BlueCross BlueShield Nebraska

# GENETIC TESTING: HEREDITARY CANCER SUSCEPTIBILITY SYNDROMES (REQUIRES PREAUTHORIZATION)

V.59

## V.59 GENETIC TESTING: HEREDITARY CANCER SUSCEPTIBILITY SYNDROMES (REQUIRES PREAUTHORIZATION)

## DESCRIPTION

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

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

Of note, the National Society of Genetic Counselors (NSGC) endorses the use of multi-gene panel tests when clinically warranted and appropriately applied. Specifically, the NSGC recommends thorough evaluation of the analytic and clinical validity of the test, as well as its clinical utility[3]. For this reason, several of the criteria in

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

Targeted germline genetic testing may also be recommended when there is a P/LP variant found on somatic tumor profiling. It should be noted that there is language in several National Comprehensive Cancer Network (NCCN) guidelines stating that somatic P/LP variants are common in some genes and may not indicate the need for germline testing unless the clinical/family history is consistent with a P/LP variant in the germline. However, given these tests are targeted and have significant implications for a patient's medical management, it is clinically appropriate to allow for a path to coverage for this type of testing.

## Dates

Original Effective
**07-01-2020**
Last Review
**08-07-2024**
Next Review
**08-11-2025**

## RELATED POLICIES

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

***V.57 Oncology: Cancer Screening*** for coverage criteria related to tests that screen for the presence of cancer.

***V.58 Oncology: Algorithmic Testing*** for coverage criteria related to tests that give prognostic information for an individual with cancer, or any oncology related test that involved an algorithmic portion.

***V.60 Oncology: Molecular Analysis of Solid Tumors and Hematologic Malignancies*** for coverage criteria related to somatic

***V.61 Oncology: Circulating Tumor DNA and Circulating Tumor Cells (Liquid Biopsy)*** for coverage criteria related to the testing of tumor DNA circulating in an individual's blood stream.

***V.62 Genetic Testing: Multisystem Inherited Disorders, Intellectual Disability, and Developmental Delay*** for coverage criteria related to diagnostic testing for Fanconi anemia.

***V.74 Genetic Testing: General Approach to Genetic and Molecular Testing*** for coverage criteria related to hereditary cancer susceptibility that is not specifically discussed in this or other non-general policies.

## REFERENCE TABLE

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

| Coverage Criteria Sections | Example Tests (Labs) | Common CPT Codes | Common ICD10 Codes | Ref |
|---|---|---|---|---|
| Pan-Cancer Hereditary Cancer Susceptibility Panels | MyRisk (Myriad Genetics) | 81432, 81433 | C15-26, C50-58 Z17, Z80, Z85.0-Z85.9 | 1, 2, 3, 11 |
| | Common Hereditary Cancers Panel (Invitae) | | | |
| | CancerNext (Ambry Genetics) | | | |
| | Tempus xG Hereditary Cancer Panel | | | |
| | +RNAinsight with CancerNext (Ambry Genetics) | 0134U | | |
| | GeneticsNow Comprehensive Germline Panel (GoPath Diagnostics) | 0474U | | |
| Hereditary Breast Cancer Susceptibility | VistaSeq Breast Cancer Panel (Labcorp) | 81162, 81163, | C50, Z80.3, Z83, Z84, Z85, Z86 | 1, 21 |

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|---|---|---|---|---|
| | Panel (Sequencing & Deletion/Duplication) (Fulgent Genetics)<br>Breast Cancer - High Risk Panel (PreventionGenetics, part of Exact Sciences)<br>Breast Cancer High-Risk Panel plus PALB2 (GeneDx) | 81167, 81216, 81307, 81321, 81351, 81432, 81433 | | |
| | BRCAplus (Ambry Genetics) | 0129U | | |
| Hereditary GI/Colon Cancer Susceptibility Panels | Colorectal Cancer Panel (Invitae) | 81435, 81436 | C15-26, Z80, Z83, Z84, Z85, Z86 | 2 |
| | ColoNext (Ambry Genetics) | 0101U | | |
| | +RNAinsight for ColoNext (Ambry Genetics) | 0130U, 0162U | | |
| Hereditary Gastric Cancer Susceptibility Panels | Invitae Gastric Cancer Panel (Invitae) | 81201, 81203, 81292, 81294, 81295, 81297, 81298, | C16, Z80, Z85, Z86 | 7 |
| | Gastric Cancer Panel (PreventionGenetics, part of Exact Sciences) | 81300, 81317, 81319, 81403, 81404, 81405, 81406, 81408, 81479 | | |
| Hereditary Pancreatic Cancer Susceptibility Panels | Pancreatic Cancer Panel (Invitae) | 81162, 81163, 81201, 81292, 81295, 81298, 81351, 81433 81479 | C25, Z80, Z84, Z85, Z86 | 1 |
| | PancNext (Ambry Genetics) | | | |
| Hereditary Polyposis Susceptibility Panels | Hereditary Polyposis Panel (PreventionGenetics, part of | 81201, 81203, | D12, K63.5, Z80, Z84, Z85, Z86 | 2 |

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

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|---|---|---|---|---|
| Analysis | PALB2 with +RNA insight (Ambry Genetics) | 0137U | | |
| ***ATM* and/or *CHEK2* Gene Testing** | | | | |
| *ATM* or *CHEK2* Targeted Variant Analysis | ATM Targeted Variant - Single Test (GeneDx) | 81479 | C50, D05, Z80, Z84, Z85, Z86 | 1 |
| | CHEK2 Targeted Variant - Single Test (GeneDx) | | | |
| *ATM* or *CHEK2* Sequencing and/or Deletion/Duplication Analysis | ATM Full Gene Sequencing and Deletion/Duplication (Invitae) | 81408, 81479 | | |
| | Hereditary Breast Cancer via the CHEK2 Gene (PreventionGenetics, part of Exact Sciences) | 81479 | | |
| | +RNAinsight for ATM (Ambry Genetics) | 0136U | | |
| **Lynch Syndrome / Hereditary Nonpolyposis Colorectal Cancer (HNPCC)** | | | | |
| *MLH1, MSH2, MSH6*, *PMS2*, or *EPCAM* Targeted Variant Analysis | MSH6 Targeted Variant; PMS2 Targeted Variant; EPCAM Targeted Variant (GeneDx) | 81299, 81318, 81479 | C15-22, C24-6, C26 C53-57 Z80, Z84, Z85, Z86 | 2 |
| | Hereditary Nonpolyposis Colorectal Cancer (HNPCC): MLH1 (Known Mutation) (Labcorp) | 81293 | | |
| | Hereditary Nonpolyposis Colorectal Cancer (HNPCC): MSH2 (Known Mutation) (Labcorp) | 81296 | | |
| *MLH1, MSH2, MSH6 PMS2*, and/or *EPCAM* Sequencing and/or Deletion/Duplication Analysis | HNPCC Concurrent (Ambry Genetics) | 81292, 81294, 81295, 81297, 81298, 81300, 81317, 81319, 81403 | | |
| | Lynch Syndrome Panel (Invitae) | | | |
| | CustomNext + RNA: MLH1, MSH2, MSH6, and/or PMS2 | 0158U, 0159U, | | |

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|---|---|---|---|---|
| **B*AP1*-Tumor Predisposition Syndrome** | | | | |
| *BAP1* Targeted Variant Analysis | BAP1: Site Specific Analysis (familial) (Univ of Pennsylvania School of Medicine-Genetic Diagnostic Laboratory) | 81403 | C22, C45, C64 C69, D22, D32, Z80, Z84, Z85, Z86 | 8 |
| *BAP1* Sequencing and/or Deletion/Duplication Analysis | BAP1 Full Gene Sequencing and Deletion/Duplication (Invitae) | 81479 | | 5, 8, 12, 13, 14 |
| **Birt-Hogg-Dube syndrome (BHDS)** | | | | |
| *FLCN* Targeted Variant Analysis | FLCN Targeted Variant - Single Test (GeneDx) | 81479 | C65, D14.3, D23.9, Z84, Z85, Z86 | 8 |
| *FLCN* Sequencing and/or Deletion/Duplication Analysis | Birt-Hogg-Dube Syndrome Test (Invitae) | 81479 | | 8, 10 |
| **Cowden Syndrome (CS)/PTEN Hamartoma Tumor Syndrome (PHTS)** | | | | |
| *PTEN* Targeted Variant Analysis | PTEN Targeted Variant - Single Test (GeneDx) | 81322 | C15-21, C26, C50, C54, C55, C64, C73, D12, D13, D17, D23, D24, F78, F84.0, Q75.3, Q87.89, Z80, Z84, Z85, Z86 | 1 |
| *PTEN* Sequencing and/or Deletion/Duplication Analysis | PTEN Gene Sequencing and Del/Dup (GeneDx) | 81321, 81323 | | |
| **Adenomatous Polyposis Conditions (Familial Adenomatous Polyposis Syndrome (FAP)/Attenuated FAP (AFAP) and *MUTYH*-Associated Polyposis Syndrome (MAP))** | | | | |
| *APC* and/or *MUTYH* Targeted Variant Analysis | APC Targeted Variant - Single Test (GeneDx) | 81202 | C15-21, D12, Z80, Z84, Z85, Z86 | 2 |
| | MUTYH Targeted Variant - Single Test (GeneDx) | 81403, 81401 | | |
| *APC* and/or *MUTYH* Sequencing and/or Deletion/Duplication Analysis | APC Seq and Del/Dup (Ambry Genetics) | 81201, 81203 | | |
| | Familial Adenomatous Polyposis Test (Invitae) | | | |
| | +RNAInsight for APC (Ambry Genetics) | 0157U | | |

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| **Familial Atypical Multiple Mole Melanoma Syndrome (FAMMM)** | | | | |
| *CDKN2A* Targeted Variant Analysis | CDKN2A Targeted Variant - Single Test (GeneDx) | 81479 | C43, Z12.83, Z80, Z84, Z85, Z86 | 1 |
| *CDKN2A* Sequencing and/or Deletion/Duplication Analysis | CDKN2A Full Gene Sequencing and Deletion/Duplication (Invitae) | 81404, 81479 | | 1, 5, 20 |
| **Hereditary Diffuse Gastric Cancer** (aka, Signet Ring Cell Gastric Cancer) | | | | |
| *CDH1* Targeted Variant Analysis | CDH1 Targeted Variant - Single Test (GeneDx) | 81479 | C16, C50, Q35, Q36, Z80, Z84, Z85, Z86 | 1, 7 |
| *CDH1* Sequencing and/or Deletion/Duplication Analysis | CDH1 Full Gene Sequencing and Deletion/Duplication (Invitae) | 81406, 81479 | | 7 |
| **Juvenile Polyposis Syndrome (JPS)** | | | | |
| *SMAD4* and/or *BMPR1A* Targeted Variant Analysis | Targeted Variant: SMAD4 (PreventionGenetics, part of Exact Sciences) | 81403 | C15-C26, D12, Z80, Z84, Z85, Z86 | 2 |
| | Targeted Variant: BMPR1A (PreventionGenetics, part of Exact Sciences) | 81403 | | |
| *SMAD4* and/or *BMPR1A* Sequencing and/or Deletion/Duplication Analysis | Juvenile Polyposis Syndrome Panel (Invitae) | 81405, 81406, 81479 | | |
| | BMPR1A, SMAD4 Gene Sequencing and Del/Dup (GeneDx) | | | |
| **Hereditary Leiomyomatosis and Renal Cell Cancer (HLRCC)** | | | | |
| *FH* Targeted Variant Analysis | FH Known Familial Mutation Analysis (University Hospitals) | 81403 | C44, C55, C64, D23, D25, Z84, Z85, Z86 | 8 |
| *FH* Sequencing and/or Deletion/Duplication Analysis | Hereditary Leiomyomatosis and Renal Cell Carcinoma (Ambry Genetics) | 81405, 81479 | | 8, 18 |
| **Li-Fraumeni Syndrome (LFS)** | | | | |
| *TP53* Targeted Variant Analysis | TP53 Targeted Variant - Single Test (GeneDx) | 81352 | C30-41, C15-26, C45, C47-49, C50, C71, C95.9, | 1 |

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|---|---|---|---|---|
| Analysis | Li-Fraumeni Syndrome, TP53 Sequencing and Deletion/Duplication (Quest Diagnostics) | | | |
| **Multiple Endocrine Neoplasia - Type 1 (MEN1)** | | | | |
| *MEN1* Targeted Variant Analysis | MEN1 Targeted Variant - Single Test (GeneDx) | 81479 | C25, C75.0, D35.2, E31.2, Z80, Z84, Z85, Z86 | 6 |
| *MEN1* Sequencing and/or Deletion/Duplication Analysis | MEN1 Gene Sequencing and Del/Dup (GeneDx) | 81404, 81405 | | |
| | Multiple Endocrine Neoplasia Type 1 Test (Invitae) | | | |
| **Multiple Endocrine Neoplasia Type 2 (MEN2)** | | | | |
| *RET* Targeted Variant Analysis | RET Targeted Variant - Single Test (GeneDx) | 81404 | C73-75, C7A, D3A, Z80, Z84, Z85, Z86 | 6 |
| *RET* Sequencing and/or Deletion/Duplication Analysis | RET Full Gene Sequencing and Deletion/Duplication (Invitae) | 81406, 81479, S3840 | | 6, 17 |
| **Nevoid Basal Cell Carcinoma Syndrome (NBCCS) (aka Gorlin syndrome)** | | | | |
| *PTCH1* and/or *SUFU* Targeted Variant Analysis | Targeted Variant: PTCH1 or SUFU (GeneDx) | 81479 | C44, C71.6, G93, M27.4, Z84, Z85, Z86 | 15 |
| *PTCH1* and *SUFU* Sequencing and/or Deletion/Duplication Analysis | Basal Cell Nevus Syndrome Panel (Invitae) | 81479 | | |
| **Hereditary Paraganglioma/Pheochromocytoma Syndrome (PGL/PCC)** | | | | |
| *MAX, SDHA, SDHAF2, SDHB, SDHC, SDHD,* or *TMEM127* Targeted Variant Analysis | SDHB, SDHD, SDHC, MAX, SDHAF2, or TMEM127 Targeted Variant - Single Test (GeneDx)<br>Targeted Variants: MAX, SDHAF2, TMEM127 (PreventionGenetics, part of Exact Sciences) | 81479 | C7A, C74.1, D35.00, D44.7, Z84, Z85, Z86 | 8 |
| *MAX, SDHA, SDHAF2, SDHB, SDHC, SDHD,* and *TMEM127* Sequencing and/or | SHDB Full Gene Sequencing and Deletion/Duplication (Invitae) | 81405, 81479 | | 6, 16 |

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|---|---|---|---|---|
| | SDHC Full Gene Sequencing and Deletion/Duplication (Invitae) | 81404, 81405 | | |
| | SDHD Full Gene Sequencing and Deletion/Duplication (Invitae) | 81404, 81479 | | |
| | MAX Full Gene Sequencing and Deletion/Duplication (Invitae) | 81479 | | |
| | SDHAF2 Full Gene Sequencing and Deletion/Duplication (Invitae) | | | |
| | TMEM127 Full Gene Sequencing and Deletion/Duplication (Invitae) | | | |
| **Peutz-Jeghers Syndrome (PJS)** | | | | |
| *STK11* Targeted Variant Analysis | STK11 Targeted Variant - Single Test (GeneDx) | 81479 | C50, Q85.8, Z80, Z84, Z85, Z86 | 2 |
| *STK11* Sequencing and/or Deletion/Duplication Analysis | STK11 Gene Sequencing & Del/Dup (GeneDx) | 81404, 81405 | | |
| **Retinoblastoma** | | | | |
| *RB1* Targeted Variant Analysis | Retinoblastoma: Site Specific Analysis (Familial) (Univ of Pennsylvania School of Medicine-Genetic Diagnostic Laboratory) | 81403 | C69, C75.3, Z80, Z84, Z85, Z86 | 9 |
| *RB1* Sequencing and/or Deletion/Duplication Analysis | RB1 Full Gene Sequencing and Deletion/Duplication (Invitae) | 81479, S3841 | | |
| **Von Hippel-Lindau Syndrome (VHL)** | | | | |
| *VHL* Targeted Variant Analysis | VHL Known Mutation (Children's Hospital of Philadelphia - Division of Genomic Diagnostics) | 81403 | C64, C7A, D3A, D35.00, K86.2, N28, N50.3, Q85.8, Z80, Z84, Z85, Z86 | 8 |

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|---|---|---|---|---|
| Analysis | VHL Gene Sequencing and Del/Dup (GeneDx) | | | |

# POLICY

**PAN-CANCER HEREDITARY CANCER SUSCEPTBILITY PANELS**

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

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

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

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

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

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

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

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

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

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

**HEREDITARY BREAST CANCER SUSCEPTIBILITY PANELS**

I. Genetic testing using a hereditary breast cancer susceptibility panel (81162, 81163, 81164, 81165, 81166, 81167, 81216, 81307, 81321, 81351, 81432, 81433, 0129U) is considered **medically necessary** when:
   A. The member meets *BRCA1* and *BRCA2* Sequencing and Deletion/Duplication analysis, **AND**
   B. The panel includes, at a minimum, sequencing of the following genes: *BRCA1*, *BRCA2*.

II. Genetic testing using a STAT hereditary breast cancer panel (81162, 81163, 81164, 81165, 81166, 81167, 81216) is considered **medically necessary** when:
   A. The member meets any of the above criteria, **AND**
   B. The member requires a rapid turn-around-time for decision making related to surgical interventions and treatment.

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

**HEREDITARY GI/COLON CANCER SUSCEPTIBILITY PANELS**

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

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

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

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

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

**NOTE:** If a multigene cancer panel is peformed, the appropriate panel codes should be used.

**HEREDITARY GASTRIC CANCER SUSCEPTIBILITY PANELS**

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

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

A. The member 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/Hereitary Nonpolyposis colorectal cancer **OR**
2. Hereditary Difusee Gastci cancer **OR**
3. Juvenile Polyposis Syndrome **OR**
4. Peutz-Heghers Syndrome **OR**
5. Adenomatous Polyposis Syndromes **AND**

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

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

**HEREDITARY PANCREATIC CANCER SUSCEPTIBILITY PANELS**

**pancreatic cancer.**

I. Genetic testing using a hereditary pancreatic cancer susceptibility panel (81162, 81163, 81201, 81292, 81295, 81298, 81351, 81433, 81479) is considered **medically necessary** when:
   A. The member is 18 years or older, **AND**
   B. The member meets criteria for *BRCA1* and *BRCA2* sequencing and/or deletion/duplication analysis, **AND**
   C. The panel includes, at a minimum, sequencing of the following genes: *ATM, BRCA1, BRCA2, CDKN2A, EPCAM, MLH1, MSH2, MSH6, PALB2, STK11*, *TP53*.

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

**HEREDITARY POLYPOSIS SUSCEPTIBILITY PANELS**

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

I. Genetic testing using a hereditary polyposis panel (81201, 81203, 81406, 81479) is considered **medically necessary** when:
   A. The member meets criteria for sequencing and/or deletion/duplication analysis for Adenomatous Polyposis conditions (Familial Adenomatous Polyposis Syndrome (FAP)/Attenuated FAP (AFAP) and *MUTYH*-Associated Polyposis Syndrome (MAP), **AND**
   B. The panel includes, at a minimum, sequencing of the following genes: *APC* and *MUTYH*.

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

**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 hereditary prostate cancer susceptibility panel (81162, 81292, 81295, 81351, 81479) 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:

3. Intermediate risk prostate cancer with intraductal/cribrifom history **OR**

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

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

a. Breast cancer at or under the 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. Exocrine pancreatic cancer at any age **OR**
f. Metastatic, very high risk, 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 patient with prostate cancer **OR**

3. Ashkenazi Jewish ancestry **OR**

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

E. The member's probability of having 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 a minimum of sequencing of the following genes: BRCA1, BRCA2

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

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

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

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

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

1. Adrenocortical carcinoma **OR**
2. Paraganglioma/pheochromocytoma **OR**
3. Parathyoid 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. At 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 (81437, 81438) is considered **investigational** for all other indications.

NOTE: If a multigene cancer panel is peformed, the appropriate panel codes should be used

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

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

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

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

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

I. *BRCA1* and *BRCA2* (81212) targeted variant analysis for the 185delAG, 5385insC, 6174delT variants is considered **medically necessary** when:
   A. The member is 18 years or older, **AND**
   B. The member is of Ashkenazi Jewish ancestry (at least one grandparent of Ashkenazi Jewish ancestry).

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

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

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

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

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

1. Male (sex assigned at birth) breast cancer **OR**

2. Triple negative breast cancer **OR**
3. Breast cancer diagnosed at age 65 or younger **OR**

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

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

8. Multiple primary breast cancers (diagnosed synchoronously or metachronously) **OR**

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

1. Ashkenazi Jewish ancestry **OR**

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

a. Female (sex assigned at birth) breast cancer diagnosed at age 50 years or younger **OR**

b. Male (sex assigned at birth) breast cancer **OR**

c. Ovarian cancer **OR**

d. Pancreatic cancer **OR**

e. Prostate cancer that is either metastatic, intermediate risk with intraductal/cribriform histology, or high or very high risk group **OR**

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

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

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

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

II. BRAC1 and BRCA2 (81162, 81163, 81164, 81165, 81166, 81167, 81216) sequencing and/or deletion/duplication analysis for hereditray breast and/or ovarian cancer susceptibility is considered **investigational** for all other indications

III. BRCA1 and BRCA2 mRNA sequencing analysis for the interpretation of variants of unknown significance (0138U) when billed in addition is considered **investigational** because it is typically either considered an existing component of the genetic testing process for quality assurance or follow up testing without proven utility.

### ***PALB2*** **GENE TESTING**

BlueCross BlueShield Nebraska

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 (81308) for hereditary breast and/or ovarian cancer susceptibility is considered **investigational** for all other indications

***PALB2* Sequencing and/or Deletion/Duplication Analysis**

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

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

B. One of the following:

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

a) Male (sex assigned at birth) breast cancer, **OR**
b) Triple-negative breast cancer, **OR,**
c) Breast cancer diagnosed at age 50 or younger, **OR**
d) Epithelial ovarian cancer (including fallopian tube cancer or peritoneal cancer), **OR**
e) Exocrine pancreatic or ampullary cancer, **OR**
f) Multiple primary breast cancers (diagnosed synchronously or metachronously, **OR**
g) Metastatic prostate cancer, **OR**

a) Ashkenazi Jewish ancestry, **OR**

b) One or more close relatives with any of the following:
   (1) Female (sex assigned at birth) breast cancer diagnosed at age 50 years or younger, **OR**
   (2) Male (sex assigned at birth) breast cancer, **OR**
   (3) Ovarian cancer, **OR**
   (4) Exocrine pancreatic cancer, **OR**

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

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

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

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

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

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

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

### *ATM* AND/OR *CHEK2* GENE TESTING

#### *ATM* or *CHEK2* Targeted Variant Analysis

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

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

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

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

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

## LYNCH SYNDROME / HEREDITARY NONPOLYPOSIS COLORECTAL CANCER (HNPCC) TESTING

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

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

A. The member 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.

indications

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

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

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

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

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

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

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

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

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

1. One or more first-degree relatives diagnosed with colorectal or endometrial cancer before age 50, **OR**

2. One or more first-degree relatives diagnosed with colorectal or endometrial cancer and an additional Lynch syndrome-related cancer, **OR**

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

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

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

### *BAP1*-TUMOR PREDISPOSITION SYNDROME

#### *BAP1* Targeted Variant Analysis

I. *BAP1* targeted variant analysis (81403) for *BAP1*-tumor predisposition syndrome is considered **medically necessary** when:
   A. The member 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 (81403) for *BAP1*-tumor predisposition syndrome is considered **investigational** for all other indications.

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

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

A. The member has a personal history of:

1. Two or more of the following:

c) Malignant mesothelioma, **OR**
d) Renal cell carcinoma, **OR**
e) Hepatocellular carcinoma, **OR**
f) Cholangiocarcinoma, **OR**
g) Meningioma, **OR**

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

a) A cutaneous melanoma, **OR**
b) A basal cell carcinoma, **OR**

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

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

4. 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) Hepatocellular carcinoma, **OR**
(6) Cholangiocarcinoma, **OR**
(7) Meningioma.

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

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

*FLCN* Sequencing and/or Deletion/Duplication Analysis

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

A. The member 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 (81479) for Birt-Hogg-Dube syndrome (BHDS) is considered **investigational** for all other indications.

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

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

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

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

A. The member 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

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. Macrocephaly (greater than or equal to 97 percentile), **OR**
6. Macular pigmentation of the glans penis, **OR**

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**

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**

e) Intellectual disability (i.e., IQ less than or equal to 75), **OR**
f) Thyroid cancer (papillary or follicular variant of papillary thyroid cancer), **OR**
g) Thyroid structural lesions (such as adenoma, multinodular goiter), **OR**
h) Renal cell carcinoma, **OR**
i) Single GI hamartoma or ganglioneuroma, **OR**
j) Testicular lipomatosis, **OR**
k) Vascular anomalies (including multiple intracranial developmental venous anomalies).

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

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

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

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

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

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

considered **medically necessary** when:

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, **OR**

7. Duodenal cancer, **OR**

8. Duodenal adenomas.

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

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

**FAMILIAL ATYPICAL MULTIPLE MOLE MELANOMA (FAMMM) SYNDROME**

***CDKN2A* Targeted Variant Analysis**

**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 (81479) for familial atypical multiple mole melanoma (FAMMM) syndrome, also known as melanoma-pancreatic cancer syndrome is considered **investigational** for all other indications

### ***CDKN2A* Sequencing and/or Deletion/Duplication Analysis**

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

A. The member 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**

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

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

### ***CDH1* Targeted Variant Analysis**

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

A. The member 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**

performed.

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

### *CDH1* Sequencing and/or Deletion/Duplication Analysis

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

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

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

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

2. Diffuse gastric cancer diagnosed at any age in a member with Maori ancestry, **OR**

3. Diffuse gastric cancer diagnosed at any age in a member with a personal or family history of cleft lip/cleft palate, **OR**

4. Bilateral lobular breast cancer diagnosed before age 70 years, **OR**

5. Personal or family history of diffuse gastric cancer and lobular breast cancer, one diagnosed before age 70 years, **OR**

6. Two cases of gastric cancer in the family, at least one of which is a confirmed case of diffuse gastric cancer, diagnosed at any age, **OR**

7. Two cases of lobular breast cancer in family members before 50 years of age**.**

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

# JUVENILE POLYPOSIS SYNDROME (JPS)

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

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

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

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

## HEREDITARY LEIOMYOMATOSIS AND RENAL CELL CANCER (HLRCC)

### *FH* Targeted Variant Analysis

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

   A. The member 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 (81403) for hereditary leiomyomatosis and renal cell cancer (HLRCC) is considered **investigational** for all other indications.

### *FH* Sequencing and/or Deletion/Duplication Analysis

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 (81405, 81479) for hereditary leiomyomatosis and renal cell cancer (HLRCC) is considered **investigational** for all other indications.

**LI-FRAUMENI SYNDROME (LFS)**

***TP53* Targeted Variant Analysis**

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

A. The member 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 (81352) for Li-Fraumeni syndrome (LFS) is considered **investigational** for all other indications.

*TP53* Sequencing and/or Deletion/Duplication Analysis

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

A. The member 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**

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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.

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

## MULTIPLE ENDOCRINE NEOPLASIA TYPE 1 (MEN1)

### *MEN1* Targeted Variant Analysis

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

identified by tumor profiling in the member and germline analysis has not yet been performed.

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

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

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

A. The member 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. **T**he member has a close relative with at least one of the above.

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

## MULTIPLE ENDOCRINE NEOPLASIA TYPE 2 (MEN2)

### *RET* Targeted Variant Analysis

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

A. The member 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.

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

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

A. The member 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 (81406, 81479, S3840) for multiple endocrine neoplasia type 2 (MEN2) is considered **investigational** for all other indications.

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

### *PTCH1* or *SUFU* Targeted Variant Analysis

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

A. The member 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 (81479) for nevoid basal cell carcinoma syndrome (NBCC), also known as Gorlin syndrome, is considered **investigational** for all other indications.

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

I. *PTCH1* and *SUFU* sequencing and/or deletion duplication analysis (81479) for nevoid basal cell carcinoma syndrome (NBCCS), also

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 (examples: 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**

**OR**

f) Pre- or post-axial polydactyly, **OR**
g) Ovarian fibromas, **OR**
h) Cardiac fibromas, **OR**
i) Ocular anomalies (examples: cataract, pigmentary changes of the retinal epithelium, developmental defects).

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

**HEREDITARY PARAGANGLIOMA/PHEOCHROMOCYTOMA SYNDROME (PGL/PCC)**

***MAX*, *SDHA*, *SDHAF2*, *SDHB*, *SDHC*, *SDHD*, or *TMEM127***

**Targeted Variant Analysis**

I. *MAX*, *SDHA*, *SDHAF2*, *SDHB*, *SDHC*, *SDHD*, or *TMEM127* targeted variant analysis (81403) for hereditary paraganglioma/pheochromocytoma syndrome (PGL/PCC) is considered **medically necessary** when:
   A. The member has a close relative with a known pathogenic or likely pathogenic variant in *MAX*, *SDHA*, *SDHAF2*, *SDHB*, *SDHC*, *SDHD*, or *TMEM127*, **OR**
   B. A 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 (81403) for hereditary paraganglioma/pheochromocytoma syndrome (PGL/PCC) is considered **investigational** for all other indications.

***MAX*, *SDHA*, *SDHAF2*, *SDHB*, *SDHC*, *SDHD*, and *TMEM127***

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

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

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

1. Pheochromocytoma, **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 *TMEM127* sequencing and/or deletion/duplication (81404, 81405, 81406, 81479) for hereditary paraganglioma/pheochromocytoma syndrome (PGL/PCC) is considered **investigational** for all other indications

**PEUTZ-JEGHERS SYNDROME (PJS)**

***STK11* Targeted Variant Analysis**

I. *STK11* targeted variant analysis (81479) for Peutz-Jeghers syndrome is considered **medically necessary** when:
   A. The member 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 (81479) for Peutz-Jeghers syndrome is considered **investigational** for all other indications.

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

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

**RETINOBLASTOMA**

***RB1* Targeted Variant Analysis**

I. *RB1* targeted variant analysis (81403) 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**

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

### *RB1* Sequencing and/or Deletion/Duplication Analysis

I. *RB1* sequencing and/or deletion/duplication analysis (81479, S3841) for retinoblastoma is considered **medically necessary** when:
   A. The member 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 (81479, S3841) for retinoblastoma is considered **investigational** for all other indications

## VON HIPPEL-LINDAU SYNDROME (VHL)

### *VHL* Targeted Variant Analysis

I. *VHL* targeted variant analysis (81403) for Von Hippel-Lindau syndrome is considered **medically necessary** when:
   A. The member 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 (81403) for Von Hippel-Lindau syndrome is considered **investigational** for all other indications.

### *VHL* Sequencing and/or Deletion/Duplication Analysis

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

A. The member 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**

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4. Pheochromocytoma or paraganglioma (in abdomen, thorax, or neck), **OR**

5. Retinal angiomas, **OR**

6. Endolymphatic sac tumor, **OR**

7. Epididymal or adnexal papillary cystadenoma, **OR**

8. Pancreatic serous cystadenoma, **OR**

9. Pancreatic neuroendocrine tumors, **OR**

10. Multiple renal, pancreatic or hepatic cysts.

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

## DEFINITIONS

1. **Close relatives** include first, second, and third degree blood relatives on the same side of the family:
    a. **First-degree relatives** are parents, siblings, and children
    b. **Second-degree relatives** are grandparents, aunts, uncles, nieces, nephews, grandchildren, and half siblings
    c. **Third-degree relatives** are great grandparents, great aunts, great uncles, great grandchildren, and first cousins
2. **Breast cancer**: Term that applies to patients with invasive cancer or ductal carcinoma in situ (DCIS).
3. **High-risk breast cancer** is defined by NCCN as “those with ≥4

positive lymph nodes (confirmed preoperatively and/or at surgery), or 1–3 positive lymph nodes with either grade 3 disease or tumor size ≥5 cm (on pre-operative imaging and/ or at surgery)". (p. BINV-K)

edema and inflammation within the lamina propria, cystic glands filled with thick mucin, and some degree of smooth muscle proliferation.

5. **Maori ancestry:** Describes individuals who are of indigenous New Zealand ethnic background
6. **High-risk prostate cancer:** Defined by NCCN as an individual who has no very-high-risk features but has exactly one of the following high-risk features:
    a. cT3a, OR
    b. Grade Group 4 or Grade Group 5, **OR**
    c. PSA > 20ng/ml
7. **Very-high-risk prostate cancer:** Defined by NCCN as an individual who has at least one of the following:
    a. CT3b-cT4
    b. Primary Gleason pattern 5
    c. 2 or 3 high-risk features
    d. >4 cores with Grade Group 4 or 5
8. **Adenomatous polyposis:** Conditions that cause multiple adenomas (i.e., benign polyps) in the gastrointestinal tract
9. **Lynch syndrome-related cancer**: Defined as any of the following cancer types: colorectal, endometrial, gastric, ovarian, pancreatic, ureter and renal pelvic, brain (usually glioblastoma), biliary tract, small intestinal, sebaceous adenoma, sebaceous carcinoma, or keratoacanthoma.

# BACKGROUND

**Pan-Cancer Hereditary Susceptibility Panels**

*National Comprehensive Cancer Network (NCCN)*

NCCN Breast, Ovarian, and/or Pancreatic Cancer Genetic Assessment guidelines (3.2024) define multi-gene testing as analysis of a set of genes that are associated with one or more cancer phenotypes in a family. It is possible for a personal or family history of cancer to be due to more than one hereditary cancer syndrome. This testing approach can be more efficient and/or cost effective than single-gene testing and is also available for individuals who have previously tested negative for a single syndrome but have a history concerning for a hereditary predisposition or for individuals who are

in a gene with uncertain clinical management. These types of findings increase as additional genes are included in the multi-gene panel. It is recommended that multi-gene panel testing be offered by a professional genetic expert that provides detailed pre- and post-test counseling. (p. EVAL-A 1-3 of 10)

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

NCCN Guidelines for Genetic/Familial High-Risk Assessment Colorectal (2.2023) recommend germline multigene panel testing in individuals with a personal history of colorectal cancer who are under age 50 at diagnosis and in some other clinical scenarios (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 2)

*National Society of Genetic Counselors (NSGC)*

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

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

hereditary cancer syndromes and risk assessment that included the following recommendations:

- A hereditary cancer risk assessment is the key to identifying patients and families who may be at increased risk of developing certain types of cancer. Assessments should be performed by obstetrician–gynecologists or other obstetric–gynecologic care providers and should be updated regularly.
- If a hereditary cancer risk assessment suggests an increased risk of a hereditary cancer syndrome, referral to a specialist in cancer genetics or a health care provider with expertise in genetics is recommended for expanded gathering of family history information, risk assessment, education, and counseling, which may lead to genetic testing and tailored cancer screening or risk reduction measures, or both.
- Genetic testing may be performed using a panel of multiple genes through next-generation sequencing technology. This multigene testing process increases the likelihood of finding variants of unknown significance, and it also allows for testing for pathogenic and likely pathogenic variants in multiple genes that may be associated with a specific cancer syndrome or family cancer phenotype (or multiple phenotypes). (p. e143)

**Hereditary Breast Cancer Susceptibility Panels**

*National Comprehensive Cancer Network (NCCN)*

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

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

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

- Treatment indications
    - To aid in systemic treatment decisions using PARP inhibitors for metastatic breast cancer
- To aid in adjuvant treatment decisions with olaparib for high-risk, HER2-negative breast cancer, including triple-negative breast cancer

metachronous)
    - Male breast cancer
- Ashkenazi Jewish ancestry
- Family history of at least 1 close blood relative with:
    - Breast cancer at age 50 years or younger
    - Male breast cancer
    - Ovarian cancer
    - Pancreatic cancer
    - Prostate cancer with metastatic, or high- or very-high-risk group
    - 3 or more total diagnoses of breast cancer and/or prostate cancer in patient and/or close blood relatives on the same side of the family

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

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

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

*American Society of Clinical Oncology/Society of Surgical Oncology*

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

*National Comprehensive Cancer Network (NCCN)*

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

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

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

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

**Hereditary Gastric Cancer Susceptibility Panels**

*National Comprehensive Cancer Network (NCCN)*

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

**Hereditary Pancreatic Cancer Susceptibility Panels**

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

**Hereditary Polyposis Susceptibility Panels**

*National Comprehensive Cancer Network (NCCN)*

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

**Hereditary Prostate Cancer Susceptibility Panels**

*National Comprehensive Cancer Network (NCCN)*

NCCN Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic guidelines (3.2024) recommend 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, high- or very-high risk group at any age
- 3 or more close blood relatives with either breast or prostate cancer (any grade) on the same side of the family including the patient with prostate cancer;
- Ashkenazi Jewish ancestry
- Another fulfilling criterion is an individual with or without prostate cancer affected (not meeting testing criteria listed above) with a first-degree blood relative meeting any of the

These guidelines also recommend consideration of testing for:

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

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

**Hereditary Neuroendocrine Cancer Susceptibility Panels**

*National Comprehensive Cancer Network (NCCN)*

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

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

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

NCCN also recommends consideration of testing for patients with:

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

*National Comprehensive Cancer Network (NCCN)*

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

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

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

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

*National Comprehensive Cancer Network (NCCN)*

The NCCN Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic guidelines (3.2024) 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)

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

*National Comprehensive Cancer Network (NCCN)*

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

Personal history of breast cancer with specific features:

- Diagnosed 50 years of age or younger
- Diagnosed at any age: To aid in systemic treatment decisions using PARP inhibitors for breast cancer in the metastatic setting; to aid in adjuvant treatment decisions with olaparib for high-risk, HER2-negative breast cancer; triple-negative breast cancer; multiple primary breast cancers (synchronous or metachronous); Male breast

prostate cancer with metastatic, or high- or very-high-risk group, 3 or more total diagnoses of breast or prostate cancer in patient and/or close blood relatives on the same side of the family.

Family history-based criteria:

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

NCCN recommends consideration of testing for the following clinical scenarios:

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

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

The NCCN guidelines for Ampullary Adenocarcinoma (2.2024) recommend consideration of genetic testing for inherited mutations for any patient with confirmed ampullary cancer. A comprehensive gene panel should be utilized. Genetic counseling is recommended for patients who test positive for a pathogenic mutation (*ATM, BRCA1,*

*US Preventive Services Task Force (USPSTF)*

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

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

*American Society of Clinical Oncology/Society of Surgical Oncology*

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

## ***PALB2* GENE TESTING**

### ***PALB2* Targeted Variant Analysis**

*National Comprehensive Cancer Network (NCCN)*

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

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

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

Personal history of breast cancer with specific features:

- Diagnosed 50 years of age or younger
- Diagnosed at any age: To aid in systemic treatment decisions using PARP inhibitors for breast cancer in the metastatic setting; to aid in adjuvant treatment decisions with olaparib for high-risk, HER2-negative breast cancer, triple-negative breast cancer; multiple primary breast cancers (synchronous or metachronous); Male breast cancer; Ashkenazi Jewish ancestry; at least 1 close blood relative with: breast cancer at age 50 years or younger, male breast cancer, ovarian cancer, pancreatic cancer, prostate cancer with metastatic, or high- or very-high-risk group, 3 or more total diagnoses of breast cancer in patient and/or close blood relatives, 2 or more close blood relatives with either breast or prostate cancer (any grade),

Family history-based criteria:

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

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

NCCN recommends consideration of testing for the following clinical scenarios:

- An individual with breast cancer who was diagnosed at any age with at least one close blood relative with intermediate-risk prostate cancer with intraductal/ cribriform histology

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

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

## *ATM* AND *CHEK2* GENE TESTING

### *ATM* or *CHEK2* Targeted Variant Analysis

*National Comprehensive Cancer Network (NCCN)*

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

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

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

*National Comprehensive Cancer Network (NCCN)*

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

In order to help further clarify variants of unknown significance, NCCN recommends consideration of RNA studies as well as a clinical trials referral to help define the functional impact of variants. (p. EVAL-A, 9 of 10)

**LYNCH SYNDROME/HEREDITARY NONPOLYPOSIS COLORECTAL CANCER (HNPCC) TESTING**

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

*National Comprehensive Cancer Network (NCCN)*

NCCN Genetic/Familial High-Risk Assessment: Colorectal guidelines (2.2023) outline testing criteria for the evaluation of Lynch syndrome. If there is a known pathogenic variant in a Lynch syndrome gene (*MLH1, MSH2, MSH6, PMS2,* or *EPCAM),* genetic testing for the known variant is recommended. (p. LS-2) Additionally, it is possible that pathogenic or likely pathogenic variants identified through tumor profiling could be of germline origin. Confirmatory germline testing is indicated for pathogenic/likely pathogenic variants identified via tumor profiling when there is a reasonable clinical suspicion of being of germline origin. (p. HRS-B 5 of 9)

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

*National Comprehensive Cancer Network (NCCN)*

NCCN Genetic/Familial High-Risk Assessment: Colorectal guidelines (2.2023) outline testing criteria for the evaluation of Lynch syndrome. These criteria include:

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

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.

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

**_BAP1_ TUMOR PREDISPOSITION SYNDROME**

**_BAP1_ Targeted Variant Analysis**

*National Comprehensive Cancer Network (NCCN)*

NCCN guidelines for Kidney Cancer (1.2025) include *BAP1* tumor predisposition syndrome in their overview of hereditary renal cell carcinoma syndromes, and recommend 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)

**_BAP1_ Sequencing and/or Deletion/Duplication Analysis**

*National Comprehensive Cancer Network (NCCN)*

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

NCCN guidelines for Uveal Melanoma (1.2024) include germline *BAP1* mutations as a risk factor for developing uveal melanoma. (p. UM-A 1 of 2)

5 of 8)

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

*GeneReviews: BAP1 Tumor Predisposition Syndrome (BAP1-TPDS)*

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

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

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

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

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

**BIRT-HOGG DUBE SYNDROME (BHDS)**

***FLCN* Targeted Variant Analysis**

*National Comprehensive Cancer Network (NCCN)*

NCCN guidelines for Kidney Cancer (1.2025) includes Birt-Hogg-Dube syndrome in their overview of hereditary renal cell carcinoma syndromes, and recommend 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)

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

*National Comprehensive Cancer Network (NCCN)*

oncocytic tumors, clear cell, oncocytomas, angiomyolipomas, and papillary RCC. (p. HERED-RCC-2)

*GeneReviews: Birt-Hogg-Dube Syndrome (BHDS)*

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

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

Major criteria

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

Minor criteria

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

The diagnosis of BHDS is established in a proband with:

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

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

***PTEN* Targeted Variant Analysis**

*National Comprehensive Cancer Network (NCCN)*

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

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

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

*National Comprehensive Cancer Network (NCCN)*

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

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

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

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

**SYNDROME (MAP))**

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

*National Comprehensive Cancer Network (NCCN)*

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

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)

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

*National Comprehensive Cancer Network (NCCN)*

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

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

Some individuals will have variants of uncertain significance (VUS); post test counseling should include considering referral to research

**FAMILIAL ATYPICAL MULTIPLE MOLE MELANOMA (FAMMM) SYNDROME**

***CDKN2A* Targeted Variant Analysis**

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

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

***CDKN2A* Sequencing and/or Deletion/Duplication Analysis**

*National Comprehensive Cancer Network (NCCN)*

NCCN Cutaneous Melanoma guidelines (1.2024) recommend 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)

NCCN Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic guidelines (3.2024) recognize 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).

*American Academy of Dermatology*

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

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

***CDH1* Targeted Variant Analysis**

risk assessment for high risk gastric cancer syndromes, which recommend risk evaluation when there is a known mutation in a gastric cancer susceptibility gene in a close relative. (p. GAST-D 1 of 8)

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

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

***CDH1* Sequencing and/or Deletion/Duplication Analysis**

*National Comprehensive Cancer Network (NCCN)*

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

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

**JUVENILE POLYPOSIS SYNDROME (JPS)**

***SMAD4* and *BMPR1A* Targeted Variant Analysis**

*National Comprehensive Cancer Network (NCCN)*

NCCN Genetic/Familial High-Risk Assessment: Colorectal guidelines (2.2023) outline clinical criteria for genetic testing for Juvenile

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)

**_SMAD4_ and _BMPR1A_ Sequencing and/or Deletion/Duplication Analysis**

*National Comprehensive Cancer Network (NCCN)*

NCCN Genetic/Familial High-Risk Assessment: Colorectal guidelines (2.2023) outline clinical criteria for 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)

**HEREDITARY LEIOMYOMATOSIS AND RENAL CELL CANCER (HLRCC)**

**_FH_ Targeted Variant Analysis**

*National Comprehensive Cancer Network (NCCN)*

NCCN guidelines for Kidney Cancer (1.2025) include 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)

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

*National Comprehensive Cancer Network (NCCN)*

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

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.

**LI-FRAUMENI SYNDROME (LFS)**

***TP53* Targeted Variant Analysis**

*National Comprehensive Cancer Network (NCCN)*

The NCCN Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic guidelines (3.2024) 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)

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

- Classic Li-Fraumeni syndrome (LFS) criteria:
- Combination of an individual diagnosed at age younger than 45 years with a sarcoma **AND**
- A first-degree relative diagnosed at age younger than 45 years with cancer **AND**
- An additional first- or second-degree relative in the same lineage with cancer diagnosed at age younger than 45 years, or a sarcoma at any age

Chompret criteria:

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

Personal/Family history criteria:

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

**MULTIPLE ENDOCRINE NEOPLASIA TYPE 1 (MEN1)**

***MEN1* Targeted Variant Analysis**

*National Comprehensive Cancer Network (NCCN)*

NCCN Neuroendocrine and Adrenal Tumors guidelines (2.2024) recommend that targeted genetic testing for *MEN1* be performed for

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

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

*National Comprehensive Cancer Network (NCCN)*

NCCN Neuroendocrine and Adrenal Tumors guidelines (1.2023) recommend that patients with two or more of the following, or one 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-E 3 of 8)

**MULTIPLE ENDOCRINE NEOPLASIA TYPE 2 (MEN2)**

***RET* Targeted Variant Analysis**

*National Comprehensive Cancer Network (NCCN)*

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

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

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

*GeneReviews: Multiple Endocrine Neoplasia Type 2*

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

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

*National Comprehensive Cancer Network (NCCN)*

NCCN Neuroendocrine and Adrenal Tumors guidelines (2.2024) also recommends MEN2 testing when there is clinical suspicion of MEN2 due to the presence of medullary thyroid cancer or other combination of MEN2-related features. Genetic testing is recommended for a first degree relative meeting this criteria, where the relative is not available for testing. (p. NE-E 3 of 8)

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

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

*GeneReviews: Nevoid Basal Cell Carcinoma Syndrome*

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

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

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

*GeneReviews: Nevoid Basal Cell Carcinoma Syndrome*

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

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).

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

*National Comprehensive Cancer Network (NCCN)*

NCCN guidelines for Kidney Cancer (1.2025) include 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)

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

*National Comprehensive Cancer Network (NCCN)*

NCCN guidelines for Neuroendocrine and Adrenal Tumors (2.2024) recommend genetic testing for hereditary endocrine neoplasia syndromes such as Hereditary Paraganglioma/Pheochromocytoma Syndrome for patients with either a paraganglioma or pheochromocytoma or with a first degree relative with either of these tumors who is unavailable for testing (p. NE-E, 3 of 8). Other manifestations of this syndrome include gastrointestinal stromal tumor and renal cell cancer (p. NE-E, 4 of 8).

*GeneReviews: Hereditary Paraganglioma-Pheochromocytoma Syndromes*

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

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

The diagnosis of hereditary PGL/PCC should be strongly suspected in an individual with multiple, multifocal, recurrent, or early-onset

**PEUTZ-JEGHERS SYNDROME (PJS)**

***STK11* Targeted Variant Analysis**

*National Comprehensive Cancer Network (NCCN)*

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

Additionally, 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)

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

*National Comprehensive Cancer Network (NCCN)*

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

**RETINOBLASTOMA**

***RB1* Targeted Variant Analysis**

*American Association of Ophthalmic Oncologists and Pathologists (AAOOP)*

The AAOOP with support of the American Association for Pediatric Ophthalmology and Strabismus and the American Academy of Pediatrics (AAP) developed expert consensus guidelines for children at risk for development of retinoblastoma (2018). These guidelines indicate that identification of a germline mutation in RB1 in a patient

testing for the mutation, allows for recommendations for screening and genetic testing for family members. (p. 455)

**_RB1_ Sequencing and/or Deletion/Duplication Analysis**

*American Association of Ophthalmic Oncologists and Pathologists (AAOOP)*

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

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

**VON HIPPEL-LINDAU SYNDROME (VHL)**

**_VHL_ Targeted Variant Analysis**

*National Comprehensive Cancer Network (NCCN)*

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

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

*National Comprehensive Cancer Network (NCCN)*

NCCN Kidney Cancer guidelines (1.2025) outline clinical features seen in Von Hippel-Lindau syndrome including: hemangioblastomas (in the retina, spine, or brain), clear cell RCC (diagnosed before age 40 years or multiple/bilateral RCC diagnosed at any age), pheochromocytomas, paragangliomas (in the abdomen, thorax, or neck), retinal angiomas, endolymphatic sac tumors, epididymal or broad ligament papillary cystadenomas, multiple pancreatic serous cystadenomas, pancreatic neuroendocrine tumors, or multiple cysts in

HERED-RCC-A)

## Quick Code Search

Use this feature to find out if a procedure and diagnosis code pair will be approved, denied or held for review. Simply put in the procedure code, then the diagnosis code, then click "Add Code Pair". If the codes are listed in this policy, we will help you by showing a dropdown to help you.

### Procedure

Please type a procedure code

Enter at least the first 3 characters of the code

### Diagnosis

Please type a diagnosis code

Enter at least the first 3 characters of the code

Add

## CODES

+ **CPT-PLA**
+ **CPT4**
+ **HCPCS**

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## REVISIONS

Update to Pan Cancer criteria. Adding an "AND" between A and B.

**12-30-2024**
Policy and version updated for 01/01/2025

**06-28-2024**
Added new 07/01/2024 PLA codes: 0474U 0475U

**01-01-2024**
Updated criteria for hereditary breast cancer susceptibility panel, hereditary colon cancer panel, hereditary prostate cancer susceptibility panel, PALB2 sequencing and/or deletion/duplication analysis, MLH1, MSH2, MSH6, PMS2, or EPCM criteria, PTEN criteria, APC and/or MUTYH criteria, PTCH1 and SUFU criteria. Background and references updated.

**09-29-2023**
Changed "may be considered medically necessary" to "may be considered scientifically validated"

Added: "investigational when the above criteria is not met and for all other indications"

**06-27-2023**
Expanded criteria: for breast panel, BRCA and PALB2: (i.e., personal history of breast cancer was change from age 45

or younger to age 50 or younger;

**02-01-2023**

**Added the following criteria under BRCA1 and BRCA2 Sequencing and/or Deletion/Duplication Analysis**

c. epithelial ovarian cancer (including fallopian tube cancer or peritoneal cancer)

d. pancreatic cancer

e. metastatic prostate cancer

f. high or very high risk group prostate cancer **OR**

**06-13-2022**

**09-01-2021**
Updated policy criteria and codes

**04-22-2021**
Breast and ovarian panel update:  Changed the AND to an OR in between A and B.

**02-15-2021**
Error in Pan-Cancer criteria:  Changed OR to AND after A and B.

**01-22-2021**
Removed code 0104U - termed 9/30/2019

**12-30-2020**
Added new 2021 CPT codes: 81351 81352 81353