Clinical Policy: Genetic Testing Hereditary Cancer Susceptibility
Reference Number: CP.MP.225
Date of Last Revision: 02/22

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.

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

<table>
<thead>
<tr>
<th>CPT® Codes</th>
<th>Example Tests (Labs)</th>
<th>Criteria Section</th>
<th>Common ICD Codes</th>
</tr>
</thead>
<tbody>
<tr>
<td>81432, 81433,</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>81435, 81436</td>
<td>MyRisk (Myriad)</td>
<td>Pan-Cancer Hereditary Cancer Susceptibility Panels</td>
<td>C15-26, C50-58</td>
</tr>
<tr>
<td></td>
<td>VistaSeq (LabCorp)</td>
<td></td>
<td>Z17, Z80, Z83, Z84, Z85, Z86</td>
</tr>
<tr>
<td></td>
<td>Comprehensive Common Cancer Panel (GeneDx)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Common Hereditary Cancer Panel (Invitae)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Riscover - Comprehensive (Progenity)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Breast &amp; Gyn Cancer Panel (Invitae)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Genetic Testing Hereditary Cancer Susceptibility

<table>
<thead>
<tr>
<th>CPT® Codes</th>
<th>Example Tests (Labs)</th>
<th>Criteria Section</th>
<th>Common ICD Codes</th>
</tr>
</thead>
<tbody>
<tr>
<td>0104U</td>
<td>CancerNext (Ambry Genetics)</td>
<td><strong>Pan-Cancer Hereditary Cancer Susceptibility Panels</strong></td>
<td>C15-26, C50-58 Z17, Z80, Z83, Z84, Z85, Z86</td>
</tr>
<tr>
<td>0103U</td>
<td>OvaNext (Ambry Genetics)</td>
<td><strong>Pan-Cancer Hereditary Cancer Susceptibility Panels</strong></td>
<td>C15-26, C50-58 Z17, Z80, Z83, Z84, Z85, Z86</td>
</tr>
<tr>
<td>0132U</td>
<td>RNAinsight for OvaNext (Ambry Genetics)</td>
<td><strong>Pan-Cancer Hereditary Cancer Susceptibility Panels</strong></td>
<td>C15-26, C50-58 Z17, Z80, Z83, Z84, Z85, Z86</td>
</tr>
<tr>
<td>0134U</td>
<td>RNAinsight for CancerNext (Ambry Genetics)</td>
<td><strong>Pan-Cancer Hereditary Cancer Susceptibility Panels</strong></td>
<td>C15-26, C50-58 Z17, Z80, Z83, Z84, Z85, Z86</td>
</tr>
<tr>
<td>0135U</td>
<td>RNAinsight for GYNPlus (Ambry Genetics)</td>
<td><strong>Pan-Cancer Hereditary Cancer Susceptibility Panels</strong></td>
<td>C15-26, C50-58 Z17, Z80, Z83, Z84, Z85, Z86</td>
</tr>
<tr>
<td>81162,81163, 81164,81165, 81166,81167, 81216, 81432, 81433</td>
<td>Breast Cancer Panel (LabCorp)</td>
<td><strong>Hereditary Breast Cancer Susceptibility Panels</strong></td>
<td>C50, Z80.3, Z83, Z84, Z85, Z86</td>
</tr>
<tr>
<td>81162,81163, 81164,81165, 81166,81167, 81216, 81432, 81433</td>
<td>Breast Cancer Panel (Invitae)</td>
<td><strong>Hereditary Breast Cancer Susceptibility Panels</strong></td>
<td>C50, Z80.3, Z83, Z84, Z85, Z86</td>
</tr>
<tr>
<td>81162,81163, 81164,81165, 81166,81167, 81216, 81432, 81433</td>
<td>Breast Cancer - Comprehensive Risk Panel (PreventionGenetics)</td>
<td><strong>Hereditary Breast Cancer Susceptibility Panels</strong></td>
<td>C50, Z80.3, Z83, Z84, Z85, Z86</td>
</tr>
<tr>
<td>81162,81163, 81164,81165, 81166,81167, 81216, 81432, 81433</td>
<td>Breast Cancer High Risk Panel (GeneDx)</td>
<td><strong>Hereditary Breast Cancer Susceptibility Panels</strong></td>
<td>C50, Z80.3, Z83, Z84, Z85, Z86</td>
</tr>
<tr>
<td>0102U</td>
<td>BreastNext (Ambry Genetics)</td>
<td><strong>Hereditary Breast Cancer Susceptibility Panels</strong></td>
<td>C50, Z80.3, Z83, Z84, Z85, Z86</td>
</tr>
<tr>
<td>0129U</td>
<td>BRCAplus (Ambry Genetics)</td>
<td><strong>Hereditary Breast Cancer Susceptibility Panels</strong></td>
<td>C50, Z80.3, Z83, Z84, Z85, Z86</td>
</tr>
<tr>
<td>0131U</td>
<td>RNAinsight for BreastNext (Ambry Genetics)</td>
<td><strong>Hereditary Breast Cancer Susceptibility Panels</strong></td>
<td>C50, Z80.3, Z83, Z84, Z85, Z86</td>
</tr>
<tr>
<td>CPT® Codes</td>
<td>Example Tests (Labs)</td>
<td>Criteria Section</td>
<td>Common ICD Codes</td>
</tr>
<tr>
<td>------------</td>
<td>---------------------</td>
<td>------------------</td>
<td>------------------</td>
</tr>
<tr>
<td>81435, 81436</td>
<td>Colorectal Cancer Panel (PreventionGenetics)</td>
<td>Hereditary Colorectal Cancer Susceptibility Panels</td>
<td>C15-26, Z23, Z80, Z83, Z84, Z85, Z86</td>
</tr>
<tr>
<td></td>
<td>VistaSeq Colorectal Cancer Panel (LabCorp)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Colorectal Cancer Guidelines-based Panel (Invitae)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Riscover - Lynch Syndrome (Progenity)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Colaris (Myriad)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0101U</td>
<td>ColoNext (Ambry Genetics)</td>
<td>Hereditary Colorectal Cancer Susceptibility Panels</td>
<td>C15-26, Z23, Z80, Z83, Z84, Z85, Z86</td>
</tr>
<tr>
<td>0130U</td>
<td>RNAinsight for ColoNext (Ambry Genetics)</td>
<td>Hereditary Colorectal Cancer Susceptibility Panels</td>
<td>C15-26, Z23, Z80, Z83, Z84, Z85, Z86</td>
</tr>
<tr>
<td>81292,81294, 81295,81297, 81298,81300, 81317,81319, 81403,81406, 81479</td>
<td>Invitae Gastric Cancer Panel (Invitae)</td>
<td>Hereditary Gastric Cancer Susceptibility Panels</td>
<td>C16, Z80, Z85, Z86</td>
</tr>
<tr>
<td></td>
<td>Gastric Cancer Panel (Fulgent Genetics)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>81162,81163, 81164, 81165, 81166,81167, 81216,81292, 81294,81295, 81297,81298, 81300,81307, 81317, 1319, 81404,81405, 81479</td>
<td>Pancreatic Cancer Panel (GeneDx)</td>
<td>Hereditary Pancreatic Cancer Susceptibility Panels</td>
<td>C25, Z80, Z84, Z85, Z86</td>
</tr>
<tr>
<td></td>
<td>Invitae Pancreatic Cancer Panel (Invitae)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pancreatic Cancer Panel (PreventionGenetics)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>PancNext (Ambry Genetics)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>81201,81203, 81406,81479, S3833</td>
<td>Hereditary Polyposis Panel (PreventionGenetics)</td>
<td>Hereditary Polyposis Panels</td>
<td>D12, K63.5, Z80, Z84, Z85, Z86</td>
</tr>
<tr>
<td></td>
<td>Familial Adenomatous Polyposis Panel (ARUP)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>81162, 1163, 81164,81165, 81166,81167, 81216,81292, 81294,81295, 81297,81298,</td>
<td>Prostate Cancer Panel (PreventionGenetics)</td>
<td>Hereditary Prostate Cancer Susceptibility Panels</td>
<td>C61, Z80, Z84, Z85, Z86</td>
</tr>
<tr>
<td></td>
<td>Invitae Prostate Cancer Panel (Invitae)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Genetic Testing Hereditary Cancer Susceptibility

<table>
<thead>
<tr>
<th>CPT® Codes</th>
<th>Example Tests (Labs)</th>
<th>Criteria Section</th>
<th>Common ICD Codes</th>
</tr>
</thead>
<tbody>
<tr>
<td>81300, 81317, 81319</td>
<td>Hereditary Prostate Cancer Panel (GeneDx)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>ProstateNext (Ambry Genetics)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0133 U</td>
<td>RNAinsight for ProstateNext (Ambry Genetics)</td>
<td>Hereditary Prostate Cancer Susceptibility Panels</td>
<td>C61, Z80, Z84, Z85, Z86</td>
</tr>
<tr>
<td>81437, 81438</td>
<td>Hereditary Paraganglioma-Pheochromocytoma syndrome Panel (PreventionGenetics)</td>
<td>Hereditary Neuroendocrine Cancer Susceptibility Panels</td>
<td>C74-75, C7A Z80, Z84, Z85, Z86</td>
</tr>
<tr>
<td></td>
<td>Invitae Hereditary Paraganglioma-Pheochromocytoma syndrome Panel (Invitae)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>PGL/PCC (Paraganglioma/Pheochromocytoma) Panel (GeneDx)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>PGLNext (Ambry Genetics)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>81432, 81433, 81435, 81436, 81437, 81438, 81445, 81450, 81455</td>
<td>CancerNext-Expanded (Ambry Genetics) with MI Profile (Caris Life Sciences)</td>
<td>Simultaneous Germline and Tumor Molecular Profiling</td>
<td>C00-D49, Z85</td>
</tr>
<tr>
<td>81215, 81217</td>
<td>BRCA1 Targeted Mutation Tests</td>
<td>BRCA1/BRCA2 Targeted Variant Analysis</td>
<td>C50-58, D05, Z17, Z80, Z83, Z84, Z85, Z86</td>
</tr>
<tr>
<td></td>
<td>BRCA2 Targeted Mutation Tests</td>
<td></td>
<td></td>
</tr>
<tr>
<td>81212</td>
<td>BRCA Ashkenazi Jewish Panel (185delAG, 5385insC, and 6174delT)</td>
<td>BRCA1/BRCA2 Targeted Variant Analysis</td>
<td>C50-58, D05, Z17, Z80, Z83, Z84, Z85, Z86</td>
</tr>
<tr>
<td>81162, 81163, 81164, 81165, 81166, 81167, 81216</td>
<td>BRCA1 Sequencing BRCA2 Sequencing</td>
<td>BRCA1/BRCA2 Sequencing and/or Deletion Duplication Analysis</td>
<td>C50-58, D05, Z17, Z80, Z83, Z84, Z85, Z86</td>
</tr>
<tr>
<td>0138 U</td>
<td>RNAinsight for BRCA1/2 (Ambry Genetics)</td>
<td>BRCA1/BRCA2 Sequencing and/or Deletion Duplication Analysis</td>
<td>C50-58, D05, Z17, Z80, Z83, Z84, Z85, Z86</td>
</tr>
</tbody>
</table>
### Genetic Testing Hereditary Cancer Susceptibility

<table>
<thead>
<tr>
<th>CPT® Codes</th>
<th>Example Tests (Labs)</th>
<th>Criteria Section</th>
<th>Common ICD Codes</th>
</tr>
</thead>
<tbody>
<tr>
<td>81308</td>
<td>PALB2 Targeted Mutation Tests</td>
<td>PALB2 Targeted Variant Analysis</td>
<td>C15-26, Z80, Z84, Z85, Z86</td>
</tr>
<tr>
<td>81307, 81479</td>
<td>PALB2 Sequencing PALB2 Deletion/Duplication</td>
<td>PALB2 Sequencing and/or Deletion/Duplication Analysis</td>
<td>C15-26, Z80, Z84, Z85, Z86</td>
</tr>
<tr>
<td>0137U</td>
<td>RNAinsight for PALB2 (Ambry Genetics)</td>
<td>PALB2 Sequencing and/or Deletion/Duplication Analysis</td>
<td>C15-26, Z80, Z84, Z85, Z86</td>
</tr>
<tr>
<td>81403</td>
<td>ATM Targeted Mutation Tests CHEK2 Targeted Mutation Tests</td>
<td>ATM or CHECK2 Targeted Variant Analysis</td>
<td>C50, D05, Z80, Z84, Z85, Z86</td>
</tr>
<tr>
<td>81408, 81479</td>
<td>ATM Sequencing Tests ATM Deletion/Duplication Tests CHEK2 Sequencing Tests CHEK2 Deletion/Duplication Tests</td>
<td>ATM or CHECK2 Sequencing and/or Deletion/Duplication Analysis</td>
<td>C50, D05, Z80, Z84, Z85, Z86</td>
</tr>
<tr>
<td>0136U</td>
<td>RNAinsight for ATM (Ambry Genetics)</td>
<td>ATM or CHECK2 Sequencing and/or Deletion/Duplication Analysis</td>
<td>C50, D05, Z80, Z84, Z85, Z86</td>
</tr>
<tr>
<td>0157U</td>
<td>CustomNext + RNA: APC (Ambry Genetics)</td>
<td>ATM or CHECK2 Sequencing and/or Deletion/Duplication Analysis</td>
<td>C50, D05, Z80, Z84, Z85, Z86</td>
</tr>
<tr>
<td>81293, 81296, 81299, 81318</td>
<td>MLH1 Targeted Mutation Tests MSH2 Targeted Mutation Tests MSH6 Targeted Mutation Tests PMS2 Targeted Mutation Tests</td>
<td>MLH1, MSH2, MSH6, PMS2, EPCAM Sequencing and/or Deletion/Duplication Analysis</td>
<td>C15-26, C50-58 Z23, Z80, Z84, Z85, Z86</td>
</tr>
<tr>
<td>CPT® Codes</td>
<td>Example Tests (Labs)</td>
<td>Criteria Section</td>
<td>Common ICD Codes</td>
</tr>
<tr>
<td>------------</td>
<td>----------------------</td>
<td>------------------</td>
<td>------------------</td>
</tr>
<tr>
<td>81292,81294, 81295, 81297, 81298, 81300, 81317, 81319, 81403</td>
<td>Lynch Syndrome Panel (Quest Diagnostics)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>HNPCC Seq and del/dup (Ambry Genetics)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lynch Syndrome Panel (GeneDx)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lynch Syndrome (Invitae)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>MLH1, MSH2, MSH6, PMS2, EPCAM Sequencing and/or Deletion/Duplication Analysis</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>C15-26, C50-58, Z23, Z80, Z84, Z85, Z86</td>
<td></td>
</tr>
<tr>
<td>0238U</td>
<td>Genomic Unity Lynch Syndrome Analysis (Variantyx Inc)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>MLH1, MSH2, MSH6, PMS2, EPCAM Sequencing and/or Deletion/Duplication Analysis</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>C15-26, C50-58, Z23, Z80, Z84, Z85, Z86</td>
<td></td>
</tr>
<tr>
<td>81403</td>
<td>BAP1 Targeted Mutation Tests</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>BAP1 Targeted Variant Analysis</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>C22, C45, C64 C69, D22, D32, Z80, Z84, Z85, Z86</td>
<td></td>
</tr>
<tr>
<td>81479</td>
<td>BAP1 Sequencing Tests</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>BAP1 Sequencing and/or Deletion/Duplication Analysis</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>C22, C45, C64 C69, D22, D32, Z80, Z84, Z85, Z86</td>
<td></td>
</tr>
<tr>
<td>81403</td>
<td>FLCN Targeted Mutation Tests</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>FLCN Targeted Variant Analysis</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>C65, Z84, Z85, Z86</td>
<td></td>
</tr>
<tr>
<td>81479</td>
<td>FLCN Sequencing Tests</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>FLCN Sequencing and/or Deletion/Duplication Analysis</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>C65, Z84, Z85, Z86</td>
<td></td>
</tr>
<tr>
<td>81322</td>
<td>PTEN Targeted Mutation Tests</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>PTEN Targeted Variant Analysis</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>C15-26, C50-58, C73-75, D10-36, Q87.89, Z80, Z84, Z85, Z86</td>
<td></td>
</tr>
<tr>
<td>81321, 81323</td>
<td>PTEN Sequencing Tests</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>PTEN Sequencing and/or Deletion/Duplication Analysis</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>C15-26, C50-58, C73-75, D10-36, Q87.89, Z80, Z84, Z85, Z86</td>
<td></td>
</tr>
<tr>
<td>0235U</td>
<td>Genomic Unity® PTEN Analysis (Variantyx Inc)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>PTEN Sequencing and/or Deletion/Duplication Analysis</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>C15-26, C50-58, C73-75, D10-36, Q87.89, Z80, Z84, Z85, Z86</td>
<td></td>
</tr>
<tr>
<td>81202, S3834</td>
<td>APC Targeted Mutation Tests</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>APC Targeted Variant Analysis</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>C15-26, Z80, Z84, Z85, Z86</td>
<td></td>
</tr>
<tr>
<td>CPT® Codes</td>
<td>Example Tests (Labs)</td>
<td>Criteria Section</td>
<td>Common ICD Codes</td>
</tr>
<tr>
<td>----------------------</td>
<td>----------------------------------------------------------</td>
<td>-------------------------------------------------------</td>
<td>--------------------------------------</td>
</tr>
<tr>
<td>81201, 81203, S3833</td>
<td>APC Sequencing Tests</td>
<td>APC Sequencing and/or Deletion/Duplication Analysis</td>
<td>C15-26, Z80, Z84, Z85, Z86</td>
</tr>
<tr>
<td></td>
<td>APC Deletion/Duplication Tests</td>
<td></td>
<td></td>
</tr>
<tr>
<td>81403</td>
<td>CDKN2A Targeted Mutation Tests</td>
<td>CDKN2A Targeted Variant Analysis</td>
<td>C43, Z12.83, Z80, Z84, Z85, Z86</td>
</tr>
<tr>
<td></td>
<td>CDKN2A Sequencing Tests</td>
<td>CDKN2A Sequencing and/or Deletion/Duplication Analysis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CDKN2A Deletion/Duplication Tests</td>
<td></td>
<td></td>
</tr>
<tr>
<td>81403</td>
<td>CDH1 Targeted Mutation Tests</td>
<td>CDH1 Targeted Mutation Tests</td>
<td>C16, Z80, Z84, Z85, Z86</td>
</tr>
<tr>
<td></td>
<td>CDH1 Sequencing Tests</td>
<td>CDH1 Sequencing and/or Deletion/Duplication</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CDH1 Deletion/Duplication Tests</td>
<td>Deletion/Duplication Analysis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CDH1 Deletion/Duplication Tests</td>
<td></td>
<td></td>
</tr>
<tr>
<td>81403</td>
<td>SMAD4 Targeted Mutation Tests</td>
<td>SMAD4 and/or BMPR1A Sequencing and/or Deletion/Duplication Analysis</td>
<td>C15-C26, Z80, Z84, Z85, Z86</td>
</tr>
<tr>
<td></td>
<td>BMPR1A Targeted Mutation Tests</td>
<td></td>
<td></td>
</tr>
<tr>
<td>81405, 81406</td>
<td>SMAD4 Sequencing Tests</td>
<td>SMAD4 and/or BMPR1A Sequencing and/or Deletion/Duplication Analysis</td>
<td>C15-C26, Z80, Z84, Z85, Z86</td>
</tr>
<tr>
<td></td>
<td>BMPR1A Sequencing Tests</td>
<td></td>
<td></td>
</tr>
<tr>
<td>81403</td>
<td>FH Targeted Mutation Tests</td>
<td>FH Targeted Variant Analysis</td>
<td>C44, C55, C64, D23, D25, Z84, Z85, Z86</td>
</tr>
<tr>
<td></td>
<td>FH Sequencing Tests</td>
<td>FH Sequencing and/or Deletion/Duplication Analysis</td>
<td>C44, C55, C64, D23, D25, Z84, Z85, Z86</td>
</tr>
<tr>
<td></td>
<td>FH Deletion/Duplication Tests</td>
<td></td>
<td></td>
</tr>
<tr>
<td>81404, 81352, 81353</td>
<td>TP53 Targeted Mutation Tests</td>
<td>TP53 Targeted Variant Analysis</td>
<td>C30-41, C15-26, C45-58, Z80, Z84, Z85, Z86</td>
</tr>
<tr>
<td></td>
<td>TP53 Sequencing Tests</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>TP53 Deletion/Duplication Tests</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CPT® Codes</td>
<td>Example Tests (Labs)</td>
<td>Criteria Section</td>
<td>Common ICD Codes</td>
</tr>
<tr>
<td>----------------</td>
<td>-----------------------------------------------</td>
<td>-------------------------------------------------------</td>
<td>-------------------------------</td>
</tr>
</tbody>
</table>
| 81351, 81405, 81479 | TP53 Sequencing Tests  
                   | TP53 Deletion/Duplication Tests                   | **TP53 Sequencing and/or Deletion/Duplication Analysis** | C30-41, C15-26, C45-58, Z80, Z84, Z85, Z86 |
| 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                 | **PTCH1 and/or SUFU Targeted Variant Analysis**       | C44, G93, M27, Z84, Z85, Z86   |
| 81479          | PTCH1 Sequencing Tests  
                   | PTCH1 Deletion/Duplication Tests                    | **PTCH1 and SUFU Sequencing and/or Duplication Analysis** | C44, G93, M27, Z84, Z85, Z86 |
| 81403          | SDHB Targeted Mutation Tests                  | **MAX, SDHA, SDHAF2, SDHB, SDHC, SDHD, or TMEM127 Targeted Variant Analysis** | C7A, C74.10, D35.00, Z84, Z85, Z86 |

**Clinical Policy**
Genetic Testing Hereditary Cancer Susceptibility

---

*Note: The above table provides a summary of CPT codes for genetic testing, including specific tests and their associated criteria sections. The Common ICD Codes listed correspond to the diagnostic codes used in clinical coding.*
This policy document provides criteria for genetic testing for hereditary cancer susceptibility.

Please refer to:

- **CP.MP.230 Genetic Testing: Multisystem Inherited Disorders, Intellectual Disability, and Developmental Delay** for criteria related to diagnostic testing for Fanconi anemia.
Clinical Policy
Genetic Testing Hereditary Cancer Susceptibility

- **CP.MP.237 Oncology: Algorithmic Testing** for criteria related to tests that give prognostic information for an individual with cancer, or any oncology related test that involved an algorithmic portion.

- **CP.MP.241 Oncology: Molecular Analysis of Solid Tumors and Hematologic Malignancies** for criteria related to somatic tumor testing, including Microsatellite Instability for colon cancer, and blood cancer testing.

- **CP.MP.238 Oncology: Cancer Screening** for criteria related to tests that screen for the presence of cancer.

- **CP.MP.239 Oncology: Circulating Tumor DNA and Circulating Tumor Cells (Liquid Biopsy)** for criteria related to the testing of tumor DNA circulating in an individual's blood stream.

- **CP.MP.222 Genetic Testing: General Approach to Genetic Testing** for criteria related to hereditary cancer susceptibility that is not specifically discussed in this or other non-general policies.

Policy/Criteria
Pan-Cancer Hereditary Cancer Susceptibility Panels
A pan-cancer hereditary cancer susceptibility panel includes genes that are associated with inherited susceptibility to several different types of cancer (e.g., breast cancer, colon cancer, stomach cancer, etc.).

I. It is the policy of health plans affiliated with Centene Corporation© 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 of 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 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)

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

   D. The panel does not include genes without a known association with cancer by ClinGen.
II. It is the policy of health plans affiliated with Centene Corporation 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.

III. It is the policy of health plans affiliated with Centene Corporation 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.

Hereditary Breast Cancer Susceptibility Panels

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

I. It is the policy of health plans affiliated with Centene Corporation 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 all of 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 has a personal history of any of the following:
   a) Male breast cancer
   b) Bilateral breast cancer
   c) Triple-negative breast cancer

2. The member/enrollee is a female who has a personal history of breast cancer and one of the following:
   a) Diagnosed ≤50 years
   b) Diagnosed >50 years and one of the following:
      (1) One or more close relatives with breast cancer <50 years
      (2) Two or more close relatives with breast at any age
      (3) An unknown or limited family history

3. The member/enrollee does not meet any of the above criteria, but has one or more first- or second-degree relatives meeting any of the above criteria.
C. The panel includes, at a minimum, sequencing of the following genes: *BRCA1*, *BRCA2*;

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

II. It is the policy of health plans affiliated with Centene Corporation 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:

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

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

III. It is the policy of health plans affiliated with Centene Corporation 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.

IV. It is the policy of health plans affiliated with Centene Corporation 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.

Hereditary Colorectal Cancer Susceptibility

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

I. It is the policy of health plans affiliated with Centene Corporation that genetic testing using a hereditary colorectal cancer susceptibility panel (81435, 81436, 0101U) is considered medically necessary when meeting all of 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) Familial Adenomatous Polyposis (FAP)/Attenuated FAP (AFAP)

   b) Cowden Syndrome (CS)/PTEN Hamartoma Tumor Syndrome (PHTS)
CLINICAL POLICY
Genetic Testing Hereditary Cancer Susceptibility

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

d) Juvenile Polyposis Syndrome (JPS)

e) MUTYH-associated Polyposis (MAP)

f) Peutz-Jeghers Syndrome (PJS)

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.

II. It is the policy of health plans affiliated with Centene Corporation that current evidence does not support genetic testing using a hereditary colorectal cancer susceptibility panel (81435, 81436, 0101U) for all other indications.

III. It is the policy of health plans affiliated with Centene Corporation 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.

Hereditary Gastric Cancer Susceptibility Panels
A hereditary gastric cancer susceptibility panel includes genes that are associated with inherited susceptibility to gastric (stomach) cancer.

I. It is the policy of health plans affiliated with Centene Corporation 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 of 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)
CLINICAL POLICY
Genetic Testing Hereditary Cancer Susceptibility

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.

II. It is the policy of health plans affiliated with Centene Corporation 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.

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

I. It is the policy of health plans affiliated with Centene Corporation 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 of 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, CDKN2A, MLH1, MSH2, MSH6, PALB2, PMS2, STK11;

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

II. It is the policy of health plans affiliated with Centene Corporation 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.

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

I. It is the policy of health plans affiliated with Centene Corporation that genetic testing using a hereditary polyposis panel (81201, 81203, 81406, 81479, S3833) 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):
Genetic Testing Hereditary Cancer Susceptibility

1. Familial Adenomatous Polyposis (FAP)/Attenuated FAP

2. MUTYH associated polyposis (MAP)

   B. The panel includes, at a minimum, sequencing of the following genes: \( \textit{APC} \) and \( \textit{MUTYH} \);

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

II. It is the policy of health plans affiliated with Centene Corporation that current evidence does not support genetic testing using a hereditary polyposis panel (81201, 81203, 81406, 81479, S3833) for all other indications.

Hereditary Prostate Cancer Susceptibility Panels
A hereditary prostate cancer susceptibility panel is one that includes genes that are associated with inherited susceptibility to prostate cancer.

I. It is the policy of health plans affiliated with Centene Corporation 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 \textbf{medically necessary} when meeting all of 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 \( \textit{BRCA1} \) and \( \textit{BRCA2} \) sequencing and/or deletion/duplication gene testing (see \textit{BRCA1} and \textit{BRCA2} sequencing and/or deletion/duplication criteria below)

   C. The panel includes, at a minimum, sequencing of the following genes: \( \textit{BRCA1}, \textit{BRCA2}, \textit{MLH1}, \textit{MSH2}, \textit{MSH6}, \textit{PMS2}, \textit{HOXB13} \);

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

II. It is the policy of health plans affiliated with Centene Corporation that current evidence does not support genetic testing using a hereditary prostate cancer susceptibility panel (81479, 0133U for all other indications.

III. It is the policy of health plans affiliated with Centene Corporation 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.

Hereditary Neuroendocrine Cancer Susceptibility Panels
A hereditary neuroendocrine cancer susceptibility panel is one that includes genes that are associated with inherited susceptibility to a neuroendocrine cancer.
I. It is the policy of health plans affiliated with Centene Corporation that genetic testing using a hereditary neuroendocrine cancer susceptibility panel (81437, 81438) is considered **medically necessary** when meeting all of 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.

II. It is the policy of health plans affiliated with Centene Corporation 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.

**Simultaneous Germline and Tumor Molecular Profiling**

I. It is the policy of health plans affiliated with Centene Corporation that current evidence does not support the use of **hereditary cancer susceptibility panels** (81432, 81433, 81435, 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 panel criteria above).

**BRCA1 and BRCA2 Gene Testing**

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

I. It is the policy of health plans affiliated with Centene Corporation that **BRCA1 (81215)** or **BRCA2 (81217)** targeted variant analysis for hereditary 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 **BRCA1** or **BRCA2** pathogenic or likely pathogenic variant
      2. The member/enrollee is seeking confirmatory testing for a **BRCA1** or **BRCA2** variant detected by an Food and Drug Administration (FDA)-authorized direct-to-consumer (DTC) test report;
CLINICAL POLICY
Genetic Testing Hereditary Cancer Susceptibility

3. A **BRCA1** or **BRCA2** pathogenic or likely pathogenic variant was detected by tumor profiling and germline analysis has not yet been performed.

II. It is the policy of health plans affiliated with Centene Corporation that current evidence does not support **BRCA1** (81215) or **BRCA2** (81217) targeted variant analysis for hereditary cancer susceptibility for all other indications.

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

I. It is the policy of health plans affiliated with Centene Corporation that **BRCA1** and **BRCA2** (81212) targeted variant analysis for the 185delAG, 5385insC, 6174delT variants is considered medically necessary when meeting both of the following:

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

   B. The member/enrollee is of Ashkenazi Jewish ancestry.

II. It is the policy of health plans affiliated with Centene Corporation that current evidence does not support **BRCA1** and **BRCA2** (81212) targeted variant analysis for the 185delAG, 5385insC, 6174delT variants for all other indications.

BRCA1 and BRCA2 Sequencing and/or Deletion/Duplication Analysis

I. It is the policy of health plans affiliated with Centene Corporation that **BRCA1** and **BRCA2** sequencing and/or deletion/duplication analysis (81162, 81163, 81164, 81165, 81166, 81167, 81216, 0138U) for hereditary cancer susceptibility is considered medically necessary when:

   A. The member/enrollee is 18 years or older and one of the following:

   1. 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
      h) Metastatic prostate cancer;

   2. The member/enrollee is a female who has a personal history of breast cancer³ and one of the following:

      a) Diagnosed ≤50 years;

      b) Diagnosed >50 years and one of the following:

         (1) One or more close relative¹ with ovarian, pancreatic, or metastatic prostate cancer at any age
**CLINICAL POLICY**  
Genetic Testing Hereditary Cancer Susceptibility

(2) One or more close relatives\(^1\) with breast cancer <50 years

(3) Two or more close relatives\(^1\) with breast or prostate cancer at any age

(4) An unknown or limited family history\(^2\)

3. Personal history of high-grade prostate cancer (Gleason score $\geq 7$) at any age with one of the following:
   
a) One or more close relatives\(^1\) with ovarian, pancreatic, or metastatic prostate cancer at any age

b) One or more close relatives\(^1\) with breast cancer <50 years

c) Two or more close relatives\(^1\) with breast or prostate cancer at any age;

4. 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

5. The member/enrollee is being considered for PARP inhibitor therapy and has a personal history of recurrent or metastatic breast cancer;

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

II. It is the policy of health plans affiliated with Centene Corporation that current evidence does not support BRCA1 and BRCA2 sequencing and/or deletion/duplication analysis (81162, 81163, 81164, 81165, 81166, 81167, 81216, 0138U) for hereditary cancer susceptibility for all other indications.

III. It is the policy of health plans affiliated with Centene Corporation that current evidence does not support BRCA1 and BRCA2 mRNA sequencing analysis for the interpretation of variants of unknown significance (0138U), 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.

**PALB2 Gene Testing**

**PALB2 Targeted Variant Analysis**

I. It is the policy of health plans affiliated with Centene Corporation 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:
CLINICAL POLICY
Genetic Testing Hereditary Cancer Susceptibility

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.

II. It is the policy of health plans affiliated with Centene Corporation that current evidence does not support *PALB2* targeted variant analysis (81308) for hereditary breast and/or ovarian cancer susceptibility for all other indications.

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

I. It is the policy of health plans affiliated with Centene Corporation 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:

A. The member/enrollee is 18 years or older

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

1. 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;

2. The member/enrollee is a female who has a personal history of breast cancer\(^3\) and one of the following:
   a) Diagnosed ≤50 years;
   b) Diagnosed >50 years and one of the following:
      (1) One or more close relative\(^1\) with ovarian or pancreatic cancer at any age
      (2) One or more close relatives\(^1\) with breast cancer <50 years
      (3) Two or more close relatives\(^1\) with breast cancer at any age
      (4) An unknown or limited family history\(^2\);
Clinical Policy
Genetic Testing Hereditary Cancer Susceptibility

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

4. The member/enrollee is being considered for PARP inhibitor therapy and has a personal history of metastatic HER2-negative breast cancer;

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

II. It is the policy of health plans affiliated with Centene Corporation 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.

III. It is the policy of health plans affiliated with Centene Corporation 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.

ATM and/or CHEK2 Gene Testing
ATM or CHEK2 Targeted Variant Analysis

I. It is the policy of health plans affiliated with Centene Corporation 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 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.

II. It is the policy of health plans affiliated with Centene Corporation 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.

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

I. It is the policy of health plans affiliated with Centene Corporation 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.

II. It is the policy of health plans affiliated with Centene Corporation 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
Clinical Policy
Genetic Testing Hereditary Cancer Susceptibility

either considered an existing component of the genetic testing process for quality
assurance, or follow up testing without proven utility.

Lynch Syndrome / Hereditary Nonpolyposis Colorectal Cancer (HNPCC) Testing
MLH1, MSH2, MSH6, PMS2 Targeted Variant Analysis

I. It is the policy of health plans affiliated with Centene Corporation 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:

A. The member/enrollee has a [close relative](#) with a known pathogenic or likely
pathogenic variant in MLH1, MSH2, MSH6, or PMS2;

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

II. It is the policy of health plans affiliated with Centene Corporation that current evidence
does not support MLH1 (81293), MSH2 (81296), MSH6 (81299), or PMS2 (81318)
targeted variant analysis for Lynch syndrome/HNPCC for all other indications.

MLH1, MSH2, MSH6, PMS2, or EPCAM Sequencing and/or Deletion/Duplication Analysis
Familial Hypercholesterolemia (FH) Panels

I. It is the policy of health plans affiliated with Centene Corporation 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.

II. It is the policy of health plans affiliated with Centene Corporation 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.

III. It is the policy of health plans affiliated with Centene Corporation 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.
CLINICAL POLICY
Genetic Testing Hereditary Cancer Susceptibility

BAP1-Tumor Predisposition Syndrome
BAP1 Targeted Variant Analysis
I. It is the policy of health plans affiliated with Centene Corporation 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.

II. It is the policy of health plans affiliated with Centene Corporation that current evidence does not support BAP1 targeted variant analysis (81479) for BAP1-tumor predisposition syndrome for all other indications.

BAP1 Sequencing and/or Deletion/Duplication Analysis
I. It is the policy of health plans affiliated with Centene Corporation 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.

II. It is the policy of health plans affiliated with Centene Corporation that current evidence does not support BAP1 sequencing and/or deletion/duplication analysis (81479) for BAP1-tumor predisposition syndrome for all other indications.
CLINICAL POLICY
Genetic Testing Hereditary Cancer Susceptibility

Birt-Hogg-Dube Syndrome (BHDS)

FLCN Targeted Variant Analysis

I. It is the policy of health plans affiliated with Centene Corporation 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 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.

II. It is the policy of health plans affiliated with Centene Corporation that current evidence does not support FLCN targeted variant analysis (81403) for Birt-Hogg-Dube syndrome (BHDS) for all other indications.

FLCN Sequencing and/or Deletion/Duplication Analysis

I. It is the policy of health plans affiliated with Centene Corporation 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 with BHDS.

II. It is the policy of health plans affiliated with Centene Corporation that current evidence does not support FLCN sequencing and/or deletion/duplication analysis (81479) for Birt-Hogg-Dube syndrome (BHDS) for all other indications.

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

PTEN Targeted Variant Analysis

I. It is the policy of health plans affiliated with Centene Corporation 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 with a known pathogenic or likely pathogenic variant in PTEN.
II. It is the policy of health plans affiliated with Centene Corporation 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.

PTEN Sequencing and/or Deletion/Duplication Analysis
I. It is the policy of health plans affiliated with Centene Corporation 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 relative1 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)

<table>
<thead>
<tr>
<th>Major Criteria:</th>
<th>Minor Criteria:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Breast Cancer</td>
<td>• Autism Spectrum Disorder</td>
</tr>
<tr>
<td>• Endometrial Cancer (epithelial)</td>
<td>• Colon Cancer</td>
</tr>
<tr>
<td>• Thyroid Cancer (follicular)</td>
<td>• Esophageal glycogenic acanthosis (≥3)</td>
</tr>
<tr>
<td>• Gastrointestinal hamartomas</td>
<td>• Lipomas (≥3)</td>
</tr>
<tr>
<td>• Macrocephaly (≥97 percentile)</td>
<td>• Intellectual disability (ie, IQ ≤ 75)</td>
</tr>
<tr>
<td>• Macular pigmentation of the glans penis</td>
<td>• Thyroid cancer (papillary or follicular)</td>
</tr>
<tr>
<td>• Multiple mucocutaneous lesions:</td>
<td>• Thyroid structural lesions (eg, adenoma, multinodular goiter)</td>
</tr>
<tr>
<td>○ One biopsy-proven trichilemmoma</td>
<td>• Renal cell carcinoma</td>
</tr>
<tr>
<td>○ Multiple palmoplantar keratoses</td>
<td>• Single GI hamartoma or ganglieneuroma</td>
</tr>
<tr>
<td>○ Multifocal or extensive oral mucosal</td>
<td>• Testicular lipomatosis</td>
</tr>
<tr>
<td>papillomatosis</td>
<td>• Vascular anomalies (including multiple intracranial developmental venous)</td>
</tr>
<tr>
<td>○ Multiple cutaneous facial papules</td>
<td></td>
</tr>
<tr>
<td>(often verrucous)</td>
<td></td>
</tr>
</tbody>
</table>
II. It is the policy of health plans affiliated with Centene Corporation 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.

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

APC Targeted Variant Analysis
I. It is the policy of health plans affiliated with Centene Corporation that APC targeted variant analysis (81202, S3834) for familial adenomatous polyposis (FAP) 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 APC;

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

II. It is the policy of health plans affiliated with Centene Corporation 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
I. It is the policy of health plans affiliated with Centene Corporation 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:

A. The member/enrollee has a history of any of the following:
   1. 10 or more cumulative colorectal adenomas
   2. Hepatoblastoma
   3. Congenital hypertrophy of the retinal pigment epithelium (CHRPE)
   4. A desmoid tumor
   5. Gastric fundus gland polyps;

B. The member/enrollee has a history of colorectal adenomas and one of the following:
   1. Duodenal or other small bowel adenomas
   2. Papillary thyroid carcinoma
   3. Medulloblastoma;
CLINICAL POLICY
Genetic Testing Hereditary Cancer Susceptibility

C. The member/enrollee has a first-degree relative\textsuperscript{1a} that meets at least one of the above criteria and has not previously undergone APC sequencing and/or deletion duplication analysis.

II. It is the policy of health plans affiliated with Centene Corporation 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.

Familial Atypical Multiple Mole Melanoma (FAMMM) Syndrome
CDKN2A Targeted Variant Analysis
I. It is the policy of health plans affiliated with Centene Corporation 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\textsuperscript{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.

II. It is the policy of health plans affiliated with Centene Corporation that current evidence does not support CDKN2A targeted variant analysis (81403) for familial cutaneous malignant melanoma for all other indications.

CDKN2A Sequencing and/or Deletion/Duplication Analysis
I. It is the policy of health plans affiliated with Centene Corporation 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.

Hereditary Diffuse Gastric Cancer (Aka, Signet Ring Cell Gastric Cancer):
CDH1 Targeted Variant Analysis
I. It is the policy of health plans affiliated with Centene Corporation 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\textsuperscript{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.

II. It is the policy of health plans affiliated with Centene Corporation 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.

CDH1 Sequencing and/or Deletion/Duplication Analysis

I. It is the policy of health plans affiliated with Centene Corporation 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:

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

B. One of the following:

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

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

3. The member/enrollee has diffuse gastric cancer and one or more first-\(^{1a}\) or second-degree\(^{1b}\) relatives diagnosed with gastric cancer;

4. The member/enrollee has a close relative\(^1\) with diffuse gastric cancer and a close relative with lobular breast cancer

5. 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.

II. It is the policy of health plans affiliated with Centene Corporation 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.

Juvenile Polyposis Syndrome (JSP)
SMAD4 or BMPR1A Targeted Variant Analysis

I. It is the policy of health plans affiliated with Centene Corporation 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.
II. It is the policy of health plans affiliated with Centene Corporation that current evidence does not support *SMAD4* and/or *BMPR1A* targeted variant analysis (81403) for juvenile polyposis syndrome (JPS) for all other indications.

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

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

A. The member/enrollee has 5 or more juvenile polyps\(^d\) in the colon

B. The member/enrollee has multiple juvenile polyps\(^4\) throughout the gastrointestinal tract;

C. 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.

II. It is the policy of health plans affiliated with Centene Corporation 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.

**Hereditary Leiomyomatosis and Renal Cell Cancer (HLREE)**

**FH Targeted Variant Analysis**

I. It is the policy of health plans affiliated with Centene Corporation 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.

II. It is the policy of health plans affiliated with Centene Corporation that current evidence does not support *FH* targeted variant analysis (81403) for hereditary leiomyomatosis and renal cell cancer (HLRCC) for all other indications.

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

I. It is the policy of health plans affiliated with Centene Corporation 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:

A. The member/enrollee is 18 years or older
CLINICAL POLICY
Genetic Testing Hereditary Cancer Susceptibility

B. One of the following:

1. The member/enrollee has one or more biopsy proven cutaneous
leiomyoma(s)

2. The member/enrollee has cutaneous leiomyosarcoma

3. The member/enrollee is a female with one of the following:
   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.

II. It is the policy of health plans affiliated with Centene Corporation 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.

FH Sequencing and/or Deletion/Duplication Analysis

I. It is the policy of health plans affiliated with Centene Corporation 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:

A. The member/enrollee is 18 years or older

B. One of the following:

1. The member/enrollee has one or more biopsy proven cutaneous
leiomyoma(s)

2. 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
CLINICAL POLICY
Genetic Testing Hereditary Cancer Susceptibility

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

II. It is the policy of health plans affiliated with Centene Corporation 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.

Li-Fraumeni Syndrome (LFS)
TP53 Targeted Variant Analysis

I. It is the policy of health plans affiliated with Centene Corporation 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.

II. It is the policy of health plans affiliated with Centene Corporation that current evidence does not support TP53 targeted variant analysis (81404) for Li-Fraumeni syndrome (LFS) for all other indications.

TP53 Sequencing and/or Deletion/Duplication Analysis

I. It is the policy of health plans affiliated with Centene Corporation 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:

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

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

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

2. 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:
CLINICAL POLICY
Genetic Testing Hereditary Cancer Susceptibility

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-\textsuperscript{1a} or second-degree\textsuperscript{1b} relative diagnosed with soft tissue sarcoma, osteosarcoma, CNS tumor, breast cancer, adrenocortical carcinoma before 56 years of age.

II. It is the policy of health plans affiliated with Centene Corporation that current evidence does not support \textit{TP53} sequencing and/or deletion/duplication analysis (81405, 81479) for Li-Fraumeni syndrome (LFS) for all other indications.

Multiple Endocrine Neoplasia Type 1 (MEN1)

MEN1 Targeted Variant Analysis

I. It is the policy of health plans affiliated with Centene Corporation that \textit{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\textsuperscript{1} with a known pathogenic or likely pathogenic variant in \textit{MEN1};

B. An \textit{MEN1} pathogenic or likely pathogenic variant was detected by tumor profiling and germline analysis has not yet been performed.

II. It is the policy of health plans affiliated with Centene Corporation that current evidence does not support \textit{MEN1} targeted variant analysis (81403) for multiple endocrine neoplasia type 1 (MEN1) for all other indications.

MEN1 Sequencing and/or Deletion/Duplication Analysis

I. It is the policy of health plans affiliated with Centene Corporation that \textit{MEN1} sequencing and/or deletion/duplication analysis (81404, 81405) for multiple endocrine neoplasia type 1 (MEN1) is considered medically necessary when:

A. The member/enrollee has a personal history of at least two of the following:

1. Pancreatic neuroendocrine tumor (islet cell tumor)

2. Multi-gland parathyroid hyperplasia

3. Pituitary adenoma

II. It is the policy of health plans affiliated with Centene Corporation that current evidence does not support \textit{MEN1} sequencing and/or deletion/duplication analysis (81404, 81405) for multiple endocrine neoplasia type 1 (MEN1) for all other indications.
Clinical Policy
Genetic Testing Hereditary Cancer Susceptibility

Multiple Endocrine Neoplasia Type 2 (MEN2)

RET Targeted Variant Analysis
I. It is the policy of health plans affiliated with Centene Corporation 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.

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

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

A. The member/enrollee has a diagnosis of medullary thyroid cancer

B. The member/enrollee has a diagnosis of primary C-cell hyperplasia

C. The member/enrollee has a personal history of an adrenal pheochromocytoma and parathyroid hyperplasia

D. The member/enrollee has a first-degree relative\(^1\) that meets at least one of the above criteria and has not previously undergone RET sequencing and/or deletion duplication analysis.

II. It is the policy of health plans affiliated with Centene Corporation 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.

Mutyh-Associated Polyposis (MAP)

MUTYH Targeted Variant Analysis
I. It is the policy of health plans affiliated with Centene Corporation 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.

II. It is the policy of health plans affiliated with Centene Corporation that current evidence does not support MUTYH targeted variant analysis (81401) for MYH-associated polyposis (MAP) for all other indications.
**CLINICAL POLICY**

**Genetic Testing Hereditary Cancer Susceptibility**

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

I. It is the policy of health plans affiliated with Centene Corporation 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:

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

B. The member/enrollee has a history of colorectal adenomas and meets one of the following:
   1. Duodenal adenomas or carcinoma
   2. 5 or more serrated polyps proximal to the rectum with at least 2 greater than 10mm;
   3. More than 20 serrated polyps of any size distributed throughout the large bowel with at least 4 proximal to the rectum.

II. It is the policy of health plans affiliated with Centene Corporation that current evidence does not support *MUTYH* sequencing and/or deletion/duplication analysis (81406, 81479) for MYH-associated polyposis (MAP) for all other indications.

**Nevoid Basal Cell Carcinoma Syndrome (Aka Gorlin Syndrome)**

**PTCH1 or SUFU Targeted Variant Analysis**

I. It is the policy of health plans affiliated with Centene Corporation that *PTCH1* or *SUFU* targeted variant analysis (81403) for nevoid basal cell carcinoma syndrome (NBCC), also known as 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.

II. It is the policy of health plans affiliated with Centene Corporation 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.

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

I. It is the policy of health plans affiliated with Centene Corporation 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:

A. The member/enrollee has a personal history of any of the following:
   1. Two major and one minor criteria (see below);
   2. One major and three minor criteria (see below)
### Clinical Policy

**Genetic Testing Hereditary Cancer Susceptibility**

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

II. It is the policy of health plans affiliated with Centene Corporation that current evidence does not support *PTCH1* and *SUFU* sequencing and/or deletion/duplication analysis (81479) for all other indications.

**Hereditary Paraganglioma/Pheochromocytoma Syndrome (PGL/PCC)**

**MAX, SDHA, SDHAF2, SDHB, SDHC, SDHD, or TEM127 Targeted Variant Analysis**

I. It is the policy of health plans affiliated with Centene Corporation 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 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.

II. It is the policy of health plans affiliated with Centene Corporation 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.

**MAX, SDHA, SDHAF2, SDHB, SDHC, SDHD, and TEM127 Sequencing and Deletion Duplication Analysis**

I. It is the policy of health plans affiliated with Centene Corporation that *MAX, SDHA, SDHAF2, SDHB, SDHC, SDHD*, and *TMEM127* sequencing and/or deletion/duplication analysis...
Genetic Testing Hereditary Cancer Susceptibility

analysis (81404, 81405, 81406, 81479) for hereditary paraganglioma/pheochromocytoma syndrome (PGL/PCC) is considered medically necessary when meeting both of the following:

A. The member/enrollee has a diagnosis of one or more of the following:
   1. Pheochromocytoma, including bilateral adrenal pheochromocytoma
   2. Paraganglioma, including paravertebral, carotid body, vagal, and/or jugulotympanic
   3. Clear cell renal cell cancer
   4. Gastrointestinal stromal tumor (GIST)
   5. Pulmonary chondromas

B. The member/enrollee has a close relative\(^1\) who meets the above criteria.

II. It is the policy of health plans affiliated with Centene Corporation that current evidence does not support \(\text{MAX, SDHA, SDHAF2, SDHB, SDHC, SDHD, and TMEM127}\) sequencing and/or deletion/duplication (81404, 81405, 81406, 81479) for hereditary paraganglioma/pheochromocytoma syndrome (PGL/PCC) for all other indications.

Peutz-Jeghers Syndrome (PJS)

STK11 Targeted Variant Analysis
I. It is the policy of health plans affiliated with Centene Corporation that \(\text{STK11}\) 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 \(\text{STK11}\).

II. It is the policy of health plans affiliated with Centene Corporation that current evidence does not support \(\text{STK11}\) targeted variant analysis (81403) for Peutz-Jeghers syndrome for all other indications.

STK11 Sequencing and/or Deletion/Duplication Analysis
I. It is the policy of health plans affiliated with Centene Corporation that \(\text{STK11}\) sequencing and/or deletion/duplication analysis (81404, 81405) for Peutz-Jeghers syndrome is considered medically necessary when:

   A. 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.
II. It is the policy of health plans affiliated with Centene Corporation that current evidence does not support STK11 sequencing and/or deletion/duplication analysis (81404, 81405) for Peutz-Jeghers syndrome for all other indications.

Retinoblastoma

RB1 Targeted Variant Analysis

I. It is the policy of health plans affiliated with Centene Corporation 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 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.

II. It is the policy of health plans affiliated with Centene Corporation that current evidence does not support RB1 targeted variant analysis (81403, S3841) for retinoblastoma for all other indications.

RB1 Sequencing and/or Deletion/Duplication Analysis

I. It is the policy of health plans affiliated with Centene Corporation that RB1 sequencing and/or deletion/duplication analysis (81403, S3841) for retinoblastoma is considered medically necessary when meeting one of the following:

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

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

II. It is the policy of health plans affiliated with Centene Corporation that current evidence does not support RB1 sequencing and/or deletion/duplication analysis (81403, S3841) for retinoblastoma for all other indications.

Von Hippel-Lindau Syndrome (VHL)

VHL Targeted Variant Analysis

I. It is the policy of health plans affiliated with Centene Corporation 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 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.

II. It is the policy of health plans affiliated with Centene Corporation that current evidence does not support VHL targeted variant analysis (81403, S3842) for Von Hippel-Lindau syndrome for all other indications.
VHL Sequencing and/or Deletion/Duplication Analysis

I. It is the policy of health plans affiliated with Centene Corporation 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:

A. 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

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

II. It is the policy of health plans affiliated with Centene Corporation 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
Clinical Policy
Genetic Testing Hereditary Cancer Susceptibility

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.

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 BMPRIA 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**
CLINICAL POLICY
Genetic Testing Hereditary Cancer Susceptibility

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:
Clinical Policy
Genetic Testing Hereditary Cancer Susceptibility

- 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 healthcare 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:
CLINICAL POLICY
Genetic Testing Hereditary Cancer Susceptibility

“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. 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.

<table>
<thead>
<tr>
<th>Reviews, Revisions, and Approvals</th>
<th>Revision Date</th>
<th>Approval Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Policy Implemented</td>
<td>02/22</td>
<td>02/22</td>
</tr>
</tbody>
</table>

References


**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. The Health Plan 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.
“Health Plan” means a health plan that has adopted this clinical policy and that is operated or
administered, in whole or in part, by Centene Management Company, LLC, or any of such health plan’s
affiliates, as applicable.

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 Health Plan-level administrative policies and procedures.

This clinical policy is effective as of the date determined by the Health Plan. The date of posting may not
be the effective date of this clinical policy. This clinical policy may be subject to applicable legal and
regulatory requirements relating to provider notification. If there is a discrepancy between the effective
date of this clinical policy and any applicable legal or regulatory requirement, the requirements of law and
regulation shall govern. The Health Plan retains the right to change, amend or withdraw this clinical
policy, and additional clinical policies may be developed and adopted as needed, at any time.

This clinical policy does not constitute medical advice, medical treatment or medical care. It is not
intended to dictate to providers how to practice medicine. Providers are expected to exercise professional
medical judgment in providing the most appropriate care, and are solely responsible for the medical
advice and treatment of members/enrollees. This clinical policy is not intended to recommend treatment
for members/enrollees. Members/enrollees should consult with their treating physician in connection with
diagnosis and treatment decisions.

Providers referred to in this clinical policy are independent contractors who exercise independent
judgment and over whom the Health Plan has no control or right of control. Providers are not agents or
employees of the Health Plan.

This clinical policy is the property of the Health Plan. Unauthorized copying, use, and distribution of this
clinical policy or any information contained herein are strictly prohibited. Providers, members/enrollees
and their representatives are bound to the terms and conditions expressed herein through the terms of their
contracts. Where no such contract exists, providers, members/enrollees and their representatives agree to
be bound by such terms and conditions by providing services to members/enrollees and/or submitting
claims for payment for such services.

Note: For Medicaid members/enrollees, when state Medicaid coverage provisions conflict with the
coverage provisions in this clinical policy, state Medicaid coverage provisions take precedence. Please
refer to the state Medicaid manual for any coverage provisions pertaining to this clinical policy.

Note: For Medicare members/enrollees, to ensure consistency with the Medicare National Coverage
Determinations (NCD) and Local Coverage Determinations (LCD), all applicable NCDs, LCDs, and
Medicare Coverage Articles should be reviewed prior to applying the criteria set forth in this clinical