3.2021) outline endocrine neoplasia manifestations found in various hereditary endocrine neoplasia syndromes. The guidelines outline principles of genetic risk assessment that include pre- and post-test counseling, consideration of the most appropriate testing strategy, and recommends that one of a number of professionals with expertise and experience in cancer genetics be involved whenever possible.

Multiple Endocrine Neoplasia Syndrome Type 2

NCCN guidelines (3.2021) outline endocrine neoplasia manifestations found in various hereditary endocrine neoplasia syndromes. The guidelines outline principles of genetic risk assessment that include pre- and post-test counseling, consideration of the most appropriate testing strategy, and recommends that one of a number of professionals with expertise and experience in cancer genetics be involved whenever possible.

MUTYH-associated Polyposis (MAP)

NCCN guidelines (1.2021) outline clinical criteria for the genetic testing for MAP in individuals with a personal and/or family history suggestive of MAP.

Hereditary Paraganglioma/Pheochromocytoma Syndrome (PGL/PCC)

NCCN guidelines do not currently include recommendations for genetic testing for hereditary PGL/PCC. However, the guidelines include discussion that refers to the Endocrine Society's published guidelines with a genetic testing decision algorithm for genetic testing in patients with pheochromocytomas/paragangliomas.

Peutz-Jeghers Syndrome (PJS)

NCCN guidelines (1.2021) outline clinical criteria for the genetic testing for PJS in

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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.

Retinoblastoma

NCCN guidelines do not currently include genetic testing recommendations for retinoblastoma.

Von Hippel-Lindau Syndrome (VHL)

NCCN guidelines (2.2022) outline criteria for further genetic risk evaluation for hereditary renal cell carcinoma syndromes, including VHL.

American Society of Clinical Oncologists (ASCO)

Germline Implications of Somatic Mutation Profiling

ASCO (2015) published the following statement regarding germline implications of somatic mutation profiling:

> "ASCO supports the communication to patients of medically relevant incidental germline findings from somatic mutation profiling conducted in the clinical setting. Only laboratories equipped to provide analytically and clinically valid results should conduct secondary analyses to identify germline variants. Laboratories that are not resourced to provide clinically valid information from secondary analysis of the normal sample in tumor-normal subtractive analyses should only report tumor-associated variants and should not be obligated to seek germline variants. Oncology providers should communicate the potential for incidental and secondary germline information to patients before conducting somatic mutation profiling and should review the potential benefits, limitations, and risks before testing. Providers should carefully ascertain patient preferences regarding the receipt of germline information and allow patients to decline receipt of germline information. This may require referral for additional counseling to help the patient clarify his or her preferences. In the setting of tumor-normal sequencing, laboratories conducting secondary analyses should develop mechanisms to report only somatic results for patients who choose to decline receipt of germline findings. ASCO supports research to determine how to best deliver pretest education, support patient preferences, and understand outcomes of providing incidental and secondary germline information with somatic testing."

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ASCO made the following recommendations (2015) for individuals diagnosed with colorectal cancer:

- Tumor testing for DNA mismatch repair (MMR) deficiency with immunohistochemistry for MMR proteins and/or MSI should be assessed in all CRC patients.
- If loss of MLH1/PMS2 protein expression is observed in the tumor, analysis of BRAF V600E mutation or analysis of methylation of the MLH1 promoter should be carried out first to rule out a sporadic case. If the tumor is MMR deficient and somatic BRAF mutation is not detected or MLH1 promoter methylation is not identified, testing for germline mutations is indicated.
- If loss of any of the other proteins (MSH2, MSH6, PMS2) is observed, germline genetic testing should be carried out for the genes corresponding to the absent proteins (eg, MSH2, MSH6, EPCAM, PMS2, or MLH1).
- Full germline genetic testing for Lynch syndrome should include DNA sequencing and large rearrangement analysis.
- Patients with multiple colorectal adenomas (> 10) should be considered for germline genetic testing of APC and/or MUTYH.
- Full germline genetic testing of APC should include DNA sequencing and large rearrangement analysis.
- Germline testing of MUTYH can be initiated by screening for the most common mutations (G396D, Y179C) in the white population followed by analysis of the entire gene in heterozygotes. Founder mutations among ethnic groups should be taken into account. For nonwhite individuals, full sequencing of MUTYH should be considered.

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.

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- 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.

American College of Medical Genetics and Genomics and the National Society of Genetic Counselors

ACMG and NSGC outlined referral indications for cancer predisposition assessment (2014). The document was reaffirmed in 2019 with the following caveat:

> "While the principles outlined for genetics referral for the specific tumors and syndromes listed remain valid, in many cases the indications for referral have expanded. The field of cancer genetics is rapidly evolving, including frequent discovery of additional genes and new clinical presentations, expanded gene panel testing, paired tumor and germline sequencing, and expanded utility of molecular testing in treatment planning. These changes have impacted referral considerations outlined in this document. We encourage clinicians to consult additional updated sources in making final decisions regarding referral. These include more recent versions of the National Comprehensive Cancer Network guidelines (https://www.nccn. org/professionals/physician_gls/default.aspx) and GeneReviews (https://www.ncbi.nlm.nih.gov/books/NBK1116/)."

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

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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."

The National Society of Genetic Counselors updated a position statement (2017) regarding the genetic testing of minors for adult-onset conditions, stating the following:

"[NSGC] encourages deferring predictive genetic testing of minors for adult-onset conditions when results will not impact childhood medical management or significantly benefit the child. Predictive testing should optimally be deferred until the individual has the capacity to weigh the associated risks, benefits, and limitations of this information, taking his/her circumstances, preferences, and beliefs into account to preserve his/her autonomy and right to an open future."

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

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based on their individual risk factors."

The American College of Obstetricians and Gynecologists (ACOG)

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).

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)."

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Endocrine Society

The Endocrine Society published a clinical practice guideline (2014) for pheochromocytoma and paraganglioma that included the following recommendations regarding genetic testing:

> 3.1 We recommend that all patients with PPGLs should be engaged in shared decision making for genetic testing.
>
> 3.2 We recommend the use of a clinical feature-driven diagnostic algorithm to establish the priorities for specific genetic testing in PPGL patients with suspected germline mutations.
>
> 3.3 We suggest that patients with paraganglioma undergo testing of SDH mutations and that patients with metastatic disease undergo testing for *SDHB* mutations.
>
> 3.4 We recommend that genetic testing for PPGL be delivered within the framework of health care. Specifically, pretest and post-test counseling should be available. All tests for PPGL genetic testing should be performed by accredited laboratories. (Ungraded recommendation).

American Association of Ophthalmic Oncologists and Pathologists

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:

- We recommend screening for at-risk children from birth up to the age of 7 years. After age 7 years, no further screening of asymptomatic children is recommended, unless they are known to carry an RB1 mutation. We suggest that individuals who are known RB1 mutation carriers be followed indefinitely with examinations every 1 to 2 years after the age of 7 years. A single dilated fundus examination to evaluate for asymptomatic spontaneously regressed retinoblastoma or retinoma is recommended for all first-degree relatives of a retinoblastoma proband, including older siblings if the RB1 genetic status of the relatives is unknown (grade C).
- 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

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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).

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