Medica Central Coverage Policy

Policy Name:	**Genetic Testing - Oncology Testing: Hereditary Cancer**
Effective Date:	**01/01/2026**

Important Information – Please Read Before Using This Policy

These services may or may not be covered by all Medica Central plans. Coverage is subject to requirements in applicable federal or state laws. Please refer to the member's plan document for other specific coverage information. If there is a difference between this general information and the member's plan document, the member's plan document will be used to determine coverage. With respect to Medicare, Medicaid, and other government programs, this policy will apply unless these programs require different coverage.

Members may contact Medica Customer Service at the phone number listed on their member identification card to discuss their benefits more specifically. Providers with questions may call the Provider Service Center. Please use the Quick Reference Guide on the Provider Communications page for the appropriate phone number. https://mo-central.medica.com/Providers/SSM-employee-health-plan-for-IL-MO-OK-providers

Medica Central coverage policies are not medical advice. Members should consult with appropriate health care providers to obtain needed medical advice, care, and treatment.

OVERVIEW

This policy addresses the use of genetic testing for hereditary cancer susceptibility. Pre-test and post-test genetic counseling that facilitates informed decision-making, addresses the possibility of secondary or incidental findings, and a plan for returning results before testing occurs is strongly advised.
For additional information see the Rationale and References section.
The tests, CPT codes, and ICD codes referenced in this policy are not comprehensive, and their inclusion does not represent a guarantee of coverage or non-coverage. Please see the Concert Platform for additional registered tests.

POLICY REFERENCE TABLE

COVERAGE CRITERIA SECTIONS	EXAMPLE TESTS (LABS)	COMMON BILLING CODES	SUPPORT
Hereditary Cancer Panels			
Pan-Cancer Hereditary Cancer Susceptibility Panels	MyRisk (Myriad Genetics)	81432, 81433, 0134U, 0474U, C15-26, C50-58, Z17, Z80, Z85.0-85.9	Rationale/ References
	Common Hereditary Cancers Panel (Invitae Corporation)		
	CancerNext (Ambry Genetics)		

COVERAGE CRITERIA SECTIONS	EXAMPLE TESTS (LABS)	COMMON BILLING CODES	SUPPORT
	Tempus xG Hereditary Cancer Panel (Tempus)		
	RNAinsight with CancerNext - 0134U (Ambry Genetics)		
	GeneticsNow Comprehensive Germline Panel - 0474U (GoPath Diagnostics)		
Hereditary Breast and/or Ovarian Cancer Susceptibility Panels	BRCA1 and BRCA2 Panel (Invitae Corporation)	81162, 81166, 81167, 81216, 81307, 81321, 81351, 81432, 81433, 0129U, 0131U, 0132U, 0133U, 0134U, 0135U, 0138U, Z85, Z86	Rationale/ References
	VistaSeq Breast Cancer Panel (LabCorp)		
	Breast Cancer Panel (Invitae Corporation)		
	Breast Cancer STAT NGS Panel (Sequencing & Deletion/Duplication) (Fulgent Genetics)		
	Breast Cancer - High Risk Panel (PreventionGenetics, part of Exact Sciences)		
	BRCA1/2 Seq and Del/Dup (Ambry Genetics)		
	BRCAplus - 0129U (Ambry Genetics)		
	RNAinsight for BreastNext - 0131U (Ambry Genetics)		
	RNAinsight for CancerNext - 0134U (Ambry Genetics)		
	RNAinsight for OvaNext - 0132U (Ambry Genetics)		
	RNAinsight for ProstateNext - 0133U (Ambry Genetics)		
	RNAinsight for GYNPlus - 0135U (Ambry Genetics)		

COVERAGE CRITERIA SECTIONS	EXAMPLE TESTS (LABS)	COMMON BILLING CODES	SUPPORT
	RNAinsight for BRCA1/2 - 0138U (Ambry Genetics)		
Hereditary Gastrointestinal/Colorectal Cancer Susceptibility Panels	Hereditary Colorectal Cancer Panel (Invitae Corporation)	81435, 81436, 0101U, 0130U, 0134U, 0158U, 0159U, 0160U, 0161U, 0162U, C15-26, Z80, Z83, Z84, Z85, Z86	Rationale/ References
	ColoNext - 0101U (Ambry Genetics)		
	RNAinsight for ColoNext - 0130U (Ambry Genetics)		
	RNAinsight for CustomNext + RNA: Lynch (MLH1, MSH2, MSH6, PMS2) - 0162U (Ambry Genetics)		
	RNAinsight for CancerNext - 0134U (Ambry Genetics)		
	CustomNext RNA: MLH1, MSH2, MSH6, and/or PMS2 - 0158U, 0159U, 0160U, 0161U (Ambry Genetics)		
Hereditary Gastric Cancer Susceptibility Panels	Gastric Cancer Panel (Invitae Corporation)	81201, 81203, 81292, 81294, 81295, 81297, 81298, 81300, 81317, 81319, 81403, 81404, 81405, 81406, 81408, 81479, C16, Z80, Z85, Z86	Rationale/ References
	Gastric Cancer Panel (PreventionGenetics, part of Exact Sciences)		
Hereditary Pancreatic Cancer Susceptibility Panels	Pancreatic Cancer Panel (Invitae Corporation)	81162, 81163, 81201, 81292, 81295, 81298, 81351, 81432, 81433, 81479, C25, Z80, Z84, Z85, Z86	Rationale/ References
	Pancreatic Cancer Panel (GeneDx)		
Hereditary Polyposis Susceptibility Panels	Hereditary Polyposis Panel (PreventionGenetics, part of Exact Sciences)	81201, 81203, 81406, 81479, D12, K63.5, Z80, Z84, Z85, Z86	Rationale/ References
	Adenomatous Polyposis Panel (Invitae Corporation)		

COVERAGE CRITERIA SECTIONS	EXAMPLE TESTS (LABS)	COMMON BILLING CODES	SUPPORT
Hereditary Prostate Cancer Susceptibility Panels	Hereditary Prostate Cancer Panel (Invitae Corporation)	81162, 81292, 81295, 81351, 81479, 0133U, 0475U, C61, Z80, Z84, Z85, Z86	Rationale/ References
	ProstateNext (Ambry Genetics)		
	RNAinsight for ProstateNext - 0133U (Ambry Genetics)		
	ProstateNow Prostate Germline Panel - 0475U (GoPath Diagnostics)		
Hereditary Neuroendocrine Cancer Susceptibility Panels	Hereditary Paraganglioma-Pheochromocytoma Panel (Invitae Corporation)	81437, C74, C75, C7A, Z80, Z84, Z85, Z86	Rationale/ References
	Hereditary Paraganglioma and Pheochromocytoma Panel (PreventionGenetics, part of Exact Sciences)		
BRCA1 and BRCA2 Gene Testing			
BRCA1 or *BRCA2* Targeted Variant or Known Familial Variant Analysis	BRCA1 or BRCA2 Targeted Variant-Single Test (GeneDx)	81215, 81217, C24.1, C50, C56, D05, Z17, Z80, Z83, Z84, Z85, Z86	Rationale/ References
BRCA1 and *BRCA2* Targeted Variant Analysis - Ashkenazi Jewish Founder Variants	BRCA1/2 Ashkenazi Jewish 3-Site Mutation Panel (Ambry Genetics)	81212, C24.1, C50, C56, D05, Z17, Z80, Z83, Z84, Z85, Z86	Rationale/ References
	MultiSite 3 BRCAnalysis (Myriad Genetics)		
PALB2 Gene Testing			
PALB2 Targeted Variant Analysis	PALB2 Targeted Variant (GeneDx)	81308, C15-26, Z80, Z84, Z85, Z86	Rationale/ References
ATM and/or CHEK2 Gene Testing			
ATM or *CHEK2* Targeted Variant Analysis	ATM Targeted Variant - Single Test (GeneDx)	81479, C50, D05, Z80, Z84, Z85, Z86	Rationale/ References
	CHEK2 Targeted Variant - Single Test (GeneDx)		
Lynch Syndrome / Hereditary Nonpolyposis Colorectal Cancer (HNPCC)			

COVERAGE CRITERIA SECTIONS	EXAMPLE TESTS (LABS)	COMMON BILLING CODES	SUPPORT
MLH1, MSH2, MSH6, PMS2, or *EPCAM* Targeted Variant Analysis	MSH6 Targeted Variant; PMS2 Targeted Variant; EPCAM Targeted Variant (GeneDx)	81293, 81296, 81299, 81318, 81479, C15-22, C24-6, C26, C53-57 Z80, Z84, Z85, Z86	Rationale/ References
	Hereditary Nonpolyposis Colorectal Cancer (HNPCC): MLH1 (Known Mutation) (LabCorp)		
	Hereditary Nonpolyposis Colorectal Cancer (HNPCC): MSH2 (Known Mutation) (LabCorp)		
MLH1, MSH2, MSH6, PMS2, and/or *EPCAM* Sequencing and/or Deletion/Duplication Analysis	VistaSeq Lynch Syndrome Panel (LabCorp)	81292, 81294, 81295, 81297, 81298, 81300, 81317, 81319, 81403, 0158U, 0159U, 0160U, 0161U, 0162U, 0238U, C15-22, C24-6, C26, C53-57, Z80, Z84, Z85, Z86	Rationale/ References
	Lynch Syndrome Panel (Invitae Corporation)		
	Genomic Unity Lynch Syndrome Analysis - 0238U (Variantyx)		
	CustomNext + RNA: MLH1, MSH2, MSH6, and/or PMS2 - 0158U, 0159U, 0160U, 0161U, or 0162U (Ambry Genetics)		
Adenomatous Polyposis Conditions			
APC or *MUTYH* Targeted Variant Analysis	APC Targeted Variant - Single Test (GeneDx)	81202, 81403, 81401, C15-21, D12, Z80, Z84, Z85, Z86	Rationale/ References
	MUTYH Targeted Variant - Single Test (GeneDx)		
BAP1-Tumor Predisposition Syndrome			
BAP1 Targeted Variant Analysis	BAP1: Site Specific Analysis (familial) (Univ of Pennsylvania School of Medicine-Genetic Diagnostic Laboratory)	81403, C22, C45, C64, C69, D22, D32, Z80, Z84, Z85, Z86	Rationale/ References
BAP1 Sequencing and/or Deletion/Duplication Analysis	BAP1 Full Gene Sequencing and Deletion/Duplication	81479, C22, C45, C64, C69, D22, D32, Z80, Z84, Z85, Z86	Rationale/ References

COVERAGE CRITERIA SECTIONS	EXAMPLE TESTS (LABS)	COMMON BILLING CODES	SUPPORT
	(Invitae Corporation)		
Birt-Hogg-Dube Syndrome (BHDS)			
FLCN Targeted Variant Analysis	FLCN Targeted Variant - Single Test (GeneDx)	81479, C65, D14.3, D23.9, Z84, Z85, Z86	Rationale/ References
FLCN Sequencing and/or Deletion/Duplication Analysis	Birt-Hogg-Dube Syndrome Test (Invitae Corporation)	81479, C65, D14.3, D23.9, Z84, Z85, Z86	Rationale/ References
Cowden Syndrome (CS)/PTEN Hamartoma Tumor Syndrome (PHTS)			
PTEN Targeted Variant Analysis	PTEN Targeted Variant - Single Test (GeneDx)	81322, C15-21, C26, C50, C54, C55, C64, C73, D12, D13, D17, D23, D24, F78, F84.0, Q75.3, Q87.89, Z80, Z84, Z85, Z86	Rationale/ References
PTEN Sequencing and/or Deletion/Duplication Analysis	PTEN Gene Sequencing and Del/Dup (GeneDx)	81321, 81323, C15-21, C26, C50, C54, C55, C64, C73, D12, D13, D17, D23, D24, F78, F84.0, Q75.3, Q87.89, Z80, Z84, Z85, Z86	Rationale/ References
Familial Atypical Multiple Mole Melanoma Syndrome (FAMMM)			
CDKN2A Targeted Variant Analysis	CDKN2A Targeted Variant - Single Test (GeneDx)	81479, C43, Z12.83, Z80, Z84, Z85, Z86	Rationale/ References
CDKN2A Sequencing and/or Deletion/Duplication Analysis	CDKN2A Full Gene Sequencing and Deletion/Duplication (Invitae Corporation)	81404, 81479, C43, Z12.83, Z80, Z84, Z85, Z86	Rationale/ References
Hereditary Diffuse Gastric Cancer (aka, Signet Ring Cell Gastric Cancer)			
CDH1 Targeted Variant Analysis	CDH1 Targeted Variant - Single Test (GeneDx)	81479, C16, C50, Q35, Q36, Z80, Z84, Z85, Z86	Rationale/ References
CDH1 Sequencing and/or Deletion/Duplication Analysis	CDH1 Full Gene Sequencing and Deletion/Duplication (Invitae Corporation)	81406, 81479, C16, C50, Q35, Q36, Z80, Z84, Z85, Z86	Rationale/ References
Juvenile Polyposis Syndrome (JPS)			

COVERAGE CRITERIA SECTIONS	EXAMPLE TESTS (LABS)	COMMON BILLING CODES	SUPPORT
SMAD4 or *BMPR1A* Targeted Variant Analysis	Targeted Variant: SMAD4 (PreventionGenetics, part of Exact Sciences) Targeted Variant: BMPR1A (PreventionGenetics, part of Exact Sciences)	81403, C15-C26, D12, Z80, Z84, Z85, Z86	Rationale/ References
SMAD4 and/or *BMPR1A* Sequencing and/or Deletion/Duplication Analysis	Hereditary Juvenile Polyposis Syndrome Panel (Invitae Corporation) Juvenile Polyposis Panel (BMPR1A and SAMD4) (Quest Diagnostics)	81405, 81406, 81479, C15-C26, D12, Z80, Z84, Z85, Z86	Rationale/ References
Hereditary Leiomyomatosis and Renal Cell Cancer (HLRCC)			
FH Targeted Variant Analysis	FH Known Familial Mutation Analysis (University Hospitals)	81403, C44, C55, C64, D23, D25, Z84, Z85, Z86	Rationale/ References
FH Sequencing and/or Deletion/Duplication Analysis	Hereditary Leiomyomatosis and Renal Cell Carcinoma (Ambry Genetics)	81405, 81479, C44, C55, C64, D23, D25, Z84, Z85, Z86	Rationale/ References
Li-Fraumeni Syndrome (LFS)			
TP53 Targeted Variant Analysis	TP53 Targeted Variant - Single Test (GeneDx)	81352, 81353, C15-26, C30-41, C45, C47-49, C50, C71, C95.9, Z80, Z84, Z85, Z86	Rationale/ References
TP53 Sequencing and/or Deletion/Duplication Analysis	Li-Fraumeni Syndrome, TP53 Sequencing and Deletion/Duplication (Quest Diagnostics)	81351, 81479, C15-26, C30-41, C45, C47-49, C50, C71, C95.9, Z80, Z84, Z85, Z86	Rationale/ References
Multiple Endocrine Neoplasia - Type 1 (MEN1)			
MEN1 Targeted Variant Analysis	MEN1 Targeted Variant - Single Test (GeneDx)	81479, C25, C75.0, D35.2, E31.2, Z80, Z84, Z85, Z86	Rationale/ References
MEN1 Sequencing and/or Deletion/Duplication Analysis	MEN1 Sequencing and Deletion/Duplication (Quest Diagnostics)	81404, 81405, C25, C75.0, D35.2, E31.2, Z80, Z84, Z85, Z86	Rationale/ References

COVERAGE CRITERIA SECTIONS	EXAMPLE TESTS (LABS)	COMMON BILLING CODES	SUPPORT
	MEN1 Full Gene Sequencing and Deletion/Duplication (Invitae Corporation)		
Multiple Endocrine Neoplasia Type 2 (MEN2)			
RET Targeted Variant Analysis	RET Targeted Variant - Single Test (GeneDx)	81404, C7A, C73-75, D3A, Z80, Z84, Z85, Z86	Rationale/ References
RET Sequencing and/or Deletion/Duplication Analysis	RET Full Gene Sequencing and Deletion/Duplication (Invitae Corporation)	81406, 81479, S3840, C7A, C73-75, D3A, Z80, Z84, Z85, Z86	Rationale/ References
Nevoid Basal Cell Carcinoma Syndrome (NBCCS) (aka Gorlin syndrome)			
PTCH1 or *SUFU* Targeted Variant Analysis	Targeted Variant: PTCH1 or SUFU (GeneDx)	81479, C44, C71.6, G93, M27.4, Z84, Z85, Z86	Rationale/ References
PTCH1 and/or *SUFU* Sequencing and/or Deletion/Duplication Analysis	Basal Cell Nevus Syndrome Panel (Invitae Corporation)	81479, C44, C71.6, G93, M27.4, Z84, Z85, Z86	Rationale/ References
Hereditary Paraganglioma/Pheochromocytoma Syndrome (PGL/PCC)			
MAX, SDHA, SDHAF2, SDHB, SDHC, SDHD, or *TMEM127* Targeted Variant Analysis	SDHB, SDHD, SDHC, MAX, SDHAF2, or TMEM127 Targeted Variant - Single Test (GeneDx)	81479, C7A, C74.1, D35.00, D44.7, Z84, Z85, Z86	Rationale/ References
	Targeted Variants: MAX, SDHAF2, TMEM127 (PreventionGenetics, part of Exact Sciences)		
MAX, SDHA, SDHAF2, SDHB, SDHC, SDHD, and/or *TMEM127* Sequencing and/or Deletion/Duplication Analysis	SDHB Full Gene Sequencing and Deletion/Duplication (Invitae Corporation)	81404, 81405, 81406, 81479, C7A, C74.1, D35.00, D44.7, Z84, Z85, Z86	Rationale/ References
	SDHA Full Gene Sequencing and Deletion/Duplication (Invitae Corporation)		

COVERAGE CRITERIA SECTIONS	EXAMPLE TESTS (LABS)	COMMON BILLING CODES	SUPPORT
	SDHC Full Gene Sequencing and Deletion/Duplication (Invitae Corporation)		
	SDHD Full Gene Sequencing and Deletion/Duplication (Invitae Corporation)		
	MAX Full Gene Sequencing and Deletion/Duplication (Invitae Corporation)		
	SDHAF2 Full Gene Sequencing and Deletion/Duplication (Invitae Corporation)		
	TMEM127 Full Gene Sequencing and Deletion/Duplication (Invitae Corporation)		
Peutz-Jeghers Syndrome (PJS)			
STK11 Targeted Variant Analysis	STK11 Targeted Variant - Single Test (GeneDx)	81479, C50, Q85.8, Z80, Z84, Z85, Z86	Rationale/ References
STK11 Sequencing and/or Deletion/Duplication Analysis	STK11 Full Gene Sequencing and Deletion/Duplication (Invitae Corporation)	81404, 81405, C50, Q85.8, Z80, Z84, Z85, Z86	Rationale/ References
Retinoblastoma			
RB1 Targeted Variant Analysis	Retinoblastoma: Site Specific Analysis (Familial) (Univ of Pennsylvania School of Medicine-Genetic Diagnostic Laboratory)	81403, C69, C75.3, Z80, Z84, Z85, Z86	Rationale/ References
RB1 Sequencing and/or Deletion/Duplication Analysis	RB1 Full Gene Sequencing and Deletion/Duplication (Invitae Corporation)	81479, S3841, C69, C75.3, Z80, Z84, Z85, Z86	Rationale/ References
Von Hippel-Lindau Syndrome (VHL)			

COVERAGE CRITERIA SECTIONS	EXAMPLE TESTS (LABS)	COMMON BILLING CODES	SUPPORT
VHL Targeted Variant Analysis	VHL Targeted Variant - Single Test (GeneDx)	81403, C64, C7A, D3A, D35.00, K86.2, N28, N50.3, Q85.8, Z80, Z84, Z85, Z86	Rationale/ References
VHL Sequencing and/or Deletion/Duplication Analysis	VHL Full Gene Sequencing and Deletion/Duplication (Invitae Corporation)	81403, 81404, S3842, C64, C7A, D3A, D35.00, K86.2, N28, N50.3, Q85.8, Z80, Z84, Z85, Z86	Rationale/ References
	VHL Gene Sequencing and Deletion/Duplication (Quest Diagnostics)		

RELATED POLICIES

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

- ***Oncology Testing: Algorithmic Assays*** for coverage criteria related to gene expression profiling and tumor biomarker tests with algorithmic analyses.
- ***Oncology Testing: Cancer Screening and Surveillance*** for coverage criteria related to screening and biomarker cancer tests.
- ***Oncology Testing: Hematologic Malignancy Molecular Diagnostics*** for coverage criteria related to molecular profiling of a known or suspected blood cancer (e.g., broad molecular profiling, including Minimal Residual Disease (MRD) Testing, Tumor Mutational Burden (TMB), and cytogenetic / fusion testing).
- ***Oncology Testing: Solid Tumor Molecular Diagnostics*** for coverage criteria related to molecular profiling of a known or suspected cancer (e.g., broad molecular profiling, including Minimal Residual Disease (MRD) Testing, Tumor Mutational Burden (TMB), and cytogenetic / fusion testing).
- ***Specialty Testing: Hematology*** for coverage criteria related to diagnostic tests for benign (non-cancerous) hematologic conditions including sickle cell disease, inherited anemias, and hemophilias.
- ***General Approach to Laboratory Testing*** for coverage criteria related to hereditary cancer susceptibility, including known familial variant testing, that is not specifically discussed in this or another non-general policy.

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COVERAGE CRITERIA

HEREDITARY CANCER PANELS

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 is considered **medically necessary** when the member meets **BOTH** A and B:

A. The member has one of the following:

1. A personal history, or a close relative with a personal history, of one of the following cancers less than or equal to 50 years of age:

a) Breast cancer, **OR**

b) Colorectal cancer, **OR**

c) Endometrial cancer, **OR**

2. The member has a personal history of one of the following:

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

b) Metastatic prostate cancer at any age**, OR**

c) Ovarian, peritoneal, or fallopian tube cancer at any age, **OR**

3. The member's personal or family history is suspicious for more than one hereditary cancer syndrome, **AND**

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

II. Genetic testing using a pan-cancer hereditary cancer susceptibility panel is considered **investigational** for all other indications.

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

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

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Hereditary Breast and/or Ovarian Cancer Susceptibility Panels

A hereditary breast and/or ovarian cancer susceptibility panel includes genes that are associated with an inherited susceptibility to breast cancer, ovarian cancer, or both.

I. Genetic testing using a hereditary breast and/or ovarian cancer susceptibility panel is considered **medically necessary** when:

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

B. The member has one of the following:

1. The member has a personal history of breast cancer ≤ age 65, **OR**

2. The member has a personal history of ovarian cancer (including fallopian tube cancer or peritoneal cancer), **OR**

3. The member has a personal history of breast cancer, **AND**
    a) One of the following:
        (1) Ashkenazi Jewish ancestry, **OR**
        (2) Male (sex assigned at birth), **OR**
        (3) Triple-negative breast cancer, **OR**
        (4) Pancreatic or ampullary cancer, **OR**
        (5) Metastatic prostate cancer, **OR**
        (6) High- or very-high-risk group prostate cancer, **OR**
        (7) Multiple primary breast cancers (diagnosed synchronously or metachronously), **OR**
        (8) The member has a close relative with any one of the following:
            (a) Breast cancer diagnosed ≤age 50, **OR**
            (b) Male breast cancer, **OR**
            (c) Ovarian cancer, **OR**
            (d) Pancreatic cancer, **OR**
            (e) Prostate cancer that is either metastatic, intermediate-risk or high- or very-high-risk group, **OR**
    b) There are 3 or more total diagnoses of breast cancer and/or prostate cancer (any grade) on the same side of the family including the member with breast cancer, **OR**
4. The member has a personal history of lobular breast cancer, **AND**
    a) A personal or family history of diffuse gastric cancer, **OR**
5. The member is unaffected or the member does not have a personal history of breast cancer that meets the above criteria, **AND**
    a) The member has a first- or second-degree relative diagnosed with breast cancer at or before age 50 years, **OR**
    b) The member has a first- or second-degree relative meeting any of criteria I.B.2, I.B.3, or I.B.4, **OR**
    c) The member's probability of having a *BRCA1* or *BRCA2* pathogenic variant is greater than 2.5% based on prior probability models (e.g., Tyrer-Cuzick, BRCApro, CanRisk), **OR**
6. The member has a personal history of breast cancer, **AND**

a) The member has recurrent unresectable or metastatic breast cancer and is being considered for systemic treatment using PARP inhibitors, **OR**

b) The member has recurrent or metastatic breast cancer and is being considered for adjuvant treatment with olaparib therapy.

II. Genetic testing using a STAT hereditary breast cancer panel is considered **medically necessary** when:

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

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

III. Genetic testing using a hereditary breast and/or ovarian cancer susceptibility panel is considered **investigational** for all other indications.

IV. *BRCA1/BRCA2* mRNA sequencing analysis in genes associated with breast and/or ovarian cancers for the interpretation of variants of unknown significance 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 Gastrointestinal/Colorectal Cancer Susceptibility Panels

I. Genetic testing using a hereditary gastrointestinal/colorectal cancer susceptibility panel is considered **medically necessary** when:

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

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

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

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

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

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

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

II. Genetic testing using a hereditary gastrointestinal/colorectal cancer susceptibility panel is considered **investigational** for all other indications.

III. Hereditary gastrointestinal/colorectal cancer susceptibility panel targeted mRNA sequencing analysis for the interpretation of variants of unknown significance is considered **investigational** because it is typically either considered an existing

component of the genetic testing process for quality assurance or follow up testing without proven utility.

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

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Hereditary Gastric Cancer Susceptibility Panels

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

I. Genetic testing using a hereditary gastric susceptibility panel is considered **medically necessary** when:

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

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

      1. Lynch syndrome/Hereditary Nonpolyposis Colorectal Cancer, **OR**

      2. Hereditary Diffuse Gastric Cancer, **OR**

      3. Juvenile Polyposis Syndrome, **OR**

      4. Peutz-Jeghers Syndrome, **OR**

      5. Hereditary Polyposis Susceptibility Panels, **AND**

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

II. Genetic testing using a hereditary gastric cancer susceptibility panel is considered **investigational** for all other indications.

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Hereditary Pancreatic Cancer Susceptibility Panels

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

I. Genetic testing using a hereditary pancreatic cancer susceptibility panel is considered **medically necessary** when:

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

   B. The member has one of the following:

      1. Pancreatic or ampullary cancer, **OR**

      2. A first-degree relative with pancreatic cancer.

II. Genetic testing using a hereditary pancreatic cancer susceptibility panel is considered **investigational** for all other indications.

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Hereditary Polyposis Susceptibility Panels

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

I. Genetic testing using a hereditary polyposis susceptibility panel is considered **medically necessary** when the member meets **BOTH** A and B:

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

      1. 10 or more cumulative adenomas, **OR**
      2. Congenital hypertrophy of the retinal pigment epithelium (CHRPE), **OR**
      3. Desmoid tumor, **OR**
      4. Hepatoblastoma, **OR**
      5. Cribriform-morular variant of papillary thyroid cancer, **OR**
      6. A clinical diagnosis of serrated polyposis syndrome, with at least some adenomas, based on one of the following:
         a) 5 or more serrated polyps proximal to the rectum, all being 5mm or greater in size and at least 2 being 10mm or greater in size, **OR**
         b) More than 20 serrated polyps of any size distributed throughout the large bowel, with at least 5 or more being proximal to the rectum, **AND**

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

II. Genetic testing using a hereditary polyposis susceptibility panel is considered **investigational** for all other indications.

III. mRNA sequencing analysis in genes associated with polyposis syndromes for the interpretation of variants of unknown significance 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 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 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. Metastatic or node-positive prostate cancer, **OR**

2. High-risk localized prostate cancer or very-high-risk localized prostate cancer, **OR**
3. Intermediate risk prostate cancer with intraductal/cribriform histology, **OR**
4. Prostate cancer diagnosed ≤ 55 years of age, **OR**

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

1. One or more close relatives with any of the following:
   a) Breast cancer at or under age 50, **OR**
   b) Triple-negative breast cancer at any age, **OR**
   c) Male (sex assigned at birth) breast cancer at any age, **OR**
   d) Ovarian cancer at any age, **OR**
   e) Pancreatic cancer at any age, **OR**
   f) Metastatic, node positive, very-high-risk prostate cancer, or high-risk prostate cancer at any age, **OR**
2. Three or more close relatives with prostate cancer (any grade) and/or breast cancer on the same side of the family including the member with prostate cancer, **OR**
3. Ashkenazi Jewish ancestry, **OR**

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

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

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

II. Genetic testing using a hereditary prostate cancer susceptibility panel 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 is considered **investigational** because it is typically either considered an existing component of the genetic testing process for quality assurance, or follow up testing without proven utility.

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Hereditary Neuroendocrine Cancer Susceptibility Panels

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

I. Genetic testing using a hereditary neuroendocrine cancer susceptibility panel is considered **medically necessary** when:

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

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

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

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

II. Genetic testing using a hereditary neuroendocrine cancer susceptibility panel is considered **investigational** for all other indications.

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

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BRCA1 AND BRCA2 GENE TESTING

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

I. *BRCA1* or *BRCA2* targeted variant or known familial 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 family history of a known *BRCA1* or *BRCA2* pathogenic or likely pathogenic variant, **OR**
2. A pathogenic or likely pathogenic variant in *BRCA1* or *BRCA2* was identified by tumor profiling in the member and germline analysis has not yet been performed.

II. *BRCA1* or *BRCA2* targeted variant or known familial variant analysis for hereditary cancer susceptibility is considered **investigational** for all other indications.

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

I. *BRCA1* and *BRCA2* 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 (at least one grandparent of Ashkenazi Jewish ancestry).

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

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PALB2 GENE TESTING

PALB2 Targeted Variant Analysis

I. *PALB2* 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:

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

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

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

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ATM AND/OR CHEK2 GENE TESTING

ATM or *CHEK2* Targeted Variant Analysis

I. *ATM* or *CHEK2* 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:

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 in *ATM* or *CHEK2* was identified by tumor profiling in the member and germline analysis has not yet been performed.

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

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LYNCH SYNDROME / HEREDITARY NONPOLYPOSIS COLORECTAL CANCER (HNPCC)

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

I. *MLH1*, *MSH2*, *MSH6*, *PMS2*, or *EPCAM* targeted variant analysis for Lynch syndrome/HNPCC is considered **medically necessary** when:

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

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

II. *MLH1*, *MSH2*, *MSH6*, *PMS2*, or *EPCAM* targeted variant analysis for Lynch syndrome/HNPCC is considered **investigational** for all other indications.

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

I. Lynch syndrome panels, *MLH1*, *MSH2*, *MSH6*, *PMS2*, and/or *EPCAM* sequencing and/or duplication analysis for Lynch syndrome/HNPCC is considered **medically necessary** when:

A. The member has a tumor that 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 a Lynch syndrome-related cancer (colorectal, endometrial, gastric, ovarian, pancreatic, urothelial, brain (usually glioblastoma), biliary tract, small intestinal, sebaceous adenoma, sebaceous carcinoma, or keratoacanthoma), **AND** any of the following:

1. Diagnosed before age 50, **OR**

2. Diagnosed at any age with an additional Lynch syndrome-related cancer, **OR**

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

4. Diagnosed at any age with two or more first- or second-degree relatives diagnosed at any age with a Lynch syndrome-related cancer, **OR**

C. The member 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- or second-degree relatives diagnosed with colorectal or endometrial cancer and an additional Lynch syndrome-related cancer, **OR**

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

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

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

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

II. Lynch syndrome panel, *MLH1*, *MSH2*, *MSH6*, *PMS2*, and/or *EPCAM* sequencing and/or duplication analysis for Lynch syndrome/HNPCC is considered **investigational** for all other indications.

III. *MLH1, MSH2, MSH6, PMS2* and *EPCAM* mRNA sequencing analysis for the interpretation of variants of unknown significance 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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ADENOMATOUS POLYPOSIS CONDITIONS

***APC* or *MUTYH* Targeted Variant Analysis**

I. *APC* or *MUTYH* targeted variant analysis for adenomatous polyposis testing is considered **medically necessary** when:

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

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

II. *APC* or *MUTYH* targeted variant analysis for adenomatous polyposis conditions is considered **investigational** for all other indications.

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BAP1-TUMOR PREDISPOSITION SYNDROME

***BAP1* Targeted Variant Analysis**

I. *BAP1* targeted variant analysis 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 by tumor profiling in the member and germline analysis has not yet been performed.

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

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***BAP1* Sequencing and/or Deletion/Duplication Analysis**

I. *BAP1* sequencing and/or deletion/duplication analysis 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), **OR**

b) Uveal melanoma, **OR**

c) Malignant mesothelioma, **OR**

d) Renal cell carcinoma, **OR**

e) Cholangiocarcinoma, **OR**

f) Meningioma, **OR**

2. One of the tumors/cancers listed in the criteria A.1., **AND**

a) A cutaneous melanoma, **OR**

b) A basal cell carcinoma, **OR**

3. One of the tumors/cancers listed in the criteria A.1., **AND**

a) A first- or second-degree relative with any of the following tumors/cancers:

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

(2) Uveal melanoma, **OR**

(3) Malignant mesothelioma, **OR**

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

(5) Cholangiocarcinoma, **OR**

(6) Meningioma, **OR**

(7) Cutaneous melanoma, **OR**

(8) Basal cell carcinoma, **OR**

4. Both of the following:
    a) A diagnosis of:
        (1) Cutaneous melanoma, **OR**
        (2) Basal cell carcinoma, **AND**
    b) A first- or second-degree relative with any of the following tumors/cancer:
        (1) *BAP1*-inactivated melanocytic tumors (aka atypical spitz tumor), **OR**
        (2) Uveal melanoma, **OR**
        (3) Malignant mesothelioma, **OR**
        (4) Renal cell carcinoma, **OR**
        (5) Cholangiocarcinoma, **OR**
        (6) Meningioma.

II. *BAP1* sequencing and/or deletion/duplication analysis 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 for Birt-Hogg-Dube syndrome (BHDS) is considered **medically necessary** when:
    A. The member has a first- or second-degree relative with a known pathogenic or likely pathogenic variant in *FLCN*, **OR**
    B. A pathogenic or likely pathogenic variant in *FLCN* was identified by tumor profiling in the member and germline analysis has not yet been performed.

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

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

I. *FLCN* sequencing and/or deletion/duplication analysis for Birt-Hogg-Dube syndrome (BHDS) is considered **medically necessary** when:
    A. The member has a personal history of any of the following:
        1. 5 or more fibrofolliculomas/trichodiscomas with at least one confirmed histologically, **OR**

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

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

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

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

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

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

I. *PTEN* sequencing and/or deletion/duplication analysis 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**
2. Adult Lhermitte-Duclos disease (LDD) (defined as the presence of a cerebellar dysplastic gangliocytoma), **OR**
3. Autism-spectrum disorder and macrocephaly, **OR**
4. At least 2 biopsy-proven trichilemmomas, **OR**

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

1. Macrocephaly (greater than or equal to 97 percentile), **OR**
2. Lhermitte-Duclos disease, **OR**
3. Gastrointestinal hamartomas or ganglioneuromas, **AND**
4. At least two of the following:
    a) Breast cancer, **OR**
    b) Endometrial cancer, **OR**
    c) Thyroid cancer (follicular), **OR**
    d) Macular pigmentation of the glans penis, **OR**
    e) Mucocutaneous lesions (One biopsy-proven trichilemmoma; multiple palmoplantar keratoses; multifocal or extensive oral mucosal papillomatosis; multiple cutaneous facial papules), **OR**

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

1. Breast cancer, **OR**
2. Endometrial cancer, **OR**
3. Thyroid cancer (follicular), **OR**
4. Multiple gastrointestinal hamartomas or ganglioneuromas, **OR**
5. Macrocephaly (greater than or equal to 97 percentile), **OR**
6. Macular pigmentation of the glans penis, **OR**
7. Mucocutaneous lesions (one biopsy-proven trichilemmoma; multiple palmoplantar keratoses; multifocal or extensive oral mucosal papillomatosis; multiple cutaneous facial papules), **AND**
8. At least three of the following:
    a) Autism spectrum disorder, **OR**
    b) Colon cancer, **OR**
    c) Esophageal glycogenic acanthosis (3 or more), **OR**
    d) Lipomas, **OR**
    e) Intellectual disability (i.e., IQ less than or equal to 75), **OR**
    f) Thyroid cancer (papillary or follicular variant of papillary thyroid cancer), **OR**
    g) Thyroid structural lesions (such as adenoma, multinodular goiter), **OR**
    h) Renal cell carcinoma, **OR**

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

j) Testicular lipomatosis, **OR**

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

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

1. Breast cancer, **OR**
2. Endometrial cancer, **OR**
3. Thyroid cancer (follicular), **OR**
4. Multiple gastrointestinal hamartomas or ganglioneuromas, **OR**
5. Macular pigmentation of the glans penis, **OR**
6. Mucocutaneous lesions (one biopsy-proven trichilemmoma; multiple palmoplantar keratoses; multifocal or extensive oral mucosal papillomatosis; multiple cutaneous facial papules), **OR**

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

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

F. The member has any of the following:

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

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

8. At least three of the following:

    a) Autism spectrum disorder, **OR**

    b) Colon cancer, **OR**

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

    d) Lipomas, **OR**

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

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

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

    h) Renal cell carcinoma, **OR**

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

    j) Testicular lipomatosis, **OR**

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

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

1. Autism spectrum disorder, **OR**

2. Colon cancer, **OR**

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

4. Lipomas, **OR**

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

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

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

8. Renal cell carcinoma, **OR**

9. Single GI hamartoma or ganglioneuroma, **OR**

10. Testicular lipomatosis, **OR**

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

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

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

a) Breast cancer, **OR**

b) Endometrial Cancer, **OR**

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

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

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

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

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

2. At least two of the following:

a) Autism spectrum disorder, **OR**

b) Colon cancer, **OR**

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

d) Lipomas, **OR**

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

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

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

h) Renal cell carcinoma, **OR**

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

j) Testicular lipomatosis, **OR**

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

I. The member has a first- or second-degree relative who is untested, deceased, and meets any of the above criteria.

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

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FAMILIAL ATYPICAL MULTIPLE MOLE MELANOMA SYNDROME (FAMMM)

CDKN2A Targeted Variant Analysis

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

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

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

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

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CDKN2A Sequencing and/or Deletion/Duplication Analysis

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

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

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

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

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

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

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

CDH1 Targeted Variant Analysis

I. *CDH1* targeted variant analysis for Hereditary Diffuse Gastric Cancer (aka gastric signet ring cell carcinoma) 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 pathogenic or likely pathogenic variant in *CDH1* was identified by tumor profiling in the member and germline analysis has not yet been performed.

II. *CDH1* targeted variant analysis for Hereditary Diffuse Gastric Cancer (aka gastric signet ring cell carcinoma) is considered **investigational** for all other indications.

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CDH1 Sequencing and/or Deletion/Duplication Analysis

I. *CDH1* sequencing and/or deletion/duplication analysis for Hereditary Diffuse Gastric Cancer (aka gastric signet ring cell carcinoma) 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. Diffuse gastric cancer (aka gastric signet ring cell carcinoma, or SRCC) at any age, **OR**

2. Lobular breast cancer at any age with a personal or family history of diffuse gastric cancer/gastric SRCC, **OR**

3. Two or more close relatives with a history of gastric cancer, **AND**

a) One case was diagnosed at or before age 50, **OR,**

b) One case was confirmed to be diffuse gastric cancer/SRCC, **OR**

4. A close relative with a history of diffuse gastric cancer/SRCC, **AND**

a) A family history of Maori ancestry, **OR**

b) A family history of cleft lip/palate.

II. *CDH1* sequencing and/or deletion/duplication analysis for Hereditary Diffuse Gastric Cancer (aka, gastric signet ring cell carcinoma) is considered **investigational** for all other indications.

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JUVENILE POLYPOSIS SYNDROME (JPS)

SMAD4 or *BMPR1A* Targeted Variant Analysis

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

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

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

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

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

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

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 family history of JPS.

II. *SMAD4* and/or *BMPR1A* sequencing and/or deletion/duplication analysis 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 for hereditary leiomyomatosis and renal cell cancer (HLRCC) is considered **medically necessary** when:

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

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

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

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

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

1. Cutaneous leiomyomata, **OR**

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

3. Renal cell carcinoma.

II. *FH* sequencing and/or deletion/duplication analysis 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 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*, **OR**

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

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

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***TP53* Sequencing and/or Deletion/Duplication Analysis**

I. *TP53* sequencing and/or deletion/duplication analysis 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 has a personal or family history of pediatric hypodiploid acute lymphoblastic leukemia, **OR**

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

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

2. At least one of the following:

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

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

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

1. Adrenocortical carcinoma, **OR**

2. Choroid plexus carcinoma, **OR**

3. Rhabdomyosarcoma of embryonal anaplastic subtype, **OR**

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

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

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

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

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

F. The member has a first- or second-degree relative who is untested, deceased, and meets any of the criteria above.

II. *TP53* sequencing and/or deletion/duplication analysis 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 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. A pathogenic or likely pathogenic variant in *MEN1* was identified by tumor profiling in the member and germline analysis has not yet been performed.

II. *MEN1* targeted variant analysis 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 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. Duodenal/pancreatic neuroendocrine tumor, **OR**

2. Primary hyperparathyroidism, **OR**
3. Pituitary adenoma, **OR**
4. Foregut (bronchial, thymic, or gastric) carcinoid, **OR**

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

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

II. *MEN1* sequencing and/or deletion/duplication analysis 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 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 pathogenic or likely pathogenic variant in *RET* was identified by tumor profiling in the member and germline analysis has not yet been performed.

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

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

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

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

1. Medullary thyroid cancer, **OR**
2. Adrenal pheochromocytoma, **OR**
3. Parathyroid adenoma or hyperplasia, **OR**

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

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

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

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NEVOID BASAL CELL CARCINOMA SYNDROME (NBCCS) (AKA GORLIN SYNDROME)

PTCH1 or *SUFU* Targeted Variant Analysis

I. *PTCH1* or *SUFU* targeted variant analysis for nevoid basal cell carcinoma syndrome (NBCCS), also known as 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 pathogenic or likely pathogenic variant in *PTCH1* or *SUFU* was identified by tumor profiling in the member and germline analysis has not yet been performed.

II. *PTCH1* or *SUFU* targeted variant analysis 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/or *SUFU* Sequencing and/or Deletion/Duplication Analysis

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

   A. The member has a personal history of:

      1. At least two of the following:

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

         b) Jaw keratocyst, **OR**

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

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

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

      2. At least one of the following:

         a) Childhood medulloblastoma, **OR**

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

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

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

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

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

         g) Ovarian fibromas, **OR**

h) Cardiac fibromas, **OR**

i) Ocular anomalies (e.g., cataract, pigmentary changes of the retinal epithelium, developmental defects), **OR**

B. The member has a personal history of:

1. At least one of the following:

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

b) Jaw keratocyst, **OR**

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

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

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

2. At least three of the following:

a) Childhood medulloblastoma, **OR**

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

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

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

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

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

g) Ovarian fibromas, **OR**

h) Cardiac fibromas, **OR**

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

II. *PTCH1* and/or *SUFU* sequencing and/or deletion/duplication analysis 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 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 pathogenic or likely pathogenic variant in *MAX*, *SDHA*, *SDHAF2*, *SDHB*, *SDHC*, *SDHD*, or *TMEM127* was identified by tumor profiling in the member and germline analysis has not yet been performed.

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

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MAX, _SDHA_, _SDHAF2_, _SDHB_, _SDHC_, _SDHD_, and/or _TMEM127_ Sequencing and/or Deletion/Duplication Analysis

I. *MAX*, *SDHA*, *SDHAF2*, *SDHB*, *SDHC*, *SDHD*, and/or *TMEM127* sequencing and/or deletion/duplication analysis 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, **OR**
2. Paraganglioma, **OR**
3. Clear cell renal cell cancer, **OR**
4. Gastrointestinal stromal tumor (GIST), **OR**

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

II. *MAX*, *SDHA*, *SDHAF2*, *SDHB*, *SDHC*, *SDHD*, and/or *TMEM127* sequencing and/or deletion/duplication 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 for Peutz-Jeghers syndrome (PJS) is considered **medically necessary** when:

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

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

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

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STK11 Sequencing and/or Deletion/Duplication Analysis

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

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

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

   C. The member has a family history of PJS.

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

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RETINOBLASTOMA

RB1 Targeted Variant Analysis

I. *RB1* targeted variant analysis 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. A pathogenic or likely pathogenic variant in *RB1* was identified by tumor profiling in the member and germline analysis has not yet been performed.

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

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RB1 Sequencing and/or Deletion/Duplication Analysis

I. *RB1* sequencing and/or deletion/duplication analysis 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 with retinoblastoma in one or both eyes.

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

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

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

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

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VHL Sequencing and/or Deletion/Duplication Analysis

I. *VHL* sequencing and/or deletion/duplication analysis 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, **OR**
2. Renal cell carcinoma diagnosed before age 40 years, **OR**
3. Multiple and/or bilateral renal cell carcinoma diagnosed at any age, **OR**
4. Pheochromocytoma or paraganglioma (in abdomen, thorax, or neck), **OR**
5. Retinal angiomas, **OR**
6. Endolymphatic sac tumor, **OR**
7. Epididymal or adnexal papillary cystadenoma, **OR**
8. Pancreatic serous cystadenoma, **OR**
9. Pancreatic neuroendocrine tumors, **OR**
10. Multiple renal, pancreatic or hepatic cysts.

II. *VHL* sequencing and/or deletion/duplication analysis for Von Hippel-Lindau syndrome is considered **investigational** for all other indications**.**

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RATIONALE AND REFERENCES

Pan-Cancer Hereditary Cancer Susceptibility Panels

National Comprehensive Cancer Network (NCCN): Genetic/Familial High-Risk Assessment: Breast, Ovarian, Pancreatic, and Prostate (1.2026)

This guideline defines multigene testing as analysis of a set of genes that fare associated with one or more cancer phenotypes in a family. NCCN states that in some families, there is suspicion for more than one hereditary cancer syndrome. In those cases, phenotype-directed testing via a “tailored multigene panel” is a more efficient and cost-effective method of testing. They state that “intermediate penetrant (moderate-risk) genes” may also be included in the multigene panels (p. EVAL-A 3 of 11).

These guidelines also recommend consideration of RNA studies, to further define the meaning of variants of unknown significance. Research studies designed to explore the functional impact of variants, such as variant reclassification programs through clinical labs or registries should be considered (p. EVAL-A, 9 of 11).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Genetic/Familial High-Risk Assessment: Breast, Ovarian, Pancreatic, and Prostate 1.2026 https://www.nccn.org/professionals/physician_gls/pdf/genetics_bopp.pdf

National Comprehensive Cancer Network (NCCN): Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric (1.2025)

This guideline recommends germline multigene panel testing in individuals with a personal history of colorectal cancer who are under age 50 at diagnosis as well as for other Lynch-syndrome related cancers, including ovarian and pancreatic cancer (p. HRS-3). Test selection should include at a minimum selected genes associated with colorectal cancer risk but additional genes can be included based on a patient's personal and family history of cancer (p. HRS-A, 2 of 3).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric 1.2025 https://www.nccn.org/professionals/physician_gls/pdf/genetics_ceg.pdf

National Society of Genetic Counselors (NSGC)

The National Society of Genetic Counselors released a position statement (Adopted 2017, reaffirmed 2020 and 2023) endorsing the use of multigene panels when clinically warranted and appropriately applied, stating the following:

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

Use of Multi-Gene Panel Testing. Position Statement from National Society of Genetic Counselors. https://www.nsgc.org/Policy-Research-and-Publications/Position-Statements/Position-Statements/Post/use-of-multi-gene-panel-tests. Released March 14, 2017. Reaffirmed 2020 and 2023.

American Society of Clinical Oncology (ASCO)

ASCO released guidelines in 2024 regarding appropriate use of multigene panel germline testing for individuals with cancer. As part of the guideline, they recommend germline genetic testing via a multigene panel for patients with cancer who have suspicion for more than one gene related to that cancer type (Table 4, p. 2605). Several genes are listed in Table 1 (p. 2603), which they recommend be included for specific populations of people with cancer (Table 4, p. 2605).

Selection of Germline Genetic Testing Panels in Patients With Cancer: ASCO Guideline. Practice Guideline from The American Society of Clinical Oncology. https://ascopubs.org/doi/pdfdirect/10.1200/JCO.24.00662. Published May 17, 2024.

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Hereditary Breast and/or Ovarian Cancer Susceptibility Panels

National Comprehensive Cancer Network (NCCN): Genetic/Familial High-Risk Assessment: Breast, Ovarian, Pancreatic, and Prostate (1.2026)

This guideline outlines clinical criteria for germline genetic testing of high-penetrance breast cancer genes. Criteria include:

1) Personal history of breast cancer at 50 years of age or younger (p. CRIT-2).

2) Personal history of breast cancer at any age with specific features (p. CRIT-2):

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

3) Family history-based criteria (p. CRIT-2): Testing is also recommended in select unaffected individuals and those with a personal history that does not meet the above criteria. Qualifying scenarios include the presence of a first- or second-degree blood relative meeting any of the criteria listed above with the exception of relatives who meet criteria only for systemic therapy selection. If the affected relative has pancreatic cancer or prostate cancer, then only first-degree relatives should be offered testing unless indicated based on additional family history.

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

These guidelines also recommend consideration of testing for patients with a personal history of breast cancer diagnosed at or before age 65, patients diagnosed with breast cancer at any age with ≥1 close blood relative with intermediate-risk prostate cancer with intraductal/cribriform histology, and for patients affected or unaffected with breast cancer who otherwise do not meet

any of the above criteria but with a 2.5%–5% probability of BRCA1/2 P/LP variant based on prior probability models (e.g., Tyrer-Cuzick, BRCAPro, CanRisk) (p. CRIT-3).

The NCCN guidelines further recommend that patients with epithelial ovarian cancer be offered germline genetic testing for genes including *ATM*, *BRCA1, BRCA2, BRIP1, MLH1, MSH2, MSH6, EPCAM, PALB2, RAD51,* and *RAD51D* (p. CRIT-4). The guideline goes on to list non-epithelial ovarian cancers with a known genetic association, including Peutz-Jeghers (*STK11*), *DICER1*-related disease, and *SMARCA4* (p. CRIT-4).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Genetic/Familial High-Risk Assessment: Breast, Ovarian, Pancreatic, and Prostate 1.2026 https://www.nccn.org/professionals/physician_gls/pdf/genetics_bopp.pdf

National Comprehensive Cancer Network (NCCN): Breast Cancer (4.2025)

This guideline recommends germline *BRCA1, BRCA2,* and *PALB2* sequencing to determine eligibility for the FDA approved therapies olaparib and talazoparib in patients with "recurrent unresectable (local or regional) or stage IV (M1) disease" (p. BINV-Q 7 of 15).

The guideline also recommends germline *BRCA1* and *BRCA2* germline testing in patients with recurrent or metastatic breast cancer, regardless of HER2 status, to assess for PARPi eligibility (p. BINV-Q 2, 3, and 4 of 15).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Breast Cancer 4.2025
https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf

American Society of Clinical Oncology (ASCO) and Society of Surgical Oncology (SSO)

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

Bedrosian I, Somerfield MR, Achatz MI, et al. Germline testing in patients with breast cancer: ASCO-Society of Surgical Oncology Guideline. J Clin Oncol. 2024;42(5):584-604. doi:10.1200/JCO.23.02225

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Hereditary Gastrointestinal/Colorectal Cancer Susceptibility Panels

National Comprehensive Cancer Network (NCCN): Colorectal, Endometrial, and Gastric (1.2025)

This guideline outlines criteria for assessment for hereditary colorectal syndromes as follows:

- Polyposis: Patient with a personal history of, or a single family member with, at least 10 adenomatous polyps, at least 2 hamartomatous polyps, or at least 5 serrated polyps/lesions proximal to the rectum (p. HRS-1)
- Individuals meeting LS testing criteria (p. HRS-1, HRS-3, LS-1) (see *MLH1, MSH2, MSH6, PMS2, EPCAM* Sequencing and/or Deletion/Duplication Analysis).

NCCN also states that the CRC-risk associated genes to include in germline multigene panel testing are as follows: *APC, BMPR1A, EPCAM, MUTYH, MLH1, MSH2, MSH6, PMS2, PTEN, SMAD4, STK11,* and *TP53* (p. HRS-A 2 of 3).

Some individuals will have variants of uncertain significance (VUS); post-test counseling should include considering referral to research studies for the purpose of learning the functional impact of VUSs such as variant reclassification programs through clinical labs or registries (p. EVAL-A 8 of 9).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric 1.2025 https://www.nccn.org/professionals/physician_gls/pdf/genetics_ceg.pdf

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Hereditary Gastric Cancer Susceptibility Panels

National Comprehensive Cancer Network (NCCN): Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric (1.2025)

This guideline outlines criteria for genetic testing for high-risk syndromes associated with gastric cancer, including: hereditary diffuse gastric cancer, Lynch syndrome, Juvenile Polyposis Syndrome, Peutz-Jeghers syndrome, and Familial Adenomatous Polyposis (p. HRS-1, p. HGAST-1).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric 1.2025 https://www.nccn.org/professionals/physician_gls/pdf/genetics_ceg.pdf

National Comprehensive Cancer Network (NCCN): Genetic/Familial High-Risk Assessment: Breast, Ovarian, Pancreatic, and Prostate (1.2026)

This guideline outlines additional criteria for genetic testing for hereditary diffuse gastric cancer in patients with a history of lobular breast cancer (p. CRIT-2).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Genetic/Familial High-Risk Assessment: Breast, Ovarian, Pancreatic, and Prostate 1.2026 https://www.nccn.org/professionals/physician_gls/pdf/genetics_bopp.pdf

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Hereditary Pancreatic Cancer Susceptibility Panels

National Comprehensive Cancer Network (NCCN): Genetic/Familial High-Risk Assessment: Breast, Ovarian, Pancreatic, and Prostate (1.2026)

This guideline recommends genetic counseling and germline testing for all individuals diagnosed with exocrine pancreatic cancer, as well as individuals with a first-degree relative diagnosed with exocrine pancreatic cancer. These guidelines list the following genes as those that are typically tested for pancreatic cancer risks: *ATM, BRCA1, BRCA2, CDKN2A, MLH1, MSH2, MSH6, EPCAM, PALB2, STK11, TP53* (p. CRIT-5).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Genetic/Familial High-Risk Assessment: Breast, Ovarian, Pancreatic, and Prostate 1.2026 https://www.nccn.org/professionals/physician_gls/pdf/genetics_bopp.pdf

National Comprehensive Cancer Network (NCCN): Ampullary Adenocarcinoma (2.2025)

This guideline recommends genetic testing to include *ATM, BRCA1, BRCA2, CDKN2A, MLH1, MSH2, MSH6, PALB2, PMS2, STK11*, and *TP53* for individuals diagnosed with ampullary adenocarcinoma (AMP-1, AMP-3).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Ampullary Adenocarcinoma 2.2025 https://www.nccn.org/professionals/physician_gls/pdf/ampullary.pdf

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Hereditary Polyposis Susceptibility Panels

National Comprehensive Cancer Network (NCCN): Genetic/Familial High-Risk Assessment:

Colorectal, Endometrial, and Gastric (1.2025)

This guideline outlines scenarios in which individuals meet criteria for germline genetic testing for “all polyposis and [colorectal cancer] genes” (p.POLYP-1A). These include: personal history of 10-20 cumulative adenomas, congenital hypertrophy of retinal pigment epithelium (CHRPE), desmoid tumor, hepatoblastoma, cribriform-morular variant of papillary thyroid cancer, and clinically diagnosed serrated polyposis syndrome if adenomas are present (p. POLYP-1).

This guideline also notes that some individuals with a clinical diagnosis of serrated polyposis syndrome (defined as 5 or more serrated polyps proximal to the rectum all being 5mm or larger with 2 or more being 10 or more mm in size, or more than 20 serrated polyps of any size distributed throughout the colon, with 5 or more being proximal to the rectum) may carry pathogenic variants in *MUTYH* (biallelic) or *RNF43* (monoallelic)(p. SPS-1).

Some individuals will have variants of uncertain significance (VUS); post-test counseling should include considering referral to research studies for the purpose of learning the functional impact of VUSs such as variant reclassification programs through clinical labs or registries (p. EVAL-A, 8 of 9).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric 1.2025 https://www.nccn.org/professionals/physician_gls/pdf/genetics_ceg.pdf

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Hereditary Prostate Cancer Susceptibility Panels

National Comprehensive Cancer Network (NCCN): Genetic/Familial High-Risk Assessment: Breast, Ovarian, Pancreatic, and Prostate (1.2026)

This guideline recommends the following testing criteria for prostate cancer susceptibility genes:

Personal history of prostate cancer with specific clinical features: metastatic disease, high- or very-high risk group, or with 1 or more close relatives with:

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

This guideline also recommends consideration of testing for:

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

CRIT-6).

This guideline also recommends consideration of RNA studies to further define the meaning of variants of unknown significance. Research studies designed to explore the functional impact of variants, such as variant reclassification programs through clinical labs or registries should be considered (p. EVAL-A, 9 of 11).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Genetic/Familial High-Risk Assessment: Breast, Ovarian, Pancreatic, and Prostate 1.2026 https://www.nccn.org/professionals/physician_gls/pdf/genetics_bopp.pdf

American Society for Clinical Oncology (ASCO)

In a 2025 ASCO guideline, germline testing via a next-generation sequencing (NGS) panel is strongly recommended for all patients with metastatic prostate cancer. The guideline goes on to recommend targeted treatment for patients found to carry a pathogenic variant specifically in *BRCA1* or *BRCA2* (p. 751). The guideline further outlines that germline testing via targeted gene panels covering "a specific set of genes known to be associated with prostate cancer" is the current standard of care (p. 755).

Yu EY, Rumble RB, Agarwal N, et al. Germline and Somatic Genomic Testing for Metastatic Prostate Cancer: ASCO Guideline. Journal of Clinical Oncology. 2025;43(6):748-758. doi:doi:/10.1200/jco-24-02608doi:https://doi.org/10.1200/jco-24-02608

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Hereditary Neuroendocrine Cancer Susceptibility Panels

National Comprehensive Cancer Network (NCCN): Neuroendocrine and Adrenal Tumors (2.2025)

This guideline states that multigene panel testing may be a more efficient and cost-effective solution for evaluating a patient for a hereditary endocrine cancer syndrome, as there is clinical overlap between several genetic conditions that predispose to endocrine neoplasms (p. NE-G 2 of 8).

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

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

NCCN also recommends consideration of testing for patients with:

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

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Neuroendocrine and Adrenal Tumors 2.2025 https://www.nccn.org/professionals/physician_gls/pdf/neuroendocrine.pdf

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

National Comprehensive Cancer Network (NCCN): Genetic/Familial High-Risk Assessment: Breast, Ovarian, Pancreatic, and Prostate (1.2026)

This guideline states that testing for hereditary cancer susceptibility should be performed in the following situations:

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

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Genetic/Familial High-Risk Assessment: Breast, Ovarian, Pancreatic, and Prostate 1.2026 https://www.nccn.org/professionals/physician_gls/pdf/genetics_bopp.pdf

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

National Comprehensive Cancer Network (NCCN): Genetic/Familial High-Risk Assessment: Breast, Ovarian, Pancreatic, and Prostate (1.2026)

This guideline recommends consideration of testing for the three known Ashkenazi Jewish founder *BRCA1/2* mutations for individuals who are age 18 years or older and have at least one grandparent who is of Ashkenazi Jewish ancestry (p. CRIT-1 and p. CRIT-1A).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Genetic/Familial High-Risk Assessment: Breast, Ovarian, Pancreatic, and Prostate 1.2026 https://www.nccn.org/professionals/physician_gls/pdf/genetics_bopp.pdf

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PALB2 Targeted Variant Analysis

National Comprehensive Cancer Network (NCCN): Genetic/Familial High-Risk Assessment: Breast, Ovarian, Pancreatic, and Prostate (1.2026)

This guideline states that testing for hereditary cancer susceptibility should be performed in multiple scenarios, including the following situations:

- Individuals with a known pathogenic/likely pathogenic variant in a cancer susceptibility gene in a blood relative
- Individuals who were found to have a pathogenic/likely pathogenic (P/LP) variant on tumor genomic testing in a gene with clinical implications if confirmed to be a germline variant (p. CRIT-1).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Genetic/Familial High-Risk Assessment: Breast, Ovarian, Pancreatic, and Prostate 1.2026 https://www.nccn.org/professionals/physician_gls/pdf/genetics_bopp.pdf

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ATM or *CHEK2* Targeted Variant Analysis

National Comprehensive Cancer Network (NCCN): Genetic/Familial High-Risk Assessment: Breast, Ovarian, Pancreatic, and Prostate (1.2026)

This guideline states that testing for hereditary cancer susceptibility should be performed in multiple scenarios, including the following situations:

- Individuals with a known pathogenic/likely pathogenic variant in a cancer susceptibility gene in a blood relative
- Individuals who were found to have a pathogenic/likely pathogenic variant on tumor genomic testing in a gene with clinical implications if confirmed to be a germline variant (p. CRIT-1).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Genetic/Familial High-Risk Assessment: Breast, Ovarian, Pancreatic, and Prostate 1.2026 https://www.nccn.org/professionals/physician_gls/pdf/genetics_bopp.pdf

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

National Comprehensive Cancer Network (NCCN): Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric (1.2025)

This guideline outlines testing criteria for the evaluation of Lynch syndrome. If there is a known familial pathogenic variant in a Lynch syndrome gene (*MLH1, MSH2, MSH6, PMS2,* or *EPCAM),* genetic testing for the known variant is recommended (p. LS-1). Additionally, it is possible that pathogenic or likely pathogenic variants identified through tumor profiling could be of germline origin. Confirmatory germline testing is indicated for pathogenic/likely pathogenic variants identified via tumor profiling when there is a reasonable clinical suspicion of being of germline origin (p. EVAL-A 5 of 9).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric 1.2025 https://www.nccn.org/professionals/physician_gls/pdf/genetics_ceg.pdf

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

National Comprehensive Cancer Network (NCCN): Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric (1.2025)

This guideline outlines testing criteria for the evaluation of Lynch syndrome. These criteria include:

- An individual with a Lynch-syndrome (LS)-related cancer (colorectal, endometrial, gastric, ovarian, pancreatic, urothelial, brain (usually glioblastoma), biliary tract, and small intestine, as well as sebaceous adenomas, sebaceous carcinomas, and keratoacanthomas) and any of the following:
    - Diagnosed younger than 50 years
    - A synchronous or metachronous LS-related cancer regardless of age
    - 1 first-degree or second-degree relative with an LS-related cancer diagnosed younger than 50 years
    - 2 or more first-degree or second-degree relatives with an LS-related cancer regardless of age
- Family history of any of the following
    - At least 1 first-degree relative with a colorectal or endometrial cancer diagnosed

younger than 50 years
    - At least 1 first- or second-degree relative with a colorectal or endometrial cancer and a synchronous or metachronous LS-related cancer regardless of age
    - 2 or more first-degree or second-degree relatives with LS-related cancers, one of whom was diagnosed before age 50
    - 3 or more first-degree or second-degree relatives with LS-related cancers regardless of age
- An individual with a 5% risk or greater of having an MMR gene pathogenic variant based on predictive models (i.e., PREMM5, MMRpro, MMRpredict)
- An individual with a personal history of CRC and/or endometrial cancer with a PREMM5 score of 2.5% or greater.
- A personal history of mismatch repair deficiency in any solid tumor

Some individuals will have variants of uncertain significance (VUS); post-test counseling should include considering referral to research studies for the purpose of learning the functional impact of VUSs such as variant reclassification programs through clinical labs or registries (p. HRS-3 and EVAL-A 8 of 9).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric 1.2025 https://www.nccn.org/professionals/physician_gls/pdf/genetics_ceg.pdf

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APC or _MUTYH_ Targeted Variant Analysis

National Comprehensive Cancer Network (NCCN): Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric (1.2025)

This guideline outlines clinical criteria for the genetic testing, which includes a known pathogenic variant in an adenomatous polyposis gene in the family (p. POLYP-1). and recommend targeted *APC* or *MUTYH* gene testing when the familial pathogenic variant is known (p. FAP-2, MAP-1).

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

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric 1.2025 https://www.nccn.org/professionals/physician_gls/pdf/genetics_ceg.pdf

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BAP1 Targeted Variant Analysis

National Comprehensive Cancer Network (NCCN): Kidney Cancer (3.2025)

This guideline includes *BAP1* tumor predisposition syndrome in their overview of hereditary renal cell carcinoma syndromes, and recommends testing for an individual with a close blood relative with a known pathogenic/likely pathogenic variant in a cancer susceptibility gene (p. HERED-RCC-1 and HERED-RCC-2).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Kidney Cancer 3.2025 https://www.nccn.org/professionals/physician_gls/pdf/kidney.pdf

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BAP1 Sequencing and/or Deletion/Duplication Analysis

National Comprehensive Cancer Network (NCCN): Cutaneous Melanoma (2.2025)

This guideline states that individuals with germline mutations in several genes, including *BAP1*, are at risk to develop single or multiple primary melanomas (p. ME-A 1 of 2).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Melanoma: Cutaneous 2.2025
https://www.nccn.org/professionals/physician_gls/pdf/cutaneous_melanoma.pdf

National Comprehensive Cancer Network (NCCN): Uveal Melanoma (1.2025)

This guideline includes germline *BAP1* mutations as a risk factor for developing uveal melanoma (p. UM-A 1 of 2).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Melanoma: Uveal 1.2025
https://www.nccn.org/professionals/physician_gls/pdf/uveal.pdf

National Comprehensive Cancer Network (NCCN): Malignant Pleural Mesothelioma (2.2025)

This guideline states that approximately 12-16% of patients with pleural or peritoneal mesothelioma have a germline mutation, including in *BAP1* (p. PM-A 5 of 8).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Mesothelioma: Pleural 2.2025
https://www.nccn.org/professionals/physician_gls/pdf/meso_pleural.pdf

National Comprehensive Cancer Network (NCCN): Kidney Cancer (3.2025)

This guideline includes *BAP1* tumor predisposition syndrome in their overview of hereditary renal cell carcinoma syndromes (p. HERED-RCC-2).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Kidney Cancer 3.2025
https://www.nccn.org/professionals/physician_gls/pdf/kidney.pdf

GeneReviews: BAP1 Tumor Predisposition Syndrome (BAP1-TPDS)

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

The clinical description and testing indications for *BAP1* Tumor Predisposition syndrome (*BAP1*-TPDS) are as follows:

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

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

**BAP1*-inactivated melanocytic tumors, uveal melanoma, malignant mesothelioma, cutaneous melanoma, renal cell carcinoma, basal cell carcinoma, meningioma, and cholangiocarcinoma.

**See above cancers. Exceptions include two basal cell cancers and/or cutaneous melanomas in the affected individuals, given their high frequency in the general population.

Pilarski R, Carlo M, Cebulla C, and Abdel-Rahman M. BAP1 Tumor Predisposition Syndrome. 2016 Oct 13 [Updated 2024 Dec 04]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2025.

Available from: https://www.ncbi.nlm.nih.gov/books/NBK390611/

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FLCN Targeted Variant Analysis

National Comprehensive Cancer Network (NCCN): Kidney Cancer (3.2025)

This guideline includes Birt-Hogg-Dube syndrome in an overview of hereditary renal cell carcinoma syndromes, and recommends testing for an individual with a close blood relative with a known pathogenic/likely pathogenic variant in a cancer predisposition gene (p. HERED-RCC-1 and HERED-RCC-2).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Kidney Cancer 3.2025
https://www.nccn.org/professionals/physician_gls/pdf/kidney.pdf

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FLCN Sequencing and/or Deletion/Duplication Analysis

National Comprehensive Cancer Network (NCCN): Kidney Cancer (3.2025)

This guideline includes Birt-Hogg-Dube syndrome in their overview of hereditary renal cell carcinoma syndromes. Commonly seen histologies include chromophobe, hybrid oncocytic tumors, clear cell, oncocytomas, angiomyolipomas, and papillary RCC (p. HERED-RCC-2).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Kidney Cancer 3.2025
https://www.nccn.org/professionals/physician_gls/pdf/kidney.pdf

GeneReviews: Birt-Hogg-Dube Syndrome (BHDS)

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

The clinical description and testing indications for Birt-Hogg-Dube syndrome (BHDS) are as follows:

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

Major criteria

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

Minor criteria

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

The diagnosis of BHDS is established in a proband with:

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

Sattler EC, Steinlein OK. Birt-Hogg-Dube Syndrome. 2006 Feb 27 [Updated 2024 Dec 05]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2025. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1522/

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PTEN Targeted Variant Analysis

National Comprehensive Cancer Network (NCCN): Genetic/Familial High-Risk Assessment: Breast, Ovarian, Pancreatic, and Prostate (1.2026)

This guideline states that testing for hereditary cancer susceptibility should be performed in multiple scenarios, including the following situations:

- Individuals with a known pathogenic/likely pathogenic variant in a cancer susceptibility gene in a blood relative
- Individuals who were found to have a pathogenic/likely pathogenic variant on tumor genomic testing in a gene with clinical implications if confirmed to be a germline variant (p. CRIT-1).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Genetic/Familial High-Risk Assessment: Breast, Ovarian, Pancreatic, and Prostate 1.2026 https://www.nccn.org/professionals/physician_gls/pdf/genetics_bopp.pdf

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PTEN Sequencing and/or Deletion/Duplication Analysis

National Comprehensive Cancer Network (NCCN): Genetic/Familial High-Risk Assessment: Breast, Ovarian, Pancreatic, and Prostate (1.2026)

This guideline outlines clinical criteria for the genetic testing for Cowden syndrome (CS)/*PTEN* hamartoma tumor syndrome (PHTS). These include:

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

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

following:

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

This guideline also recommends testing for individuals with a first- or second-degree relative who is untested and deceased, and who meets any of the clinical coverage criteria outlined (p. CRIT-8).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Genetic/Familial High-Risk Assessment: Breast, Ovarian, Pancreatic, and Prostate 1.2026 https://www.nccn.org/professionals/physician_gls/pdf/genetics_bopp.pdf

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CDKN2A Targeted Variant Analysis

National Comprehensive Cancer Network (NCCN): Genetic/Familial High-Risk Assessment: Breast, Ovarian, Pancreatic, and Prostate (1.2026)

This guideline states that testing for hereditary cancer susceptibility should be performed in multiple scenarios, including the following situations:

- Individuals with a known pathogenic/likely pathogenic variant in a cancer susceptibility gene in a blood relative
- Individuals who were found to have a pathogenic/likely pathogenic (P/LP) variant on tumor genomic testing in a gene with clinical implications if confirmed to be a germline variant (p.CRIT-1).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Genetic/Familial High-Risk Assessment: Breast, Ovarian, Pancreatic, and Prostate 1.2026 https://www.nccn.org/professionals/physician_gls/pdf/genetics_bopp.pdf

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CDKN2A Sequencing and/or Deletion/Duplication Analysis

National Comprehensive Cancer Network (NCCN): Cutaneous Melanoma (2.2025)

This guideline recommends consideration of a genetic counseling referral for *p16*/*CDKN2A* mutation testing (and possibly other genes) when a patient has 3 or more invasive cutaneous melanomas, or a personal or family history of invasive melanoma, pancreatic cancer, and/or astrocytoma diagnoses (p. ME-12).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Melanoma: Cutaneous 2.2025 https://www.nccn.org/professionals/physician_gls/pdf/cutaneous_melanoma.pdf

National Comprehensive Cancer Network (NCCN): Genetic/Familial High-Risk Assessment: Breast, Ovarian, Pancreatic, and Prostate (1.2026)

This guideline recognizes CDKN2A as a pancreatic cancer susceptibility gene; testing is recommended in an individual with exocrine pancreatic cancer or a first degree relative with exocrine pancreatic cancer (p. CRIT-5).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Genetic/Familial High-Risk Assessment: Breast, Ovarian, Pancreatic, and Prostate 1.2026 https://www.nccn.org/professionals/physician_gls/pdf/genetics_bopp.pdf

American Academy of Dermatology (AAD)

A guideline published in 2018 by the AAD regarding the care and management primary cutaneous melanoma recommends genetic risk assessment for patients with cutaneous melanoma who have two or more relatives with cutaneous melanoma and/or pancreatic cancer, especially when a first degree relative is involved (p. 237).

Swetter SM, Tsao H, Bichakjian CK, et al. Guidelines of care for the management of primary cutaneous melanoma. J Am Acad Dermatol. 2019;80(1):208-250. doi:10.1016/j.jaad.2018.08.055

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CDH1 Targeted Variant Analysis

National Comprehensive Cancer Network (NCCN): Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric (1.2025)

This guideline recommends targeted testing for *CDH1* variants when a relative has a known pathogenic variant in the *CDH1* gene (p. HGAST-1). This guideline also states that somatic testing (tumor genomic testing) can sometimes result in a possible germline finding. Pathogenic and likely pathogenic variants found in the tumor may be of somatic or germline origin (p. EVAL-A 5 of 9).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric 1.2025 https://www.nccn.org/professionals/physician_gls/pdf/genetics_ceg.pdf

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CDH1 Sequencing and/or Deletion/Duplication Analysis

National Comprehensive Cancer Network (NCCN): Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric (1.2025)

This guideline outlines testing criteria for germline *CDH1* testing, including:

- Personal history of diffuse gastric cancer at any age
- Family history of two or more first- or second-degree relatives with gastric cancer, at least one of whom was either diagnosed at or before age 50 OR had confirmed diffuse gastric cancer (DGC) at any age (p. HGAST-1).

The guideline footnotes note that testing in families with diffuse gastric cancer and cleft lip/palate or with Maori ancestry may also be “warranted” (p. HGAST-1); the footnote also includes the following synonyms and histologic descriptors for DGC:

- Intramucosal signet ring cell carcinoma (SRCC), diffuse-type, poorly cohesive gastric cancer, and “linitis plastica.”

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric 1.2025 https://www.nccn.org/professionals/physician_gls/pdf/genetics_ceg.pdf

National Comprehensive Cancer Network (NCCN): Genetic/Familial High-Risk Assessment: Breast, Ovarian, Pancreatic, and Prostate (1.2026)

This guideline states that germline testing for high-penetrance breast cancer predisposition genes, including *CDH1*, is indicated in patients who have lobular breast cancer at any age and a family history of diffuse gastric cancer (p. CRIT-2).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Genetic/Familial High-Risk Assessment: Breast, Ovarian, Pancreatic, and Prostate 1.2026 https://www.nccn.org/professionals/physician_gls/pdf/genetics_bopp.pdf

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SMAD4 or *BMPR1A* Targeted Variant Analysis

National Comprehensive Cancer Network (NCCN): Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric (1.2025)

This guideline outlines clinical criteria for genetic testing for Juvenile Polyposis syndrome. Testing is recommended when there is a known *BMPR1A* or *SMAD4* pathogenic variant in the family (p. JPS-1).

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

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric 1.2025 https://www.nccn.org/professionals/physician_gls/pdf/genetics_ceg.pdf

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

National Comprehensive Cancer Network (NCCN): Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric (1.2025)

This guideline outlines clinical criteria for genetic testing for juvenile polyposis syndrome (JPS) in individuals with a personal and/or family history suggestive of JPS. Genetic testing is recommended when criteria are met or when there is a family history of JPS.

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

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric 1.2025 https://www.nccn.org/professionals/physician_gls/pdf/genetics_ceg.pdf

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FH Targeted Variant Analysis

National Comprehensive Cancer Network (NCCN): Kidney Cancer (3.2025)

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

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Kidney Cancer 3.2025 https://www.nccn.org/professionals/physician_gls/pdf/kidney.pdf

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FH Sequencing and/or Deletion/Duplication Analysis

National Comprehensive Cancer Network (NCCN): Kidney Cancer (3.2025)

This guideline outlines criteria for further genetic risk evaluation for hereditary renal cell carcinoma syndromes, including HLRCC-associated renal cell carcinoma. Testing is recommended for an individual whose tumor is HLRCC-associated renal cell carcinoma, FH

deficient renal cell carcinoma, or has other histologic features of HLRCC (p. HERED-RCC-1).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Kidney Cancer 3.2025 https://www.nccn.org/professionals/physician_gls/pdf/kidney.pdf

GeneReviews: FH Tumor Predisposition Syndrome

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

The recommended testing for FH tumor predisposition syndrome (HLRCC) is as follows:

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

Cutaneous leiomyomata (~50%):

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

Uterine leiomyomata (uterine fibroids) (~90% of females):

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

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

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

Kamihara J, Schultz KA, Rana H. FH Tumor Predisposition Syndrome. 2006 Jul 31. [Updated 2020 Aug 13]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2025. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1252/

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TP53 Targeted Variant Analysis

National Comprehensive Cancer Network (NCCN): Genetic/Familial High-Risk Assessment: Breast, Ovarian, Pancreatic, and Prostate (1.2026)

This guideline states that testing for hereditary cancer susceptibility should be performed in the following situations:

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

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Genetic/Familial High-Risk Assessment: Breast, Ovarian, Pancreatic, and Prostate 1.2026 https://www.nccn.org/professionals/physician_gls/pdf/genetics_bopp.pdf

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TP53 Sequencing and/or Deletion/Duplication Analysis

National Comprehensive Cancer Network (NCCN): Genetic/Familial High-Risk Assessment: Breast, Ovarian, Pancreatic, and Prostate (1.2026)

This guideline outlines clinical testing criteria for the genetic testing for Li-Fraumeni syndrome. This Includes classic Li-Fraumeni syndrome criteria and Chompret criteria and considerations for family history:

Classic Li-Fraumeni syndrome (LFS) criteria:

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

Chompret criteria:

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

Personal/Family history criteria:

- Personal or family history of pediatric hypodiploid acute lymphoblastic leukemia
- A first- or second-degree relative who is untested and deceased, and who meets these clinical criteria (p. CRIT-7).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Genetic/Familial High-Risk Assessment: Breast, Ovarian, Pancreatic, and Prostate 1.2026 https://www.nccn.org/professionals/physician_gls/pdf/genetics_bopp.pdf

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MEN1 Targeted Variant Analysis

National Comprehensive Cancer Network (NCCN): Neuroendocrine and Adrenal Tumors (2.2025)

This guideline recommends that targeted genetic testing for *MEN1* be performed for individuals with a close blood relative with a known pathogenic variant/likely pathogenic variant in a cancer susceptibility gene (p. NE-G 3 of 8).

Additionally, NCCN recommends genetic risk evaluation and genetic testing for Hereditary Endocrine Neoplasia Syndromes when a mutation is identified on tumor genomic testing that

has clinical implications if also identified in the germline (p NE-G 3 of 8).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Neuroendocrine and Adrenal Tumors 2.2025 https://www.nccn.org/professionals/physician_gls/pdf/neuroendocrine.pdf

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MEN1 Sequencing and/or Deletion/Duplication Analysis

National Comprehensive Cancer Network (NCCN): Neuroendocrine and Adrenal Tumors (2.2025)

This guideline recommends that patients with history of two or more of the following, **or** a patient with one of the following AND a family history of one or more of the following, be evaluated for *MEN1* germline mutations:

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

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Neuroendocrine and Adrenal Tumors 2.2025 https://www.nccn.org/professionals/physician_gls/pdf/neuroendocrine.pdf

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RET Targeted Variant Analysis

National Comprehensive Cancer Network (NCCN): Neuroendocrine and Adrenal Tumors (2.2025)

This guideline recommends that targeted genetic testing for *MEN2* be performed for individuals with a close blood relative with a known pathogenic variant/likely pathogenic variant in a cancer susceptibility gene (p. NE-G 3 of 8). Additionally, NCCN states that testing is recommended when a mutation is identified on tumor genomic testing that has clinical implications if also identified in the germline (p NE-G 3 of 8).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Neuroendocrine and Adrenal Tumors 2.2025 https://www.nccn.org/professionals/physician_gls/pdf/neuroendocrine.pdf

National Comprehensive Cancer Network (NCCN): Thyroid Carcinoma (1.2025)

This guideline recommends “prompt specific mutation testing” in family members when a germline mutation is identified in an affected individual (p. MEDU-1).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Thyroid Carcinoma 1.2025 https://www.nccn.org/professionals/physician_gls/pdf/thyroid.pdf

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RET Sequencing and/or Deletion/Duplication Analysis

GeneReviews: Multiple Endocrine Neoplasia Type 2

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

The clinical description for the multiple endocrine neoplasia type 2 (MEN2) phenotypes are as follows:

- Multiple endocrine neoplasia type 2A (MEN2A) should be suspected in any individual with one of the following:
    - Medullary thyroid carcinoma (MTC)
    - Pheochromocytoma
    - Parathyroid adenoma/hyperplasia.
- Familial Medullary Thyroid Carcinoma (FMTC) should be suspected in families with both of the following:
    - More than one individual (two or more) with MTC
    - No pheochromocytoma or parathyroid adenoma/hyperplasia.
- Multiple endocrine neoplasia type 2B (MEN2B) should be suspected in individuals with the following:
    - Distinctive facies including lip mucosal neuromas resulting in thick vermilion of the upper and lower lip
    - Mucosal neuromas of the lips and tongue
    - Medullated corneal nerve fibers
    - Marfanoid habitus
    - Early-onset MTC.

Eng C, Plitt, G. Multiple Endocrine Neoplasia Type 2. 1999 Sep 27 [Updated 2023 Aug 10]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2025. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1257/

National Comprehensive Cancer Network (NCCN): Neuroendocrine and Adrenal Tumors (2.2025)

This guideline recommends *MEN2* testing when there is clinical suspicion of MEN2 due to the presence of medullary thyroid cancer or other combination of MEN2-related features. Genetic testing is recommended for a first degree relative meeting this criteria, where the relative is not available for testing (p. NE-G 3 of 8).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Neuroendocrine and Adrenal Tumors 2.2025 https://www.nccn.org/professionals/physician_gls/pdf/neuroendocrine.pdf

National Comprehensive Cancer Network (NCCN): Thyroid Carcinoma (1.2025)

This guideline recommends germline *RET* testing for individuals with medullary thyroid cancer during the diagnostic work-up (p. MEDU-1). The additional workup and subsequent treatment recommendations are partially based on the specific *RET* pathogenic variant (p. MEDU-3 and MEDU-4).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Thyroid Carcinoma 1.2025 https://www.nccn.org/professionals/physician_gls/pdf/thyroid.pdf

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PTCH1 or *SUFU* Targeted Variant Analysis

GeneReviews: Nevoid Basal Cell Carcinoma Syndrome

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

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

Evans DG, Farndon PA. Nevoid Basal Cell Carcinoma Syndrome. 2002 Jun 20 [Updated 2024 Feb 22]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2025. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1151/

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

GeneReviews: Nevoid Basal Cell Carcinoma Syndrome

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

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

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

Major criteria

- Lamellar (sheet-like) calcification of the falx or clear evidence of calcification in an individual younger than age 20 years. Falx calcification is nearly always present and is visible on anteroposterior (AP) x-rays of the skull after age 20 years (see Notes regarding radiographs)
- Jaw keratocyst. Odontogenic keratocyst histologically; seen on orthopantomogram as an area of translucency
- Palmar/plantar pits (at least 2); particularly useful in diagnosis and more pronounced when the hands and feet are soaked in warm water for up to ten minutes. Pits may appear as white "punched-out" or pink "pin-prick" lesions
- Multiple basal cell carcinomas (BCCs) (more than 5 in a lifetime) or a BCC before age 30 years. Provision needs to be made for decreased risk of BCC in individuals with dark skin and increased risk in those with light skin living in hot sunny climates, particularly those with type 1 Celtic skin and red hair, and of this group, particularly those with the common *MC1R* variant (rs1805007), which can modify age of onset for NBCCS
- First-degree relative with NBCCS.

Minor criteria

- Childhood medulloblastoma (also called primitive neuroectodermal tumor)
- Lympho-mesenteric or pleural cysts

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

Evans DG, Farndon PA. Nevoid Basal Cell Carcinoma Syndrome. 2002 Jun 20 [Updated 2024 Feb 22]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2025. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1151/

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MAX, SDHA, SDHAF2, SDHB, SDHC, SDHD, or _TMEM127_ Targeted Variant Analysis

National Comprehensive Cancer Network (NCCN): Kidney Cancer (3.2025)

This guideline includes hereditary paraganglioma/pheochromocytoma (PGL/PCC) syndrome in their overview of hereditary renal cell carcinoma syndromes. Genetic testing is recommended for an individual with a close blood relative with a known pathogenic/likely pathogenic variant in a cancer susceptibility gene (p. HERED-RCC-1 and HERED-RCC-2).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Kidney Cancer 3.2025 https://www.nccn.org/professionals/physician_gls/pdf/kidney.pdf

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MAX, SDHA, SDHAF2, SDHB, SDHC, SDHD, and/or _TMEM127_ Sequencing and/or Deletion/Duplication Analysis

National Comprehensive Cancer Network (NCCN): Neuroendocrine and Adrenal Tumors (2.2025)

This guideline recommends genetic testing for hereditary endocrine neoplasia syndromes such as hereditary paraganglioma/pheochromocytoma syndrome for patients with either a paraganglioma or pheochromocytoma or with a first degree relative with either of these tumors who is unavailable for testing (p. NE-G, 3 of 8). Other manifestations of this syndrome include gastrointestinal stromal tumor and renal cell cancer (p. NE-E, 4 of 8).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Neuroendocrine and Adrenal Tumors 2.2025 https://www.nccn.org/professionals/physician_gls/pdf/neuroendocrine.pdf

GeneReviews: Hereditary Paraganglioma-Pheochromocytoma Syndromes

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

Per GeneReviews, hereditary paraganglioma-pheochromocytoma (PGL/PCC) syndromes should be suspected in individuals with any of the following:

- Paraganglioma, particularly if the individual has multiple

- Pheochromocytoma, particularly if the individual has multiple (includes bilateral)
- A family history of paraganglioma or pheochromocytoma
- Gastrointestinal stromal tumors (GIST)

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

Else T, Greenberg S, Fishbein L. Hereditary Paraganglioma-Pheochromocytoma Syndromes. 2008 May 21 [Updated 2023 September 21]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2025. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1548/

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STK11 Targeted Variant Analysis

National Comprehensive Cancer Network (NCCN): Genetic/Familial High- Risk Assessment: Colorectal, Endometrial, and Gastric (1.2025)

This guideline outlines testing criteria for the evaluation of Peutz-Jeghers Syndrome (PJS) and recommends clinical genetic testing when there is a family history of confirmed PJS. NCCN states that pathogenic mutations in *STK11* cause the majority of PJS cases (p. PJS-1).

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

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric 1.2025 https://www.nccn.org/professionals/physician_gls/pdf/genetics_ceg.pdf

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STK11 Sequencing and/or Deletion/Duplication Analysis

National Comprehensive Cancer Network (NCCN): Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric (1.2025)

This guideline outlines clinical criteria for Peutz-Jeghers Syndrome (PJS) genetic testing in individuals with a personal and/or family history suggestive of PJS, as a majority of cases occur due to pathogenic variants in the *STK11* (*LKB1*) gene. These criteria include: two or more PJS-type hamartomas in the GI tract, hyperpigmentation in mucocutaneous membranes (such as the mouth, lips, nose, eyes, genitals, or fingers) and a family history of PJS (p. PJS-1).

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Genetic/Familial High-Risk Assessment: Colorectal, Endometrial, and Gastric 1.2025 https://www.nccn.org/professionals/physician_gls/pdf/genetics_ceg.pdf

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RB1 Targeted Variant Analysis

American Association for Cancer Research (AACR)

The Childhood Cancer Predisposition Workshop published updated recommendations in 2025 for retinoblastoma predisposition and surveillance recommendations for children. In regards to targeted variant analysis, the recommendations state that when *RB1* variants are detected in the retinoblastoma tumor, germline testing for these variants can then be pursued (p. 1574).

Kamihara J, Schienda J, McGee RB, et al. Update on Retinoblastoma Predisposition and Surveillance Recommendations for Children. Clin Cancer Res. 2025 May 1;31(9):1573-1579. Published online February 25, 2025. doi:10.1158/1078-0432.CCR-24-3271

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RB1 Sequencing and/or Deletion/Duplication Analysis

American Association for Cancer Research (AACR)

The Childhood Cancer Predisposition Workshop published updated recommendations in 2025 for retinoblastoma predisposition and surveillance recommendations for children. Germline testing for *RB1* is recommended for all children who have been diagnosed with retinoblastoma, either unilaterally or bilaterally (p. 1573).

Kamihara J, Schienda J, McGee RB, et al. Update on Retinoblastoma Predisposition and Surveillance Recommendations for Children. Clin Cancer Res. 2025 May 1;31(9):1573-1579. Published online February 25, 2025. doi:10.1158/1078-0432.CCR-24-3271

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VHL Targeted Variant Analysis

National Comprehensive Cancer Network (NCCN): Kidney Cancer (3.2025)

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

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Kidney Cancer 3.2025
https://www.nccn.org/professionals/physician_gls/pdf/kidney.pdf

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VHL Sequencing and/or Deletion/Duplication Analysis

National Comprehensive Cancer Network (NCCN): Kidney Cancer (3.2025)

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

National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Kidney Cancer 3.2025
https://www.nccn.org/professionals/physician_gls/pdf/kidney.pdf

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DEFINITIONS

1. **Adenomatous polyposis** are conditions that cause multiple adenomas (i.e., benign polyps) in the gastrointestinal tract.
2. **Breast cancer** is a term that applies to patients with invasive cancer or ductal carcinoma in situ (DCIS).

3. **Close relatives** include first, second, and third degree blood relatives:
    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
4. **Adjuvant treatment with olaparib therapy** may be indicated for cancer defined as
    a. Triple-negative breast cancer treated with either:
        i. Adjuvant chemotherapy with axillary node-positive disease or an invasive primary tumor greater than or equal to 2 cm on pathology analysis, **OR**
        ii. Neoadjuvant chemotherapy with residual invasive breast cancer in the breast or resected lymph nodes, **OR**
    b. Hormone receptor positive disease treated with either:
        i. Adjuvant chemotherapy with four or more positive pathologically confirmed lymph nodes, **OR**
        ii. Neoadjuvant chemotherapy which did not have a complete pathologic response, with a CPS+CG score [pre-treatment clinical (CS) and post-treatment pathological stage (PS), estrogen-receptor status (E) and grade (G)] of 3 or higher.
5. **High-risk prostate cancer** is defined by NCCN as an individual who has one or more of the following high-risk features, but does not meet criteria for very-high-risk features:
    a. cT3-cT4
    b. Grade Group 4 or 5
    a. PSA > 20ng/ml
6. **Juvenile polyps** are 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.
7. **Lynch syndrome-related cancer** is defined as any of the following cancer types: colorectal, endometrial, gastric, ovarian, pancreatic, urothelial, brain (usually glioblastoma), biliary tract, small intestinal, sebaceous adenoma, sebaceous carcinoma, or keratoacanthoma.
8. **Maori ancestry** describes individuals who are of indigenous New Zealand ethnic background.
9. **Very-high-risk prostate cancer** is defined by NCCN as an individual who has at least two of the following:
    a. cT3-cT4
    b. PSA >40 ng/mL
    a. Grade Group 4 or 5

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Note: The Health Plan uses the genetic testing clinical criteria developed by Concert Genetics, an industry-leader in genetic testing technology assessment and policy development.

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