Colorectal cancer (CRC) is a major cause of morbidity and mortality around the world, and approximately 5% develop in the context of inherited mutations leading to some form of familial colon cancer syndrome. The features suggestive of a hereditary CRC predisposition include: young age at diagnosis, history of CRC or adenomatous polyps in one or more close relatives, multiple primary cancers in a single individual, and several relatives affected with cancer spanning multiple generations. Of the cases that are suspected of having a hereditary predisposition to CRC, the most common causes are Lynch syndrome, familial adenomatous polyposis (FAP) and attenuated FAP (AFAP) [1, 2]. Individuals with hereditary CRC syndromes often have a high risk of developing gastrointestinal cancers and require increased screening and surveillance to reduce their cancer risk.

Our Comprehensive Hereditary Colorectal Cancer Panel includes sequence and deletion/duplication analysis of the 21 genes listed below. Other smaller panels are also available, please see below for more details.

<table>
<thead>
<tr>
<th>Gene</th>
<th>Associated Syndrome</th>
<th>Cancer Risk</th>
<th>Management Guidelines</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>APC</td>
<td>Familial adenomatous polyposis</td>
<td>Nearly a 100% lifetime risk of CRC in untreated individuals.</td>
<td>NCCN-CRC</td>
<td>[1]</td>
</tr>
<tr>
<td>AXIN2</td>
<td>NA</td>
<td>Associated with an apparently milder form of familial polyposis and increased risk of CRC.</td>
<td>N/A</td>
<td>[3]</td>
</tr>
<tr>
<td>BMPR1A</td>
<td>Juvenile Polyposis Syndrome</td>
<td>The risk of CRC is 40-50%. The risk of stomach cancer is 21% if gastric polyps are present.</td>
<td>NCCN-CRC</td>
<td>[1]</td>
</tr>
<tr>
<td>SMAD4</td>
<td></td>
<td>Homozygosity for BUB1B mutations is associated with an increased susceptibility to gastrointestinal neoplasia.</td>
<td>N/A</td>
<td>[4]</td>
</tr>
<tr>
<td>CDH1</td>
<td>N/A</td>
<td>Increased risk for hereditary diffuse gastric cancer, lobular breast cancer, colon cancer, or signet ring cell colon cancer.</td>
<td>NCCN-Gastric</td>
<td>[5]</td>
</tr>
<tr>
<td>CHEK2</td>
<td>N/A</td>
<td>The relative risk of breast cancer in males is 10.3 (95% CI 3.5–30.0); females is 1.70 (95% CI 1.3–2.2). The risk of other types of cancer is also increased including prostate and colon cancer.</td>
<td>NCCN-BR/OV, ACS Breast MRI</td>
<td>[6, 7]</td>
</tr>
<tr>
<td>ENG</td>
<td>N/A</td>
<td>Associated with moderate-load colorectal polyps and increased risk of CRC.</td>
<td>N/A</td>
<td>[8]</td>
</tr>
<tr>
<td>EPCAM</td>
<td>Lynch syndrome, Turcot syndrome, Muir-Torre syndrome</td>
<td>The lifetime risk of colon cancer is 70-80%, endometrial cancer is 20-60%, ovarian cancer is 0.3-20%, gastric cancer is 5-10%, small bowel cancer is 0.4-12%, and urinary tract cancers is 0.2-25%.</td>
<td>NCCN-CRC, CAPS</td>
<td>[9, 10]</td>
</tr>
<tr>
<td>MSH6</td>
<td></td>
<td>Increased risk for CRC.</td>
<td>N/A</td>
<td>[11]</td>
</tr>
<tr>
<td>MUTYH</td>
<td>MUTYH-associated polyposis</td>
<td>MUTYH-associated polyposis is associated with a 28-fold increased risk of CRC, with a penetrance of 19% by age 50 years, 43% by 60 years, and 80% by 70 years.</td>
<td>NCCN-CRC</td>
<td>[1]</td>
</tr>
<tr>
<td>POLD1</td>
<td>polymerase proofreading-associated polyposis</td>
<td>Increased risk for CRC and endometrial cancer.</td>
<td>N/A</td>
<td>[13, 14]</td>
</tr>
</tbody>
</table>

References:
[1] 1999. 2
[8] 1999. 17
[10] 1999. 1
[14] 1999. 16
<table>
<thead>
<tr>
<th>Gene</th>
<th>Syndrome</th>
<th>Description</th>
<th>Test Code</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>POLE</td>
<td>polymerase proofreading-associated polyposis</td>
<td>Increased risk for CRC.</td>
<td>N/A</td>
<td>[13]</td>
</tr>
<tr>
<td>PTEN</td>
<td>Cowden syndrome</td>
<td>Of all of the PTEN mutation carriers, 7% have been diagnosed with CRC. The lifetime risk in PTEN mutation carriers is 85% for breast cancer, 35% for nonmedullary thyroid cancer, and 28% for endometrial cancer.</td>
<td>NCCN-BR/OV</td>
<td>[1]</td>
</tr>
<tr>
<td>STK11</td>
<td>Peutz-Jeghers syndrome</td>
<td>The lifetime risk for breast cancer is 54%, 39% for colon cancer, 11-36% for pancreatic cancer, 29% for stomach cancer, 13% for small bowel cancer, 21% for ovary cancer, 11% for endometrial cancer, 15% for lung cancer.</td>
<td>NCCN-CRC, CAPS#</td>
<td>[1]</td>
</tr>
<tr>
<td>TP53</td>
<td>Li-Fraumeni syndrome</td>
<td>Extremely high risk for a multitude of tumor types including breast cancer, sarcoma, brain cancer, hematologic malignancies, adrenocortical, among others.</td>
<td>NCCN-BR/OV</td>
<td>[15]</td>
</tr>
</tbody>
</table>

N/A: Not available.

*Please note variations within exons 1-5, 9 and 11-15 of the PMS2 gene may not be analyzed or reported due to homology issues.

**Testing of GREM1 includes analysis of the founder duplication in SCG5 intron 2, upstream of the GREM1 gene.

Testing Options

**Lynch Syndrome Panel (sequence and deletion/duplication analysis of 7 genes: MLH1, MSH2, MSH6, PMS2*, EPCAM, POLE, POLD1)**

Cost: $3,700
CPT codes: 81292, 81294, 81295, 81297, 81317, 81319, 81298, 81300
Turn-around time: 4-6 weeks

**Hereditary Colorectal Cancer High Risk panel (sequence and deletion/duplication analysis of 9 genes: MLH1, MSH2, MSH6, PMS2*, EPCAM, POLE, POLD1, APC, MUTYH)**

Cost: $3,800
CPT codes: 81292, 81294, 81295, 81297, 81317, 81319, 81298, 81300, 81201, 81203
Turn-around time: 4-6 weeks

**Colorectal polyposis panel (sequence and deletion/duplication analysis of 10 genes: APC, MUTYH, BMPR1A, SMAD4, AXIN2, ENG, GREM1, BUB1B, PTEN, STK11)**

Cost: $3,800
CPT codes: 81321, 81323, 81201, 81203
Turn-around time: 4-6 weeks

**Comprehensive Hereditary Colorectal Cancer (sequence and deletion/duplication analysis of 21 genes*)**

Cost: $3,950
CPT codes: 81435, 81436
Turn-around time: 4-6 weeks

*Please note variations within exons 1-5, 9 and 11-15 of the PMS2 gene may not be analyzed or reported due to homology issues.

**Testing methods:**

Comprehensive sequence coverage of the coding regions and splice junctions of all genes in this panel is performed. Targets of interests are enriched and prepared for sequencing using the Agilent SureSelect system. Sequencing is performed using Illumina technology and reads are aligned to the reference sequence. Variants are identified and evaluated using a custom collection of bioinformatic tools and comprehensively interpreted by our team of directors and genetic counselors. Please note variations within exons 1-5, 9 and 11-15 of the PMS2 gene may not be analyzed or reported due to homology issues. All pathogenic and likely pathogenic variants are confirmed by Sanger sequencing. The technical sensitivity of this test is estimated to be >99% for single nucleotide changes and insertions and deletions of less than 20 bp. Deletion/duplication analysis of the panel genes is performed by oligonucleotide array-CGH. Partial exonic copy number changes and rearrangements of less than 400 bp may not be detected by array-CGH. Array-CGH will not detect low-level
mosaicism, balanced translocations, inversions, or point mutations that may be responsible for the clinical phenotype. The sensitivity of this assay may be reduced when DNA is extracted by an outside laboratory.

Results:
Results, along with an interpretive report, are faxed to the referring physician as soon as they are completed. One report will be issued for the entire panel. All abnormal results are reported by telephone.

References:

Committed to CUSTOMIZED DIAGNOSTICS, TRANSLATIONAL RESEARCH & YOUR PATIENTS’ NEEDS