ColoTrue®

Analyzing 14 genes associated with hereditary colon cancer

The Test
ColoTrue® is a 14-gene hereditary cancer panel for individuals and families with features suggestive of hereditary colorectal cancer. This panel includes full sequencing and deletion/duplication analysis of 13 genes as well as deletion/duplication analysis of the EPCAM gene. In addition, this test also offers site-specific analysis of the MDM2–SNP309 allele. A pathogenic variant in any of these genes warrants consideration of increased colorectal cancer surveillance.1-2

Overview
Colon cancer is both the third most commonly diagnosed cancer and the third most common cause of cancer-related death in men and women in the United States. Overall, 1 in 20 individuals will develop colon cancer at some point during their life – equating to an approximately 5% lifetime risk to develop colon cancer. In 2012, it was estimated that there were almost 1.2 million individuals living in the United States with a history of colon cancer.3 Although the majority of colorectal cancer is sporadic, and caused by a variety of genetic and non-genetic factors, research has shown that approximately 5% of colon cancers are due to hereditary changes in single genes.4-5

Why Use ColoTrue®?
Past studies have estimated that pathogenic variants in the five genes associated with Lynch syndrome (EPCAM, MLH1, MSH2, MSH6, and PMS2) account for approximately 40-80% of all inherited cases of colorectal cancer.5-6 The remaining 20-60% of cases are caused by pathogenic variants in a variety of other genes that convey an increased risk of developing colon cancer, among other assorted cancers. The ColoTrue® test is a fourteen gene hereditary cancer panel designed to detect pathogenic variants both in the five genes associated with Lynch syndrome as well as in nine additional genes associated with an increased risk of colon cancer.

Given the genetic heterogeneity associated with inherited colorectal cancer, utilizing a multigene panel, such as ColoTrue®, may be the ideal testing option for a patient with a personal and family cancer history suggestive of hereditary colorectal cancer.1,7 Furthermore, many of the genes associated with hereditary cancer syndromes have very similar, and overlapping, clinical presentations, which may make it difficult to pinpoint what gene(s) is most appropriate for targeted testing.8

Thus, for cancer types that are prevalent in the clinical spectrum of several hereditary cancer syndromes, such as colorectal cancer, multigene panel testing may be the most time-efficient and economical testing method.8

When to consider using ColoTrue®?
Individuals with a personal and/or family history of the following risk factors should consider ColoTrue®:
- Early onset colorectal or endometrial cancer (diagnosed when less than 50 years old)
- Presence or history of ≥10 adenomas
- Multiple colon cancer diagnoses in the same individual
- Two or more associated cancers in the same individual (see figure 2)
- Two or more relatives, on the same side of the family, with associated cancers, with at least one diagnosed under 50 years old (see figure 2)
- Three or more relatives, on the same side of the family, with associated cancers at any age (see figure 2)
- Abnormal microsatellite instability (MSI) and/or immunohistochemistry (IHC) testing
Colon Cancer Risks
The lifetime colon cancer risk for each of the genes included on the ColoTrue® test is shown in Figure 1.

![Figure 1: Average Lifetime Colorectal Cancer Risks for the 14 genes in ColoTrue™](image)

Other Associated Cancer Risks
In addition to colon cancer, pathogenic variants in each of the genes in ColoTrue® are associated also with increased risks for other cancers. Being aware of these additional cancer risks is important for effective screening for each individual patient. Other cancers associated with each gene in the panel are shown in Figure 2.

![Figure 2: Cancer types associated with pathological variants in each of the respective genes on ColoTrue®](image)

Test Specifications
ColoTrue® analyzes the coding and flanking regions (+/- 20 bp) of 13 genes associated with hereditary colorectal cancer (APC, BMPR1A, CDH1, CHEK2, MLH1, MSH2, MSH6, MUTYH, PMS2, PTEN, SMAD4, STK11, TP53) by next-generation sequencing-based (NGS) and Sanger confirmation of reported gene variants. Additionally, site-specific analysis is performed to test for the variant defined as SNP309T>G in the MDM2 gene. Sanger fill-in is used for all genes in areas of low coverage, which is defined as a read depth of less than 25x. Gross deletions and duplications in the aforementioned 13 genes and EPCAM are identified by microarray analysis and multiplex ligation-dependent probe amplification (MLPA). Suspected deletions in exons 13-15 of PMS2 are confirmed with long range PCR to exclude the pseudogene signal.
References


