ALBERTA PRECISION LABORATORIES
Leaders in Laboratory Medicine

Gastrointestinal Cancers and Polyposis Panel: Information for Ordering Providers

Gastrointestinal cancer refers to malignant conditions of the gastrointestinal tract (GI tract) and accessory organs of digestion, including the esophagus, stomach, biliary system, small intestine, large intestine, rectum and anus. Gastrointestinal polyps may precede malignancy and are an important characteristic of some hereditary cancer conditions. Most cases of gastrointestinal cancer are sporadic; however, roughly 5% are due to a hereditary predisposition.[1]

Features suggestive of a hereditary cancer predisposition include:

- younger age at diagnosis
- multiple primary cancers in a single individual
- several relatives affected with related cancers spanning multiple generations
- large number of polyps
- less common polyp pathology such as hamartomatous or serrated polyps[2]

Individuals who carry a pathogenic variant in a hereditary cancer gene have an increased risk of certain cancers compared to the general population. Cancer risks depend on the gene(s) in which the variant(s) is identified. These individuals are eligible for increased cancer screening and/or risk reducing surgeries and therapeutic interventions. In addition, results may influence treatment plans for individuals with cancer.

If a pathogenic variant is identified in one of these genes, the patient and/or their family members may be at increased risk for specific cancers or other conditions. Genetic counselling is recommended for these families.

Indications for Testing

Patients with a personal and/or family history suggestive of a predisposition to gastrointestinal cancer or polyps may be eligible for testing. Testing may also be considered for patients diagnosed at a very young age or with an unusual presentation.

Ordering Privileges

Please refer to the APL Test Directory (http://ahsweb.ca/lab/apl-td-lab-test-directory) for specific ordering restrictions.

Gastrointestinal Cancer NGS panel:

Gene(s)	Associated cancers and/or clinical features[3]	Associated Hereditary Syndrome[3]
BAP1	*BAP1*-inactivated melanocytic tumours, uveal melanoma, malignant mesothelioma, cutaneous melanoma, renal cell carcinoma and basal cell carcinoma	*BAP1* tumor predisposition syndrome
CHEK2	colon, breast and prostate cancers	N/A
POLD1	colon and endometrial polyps and cancers	N/A
POLE	colon polyps and cancer	N/A
RHBDF2	esophageal cancers	N/A
MLH1 *MSH2* *MSH6* *PMS2* *EPCAM*	Colorectal cancer (up to 82% lifetime risk), uterine cancer, ovarian cancer and stomach cancer	Lynch syndrome
APC	Colonic polyps, colon cancer, hepatoblastoma	*APC*- associated polyposis conditions
CDH1	Diffuse gastric cancer (up to 70% lifetime risk for men and 56% for women), lobular breast cancer (up to 42% lifetime risk for women)	Hereditary diffuse gastric cancer

BMPR1A *SMAD4*	Increased risk of Juvenile polyps, colon cancer, stomach cancer, iron deficient anemia, GI bleeding. Increased risk of HHT in *SMAD4* carriers.	Juvenile polyposis syndrome
STK11	Gastrointestinal polyposis, mucocutaneous pigmentation, increased risk of cancer (colon, stomach, pancreatic, breast, ovarian), sex cord tumours	Peutz-Jeghers syndrome
TP53	Lifetime risk of 68%-93% to develop cancer. The most common tumor types include soft tissue, osteosarcomas, breast cancer, and brain cancer	Li-Fraumeni syndrome
PTEN	Multiple hamartoma syndrome with an increased risk of breast, thyroid, endometrial, and renal cancers	*PTEN* Hamartoma syndrome (Includes Cowden syndrome, Bannayan-Riley-Ruvalcaba syndrome)
MUTYH	Polyposis or colon cancers. Autosomal recessive inheritance. Caused by biallelic pathogenic variants	*MUTYH* associated polyposis

Associated Disorders[4]
Hereditary cancer predispositions are typically inherited in an autosomal dominant fashion. Some of the genes on this panel are associated with other rare disorders including:

Constitutional mismatch repair deficiency syndrome is a rare autosomal recessive condition that occurs in individuals who have two pathogenic variants in one of the following genes: *EPCAM, MLH1, MSH2, MSH6 or PMS2.* Affected individuals often have onset of colon/intestinal cancer before the age of 20 years and may have a cutaneous phenotype similar to that seen in neurofibromatosis type I.

Facial dysmorphism, immunodeficiency, livedo and short stature (FILS) is characterized by mild facial dysmorphism, mainly malar hypoplasia, livedo on the skin since birth, immunodeficiency resulting in recurrent infections, and short stature. It is inherited in an autosomal recessive manner and associated with *POLE* pathogenic variants.

Hereditary Hemorrhagic Telangiectasia (HHT) is characterized by multiple arteriovenous malformations resulting in epistaxis and mucocutaneous telangiectasias**.** HHT is caused by pathogenic variants in *ACVRL1*, *ENG* and *SMAD4*. *SMAD4* is also associated with intestinal polyps.

When can I expect results?
Results may take up to 4 months.

How are results reported?
Results are sent to the ordering provider and available in Netcare and Connect Care.

Contact Information
Genetics Counsellors, Genetics & Genomics
Edmonton: 780-407-1015
Calgary: 403-955-3097

Requisition forms, contact information and other resources can be found at:
http://ahsweb.ca/lab/if-lab-genetics-and-genomics

References

1. American Cancer Society. Colorectal Cancer Risk Factors. Available from: https://www.cancer.org/cancer/colon-rectal-cancer/causes-risks-prevention/risk-factors.html (accessed [2022 August])
2. NCCN Guidelines®. Genetic/Familial High-Risk Assessment: Colorectal. Available from: genetics_colon.pdf (tri-kobe.org) (accessed [2022 September]).
3. Online Mendelian Inheritance in Man, OMIM® . McKusick-Nathans Institute of Genetic Medicine, Johns Hopkins University (Baltimore, MD), Available from: https://omim.org/ (accessed [2022 August])
4. Adam MP, Mirzaa GM, Pagon RA, et al., editors. GeneReviews®. Seattle (WA): University of Washington, Seattle; 1993-2022. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1116/ (accessed [2022 September])