Clinical Policy: Genetic Testing Hereditary Cancer Susceptibility

Reference Number: LA.CP.MP.225c
Date of Last Revision: 2/23

Coding Implications
Revision Log

See Important Reminder at the end of this policy for important regulatory and legal information.

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 more limited number of genes associated with hereditary susceptibility to one specific type of cancer (e.g., breast cancer panel), or a pan-cancer hereditary cancer susceptibility panel (i.e., a panel that tests for many genes associated with hereditary cancer susceptibility at the same time).

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.

Genetic testing for a particular disease should generally be performed once per lifetime; however, there are rare instances in which testing may be performed more than once in a lifetime (e.g., previous testing methodology is inaccurate, or a new discovery has added significant relevant mutations for a disease).

For members who are 20 years or younger, LHCC will review any tests that are that are excluded from the LDH fee schedule on a case-by-case basis for medical necessity*

For members who are 21 years old and older, coverage for testing is subject to review for inclusion of the requested testing panel(s) on the most current LDH fee schedule by LHCC.

All genetic testing requires a prior authorization. Failure to submit an authorization timely may result in a denial or partial approval of requested services.

Genetic Counseling and Testing Genetic Counseling
Counseling is required before and after all genetic testing. Counseling, at a minimum, must

consist of the following and be documented in the beneficiary's medical record:
• Obtaining a structured family genetic history;
• Genetic risk assessment; and
• Counseling of the beneficiary and family about diagnosis, prognosis, and treatment.

When performed by licensed genetic counselors, services are reimbursed using the procedure code specific to genetic counseling. Reimbursement for this service is "incident to" the services of a supervising physician and is limited to no more than 90 minutes on a single day of service.

When performed by providers other than licensed genetic counselors, an applicable evaluation and management code must be used

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

CPT® Codes	Example Tests (Labs)	Criteria Section	Common ICD Codes
*81432,*81433, *81435, *81436	MyRisk (Myriad) VistaSeq (LabCorp) Comprehensive Common Cancer Panel (GeneDx) Common Hereditary Cancer Panel (Invitae) Riscover - Comprehensive (Progenity) Breast & Gyn Cancer Panel (Invitae	Pan-Cancer Hereditary Cancer Susceptibility Panels	C15-26, C50-58 Z17, Z80, Z83, Z84, Z85, Z86
*0104U	CancerNext (Ambry Genetics)	Pan-Cancer Hereditary Cancer Susceptibility Panels	C15-26, C50-58 Z17, Z80, Z83, Z84, Z85, Z86
*0103U	OvaNext (Ambry Genetics)	Pan-Cancer Hereditary Cancer Susceptibility Panels	C15-26, C50-58 Z17, Z80, Z83, Z84, Z85, Z86
*0132U	RNAinsight for OvaNext (Ambry Genetics)	Pan-Cancer Hereditary Cancer Susceptibility Panels	C15-26, C50-58 Z17, Z80, Z83, Z84, Z85, Z86

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CPT® Codes	Example Tests (Labs)	Criteria Section	Common ICD Codes
*0134U	RNAinsight for CancerNext (Ambry Genetics)	Pan-Cancer Hereditary Cancer Susceptibility Panels	C15-26, C50-58 Z17, Z80, Z83, Z84, Z85, Z86
*0135U	RNAinsight for GYNPlus (Ambry Genetics)	Pan-Cancer Hereditary Cancer Susceptibility Panels	C15-26, C50-58 Z17, Z80, Z83, Z84, Z85, Z86
81162,81163, 81164,81165, 81166,81167, 81216, *81432, *81433	Breast Cancer Panel (LabCorp) Breast Cancer Panel (Invitae) Breast Cancer STAT NGS Panel (Sequencing & Deletion/Duplication) (Invitae) Breast Cancer - Comprehensive Risk Panel (PreventionGenetics) Breast Cancer High Risk Panel (GeneDx)	Hereditary Breast Cancer Susceptibility Panels	C50, Z80.3, Z83, Z84, Z85, Z86
*0102U	BreastNext (Ambry Genetics)	Hereditary Breast Cancer Susceptibility Panels	C50, Z80.3, Z83, Z84, Z85, Z86
*0129U	BRCAplus (Ambry Genetics)	Hereditary Breast Cancer Susceptibility Panels	C50, Z80.3, Z83, Z84, Z85, Z86
*0131U	RNAinsight for BreastNext (Ambry Genetics)	Hereditary Breast Cancer Susceptibility Panels	C50, Z80.3, Z83, Z84, Z85, Z86
*81435, *81436	Colorectal Cancer Panel (PreventionGenetics) VistaSeq Colorectal Cancer Panel (LabCorp) Colorectal Cancer Guidelines-based Panel (Invitae) Riscover - Lynch Syndrome	Hereditary Colorectal Cancer Susceptibility Panels	C15-26, Z23, Z80, Z83, Z84, Z85, Z86

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CPT® Codes	Example Tests (Labs)	Criteria Section	Common ICD Codes
	(Progenity) Colaris (Myriad		
*0101U	ColoNext (Ambry Genetics)	Hereditary Colorectal Cancer Susceptibility Panels	C15-26, Z23, Z80, Z83, Z84, Z85, Z86
*0130U	RNAinsight for ColoNext (Ambry Genetics)	Hereditary Colorectal Cancer Susceptibility Panels	C15-26, Z23, Z80, Z83, Z84, Z85, Z86
81292,81294, 81295,81297, 81298,81300, 81317,81319, *81403,*81406, 81479	Invitae Gastric Cancer Panel (Invitae) Gastric Cancer Panel (Fulgent Genetics)	Hereditary Gastric Cancer Susceptibility Panels	C16, Z80, Z85, Z86
81162,81163, 81164, 1165, 81166,81167, 81216,81292, 81294,81295, 81297,81298, 81300,81307, 81317, 1319, *81404,*81405, 81479	Pancreatic Cancer Panel (GeneDx) Invitae Pancreatic Cancer Panel (Invitae) Pancreatic Cancer Panel (PreventionGenetics) PancNext (Ambry Genetics)	Hereditary Pancreatic Cancer Susceptibility Panels	C25, Z80, Z84, Z85, Z86
81201,81203, *81406,81479, *S3833	Hereditary Polyposis Panel (PreventionGenetics) Familial Adenomatous Polyposis Panel (ARUP)	Hereditary Polyposis Panels	D12, K63.5, Z80, Z84, Z85, Z86
81162, 1163, 81164,81165, 81166,81167, 81216,81292, 81294,81295, 81297,81298, 81300,81317, 81319	Prostate Cancer Panel (PreventionGenetics) Invitae Prostate Cancer Panel (Invitae) Hereditary Prostate Cancer Panel (GeneDx) ProstateNext (Ambry Genetics)	Hereditary Prostate Cancer Susceptibility Panels	C61, Z80, Z84, Z85, Z86

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CPT® Codes	Example Tests (Labs)	Criteria Section	Common ICD Codes
*0133U	RNAinsight for ProstateNext (Ambry Genetics)	Hereditary Prostate Cancer Susceptibility Panels	C61, Z80, Z84, Z85, Z86
*81437, *81438	Hereditary Paraganglioma-Pheochromocytoma syndrome Panel (PreventionGenetics) Invitae Hereditary Paraganglioma-Pheochromocytoma syndrome Panel (Invitae) PGL/PCC (Paraganglioma/ Pheochromocytoma) Panel (GeneDx) PGLNext (Ambry Genetics)	Hereditary Neuroendocrine Cancer Susceptibility Panels	C74-75, C7A Z80, Z84, Z85, Z86
*81432,*81433, *81435,*81436, *81437,*81438, *81445,*81450, *81455	CancerNext-*Expanded* (Ambry Genetics) with MI Profile (Caris Life Sciences)	Simultaneous Germline and Tumor Molecular Profiling	C00-D49, Z85
81215, 81217	BRCA1 Targeted Mutation Tests BRCA2 Targeted Mutation Tests	BRCA1/BRCA2 Targeted Variant Analysis	C50-58, D05, Z17, Z80, Z83, Z84, Z85, Z86
81212	BRCA Ashkenazi Jewish Panel (185delAG, 5385insC, and 6174delT)	BRCA1/BRCA2 Targeted Variant Analysis	C50-58, D05, Z17, Z80, Z83, Z84, Z85, Z86
81162,81163, 81164,81165, 81166,81167, 81216	BRCA1 Sequencing BRCA2 Sequencing	BRCA1/BRCA2 Sequencing and/or Deletion Duplication Analysis	C50-58, D05, Z17, Z80, Z83, Z84, Z85, Z86
*0138U	RNAinsight for BRCA1/2 (Ambry Genetics)	BRCA1/BRCA2 Sequencing and/or Deletion Duplication Analysis	C50-58, D05, Z17, Z80, Z83, Z84, Z85, Z86
81308	PALB2 Targeted Mutation Tests	PALB2 Targeted Variant Analysis	C15-26, Z80, Z84, Z85, Z86

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CPT® Codes	Example Tests (Labs)	Criteria Section	Common ICD Codes
81307, 81479	PALB2 Sequencing PALB2 Deletion/Duplication	PALB2 Sequencing and/or Deletion/Duplication Analysis	C15-26, Z80, Z84, Z85, Z86
*0137U	RNAinsight for PALB2 (Ambry Genetics)	PALB2 Sequencing and/or Deletion/Duplication Analysis	C15-26, Z80, Z84, Z85, Z86
*81403	ATM Targeted Mutation Tests CHEK2 Targeted Mutation Tests	ATM or CHECK2 Targeted Variant Analysis	C50, D05, Z80, Z84, Z85, Z86
*81408, 81479	ATM Sequencing Tests ATM Deletion/Duplication Tests CHEK2 Sequencing Tests CHEK2 Deletion/Duplication Tests	ATM or CHEK2 Sequencing and/or Deletion/Duplication Analysis	C50, D05, Z80, Z84, Z85, Z86
*0136U	RNAinsight for ATM (Ambry Genetics)	ATM or CHEK2 Sequencing and/or Deletion/Duplication Analysis	C50, D05, Z80, Z84, Z85, Z86
*0157U	CustomNext + RNA: APC (Ambry Genetics)	ATM or CHEK2 Sequencing and/or Deletion/Duplication Analysis	C50, D05, Z80, Z84, Z85, Z86
81293,81296, 81299, 81318	MLH1 Targeted Mutation Tests MSH2 Targeted Mutation Tests MSH6 Targeted Mutation Tests PMS2 Targeted Mutation Tests	MLH1, MSH2, MSH6, PMS2, EPCAM Sequencing and/or Deletion/Duplication Analysis	C15-26, C50-58 Z23, Z80, Z84, Z85, Z86
81292,81294, 81295,81297, 81298,81300,	Lynch Syndrome Panel (Quest Diagnostics)	MLH1, MSH2, MSH6, PMS2, EPCAM Sequencing	C15-26, C50-58 Z23, Z80, Z84, Z85, Z86

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CPT® Codes	Example Tests (Labs)	Criteria Section	Common ICD Codes
81317,81319, *81403	HNPCC Seq and del/dup (Ambry Genetics) Lynch Syndrome Panel (GeneDx) Lynch Syndrome (Invitae)	and/or Deletion/Duplication Analysis	
*0238U	Genomic Unity Lynch Syndrome Analysis (Variantyx Inc)	MLH1, MSH2, MSH6, PMS2, EPCAM Sequencing and/or Deletion/Duplication Analysis	C15-26, C50-58 Z23, Z80, Z84, Z85, Z86
*81403	BAP1 Targeted Mutation Tests	BAP1 Targeted Variant Analysis	C22, C45, C64 C69, D22, D32, Z80, Z84, Z85, Z86
81479	BAP1 Sequencing Tests BAP1 Deletion/Duplication Tests	BAP1 Sequencing and/or Deletion/Duplication Analysis	C22, C45, C64 C69, D22, D32, Z80, Z84, Z85, Z86
*81403	FLCN Targeted Mutation Tests	FLCN Targeted Variant Analysis	C65, Z84, Z85, Z86
81479	FLCN Sequencing Tests FLCN Deletion/Duplication Tests	FLCN Sequencing and/or Deletion/Duplication Analysis	C65, Z84, Z85, Z86
*81322	PTEN Targeted Mutation Tests	PTEN Targeted Variant Analysis	C15-26, C50-58, C73-75, D10-36, Q87.89, Z80, Z84, Z85, Z86
*81321, *81323	PTEN Sequencing Tests PTEN Deletion/Duplication Tests	PTEN Sequencing and/or Deletion/Duplication Analysis	C15-26, C50-58, C73-75, D10-36, Q87.89, Z80, Z84, Z85, Z86
*0235U	Genomic Unity® PTEN Analysis (Variantyx Inc)	PTEN Sequencing and/or Deletion/Duplication Analysis	C15-26, C50-58, C73-75, D10-36, Q87.89, Z80, Z84, Z85, Z86
*81202,*S3834	APC Targeted Mutation Tests	APC Targeted Variant Analysis	C15-26, Z80, Z84, Z85, Z86
81201,81203, *S3833	APC Sequencing Tests APC Deletion/Duplication Tests	APC Sequencing and/or Deletion/Duplication Analysis	C15-26, Z80, Z84, Z85, Z86

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CPT® Codes	Example Tests (Labs)	Criteria Section	Common ICD Codes
*81403	CDKN2A Targeted Mutation Tests	CDKN2A Targeted Variant Analysis	C43, Z12.83, Z80, Z84, Z85, Z86
*81404, 81479	CDKN2A Sequencing Tests CDKN2A Deletion/Duplication Tests	CDKNA2A Sequencing and/or Deletion/Duplication Analysis	C43, Z12.83, Z80, Z84, Z85, Z86
*81403	CDH1 Targeted Mutation Tests	CDH1 Targeted Mutation Tests	C16, Z80, Z84, Z85, Z86
*81406, 81479	CDH1 Sequencing Tests CDH1 Deletion/Duplication Tests Analysis	CDH1 Sequencing and/or Deletion/Duplication	C16, Z80, Z84, Z85, Z86
*81403	SMAD4 Targeted Mutation Tests BMPR1A Targeted Mutation Tests	SMAD4 and/or BMPR1A Sequencing and/or Deletion/Duplication Analysis	C15-C26, Z80, Z84, Z85, Z86
*81405, *81406	SMAD4 Sequencing Tests BMPR1A Sequencing Tests SMAD4 Deletion/Duplication Tests BMPR1A Deletion/Duplication Tests	SMAD4 and/or BMPR1A Sequencing and/or Deletion/Duplication Analysis	C15-C26, Z80, Z84, Z85, Z86
*81403	FH Targeted Mutation Tests	FH Targeted Variant Analysis	C44, C55, C64, D23, D25, Z84, Z85, Z86
*81405, 81479	FH Sequencing Tests FH Deletion/Duplication Tests	FH Sequencing and/or Deletion/Duplication Analysis	C44, C55, C64, D23, D25, Z84, Z85, Z86
*81404, 81352, 81353	TP53 Targeted Mutation Tests	TP53 Targeted Variant Analysis	C30-41, C15-26, C45-58, Z80, Z84, Z85, Z86
81351, *81405, 81479	TP53 Sequencing Tests TP53 Deletion/Duplication	TP53 Sequencing and/or Deletion/Duplication Analysis	C30-41, C15-26, C45-58, Z80, Z84, Z85, Z86

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CPT® Codes	Example Tests (Labs)	Criteria Section	Common ICD Codes
	Tests		
*81403	MEN1 Targeted Mutation Tests	MEN1 Targeted Variant Analysis	C73-75, E31.2, Z80, Z84, Z85, Z86
*81404, *81405	MEN1 Sequencing Tests MEN1 Deletion/Duplication Tests	MEN1 Sequencing and/or Deletion/Duplication Analysis	C73-75, E31.2, Z80, Z84, Z85, Z86
*81404, *81405	RET Targeted Mutation Tests	RET Targeted Variant Analysis	C73-75, C7A, D3A, Z80, Z84, Z85, Z86
*81406,81479, *S3840	RET Sequencing Tests RET Deletion/Duplication Tests	RET Sequencing and/or Deletion/Duplication Analysis	C73-75, C7A, D3A, Z80, Z84, Z85, Z86
*81401	MUTYH Targeted Mutation Tests	MUTYH Targeted Variant Analysis	C15-26, Z80, Z84, Z85, Z86
*81406, 81479	MUTYH Sequencing Tests MUTYH Deletion/Duplication Tests	MUTYH Sequencing and/or Deletion/Duplication Analysis	C15-26, Z80, Z84, Z85, Z86
*81403	PTCH1 Targeted Mutation Tests SUFU Targeted Mutation Tests	PTCH1 and/or SUFU Targeted Variant Analysis	C44, G93, M27, Z84, Z85, Z86
81479	PTCH1 Sequencing Tests SUFU Sequencing Tests PTCH1 Deletion/Duplication Tests SUFU Deletion/Duplication Tests	PTCH1 and SUFU Sequencing and/or Duplication Analysis	C44, G93, M27, Z84, Z85, Z86
*81403	SDHB Targeted Mutation Tests SDHD Targeted Mutation	MAX, SDHA, SDHAF2, SDHB, SDHC, SDHD, or TMEM127 Targeted Variant Analysis	C7A, C74.10, D35.00, Z84, Z85, Z86

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CPT® Codes	Example Tests (Labs)	Criteria Section	Common ICD Codes
	Tests MAX Targeted Mutation Tests SDHAF2 Targeted Mutation Tests SDHC Targeted Mutation Tests TMEM127 Targeted Mutation Tests		
*81404,*81405, *81406, 81479	SDHB Sequencing Tests SDHD Sequencing Tests SDHB Deletion/Duplication Tests SDHD Deletion/Duplication Tests	MAX, SDHA, SDHAF2, SDHB, SDHC, SDHD, and/or TEMEM127 Sequencing and/or Deletion/Duplication Analysis	C7A, C74.10, D35.00, Z84, Z85, Z86
*81403	STK11 Targeted Mutation Tests	STK11 Targeted Variant Analysis	C50, Q85, Z80, Z84, Z85, Z86
*81404, *81405	STK11 Sequencing Tests STK11 Deletion/Duplication Tests	STK11 Sequencing and/or Deletion/Duplication Analysis	C50, Q85, Z80, Z84, Z85, Z86
*81403,*S3841	RB1 Targeted Mutation Tests	RB1 Targeted Variant Analysis	C69, Z80, Z84, Z85, Z86
81479,*S3841	RB1 Sequencing Tests RB1 Deletion/Duplication Tests	RB1 Sequencing and/or Deletion/Duplication Analysis	C69, Z80, Z84, Z85, Z86
*81403, *S3842	VHL Targeted Mutation Tests	VHL Targeted Variant Analysis	C64, Q85, Z80, Z84, Z85, Z86

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I. **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.).

A. It is the policy of Louisiana Health Care Connections that genetic testing using a pan-cancer hereditary cancer susceptibility panel (including hereditary breast and gynecological panels) (81432, 81433, 81435, 81436) is considered **medically necessary** when meeting all the following:

B. The member/enrollee is 18 years or older

C. The member/enrollee meets at least one of the following:

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

2. The member/enrollee meets at least one criteria for Lynch syndrome/HNPCC sequencing and/or deletion duplication gene testing (see Lynch syndrome/HNPCC sequencing and/or deletion/duplication gene testing criteria below)

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

E. The panel does not include genes without a known association with cancer by ClinGen.

F. It is the policy of Louisiana Health Care Connections that current evidence does not support genetic testing using a pan-cancer hereditary cancer susceptibility panel (including hereditary breast and gynecological panels) (81432, 81433, 81435, 81436) for all other indications.

G. It is the policy of Louisiana Health Care Connections that current evidence does not support hereditary cancer susceptibility panel targeted mRNA sequencing analysis for the interpretation of variants of unknown significance (0132U, 0134U, 0135U), when billed in addition, 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.

A. **Hereditary Breast Cancer Susceptibility Panels-**A hereditary breast cancer susceptibility panel includes genes that are associated with inherited susceptibility to breast cancer. It is the policy of Louisiana Health Care Connections that current evidence does not support genetic testing using a hereditary breast cancer susceptibility panel

(81162, 81163, 81164, 81165, 81166, 81167, 81216, 81432, 81433, 0102U, 0129U) for all other indications. It is the policy of Louisiana Health Care Connections that current evidence does not support hereditary breast cancer susceptibility panel targeted mRNA sequencing analysis for the interpretation of variants of unknown significance (0131U), when billed in addition because it is typically either considered an existing component of the genetic testing process for quality assurance or follow up testing without proven utility.

A. It is the policy of Louisiana Health Care Connections that genetic testing using a hereditary breast cancer susceptibility panel (81162, 81163, 81164, 81165, 81166, 81167, 81216, 81432, 81433, 0102U, 0129U) is considered **medically necessary** when meeting (one or more of the following criteria):

B. Individuals with any blood relative with a known BRCA1/BRCA2 mutation

C. Individuals meeting the criteria below but with previous limited testing (e.g., single gene and/or absent deletion duplication analysis) interested in pursuing multi-gene testing;

D. Individuals with a personal history of cancer, defined as one or more of the following:

1. Breast cancer and one or more of the following:

   a. Diagnosed age ≤45 years;

   b. Diagnosed at age 45—50 years with:

      i. Unknown or limited family history; or
      ii. A second breast cancer diagnosed at any age; or
      iii. ≥1 close blood relative* with breast, ovarian, pancreatic, or high-grade (Gleason score ≥7) or intraductal prostate cancer at any age

E. Diagnosed at age ≤60 years with triple negative (ER–, PR–, HER2) breast cancer;

F. Diagnosed at any age with:

1. Ashkenazi Jewish ancestry or
2. ≥1 close blood relative* with breast cancer at age ≤50 years or ovarian, pancreatic, or metastatic or intraductal prostate cancer at any age; or
3. ≥3 total diagnoses of breast cancer in patient and/or close blood relatives
4. Bilateral breast cancer

G. Diagnosed at any age with male breast cancer

H. Epithelial ovarian cancer (including fallopian tube cancer or peritoneal cancer) at any age.

I. Exocrine pancreatic cancer at any age

J. Metastatic or intraductal prostate cancer at any age

K. High-grade (Gleason score ≥7) prostate cancer at any age with:

1. Ashkenazi Jewish ancestry;
2. ≥1 close blood relative* with breast cancer at age ≤50 years or ovarian, pancreatic, or metastatic or intraductal prostate cancer at any age.
3. ≥2 close blood relatives* with breast or prostate cancer (any grade) at any age.

L. A mutation identified on tumor genomic testing that has clinical implications if also identified in the germline.

M. To aid in systemic therapy decision-making, such as for HER2-negative metastatic breast cancer.

N. Individuals with a family history of cancer, including unaffected individuals, defined as one or more of the following:

1. An affected or unaffected individual with a 1st- or 2nd-degree blood relative meeting any of the criterion listed above (except individuals who meet criteria only for systemic therapy decision-making)

2. *For the purpose of familial assessment, close blood relatives include first-, second-, and third-degree relatives on the same side of the family (maternal or paternal):
   a. 1st-degree relatives are parents, siblings, and children;
   b. 2nd-degree relatives are grandparents, aunts, uncles, nieces, nephews, grandchildren, and half siblings; or
   c. 3rd-degree relatives are great-grandparents, great-aunts, great-uncles, great grandchildren and first cousins.

3. An affected or unaffected individual who otherwise does not met criteria above but also has a probability >5% of a BRCA1/2 pathogenic variant based on prior probability models (eg, Tyer-Cuzick, BRCAPro, Pennll).

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

P. The panel does not include genes without known association with breast cancer by ClinGen.

Q. It is the policy of Louisiana Health Care Connections that genetic testing using a STAT hereditary breast cancer panel (81162, 81163, 81164, 81165, 81166, 81167, 81216) is considered medically necessary when meeting both of the following:

1. The member/enrollee meets one of the above criteria

2. The member/enrollee requires a rapid turn-around-time for decision making related to surgical interventions and treatment decisions.

III. Hereditary Colorectal Cancer Susceptibility- A hereditary colorectal cancer susceptibility panel includes genes that are associated with inherited susceptibility to colorectal cancer. It is the policy of Louisiana Health Care Connections that genetic testing using a hereditary colorectal cancer susceptibility panel (81435, 81436, 0101U) is considered **medically necessary** when meeting all the following:

A. The member/enrollee is 18 years or older

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

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

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

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

b. Hereditary Diffuse Gastric Cancer (aka, Signet Ring Cell Gastric Cancer),

c. Juvenile Polyposis Syndrome (JPS)

d. MUTYH-associated Polyposis (MAP)

e. Peutz-Jeghers Syndrome (PJS)

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

D. The panel does not include genes without a known association with colorectal or gastrointestinal cancer by ClinGen.

E. It is the policy of Louisiana Health Care Connections that current evidence does not support genetic testing using a hereditary colorectal cancer susceptibility panel (81435, 81436, 0101U) for all other indications.

F. It is the policy of Louisiana Health Care Connections that current evidence does not support hereditary colorectal cancer susceptibility panel targeted mRNA sequencing analysis for the interpretation of variants of unknown significance (0130U), when billed in addition 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.

IV. Hereditary Gastric Cancer Susceptibility Panels- A hereditary gastric cancer susceptibility panel includes genes that are associated with inherited susceptibility to gastric (stomach) cancer**.** It is the policy of Louisiana Health Care Connections that genetic testing using a hereditary gastric susceptibility panel (81292, 81294, 81295, 81297, 81298, 81300, 81317, 81319, 81403, 81406, 81479) is considered medically necessary when meeting all the following:

A. The member/enrollee is 18 years or older

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

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

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

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

D. The panel does not include genes without a known association with gastric (stomach) cancer by ClinGen.

E. It is the policy of Louisiana Health Care Connections that current evidence does not support genetic testing using a hereditary breast cancer susceptibility panel (81162, 81163, 81164, 81165, 81166, 81167, 81216, 81432, 81433, 0102U, 0129U) for all other indications.

F. It is the policy of Louisiana Health Care Connections that current evidence does not support hereditary breast cancer susceptibility panel targeted mRNA sequencing analysis for the interpretation of variants of unknown significance

(0131U), when billed in addition because it is typically either considered an existing component of the genetic testing process for quality assurance, or follow up testing without proven utility.

G. It is the policy of Louisiana Health Care Connections that current evidence does not support genetic testing using a hereditary gastric cancer susceptibility panel (81292, 81294, 81295, 81297, 81298, 81300, 81317, 81319, 81403, 81406, 81479) for all other indications.

V. Hereditary Pancreatic Cancer Susceptibility Panels- A hereditary pancreatic cancer susceptibility panel includes genes that are associated with inherited susceptibility to pancreatic cancer.

A. It is the policy of Louisiana Health Care Connections that genetic testing using a hereditary pancreatic cancer susceptibility panel (81162, 81163, 81164, 81165, 81166, 81167, 81216, 81292, 81294, 81295, 81297, 81298, 81300, 81307, 81317, 81319, 81404, 81405, 81479) is considered **medically necessary** when meeting all the following:

B. The member/enrollee is 18 years or older

C. The member/enrollee meets at least one of the following:

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

D. The panel includes, at a minimum, sequencing of the following genes: *BRCA1, BRCA2, CDKN2A, MLH1, MSH2, MSH6, PALB2, PMS2, STK11*;

E. The panel does not include genes without a known association with pancreatic cancer by ClinGen.

F. It is the policy of Louisiana Health Care Connections that current evidence does not support genetic testing using a hereditary pancreatic cancer susceptibility panel (81162, 81163, 81164, 81165, 81166, 81167, 81216, 81292, 81294, 81295, 81297, 81298, 81300, 81307, 81317, 81319, 81404, 81405, 81479) for all other indications.

VI. Hereditary Polyposis Panels- A hereditary polyposis panel is one that includes genes that are associated with inherited susceptibility to colon polyposis. It is the policy of Louisiana Health Care Connections that genetic testing using a hereditary polyposis panel

(81201, 81203, 81406, 81479, S3833) is considered medically necessary when the member meets the following criteria:

A. The member/enrollee meets criteria for sequencing and/or deletion/duplication analysis for at least one of the following (see specific criteria sections below):
   1. Familial Adenomatous Polyposis (FAP)/Attenuated FAP
   2. MUTYH associated polyposis (MAP)

B. Personal history of > 20 cumulative adenomas; or

C. Known deleterious APC mutation in first-degree family member

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

E. The panel does not include genes without a known association with colon polyposis by ClinGen.

F. It is the policy of Louisiana Health Care Connections that current evidence does not support genetic testing using a hereditary polyposis panel (81201, 81203, 81406, 81479, S3833) for all other indications.

VII. Lynch Syndrome- It is the policy of Louisiana Health care Connections that *MLH1* (81293), *MSH2* (81296), *MSH6* (81299), or *PMS2* (81318) targeted variant analysis for Lynch syndrome/HNPCC is considered **medically necessary** when meeting one of the following genetic testing for Lynch syndrome to be medically necessary when a member meets the following criteria using either diagnostic tool as described below:

A. **Amsterdam II criteria**: All of the following must be met:

   1. There must be at least three relatives with a Lynch syndrome associated cancer (cancer of the colorectal, endometrium, small bowel, ureter or renal pelvis) and all of the following criteria should be present:

      a. One must be a first-degree relative to the other two

      b. Two or more successive generations must be affected.

      c. One or more must be diagnosed before 50 years of age

      d. Familial adenomatous polyposis should be excluded in the colorectal cancer

      e. Tumors must be verified by pathological examination

OR

B. **Revised Bethesda Guidelines**-One or more of following must be met

1. Colorectal or uterine cancer diagnosed in a patient who is less than 50 years of age
2. Presence of synchronous (coexist at the same time), metachronous (previous or recurring) colorectal cancer, or other *Lynch syndrome associated tumors*. Hereditary nonpolyposis colorectal cancer (HNPCC)-related tumors include colorectal, endometrial, stomach, ovarian, pancreas, ureter and renal pelvis, biliary tract, and brain (usually glioblastoma as seen in Turcot syndrome) tumors, sebaceous gland adenomas and keratoacanthomas in Muir-Torre syndrome, and carcinoma of the small bowel
3. Colorectal cancer with the MSI-H (*microsatellite instability–high in tumors)* refers to changes in two or more of the five National Cancer Institute-recommended panels of microsatellite markers *histology*; as defined by the presence of tumor infiltrating lymphocytes, Crohn's-like lymphocytic reaction, mucinous/signet-ring differentiation, or medullary growth pattern diagnosed in a patient who is less than 60 years of age);
4. Colorectal cancer diagnosed in one or more first-degree relatives with a Lynch syndrome related tumor, with one of the cancers being diagnosed under 50 years of age; and/or
5. Colorectal cancer diagnosed in two or more first- or second-degree relatives with Lynch syndrome related tumors, regardless of age.

OR

C. Estimated risk ≥ 5 percent based on predictive models (MMRpro, PREMM5, or MMRpredict).

VIII. 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. It is the policy of Louisiana Health Care Connections that genetic testing using a hereditary prostate cancer susceptibility panel (0133U, 81162, 81163, 81164, 81165, 81166, 81167, 81216, 81292, 81294, 81295, 81297, 81298, 81300, 81317, 81319) is considered medically necessary when meeting all the following:

A. The member/enrollee is 18 years or older

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

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

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

D. The panel does not include genes without a known association with prostate cancer by ClinGen.

E. It is the policy of Louisiana Health Care Connections that current evidence does not support genetic testing using a hereditary prostate cancer susceptibility panel (81479, 0133U for all other indications.

F. It is the policy of Louisiana Health Care Connections that hereditary prostate cancer susceptibility panel targeted mRNA sequencing analysis for the interpretation of variants of unknown significance (0133U), when billed in addition because it is typically either considered an existing component of the genetic testing process for quality assurance or follow up testing without proven utility.

IX. 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. It is the policy of Louisiana Health Care Connections that genetic testing using a hereditary neuroendocrine cancer susceptibility panel (81437, 81438) is considered **medically necessary** when meeting all the following:

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

1. Von-Hippel Lindau syndrome (VHL)

2. Hereditary Paraganglioma-Pheochromocytoma syndrome (PGL/PCC);

B. The panel includes, at a minimum, sequencing of the following genes: *MAX, SDHB, SDHC, SDHD, TMEM127, VHL*;

C. The panel does not include genes without a known association with a neuroendocrine cancer by ClinGen.

D. It is the policy of Louisiana Health Care Connections that current evidence does not support genetic testing using a hereditary neuroendocrine cancer susceptibility panel (81437, 81438) for all other indications.

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

X. Simultaneous Germline and Tumor Molecular Profiling

A. It is the policy of Louisiana Health Care Connections that current evidence does not support the use of **hereditary cancer susceptibility panels** (81432, 81433, 81435, 81436, 81437, 81438) simultaneously with **comprehensive tumor molecular profiling panels** (81445, 81450, 81455) when the member/enrollee

does not independently meet criteria for the hereditary cancer susceptibility panel *(see specific criteria for* BRCA1 and BRCA2 Gene Testing in section II

XI. PALB2 Gene Testing- PALB2 Targeted Variant Analysis-It is the policy of Louisiana Health Care Connections that *PALB2* targeted variant analysis (81308) for hereditary breast and/or ovarian cancer susceptibility is considered **medically necessary** when meeting both of the following:

A. The member/enrollee is 18 years or older

B. One of the following:

1. The member/enrollee has a close relative[1] with 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.

C. It is the policy of Louisiana Health Care Connections that current evidence does not support *PALB2* targeted variant analysis (81308) for hereditary breast and/or ovarian cancer susceptibility for all other indications.

D PALB2 Sequencing and/or Deletion/Duplication Analysis-It is the policy of Louisiana Health Care Connections that *PALB2* (81307, 0137U) sequencing and/or deletion/duplication analysis for hereditary breast and/or ovarian cancer susceptibility is considered medically necessary when meeting all of the following**:**

1. The member/enrollee is 18 years or older

2. The member/enrollee meets at least one of the following criteria:

3. The member/enrollee has a personal history of any of the following:

a. Epithelial ovarian cancer

b. Fallopian tube cancer

c. Primary peritoneal cancer

d. Male breast cancer

e. Pancreatic cancer

f. Bilateral breast cancer

g. Triple-negative breast cancer;

4. The member/enrollee is a female who has a personal history of breast cancer[3] and one of the following:
    a. Diagnosed ≤45 years;
    b. Diagnosed at 45-50 years and one of the following:
        i. One or more close relative[1] with ovarian or pancreatic cancer at any age
        ii. One or more close relatives[1] with breast cancer <50 years
        iii. Two or more close relatives[1] with breast cancer at any age
        iv. An unknown or limited family history[2];
5. The member/enrollee does not meet any of the above criteria, but has one or more first[1a]- or second-degree[1b] relatives meeting any of the above criteria;
6. The member/enrollee is being considered for PARP inhibitor therapy and has a personal history of metastatic HER2-negative breast cancer;

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

F. It is the policy of Louisiana Health Care Connections that current evidence does not support *PALB2* (81307, 0137U) sequencing and/or deletion/duplication analysis for hereditary breast and/or ovarian cancer susceptibility for all other indications.

G. It is the policy of Louisiana Health Care Connections that current evidence does not support *PALB2* mRNA sequencing analysis for the interpretation of variants of unknown significance (0137U), when billed in addition because it is typically either considered an existing component of the genetic testing process for quality assurance or follow up testing without proven utility.

XII. ATM and/or CHEK2 Gene Testing- ATM or CHEK2 Targeted Variant Analysis
It is the policy of Louisiana Health Care Connections that *ATM* (81403) or *CHEK2* (81403) targeted variant analysis for hereditary breast and/or ovarian cancer susceptibility is considered **medically necessary** when meeting both of the following:

A. The member/enrollee is 18 years or older

B. One of the following:

1. The member/enrollee has a close relative[1] 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.

C. It is the policy of Louisiana Health Care Connections that current evidence does not support *ATM* (81403) or *CHEK2* (81403) targeted variant analysis for hereditary breast and/or ovarian cancer susceptibility for all other indications.

D. ATM and/or CHEK2 Sequencing and/or Deletion/Duplication Analysis
1. It is the policy of Louisiana Health Care Connections that current evidence does not support *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.

2. It is the policy of Louisiana Health Care Connections that current evidence does not support *ATM* mRNA sequencing analysis for the interpretation of variants of unknown significance (0136U, 0157U), when billed in addition because it is typically either considered an existing component of the genetic testing process for quality assurance or follow up testing without proven utility.

XIII. MLH1, MSH2, MSH6, PMS2, or EPCAM Sequencing and/or Deletion/Duplication Analysis. It is the policy of Louisiana Health Care Connections that *MLH1* (81292, 81294), *MSH2* (81295, 81297), *MSH6* (81298, 81300), *PMS2* (81317, 81319), and/or *EPCAM* (81403) (0238U) sequencing and/or duplication analysis for Lynch syndrome/HNPCC is considered medically necessary when meeting any of the following:

A. The member/enrollee has a Lynch syndrome-related cancer (i.e., colorectal, endometrial, gastric, ovarian, pancreatic, ureter and renal pelvic, brain (usually glioblastoma), biliary tract, small intestinal, sebaceous adenoma, sebaceous carcinoma, or keratoacanthoma) **and** the tumor shows evidence of mismatch repair (MMR) deficiency (either by microsatellite instability (MSI) or loss of MMR protein expression)

B. The member/enrollee has a diagnosis of colorectal cancer or endometrial cancer and any of the following:

1. Diagnosed before age 50

2. Diagnosed at any age with an additional Lynch syndrome-related cancer (i.e., colorectal, endometrial, gastric, ovarian, pancreatic, ureter and renal pelvic, brain (usually glioblastoma), biliary tract, small intestinal, sebaceous adenoma, sebaceous carcinoma, or keratoacanthoma)

3. Diagnosed at any age with one or more first[1a]- or second-degree[1b] relatives diagnosed before age 50 with a Lynch syndrome-related cancer (i.e., colorectal, endometrial, gastric, ovarian, pancreatic, ureter and renal

pelvic, brain (usually glioblastoma), biliary tract, small intestinal, sebaceous adenoma, sebaceous carcinoma, or keratoacanthoma)

4. Diagnosed at any age with two or more first[1a]- or second-degree[1b] relatives diagnosed at any age with a Lynch syndrome-related cancer (i.e., colorectal, endometrial, gastric, ovarian, pancreatic, ureter and renal pelvic, brain (usually glioblastoma), biliary tract, small intestinal, sebaceous adenoma, sebaceous carcinoma, or keratoacanthoma);

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

1. One or more first-degree[1a] relatives diagnosed with colorectal or endometrial cancer before age 50

2. One or more first-degree[1a] relatives diagnosed with colorectal or endometrial cancer and an additional Lynch syndrome-related cancer (i.e., colorectal, endometrial, gastric, ovarian, pancreatic, ureter and renal pelvic, brain (usually glioblastoma), biliary tract, small intestinal, sebaceous adenoma, sebaceous carcinoma, or keratoacanthoma)

3. Two or more first[1a]- or second-degree[1b] relatives diagnosed with a Lynch syndrome-related cancer (i.e., colorectal, endometrial, gastric, ovarian, pancreatic, ureter and renal pelvic, brain (usually glioblastoma), biliary tract, small intestinal, sebaceous adenoma, sebaceous carcinoma, or keratoacanthoma), one of which was diagnosed before age 50

4. Three or more first[1a]- or second-degree[1b] relatives diagnosed with a Lynch syndrome-related cancer (i.e., colorectal, endometrial, gastric, ovarian, pancreatic, ureter and renal pelvic, brain (usually glioblastoma), biliary tract, small intestinal, sebaceous adenoma, sebaceous carcinoma, or keratoacanthoma);

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

E. It is the policy of Louisiana Health Care Connections that current evidence does not support *MLH1* (81292, 81294), *MSH2* (81295, 81297), *MSH6* (81298, 81300), *PMS2* (81317, 81319), and/or *EPCAM* (81403) (0238U) sequencing and/or duplication analysis for Lynch syndrome/HNPCC for all other indications.

F. It is the policy of Louisiana Health Care Connections that current evidence does not support *MLH1, MSH2, MSH6, and PMS2* mRNA sequencing analysis for the interpretation of variants of unknown significance (0158U, 0159U, 0160U, 0161U, 0162U), when billed in addition because it is typically either considered an existing component of the genetic testing process for quality assurance, or follow up testing without proven utility.

XIV. BAP1-Tumor Predisposition Syndrome- BAP1 Targeted Variant Analysis-It is the policy of Louisiana Health Care Connections that *BAP1* targeted variant analysis (81479) for *BAP1*-tumor predisposition syndrome is considered medically necessary when meeting one of the following:

A. The member/enrollee has a close relative[1] 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.

C. It is the policy of Louisiana Health Care Connections that current evidence does not support *BAP1* targeted variant analysis (81479) for *BAP1*-tumor predisposition syndrome for all other indications.

XV. BAP1 Sequencing and/or Deletion/Duplication Analysis- It is the policy of Louisiana Health Care Connections that *BAP1* sequencing and/or deletion/duplication analysis (81479) for *BAP1*-tumor predisposition syndrome is considered medically necessary when:

A. The member/enrollee has a personal history of:

1. Two or more of the following:

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

b. Uveal melanoma

c. Malignant mesothelioma

d. Renal cell carcinoma

e. Hepatocellular carcinoma

f. Cholangiocarcinoma

g. Meningioma;

2. One or more of the above listed tumors/cancer and a first[1a]- or second[1b]-degree relative with any of the above listed tumors/cancers.

B. It is the policy of Louisiana Health Care Connections that current evidence does not support *BAP1* sequencing and/or deletion/duplication analysis (81479) for *BAP1*-tumor predisposition syndrome for all other indications.

I. Birt-Hogg-Dube Syndrome (BHDS) FLCN Targeted Variant Analysis- It is the policy of Louisiana Health Care Connections that *FLCN* targeted variant analysis (81403)

for Birt-Hogg-Dube syndrome (BHDS) is considered medically necessary when meeting one of the following:

A. The member/enrollee has a close relative[1] 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.

C. It is the policy of Louisiana Health Care Connections that current evidence does not support *FLCN* targeted variant analysis (81403) for Birt-Hogg-Dube syndrome (BHDS) for all other indications.

II. FLCN Sequencing and/or Deletion/Duplication Analysis- It is the policy of Louisiana Health Care Connections that *FLCN* sequencing and/or deletion/duplication analysis (81479) for Birt-Hogg-Dube syndrome (BHDS) is considered medically necessary when meeting one of the following:

A. The member/enrollee has a personal history of:

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

2. Two or more of the following:

a. Multiple lung cysts with no apparent cause

b. Renal cancer before 50 years of age

c. Multifocal or bilateral renal cancer

d. Renal cancer of mixed chromophobe and oncocytic histology

e. A first-degree relative[1a] with BHDS.

B. It is the policy of Louisiana Health Care Connections that current evidence does not support *FLCN* sequencing and/or deletion/duplication analysis (81479) for Birt-Hogg-Dube syndrome (BHDS) for all other indications.

III. Cowden Syndrome (CS)/PTEN Hamartoma Tumor Syndrome (PHTS)-
PTEN Targeted Variant Analysis It is the policy of Louisiana Health Care Connections that *PTEN* targeted variant analysis (81322) for Cowden syndrome (CS)/PTEN hamartoma tumor syndrome (PHTS) is considered medically necessary when:

A. The member/enrollee has a close relative[1] with a known pathogenic or likely pathogenic variant in *PTEN*.

B. It is the policy of Louisiana Health Care Connections that current evidence does not support *PTEN* targeted variant analysis analysis (81322) for Cowden syndrome (CS)/PTEN hamartoma tumor syndrome (PHTS) for all other indications.

IV. PTEN Sequencing and/or Deletion/Duplication Analysis- It is the policy of Louisiana Health Care Connections that *PTEN* sequencing and/or deletion/duplication analysis (81321, 81323, 0235U) for Cowden syndrome (CS)/PTEN hamartoma tumor syndrome (PHTS) is considered medically necessary when meeting one of the following**:**

A. The member/enrollee 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
5. Macrocephaly and at least one other major criteria (see below)
6. Three major criteria (see below) without macrocephaly
7. One major and at least three minor criteria (see below)
8. Four or more minor criteria (see below)

B. The member/enrollee meets both of the following:

1. Has a close relative[1] with a clinical diagnosis of CS/PHTS or BRRS for whom testing has not been performed
2. Meets one major or two minor criteria (see below)

Major Criteria:	Minor Criteria:
● Breast Cancer ● Endometrial Cancer (epithelial) ● Thyroid Cancer (follicular) ● Gastrointestinal hamartomas ● Macrocephaly (≥97 percentile) ● Macular pigmentation of the glans penis ● Multiple mucocutaneous lesions: ○ One biopsy-proven trichilemmoma ○ Multiple palmoplantar keratoses ○ Multifocal or extensive oral mucosal papillomatosis	● Autism Spectrum Disorder ● Colon Cancer ● Esophageal glycogenic acanthosis (≥3) ● Lipomas (≥3) ● Intellectual disability (ie, IQ ≤ 75) ● Thyroid cancer (papillary or follicular) ● Thyroid structural lesions (eg, adenoma, multinodular goiter) ● Renal cell carcinoma ● Single GI hamartoma or ganglioneuroma ● Testicular lipomatosis

○ Multiple cutaneous facial papules (often verrucous)	● Vascular anomalies (including multiple intracranial developmental venous anomalies)

C. It is the policy of Louisiana Health Care Connections that current evidence does not support *PTEN* sequencing and/or deletion/duplication analysis (81321, 81323, 0235U) for Cowden syndrome (CS)/PTEN hamartoma tumor syndrome (PHTS) for all other indications**.**

XX. Familial Adenomatous Polyposis (FAP)/Attenuated Fap (AFAP)

APC Targeted Variant Analysis

A. It is the policy of Louisiana Health Care Connections that *APC* targeted variant analysis (81202, S3834) for familial adenomatous polyposis (FAP) is considered **medically necessary** when meeting one of the following:

1. The member/enrollee has a close relative[1] with a known pathogenic or likely pathogenic variant in *APC*;

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

B. It is the policy of Louisiana Health Care Connections that current evidence does not support *APC* targeted variant analysis (81202, S3834) for familial adenomatous polyposis (FAP) for all other indications.

APC Sequencing and/or Deletion/Duplication Analysis

A. It is the policy of Louisiana Health Care Connections that *APC* sequencing and/or deletion/duplication analysis (81201, 81203, S3833) for familial adenomatous polyposis (FAP) is considered **medically necessary** when meeting one of the following:

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

a. 10 or more cumulative colorectal adenomas

b. Hepatoblastoma

c. Congenital hypertrophy of the retinal pigment epithelium (CHRPE)

d. A desmoid tumor

e. Gastric fundus gland polyps;

2. The member/enrollee has a history of colorectal adenomas and one of the following:

a. Duodenal or other small bowel adenomas

b. Papillary thyroid carcinoma

c. Medulloblastoma;

3. The member/enrollee has a first-degree relative[1a] that meets at least one of the above criteria and has not previously undergone *APC* sequencing and/or deletion duplication analysis.

B. It is the policy of Louisiana Health Care Connections that current evidence does not support *APC* sequencing and/or deletion/duplication analysis (81201, 81203, S3833) for familial adenomatous polyposis (FAP) for all other indications.

XXI. Familial Atypical Multiple Mole Melanoma (FAMMM) Syndrome

CDKN2A Targeted Variant Analysis It is the policy of Louisiana Health Care Connections that *CDKN2A* targeted variant analysis (81403) for familial atypical multiple mole melanoma (FAMMM) syndrome, also known as melanoma-pancreatic cancer syndrome, is considered medically necessary when meeting both of the following:

A. The member/enrollee is 18 years or older;

B. One of the following:

1. The member/enrollee has a close relative[1] 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.

C. It is the policy of Louisiana Health Care Connections that current evidence does not support *CDKN2A* targeted variant analysis (81403) for familial cutaneous malignant melanoma for all other indications.

D. CDKN2A Sequencing and/or Deletion/Duplication Analysis It is the policy of Louisiana Health Care Connections that current evidence does not support *CDKN2A* sequencing and/or deletion/duplication analysis (81404, 81479) for familial atypical multiple mole melanoma (FAMMM) syndrome, also known as melanoma-pancreatic cancer syndrome, as a standalone test.

XXII. Hereditary Diffuse Gastric Cancer (Aka, Signet Ring Cell Gastric Cancer): CDH1 Targeted Variant Analysis- It is the policy of Louisiana Health Care Connections that *CDH1* targeted variant analysis (81403) for Hereditary Diffuse Gastric Cancer (aka, Signet Ring Cell Gastric Cancer) is considered medically necessary when meeting both of the following:

A. The member/enrollee is 18 years or older;

B. One of the following:

1. The member/enrollee has a close relative[1] 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.

C. It is the policy of Louisiana Health Care Connections that current evidence does not support *CDH1* targeted variant analysis (81403) for Hereditary Diffuse Gastric Cancer (aka, Signet Ring Cell Gastric Cancer) for all other indications.

D. CDH1 Sequencing and/or Deletion/Duplication Analysis-It is the policy of Louisiana Health Care Connections that *CDH1* sequencing and/or deletion/duplication analysis for Hereditary Diffuse Gastric Cancer (aka, Signet Ring Cell Gastric Cancer) (81406, 81479) is considered medically necessary when meeting both of the following:

1. The member/enrollee is 18 years or older;

2. One of the following:

a. The member/enrollee has diffuse gastric cancer diagnosed before 40 years of age;

b. The member/enrollee has a personal history of diffuse gastric cancer and lobular breast cancer;

c. The member/enrollee has diffuse gastric cancer and one or more first-[1a] or second-degree[1b] relatives diagnosed with gastric cancer;

d. The member/enrollee has a close relative[1] with diffuse gastric cancer and a close relative with lobular breast cancer

e. The member/enrollee has a first-degree relative[1a] that meets at least one of the above criteria and has not previously undergone *CDH1* sequencing and/or deletion duplication analysis.

E. It is the policy of Louisiana Health Care Connections that current evidence does not support *CDH1* sequencing and/or deletion/duplication analysis for Hereditary Diffuse Gastric Cancer (aka, Signet Ring Cell Gastric Cancer) (81406, 81479) for all other indications.

XXIII. Juvenile Polyposis Syndrome (JSP)- SMAD4 or BMPR1A Targeted Variant Analysis It is the policy of Louisiana Health Care Connections that *SMAD4* and/or *BMPR1A* targeted variant analysis (81403) for juvenile polyposis syndrome (JPS) is considered medically necessary when meeting one of the following:

A. The member/enrollee has a close relative[1] 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.

C. It is the policy of Louisiana Health Care Connections that current evidence does not support *SMAD4* and/or *BMPR1A* targeted variant analysis (81403) for juvenile polyposis syndrome (JPS) for all other indications.

D. SMAD4 and/or BMPR1A Sequencing and/or Deletion/Duplication Analysis *SMAD4* and/or *BMPR1A* sequencing and/or deletion/duplication analysis (81405, 81406) for juvenile polyposis syndrome (JPS) is considered medically necessary when meeting one of the following:

1. The member/enrollee has 5 or more juvenile polyps[4] in the colon
2. The member/enrollee has multiple juvenile polyps[4] throughout the gastrointestinal tract;
3. The member/enrollee has a first-degree relative[1a] that meets at least one of the above criteria and has not previously undergone *SMAD4* and/or *BMPR1A* sequencing and/or deletion duplication analysis.

E. It is the policy of Louisiana Health Care Connections that current evidence does not support *SMAD4* and/or *BMPR1A* sequencing and/or deletion/duplication analysis (81405, 81406) for juvenile polyposis syndrome (JPS) for all other indications.

XXIV. Hereditary Leiomyomatosis and Renal Cell Cancer (HLREE)- FH Targeted Variant Analysi It is the policy of Louisiana Health Care Connections that *FH* targeted variant analysis (81403) for hereditary leiomyomatosis and renal cell cancer (HLRCC) is considered medically necessary when meeting both of the following:

A. The member/enrollee is 18 years or older

B. One of the following:

1. The member/enrollee has a close relative[1] 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.

C. It is the policy of Louisiana Health Care Connections that current evidence does not support *FH* targeted variant analysis (81403) for hereditary leiomyomatosis and renal cell cancer (HLRCC) for all other indications.

D. FH Sequencing and/or Deletion/Duplication Analysis It is the policy of Louisiana Health Care Connections that *FH* sequencing and/or deletion/duplication analysis (81405, 81479) for hereditary leiomyomatosis and renal cell cancer (HLRCC) is considered medically necessary when meeting one of the following:

1. The member/enrollee is 18 years or older
2. One of the following:
    a. The member/enrollee has one or more biopsy proven cutaneous leiomyoma(s)
    b. The member/enrollee has cutaneous leiomyosarcoma
    c. The member/enrollee is a female with one of the following:
        i. Multiple or large uterine fibroids
        ii. Hysterectomy or myomectomy before 40 years of age due to large or numerous uterine fibroids
        iii. A single uterine fibroid with loss of FH staining on IHC analysis
        iv. Uterine leiomyosarcoma;
3. The member/enrollee has renal cell cancer diagnosed before 45 years of age.

E. It is the policy of Louisiana Health Care Connections that current evidence does not support *FH* sequencing and/or deletion/duplication analysis for hereditary leiomyomatosis and renal cell cancer (HLRCC) for all other indications.

F. FH Sequencing and/or Deletion/Duplication Analysis It is the policy of Louisiana Health Care Connections that *FH* sequencing and/or deletion/duplication analysis (81405, 81479) for hereditary leiomyomatosis and renal cell cancer (HLRCC) is considered medically necessary when meeting both of the following:

1. The member/enrollee is 18 years or older
2. One of the following:
    a. The member/enrollee has one or more biopsy proven cutaneous leiomyoma(s)
    b. The member/enrollee has cutaneous leiomyosarcoma
3. The member/enrollee is a female with:

a. Multiple or large uterine fibroids

b. Hysterectomy or myomectomy before 40 years of age due to large or numerous uterine fibroids

c. A single uterine fibroid with loss of FH staining on IHC analysis

d. Uterine leiomyosarcoma

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

G. It is the policy of Louisiana Health Care Connections that current evidence does not support *FH* sequencing and/or deletion/duplication analysis for hereditary leiomyomatosis and renal cell cancer (HLRCC) for all other indications.

XXV. Li-Fraumeni Syndrome (LFS) TP53 Targeted Variant Analysis- It is the policy of Louisiana Health Care Connections that *TP53* targeted variant analysis (81404) for Li-Fraumeni syndrome (LFS) is considered medically necessary when the member/enrollee has a close relative[1] with a known pathogenic or likely pathogenic variant in *TP53*.

A. It is the policy of Louisiana Health Care Connections that current evidence does not support *TP53* targeted variant analysis (81404) for Li-Fraumeni syndrome (LFS) for all other indications.

B. TP53 Sequencing and/or Deletion/Duplication Analysis It is the policy of Louisiana Health Care Connections that *TP53* sequencing and/or deletion/duplication analysis (81405, 81479) for Li-Fraumeni syndrome (LFS) is considered medically necessary when meeting any of the following:

1. The member/enrollee was diagnosed with breast cancer before 31 years of age

2. The member/enrollee meets all of the following *Classic LFS* criteria:

a. The member/enrollee was diagnosed with a sarcoma before 45 years of age

b. The member/enrollee has a first-degree relative[1a] diagnosed with any cancer before 45 years of age

3. At least one of the following:

a. The member/enrollee has a first-[1a] or second-degree[1b] relative diagnosed with any cancer before 45 years of age

b. The member/enrollee has a first-[1a] or second-degree[1b] relative diagnosed with sarcoma at any age

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

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

2. The member/enrollee has three or more primary tumors

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

   a. Soft tissue sarcoma
   b. Osteosarcoma
   c. Central nervous system tumor
   d. Breast cancer

4. The member/enrollee meets both of the following:

   a. Has a diagnosis of soft tissue sarcoma, osteosarcoma, CNS tumor, breast cancer diagnosed before 46 years of age

   b. Has a first-[1a] or second-degree[1b] relative diagnosed with soft tissue sarcoma, osteosarcoma, CNS tumor, breast cancer, adrenocortical carcinoma before 56 years of age.

D. It is the policy of Louisiana Health Care Connections that current evidence does not support *TP53* sequencing and/or deletion/duplication analysis (81405, 81479) for Li-Fraumeni syndrome (LFS) for all other indications**.**

XXVI. Multiple Endocrine Neoplasia Type 1 (MEN1)- MEN1 Targeted Variant Analysis It is the policy of Louisiana Health Care Connections that *MEN1* targeted variant analysis (81403) for multiple endocrine neoplasia type 1 (MEN1) is considered medically necessary when meeting one of the following:

A. The member/enrollee has a close relative[1] 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.

C. It is the policy of Louisiana Health Care Connections that current evidence does not support *MEN1* targeted variant analysis (81403) for multiple endocrine neoplasia type 1 (MEN1) for all other indications.

D. MEN1 Sequencing and/or Deletion/Duplication Analysis It is the policy of Louisiana Health Care Connections that *MEN1* sequencing and/or

deletion/duplication analysis (81404, 81405) for multiple endocrine neoplasia type 1 (MEN1) is considered medically necessary when:

1. The member/enrollee has a personal history of at least two of the following:
    a. Pancreatic neuroendocrine tumor (islet cell tumor)
    b. Multi-gland parathyroid hyperplasia
    c. Pituitary adenoma

E. It is the policy of Louisiana Health Care Connections that current evidence does not support *MEN1* sequencing and/or deletion/duplication analysis (81404, 81405) for multiple endocrine neoplasia type 1 (MEN1) for all other indications**.**

XXVII. Multiple Endocrine Neoplasia Type 2 (MEN2) RET Targeted Variant Analysis It is the policy of Louisiana Health Care Connections that *RET* targeted variant analysis (81404, 81405) for multiple endocrine neoplasia type 2 (MEN2) is considered medically necessary when meeting one of the following:

A. The member/enrollee has a close relative[1] 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.

C. *RET* targeted variant analysis (81404, 81405) for multiple endocrine neoplasia type 2 (MEN2) is considered **investigational** for all other indications.

D. RET Sequencing and/or Deletion/Duplication Analysis *RET* sequencing and/or deletion/duplication analysis (81406, 81479, S3840) for multiple endocrine neoplasia type 2 (MEN2) is considered **medically necessary** when meeting one of the following:

1. The member/enrollee has a diagnosis of medullary thyroid cancer
2. The member/enrollee has a diagnosis of primary C-cell hyperplasia
3. The member/enrollee has a personal history of an adrenal pheochromocytoma and parathyroid hyperplasiaThe member/enrollee has a first-degree relative[1a] that meets at least one of the above criteria and has not previously undergone *RET* sequencing and/or deletion duplication analysis.

E. It is the policy of Louisiana Health Care Connections that current evidence does not support *RET* sequencing and/or deletion/duplication analysis (81406, 81479, S3840) for multiple endocrine neoplasia type 2 (MEN2) for all other indications.

XXVIII. **Mutyh-Associated Polyposis (MAP)** MUTYH Targeted Variant Analysis

I. It is the policy of Louisiana Health Care Connections that *MUTYH* targeted variant analysis (81401) for MYH-associated polyposis (MAP) is considered **medically necessary** when meeting one of the following:

A. The member/enrollee has a close relative[1] with a known pathogenic or likely pathogenic variant in *MUTYH*

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

C. It is the policy of Louisiana Health Care Connections that current evidence does not support *MUTYH* targeted variant analysis (81401) for MYH-associated polyposis (MAP) for all other indications.

D. MUTYH Sequencing and/or Deletion/Duplication Analysis It is the policy of Louisiana Health Care Connections that *MUTYH* sequencing and/or deletion/duplication analysis (81406, 81479) for MYH-associated polyposis (MAP) is considered medically necessary when meeting one of the following:

1. The member/enrollee has 10 or more cumulative colorectal adenomas;

2. The member/enrollee has a history of colorectal adenomas and meets one of the following:

   a. Duodenal adenomas or carcinoma

   b. 5 or more serrated polyps proximal to the rectum with at least 2 greater than 10mm;

   c. More than 20 serrated polyps of any size distributed throughout the large bowel with at least 4 proximal to the rectum.

E. It is the policy of Louisiana Health Care Connections that current evidence does not support *MUTYH* sequencing and/or deletion/duplication analysis (81406, 81479) for MYH-associated polyposis (MAP) for all other indications.

XXIX. **Nevoid Basal Cell Carcinoma Syndrome (Aka Gorlin Syndrome) PTCH1 or SUFU Targeted Variant Analysis** It is the policy of Louisiana Health Care Connections that *PTCH1* or *SUFU* targeted variant analysis (81403) for nevoid basal cell carcinoma syndrome (NBCC), also known was Gorlin syndrome, is considered medically necessary when meeting one of the following:

A. The member/enrollee has a close relative[1] 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.

C. It is the policy of Louisiana Health Care Connections that current evidence does not support *PTCH1* or *SUFU* targeted variant analysis (81403) for nevoid basal cell carcinoma syndrome (NBCC), also known as Gorlin syndrome, for all other indications.

D. PTCH1 and SUFU Sequencing and/or Deletion/Duplication Analysis It is the policy of Louisiana Health Care Connections that *PTCH1* and *SUFU* sequencing and/or deletion duplication analysis (81479) for nevoid basal cell carcinoma syndrome (NBCC), also known as Gorlin syndrome, is considered medically necessary when:

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

2. Two major and one minor criteria (see below);

3. One major and three minor criteria (see below)

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

E. It is the policy of Louisiana Health Care Connections that current evidence does not support *PTCH1* and *SUFU* sequencing and/or deletion/duplication analysis (81479) for all other indications.

XXX. Hereditary Paraganglioma/Pheochromocytoma Syndrome (PGL/PCC) MAX, SDHA, SDHAF2, SDHB, SDHC, SDHD, or TEM127 Targeted Variant Analysis It is the policy of Louisiana Health Care Connections that *MAX*, *SDHA*, *SDHAF2*, *SDHB*, *SDHC*, *SDHD*, or *TMEM127* targeted variant analysis (81403) for hereditary

paraganglioma/pheochromocytoma syndrome (PGL/PCC) is considered medically necessary when meeting one of the following:

A. The member/enrollee has a close relative[1] 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.

C. It is the policy of Louisiana Health Care Connections that current evidence does not support *MAX*, *SDHA*, *SDHAF2*, *SDHB*, *SDHC*, *SDHD*, or *TMEM127* targeted variant analysis (81403) for hereditary paraganglioma/pheochromocytoma syndrome (PGL/PCC) for all other indications.

D. MAX, SDHA, SDHAF2, SDHB, SDHC, SDHD, and TEM127 Sequencing and Deletion Duplication Analysis It is the policy of Louisiana Health Care Connections that *MAX*, *SDHA*, *SDHAF2*, *SDHB*, *SDHC*, *SDHD*, and *TMEM127* sequencing and/or deletion/duplication analysis (81404, 81405, 81406, 81479) for hereditary paraganglioma/pheochromocytoma syndrome (PGL/PCC) is considered medically necessary when meeting both of the following:

1. The member/enrollee has a diagnosis of one or more of the following:

    a. Pheochromocytoma, including bilateral adrenal pheochromocytoma

    b. Paraganglioma, including paravertebral, carotid body, vagal, and/or jugulotympanic

    c. Clear cell renal cell cancer

    d. Gastrointestinal stromal tumor (GIST)

    e. Pulmonary chondromas

2. The member/enrollee has a close relative[1] who meets the above criteria.

E. It is the policy of Louisiana Health Care Connections that current evidence does not support *MAX*, *SDHA*, *SDHAF2*, *SDHB*, *SDHC*, *SDHD*, and *TMEM127* sequencing and/or deletion/duplication (81404, 81405, 81406, 81479) for hereditary paraganglioma/pheochromocytoma syndrome (PGL/PCC) for all other indications.

XXXI. Peutz-Jeghers Syndrome (PJS) STK11 Targeted Variant Analysis- It is the policy of Louisiana Health Care Connections that *STK11* targeted variant analysis (81403) for

Peutz-Jeghers syndrome is considered medically necessary when the member/enrollee has a close relative[1] with a known pathogenic or likely pathogenic variant in *STK11*.

A. It is the policy of Louisiana Health Care Connections that current evidence does not support *STK11* targeted variant analysis (81403) for Peutz-Jeghers syndrome for all other indications.

B. **STK11 Sequencing and/or Deletion/Duplication Analysis** It is the policy of Louisiana Health Care Connections that *STK11* sequencing and/or deletion/duplication analysis (81404, 81405) for Peutz-Jeghers syndrome is considered **medically necessary** when: The member/enrollee has a clinical diagnosis of Peutz-Jeghers syndrome based on the presence of any two of the following:

1. Two or more histologically confirmed Peutz-Jeghers-type hamartomatous polyps of the GI tract
2. Mucocutaneous pigmentation of the mouth, lips, nose, eyes, genitalia, or fingers
3. Close relative[1] with a clinical diagnosis of PJS.

C. It is the policy of Louisiana Health Care Connections that current evidence does not support *STK11* sequencing and/or deletion/duplication analysis (81404, 81405) for Peutz-Jeghers syndrome for all other indications.

XXXII. Retinoblastoma RB1 Targeted Variant Analysis It is the policy Louisiana Health Care Connections that *RB1* targeted variant analysis (81403, S3841) for retinoblastoma is considered medically necessary when meeting one of the following:

A. The member/enrollee has a close relative[1] 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. It is the policy of Louisiana Health Care Connections that current evidence does not support *RB1* targeted variant analysis (81403, S3841) for retinoblastoma for all other indications.

D. RB1 Sequencing and/or Deletion/Duplication Analysis It is the policy of Louisiana Health Care Connections that *RB1* sequencing and/or deletion/duplication analysis (81403, S3841) for retinoblastoma is considered **medically necessary** when meeting one of the following:

1. The member/enrollee has a diagnosis of retinoblastoma in one or both eyes;

2. The member/enrollee has a close relative[1] diagnosed with retinoblastoma in one or both eyes and has not previously undergone *RB1* sequencing and/or deletion duplication analysis.

E. It is the policy of Louisiana Health Care Connections that current evidence does not support *RB1* sequencing and/or deletion/duplication analysis (81403, S3841) for retinoblastoma for all other indications.

XXXIII. Von Hippel-Lindau Syndrome (VHL) VHL Targeted Variant Analysis It is the policy of Louisiana Health Care Connections that *VHL* targeted variant analysis (81403, S3842) for Von Hippel-Lindau syndrome is considered medically necessary when meeting one of the following:

A. The member/enrollee has a close relative[1] 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.

C. It is the policy of Louisiana Health Care Connections that current evidence does not support *VHL* targeted variant analysis (81403, S3842) for Von Hippel-Lindau syndrome for all other indications.

D. VHL Sequencing and/or Deletion/Duplication Analysis It is the policy of Louisiana Health Care Connections that *VHL* sequencing and/or deletion/duplication analysis (81403, 81404, S3842) for Von Hippel-Lindau syndrome is considered medically necessary when meeting one of the following:

E. The member/enrollee has a diagnosis of one or more of the following:

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

F. The member/enrollee has a close relative[1] diagnosed with VHL.

G. It is the policy of Louisiana Health Care Connections that current evidence does not support *VHL* sequencing and/or deletion/duplication analysis (81403, 81404, S3842) for Von Hippel-Lindau syndrome for all other indications**.**

Notes and Definitions

1. Close relatives include first, second, and third degree blood relatives:

   a. **First-degree relatives** are parents, siblings, and children

   b. **Second-degree relatives** are grandparents, aunts, uncles, nieces, nephews, grandchildren, and half siblings

   c. **Third-degree relatives** are great grandparents, great aunts, great uncles, great grandchildren, and first cousins

See *Marcus, et. al. 2010* for details regarding major and minor criteria

Background

National Comprehensive Cancer Network (NCCN)

Multi-gene Panel Testing

NCCN guidelines (1.2022) recognize that next-generation sequencing technology has rapidly altered the clinical approach to testing at-risk patients and their families for hereditary forms of cancer and that when more than one gene can explain an inherited cancer syndrome, tailored multi-gene testing is often more efficient and/or cost effective than single-gene testing. NCCN guidelines recognize that there are pros and cons to multi-gene panel testing, one con being that there is a chance of finding a variant of uncertain significance or a pathogenic variant with uncertain clinical management increase as the number of genes included in the multi-gene panel increases. Because of these pros and cons, it is recommended that multi-gene panel testing be offered by a professional genetic expert that provides detailed pre- and post-test counseling.

Germline Testing after Tumor Profiling

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

High-Penetrance Breast and Ovarian Cancer Susceptibility Genes Testing

NCCN guidelines (1.2022) outline testing criteria for high-penetrance breast and/or ovarian cancer susceptibility genes, specifically *BRCA1/2*, *CDH1*, *PALB2*, *PTEN*, and *TP53*. NCCN recommends this testing in individuals with a personal and/or family history of HBOC-related cancers, such as breast, ovarian, prostate, and pancreatic cancer. Additionally, current guidelines (8.2021) recommends assessing for germline *BRCA1/2* mutations in all patients with recurrent or metastatic breast cancer to identify candidates for PARP inhibitor therapy.

Pancreatic Cancer Susceptibility Genes Testing

NCCN guidelines (1.2022) recommend genetic counseling and germline testing for all individuals diagnosed with exocrine pancreatic cancer, as well as individuals with a first-degree relative diagnosed with exocrine pancreatic cancer.

Lynch Syndrome/HNPCC

NCCN guidelines (1.2021) outline testing criteria for the evaluation of Lynch syndrome. NCCN recommends analysis of *MLH1*, *MSH2*, *MSH6*, *PMS2* and/or *EPCAM* in individuals with a personal and/or family history of Lynch syndrome-related cancers, such as colorectal, endometrial, gastric, ovarian, pancreatic, ureter and renal pelvic, brain (usually glioblastoma), biliary tract, small intestinal, sebaceous adenoma, sebaceous carcinoma, or keratoacanthoma.

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

NCCN guidelines (1.2022) outline clinical criteria for the genetic testing for Cowden syndrome (CS)/*PTEN* hamartoma tumor syndrome (PHTS) in individuals with a personal or family history of PHTS/CS.

Familial Adenomatous Polyposis (FAP)/Attenuated (AFAP)

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

Familial Cutaneous Malignant Melanoma

NCCN guidelines (2.2021) recommend considering genetic counseling referral for *p16*/*CDKN2A* mutation testing (and possibly other genes) when a patient has 3 or more invasive cutaneous melanomas, or a personal or family history of a mix of invasive melanoma, pancreatic cancer, and/or astrocytoma diagnoses.

NCCN guidelines (2.2021) also state that individuals with the presence of germline mutations in *CDKN2a*, *CDK4*, *MC1R*, *BRCA2*, *BAP1* and potentially other genes, are predisposed to develop single or multiple primary melanomas.

Hereditary Diffuse Gastric Cancer

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

Juvenile Polyposis Syndrome (JPS)

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

Hereditary Leiomyomatosis and Renal Cell Cancer (HLRCC)

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

Li-Fraumeni Syndrome (LFS)

NCCN guidelines (1.2022) outline clinical testing criteria for the genetic testing for Li-Fraumeni syndrome including classic Li-Fraumeni syndrome criteria and Chompret criteria and considerations for family history.

Multiple Endocrine Neoplasia Syndrome Type 1

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

experience in cancer genetics be involved whenever possible.

Multiple Endocrine Neoplasia Syndrome Type 2

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

MUTYH-associated Polyposis (MAP)

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

Hereditary Paraganglioma/Pheochromocytoma Syndrome (PGL/PCC)

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

Peutz-Jeghers Syndrome (PJS)

NCCN guidelines (1.2021) outline clinical criteria for the genetic testing for PJS in individuals with a personal and/or family history suggestive of PJS, as a majority of cases occur due to pathogenic variants in the *STK11* (*LKB1*) gene.

Retinoblastoma

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

Von Hippel-Lindau Syndrome (VHL)

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

American Society of Clinical Oncologists (ASCO)

Germline Implications of Somatic Mutation Profiling

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

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

preferences, and understand outcomes of providing incidental and secondary germline information with somatic testing."

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

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

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

- All women diagnosed with epithelial ovarian cancer should have germline genetic testing for *BRCA1/2* and other ovarian cancer susceptibility genes. In women who do not carry a germline pathogenic or likely pathogenic *BRCA1/2* variant, somatic tumor testing for *BRCA1/2* pathogenic or likely pathogenic variants should be performed. Women with identified germline or somatic pathogenic or likely pathogenic variants in *BRCA1/2* genes should be offered treatments that are US Food and Drug Administration (FDA) approved in the upfront and the recurrent setting.
- Women diagnosed with clear cell, endometrioid, or mucinous ovarian cancer should be offered somatic tumor testing for mismatch repair deficiency (dMMR). Women with identified dMMR should be offered FDA-approved treatment based on these results.
- Genetic evaluations should be conducted in conjunction with health care providers familiar with the diagnosis and management of hereditary cancer.
- First- or second-degree blood relatives of a patient with ovarian cancer with a known germline pathogenic cancer susceptibility gene variant should be offered individualized genetic risk evaluation, counseling, and genetic testing.
- Clinical decision making should not be made based on a variant of uncertain significance.

- Women with epithelial ovarian cancer should have testing at the time of diagnosis.

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

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

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

National Society of Genetic Counselors (NSGC)

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

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

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

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

American Society of Breast Surgeons

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

> "Genetic testing should be made available to all patients with a personal history of breast

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

The American College of Obstetricians and Gynecologists (ACOG)

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

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

US Preventive Services Task Force (USPSTF)

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

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

Endocrine Society

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

3.1 We recommend that all patients with PPGLs should be engaged in shared decision making for genetic testing.

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

American Association of Ophthalmic Oncologists and Pathologists

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

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

Coding Implications

This clinical policy references Current Procedural Terminology (CPT®). CPT® is a registered trademark of the American Medical Association. All CPT codes and descriptions are copyrighted 2021, American Medical Association. All rights reserved. CPT codes and CPT descriptions are from the current manuals and those included herein are not intended to be all-inclusive and are included for informational purposes only. Codes referenced in this clinical policy are for informational purposes only and may not support medical necessity. Inclusion or exclusion of any codes does not guarantee coverage. Providers should reference the most up-to-date sources of professional coding guidance prior to the submission of claims for reimbursement of covered services.

Reviews, Revisions, and Approvals	Revision Date	Approval Date
Policy rebranded from corporate policy and revised for Louisiana specifics	2/23	4/10/23

References

1. Louisiana Department of Health, Provider manual. Genetic Counseling and Testing criteria.
2. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Genetic/Familial High-Risk Assessment: Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic. Version 1.2022. https://www.nccn.org/professionals/physician_gls/pdf/genetics_bop.pdf.
3. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Genetic/Familial High-Risk Assessment: Colorectal. Version 1.2021. https://www.nccn.org/professionals/physician_gls/pdf/genetics_colon.pdf.
4. "Use of Multi-Gene Panel Testing." Position Statement from National Society of Genetic Counselors. https://www.nsgc.org/Policy-Research-and-Publications/Position-Statements/Position-Statements/Post/use-of-multi-gene-panel-tests. Released March 14, 2017.
5. "Genetic Testing of Minors for Adult-Onset Conditions". Position Statement from National Society of Genetic Counselors. https://www.nsgc.org/Policy-Research-and-Publications/Position-Statements/Position-Statements/Post/genetic-testing-of-minors-for-adult-onset-conditions. Released February 15, 2017. Updated April 18, 2018.
6. Stoffel EM, Mangu PB, Gruber SB, et al. Hereditary colorectal cancer syndromes: American society of clinical oncology clinical practice guideline endorsement of familial risk-colorectal cancer: European Society for medical oncology clinical practice guidelines. J Clin Oncol. 2015;33(2):209-217. doi:10.1200/JCO.2014.58.1322
7. Owens DK, Davidson KW, Krist AH, et al. Risk Assessment, Genetic Counseling, and Genetic Testing for BRCA -Related Cancer: US Preventive Services Task Force Recommendation Statement. *JAMA - J Am Med Assoc*. 2019;322(7):652-665. doi:10.1001/jama.2019.10987
8. Manahan ER, Kuerer HM, Sebastian M, et al. Consensus Guidelines on Genetic Testing for Hereditary Breast Cancer from the American Society of Breast Surgeons. *Ann Surg Oncol*. 2019;26(10):3025-3031. doi:10.1245/s10434-019-07549-8
9. Lenders JW, Duh QY, Eisenhofer G, Gimenez-Roqueplo AP, Grebe SK, Murad MH, Naruse M, Pacak K, Young WF Jr, Endocrine Society. Pheochromocytoma and paraganglioma: an endocrine society clinical practice guideline. *The Journal of Clinical Endocrinology and Metabolism.* 2014;99(6):1915-1942

10. Robson ME, Bradbury AR, Arun B, et al. American Society of Clinical Oncology Policy Statement Update: Genetic and Genomic Testing for Cancer Susceptibility. *J Clin Oncol*. 2015;33(31):3660-3667. doi:10.1200/JCO.2015.63.0996
11. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Cutaneous Melanoma. Version 2.2021. https://www.nccn.org/professionals/physician_gls/pdf/cutaneous_melanoma.pdf.
12. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Neuroendocrine and Adrenal Tumors. Version 3.2021. https://www.nccn.org/professionals/physician_gls/pdf/neuroendocrine.pdf.
13. Else T, Greenberg S, Fishbein L. Hereditary Paraganglioma-Pheochromocytoma Syndromes. 2008 May 21 [Updated 2018 Oct 4]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2020. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1548/.
14. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Gastric Cancer. Version 1.2021. https://www.nccn.org/professionals/physician_gls/pdf/gastric.pdf.
15. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Kidney Cancer. Version 2.2022. https://www.nccn.org/professionals/physician_gls/pdf/kidney.pdf.
16. Jasperson KW, Patel SG, Ahnen DJ. APC-Associated Polyposis Conditions. 1998 Dec 18 [Updated 2017 Feb 2]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2020. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1345/.
17. Kaurah P, Huntsman DG. Hereditary Diffuse Gastric Cancer. 2002 Nov 4 [Updated 2018 Mar 22]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2020. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1139/.
18. van Leeuwaarde RS, Ahmad S, Links TP, et al. Von Hippel-Lindau Syndrome. 2000 May 17 [Updated 2018 Sep 6]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2020. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1463/.
19. Skalet AH, Gombos DS, Gallie BL, et al. Screening Children at Risk for Retinoblastoma: Consensus Report from the American Association of Ophthalmic Oncologists and Pathologists. *Ophthalmology*. 2018;125(3):453-458. doi:10.1016/j.ophtha.2017.09.001
20. Hampel, H., Bennett, R., Buchanan, A. *et al.* A practice guideline from the American College of Medical Genetics and Genomics and the National Society of Genetic Counselors: referral indications for cancer predisposition assessment. *Genet Med* 17, 70–87 (2015). https://doi.org/10.1038/gim.2014.147
21. Bashford, M.T., Kohlman, W., Everett, J. *et al.* Addendum: A practice guideline from the American College of Medical Genetics and Genomics and the National Society of Genetic

Counselors: referral indications for cancer predisposition assessment. *Genet Med* 21, 2844 (2019). https://doi.org/10.1038/s41436-019-0586-y

22. Lohmann DR, Gallie BL. Retinoblastoma. 2000 Jul 18 [Updated 2018 Nov 21]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2020. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1452/.
23. Menko FH, Maher ER, Schmidt LS, et al. Hereditary leiomyomatosis and renal cell cancer (HLRCC): renal cancer risk, surveillance and treatment. *Fam Cancer*. 2014;13(4):637-644. doi:10.1007/s10689-014-9735-2
24. Schultz KAP, Rednam SP, Kamihara J, et al. *PTEN, DICER1, FH*, and Their Associated Tumor Susceptibility Syndromes: Clinical Features, Genetics, and Surveillance Recommendations in Childhood. *Clin Cancer Res*. 2017;23(12):e76-e82. doi:10.1158/1078-0432.CCR-17-0629
25. Konstantinopoulos PA, Norquist B, Lacchetti C, et al. Germline and Somatic Tumor Testing in Epithelial Ovarian Cancer: ASCO Guideline. *J Clin Oncol*. 2020;38(11):1222-1245. doi:10.1200/JCO.19.02960
26. Li MM, Chao E, Esplin ED, et al. Points to consider for reporting of germline variation in patients undergoing tumor testing: a statement of the American College of Medical Genetics and Genomics (ACMG). *Genet Med*. 2020;22(7):1142-1148. doi:10.1038/s41436-020-0783-8
27. Blair VR, McLeod M, Carneiro F, et al. Hereditary diffuse gastric cancer: updated clinical practice guidelines. *Lancet Oncol.* 2020;21(8):e386-e397. doi:10.1016/S1470-2045(20)30219-9
28. Sattler EC, Steinlein OK. Birt-Hogg-Dube Syndrome. 2006 Feb 27 [Updated 2020 Jan 30]. In: Adam MP, Ardinger HH, Pagon RA, et al., editory. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2020. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1522/
29. Evans DG, Farndon PA. Nevoid Basal Cell Carcinoma Syndrome. 2002 June 20 [Updated 2018 Mar 29]. n: Adam MP, Ardinger HH, Pagon RA, et al., editory. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2021. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1151/
30. Pilarski R, Carlo M, Cebulla C, et al. BAP1 Tumor Predisposition Syndrome. 2016 Oct 13 [Updated 2020 Sep 17]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2021. Available from: https://www.ncbi.nlm.nih.gov/books/NBK390611/
31. Hereditary Cancer Syndromes and Risk Assessment: ACOG COMMITTEE OPINION, Number 793. Obstet Gynecol. 2019;134(6):e143-e149. doi:10.1097/AOG.0000000000003562
32. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology: Breast Cancer. Version 8.2021. https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf.

Important Reminder

This clinical policy has been developed by appropriately experienced and licensed health care professionals based on a review and consideration of currently available generally accepted standards of medical practice; peer-reviewed medical literature; government agency/program approval status; evidence-based guidelines and positions of leading national health professional organizations; views of physicians practicing in relevant clinical areas affected by this clinical policy; and other available clinical information. LHCC makes no representations and accepts no liability with respect to the content of any external information used or relied upon in developing this clinical policy. This clinical policy is consistent with standards of medical practice current at the time that this clinical policy was approved.

The purpose of this clinical policy is to provide a guide to medical necessity, which is a component of the guidelines used to assist in making coverage decisions and administering benefits. It does not constitute a contract or guarantee regarding payment or results. Coverage decisions and the administration of benefits are subject to all terms, conditions, exclusions and limitations of the coverage documents (e.g., evidence of coverage, certificate of coverage, policy, contract of insurance, etc.), as well as to state and federal requirements and applicable LHCC administrative policies and procedures.

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