Example Test Table

The tests and associated laboratories and CPT 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 Genetics Platform for a comprehensive list of registered tests.

Policy Statement Sections	Example Tests (Labs)	Common CPT Codes
Pan-Cancer Hereditary Cancer Susceptibility Panels	MyRisk (Myriad Genetics)	81432, 81433
	Common Hereditary Cancers Panel (Invitae)	
	CancerNext (Ambry Genetics)	
	Tempus xG Hereditary Cancer Panel	
	+RNAinsight with CancerNext (Ambry Genetics)	0134U
Hereditary Breast Cancer Susceptibility Panels	VistaSeq Breast Cancer Panel (Labcorp) Breast Cancer Panel (Invitae) Breast Cancer STAT NGS Panel (Sequencing & Deletion/Duplication) (Fulgent Genetics) Breast Cancer - High Risk Panel (PreventionGenetics, part of Exact Sciences) Breast Cancer High-Risk Panel plus PALB2 (GeneDx)	81162, 81163, 81164, 81165, 81166, 81167, 81216, 81307, 81321, 81351, 81432, 81433
	BRCAplus (Ambry Genetics)	0129U
Hereditary GI/Colon Cancer Panel Tests	Colorectal Cancer Panel (Invitae)	81435, 81436
	ColoNext (Ambry Genetics)	0101U
	+RNAinsight for ColoNext (Ambry Genetics)	0130U, 0162U
Hereditary Gastric Cancer Panels	Invitae Gastric Cancer Panel (Invitae)	81201, 81203, 81292, 81294, 81295, 81297, 81298, 81300, 81317, 81319, 81403, 81404, 81405, 81406, 81408, 81479
	Gastric Cancer Panel (PreventionGenetics, part of Exact Sciences)	

Policy Statement Sections	Example Tests (Labs)	Common CPT Codes
Hereditary Pancreatic Cancer Susceptibility Panels	Pancreatic Cancer Panel (Invitae)	81162, 81163, 81201, 81292, 81295, 81298, 81351, 81433 81479
	PancNext (Ambry Genetics)	
Hereditary Polyposis Panels	Hereditary Polyposis Panel (PreventionGenetics, part of Exact Sciences)	81201, 81203, 81406, 81479
	COLARIS AP (Myriad Genetics)	
Hereditary Prostate Cancer Susceptibility Panels	Prostate Cancer Panel-Primary Panel (Invitae)	81162, 81292, 81295, 81351, 81479
	ProstateNext (Ambry Genetics)	
	+RNAinsight for ProstateNext (Ambry Genetics)	0133U
Hereditary Neuroendocrine Cancer Susceptibility Panels	Hereditary Paraganglioma-Pheochromocytoma Panel (Invitae)	81437, 81438
	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
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
	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
PALB2 Sequencing and/or Deletion/Duplication Analysis	PALB2 Sequencing PALB2 Deletion/Duplication (Quest)	81307, 81479
	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
	CHEK2 Targeted Variant - Single Test (GeneDx)	

Policy Statement Sections	Example Tests (Labs)	Common CPT Codes
ATM or *CHEK2* Sequencing and/or Deletion/Duplication Analysis	Ataxia-Telangiectasia Test (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 Mutation Analysis	MSH6 Targeted Variant; PMS2 Targeted Variant; EPCAM Targeted Variant (GeneDx)	81299, 81318, 81479
	Hereditary Nonpolyposis Colorectal Cancer (HNPCC): MLH1 (Known Mutation) (Labcorp)	81293
	Hereditary Nonpolyposis Colorectal Cancer (HNPCC): MSH2 (Known Mutation) (Labcorp)	81296
MLH1, MSH2, MSH6 PMS2, or *EPCAM* Sequencing and/or Deletion/Duplication Analysis	HNPCC Concurrent (Ambry Genetics)	81292, 81294, 81295, 81297, 81298, 81300, 81317, 81319, 81403
	Lynch Syndrome Panel (Invitae)	
	CustomNext + RNA: MLH1, MSH2, MSH6, and/or PMS2 (Ambry Genetics)	0158U, 0159U, 0160U, 0161U, 0162U
B*AP1*–Tumor Predisposition Syndrome		
BAP1 Targeted Variant Analysis	BAP1: Site Specific Analysis (familial) (Univ of Pennsylvania School of Medicine-Genetic Diagnostic Laboratory)	81403
BAP1 Sequencing and/or Deletion/Duplication Analysis	BAP1 Full Gene Sequencing and Deletion/Duplication (Invitae)	81479
Birt-Hogg-Dube syndrome (BHDS)		
F*LCN* Targeted Variant Analysis	FLCN Targeted Variant - Single Test (GeneDx)	81479
FLCN Sequencing and/or Deletion/Duplication Analysis	Birt-Hogg-Dube Syndrome Test (Invitae)	81479
Cowden Syndrome (CS)/PTEN Hamartoma Tumor Syndrome (PHTS)		
PTEN Targeted Variant Analysis	PTEN Targeted Variant - Single Test (GeneDx)	81322
PTEN Sequencing and/or Deletion/Duplication Analysis	PTEN Gene Sequencing and Del/Dup (GeneDx)	81321, 81323

Policy Statement Sections	Example Tests (Labs)	Common CPT Codes
Adenomatous Polyposis Conditions (Familial Adenomatous Polyposis syndrome (FAP)/Attenuated FAP (AFAP) and *MUTYH*-Associated Polyposis Syndrome (MAP))		
APC or *MUTYH* Targeted Variant Analysis	APC Targeted Variant - Single Test (GeneDx)	81202
	MUTYH Targeted Variant - Single Test (GeneDx)	81403, 81401
APC and/or *MUTYH* Sequencing and/or Deletion/Duplication Analysis	APC Seq and Del/Dup (Ambry Genetics)	81201, 81203
	Familial Adenomatous Polyposis Test (Invitae)	
	+RNAInsight for APC (Ambry Genetics)	0157U
	MUTYH Full Gene Sequencing and Deletion/Duplication (Invitae)	81406, 81479
Familial Atypical Multiple Mole Melanoma Syndrome (FAMMM)		
CDKN2A Targeted Variant Analysis	CDKN2A Targeted Variant - Single Test (GeneDx)	81479
CDKN2A Sequencing and/or Deletion/Duplication Analysis	CDKN2A Full Gene Sequencing and Deletion/Duplication (Invitae)	81404, 81479
Hereditary Diffuse Gastric Cancer (aka, Signet Ring Cell Gastric Cancer)		
CDH1 Targeted Variant Analysis	CDH1 Targeted Variant - Single Test (GeneDx)	81479
CDH1 Sequencing and/or Deletion/Duplication Analysis	Hereditary Diffuse Gastric Cancer Syndrome Test (Invitae)	81406, 81479
Juvenile Polyposis Syndrome (JPS)		
SMAD4 and/or *BMPR1A* Targeted Variant Analysis	Targeted Variant: SMAD4 (PreventionGenetics, part of Exact Sciences)	81403
	Targeted Variant: BMPR1A (PreventionGenetics, part of Exact Sciences)	81403
SMAD4 and/or *BMPR1A* Sequencing and/or Deletion/Duplication Analysis	Juvenile Polyposis Syndrome Panel (Invitae)	81405, 81406, 81479
	BMPR1A, SMAD4 Gene Sequencing and Del/Dup (GeneDx)	
Hereditary Leiomyomatosis and Renal Cell Cancer (HLRCC)		
FH Targeted Variant Analysis	FH Sequence Analysis (Familial Mutation/Variant Analysis) (Baylor Genetics)	81403
FH Sequencing and/or Deletion/Duplication Analysis	Hereditary Leiomyomatosis and Renal Cell Carcinoma (Ambry Genetics)	81405, 81479
Li-Fraumeni Syndrome (LFS)		
TP53 Targeted Variant Analysis	TP53 Targeted Variant - Single Test (GeneDx)	81352

Policy Statement Sections	Example Tests (Labs)	Common CPT Codes
TP53 Sequencing and/or Deletion/Duplication Analysis	TP53 Full Gene Sequencing and Deletion/Duplication (Invitae)	81351, 81479
	Li-Fraumeni Syndrome, TP53 Sequencing and Deletion/Duplication (Quest Diagnostics)	
Multiple Endocrine Neoplasia - Type 1 (MEN1)		
MEN1 Targeted Variant Analysis	MEN1 Targeted Variant - Single Test (GeneDx)	81479
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
RET Sequencing and/or Deletion/Duplication Analysis	RET Full Gene Sequencing and Deletion/Duplication (Invitae)	81406, 81479, S3840
Nevoid Basal Cell Carcinoma Syndrome (NBCCS) (aka Gorlin syndrome)		
PTCH1 and/or *SUFU* Targeted Variant Analysis	Targeted Variant: PTCH1 or SUFU (GeneDx)	81479
PTCH1 and *SUFU* Sequencing and/or Deletion/Duplication Analysis	Basal Cell Nevus Syndrome Panel (Invitae)	81479
Hereditary Paraganglioma/Pheochromocytoma Syndrome (PGL/PCC)		
MAX, SDHA, SDHAF2, SDHB, SDHC, SDHD, or *TMEM127* Targeted Variant Analysis	SDHB, SDHD, SDHC, MAX, SDHAF2, or TMEM127 Targeted Variant - Single Test (GeneDx) Targeted Variants: MAX, SDHAF2, TMEM127 (PreventionGenetics, part of Exact Sciences)	81479
MAX, SDHA, SDHAF2, SDHB, SDHC, SDHD, and/or *TMEM127* Sequencing and/or Deletion/Duplication Analysis	SHDB Full Gene Sequencing and Deletion/Duplication (Invitae)	81405, 81479
	SDHA Full Gene Sequencing and Deletion/Duplication (Invitae)	81406, 81479
	SDHC Full Gene Sequencing and Deletion/Duplication (Invitae)	81404, 81405
	SDHD Full Gene Sequencing and Deletion/Duplication (Invitae)	81404, 81479
	MAX Full Gene Sequencing and Deletion/Duplication (Invitae)	81479
	SDHAF2 Full Gene Sequencing and Deletion/Duplication (Invitae)	
	TMEM127 Full Gene Sequencing and Deletion/Duplication (Invitae)	

Policy Statement Sections	Example Tests (Labs)	Common CPT Codes
Peutz-Jeghers Syndrome (PJS)		
STK11 Targeted Variant Analysis	STK11 Targeted Variant - Single Test (GeneDx)	81479
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
RB1 Sequencing and/or Deletion/Duplication Analysis	RB1 Full Gene Sequencing and Deletion/Duplication (Invitae)	81479, S3841
Von Hippel-Lindau Syndrome (VHL)		
VHL Targeted Variant Analysis	VHL Sequence Analysis (Familial Mutation/Variant Analysis) (Baylor Genetics, LLC)	81403
VHL Sequencing and/or Deletion/Duplication Analysis	VHL Full Gene Sequencing and Deletion/Duplication (Invitae) VHL Gene Sequencing and Del/Dup (GeneDx)	81403, 81404, S3842

Policy Statement

PAN-CANCER HEREDITARY CANCER SUSCEPTIBILITY PANELS

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

I. Genetic testing using a pan-cancer hereditary cancer susceptibility panel (81432, 81433) may be considered **medically necessary** when **ALL** of the following criteria are met:
   A. The member is 18 years or older
   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 (statement XXV)
      2. The member meets clinical criteria for Lynch syndrome/HNPCC *MLH1, MSH2, MSH6, PMS2, or EPCAM* sequencing and/or deletion/duplication analysis (statement XXXIX)
   C. The panel includes, at a minimum, sequencing of the following genes: *BRCA1*, *BRCA2*, *EPCAM*, *MLH1*, *MSH2*, *MSH6*, *PMS2*
   D. The panel does not include genes without a known association with cancer by ClinGen.

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

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

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

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HEREDITARY BREAST CANCER SUSCEPTIBILITY PANELS

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

IV. Genetic testing using a hereditary breast cancer susceptibility panel (81162, 81163, 81164, 81165, 81166, 81167, 81216, 81307, 81321, 81351, 81432, 81433, 0129U) may be considered **medically necessary** when **ALL** of the following criteria are met:
  A. The member is 18 years or older
  B. The member meets *BRCA1* and *BRCA2* Sequencing and Deletion/Duplication analysis, (statement XXV)
  C. The panel includes, at a minimum, sequencing of the following genes: *BRCA1*, *BRCA2*
  D. The panel does not include genes without known association with breast cancer by ClinGen.

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

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

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HEREDITARY GI/COLON CANCER PANEL TESTS

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

VII. Genetic testing using a hereditary colorectal cancer susceptibility panel (81435, 81436, 0101U) may be considered **medically necessary** when **ALL** of the following criteria are met:
  A. The member is 18 years or older
  B. 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
      b. At least 2 hamartomatous polyps
      c. At least 5 serrated polyps/lesions proximal to the rectum
    2. The member has a personal history of colorectal cancer under 50 years of age
    3. The member meets clinical criteria for Lynch syndrome/HNPCC *MLH1, MSH2, MSH6, PMS2, or EPCAM* Sequencing and/or Deletion/Duplication Analysis (statement XXXIX)
  C. The panel includes, at a minimum, sequencing of the following genes: *APC, MUTYH, MLH1, MSH2, MSH6, PMS2, EPCAM, BMPR1A, SMAD4, PTEN, STK11,* and *TP53*
  D. The panel does not include genes without a known association with colorectal or gastrointestinal cancer by ClinGen.

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

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

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

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HEREDITARY GASTRIC CANCER PANELS

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

X. Genetic testing using a hereditary gastric susceptibility panel (81201, 81203, 81292, 81294, 81295, 81297, 81298, 81300, 81317, 81319, 81403, 81404, 81405, 81406, 81408, 81479) may be considered **medically necessary** when **ALL** of the following criteria are met:
   A. The member is 18 years or older
   B. The member meets sequencing and/or deletion/duplication clinical criteria for **at least one** of the following:
      1. Lynch syndrome/Hereditary Nonpolyposis Colorectal Cancer (statement XXXIX)
      2. Hereditary Diffuse Gastric Cancer (statement LXV)
      3. Juvenile Polyposis Syndrome (statement LXIX)
      4. Peutz-Jeghers Syndrome (statement XCVII)
      5. Adenomatous Polyposis Syndromes (statement LVI)
   C. The panel includes, at a minimum, sequencing of the following genes: *APC*, *BMPR1A, CDH1, EPCAM, MLH1, MSH2, MSH6, PMS2, SMAD4, STK11*
   D. The panel does not include genes without a known association with gastric (stomach) cancer by ClinGen.

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

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HEREDITARY PANCREATIC CANCER SUSCEPTIBILITY PANELS

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

XII. Genetic testing using a hereditary pancreatic cancer susceptibility panel (81162, 81163, 81201, 81292, 81295, 81298, 81351, 81433, 81479) may be considered **medically necessary** when **ALL** of the following criteria are met:
   A. The member is 18 years or older
   B. The member meets criteria for *BRCA1* and *BRCA2* sequencing and/or deletion/duplication analysis (statement XXV)
   C. The panel includes, at a minimum, sequencing of the following genes: *ATM, BRCA1, BRCA2, CDKN2A, EPCAM, MLH1, MSH2, MSH6, PALB2, STK11, TP53*
   D. The panel does not include genes without a known association with pancreatic cancer by ClinGen.

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

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HEREDITARY POLYPOSIS PANELS

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

XIV. Genetic testing using a hereditary polyposis panel (81201, 81203, 81406, 81479) may be considered **medically necessary** when **ALL** of the following criteria are met:
  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) (statement LVI)
  B. The panel includes, at a minimum, sequencing of the following genes: *APC* and *MUTYH*
  C. The panel does not include genes without a known association with colon polyposis by ClinGen.

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

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HEREDITARY PROSTATE CANCER SUSCEPTIBILITY PANELS

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

XVI. Genetic testing using a hereditary prostate cancer susceptibility panel (81162, 81292, 81295, 81351, 81479,) may be considered **medically necessary** when **ANY** of the following criteria are met:
  A. The member meets **BOTH** of the following criteria:
    1. Is 18 years or older
    2. Has a personal history of **any** of the following:
      a. Metastatic prostate cancer
      b. High- or very-high risk localized prostate cancer
      c. Regional (node positive) prostate cancer
  B. The member has a personal history of prostate cancer and **any** of the following:
    1. One or more close relatives with **any** of the following:
      a. Breast cancer at or under age 50
      b. Triple-negative breast cancer at any age
      c. Colorectal or endometrial cancer at or under age 50
      d. Male (sex assigned at birth) breast cancer at any age
      e. Ovarian cancer at any age
      f. Exocrine pancreatic cancer at any age
      g. Metastatic, regional, very-high-risk, or high-risk prostate cancer at any age
    2. One or more first-degree relatives with prostate cancer at or under age 60
    3. Two or more close relatives with **either** of the following:
      a. Breast cancer at any age
      b. Prostate cancer at any age
    4. Three or more first- or second-degree relatives with a Lynch syndrome related cancer, especially if diagnosed under age 50
    5. 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

        6. Ashkenazi Jewish ancestry
        7. A personal history of breast cancer
    C. The member meets ALL of the following criteria:
        1. The member is affected (does not meet testing criteria above) or is unaffected, with a first-degree blood relative meeting any of the criteria above
        2. The panel includes, at a minimum, sequencing of the following genes: *BRCA1, BRCA2*
        3. The panel does not include genes without a known association with prostate cancer by ClinGen.

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

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

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HEREDITARY NEUROENDOCRINE CANCER SUSCEPTIBILITY PANELS

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

XIX. Genetic testing using a hereditary neuroendocrine cancer susceptibility panel (81437, 81438) may be considered **medically necessary** when **ANY** of the following criteria are met:
    A. The member has **at least one** of the following:
        1. Adrenocortical carcinoma
        2. Paraganglioma/pheochromocytoma
        3. Parathyroid adenoma or primary hyperparathyroidism before age 30
        4. Multiple parathyroid adenomas
        5. Multigland hyperplasia without obvious secondary cause
        6. Recurrent primary hyperparathyroidism
    B. The member meets criteria for *MEN1* sequencing and/or deletion/duplication analysis (statement LXXXI)
    C. **BOTH** of the following criteria are met:
        1. The member meets criteria for *RET* sequencing and/or deletion duplication analysis (statement LXXXV)
        2. The panel does not include genes without a known association with a neuroendocrine cancer by ClinGen.

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

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

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BRCA1 AND *BRCA2* GENE TESTING

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

XXI. *BRCA1* (81215) or *BRCA2* (81217) targeted variant or known familial variant analysis for hereditary cancer susceptibility may be considered **medically necessary** when **BOTH** of the following criteria are met:
    A. The member is 18 years or older
    B. **One** of the following:

    1. The member has a family history of a known *BRCA1* or *BRCA2* pathogenic or likely pathogenic variant
    2. A *BRCA1* or *BRCA2* pathogenic or likely pathogenic variant was detected by tumor profiling and germline analysis has not yet been performed.

XXII. *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

XXIII. *BRCA1* and *BRCA2* (81212) targeted variant analysis for the 185delAG, 5385insC, 6174delT variants may be considered **medically necessary** when **BOTH** of the following criteria are met:

- A. The member is 18 years or older
- B. The member is of Ashkenazi Jewish ancestry (at least one grandparent of Ashkenazi Jewish ancestry).

XXIV. *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

XXV. *BRCA1* and *BRCA2* (81162, 81163, 81164, 81165, 81166, 81167, 81216) sequencing and/or deletion/duplication analysis for hereditary breast and/or ovarian cancer susceptibility may be considered **medically necessary** when **ANY** of the following criteria are met:

- A. **BOTH** of the following criteria are met:
    1. The member is 18 years or older
    2. The member has a personal history of **any** of the following:
        - a. Male (sex assigned at birth) breast cancer
        - b. Triple-negative breast cancer
        - c. Breast cancer diagnosed at age 50 or younger
        - d. Epithelial ovarian cancer (including fallopian tube cancer or peritoneal cancer)
        - e. Exocrine pancreatic or ampullary cancer
        - f. Metastatic prostate cancer
        - g. High- or very-high-risk group prostate cancer
        - h. Multiple primary breast cancers (diagnosed synchronously or metachronously)
- B. The member has a personal history of breast cancer **AND** any of the following:
    1. Ashkenazi Jewish ancestry
    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
        - b. Male (sex assigned at birth) breast cancer
        - c. Ovarian cancer
        - d. Pancreatic cancer
        - e. Metastatic, or high- or very-high-risk group prostate cancer
    3. Three or more total diagnoses of breast cancer and/or prostate cancer (any grade) on the same side of the family including the member with breast cancer
- C. The member does not have a personal history of a *BRCA1/2*-related cancer, but has a first- or second-degree relative meeting any of the above criteria
- D. The member has metastatic breast cancer and is being considered for systemic treatment using PARP inhibitors
- E. The member has high-risk, HER2-negative breast cancer and is being considered for adjuvant treatment with olaparib
- F. The member's probability of having a *BRCA1* or *BRCA2* pathogenic variant is greater than 5% based on prior probability models (examples: Tyrer-Cuzick, BRCApro, CanRisk).

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

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

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PALB2 GENE TESTING

PALB2 Targeted Variant Analysis

XXVIII. *PALB2* targeted variant analysis (81308) for hereditary breast and/or ovarian cancer susceptibility may be considered **medically necessary** when **BOTH** of the following criteria are met:

- A. The member is 18 years or older
- B. **One** of the following:
    1. The member has a family history of a known pathogenic or likely pathogenic variant in *PALB2*
    2. A pathogenic or likely pathogenic variant was detected by tumor profiling in *PALB2,* and germline analysis has not yet been performed.

XXIX. *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

XXX. *PALB2* (81307, 81479) sequencing and/or deletion/duplication analysis for hereditary breast and/or ovarian cancer susceptibility may be considered **medically necessary** when **BOTH** of the following criteria are met:

- A. The member is 18 years or older
- 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
        - b. Triple-negative breast cancer
        - c. Breast cancer diagnosed at age 50 or younger
        - d. Epithelial ovarian cancer (including fallopian tube cancer or peritoneal cancer)
        - e. Exocrine pancreatic or ampullary cancer
        - f. Multiple primary breast cancers (diagnosed synchronously or metachronously
    2. The member has a personal history of breast cancer **AND** any of the following:
        - a. Ashkenazi Jewish ancestry
        - b. One or more close relatives with any of the following:
            - i. Female (sex assigned at birth) breast cancer diagnosed at age 50 years or younger
            - ii. Male (sex assigned at birth) breast cancer
            - iii. Ovarian cancer
            - iv. Exocrine pancreatic cancer
        - c. Three or more total diagnoses of breast cancer in the member and/or close relatives
    3. The member does not have a personal history of a *PALB2*-related cancer (breast, ovarian or pancreatic), but has a first- or second-degree relative meeting any of the above criteria
    4. The member has metastatic breast cancer and is being considered for systemic treatment decisions using PARP inhibitors

5. The member has high-risk, HER2-negative breast cancer and is being considered for adjuvant treatment with olaparib
6. The member's probability of having a *BRCA1* or *BRCA2* pathogenic variant is greater than 5% based on prior probability models (examples: Tyrer-Curzick, BRCApro, CanRisk).

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

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

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ATM AND/OR *CHEK2* GENE TESTING

ATM or *CHEK2* Targeted Variant Analysis

XXXIII. *ATM* (81479) or *CHEK2* (81479) targeted variant analysis for hereditary breast and/or ovarian cancer susceptibility may be considered **medically necessary** when **BOTH** of the following criteria are met:

- A. The member is 18 years or older
- B. **One** of the following:
  1. The member has a close relative with a known pathogenic or likely pathogenic variant in *ATM* or *CHEK2*
  2. A pathogenic or likely pathogenic variant was detected by tumor profiling in *ATM* or *CHEK2* and germline analysis has not yet been performed.

XXXIV. *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

XXXV. *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**.

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

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LYNCH SYNDROME / HEREDITARY NONPOLYPOSIS COLORECTAL CANCER (HNPCC) TESTING

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

XXXVII. *MLH1* (81293), *MSH2* (81296), *MSH6* (81299), *PMS2* (81318), or *EPCAM* (81479) targeted variant analysis for Lynch syndrome/HNPCC may be considered **medically necessary** when **EITHER** of the following criteria are met:

- A. The member has a blood relative with a known pathogenic or likely pathogenic variant in *MLH1*, *MSH2*, *MSH6*, *PMS2*, or *EPCAM*
- B. A pathogenic or likely pathogenic variant was detected by tumor profiling in *MLH1*, *MSH2*, *MSH6*, *PMS2*, or *EPCAM* and germline analysis has not yet been performed.

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

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

XXXIX. *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 may be considered **medically necessary** when **ANY** of the following criteria are met:

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)
B. The member has a diagnosis of a Lynch syndrome-related cancer, **AND any** of the following:
   1. Diagnosed before age 50
   2. Diagnosed at any age with an additional Lynch syndrome-related cancer
   3. Diagnosed at any age with one or more first- or second-degree relatives diagnosed before age 50 with a Lynch syndrome-related cancer
   4. Diagnosed at any age with two or more first- or second-degree relatives diagnosed at any age with a Lynch syndrome-related cancer
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
   2. One or more first-degree relatives diagnosed with colorectal or endometrial cancer and an additional Lynch syndrome-related cancer
   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
   4. Three or more first- or second-degree relatives on the same side of the family diagnosed with a Lynch syndrome-related cancer
D. The member has a 5% or greater risk of Lynch syndrome on one of the following variant prediction models: MMRpro, PREMM5, MMRpredict
E. The member has a personal history of colorectal and/or endometrial cancer with a PREMM5 score of 2.5% or greater.

XL. *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.

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

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BAP1-TUMOR PREDISPOSITION SYNDROME

BAP1 Targeted Variant Analysis

XLII. *BAP1* targeted variant analysis (81403) for *BAP1*-tumor predisposition syndrome may be considered **medically necessary** when **EITHER** of the following criteria are met:

A. The member has a close relative with a known pathogenic or likely pathogenic variant in *BAP1*
B. A pathogenic or likely pathogenic variant in *BAP1* was identified on tumor profiling and germline analysis has not yet been performed.

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

BAP1 Sequencing and/or Deletion/Duplication Analysis

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

- A. The member has a personal history of **ANY** of the following:
  - 1. **Two or more** of the following:
    - a. *BAP1*-inactivated melanocytic tumors (aka atypical spitz tumor)
    - b. Uveal melanoma
    - c. Malignant mesothelioma
    - d. Renal cell carcinoma
    - e. Hepatocellular carcinoma
    - f. Cholangiocarcinoma
    - g. Meningioma
  - 2. **One** of the tumors/cancers listed in the criteria A.1., **AND EITHER** of the following:
    - a. A cutaneous melanoma
    - b. A basal cell carcinoma
  - 3. One or more of the tumors/cancers listed in the criteria A.1., **AND**
    - a. A first- or second-degree relative with any of the tumors/cancers listed in the criteria A.1.

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

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BIRT-HOGG-DUBE SYNDROME (BHDS)

FLCN Targeted Variant Analysis

XLVI. *FLCN* targeted variant analysis (81479) for Birt-Hogg-Dube syndrome (BHDS) may be considered **medically necessary** when **EITHER** of the following criteria are met:

- A. The member has a first- or second-degree relative with a known pathogenic or likely pathogenic variant in *FLCN*
- B. A pathogenic or likely pathogenic variant in *FLCN* was identified on tumor profiling and germline analysis has not yet been performed.

XLVII. *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

XLVIII. *FLCN* sequencing and/or deletion/duplication analysis (81479) for Birt-Hogg-Dube syndrome (BHDS) may be 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
  - 2. Multiple lung cysts with no apparent cause
  - 3. Renal cancer diagnosed before 50 years of age
  - 4. Multifocal or bilateral renal cancer
  - 5. Renal cancer of mixed chromophobe and oncocytic, clear cell, or papillary histology
  - 6. Oncocytoma
  - 7. Angiomyolipoma
  - 8. A first-degree relative with BHDS

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

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

PTEN Targeted Variant Analysis

L. *PTEN* targeted variant analysis (81322) for Cowden syndrome (CS)/*PTEN* hamartoma tumor syndrome (PHTS) may be considered **medically necessary** when **EITHER** of the following criteria are met:
   A. The member has a blood relative with a known pathogenic or likely pathogenic variant in *PTEN*
   B. A pathogenic or likely pathogenic variant in *PTEN* was identified on tumor profiling and germline analysis has not yet been performed.

LI. *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

LII. *PTEN* sequencing and/or deletion/duplication analysis (81321, 81323) for Cowden syndrome (CS)/*PTEN* hamartoma tumor syndrome (PHTS) may be considered **medically necessary** when **ANY** of the following criteria are met:
   A. The member has a personal history of **any** of the following:
      1. Bannayan Riley-Ruvalcaba syndrome (BRRS)
      2. Adult Lhermitte-Duclos disease (LDD) (defined as the presence of a cerebellar dysplastic gangliocytoma)
      3. Autism-spectrum disorder and macrocephaly
      4. At least 2 biopsy-proven trichilemmomas
   B. The member meets clinical criteria for CS/PHTS as shown in ANY of the following criteria:
      1. Macrocephaly (greater than or equal to 97 percentile)
      2. Lhermitte-Duclos disease (LDD) (defined as the presence of a cerebellar dysplastic gangliocytoma)
      3. Gastrointestinal hamartomas or ganglioneuromas, **AND at least two** of the following:
         a. Breast Cancer
         b. Endometrial Cancer
         c. Thyroid Cancer (follicular)
         d. Macular pigmentation of the glans penis
         e. Mucocutaneous lesions (One biopsy-proven trichilemmoma; multiple palmoplantar keratoses; multifocal or extensive oral mucosal papillomatosis; multiple cutaneous facial papules)
   C. The member has **at least two** of the following:
      1. Breast Cancer
      2. Endometrial Cancer
      3. Thyroid Cancer (follicular)
      4. Multiple gastrointestinal hamartomas or ganglioneuromas
      5. Macrocephaly (greater than or equal to 97 percentile)
      6. Macular pigmentation of the glans penis
      7. Mucocutaneous lesions (One biopsy-proven trichilemmoma; multiple palmoplantar keratoses; multifocal or extensive oral mucosal papillomatosis; multiple cutaneous facial papules), **AND at least three** of the following:
         a. Autism Spectrum Disorder
         b. Colon Cancer
         c. Esophageal glycogenic acanthosis (3 or more)
         d. Lipomas
         e. Intellectual disability (i.e., IQ less than or equal to 75)

        f. Thyroid cancer (papillary or follicular variant of papillary thyroid cancer)
        g. Thyroid structural lesions (such as adenoma, multinodular goiter)
        h. Renal cell carcinoma
        i. Single GI hamartoma or ganglioneuroma
        j. Testicular lipomatosis
        k. Vascular anomalies (including multiple intracranial developmental venous anomalies)

D. The member has macrocephaly, **AND ANY** of the following:
    1. Breast Cancer
    2. Endometrial Cancer
    3. Thyroid Cancer (follicular)
    4. Multiple gastrointestinal hamartomas or ganglioneuromas
    5. Macrocephaly (greater than or equal to 97 percentile)
    6. Macular pigmentation of the glans penis
    7. Mucocutaneous lesions (One biopsy-proven trichilemmoma; multiple palmoplantar keratoses; multifocal or extensive oral mucosal papillomatosis; multiple cutaneous facial papules)

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

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

G. The member has **at least four** of the following:
    1. Autism Spectrum Disorder
    2. Colon Cancer

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

H. The member has a close relative with a clinical diagnosis of CS/PHTS or BRRS for whom testing has not been performed, **AND EITHER** of the following:
  1. The member has **at least one** of the following:
    a. Breast Cancer
    b. Endometrial Cancer
    c. Thyroid Cancer (follicular)
    d. Multiple gastrointestinal hamartomas or ganglioneuromas
    e. Macrocephaly (greater than or equal to 97 percentile)
    f. Macular pigmentation of the glans penis
    g. Mucocutaneous lesions (One biopsy-proven trichilemmoma; multiple palmoplantar keratoses; multifocal or extensive oral mucosal papillomatosis; multiple cutaneous facial papules)
  2. **At least two** of the following:
    a. Autism Spectrum Disorder
    b. Colon Cancer
    c. Esophageal glycogenic acanthosis (3 or more)
    d. Lipomas
    e. Intellectual disability (i.e., IQ less than or equal to 75)
    f. Thyroid cancer (papillary or follicular variant of papillary thyroid cancer)
    g. Thyroid structural lesions (such as adenoma, multinodular goiter)
    h. Renal cell carcinoma
    i. Single GI hamartoma or ganglioneuroma
    j. Testicular lipomatosis
    k. Vascular anomalies (including multiple intracranial developmental venous anomalies).

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

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

APC OR MUTYH Targeted Variant Analysis

LIV. *APC* (81202) or *MUTYH* targeted variant analysis (81401, 81403) for adenomatous polyposis testing may be considered **medically necessary** when **EITHER** of the following criteria are met:
  A. The member has a family history of a known pathogenic or likely pathogenic variant in *APC* or *MUTYH*
  B. An *APC* or *MUTYH* pathogenic or likely pathogenic variant was detected by tumor profiling and germline analysis has not yet been performed.

LV. *APC* (81202) 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

LVI. *APC* sequencing and/or deletion/duplication analysis (81201, 81203) and/or *MUTYH* sequencing and/or deletion/duplication analysis (81406, 81479) for adenomatous polyposis conditions may be considered **medically necessary** when:
- A. The member has a history of **any** of the following:
  - 1. 10 or more cumulative adenomas
  - 2. Congenital hypertrophy of the retinal pigment epithelium (CHRPE)
  - 3. Desmoid tumor
  - 4. Hepatoblastoma
  - 5. Cribriform-morular variant of papillary thyroid cancer
  - 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
    - 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
  - 7. Duodenal cancer
  - 8. Duodenal adenomas.

LVII. *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.

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

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FAMILIAL ATYPICAL MULTIPLE MOLE MELANOMA (FAMMM) SYNDROME

CDKN2A Targeted Variant Analysis

LIX. *CDKN2A* targeted variant analysis (81479) for familial atypical multiple mole melanoma (FAMMM) syndrome, also known as melanoma-pancreatic cancer syndrome, may be considered **medically necessary** when **BOTH** of the following criteria are met:
- A. The member is 18 years or older
- B. **One** of the following:
  - 1. The member has a close relative with a known pathogenic or likely pathogenic variant in *CDKN2A*
  - 2. A *CDKN2A* pathogenic or likely pathogenic variant was detected by tumor profiling and germline analysis has not yet been performed.

LX. *CDKN2A* targeted variant analysis (81479) for familial cutaneous malignant melanoma is considered **investigational** for all other indications.

CDKN2A Sequencing and/or Deletion/Duplication Analysis

LXI. *CDKN2A* sequencing and/or deletion/duplication analysis (81404, 81479) for familial atypical multiple mole melanoma (FAMMM) syndrome, also known as melanoma-pancreatic cancer syndrome, may be considered **medically necessary** when **ANY** of the following criteria are met:
- A. The member has had 3 or more invasive cutaneous melanomas
- B. The member has had pancreatic adenocarcinoma
- C. The member has had at least one cutaneous melanoma, **AND**

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

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

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

CDH1 Targeted Variant Analysis

LXIII. *CDH1* targeted variant analysis (81479) for Hereditary Diffuse Gastric Cancer (aka, Signet Ring Cell Gastric Cancer) may be considered **medically necessary** when **BOTH** of the following criteria are met:

A. The member is 18 years or older
B. **One** of the following:
    1. The member has a blood relative with a known pathogenic or likely pathogenic variant in *CDH1*
    2. A *CDH1* pathogenic or likely pathogenic variant was detected by tumor profiling and germline analysis has not yet been performed.

LXIV. *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

LXV. *CDH1* sequencing and/or deletion/duplication analysis for Hereditary Diffuse Gastric Cancer (aka, Signet Ring Cell Gastric Cancer) (81406, 81479) may be considered **medically necessary** when **BOTH** of the following criteria are met:

A. The member is 18 years or older
B. The member meets **at least one** of the following criteria:
    1. Diffuse gastric cancer diagnosed before age 50 years
    2. Diffuse gastric cancer diagnosed at any age in a member with Maori ancestry
    3. Diffuse gastric cancer diagnosed at any age in a member with a personal or family history of cleft lip/cleft palate
    4. Bilateral lobular breast cancer diagnosed before age 70 years
    5. Personal or family history of diffuse gastric cancer and lobular breast cancer, one diagnosed before age 70 years
    6. Two cases of gastric cancer in the family, one of which is a confirmed case of diffuse gastric cancer, diagnosed at any age
    7. Two cases of lobular breast cancer in family members before 50 years of age.

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

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JUVENILE POLYPOSIS SYNDROME (JPS)

SMAD4 or *BMPR1A* Targeted Variant Analysis

LXVII. *SMAD4* and/or *BMPR1A* targeted variant analysis (81403) for juvenile polyposis syndrome (JPS) may be considered **medically necessary** when **EITHER** of the following criteria are met:

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

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

LXVIII. *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

LXIX. *SMAD4* and/or *BMPR1A* sequencing and/or deletion/duplication analysis (81405, 81406, 81479) for juvenile polyposis syndrome (JPS) may be considered **medically necessary** when **ANY** of the following criteria are met:

  A. The member has 5 or more juvenile polyps in the colon
  B. The member has multiple juvenile polyps throughout the gastrointestinal tract
  C. The member has juvenile polyps (any number) and a family history of JPS.

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

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HEREDITARY LEIOMYOMATOSIS AND RENAL CELL CANCER (HLRCC)

FH Targeted Variant Analysis

LXXI. *FH* targeted variant analysis (81403) for hereditary leiomyomatosis and renal cell cancer (HLRCC) may be considered **medically necessary** when **BOTH** of the following criteria are met:

  A. The member is 18 years or older
  B. **One** of the following:
    1. The member has a first- or second-degree relative with a known pathogenic or likely pathogenic variant in *FH*
    2. A *FH* pathogenic or likely pathogenic variant was detected by tumor profiling and germline analysis has not yet been performed.

LXXII. *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

LXXIII. *FH* sequencing and/or deletion/duplication analysis (81405, 81479) for hereditary leiomyomatosis and renal cell cancer (HLRCC) may be considered **medically necessary** when **BOTH** of the following criteria are met:

  A. The member is 18 years or older
  B. The member has **at least one** of the following:
    1. Cutaneous leiomyomata
    2. Uterine leiomyomata (uterine fibroids)
    3. Renal cell carcinoma.

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

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LI-FRAUMENI SYNDROME (LFS)

TP53 Targeted Variant Analysis

LXXV. *TP53* targeted variant analysis (81352) for Li-Fraumeni syndrome (LFS) may be considered **medically necessary** when **EITHER** of the following criteria are met:

- A. The member has a blood relative with a known pathogenic or likely pathogenic variant in *TP53*
- B. A *TP53* pathogenic or likely pathogenic variant was detected by tumor profiling and germline analysis has not yet been performed.

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

TP53 Sequencing and/or Deletion/Duplication Analysis

LXXVII. *TP53* sequencing and/or deletion/duplication analysis (81351, 81479) for Li-Fraumeni syndrome (LFS) may be considered **medically necessary** when **ANY** of the following criteria are met:

- A. The member was diagnosed with breast cancer before 31 years of age
- B. The member has a personal or family history of pediatric hypodiploid acute lymphoblastic leukemia
- C. The member was diagnosed with a sarcoma before 45 years of age, **AND BOTH** of the following:
  - 1. The member has a first-degree relative diagnosed with any cancer before 45 years of age
  - 2. **At least one** of the following:
    - a. The member has an additional first- or second-degree relative diagnosed with any cancer before 45 years of age
    - b. The member has an additional first- or second-degree relative diagnosed with sarcoma at any age
- D. The member was diagnosed with **any** of the following at any age:
  - 1. Adrenocortical carcinoma
  - 2. Choroid plexus carcinoma
  - 3. Rhabdomyosarcoma of embryonal anaplastic subtype
- 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
  - 2. Osteosarcoma
  - 3. Central nervous system tumor
  - 4. Breast cancer
  - 5. Adrenocortical carcinoma, **AND ANY** of the following:
    - a. The member has had a second tumor from the LFS tumor spectrum (except breast cancer if the initial cancer was breast cancer)
    - 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)
    - c. The member has a first- or second-degree relative with a history of multiple primary tumors at any age.

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

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MULTIPLE ENDOCRINE NEOPLASIA TYPE 1 (MEN1)

MEN1 Targeted Variant Analysis

LXXIX. *MEN1* targeted variant analysis (81479) for multiple endocrine neoplasia type 1 (MEN1) may be considered **medically necessary** when **EITHER** of the following criteria are met:

A. The member has a close relative with a known pathogenic or likely pathogenic variant in *MEN1*
B. An *MEN1* pathogenic or likely pathogenic variant was detected by tumor profiling and germline analysis has not yet been performed.

LXXX. *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

LXXXI. *MEN1* sequencing and/or deletion/duplication analysis (81404, 81405) for multiple endocrine neoplasia type 1 (MEN1) may be considered **medically necessary** when **EITHER** of the following criteria are met:

A. The member has a personal history of **at least two** of the following:
   1. Duodenal/pancreatic neuroendocrine tumor
   2. Primary hyperparathyroidism
   3. Pituitary adenoma
   4. Foregut (bronchial, thymic, or gastric) carcinoid
B. The member has a personal history of one of the above, **AND**
   1. The member has a close relative with at least one of the above.

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

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MULTIPLE ENDOCRINE NEOPLASIA TYPE 2 (MEN2)

RET Targeted Variant Analysis

LXXXIII. *RET* targeted variant analysis (81404) for multiple endocrine neoplasia type 2 (MEN2) may be considered **medically necessary** when **EITHER** of the following criteria are met:

A. The member has a close relative with a known pathogenic or likely pathogenic variant in *RET*
B. A *RET* pathogenic or likely pathogenic variant was detected by tumor profiling and germline analysis has not yet been performed.

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

RET Sequencing and/or Deletion/Duplication Analysis

LXXXV. *RET* sequencing and/or deletion/duplication analysis (81406, 81479, S3840) for multiple endocrine neoplasia type 2 (MEN2) may be considered **medically necessary** when **ANY** of the following criteria are met:

A. The member has a diagnosis of medullary thyroid cancer
B. The member has an adrenal pheochromocytoma
C. The member has parathyroid adenoma or hyperplasia
D. The member has a first-degree relative that meets at least one of the above criteria and has not previously undergone *RET* sequencing and/or deletion duplication analysis.

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

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

PTCH1 or *SUFU* Targeted Variant Analysis

LXXXVII. *PTCH1* or *SUFU* targeted variant analysis (81479) for nevoid basal cell carcinoma syndrome (NBCCS), also known as Gorlin syndrome, may be considered **medically necessary** when **EITHER** of the following criteria are met:

- A. The member has a close relative with a known pathogenic or likely pathogenic variant in *PTCH1* or *SUFU*
- B. A *PTCH1* or *SUFU* pathogenic or likely pathogenic variant was detected by tumor profiling and germline analysis has not yet been performed.

LXXXVIII. *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

LXXXIX. *PTCH1* and *SUFU* sequencing and/or deletion duplication analysis (81479) for nevoid basal cell carcinoma syndrome (NBCCS), also known as Gorlin syndrome, may be considered **medically necessary** when **EITHER** of the following criteria are met:

- A. The member has **BOTH** of the following:
  - 1. A personal history of **at least two** of the following:
    - a. Lamellar calcification of the falx
    - b. Jaw keratocyst
    - c. Palmar/plantar pits (2 or more)
    - d. Multiple basal cell carcinomas (more than 5 in lifetime) or a basal cell carcinoma diagnosed before 30 years of age
    - e. A first-degree relative with NBCCS
  - 2. **At least one** of the following:
    - a. Childhood medulloblastoma
    - b. Lympho-mesenteric or pleural cysts
    - c. Macrocephaly (OFC greater than 97th centile)
    - d. Cleft lip/palate
    - e. Vertebral/rib anomalies (bifid/splayed/extra ribs; bifid vertebrae)
    - f. Pre- or post-axial polydactyly
    - g. Ovarian fibromas
    - h. Cardiac fibromas
    - i. Ocular anomalies (examples: cataract, pigmentary changes of the retinal epithelium, developmental defects)
- B. The member has **BOTH** of the following:
  - 1. A personal history of **at least one** of the following:
    - a. Lamellar calcification of the falx
    - b. Jaw keratocyst
    - c. Palmar/plantar pits (2 or more)
    - d. Multiple basal cell carcinomas (more than 5 in lifetime) or a basal cell carcinoma diagnosed before 30 years of age
    - e. A first-degree relative with NBCCS
  - 2. **At least three** of the following:
    - a. Childhood medulloblastoma
    - b. Lympho-mesenteric or pleural cysts
    - c. Macrocephaly (OFC greater than 97th centile)
    - d. Cleft lip/palate
    - e. Vertebral/rib anomalies (bifid/splayed/extra ribs; bifid vertebrae)
    - f. Pre- or post-axial polydactyly
    - g. Ovarian fibromas

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

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

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HEREDITARY PARAGANGLIOMA/PHEOCHROMOCYTOMA SYNDROME (PGL/PCC)

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

XCI. *MAX*, *SDHA*, *SDHAF2*, *SDHB*, *SDHC*, *SDHD*, or *TMEM127* targeted variant analysis (81403) for hereditary paraganglioma/pheochromocytoma syndrome (PGL/PCC) may be considered **medically necessary** when **EITHER** of the following criteria are met:
  A. The member has a close relative with a known pathogenic or likely pathogenic variant in *MAX*, *SDHA*, *SDHAF2*, *SDHB*, *SDHC*, *SDHD*, or *TMEM127*
  B. A *MAX*, *SDHA*, *SDHAF2*, *SDHB*, *SDHC*, *SDHD*, or *TMEM127* pathogenic or likely pathogenic variant was detected by tumor profiling and germline analysis has not yet been performed.

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

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

XCIII. *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) may be considered **medically necessary** when **EITHER** of the following criteria are met:
  A. The member has a diagnosis of **one or more** of the following:
    1. Pheochromocytoma
    2. Paraganglioma
    3. Clear cell renal cell cancer
    4. Gastrointestinal stromal tumor (GIST)
    5. Pulmonary chondromas
  B. The member has a close relative with paraganglioma or pheochromocytoma.

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

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PEUTZ-JEGHERS SYNDROME (PJS)

STK11 Targeted Variant Analysis

XCV. *STK11* targeted variant analysis (81479) for Peutz-Jeghers syndrome may be considered **medically necessary** when **EITHER** of the following criteria are met:
  A. The member has a blood relative with a known pathogenic or likely pathogenic variant in *STK11*
  B. An *STK11* pathogenic or likely pathogenic variant was detected by tumor profiling and germline analysis has not yet been performed.

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

STK11 Sequencing and/or Deletion/Duplication Analysis

XCVII. *STK11* sequencing and/or deletion/duplication analysis (81404, 81405) for Peutz-Jeghers syndrome (PJS) may be considered **medically necessary** when:
  A. The member has a clinical diagnosis of Peutz-Jeghers syndrome based on the presence of **any two** of the following:
    1. At least two histologically confirmed Peutz-Jeghers-type hamartomatous polyps of the GI tract
    2. Mucocutaneous pigmentation of the mouth, lips, nose, eyes, genitalia, or fingers
    3. A close relative with PJS.

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

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RETINOBLASTOMA

RB1 Targeted Variant Analysis

XCIX. *RB1* targeted variant analysis (81403) for retinoblastoma may be considered **medically necessary** when **EITHER** of the following criteria are met:
  A. The member has a close relative with a known pathogenic or likely pathogenic variant in *RB1*
  B. An *RB1* pathogenic or likely pathogenic variant was detected by tumor profiling and germline analysis has not yet been performed.

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

RB1 Sequencing and/or Deletion/Duplication Analysis

CI. *RB1* sequencing and/or deletion/duplication analysis (81479, S3841) for retinoblastoma may be considered **medically necessary** when **EITHER** of the following criteria are met:
  A. The member has a diagnosis of retinoblastoma in one or both eyes
  B. The member has a close relative with retinoblastoma in one or both eyes.

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

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VON HIPPEL-LINDAU SYNDROME (VHL)

VHL Targeted Variant Analysis

CIII. *VHL* targeted variant analysis (81403) for Von Hippel-Lindau syndrome may be considered **medically necessary** when **EITHER** of the following criteria are met:
  A. The member has a first- or second-degree relative with a known pathogenic or likely pathogenic variant in *VHL*
  B. A *VHL* pathogenic or likely pathogenic variant was detected by tumor profiling and germline analysis has not yet been performed.

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

VHL Sequencing and/or Deletion/Duplication Analysis

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

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

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

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NOTE: Refer to Appendix A to see the policy statement changes (if any) from the previous version.

Policy Guidelines

DEFINITIONS

1. **Close relatives** include first, second, and third degree blood relatives on the same side of the family:
   - a. **First-degree relatives** are parents, siblings, and children
   - b. **Second-degree relatives** are grandparents, aunts, uncles, nieces, nephews, grandchildren, and half siblings
   - c. **Third-degree relatives** are great grandparents, great aunts, great uncles, great grandchildren, and first cousins
2. **Breast cancer**: Term that applies to patients with invasive cancer or ductal carcinoma in situ (DCIS).
3. **High-risk breast cancer for olaparib therapy:** Defined as
   - a. Triple negative breast cancer treated with either:
     - i. Adjuvant chemotherapy with axillary node-positive disease or an invasive primary tumor greater than or equal to 2 cm on pathology analysis, **OR**
     - ii. Neoadjustant chemotherapy with residual invasive breast cancer in the breast or resected lymph nodes, **OR**
   - b. Hormone receptor positive disease treated with either:
     - i. Adjuvant chemotherapy with four or more positive pathologically confirmed lymph nodes, OR
     - ii. Neoadjuvant chemotherapy which did not have a complete pathologic response, with a CPS+CG score [pre-treatment clinical (CS) and post-treatment pathological stage (PS), estrogen-receptor status (E) and grade (G)] of 3 or higher
4. **Juvenile polyps:** Polyps associated with Juvenile Polyposis Syndrome. These polyps are exophytic and eroded. They typically contain the following: marked edema and inflammation within the lamina propria, cystic glands filled with thick mucin, and some degree of smooth muscle proliferation.
5. **ClinGen**: National Institutes of Health (NIH)-funded resource dedicated to building a central resource that defines the clinical relevance of genes and variants for use in precision medicine and research.

6. **Maori ancestry:** Describes individuals who are of indigenous New Zealand ethnic background
7. **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
8. **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
9. **Targeted mutation testing:** The process of analyzing one specific pathogenic or likely pathogenic (P/LP) variant in one gene. This testing is typically performed when there is a known familial mutation, or in cases where a P/LP variant is identified on somatic tumor profiling.
10. **Adenomatous polyposis:** conditions that cause multiple adenomas (i.e., benign polyps) in the gastrointestinal tract.
11. **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.

Coding

See the Codes table for details.

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).

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

Targeted mutation testing 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.

Related Policies

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

- ***Genetic Testing: Multisystem Inherited Disorders, Intellectual Disability, and Developmental Delay*** for coverage criteria related to diagnostic testing for Fanconi anemia *(to be published)*
- ***Oncology: Algorithmic (Genetic Expression) Testing*** for coverage criteria related to tests that give prognostic information for an individual with cancer, or any oncology related test that involved an algorithmic portion.
- ***Oncology: Molecular Analysis of Solid Tumors and Hematologic Malignancies*** for coverage criteria related to somatic tumor testing, including Microsatellite Instability for colon cancer, and blood cancer testing
- ***Oncology: Cancer Screening*** for coverage criteria related to tests that screen for the presence of cancer.
- ***Oncology: Circulating Tumor DNA and Circulating Tumor Cells (Liquid Biopsy)*** for coverage criteria related to the testing of tumor DNA circulating in an individual's blood stream.
- ***Genetic Testing: General Approach to Genetic and Molecular Testing*** for coverage criteria related to hereditary cancer susceptibility that is not specifically discussed in this or other non-general policies.

Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

Regulatory Status

State:
Starting on July 1, 2022 (per CA law SB 535) for commercial plans regulated by the California Department of Managed Healthcare and California Department of Insurance (PPO and HMO), health care service plans and insurers shall not require prior authorization for biomarker testing,

including biomarker testing for cancer progression and recurrence, if a member has stage 3 or 4 cancer. Health care service plans and insurers can still do a medical necessity review of a biomarker test and possibly deny coverage after biomarker testing has been completed and a claim is submitted (post service review)

Rationale

Background and Rationale
Pan-Cancer Hereditary Susceptibility Panels

National Comprehensive Cancer Network (NCCN)
NCCN Breast, Ovarian, and/or Pancreatic Cancer Genetic Assessment guidelines (2.2024) recognize that next-generation sequencing technology has rapidly altered the clinical approach to testing at-risk patients and their families for hereditary forms of cancer and that when more than one gene can explain an inherited cancer syndrome, tailored multi-gene testing is often more efficient and/or cost effective than single-gene testing. However, there is the chance of finding a variant of uncertain significance in a well established gene, or finding a pathogenic variant in a gene with uncertain clinical management. These types of findings increase as additional genes are included in the multi-gene panel. It is recommended that multi-gene panel testing be offered by a professional genetic expert that provides detailed pre- and post-test counseling. (p. EVAL-A 3 of 10). These guidelines also state that RNA studies (when appropriate) may be a consideration to further define functional impact of variants, and a referral to research studies that aim to define the functional impact of variants such as variant reclassification programs through clinical labs or registries should be considered. (p. EVAL-A, 9 of 10).

NCCN Guidelines for Genetic/Familial High-Risk Assessment Colorectal (2.2023) state that when more than one gene can explain an inherited cancer syndrome, multigene testing is more efficient than single-gene testing, or sequential single syndrome testing. There is also a role for multigene testing in individuals who have tested negative (indeterminate) for a single syndrome, but whose personal or family history remains strongly suggestive of an inherited susceptibility. (p. GENE-1)

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

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

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

- A hereditary cancer risk assessment is the key to identifying patients and families who may be at increased risk of developing certain types of cancer. Assessments should be performed by obstetrician–gynecologists or other obstetric–gynecologic care providers and should be updated regularly.

- If a hereditary cancer risk assessment suggests an increased risk of a hereditary cancer syndrome, referral to a specialist in cancer genetics or a health care provider with expertise in genetics is recommended for expanded gathering of family history information, risk assessment, education, and counseling, which may lead to genetic testing and tailored cancer screening or risk reduction measures, or both.
- Genetic testing may be performed using a panel of multiple genes through next-generation sequencing technology. This multigene testing process increases the likelihood of finding variants of unknown significance, and it also allows for testing for pathogenic and likely pathogenic variants in multiple genes that may be associated with a specific cancer syndrome or family cancer phenotype (or multiple phenotypes). (p. e143)

Hereditary Breast Cancer Susceptibility Panels

National Comprehensive Cancer Network (NCCN)

The NCCN guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic Cancers (2.2024, p. CRIT-2) outline clinical criteria for germline genetic testing of high-penetrance breast cancer genes. These guidelines include:

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

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

3.) 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

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

Hereditary GI/Colon Cancer Panel Tests

National Comprehensive Cancer Network (NCCN)

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

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

NCCN also states that the minimum number of CRC-risk associated genes to include in germline multi-gene panel testing are as follows: *APC, MUTYH, MLH1, MSH2, MSH6, PMS2, EPCAM, BMPR1A, SMAD4, PTEN, STK11,* and *TP53.* (p. HRS-A 2 of 2). Many individuals will have variants of uncertain significance (VUS); post test counseling should include considering referral to research studies that aim to define 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 Panels

National Comprehensive Cancer Network (NCCN)

NCCN Gastric Cancer guidelines (2.2023) outline criteria for further genetic risk assessment for high-risk syndromes associated with gastric cancer, including: hereditary diffuse gastric cancer, Lynch syndrome, Juvenile Polyposis Syndrome, Peutz-Jeghers syndrome, and Familial Adenomatous Polyposis. (p. GAST-D 3 of 8 and p. GAST-D 4 of 8)

Hereditary Pancreatic Cancer Susceptibility Panels

National Comprehensive Cancer Network (NCCN)

NCCN Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic guidelines (2.2024) 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 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) for germline mutations in *APC* and *MUTYH.* (p. HRS-2)

Hereditary Prostate Cancer Susceptibility Panels

National Comprehensive Cancer Network (NCCN)

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

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

    - 1 or more first-degree relative (parent or sibling) with:
        - prostate cancer at age <60 y
    - 2 or more first-, second-, or third-degree relatives with:
        - breast cancer at any age
        - prostate cancer at any age
    - 3 or more first- or second-degree relatives with:
        - Lynch syndrome-related cancers, especially if diagnosed <50 y: colorectal, endometrial, gastric, ovarian, exocrine pancreas, upper tract urothelial, glioblastoma, biliary tract, and small intestinal cancer
  - A known family history of familial cancer risk mutation (pathogenic/likely pathogenic variants), especially in: *BRCA1, BRCA2, ATM, PALB2, CHEK2, MLH1, MSH2, MSH6, PMS2,* and *EPCAM*
  - Ashkenazi Jewish ancestry
  - Personal history of breast cancer

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

NCCN Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic guidelines (2.2024) recommend the following testing criteria for prostate cancer susceptibility genes:

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

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

Hereditary Neuroendocrine Cancer Susceptibility Panels

National Comprehensive Cancer Network (NCCN)

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

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

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

- Clinical suspicion for MEN2
- Clinical suspicion for MEN1 (p. NE-E, 3 of 8)

BRCA1 AND *BRCA2* GENE TESTING

BRCA1/BRCA2 Targeted Variant or Known Familial Variant Analysis

National Comprehensive Cancer Network (NCCN)
The NCCN Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic guidelines (2.2024) states that testing should be performed in the following situations:

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

BRCA1/BRCA2 Targeted Variant Analysis - Ashkenazi Jewish Founder Variants

National Comprehensive Cancer Network (NCCN)
The NCCN Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic guidelines (2.2024) states that testing for the three known Ashkenazi Jewish founder *BRCA1/2* mutations is appropriate for individuals who are age 18 years or older and have at least one grandparent who is of Ashkenazi Jewish ancestry. (p. CRIT-1 and p. CRIT-1A)

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

National Comprehensive Cancer Network (NCCN)
The NCCN guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic guidelines (2.2024) 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 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 or prostate cancer in patient and/or close blood relativesFamily 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 (e.g., Tyrer-Cuzick, BRCAPro, CanRisk) (p. CRIT-2)

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

The NCCN guidelines for Ampullary Adenocarcinoma (2.2023) recommend genetic testing for inherited mutations for any patient with confirmed ampullary cancer. A comprehensive gene panel should be utilized. Genetic counseling is recommended for patients who test positive for a pathogenic mutation (*ATM, BRCA1, BRCA2, CDKN2A, MLH1, MSH2, MSH6, PALB2, PMS2, STK11*, and *TP53*) or for patients with a positive family history of cancer, especially pancreatic/ampullary cancer, regardless of mutation status. (p. AMP-3)

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

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

PALB2 GENE TESTING
PALB2 Targeted Variant Analysis

National Comprehensive Cancer Network (NCCN)
The NCCN Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic guidelines (2.2024) states that testing should be performed in the following situations:

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

PALB2 Sequencing and/or Deletion/Duplication Analysis

National Comprehensive Cancer Network (NCCN)
The NCCN guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic guidelines (2.2024) 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 (e.g., Tyrer-Cuzick, BRCAPro, CanRisk) (p. CRIT-2)

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

The NCCN guidelines for Ampullary Adenocarcinoma (2.2023) recommend genetic testing for inherited mutations for any patient with confirmed ampullary cancer. A comprehensive gene panel should be utilized. Genetic counseling is recommended for patients who test positive for a pathogenic mutation (*ATM, BRCA1, BRCA2, CDKN2A, MLH1, MSH2, MSH6, PALB2, PMS2, STK11*, and *TP53*) or for patients with a positive family history of cancer, especially pancreatic/ampullary cancer, regardless of mutation status. (p. AMP-3)

ATM AND *CHEK2* GENE TESTING
ATM or *CHEK2* Targeted Variant Analysis

National Comprehensive Cancer Network (NCCN)
The NCCN Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic guidelines (2.2024) state that testing should be performed in the following situations:

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

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

National Comprehensive Cancer Network (NCCN)
While the NCCN Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic guidelines (2.2024) do provide surveillance recommendations for individuals with germline *ATM* and *CHEK2* mutations (p. GENE-A 1 of 10 and p. GENE-A 4 of 10), these genes are not considered high-penetrance breast cancer susceptibility genes, and the guidelines do not include gene-specific clinical criteria for *ATM* and *CHEK2* as they do for the high-penetrance breast cancer susceptibility genes.

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

LYNCH SYNDROME/HEREDITARY NONPOLYPOSIS COLORECTAL CANCER (HNPCC) TESTING
MLH1, MSH2, MSH6, PMS2, or *EPCAM* Targeted Variant Analysis

National Comprehensive Cancer Network (NCCN)
NCCN Genetic/Familial High-Risk Assessment: Colorectal guidelines (2.2023) outline testing criteria for the evaluation of Lynch syndrome. NCCN recommends analysis of *MLH1*, *MSH2*, *MSH6*, *PMS2* and/or *EPCAM* in individuals with a known pathogenic variant in the family. (p. HRS-5)

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

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

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

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

For individuals without a personal history of CRC and/or endometrial cancer, some data have suggested using a PREMM5 score threshold of 2.5% or greater rather than 5% or greater to select individuals for MMR genetic testing. Based on these data, it is reasonable for testing to be done based on the 2.5% or greater score result and clinical judgment. (p. HRS-5)

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

BAP1 TUMOR PREDISPOSITION SYNDROME

BAP1 Targeted Variant Analysis

National Comprehensive Cancer Network (NCCN)
NCCN guidelines for Kidney Cancer (1.2024) include *BAP1* tumor predisposition syndrome in their overview of hereditary renal cell carcinoma syndromes, and state that this testing is indicated for an individual with a close blood relative with a known pathogenic/likely pathogenic variant. (p. HERED-RCC-1 and HERED-RCC-2)

BAP1 Sequencing and/or Deletion/Duplication Analysis

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

NCCN guidelines for Uveal Melanoma (1.2023) include germline *BAP1* mutations as a risk factor for developing uveal melanoma. (p. UM-A 1 of 2)

NCCN guidelines for Malignant Pleural Mesothelioma (1.2023) state that approximately 12-16% of patients with pleural or peritoneal mesothelioma have a germline mutation, including in *BAP1.* (p. MPM-A 5 of 8)

NCCN guidelines for Kidney cancer (1.2024) 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 (1.2024) includes Birt-Hogg-Dube syndrome in their overview of hereditary renal cell carcinoma syndromes, and state that this testing is indicated for an individual with a close blood relative with a known pathogenic/likely pathogenic variant. (p. HERED-RCC-1 and HERED-RCC-2)

FLCN Sequencing and/or Deletion/Duplication Analysis

National Comprehensive Cancer Network (NCCN)
NCCN guidelines for Kidney Cancer (1.2024 include Birt-Hogg-Dube syndrome in their overview of hereditary renal cell carcinoma syndromes. (p. HERED-RCC-2). Commonly seen histologies include chromophobe, hybrid oncocytic tumors, clear cell, oncocytomas, angiomyolipomas, and papillary RCC. (p. HERED-RCC-2)

GeneReviews: Birt-Hogg-Dube Syndrome (BHDS)

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

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

<u>Major criteria</u>

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

<u>Minor criteria</u>

- Multiple lung cysts. Bilateral basally located lung cysts with no other apparent cause, with or without spontaneous primary pneumothorax

- Early-onset renal cancer (age <50 years)
- Multifocal or bilateral renal cancer
- Renal cancer of mixed chromophobe and oncocytic histology
- First-degree relative with BHDS

The diagnosis of BHDS is established in a proband with:

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

COWDEN SYNDROME (CS)/PTEN HAMARTOMA TUMOR SYNDROME (PHTS)
PTEN Targeted Variant Analysis

National Comprehensive Cancer Network (NCCN)
The NCCN Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic guidelines (2.2024) states that testing should be performed in the following situations:

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

PTEN Sequencing and/or Deletion/Duplication Analysis

National Comprehensive Cancer Network (NCCN)
NCCN Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic guidelines (2.2024) outline clinical criteria for the genetic testing for Cowden syndrome (CS)/*PTEN* hamartoma tumor syndrome (PHTS) These include:

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

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

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

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

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

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

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

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

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

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

FAMILIAL ATYPICAL MULTIPLE MOLE MELANOMA (FAMMM) SYNDROME
CDKN2A Targeted Variant Analysis

Genetic Support Foundation
The NCCN Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic guidelines (2.2024) state that testing should be performed in the following situations:

- Individuals with any blood relative with a known pathogenic/likely pathogenic variant in a cancer susceptibility gene
- Individuals with a pathogenic/likely pathogenic (P/LP) variant identified on tumor genomic testing that has clinical implications if also identified in the germline. (p.CRIT-1).
- Comprehensive skin exam and additional evaluations by a dermatologist are recommended for individuals with a P/LP variant (p. GENE-A, 4 of 11).

CDKN2A Sequencing and/or Deletion/Duplication Analysis

National Comprehensive Cancer Network (NCCN)
NCCN Cutaneous Melanoma guidelines (3.2023) recommend considering genetic counseling referral for *p16*/*CDKN2A* mutation testing (and possibly other genes) when a patient has 3 or more invasive

cutaneous melanomas, or a personal or family history of a mix of invasive melanoma, pancreatic cancer, and/or astrocytoma diagnoses. (p. ME-11).

NCCN Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic guidelines (2.2024) recognize CDKN2A as a pancreatic cancer susceptibility gene; testing is indicated in an individual with pancreatic cancer or a first degree relative with pancreatic cancer. (p. CRIT-5).

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

HEREDITARY DIFFUSE GASTRIC CANCER (aka, Signet Ring Cell Gastric Cancer): *CDH1* Targeted Variant Analysis

National Comprehensive Cancer Network (NCCN)
NCCN Gastric Cancer guidelines (2.2023) outline testing criteria for germline *CDH1* testing, which states that a known mutation in a gastric cancer susceptibility gene in a close relative is criteria for further risk evaluation. (p.GAST-D 1 of 8)

The NCCN Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic guidelines (2.2024) state that testing should be performed in the following situations:

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

CDH1 Sequencing and/or Deletion/Duplication Analysis

National Comprehensive Cancer Network (NCCN)
NCCN Gastric Cancer guidelines (2.2023) outline testing criteria for germline *CDH1* testing which incorporates both personal and family history of gastric cancer and lobular breast cancer. These include:

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

JUVENILE POLYPOSIS SYNDROME (JPS) *SMAD4* and *BMPR1A* Targeted Variant Analysis

National Comprehensive Cancer Network (NCCN)
NCCN Genetic/Familial High-Risk Assessment: Colorectal guidelines (2.2023) outline clinical criteria for the genetic testing, which states that genetic testing should be performed for individuals with a known pathogenic variant in BMPR1A or SMAD4. (p. JPS-1)

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

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

National Comprehensive Cancer Network (NCCN)
NCCN Genetic/Familial High-Risk Assessment: Colorectal guidelines (2.2023) outline clinical criteria for the genetic testing for juvenile polyposis syndrome (JPS) in individuals with a personal and/or family history suggestive of JPS, noting that clinical genetic testing is recommended as approximately 50% of JPS cases occurring due to pathogenic variants in *BMPR1A* and *SMAD4*. These criteria include 5 or more colonic juvenile polyps, multiple juvenile polyps throughout the gastrointestinal tract, and any number of juvenile polyps in someone with a family history of JPS. (p. JPS-1)

HEREDITARY LEIOMYOMATOSIS AND RENAL CELL CANCER (HLRCC)

FH Targeted Variant Analysis

National Comprehensive Cancer Network (NCCN)
NCCN guidelines for Kidney Cancer (1.2024) include Hereditary leiomyomatosis and renal cell carcinoma (HLRCC) in their overview of hereditary renal cell carcinoma syndromes, and state that this testing is indicated for an individual with a close blood relative with a known pathogenic/likely pathogenic variant. (p. HERED-RCC-1 and HERED-RCC-2)

FH Sequencing and/or Deletion/Duplication Analysis

National Comprehensive Cancer Network (NCCN)
NCCN guidelines for Kidney Cancer (1.2024) outline criteria for further genetic risk evaluation for hereditary renal cell carcinoma syndromes, including HLRCC-associated renal cell carcinoma. (p. HERED-RCC-2)

GeneReviews: FH Tumor Predisposition Syndrome

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

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

Cutaneous leiomyomata (~50%):

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

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

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

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

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

LI-FRAUMENI SYNDROME (LFS)

TP53 Targeted Variant Analysis

National Comprehensive Cancer Network (NCCN)
The NCCN Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic guidelines (2.2024) states that testing should be performed in the following situations:

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

TP53 Sequencing and/or Deletion/Duplication Analysis

National Comprehensive Cancer Network (NCCN)
NCCN Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic guidelines (2.2024) 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 or family history of pediatric hypodiploid acute lymphoblastic leukemia,

MULTIPLE ENDOCRINE NEOPLASIA TYPE 1 (MEN1)

MEN1 Targeted Variant Analysis

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

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

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

National Comprehensive Cancer Network (NCCN)

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

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

MULTIPLE ENDOCRINE NEOPLASIA TYPE 2 (MEN2)

RET **Targeted Variant Analysis**

National Comprehensive Cancer Network (NCCN)

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

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

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

GeneReviews: Multiple Endocrine Neoplasia Type 2

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

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

National Comprehensive Cancer Network (NCCN)

NCCN Neuroendocrine and Adrenal Tumors guidelines (1.2023) also recommends MEN2 testing when there is clinical suspicion of MEN2 due to the presence of medullary thyroid cancer or other combination of MEN2-related features. Genetic testing is indicated for a first degree relative meeting this criteria, where the relative is not available for testing. (p. NE-E 3 of 8)

NEVOID BASAL CELL CARCINOMA SYNDROME (aka Gorlin syndrome)

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

GeneReviews: Nevoid Basal Cell Carcinoma Syndrome

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

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

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

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

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

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

Major criteria

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

Minor criteria

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

HEREDITARY PARAGANGLIOMA/PHEOCHROMOCYTOMA SYNDROME (PGL/PCC)

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

National Comprehensive Cancer Network (NCCN)
NCCN guidelines for Kidney Cancer (1.2024) include Hereditary paraganglioma/pheochromocytoma (PGL/PCC) syndrome in their overview of hereditary renal cell carcinoma syndromes, and state that this testing is indicated for an individual with a close blood relative with a known pathogenic/likely pathogenic variant. (p. HERED-RCC-1 and HERED-RCC-2)

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

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

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

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

PEUTZ-JEGHERS SYNDROME (PJS)

STK11 Targeted Variant Analysis

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

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

STK11 Sequencing and/or Deletion/Duplication Analysis

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

RETINOBLASTOMA

RB1 Targeted Variant Analysis

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

RB1 Sequencing and/or Deletion/Duplication Analysis

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

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

VON HIPPEL-LINDAU SYNDROME (VHL)

VHL Targeted Variant Analysis

National Comprehensive Cancer Network (NCCN)
NCCN guidelines for Kidney Cancer (1.2024) include von Hippel-Lindau (VHL) syndrome in their overview of hereditary renal cell carcinoma syndromes, and state that this testing is indicated for an individual with a close blood relative with a known pathogenic/likely pathogenic variant. (p. HERED-RCC-1 and HERED-RCC-2)

VHL Sequencing and/or Deletion/Duplication Analysis

National Comprehensive Cancer Network (NCCN)
NCCN Kidney Cancer guidelines (1.2024) outline clinical features seen in Von Hippel-Lindau syndrome including: hemangioblastomas (in the retina, spine, or brain), clear cell RCC (diagnosed before age 40 years or multiple/bilateral RCC diagnosed at any age), pheochromocytomas, paragangliomas (in the abdomen, thorax, or neck), retinal angiomas, endolymphatic sac tumors, epididymal or broad ligament papillary cystadenomas, multiple pancreatic serous cystadenomas, pancreatic neuroendocrine tumors, or multiple cysts in the pancreas. While these clinical features are categorized within the categories "major" and "minor," the NCCN guidelines do not provide a scoring system required for patients to meet testing criteria. (p. HERED-RCC-A)

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Documentation for Clinical Review

Please provide the following documentation:

- Name of the test being requested or the Concert Genetics GTU identifier.
  The Concert Genetics GTU can be found at https://app.concertgenetics.com
- CPT codes to be billed for the particular genetic test (GTU required for unlisted codes)
- History and physical and/or consultation notes including:
  - Clinical findings:
    - Signs/symptoms leading to a suspicion of genetic condition
    - Family history if applicable
  - Prior evaluation/treatment:
    - Previous test results (i.e., imagining, lab work, etc.) related to reason for genetic testing
    - Family member's genetic test result, if applicable
  - Rationale
    - Reason for performing test
    - How test result will impact clinical decision making

Post Service (in addition to the above, please include the following):

- Results/reports of tests performed

Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy.

The following codes are included below for informational purposes. Inclusion or exclusion of a code(s) does not constitute or imply member coverage or provider reimbursement policy. Policy Statements are intended to provide member coverage information and may include the use of some codes for clarity. The Policy Guidelines section may also provide additional information for how to interpret the Policy Statements and to provide coding guidance in some cases.

Type	Code	Description
CPT®	0101U	Hereditary colon cancer disorders (e.g., Lynch syndrome, PTEN hamartoma syndrome, Cowden syndrome, familial adenomatosis polyposis), genomic sequence analysis panel utilizing a combination of NGS, Sanger, MLPA, and array CGH, with mRNA analytics to resolve variants of unknown significance when indicated (15 genes [sequencing and deletion/duplication], EPCAM and GREM1 [deletion/duplication only])
	0129U	Hereditary breast cancer-related disorders (e.g., hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer), genomic sequence analysis and deletion/duplication analysis panel (ATM, BRCA1, BRCA2, CDH1, CHEK2, PALB2, PTEN, and TP53)
	0130U	Hereditary colon cancer disorders (e.g., Lynch syndrome, PTEN hamartoma syndrome, Cowden syndrome, familial adenomatosis polyposis), targeted mRNA sequence analysis panel (APC, CDH1, CHEK2, MLH1, MSH2, MSH6, MUTYH, PMS2, PTEN, and TP53) (List separately in addition to code for primary procedure)

Type	Code	Description
	0133U	Hereditary prostate cancer-related disorders, targeted mRNA sequence analysis panel (11 genes) (List separately in addition to code for primary procedure)
	0134U	Hereditary pan cancer (e.g., hereditary breast and ovarian cancer, hereditary endometrial cancer, hereditary colorectal cancer), targeted mRNA sequence analysis panel (18 genes) (List separately in addition to code for primary procedure)
	0136U	ATM (ataxia telangiectasia mutated) (e.g., ataxia telangiectasia) mRNA sequence analysis (List separately in addition to code for primary procedure)
	0137U	PALB2 (partner and localizer of BRCA2) (e.g., breast and pancreatic cancer) mRNA sequence analysis (List separately in addition to code for primary procedure)
	0138U	BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (e.g., hereditary breast and ovarian cancer) mRNA sequence analysis (List separately in addition to code for primary procedure)
	0157U	APC (APC regulator of WNT signaling pathway) (e.g., familial adenomatosis polyposis [FAP]) mRNA sequence analysis (List separately in addition to code for primary procedure)
	0158U	MLH1 (mutL homolog 1) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) mRNA sequence analysis (List separately in addition to code for primary procedure)
	0159U	MSH2 (mutS homolog 2) (e.g., hereditary colon cancer, Lynch syndrome) mRNA sequence analysis (List separately in addition to code for primary procedure)
	0160U	MSH6 (mutS homolog 6) (e.g., hereditary colon cancer, Lynch syndrome) mRNA sequence analysis (List separately in addition to code for primary procedure)
	0161U	PMS2 (PMS1 homolog 2, mismatch repair system component) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) mRNA sequence analysis (List separately in addition to code for primary procedure)
	0162U	Hereditary colon cancer (Lynch syndrome), targeted mRNA sequence analysis panel (MLH1, MSH2, MSH6, PMS2) (List separately in addition to code for primary procedure)
	81162	BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; full sequence analysis and full duplication/deletion analysis (i.e., detection of large gene rearrangements)
	81163	BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; full sequence analysis
	81164	BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; full duplication/deletion analysis (i.e., detection of large gene rearrangements)
	81165	BRCA1 (BRCA1, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; full sequence analysis
	81166	BRCA1 (BRCA1, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; full duplication/deletion analysis (i.e., detection of large gene rearrangements)

Type	Code	Description
	81167	BRCA2 (BRCA2, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; full duplication/deletion analysis (i.e., detection of large gene rearrangements)
	81201	APC (adenomatous polyposis coli) (e.g., familial adenomatosis polyposis [FAP], attenuated FAP) gene analysis; full gene sequence
	81202	APC (adenomatous polyposis coli) (e.g., familial adenomatosis polyposis [FAP], attenuated FAP) gene analysis; known familial variants
	81203	APC (adenomatous polyposis coli) (e.g., familial adenomatosis polyposis [FAP], attenuated FAP) gene analysis; duplication/deletion variants
	81212	BRCA1 (BRCA1, DNA repair associated), BRCA2 (BRCA2, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; 185delAG, 5385insC, 6174delT variants
	81215	BRCA1 (BRCA1, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; known familial variant
	81216	BRCA2 (BRCA2, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; full sequence analysis
	81217	BRCA2 (BRCA2, DNA repair associated) (e.g., hereditary breast and ovarian cancer) gene analysis; known familial variant
	81292	MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis
	81293	MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; known familial variants
	81294	MLH1 (mutL homolog 1, colon cancer, nonpolyposis type 2) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; duplication/deletion variant
	81295	MSH2 (mutS homolog 2, colon cancer, nonpolyposis type 1) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis
	81296	MSH2 (mutS homolog 2, colon cancer, nonpolyposis type 1) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; known familial variants
	81297	MSH2 (mutS homolog 2, colon cancer, nonpolyposis type 1) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; duplication/deletion variants
	81298	MSH6 (mutS homolog 6 [E. coli]) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis
	81299	MSH6 (mutS homolog 6 [E. coli]) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; known familial variants
	81300	MSH6 (mutS homolog 6 [E. coli]) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; duplication/deletion variants
	81307	PALB2 (partner and localizer of BRCA2) (e.g., breast and pancreatic cancer) gene analysis; full gene sequence
	81308	PALB2 (partner and localizer of BRCA2) (e.g., breast and pancreatic cancer) gene analysis; known familial variant
	81317	PMS2 (postmeiotic segregation increased 2 [S. cerevisiae]) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; full sequence analysis

Type	Code	Description
	81318	PMS2 (postmeiotic segregation increased 2 [S. cerevisiae]) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; known familial variants
	81319	PMS2 (postmeiotic segregation increased 2 [S. cerevisiae]) (e.g., hereditary non-polyposis colorectal cancer, Lynch syndrome) gene analysis; duplication/deletion variants
	81321	PTEN (phosphatase and tensin homolog) (e.g., Cowden syndrome, PTEN hamartoma tumor syndrome) gene analysis; full sequence analysis
	81322	PTEN (phosphatase and tensin homolog) (e.g., Cowden syndrome, PTEN hamartoma tumor syndrome) gene analysis; known familial variant
	81323	PTEN (phosphatase and tensin homolog) (e.g., Cowden syndrome, PTEN hamartoma tumor syndrome) gene analysis; duplication/deletion variant
	81351	TP53 (tumor protein 53) (e.g., Li-Fraumeni syndrome) gene analysis; full gene sequence
	81352	TP53 (tumor protein 53) (e.g., Li-Fraumeni syndrome) gene analysis; targeted sequence analysis (e.g., 4 oncology)
	81401	Molecular pathology procedure, Level 2 (e.g., 2-10 SNPs, 1 methylated variant, or 1 somatic variant [typically using nonsequencing target variant analysis], or detection of a dynamic mutation disorder/triplet repeat)
	81403	Molecular pathology procedure, Level 4 (e.g., analysis of single exon by DNA sequence analysis, analysis of >10 amplicons using multiplex PCR in 2 or more independent reactions, mutation scanning or duplication/deletion variants of 2-5 exons)
	81404	Molecular pathology procedure, Level 5 (e.g., analysis of 2-5 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 6-10 exons, or characterization of a dynamic mutation disorder/triplet repeat by Southern blot analysis)
	81405	Molecular pathology procedure, Level 6 (e.g., analysis of 6-10 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 11-25 exons, regionally targeted cytogenomic array analysis)
	81406	Molecular pathology procedure, Level 7 (e.g., analysis of 11-25 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 26-50 exons)
	81408	Molecular pathology procedure, Level 9 (e.g., analysis of >50 exons in a single gene by DNA sequence analysis)
	81432	Hereditary breast cancer-related disorders (e.g., hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer); genomic sequence analysis panel, must include sequencing of at least 10 genes, always including BRCA1, BRCA2, CDH1, MLH1, MSH2, MSH6, PALB2, PTEN, STK11, and TP53
	81433	Hereditary breast cancer-related disorders (e.g., hereditary breast cancer, hereditary ovarian cancer, hereditary endometrial cancer); duplication/deletion analysis panel, must include analyses for BRCA1, BRCA2, MLH1, MSH2, and STK11
	81435	Hereditary colon cancer disorders (e.g., Lynch syndrome, PTEN hamartoma syndrome, Cowden syndrome, familial adenomatosis polyposis); genomic sequence analysis panel, must include sequencing of at least 10 genes, including APC, BMPR1A, CDH1, MLH1, MSH2, MSH6, MUTYH, PTEN, SMAD4, and STK11

Type	Code	Description
	81436	Hereditary colon cancer disorders (e.g., Lynch syndrome, PTEN hamartoma syndrome, Cowden syndrome, familial adenomatosis polyposis); duplication/deletion analysis panel, must include analysis of at least 5 genes, including MLH1, MSH2, EPCAM, SMAD4, and STK11
	81437	Hereditary neuroendocrine tumor disorders (e.g., medullary thyroid carcinoma, parathyroid carcinoma, malignant pheochromocytoma or paraganglioma); genomic sequence analysis panel, must include sequencing of at least 6 genes, including MAX, SDHB, SDHC, SDHD, TMEM127, and VHL
	81438	Hereditary neuroendocrine tumor disorders (e.g., medullary thyroid carcinoma, parathyroid carcinoma, malignant pheochromocytoma or paraganglioma); duplication/deletion analysis panel, must include analyses for SDHB, SDHC, SDHD, and VHL
	81479	Unlisted molecular pathology procedure
HCPCS	S3840	DNA analysis for germline mutations of the RET proto-oncogene for susceptibility to multiple endocrine neoplasia type 2
	S3841	Genetic testing for retinoblastoma
	S3842	Genetic testing for Von Hippel-Lindau disease

Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

Effective Date	Action
05/01/2024	New policy. Archived Blue Shield of California Medical Policy: 2.04.02, 2.04.08, 2.04.44, 2.04.93, 2.04.126, 2.04.148, and 2.04.149.

Definitions of Decision Determinations

Medically Necessary: Services that are Medically Necessary include only those which have been established as safe and effective, are furnished under generally accepted professional standards to treat illness, injury or medical condition, and which, as determined by Blue Shield, are: (a) consistent with Blue Shield medical policy; (b) consistent with the symptoms or diagnosis; (c) not furnished primarily for the convenience of the patient, the attending Physician or other provider; (d) furnished at the most appropriate level which can be provided safely and effectively to the patient; and (e) not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of the Member's illness, injury, or disease.

Investigational/Experimental: A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

Split Evaluation: Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

Prior Authorization Requirements and Feedback (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department at (800) 541-6652, or the Transplant Case Management Department at (800) 637-2066 ext. 3507708 or visit the provider portal at www.blueshieldca.com/provider.

We are interested in receiving feedback relative to developing, adopting, and reviewing criteria for medical policy. Any licensed practitioner who is contracted with Blue Shield of California or Blue Shield of California Promise Health Plan is welcome to provide comments, suggestions, or concerns. Our internal policy committees will receive and take your comments into consideration.

For utilization and medical policy feedback, please send comments to: MedPolicy@blueshieldca.com

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.

Appendix A

<table>
<tr><th colspan="2">POLICY STATEMENT</th></tr>
<tr><th>BEFORE</th><th>AFTER
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<tr><td>New Policy

Policy Statement:
N/A</td><td>Genetic Testing: Hereditary Cancer Susceptibility BSC_CON_2.01

Policy Statement:
PAN-CANCER HEREDITARY CANCER SUSCEPTIBILITY PANELS
A pan-cancer hereditary cancer susceptibility panel includes genes that are associated with inherited susceptibility to several different types of cancer (e.g., breast cancer, colon cancer, stomach cancer, etc.).

I. Genetic testing using a pan-cancer hereditary cancer susceptibility panel (81432, 81433) may be considered medically necessary when ALL of the following criteria are met:
A. The member is 18 years or older
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 (statement XXV)
2. The member meets clinical criteria for Lynch syndrome/HNPCC MLH1, MSH2, MSH6, PMS2, or EPCAM sequencing and/or deletion/duplication analysis (statement XXXIX)
C. The panel includes, at a minimum, sequencing of the following genes: BRCA1, BRCA2, EPCAM, MLH1, MSH2, MSH6, PMS2
D. The panel does not include genes without a known association with cancer by ClinGen.

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

III. Hereditary cancer susceptibility panel targeted mRNA sequencing analysis for the interpretation of variants of unknown significance (0134U), when billed in addition, is considered investigational because it is typically either considered an existing component of</td></tr>
</table>

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<tr><th>BEFORE</th><th>AFTER
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<tr><td></td><td>the genetic testing process for quality assurance or follow up testing without proven utility.

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

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HEREDITARY BREAST CANCER SUSCEPTIBILITY PANELS
A hereditary breast cancer susceptibility panel includes genes that are associated with inherited susceptibility to breast cancer.

IV. Genetic testing using a hereditary breast cancer susceptibility panel (81162, 81163, 81164, 81165, 81166, 81167, 81216, 81307, 81321, 81351, 81432, 81433, 0129U) may be considered **medically necessary** when **ALL** of the following criteria are met:
A. The member is 18 years or older
B. The member meets *BRCA1* and *BRCA2* Sequencing and Deletion/Duplication analysis, (statement XXV)
C. The panel includes, at a minimum, sequencing of the following genes: *BRCA1*, *BRCA2*
D. The panel does not include genes without known association with breast cancer by ClinGen.

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

VI. 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.</td></tr>
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POLICY STATEMENT	
BEFORE	AFTER Blue font: Verbiage Changes/Additions
	back to top **HEREDITARY GI/COLON CANCER PANEL TESTS** A hereditary colorectal cancer susceptibility panel includes genes that are associated with inherited susceptibility to colorectal cancer. VII. Genetic testing using a hereditary colorectal cancer susceptibility panel (81435, 81436, 0101U) may be considered **medically necessary** when **ALL** of the following criteria are met: A. The member is 18 years or older B. 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 b. At least 2 hamartomatous polyps c. At least 5 serrated polyps/lesions proximal to the rectum 2. The member has a personal history of colorectal cancer under 50 years of age 3. The member meets clinical criteria for Lynch syndrome/HNPCC *MLH1, MSH2, MSH6, PMS2,* or *EPCAM* Sequencing and/or Deletion/Duplication Analysis (statement XXXIX) C. The panel includes, at a minimum, sequencing of the following genes: *APC, MUTYH, MLH1, MSH2, MSH6, PMS2, EPCAM, BMPR1A, SMAD4, PTEN, STK11,* and *TP53* D. The panel does not include genes without a known association with colorectal or gastrointestinal cancer by ClinGen. VIII. Genetic testing using a hereditary colorectal cancer susceptibility panel (81435, 81436, 0101U) is considered **investigational** for all other indications. IX. 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

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	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. back to top **HEREDITARY GASTRIC CANCER PANELS** A hereditary gastric cancer panel includes genes that are associated with inherited susceptibility to gastric (stomach) cancer. X. Genetic testing using a hereditary gastric susceptibility panel (81201, 81203, 81292, 81294, 81295, 81297, 81298, 81300, 81317, 81319, 81403, 81404, 81405, 81406, 81408, 81479) may be considered **medically necessary** when **ALL** of the following criteria are met: A. The member is 18 years or older B. The member meets sequencing and/or deletion/duplication clinical criteria for **at least one** of the following: 1. Lynch syndrome/Hereditary Nonpolyposis Colorectal Cancer (statement XXXIX) 2. Hereditary Diffuse Gastric Cancer (statement LXV) 3. Juvenile Polyposis Syndrome (statement LXIX) 4. Peutz-Jeghers Syndrome (statement XCVII) 5. Adenomatous Polyposis Syndromes (statement LVI) C. The panel includes, at a minimum, sequencing of the following genes: *APC, BMPR1A, CDH1, EPCAM, MLH1, MSH2, MSH6, PMS2, SMAD4, STK11* D. The panel does not include genes without a known association with gastric (stomach) cancer by ClinGen. XI. Genetic testing using a hereditary gastric cancer susceptibility panel (81201, 81203, 81292, 81294, 81295, 81297, 81298, 81300, 81317, 81319, 81403, 81404, 81405, 81406, 81408, 81479) is considered **investigational** for all other indications.

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HEREDITARY PANCREATIC CANCER SUSCEPTIBILITY PANELS

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

XII. Genetic testing using a hereditary pancreatic cancer susceptibility panel (81162, 81163, 81201, 81292, 81295, 81298, 81351, 81433, 81479) may be considered **medically necessary** when **ALL** of the following criteria are met:
  A. The member is 18 years or older
  B. The member meets criteria for *BRCA1* and *BRCA2* sequencing and/or deletion/duplication analysis (statement XXV)
  C. The panel includes, at a minimum, sequencing of the following genes: *ATM, BRCA1, BRCA2, CDKN2A, EPCAM, MLH1, MSH2, MSH6, PALB2, STK11, TP53*
  D. The panel does not include genes without a known association with pancreatic cancer by ClinGen.

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

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HEREDITARY POLYPOSIS PANELS

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

XIV. Genetic testing using a hereditary polyposis panel (81201, 81203, 81406, 81479) may be considered **medically necessary** when **ALL** of the following criteria are met:
  A. The member meets criteria for sequencing and/or deletion/duplication analysis for Adenomatous Polyposis conditions (Familial Adenomatous Polyposis Syndrome

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	(FAP)/Attenuated FAP (AFAP) and *MUTYH*-Associated Polyposis Syndrome (MAP) (statement LVI) B. The panel includes, at a minimum, sequencing of the following genes: *APC* and *MUTYH* C. The panel does not include genes without a known association with colon polyposis by ClinGen. XV. Genetic testing using a hereditary polyposis panel (81201, 81203, 81406, 81479) is considered **investigational** for all other indications. back to top **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. XVI. Genetic testing using a hereditary prostate cancer susceptibility panel (81162, 81292, 81295, 81351, 81479,) may be considered **medically necessary** when **ANY** of the following criteria are met: A. The member meets **BOTH** of the following criteria: 1. Is 18 years or older 2. Has a personal history of **any** of the following: a. Metastatic prostate cancer b. High- or very-high risk localized prostate cancer c. Regional (node positive) prostate cancer B. The member has a personal history of prostate cancer and **any** of the following: 1. One or more close relatives with **any** of the following: a. Breast cancer at or under age 50 b. Triple-negative breast cancer at any age c. Colorectal or endometrial cancer at or under age 50 d. Male (sex assigned at birth) breast cancer at any age e. Ovarian cancer at any age f. Exocrine pancreatic cancer at any age g. Metastatic, regional, very-high-risk, or high-risk prostate cancer at any age

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	2. One or more first-degree relatives with prostate cancer at or under age 60 3. Two or more close relatives with **either** of the following: a. Breast cancer at any age b. Prostate cancer at any age 4. Three or more first- or second-degree relatives with a Lynch syndrome related cancer, especially if diagnosed under age 50 5. 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 6. Ashkenazi Jewish ancestry 7. A personal history of breast cancer C. The member meets ALL of the following criteria: 1. The member is affected (does not meet testing criteria above) or is unaffected, with a first-degree blood relative meeting any of the criteria above 2. The panel includes, at a minimum, sequencing of the following genes: *BRCA1, BRCA2* 3. The panel does not include genes without a known association with prostate cancer by ClinGen. XVII. Genetic testing using a hereditary prostate cancer susceptibility panel (81162, 81292, 81295, 81351, 81479, is considered **investigational** for all other indications. XVIII. Hereditary prostate cancer susceptibility panel targeted mRNA sequencing analysis for the interpretation of variants of unknown significance (0133U), when billed in addition, is considered **investigational** because it is typically either considered an existing component of the genetic testing process for quality assurance, or follow up testing without proven utility. back to top **HEREDITARY NEUROENDOCRINE CANCER SUSCEPTIBILITY PANELS**

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	A hereditary neuroendocrine cancer susceptibility panel is one that includes genes that are associated with inherited susceptibility to a neuroendocrine cancer. XIX. Genetic testing using a hereditary neuroendocrine cancer susceptibility panel (81437, 81438) may be considered **medically necessary** when **ANY** of the following criteria are met: A. The member has **at least one** of the following: 1. Adrenocortical carcinoma 2. Paraganglioma/pheochromocytoma 3. Parathyroid adenoma or primary hyperparathyroidism before age 30 4. Multiple parathyroid adenomas 5. Multigland hyperplasia without obvious secondary cause 6. Recurrent primary hyperparathyroidism B. The member meets criteria for *MEN1* sequencing and/or deletion/duplication analysis (statement LXXXI) C. **BOTH** of the following criteria are met: 1. The member meets criteria for *RET* sequencing and/or deletion duplication analysis (statement LXXXV) 2. The panel does not include genes without a known association with a neuroendocrine cancer by ClinGen. XX. Genetic testing using a hereditary neuroendocrine cancer susceptibility panel (81437, 81438) is considered **investigational** for all other indications. ***NOTE:*** If a multigene cancer panel is performed, the appropriate panel code should be used. back to top ***BRCA1* AND *BRCA2* GENE TESTING** ***BRCA1* or *BRCA2* Targeted Variant or Known Familial Variant Analysis** XXI. *BRCA1* (81215) or *BRCA2* (81217) targeted variant or known familial variant analysis for hereditary cancer susceptibility may be

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	considered **medically necessary** when **BOTH** of the following criteria are met: A. The member is 18 years or older B. **One** of the following: 1. The member has a family history of a known *BRCA1* or *BRCA2* pathogenic or likely pathogenic variant 2. A *BRCA1* or *BRCA2* pathogenic or likely pathogenic variant was detected by tumor profiling and germline analysis has not yet been performed. XXII. *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** XXIII. *BRCA1* and *BRCA2* (81212) targeted variant analysis for the 185delAG, 5385insC, 6174delT variants may be considered **medically necessary** when **BOTH** of the following criteria are met: A. The member is 18 years or older B. The member is of Ashkenazi Jewish ancestry (at least one grandparent of Ashkenazi Jewish ancestry). XXIV. *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** XXV. *BRCA1* and *BRCA2* (81162, 81163, 81164, 81165, 81166, 81167, 81216) sequencing and/or deletion/duplication analysis for hereditary breast and/or ovarian cancer susceptibility may be considered **medically necessary** when **ANY** of the following criteria are met: A. **BOTH** of the following criteria are met: 1. The member is 18 years or older 2. The member has a personal history of **any** of the following: a. Male (sex assigned at birth) breast cancer

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	b. Triple-negative breast cancer c. Breast cancer diagnosed at age 50 or younger d. Epithelial ovarian cancer (including fallopian tube cancer or peritoneal cancer) e. Exocrine pancreatic or ampullary cancer f. Metastatic prostate cancer g. High- or very-high-risk group prostate cancer h. Multiple primary breast cancers (diagnosed synchronously or metachronously) B. The member has a personal history of breast cancer **AND** any of the following: 1. Ashkenazi Jewish ancestry 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 b. Male (sex assigned at birth) breast cancer c. Ovarian cancer d. Pancreatic cancer e. Metastatic, or high- or very-high-risk group prostate cancer 3. Three or more total diagnoses of breast cancer and/or prostate cancer (any grade) on the same side of the family including the member with breast cancer C. The member does not have a personal history of a *BRCA1/2*-related cancer, but has a first- or second-degree relative meeting any of the above criteria D. The member has metastatic breast cancer and is being considered for systemic treatment using PARP inhibitors E. The member has high-risk, HER2-negative breast cancer and is being considered for adjuvant treatment with olaparib F. The member's probability of having a *BRCA1* or *BRCA2* pathogenic variant is greater than 5% based on prior probability models (examples: Tyrer-Cuzick, BRCApro, CanRisk). XXVI. *BRCA1* and *BRCA2* (81162, 81163, 81164, 81165, 81166, 81167, 81216) sequencing and/or deletion/duplication analysis for hereditary

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	breast and/or ovarian cancer susceptibility is considered **investigational** for all other indications. XXVII. *BRCA1/BRCA2* mRNA sequencing analysis for the interpretation of variants of unknown significance (0138U), when billed in addition, is considered **investigational** because it is typically either considered an existing component of the genetic testing process for quality assurance or follow up testing without proven utility. back to top *PALB2* GENE TESTING *PALB2* Targeted Variant Analysis XXVIII. *PALB2* targeted variant analysis (81308) for hereditary breast and/or ovarian cancer susceptibility may be considered **medically necessary** when **BOTH** of the following criteria are met: A. The member is 18 years or older B. **One** of the following: 1. The member has a family history of a known pathogenic or likely pathogenic variant in *PALB2* 2. A pathogenic or likely pathogenic variant was detected by tumor profiling in *PALB2,* and germline analysis has not yet been performed. XXIX. *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 XXX. *PALB2* (81307, 81479) sequencing and/or deletion/duplication analysis for hereditary breast and/or ovarian cancer susceptibility may be considered **medically necessary** when **BOTH** of the following criteria are met: A. The member is 18 years or older B. **One** of the following: 1. The member has a personal history of **any** of the following:

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	a. Male (sex assigned at birth) breast cancer b. Triple-negative breast cancer c. Breast cancer diagnosed at age 50 or younger d. Epithelial ovarian cancer (including fallopian tube cancer or peritoneal cancer) e. Exocrine pancreatic or ampullary cancer f. Multiple primary breast cancers (diagnosed synchronously or metachronously 2. The member has a personal history of breast cancer **AND** any of the following: a. Ashkenazi Jewish ancestry b. One or more close relatives with any of the following: i. Female (sex assigned at birth) breast cancer diagnosed at age 50 years or younger ii. Male (sex assigned at birth) breast cancer iii. Ovarian cancer iv. Exocrine pancreatic cancer c. Three or more total diagnoses of breast cancer in the member and/or close relatives 3. The member does not have a personal history of a *PALB2*-related cancer (breast, ovarian or pancreatic), but has a first- or second-degree relative meeting any of the above criteria 4. The member has metastatic breast cancer and is being considered for systemic treatment decisions using PARP inhibitors 5. The member has high-risk, HER2-negative breast cancer and is being considered for adjuvant treatment with olaparib 6. The member's probability of having a *BRCA1* or *BRCA2* pathogenic variant is greater than 5% based on prior probability models (examples: Tyrer-Curzick, BRCApro, CanRisk).

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	XXXI. *PALB2* (81307) sequencing and/or deletion/duplication analysis for hereditary breast and/or ovarian cancer susceptibility is considered **investigational** for all other indications. XXXII. *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. back to top ***ATM* AND/OR *CHEK2* GENE TESTING** ***ATM* or *CHEK2* Targeted Variant Analysis** XXXIII. *ATM* (81479) or *CHEK2* (81479) targeted variant analysis for hereditary breast and/or ovarian cancer susceptibility may be considered **medically necessary** when **BOTH** of the following criteria are met: A. The member is 18 years or older B. **One** of the following: 1. The member has a close relative with a known pathogenic or likely pathogenic variant in *ATM* or *CHEK2* 2. A pathogenic or likely pathogenic variant was detected by tumor profiling in *ATM* or *CHEK2* and germline analysis has not yet been performed. XXXIV. *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** XXXV. *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**.

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	XXXVI. *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. back to top **LYNCH SYNDROME / HEREDITARY NONPOLYPOSIS COLORECTAL CANCER (HNPCC) TESTING** ***MLH1, MSH2, MSH6, PMS2,* or *EPCAM* Targeted Variant Analysis** XXVII. *MLH1* (81293), *MSH2* (81296), *MSH6* (81299), *PMS2* (81318), or *EPCAM* (81479) targeted variant analysis for Lynch syndrome/HNPCC may be considered **medically necessary** when **EITHER** of the following criteria are met: A. The member has a blood relative with a known pathogenic or likely pathogenic variant in *MLH1, MSH2, MSH6, PMS2*, or *EPCAM* B. A pathogenic or likely pathogenic variant was detected by tumor profiling in *MLH1, MSH2, MSH6, PMS2*, or *EPCAM* and germline analysis has not yet been performed. XXVIII. *MLH1* (81293), *MSH2* (81296), *MSH6* (81299), *PMS2* (81318), or *EPCAM* (81479) targeted variant analysis for Lynch syndrome/HNPCC is considered **investigational** for all other indications. ***MLH1, MSH2, MSH6, PMS2,* or *EPCAM* Sequencing and/or Deletion/Duplication Analysis** XXXIX. *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 may be considered **medically necessary** when **ANY** of the following criteria are met: A. The member has a Lynch syndrome-related cancer **and** the tumor shows evidence of mismatch repair (MMR) deficiency

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	(either by microsatellite instability (MSI) or loss of MMR protein expression) B. The member has a diagnosis of a Lynch syndrome-related cancer, **AND any** of the following: 1. Diagnosed before age 50 2. Diagnosed at any age with an additional Lynch syndrome-related cancer 3. Diagnosed at any age with one or more first- or second-degree relatives diagnosed before age 50 with a Lynch syndrome-related cancer 4. Diagnosed at any age with two or more first- or second-degree relatives diagnosed at any age with a Lynch syndrome-related cancer 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 2. One or more first-degree relatives diagnosed with colorectal or endometrial cancer and an additional Lynch syndrome-related cancer 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 4. Three or more first- or second-degree relatives on the same side of the family diagnosed with a Lynch syndrome-related cancer D. The member has a 5% or greater risk of Lynch syndrome on one of the following variant prediction models: MMRpro, PREMM5, MMRpredict E. The member has a personal history of colorectal and/or endometrial cancer with a PREMM5 score of 2.5% or greater. XL. *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.

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	XLI. *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. back to top ***BAP1*-TUMOR PREDISPOSITION SYNDROME** ***BAP1* Targeted Variant Analysis** XLII. *BAP1* targeted variant analysis (81403) for *BAP1*-tumor predisposition syndrome may be considered **medically necessary** when **EITHER** of the following criteria are met: A. The member has a close relative with a known pathogenic or likely pathogenic variant in *BAP1* B. A pathogenic or likely pathogenic variant in *BAP1* was identified on tumor profiling and germline analysis has not yet been performed. XLIII. *BAP1* targeted variant analysis (81403) for *BAP1*-tumor predisposition syndrome is considered **investigational** for all other indications. ***BAP1* Sequencing and/or Deletion/Duplication Analysis** XLIV. *BAP1* sequencing and/or deletion/duplication analysis (81479) for *BAP1*-tumor predisposition syndrome may be considered **medically necessary** when: A. The member has a personal history of **ANY** of the following: 1. **Two or more** of the following: a. *BAP1*-inactivated melanocytic tumors (aka atypical spitz tumor) b. Uveal melanoma c. Malignant mesothelioma d. Renal cell carcinoma e. Hepatocellular carcinoma

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	f. Cholangiocarcinoma g. Meningioma 2. **One** of the tumors/cancers listed in the criteria A.1., **AND EITHER** of the following: a. A cutaneous melanoma b. A basal cell carcinoma 3. One or more of the tumors/cancers listed in the criteria A.1., **AND** a. A first- or second-degree relative with any of the tumors/cancers listed in the criteria A.1. XLV. *BAP1* sequencing and/or deletion/duplication analysis (81479) for *BAP1*-tumor predisposition syndrome is considered **investigational** for all other indications. back to top **BIRT-HOGG-DUBE SYNDROME (BHDS)** ***FLCN* Targeted Variant Analysis** XLVI. *FLCN* targeted variant analysis (81479) for Birt-Hogg-Dube syndrome (BHDS) may be considered **medically necessary** when **EITHER** of the following criteria are met: A. The member has a first- or second-degree relative with a known pathogenic or likely pathogenic variant in *FLCN* B. A pathogenic or likely pathogenic variant in *FLCN* was identified on tumor profiling and germline analysis has not yet been performed. XLVII. *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** XLVIII. *FLCN* sequencing and/or deletion/duplication analysis (81479) for Birt-Hogg-Dube syndrome (BHDS) may be considered **medically necessary** when:

POLICY STATEMENT	
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	A. The member has a personal history of **any** of the following: 1. 5 or more fibrofolliculomas/trichodiscomas with at least one confirmed histologically 2. Multiple lung cysts with no apparent cause 3. Renal cancer diagnosed before 50 years of age 4. Multifocal or bilateral renal cancer 5. Renal cancer of mixed chromophobe and oncocytic, clear cell, or papillary histology 6. Oncocytoma 7. Angiomyolipoma 8. A first-degree relative with BHDS XLIX. *FLCN* sequencing and/or deletion/duplication analysis (81479) for Birt-Hogg-Dube syndrome (BHDS) is considered **investigational** for all other indications. back to top **COWDEN SYNDROME (CS)/PTEN HAMARTOMA TUMOR SYNDROME (PHTS)** ***PTEN* Targeted Variant Analysis** L. *PTEN* targeted variant analysis (81322) for Cowden syndrome (CS)/*PTEN* hamartoma tumor syndrome (PHTS) may be considered **medically necessary** when **EITHER** of the following criteria are met: A. The member has a blood relative with a known pathogenic or likely pathogenic variant in *PTEN* B. A pathogenic or likely pathogenic variant in *PTEN* was identified on tumor profiling and germline analysis has not yet been performed. LI. *PTEN* targeted variant analysis (81322) for Cowden syndrome (CS)/*PTEN* hamartoma tumor syndrome (PHTS) is considered **investigational** for all other indications.

POLICY STATEMENT	
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	***PTEN* Sequencing and/or Deletion/Duplication Analysis** LII. *PTEN* sequencing and/or deletion/duplication analysis (81321, 81323) for Cowden syndrome (CS)/*PTEN* hamartoma tumor syndrome (PHTS) may be considered **medically necessary** when **ANY** of the following criteria are met: A. The member has a personal history of **any** of the following: 1. Bannayan Riley-Ruvalcaba syndrome (BRRS) 2. Adult Lhermitte-Duclos disease (LDD) (defined as the presence of a cerebellar dysplastic gangliocytoma) 3. Autism-spectrum disorder and macrocephaly 4. At least 2 biopsy-proven trichilemmomas B. The member meets clinical criteria for CS/PHTS as shown in ANY of the following criteria: 1. Macrocephaly (greater than or equal to 97 percentile) 2. Lhermitte-Duclos disease (LDD) (defined as the presence of a cerebellar dysplastic gangliocytoma) 3. Gastrointestinal hamartomas or ganglioneuromas, **AND at least two** of the following: a. Breast Cancer b. Endometrial Cancer c. Thyroid Cancer (follicular) d. Macular pigmentation of the glans penis e. Mucocutaneous lesions (One biopsy-proven trichilemmoma; multiple palmoplantar keratoses; multifocal or extensive oral mucosal papillomatosis; multiple cutaneous facial papules) C. The member has **at least two** of the following: 1. Breast Cancer 2. Endometrial Cancer 3. Thyroid Cancer (follicular) 4. Multiple gastrointestinal hamartomas or ganglioneuromas 5. Macrocephaly (greater than or equal to 97 percentile) 6. Macular pigmentation of the glans penis 7. Mucocutaneous lesions (One biopsy-proven trichilemmoma; multiple palmoplantar keratoses; multifocal or extensive oral mucosal papillomatosis;

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	multiple cutaneous facial papules), **AND at least three** of the following: a. Autism Spectrum Disorder b. Colon Cancer c. Esophageal glycogenic acanthosis (3 or more) d. Lipomas e. Intellectual disability (i.e., IQ less than or equal to 75) f. Thyroid cancer (papillary or follicular variant of papillary thyroid cancer) g. Thyroid structural lesions (such as adenoma, multinodular goiter) h. Renal cell carcinoma i. Single GI hamartoma or ganglioneuroma j. Testicular lipomatosis k. Vascular anomalies (including multiple intracranial developmental venous anomalies) D. The member has macrocephaly, **AND ANY** of the following: 1. Breast Cancer 2. Endometrial Cancer 3. Thyroid Cancer (follicular) 4. Multiple gastrointestinal hamartomas or ganglioneuromas 5. Macrocephaly (greater than or equal to 97 percentile) 6. Macular pigmentation of the glans penis 7. Mucocutaneous lesions (One biopsy-proven trichilemmoma; multiple palmoplantar keratoses; multifocal or extensive oral mucosal papillomatosis; multiple cutaneous facial papules) E. The member has **at least three** of the following: 1. Breast Cancer, 2. Endometrial Cancer 3. Thyroid Cancer (follicular) 4. Multiple gastrointestinal hamartomas or ganglioneuromas 5. Macular pigmentation of the glans penis 6. Mucocutaneous lesions (One biopsy-proven trichilemmoma; multiple palmoplantar keratoses;

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	multifocal or extensive oral mucosal papillomatosis; multiple cutaneous facial papules) 7. The member has a close relative with a clinical diagnosis of CS/PHTS or BRRS for whom testing has not been performed F. The member has **any** of the following: 1. Breast Cancer 2. Endometrial Cancer 3. Thyroid Cancer (follicular) 4. Multiple gastrointestinal hamartomas or ganglioneuromas 5. Macrocephaly (greater than or equal to 97 percentile) 6. Macular pigmentation of the glans penis 7. Mucocutaneous lesions (One biopsy-proven trichilemmoma; multiple palmoplantar keratoses; multifocal or extensive oral mucosal papillomatosis; multiple cutaneous facial papules) 8. **At least three** of the following: a. Autism Spectrum Disorder b. Colon Cancer c. Esophageal glycogenic acanthosis (3 or more) d. Lipomas e. Intellectual disability (i.e., IQ less than or equal to 75) f. Thyroid cancer (papillary or follicular variant of papillary thyroid cancer) g. Thyroid structural lesions (such as adenoma, multinodular goiter) h. Renal cell carcinoma i. Single GI hamartoma or ganglioneuroma j. Testicular lipomatosis k. Vascular anomalies (including multiple intracranial developmental venous anomalies) G. The member has **at least four** of the following: 1. Autism Spectrum Disorder 2. Colon Cancer 3. Esophageal glycogenic acanthosis (3 or more) 4. Lipomas

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	5. Intellectual disability (i.e., IQ less than or equal to 75) 6. Thyroid cancer (papillary or follicular variant of papillary thyroid cancer) 7. Thyroid structural lesions (such as adenoma, multinodular goiter) 8. Renal cell carcinoma 9. Single GI hamartoma or ganglioneuroma 10. Testicular lipomatosis 11. Vascular anomalies (including multiple intracranial developmental venous anomalies) H. The member has a close relative with a clinical diagnosis of CS/PHTS or BRRS for whom testing has not been performed, **AND EITHER** of the following: 1. The member has **at least one** of the following: a. Breast Cancer b. Endometrial Cancer c. Thyroid Cancer (follicular) d. Multiple gastrointestinal hamartomas or ganglioneuromas e. Macrocephaly (greater than or equal to 97 percentile) f. Macular pigmentation of the glans penis g. Mucocutaneous lesions (One biopsy-proven trichilemmoma; multiple palmoplantar keratoses; multifocal or extensive oral mucosal papillomatosis; multiple cutaneous facial papules) 2. **At least two** of the following: a. Autism Spectrum Disorder b. Colon Cancer c. Esophageal glycogenic acanthosis (3 or more) d. Lipomas e. Intellectual disability (i.e., IQ less than or equal to 75) f. Thyroid cancer (papillary or follicular variant of papillary thyroid cancer) g. Thyroid structural lesions (such as adenoma, multinodular goiter) h. Renal cell carcinoma

POLICY STATEMENT	
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	i. Single GI hamartoma or ganglioneuroma j. Testicular lipomatosis k. Vascular anomalies (including multiple intracranial developmental venous anomalies). LIII. *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. back to top **ADENOMATOUS POLYPOSIS CONDITIONS (Familial Adenomatous Polyposis Syndrome (FAP)/Attenuated FAP (AFAP) AND *MUTYH*-Associated Polyposis Syndrome (MAP)** ***APC OR MUTYH* Targeted Variant Analysis** LIV. *APC* (81202) or *MUTYH* targeted variant analysis (81401, 81403) for adenomatous polyposis testing may be considered **medically necessary** when **EITHER** of the following criteria are met: A. The member has a family history of a known pathogenic or likely pathogenic variant in *APC* or *MUTYH* B. An *APC* or *MUTYH* pathogenic or likely pathogenic variant was detected by tumor profiling and germline analysis has not yet been performed. LV. *APC* (81202) 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** LVI. *APC* sequencing and/or deletion/duplication analysis (81201, 81203) and/or *MUTYH* sequencing and/or deletion/duplication analysis (81406, 81479) for adenomatous polyposis conditions may be considered **medically necessary** when: A. The member has a history of **any** of the following: 1. 10 or more cumulative adenomas

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2. Congenital hypertrophy of the retinal pigment epithelium (CHRPE)
3. Desmoid tumor
4. Hepatoblastoma
5. Cribriform-morular variant of papillary thyroid cancer
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
  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
7. Duodenal cancer
8. Duodenal adenomas.

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

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

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FAMILIAL ATYPICAL MULTIPLE MOLE MELANOMA (FAMMM) SYNDROME
<i>CDKN2A</i> Targeted Variant Analysis
LIX. <i>CDKN2A</i> targeted variant analysis (81479) for familial atypical multiple mole melanoma (FAMMM) syndrome, also known as melanoma-pancreatic cancer syndrome, may be considered medically necessary when BOTH of the following criteria are met:
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	A. The member is 18 years or older B. **One** of the following: 1. The member has a close relative with a known pathogenic or likely pathogenic variant in *CDKN2A* 2. A *CDKN2A* pathogenic or likely pathogenic variant was detected by tumor profiling and germline analysis has not yet been performed. LX. *CDKN2A* targeted variant analysis (81479) for familial cutaneous malignant melanoma is considered **investigational** for all other indications. ***CDKN2A* Sequencing and/or Deletion/Duplication Analysis** LXI. *CDKN2A* sequencing and/or deletion/duplication analysis (81404, 81479) for familial atypical multiple mole melanoma (FAMMM) syndrome, also known as melanoma-pancreatic cancer syndrome, may be considered **medically necessary** when **ANY** of the following criteria are met: A. The member has had 3 or more invasive cutaneous melanomas B. The member has had pancreatic adenocarcinoma C. The member has had at least one cutaneous melanoma, **AND** 1. The member has at least two close relatives with pancreatic cancer or cutaneous melanoma on the same side of the family. LXII. *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. back to top **HEREDITARY DIFFUSE GASTRIC CANCER (AKA, SIGNET RING CELL GASTRIC CANCER):** ***CDH1* Targeted Variant Analysis**

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	LXIII. *CDH1* targeted variant analysis (81479) for Hereditary Diffuse Gastric Cancer (aka, Signet Ring Cell Gastric Cancer) may be considered **medically necessary** when **BOTH** of the following criteria are met: A. The member is 18 years or older B. **One** of the following: 1. The member has a blood relative with a known pathogenic or likely pathogenic variant in *CDH1* 2. A *CDH1* pathogenic or likely pathogenic variant was detected by tumor profiling and germline analysis has not yet been performed. LXIV. *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** LXV. *CDH1* sequencing and/or deletion/duplication analysis for Hereditary Diffuse Gastric Cancer (aka, Signet Ring Cell Gastric Cancer) (81406, 81479) may be considered **medically necessary** when **BOTH** of the following criteria are met: A. The member is 18 years or older B. The member meets **at least one** of the following criteria: 1. Diffuse gastric cancer diagnosed before age 50 years 2. Diffuse gastric cancer diagnosed at any age in a member with Maori ancestry 3. Diffuse gastric cancer diagnosed at any age in a member with a personal or family history of cleft lip/cleft palate 4. Bilateral lobular breast cancer diagnosed before age 70 years 5. Personal or family history of diffuse gastric cancer and lobular breast cancer, one diagnosed before age 70 years 6. Two cases of gastric cancer in the family, one of which is a confirmed case of diffuse gastric cancer, diagnosed at any age 7. Two cases of lobular breast cancer in family members before 50 years of age.

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	LXVI. *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. back to top **JUVENILE POLYPOSIS SYNDROME (JPS)** ***SMAD4* or *BMPR1A* Targeted Variant Analysis** LXVII. *SMAD4* and/or *BMPR1A* targeted variant analysis (81403) for juvenile polyposis syndrome (JPS) may be considered **medically necessary** when **EITHER** of the following criteria are met: A. The member has a blood relative with a known pathogenic or likely pathogenic variant in *SMAD4* and/or *BMPR1A* B. A *SMAD4* and/or *BMPR1A* pathogenic or likely pathogenic variant was detected by tumor profiling and germline analysis has not yet been performed. LXVIII. *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** LXIX. *SMAD4* and/or *BMPR1A* sequencing and/or deletion/duplication analysis (81405, 81406, 81479) for juvenile polyposis syndrome (JPS) may be considered **medically necessary** when **ANY** of the following criteria are met: A. The member has 5 or more juvenile polyps in the colon B. The member has multiple juvenile polyps throughout the gastrointestinal tract C. The member has juvenile polyps (any number) and a family history of JPS.

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<tr><td></td><td>LXX. <i>SMAD4</i> and/or <i>BMPR1A</i> sequencing and/or deletion/duplication analysis (81405, 81406, 81479) for juvenile polyposis syndrome (JPS) is considered investigational for all other indications.

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HEREDITARY LEIOMYOMATOSIS AND RENAL CELL CANCER (HLRCC)
<i>FH</i> Targeted Variant Analysis
LXXI. <i>FH</i> targeted variant analysis (81403) for hereditary leiomyomatosis and renal cell cancer (HLRCC) may be considered medically necessary when BOTH of the following criteria are met:
A. The member is 18 years or older
B. One of the following:
1. The member has a first- or second-degree relative with a known pathogenic or likely pathogenic variant in <i>FH</i>
2. A <i>FH</i> pathogenic or likely pathogenic variant was detected by tumor profiling and germline analysis has not yet been performed.

LXXII. <i>FH</i> targeted variant analysis (81403) for hereditary leiomyomatosis and renal cell cancer (HLRCC) is considered investigational for all other indications.

<i>FH</i> Sequencing and/or Deletion/Duplication Analysis
LXXIII. <i>FH</i> sequencing and/or deletion/duplication analysis (81405, 81479) for hereditary leiomyomatosis and renal cell cancer (HLRCC) may be considered medically necessary when BOTH of the following criteria are met:
A. The member is 18 years or older
B. The member has at least one of the following:
1. Cutaneous leiomyomata
2. Uterine leiomyomata (uterine fibroids)
3. Renal cell carcinoma.</td></tr>
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	LXXIV. *FH* sequencing and/or deletion/duplication analysis (81405, 81479) for hereditary leiomyomatosis and renal cell carcinoma (HLRCC) is considered **investigational** for all other indications. back to top **LI-FRAUMENI SYNDROME (LFS)** ***TP53* Targeted Variant Analysis** LXXV. *TP53* targeted variant analysis (81352) for Li-Fraumeni syndrome (LFS) may be considered **medically necessary** when **EITHER** of the following criteria are met: A. The member has a blood relative with a known pathogenic or likely pathogenic variant in *TP53* B. A *TP53* pathogenic or likely pathogenic variant was detected by tumor profiling and germline analysis has not yet been performed. XXVI. *TP53* targeted variant analysis (81352) for Li-Fraumeni syndrome (LFS) is considered **investigational** for all other indications. ***TP53* Sequencing and/or Deletion/Duplication Analysis** XXVII. *TP53* sequencing and/or deletion/duplication analysis (81351, 81479) for Li-Fraumeni syndrome (LFS) may be considered **medically necessary** when **ANY** of the following criteria are met: A. The member was diagnosed with breast cancer before 31 years of age B. The member has a personal or family history of pediatric hypodiploid acute lymphoblastic leukemia C. The member was diagnosed with a sarcoma before 45 years of age, **AND BOTH** of the following: 1. The member has a first-degree relative diagnosed with any cancer before 45 years of age 2. **At least one** of the following: a. The member has an additional first- or second-degree relative diagnosed with any cancer before 45 years of age

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	b. The member has an additional first- or second-degree relative diagnosed with sarcoma at any age D. The member was diagnosed with **any** of the following at any age: 1. Adrenocortical carcinoma 2. Choroid plexus carcinoma 3. Rhabdomyosarcoma of embryonal anaplastic subtype 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 2. Osteosarcoma 3. Central nervous system tumor 4. Breast cancer 5. Adrenocortical carcinoma, **AND ANY** of the following: a. The member has had a second tumor from the LFS tumor spectrum (except breast cancer if the initial cancer was breast cancer) 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) c. The member has a first- or second-degree relative with a history of multiple primary tumors at any age. *XXVIII.* TP53 sequencing and/or deletion/duplication analysis (81351, 81479) for Li-Fraumeni syndrome (LFS) is considered **investigational** for all other indications. back to top **MULTIPLE ENDOCRINE NEOPLASIA TYPE 1 (MEN1)** ***MEN1* Targeted Variant Analysis** LXXIX. *MEN1* targeted variant analysis (81479) for multiple endocrine neoplasia type 1 (MEN1) may be considered **medically necessary** when **EITHER** of the following criteria are met:

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	A. The member has a close relative with a known pathogenic or likely pathogenic variant in *MEN1* B. An *MEN1* pathogenic or likely pathogenic variant was detected by tumor profiling and germline analysis has not yet been performed. LXXX. *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** LXXXI. *MEN1* sequencing and/or deletion/duplication analysis (81404, 81405) for multiple endocrine neoplasia type 1 (MEN1) may be considered **medically necessary** when **EITHER** of the following criteria are met: A. The member has a personal history of **at least two** of the following: 1. Duodenal/pancreatic neuroendocrine tumor 2. Primary hyperparathyroidism 3. Pituitary adenoma 4. Foregut (bronchial, thymic, or gastric) carcinoid B. The member has a personal history of one of the above, **AND** 1. The member has a close relative with at least one of the above. XXXII. *MEN1* sequencing and/or deletion/duplication analysis (81404, 81405) for multiple endocrine neoplasia type 1 (MEN1) is considered **investigational** for all other indications. back to top **MULTIPLE ENDOCRINE NEOPLASIA TYPE 2 (MEN2)** ***RET* Targeted Variant Analysis** XXXIII. *RET* targeted variant analysis (81404) for multiple endocrine neoplasia type 2 (MEN2) may be considered **medically necessary** when **EITHER** of the following criteria are met:

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	A. The member has a close relative with a known pathogenic or likely pathogenic variant in *RET* B. A *RET* pathogenic or likely pathogenic variant was detected by tumor profiling and germline analysis has not yet been performed. XXXIV. *RET* targeted variant analysis (81404) for multiple endocrine neoplasia type 2 (MEN2) is considered **investigational** for all other indications. ***RET* Sequencing and/or Deletion/Duplication Analysis** XXXV. *RET* sequencing and/or deletion/duplication analysis (81406, 81479, S3840) for multiple endocrine neoplasia type 2 (MEN2) may be considered **medically necessary** when **ANY** of the following criteria are met: A. The member has a diagnosis of medullary thyroid cancer B. The member has an adrenal pheochromocytoma C. The member has parathyroid adenoma or hyperplasia D. The member has a first-degree relative that meets at least one of the above criteria and has not previously undergone *RET* sequencing and/or deletion duplication analysis. XXXVI. *RET* sequencing and/or deletion/duplication analysis (81406, 81479, S3840) for multiple endocrine neoplasia type 2 (MEN2) is considered **investigational** for all other indications. back to top **NEVOID BASAL CELL CARCINOMA SYNDROME (NBCCS) (aka Gorlin syndrome)** ***PTCH1* or *SUFU* Targeted Variant Analysis** XXVII. *PTCH1* or *SUFU* targeted variant analysis (81479) for nevoid basal cell carcinoma syndrome (NBCCS), also known as Gorlin syndrome, may be considered **medically necessary** when **EITHER** of the following criteria are met:

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	A. The member has a close relative with a known pathogenic or likely pathogenic variant in *PTCH1* or *SUFU* B. A *PTCH1* or *SUFU* pathogenic or likely pathogenic variant was detected by tumor profiling and germline analysis has not yet been performed. XXVIII. *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** XXXIX. *PTCH1* and *SUFU* sequencing and/or deletion duplication analysis (81479) for nevoid basal cell carcinoma syndrome (NBCCS), also known as Gorlin syndrome, may be considered **medically necessary** when **EITHER** of the following criteria are met: A. The member has **BOTH** of the following: 1. A personal history of **at least two** of the following: a. Lamellar calcification of the falx b. Jaw keratocyst c. Palmar/plantar pits (2 or more) d. Multiple basal cell carcinomas (more than 5 in lifetime) or a basal cell carcinoma diagnosed before 30 years of age e. A first-degree relative with NBCCS 2. **At least one** of the following: a. Childhood medulloblastoma b. Lympho-mesenteric or pleural cysts c. Macrocephaly (OFC greater than 97th centile) d. Cleft lip/palate e. Vertebral/rib anomalies (bifid/splayed/extra ribs; bifid vertebrae) f. Pre- or post-axial polydactyly g. Ovarian fibromas h. Cardiac fibromas

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	i. Ocular anomalies (examples: cataract, pigmentary changes of the retinal epithelium, developmental defects) B. The member has **BOTH** of the following: 1. A personal history of **at least one** of the following: a. Lamellar calcification of the falx b. Jaw keratocyst c. Palmar/plantar pits (2 or more) d. Multiple basal cell carcinomas (more than 5 in lifetime) or a basal cell carcinoma diagnosed before 30 years of age e. A first-degree relative with NBCCS 2. **At least three** of the following: a. Childhood medulloblastoma b. Lympho-mesenteric or pleural cysts c. Macrocephaly (OFC greater than 97th centile) d. Cleft lip/palate e. Vertebral/rib anomalies (bifid/splayed/extra ribs; bifid vertebrae) f. Pre- or post-axial polydactyly g. Ovarian fibromas h. Cardiac fibromas i. Ocular anomalies (examples: cataract, pigmentary changes of the retinal epithelium, developmental defects). XC. *PTCH1* and *SUFU* sequencing and/or deletion/duplication analysis (81479) is considered **investigational** for all other indications. back to top **HEREDITARY PARAGANGLIOMA/PHEOCHROMOCYTOMA SYNDROME (PGL/PCC)** ***MAX, SDHA, SDHAF2, SDHB, SDHC, SDHD*, or *TMEM127* Targeted Variant Analysis**

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	XCI. *MAX*, *SDHA*, *SDHAF2*, *SDHB*, *SDHC*, *SDHD*, or *TMEM127* targeted variant analysis (81403) for hereditary paraganglioma/pheochromocytoma syndrome (PGL/PCC) may be considered **medically necessary** when **EITHER** of the following criteria are met: A. The member has a close relative with a known pathogenic or likely pathogenic variant in *MAX*, *SDHA*, *SDHAF2*, *SDHB*, *SDHC*, *SDHD*, or *TMEM127* B. A *MAX*, *SDHA*, *SDHAF2*, *SDHB*, *SDHC*, *SDHD*, or *TMEM127* pathogenic or likely pathogenic variant was detected by tumor profiling and germline analysis has not yet been performed. XCII. *MAX*, *SDHA*, *SDHAF2*, *SDHB*, *SDHC*, *SDHD*, or *TMEM127* targeted variant analysis (81403) for hereditary paraganglioma/pheochromocytoma syndrome (PGL/PCC) is considered **investigational** for all other indications. ***MAX*, *SDHA*, *SDHAF2*, *SDHB*, *SDHC*, *SDHD*, and *TMEM127* Sequencing and Deletion Duplication Analysis** XCIII. *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) may be considered **medically necessary** when **EITHER** of the following criteria are met: A. The member has a diagnosis of **one or more** of the following: 1. Pheochromocytoma 2. Paraganglioma 3. Clear cell renal cell cancer 4. Gastrointestinal stromal tumor (GIST) 5. Pulmonary chondromas B. The member has a close relative with paraganglioma or pheochromocytoma. XCIV. *MAX*, *SDHA*, *SDHAF2*, *SDHB*, *SDHC*, *SDHD*, and *TMEM127* sequencing and/or deletion/duplication (81404, 81405, 81406, 81479)

POLICY STATEMENT	
BEFORE	AFTER Blue font: Verbiage Changes/Additions
	for hereditary paraganglioma/pheochromocytoma syndrome (PGL/PCC) is considered **investigational** for all other indications. back to top **PEUTZ-JEGHERS SYNDROME (PJS)** ***STK11* Targeted Variant Analysis** XCV. *STK11* targeted variant analysis (81479) for Peutz-Jeghers syndrome may be considered **medically necessary** when **EITHER** of the following criteria are met: A. The member has a blood relative with a known pathogenic or likely pathogenic variant in *STK11* B. An *STK11* pathogenic or likely pathogenic variant was detected by tumor profiling and germline analysis has not yet been performed. XCVI. *STK11* targeted variant analysis (81479) for Peutz-Jeghers syndrome is considered **investigational** for all other indications. ***STK11* Sequencing and/or Deletion/Duplication Analysis** XCVII. *STK11* sequencing and/or deletion/duplication analysis (81404, 81405) for Peutz-Jeghers syndrome (PJS) may be considered **medically necessary** when: A. The member has a clinical diagnosis of Peutz-Jeghers syndrome based on the presence of **any two** of the following: 1. At least two histologically confirmed Peutz-Jeghers-type hamartomatous polyps of the GI tract 2. Mucocutaneous pigmentation of the mouth, lips, nose, eyes, genitalia, or fingers 3. A close relative with PJS. XCVIII. *STK11* sequencing and/or deletion/duplication analysis (81404, 81405) for Peutz-Jeghers syndrome is considered **investigational** for all other indications. back to top

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	RETINOBLASTOMA ***RB1* Targeted Variant Analysis** XCIX. *RB1* targeted variant analysis (81403) for retinoblastoma may be considered **medically necessary** when **EITHER** of the following criteria are met: A. The member has a close relative with a known pathogenic or likely pathogenic variant in *RB1* B. An *RB1* pathogenic or likely pathogenic variant was detected by tumor profiling and germline analysis has not yet been performed. C. *RB1* targeted variant analysis (81403) for retinoblastoma is considered **investigational** for all other indications. ***RB1* Sequencing and/or Deletion/Duplication Analysis** CI. *RB1* sequencing and/or deletion/duplication analysis (81479, S3841) for retinoblastoma may be considered **medically necessary** when **EITHER** of the following criteria are met: A. The member has a diagnosis of retinoblastoma in one or both eyes B. The member has a close relative with retinoblastoma in one or both eyes. CII. *RB1* sequencing and/or deletion/duplication analysis (81479, S3841) for retinoblastoma is considered **investigational** for all other indications. back to top VON HIPPEL-LINDAU SYNDROME (VHL) ***VHL* Targeted Variant Analysis** CIII. *VHL* targeted variant analysis (81403) for Von Hippel-Lindau syndrome may be considered **medically necessary** when **EITHER** of the following criteria are met:

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	A. The member has a first- or second-degree relative with a known pathogenic or likely pathogenic variant in *VHL* B. A *VHL* pathogenic or likely pathogenic variant was detected by tumor profiling and germline analysis has not yet been performed. CIV. *VHL* targeted variant analysis (81403) for Von Hippel-Lindau syndrome is considered **investigational** for all other indications. ***VHL* Sequencing and/or Deletion/Duplication Analysis** CV. *VHL* sequencing and/or deletion/duplication analysis (81403, 81404, S3842) for Von Hippel-Lindau syndrome may be considered **medically necessary** when: A. The member has a diagnosis of **one or more** of the following: 1. Hemangioblastoma of the retina, spine, or brain 2. Clear cell renal cell carcinoma diagnosed before age 40 years 3. Multiple and/or bilateral clear cell renal cell carcinoma diagnosed at any age 4. Pheochromocytoma or paraganglioma (in abdomen, thorax, or neck) 5. Retinal angiomas 6. Endolymphatic sac tumor 7. Epididymal or adnexal papillary cystadenoma 8. Pancreatic serous cystadenoma 9. Pancreatic neuroendocrine tumors 10. Multiple renal, pancreatic or hepatic cysts. CVI. *VHL* sequencing and/or deletion/duplication analysis (81403, 81404, S3842) for Von Hippel-Lindau syndrome is considered **investigational** for all other indications. back to top