

## Hereditary Colorectal Cancer

Genetic testing with the Lynch/Colorectal High Risk Panel may be appropriate if your personal and/or family history is suggestive of Lynch syndrome or a hereditary predisposition to colorectal cancer and/or polyps. **This includes:**

- Colorectal or endometrial\* cancer diagnosed under 50 years of age
- Multiple colon polyps (especially  $\geq 20$  adenomas) at any age
- Tumor testing which indicates an increased risk for a hereditary cancer syndrome known as Lynch syndrome (e.g. microsatellite instability and/or lack of immunohistochemistry staining for a mismatch repair protein)
- Multiple cancers in one person either of the same origin (such as two separate colorectal cancers) or of different origin (such as colon and endometrial cancer in the same individual)
- Multiple relatives diagnosed with the same or related cancers (such as colon, endometrial, ovarian, urinary tract, gastric) on the same side of the family and spanning multiple generations

Your healthcare provider will determine if genetic testing is medically necessary for you.

\* if this is the primary indication for testing, a more comprehensive panel specifically geared at this diagnosis is available

## Genes Included on the Colorectal Cancer Panel are Listed in the Table Below

**High-Risk Genes** Well-studied • Greater than 4-fold risk of developing one or more cancers • Can cause a moderate risk for other cancers • National or expert opinion guidelines for screening and prevention are established

**Moderate-Risk Genes** Well-studied • Approximately 2- to 4-fold risk of developing one or more cancers • May increase risk for other cancers • Limited guidelines for screening and prevention

**Newer Genes** Not as well-studied • Precise lifetime risks and tumor spectrum not yet determined • Guidelines for screening and prevention are limited or not available

	Gene	Lifetime Cancer and/or Tumor Risks*
High-Risk Genes	APC	Colorectal (up to 93%), Duodenal or periampullary (4-12%), Gastric, Thyroid (up to 3%), Pancreatic, Brain-medulloblastoma, Liver-hepatoblastoma, Desmoid tumors, Gastrointestinal polyps
	BMPR1A	Colorectal (up to 68%), Gastric (up to 21% if gastric polyps), Small bowel, Pancreatic, Gastrointestinal polyps
	CDH1	Gastric-diffuse, Female breast-lobular (39-55%), Colorectal
	EPCAM**	Colorectal (69-75%), Endometrial (12-55%), Ovarian, Gastric, Pancreatic, Biliary tract, Urinary tract-transitional cell, Small bowel, Brain, Sebaceous neoplasms, Prostate
	MLH1	Colorectal (34-46%), Endometrial (18-54%), Ovarian (10-20%), Gastric (6-20%), Urinary tract-transitional cell (1-4%), Pancreatic (1-4%), Biliary tract (2-3%), Small bowel (4-12%), Brain, Sebaceous neoplasms, Prostate
	MSH2	Colorectal (37-48%), Endometrial (21-57%), Ovarian (10-24%), Urinary tract-transitional cell (8-20%), Gastric (<1-9%), Pancreatic (1-4%), Biliary tract, Small bowel (1%), Brain, Sebaceous neoplasms, Prostate
	MSH6**	Colorectal (20-44%), Endometrial (16-71%), Ovarian (1-13%), Gastric, Pancreatic, Biliary tract, Urinary tract-transitional cell, Small bowel, Brain, Sebaceous neoplasms, Prostate
	MUTYH	Colorectal (up to 80%), Duodenal (up to 4%), Gastrointestinal polyps
	PMS2**	Colorectal (11-20%), Endometrial (12-26%), Ovarian, Gastric, Pancreatic, Biliary tract, Urinary tract-transitional cell, Small bowel, Brain, Sebaceous neoplasms, Prostate
	PTEN	Female breast (25-85%), Thyroid (3-38%), Endometrial (5-28%), Colorectal, Renal, Melanoma, Gastrointestinal polyps, Lhermitte-Duclos disease
	SMAD4	Colorectal (up to 68%), Gastric (up to 21% if gastric polyps), Small bowel, Pancreatic, Gastrointestinal polyps
	STK11	Female breast (up to 54%), Colorectal (39%), Pancreatic (11-36%), Gastric (29%), Ovarian tumors (21%), Lung (7-17%), Small bowel (13%), Cervical (10%), Testicular tumors (9%), Endometrial (9%), Gastrointestinal polyps
	TP53	Female breast (85%), Soft tissue sarcoma, Osteosarcoma, Brain, Hematologic malignancies-Acute leukemias among others, Adrenocortical carcinoma, among others. Overall risk for cancer: up to 95% in females, 88% in males
Moderate-Risk Genes	ATM	Female breast (27-33%), Colorectal, Ovarian, Pancreatic, Prostate
	CHEK2	Female breast, Male breast, Colorectal, Gastric, Prostate, Renal, Thyroid

	Gene	Lifetime Cancer and/or Tumor Risks*
Newer Genes	<i>AXIN2</i>	Colorectal, Colon polyps
	<i>NTHL1</i>	Colorectal, Colon polyps
	<i>POLD1</i>	Colorectal, Endometrial, Colon polyps
	<i>POLE</i>	Colorectal, Colon polyps
	<i>SCG5/GREM1</i>	Colorectal, Colon polyps

\*Most commonly associated cancer/tumors listed; lifetime risks provided when available. Risks relate to carriers of a single pathogenic variant with the exception of the *MUTYH* and *NTHL1* genes.

\*\*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*.

## Possible Outcomes of Genetic Testing



### Positive

- Pathogenic or likely pathogenic variant identified
- Medical management recommendations may be available
- Family member testing may be recommended



### Negative

- No significant genetic changes identified
- Medical management based on personal and/or family history



### Variant of Uncertain Significance (VUS)

- A genetic change identified, but its association with disease is unclear
- Medical management based on personal and/or family history

## Medical Management Based on Genetic Test Results

Clinical guidelines may be available which provide options and recommendations for patients who have a **positive** (pathogenic or likely pathogenic variant) test result indicating an increased risk for cancer and/or tumors. Guidelines and recommendations for early detection and/or risk reduction are specific to the gene in which the pathogenic variant was found.

## Recommendations may include:

- Clinical exams, such as skin or eye exams
- Urine analysis
- Imaging exams, such as a MRI, CT and/or ultrasound
- Screening procedures, such as a colonoscopy or endoscopy
- Risk-reducing surgery

In some cases, guidelines for screening and prevention are limited or not available for a positive result. Once your test results are available, a discussion with your healthcare provider is recommended to determine the most appropriate medical management options for you and your family.

## Resources

### General

American Cancer Society  
[www.cancer.org](http://www.cancer.org)

GeneDx  
[www.genedx.com/oncology](http://www.genedx.com/oncology)

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

### Colorectal Cancer

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

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

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

Colon Cancer Alliance for Research and Education for Lynch Syndrome (CCARE)  
[www.fightlynch.org](http://www.fightlynch.org)

### Find a Genetic Counselor

Canadian Association of Genetic Counsellors  
[www.cagc-accg.ca](http://www.cagc-accg.ca)

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