Colorectal Cancer

Hereditary Colorectal Cancer
A Guide for Clinicians

KNOWING WHAT TO LOOK FOR       KNOWING WHERE TO LOOK       AND KNOWING WHAT IT MEANS
Colorectal Cancer Panel

Individuals in the general population have a lifetime risk of approximately 5% to develop colorectal cancer. Individuals with hereditary cancer syndromes have a higher risk to develop cancer and benefit from increased surveillance as well other medical management strategies to improve early detection and reduce cancer risk. Approximately 5% of colorectal cancers can be attributed to hereditary cancer syndromes. The most common hereditary colorectal cancer syndromes are familial adenomatous polyposis/attenuated familial adenomatous polyposis (FAP/AFAP) and Lynch syndrome, also known as hereditary non-polyposis colorectal cancer (HNPCC). For some of the well-described hereditary cancer syndromes, clinical diagnostic criteria based on personal medical history and family history are available to help identify patients most likely to have a hereditary cancer syndrome. In addition, Lynch syndrome-associated colorectal cancers often exhibit features of microsatellite instability and have loss of gene-specific protein expression. In many cases, however, the personal and family histories of patients suspected to have a hereditary predisposition do not fulfill these criteria. In addition, the patient’s personal or family history may raise suspicion for several hereditary conditions. A step-wise approach to genetic testing in these patients can be complicated, costly and time consuming. The Colorectal Cancer Panel offered at GeneDx is a comprehensive panel that utilizes next generation sequencing and exon level microarray to identify pathogenic (harmful) variants in 19 genes associated with hereditary predisposition to colorectal cancers.

Genes Included in the Colorectal Cancer Panel

The 19 genes included in the Colorectal Cancer Panel can be categorized into two main groups: High-Risk and Newer-Risk Genes as described in Table 1.

<table>
<thead>
<tr>
<th>High-Risk Genes</th>
<th>Newer-Risk Genes</th>
</tr>
</thead>
<tbody>
<tr>
<td>APC, BMPR1A, CDH1, EPCAM, MLH1, MSH2, MSH6, MUTYH, PMS2, PTEN, SMAD4, STK11, TP53</td>
<td>ATM, AXIN2, CHEK2, POLD1, POLE, SCG5/GREM1</td>
</tr>
<tr>
<td>Well studied</td>
<td>May not be well-studied with regard to colorectal or other cancer risks</td>
</tr>
<tr>
<td>Significantly increased risk of developing colorectal cancer (often at least 4-fold)</td>
<td>Data may be based on a small number of patients or patients within a specific ethnicity</td>
</tr>
<tr>
<td>Increase risk for other cancers</td>
<td>Precise lifetime risks of colorectal cancer may not be determined</td>
</tr>
<tr>
<td>Guidelines for screening and prevention established</td>
<td>May increase risk for other cancers</td>
</tr>
<tr>
<td></td>
<td>Guidelines for colorectal cancer screening and prevention not yet established</td>
</tr>
</tbody>
</table>

Table 1: Composition of Colorectal Cancer Panel
Lynch/Colorectal High Risk Panel

The Lynch/Colorectal High Risk Panel is a seven-gene test focusing analysis on the highest risk and most common hereditary colorectal cancer syndromes found on the Colorectal Panel. These genes include MLH1, MSH2, MSH6, PMS2, EPCAM, APC and MUTYH. This unique test offers clinicians the ability to focus on genes associated with highly-penetrant hereditary colorectal cancer syndromes for which explicit management guidelines have been published.

Lifetime Cancer Risks Associated with High Risk Genes

Lynch Syndrome (LS)
The MLH1, MSH2, MSH6, and PMS2 genes are involved in DNA mismatch repair. Individuals with a single pathogenic variant in one of these genes have Lynch syndrome. Deletions in the 3’ region of the EPCAM gene cause epigenetic silencing of MSH2 and thus also cause Lynch syndrome. Lynch syndrome is characterized by increased risks for cancers of the colon, rectum, endometrium (uterus), stomach, small bowel, ovaries, pancreas, biliary tract and urothelium. Some individuals with Lynch syndrome have sebaceous adenomas and keratoacanthomas of the skin (sometimes referred to as Muir-Torre syndrome) or glioblastomas (sometimes referred to as Turcot syndrome).

Colorectal and endometrial cancer are the two most common cancers observed in individuals with Lynch syndrome. Several studies have been conducted to determine the lifetime risk of colorectal, endometrial, and other Lynch syndrome-associated cancers and have resulted in a wide range of estimates. The lifetime risks for the most prevalent cancers associated with Lynch syndrome are presented in Figure 1. The average age of colorectal cancer diagnosis is 45-59 years.\(^3,4\) Individuals with Lynch syndrome who have been diagnosed with colon or endometrial cancers have an increased risk for a second primary cancer.\(^5,6\)

Figure 1: Probability of Lynch Syndrome – Associated Lifetime Risks by Cancer Type

- Colorectal: Up to 24%
- Endometrial: 12-61%
- Ovarian: 15-80%
- Gastric: Up to 20%

![Figure 1: Probability of Lynch Syndrome – Associated Lifetime Risks by Cancer Type](image-url)
Familial Adenomatous Polyposis (FAP/AFAP)

Pathogenic variants in the APC gene cause Familial Adenomatous Polyposis (FAP), which can present in a classic form or a less severe form known as attenuated FAP (AFAP).

FAP is characterized by hundreds to thousands of adenomatous polyps in the colon/rectum and elsewhere in the gastrointestinal tract, typically presenting by the second decade of life. If the polyposis is not controlled with polypectomy or colectomy, the risk of developing colorectal cancer in classic FAP is >90%. The average age of colorectal cancer diagnosis in FAP is 39 years. Individuals with classic FAP also have an increased risk to develop other types of cancers including those of the upper gastrointestinal tract, thyroid, pancreas, brain (typically medulloblastoma), and childhood hepatoblastoma. However, the lifetime risks for each of these additional cancers are estimated to be 5% or less. Individuals with FAP can also develop non-malignant stigmata, including desmoids, osteomas, epidermoid cysts, fibromas, dental abnormalities, and congenital hypertrophy of the retinal pigment epithelium (CHRPE).

Pathogenic variants in the APC gene can also cause an attenuated, or less severe, form of FAP known as attenuated FAP (AFAP). AFAP is characterized by multiple but fewer than 100 adenomatous polyps in the colon/rectum (often ~30) and elsewhere in the gastrointestinal tract, typically presenting by the second decade of life. The average age of colorectal cancer diagnosis in AFAP is 50-55 years. Individuals with AFAP also have an increased risk to develop other cancers associated with classic FAP, including those of the upper gastrointestinal tract, thyroid, pancreas, brain (typically medulloblastoma), and childhood hepatoblastoma.

Additional High Risk Genes

In addition to MLH1, MSH2, MSH6, PMS2, EPCAM and APC, the Colorectal Panel includes other highly penetrant genes associated with well-defined cancer syndromes known to increase the risk of colorectal cancer. These include BMPR1A, SMAD4 (Juvenile Polyposis syndrome), CDH1 (Hereditary Diffuse Gastric Cancer syndrome), PTEN (Cowden syndrome), STK11 (Peutz-Jeghers syndrome), MUTYH (MUTYH-Associated Polyposis) and TP53 (Li-Fraumeni syndrome). Table 2 provides lifetime cancer risks (when available).
Newer-Risk Genes
Six of the genes included in the Colorectal Cancer Panel have only recently been associated with colorectal cancer risk. Pathogenic variants in ATM, AXIN2, CHEK2, POLD1, POLE, and SCG5/GREM1 have been identified in families with colorectal cancer. However, precise lifetime cancer risks associated with pathogenic variants in these genes have not been determined. Identification of pathogenic variants in these genes may be helpful for families because, as more data becomes available, targeted cancer screening and prevention can be offered.

<table>
<thead>
<tr>
<th>Gene</th>
<th>Associated Cancers and Risks</th>
</tr>
</thead>
<tbody>
<tr>
<td>APC</td>
<td>Colorectal (up to 93%), Duodenal or periampullary (5%), Gastric, Thyroid, Pancreatic, Brain, Liver</td>
</tr>
<tr>
<td>BMPR1A</td>
<td>Colorectal (40-50%), Gastric (21% if gastric polyps)</td>
</tr>
<tr>
<td>CDH1</td>
<td>Diffuse gastric cancer (40-83%), Female Breast (39-52%), Colorectal</td>
</tr>
<tr>
<td>EPCAM*</td>
<td>Colorectal (69-75%), Endometrial (12-55%), Ovarian, Gastric, Pancreatic, Biliary tract, Urothelium, Small bowel, Brain, Sebaceous neoplasms</td>
</tr>
<tr>
<td>MLH1</td>
<td>Colorectal (22-80%), Endometrial (31-54%), Ovarian (13-20%), Gastric (6-20%), Pancreatic, Biliary tract, Urothelium, Small bowel, Brain, Sebaceous neoplasms</td>
</tr>
<tr>
<td>MSH2</td>
<td>Colorectal (22-80%), Endometrial (31-61%), Ovarian (10-24%), Gastric (&lt;1-9%), Pancreatic, Biliary tract, Urothelium, Small bowel, Brain, Sebaceous neoplasms</td>
</tr>
<tr>
<td>MSH6*</td>
<td>Colorectal (20-44%), Endometrial (44%), Ovarian (1-11%), Gastric, Pancreatic, Biliary tract, Urothelium, Small bowel, Brain, Sebaceous neoplasms</td>
</tr>
<tr>
<td>MUTYH</td>
<td>Colorectal (80%), Duodenal (4%), Endometrial</td>
</tr>
<tr>
<td>PMS2*</td>
<td>Colorectal (15-20%), Endometrial (15%), Ovarian, Gastric, Pancreatic, Biliary tract, Urothelium, Small bowel, Brain, Sebaceous neoplasms</td>
</tr>
<tr>
<td>PTEN</td>
<td>Female Breast (25-50%), Thyroid (10%), Endometrial (5-10%), Colorectal, Renal, Melanoma</td>
</tr>
<tr>
<td>SMAD4</td>
<td>Colorectal (40-50%), Gastric (21% if gastric polyps)</td>
</tr>
<tr>
<td>STK11</td>
<td>Colorectal (39%), Female Breast (32-54%), Pancreatic (11-36%), Gastric (29%), Ovarian tumors (21%), Lung (15%), Small intestine (13%), Cervical (10%), Endometrial (9%), Testicular tumors (9%)</td>
</tr>
<tr>
<td>TP53</td>
<td>Female Breast, Soft tissue sarcoma, Osteosarcoma, Brain, Hematologic malignancies, Adrenocortical carcinoma</td>
</tr>
</tbody>
</table>

Overall risk for cancer: nearly 100% in females, 73% in males

Table 2: Cancers and lifetime risks associated with genes in the colorectal cancer panel

*Tumor spectrum is representative of Lynch syndrome; data are limited with regard to the association of certain cancers with pathogenic variants in MSH6, PMS2, and EPCAM.
Inheritance of the Genes on the Colorectal Cancer Panel

The majority of genes included on the Colorectal Cancer Panel are inherited in an autosomal dominant manner. Therefore, an individual carrying a pathogenic variant has a 50% chance of transmitting the variant to a child, either male or female. In most cases, individuals with a pathogenic variant in one of the genes on the panel inherited it from a parent and, therefore, the siblings of this individual have up to a 50% chance to have the same variant. The risk for other family members to carry the familial pathogenic variant depends on which side of the family transmits the variant and how closely related the family member is to the patient.

Pathogenic variants in the MUTYH gene are inherited in an autosomal recessive manner; hence two pathogenic variants (one from each parent) are generally required to produce symptoms. Of note, some studies have shown that people who carry just one MUTYH pathogenic variant may have an increased risk for certain cancers including colon, endometrial (uterine) and...
breast cancer, but these risks are not well defined. Parents and children of an individual with two MUTYH pathogenic variants are obligate carriers (e.g. 100% risk to have at least one variant), and their full siblings have a 25% chance of having both variants and a 50% chance of having one variant in the MUTYH gene. First degree relatives of individuals who carry one MUTYH pathogenic variant have a 50% chance of also testing positive for the same variant.

While each of the dominantly inherited genes on the panel is associated with an increased risk for colorectal cancer when a single pathogenic variant in the gene is present, some of the genes on the panel are associated with rare autosomal recessive syndromes if an individual has a pathogenic variant in both copies of the gene (biallelic pathogenic variants). The genes known to be associated with recessively inherited syndromes are listed in Table 3. If both a mother and father are carriers for a pathogenic variant within the same gene*, each of their children has a 25% chance to inherit both variants, resulting in the recessive syndrome associated with that particular gene. If your patient tests positive for one of these pathogenic variants and wishes to have children in the future, then careful review of his or her partner’s family history and possibly genetic testing of the partner are needed to assess the reproductive risks associated with pathogenic variants in these genes.

<table>
<thead>
<tr>
<th>Gene</th>
<th>Autosomal Recessive Disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATM</td>
<td>Ataxia-Telangiectasia</td>
</tr>
<tr>
<td>EPCAM, MLH1, MSH2, MSH6, PMS2</td>
<td>Constitutional mismatch repair deficiency syndrome</td>
</tr>
<tr>
<td></td>
<td>*there is a case report of a child with this condition that has one pathogenic variant in EPCAM and one pathogenic variant in MSH2</td>
</tr>
<tr>
<td>POLE</td>
<td>FILS (facial dysmorphism, immunodeficiency, livedo, and short stature)</td>
</tr>
</tbody>
</table>

Table 3: Genes associated with autosomal recessive disorders

**Genetic Test Results and What They Mean**

There are three possible outcomes of genetic testing: positive, negative and variant of uncertain significance. All patients who undergo genetic testing should receive pre-test and post-test genetic counseling to understand the implications of testing. Genetic counseling services across the country can be found at: [www.nsgc.org](http://www.nsgc.org)
Positive Result
A positive result indicates that a pathogenic (harmful) variant was identified in an individual, and the risk for cancer is increased. Knowledge of a positive result provides valuable information to the patient, healthcare provider and family members. Knowledge of a patient’s genotype can assist in making management and treatment decisions. Furthermore, the patient’s family members can undergo site specific gene testing to allow for personalized cancer risk predictions.

Negative Result
A negative result means that a pathogenic variant was not identified in the individual tested. A negative result can have different interpretations based on the following scenarios:

True Negative Result: An individual who tests negative for a known familial pathogenic variant is not a carrier of a cancer-predisposing variant that has been identified in another family member. The risk for cancer in this individual is generally not expected to be higher than that of the general population. In some cases, this interpretation may be limited by the identification of a pathogenic variant in a gene with modest cancer risk or a pathogenic variant in a gene that has been recently described (i.e., newer-risk genes) with cancer risk and for which there are currently limited data to predict cancer risk. In these situations, not all of the cancer in the family may be attributed to the identified familial pathogenic variant. Therefore, clinical assessment of the complete family history of cancer and personal risk factors is important to determine appropriate management.

Uninformative Negative Result: If testing was performed on an individual with a cancer diagnosis, this means that we do not have an explanation for why this individual developed cancer. Genetic counseling is recommended, as additional testing may be considered based on the individual’s medical and family history. If testing was performed on an individual without a personal history of cancer and based only on family history, the risk for
cancer may remain increased as the exact cause of the cancer in the family remains unknown. Testing of an affected family member may help clarify this individual’s cancer risks.

**Variant of Uncertain Significance (VUS)**
A variant of uncertain significance (VUS) indicates that the effect of the variant cannot be clearly established. To further clarify the clinical significance of this variant, testing of family members may be helpful. If a relative with a related cancer is found to have the same variant, it may provide evidence that the variant may be pathogenic. The greater the number of affected family members who carry the VUS, the greater is the likelihood that the VUS is pathogenic. With consistent linkage of the VUS with family members with related cancers, in addition to other evidence, the variant found may be reclassified as pathogenic and predictive genetic testing can be offered to extended family members. Conversely, a VUS could be determined to be benign through this and other research. GeneDx may review a patient’s detailed family history to determine if family members are eligible for complementary targeted variant testing through our Variant Testing Program.

**Management**
There are a variety of management strategies available to patients who test positive for a pathogenic variant in a gene associated with an increased risk of colorectal cancer. Various guidelines outline available options and recommendations for patients who test positive for syndromes associated with hereditary colorectal cancer, including Lynch syndrome and FAP/AFAP, MUTYH-Associated Polyposis (MAP), Juvenile Polyposis syndrome, Peutz–Jeghers syndrome, Li-Fraumeni syndrome and Cowden syndrome. The guidelines below are examples of current recommendations as of 2015. Please visit [www.nccn.org](http://www.nccn.org) for the most up-to-date recommendations, including ages to begin surveillance and current recommended screening frequencies.
Lynch Syndrome-Related Cancers: MLH1, MSH2, MSH6, PMS2, EPCAM genes

Increased screening:

- Frequent colonoscopy (every 1-2 years in many cases) starting at an early age
- Consider endometrial cancer screening, which may include endometrial biopsy, transvaginal ultrasound and CA-125 blood tests
- Consider routine esophagastroduodenoscopy (EGD) with extended duodenoscopy starting at an early age
- Consider routine urinalysis starting at an early age
- Annual physical exam

Risk-Reducing Surgery:

- Consider the option of colectomy, particularly if the patient requires surgery to address a colonic neoplasm not amenable to endoscopic resection. This surgery will reduce the chance of developing colon cancer by more than 90%.
- Hysterectomy and salpingo-oopherectomy can be considered once a woman has completed childbearing. This surgery greatly reduces the chance of developing endometrial or ovarian cancer.

Classic FAP Related Cancers: APC gene

Increased screening:

- Frequent flexible sigmoidoscopy or colonoscopy (often every year), at an early age until colectomy; continued routine endoscopic evaluation post-colectomy
- Routine esophagastroduodenoscopy (EGD) starting at an early age
- Routine thyroid exam starting at an early age; consideration can be given to routine thyroid ultrasound
- Annual physical exam
- Routine abdominal palpation; if there is a family history of desmoid tumors, consideration should be given to abdominal MRI or CT scan
• If screening for desmoid tumors with MRI or CT scan, consideration should be given to adding small bowel visualization to screen for the risk of small bowel polyps and cancer.

Risk-Reducing Surgery:
• Prophylactic colectomy is recommended in individuals with classic FAP.

**Attenuated FAP (AFAP) Related Cancers: APC gene**

Increased Screening:
• Frequent colonoscopy starting at an early age; if the person has adenomas identified, increase the interval of colonoscopy.
• If the patient undergoes colectomy, continued routine endoscopic evaluation post-colectomy.
• Routine esophagogastroduodenoscopy (EGD) starting at an early age.
• Routine thyroid exam.
• Annual physical exam.

Risk-Reducing Surgery:
• Prophylactic colectomy is not always needed in AFAP. Colectomy is generally recommended for individuals who have adenomas that cannot be managed through colonoscopy.

**Other Genes**

Various screening and surgical options are available to individuals who test positive for other pathogenic variants included on the hereditary colorectal cancer panel as discussed in Table 4. For comprehensive gene specific guidelines, please visit: [www.nccn.com](http://www.nccn.com)
<table>
<thead>
<tr>
<th>Gene</th>
<th>Management Guidelines</th>
</tr>
</thead>
</table>
| TP53        | • Consider increased colonoscopy screening starting at an early age  
• Comprehensive physical exam including neurologic exams  
• Use caution regarding radiation therapy for cancer  
• Increased breast awareness including self-breast exam  
• Routine clinical breast exam  
• Breast MRI and mammography starting at an early age  
• Consider prophylactic mastectomy  
• Routine full body skin exam  
• Routine whole body MRI  
• Brain imaging as part of whole body MRI or as separate exam  
• Additional surveillance based on family history of cancer |
| PTEN        | • Routine colonoscopy  
• Consider annual dermatologic exam  
• Annual thyroid ultrasound  
• Increased breast awareness, including routine self-breast exam  
• Routine clinical breast exam  
• Breast MRI and mammography starting at an early age  
• Consider endometrial biopsy and/or transvaginal ultrasound starting at an early age; encourage patient education and prompt response to symptoms  
• Consider routine renal ultrasounds starting at an early age  
• Annual physical exam  
• Options of prophylactic mastectomy and hysterectomy can be discussed |
| CDH1        | • Routine colonoscopy  
• Routine endoscopy starting at an early age in absence of prophylactic gastrectomy  
• Prophylactic gastrectomy  
• Increased breast awareness including self-breast exam  
• Routine clinical breast exam  
• Routine breast MRI and mammography  
• Consider the use of breast cancer chemoprevention and/or prophylactic mastectomy |
| STK11       | • Frequent colonoscopy starting at an early age  
• Routine upper endoscopy starting at an early age  
• Routine pancreatic cancer screening (e.g. magnetic resonance cholangiopancreatography (MRCP) or endoscopic ultrasound) starting at an early age  
• Routine small bowel visualization starting at an early age  
• Routine pelvic exam with consideration of transvaginal ultrasound  
• Increased breast awareness including self-breast exam  
• Routine clinical breast exam  
• Routine breast MRI and mammography starting at an early age  
• Annual physical exam |
| SMAD4/BMPR1A| • Frequent colonoscopy starting at an early age  
• Routine upper endoscopy starting at an early age  
• For SMAD4 pathogenic variant carriers, screen for vascular lesions associated with hereditary hemorrhagic telangiectasia |
| MUTYH       | • Frequent colonoscopy starting at an early age  
• Consider routine esophagogastroduodenoscopy (EGD) and side viewing duodenoscopy starting at an early age  
• Annual physical exam |

Table 4: Management guidelines for pathogenic variant carriers
**Genetic Counseling**

Pre-test counseling is recommended for individuals who are interested in understanding their risks, meet the clinical criteria for testing, and/or are considering genetic testing. If a pathogenic variant has already been identified in a family member, testing of the specific variant is appropriate. If a pathogenic variant has never been identified, an affected family member with the highest likelihood for a positive result (early onset disease or multiple primaries) is the preferred person for initial testing within a family. If an affected family member is not available for testing, testing of an unaffected family member can be performed, although a negative test result will not guarantee that the individual does not have an increased cancer risk. Once patients make the decision to undergo testing, post-test genetic counseling is recommended to understand the implications of the results. Genetic counseling services across the country can be found at: [www.nsgc.org](http://www.nsgc.org)

**Resources for Patients:**

National Cancer Institute: [www.cancer.gov/cancertopics/genetics](http://www.cancer.gov/cancertopics/genetics)

GeneDx: [www.oncogenedx.com](http://www.oncogenedx.com)

Colon Cancer Alliance: [www.ccalliance.org](http://www.ccalliance.org)

C3: Colorectal Cancer Coalition: [www.fightcolorectalcancer.org](http://www.fightcolorectalcancer.org)

Hereditary Colon Cancer Takes Guts: [www.hcctakesguts.org](http://www.hcctakesguts.org)

National Society of Genetic Counselors: [www.nsgc.org](http://www.nsgc.org)

**References**


How can I order this test?
You can order this test by taking the following steps:

1. Download the OncogeneDx test requisition form from the GeneDx website: www.genedx.com/forms

2. Complete all the forms with required information

3. Ship completed forms along with two 4mL lavender top tubes of blood or at least 30 mL of the oral rinse provided by GeneDx to the following address:
   
   Accessions
   GeneDx
   207 Perry Parkway
   Gaithersburg, MD 20877

We provide shipping kits to healthcare providers upon request. To place an order for shipping kits, please visit our website: www.genedx.com/supplies or email us at: wecare@genedx.com

About GeneDx
GeneDx is a highly respected genetic testing company, founded in 2000 by two scientists from the National Institutes of Health (NIH) to address the needs of patients and clinicians concerned with rare inherited disorders. Currently, GeneDx offers whole exome sequencing, oligonucleotide microarray-based testing for detecting chromosomal abnormalities, testing for inherited eye disorders and autism spectrum disorders and gene panels for testing various forms of inherited cardiac disorders, mitochondrial disorders, neurological disorders and inherited cancer disorders. At GeneDx, our technical services are matched by our scientific expertise and customer support. Our growing staff includes more than 100 geneticists and genetic counselors specialized in clinical genetics, molecular genetics, metabolic genetics and cytogenetics who are just a phone call or email away. We invite you to visit our website: www.genedx.com to learn more about us and the services we offer.