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**Executive Summary**

This executive summary reviews the topics covered in the PDQ summary on the genetics of colorectal cancer (CRC), with hyperlinks to detailed sections below that describe the evidence on each topic.

* **Inheritance and Risk**

[Factors suggestive of a genetic contribution to CRC](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#_18) include the following: (1) a strong family history of CRC and/or polyps; (2) multiple primary cancers in a patient with CRC; (3) the existence of other cancers within the kindred consistent with known syndromes causing an inherited risk of CRC, such as endometrial cancer; and (4) early age at diagnosis of CRC. Hereditary CRC is most commonly inherited in an autosomal dominant pattern, although two syndromes are inherited in an autosomal recessive pattern (*MUTYH*-associated polyposis and *NTHL1*).

At least three validated [computer models](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#_1101) are available to estimate the probability that an individual affected with cancer carries a pathogenic variant in a mismatch repair (MMR) gene associated with Lynch syndrome, the most common inherited CRC syndrome. These include the MMRpro, MMRpredict, and PREMM5 (PREdiction Model for gene Mutations) prediction models. Individuals with a quantified risk of 2.5% or greater on PREMM5 or 5% or greater on MMRpro and MMRpredict are recommended for genetic evaluation referral and testing.

* **Associated Genes and Syndromes**

Hereditary CRC has two well-described forms: (1) polyposis (including [familial adenomatous polyposis [FAP]](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#_90) and [attenuated FAP](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#_118) (AFAP), which are caused by pathogenic variants in the [*APC*](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#_2551) gene; and [MUTYH-associated polyposis](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#_433), which is caused by pathogenic variants in the [*MUTYH*](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#_2555) gene); and (2) [Lynch syndrome](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#_2986) (often referred to as hereditary nonpolyposis colorectal cancer), which is caused by germline pathogenic variants in DNA MMR genes ([*MLH1*](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#_1114), [*MSH2*](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#_1118), [*MSH6*](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#_3102), and [*PMS2*](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#_1126)) and [*EPCAM*](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#_1130). Other CRC syndromes and their associated genes include [oligopolyposis](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#_2642) (*POLE*, *POLD1*), [*NTHL1*](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#_2826), [juvenile polyposis syndrome](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#_647) ([*BMPR1A*](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#_2563), [*SMAD4*](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#_2563)), [Cowden syndrome](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#_2559) (*PTEN*), and [Peutz-Jeghers syndrome](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#_2920) (*STK11*). Many of these syndromes are also associated with extracolonic cancers and other manifestations. [Serrated polyposis syndrome](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#_684), which is characterized by the appearance of hyperplastic polyps, appears to have a familial component, but the genetic basis remains unknown. The natural history of some of these syndromes is still being described. Many other families exhibit aggregation of CRC and/or adenomas, but with no apparent association with an identifiable hereditary syndrome, and are known collectively as [familial CRC](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#_166). In addition, most individuals with CRC diagnosed before age 50 years and without a family history of cancer do not have a pathogenic variant associated with an inherited cancer syndrome.

[Genome-wide searches](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#_2583) are showing promise in identifying common, low-penetrance susceptibility alleles for many complex diseases, including CRCs, but the clinical utility of these findings remains uncertain.

* **Clinical Management**

It is becoming the standard of care at many centers that all individuals with newly diagnosed CRC are evaluated for Lynch syndrome through molecular diagnostic tumor testing assessing MMR deficiency. A [universal screening approach to tumor testing](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#_1110) is supported, in which all CRC cases are evaluated regardless of age at diagnosis or fulfillment of existing clinical criteria for Lynch syndrome. A more cost-effective approach has been reported whereby all patients aged 70 years or younger with CRC and older patients who meet the revised Bethesda guidelines are tested for Lynch syndrome. Tumor evaluation often begins with [immunohistochemistry testing](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#_1105) for the expression of the MMR proteins associated with Lynch syndrome or [microsatellite instability (MSI) testing](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#_3119), *BRAF* testing, and *MLH1* hypermethylation analyses.

Colonoscopy for CRC screening and surveillance is commonly performed in individuals with hereditary CRC syndromes and has been associated with improved survival outcomes. For example, [surveillance of Lynch syndrome patients with colonoscopy](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#_1144) every 1 to 2 years, and in one study up to 3 years, has been shown to reduce CRC incidence and mortality. [Extracolonic surveillance](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#_2975) is also a mainstay for some hereditary CRC syndromes depending on the other cancers associated with the syndrome. For example, regular [endoscopic surveillance of the duodenum in FAP patients](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#_613) has been shown to improve survival.

Prophylactic surgery (colectomy) has also been shown to improve survival in [patients with FAP](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#_263). The timing and extent of risk-reducing surgery usually depends on the number of polyps, their size, histology, and symptomatology. For [patients with Lynch syndrome](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#_1147) and a diagnosis of CRC, extended resection is associated with fewer metachronous CRCs and additional surgical procedures for colorectal neoplasia than in patients who undergo segmental resection for CRC. The surgical decision must take into account the age of the patient, comorbidities, clinical stage of the tumor, sphincter function, and the patient’s wishes.

Chemopreventive agents have also been studied in the management of FAP and Lynch syndrome. In FAP patients, [celecoxib and sulindac](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#_265) have been associated with a decrease in polyp size and number. A double-blind, randomized, controlled trial evaluating the efficacy of sulindac plus an epidermal growth factor receptor inhibitor, [erlotinib](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#_2894), versus placebo in FAP or AFAP patients with duodenal polyps suggested that erlotinib has the potential to inhibit duodenal polyps in FAP patients. An ongoing trial will determine whether lower doses of erlotinib alone will significantly reduce duodenal polyp burden. [Aspirin](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#_1148) use (600 mg daily) was shown to have a preventive effect on cancer incidence in Lynch syndrome patients in a large randomized trial; lower doses are being examined in an ongoing study.

[Novel therapies that stimulate the immune system](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#_3076) have been evaluated in MMR-deficient tumors, including those related to Lynch syndrome. The dense immune infiltration and cytokine-rich environment in MMR-deficient tumors may improve clinical outcomes. A critical pathway responsible for mediating tumor-induced immune suppression is the programmed cell death-1 (PD-1)–mediated checkpoint pathway. Two phase 2 studies using anti–PD-1 immune checkpoint inhibitors (pembrolizumab and nivolumab) demonstrated favorable outcomes, including progression-free survival, radiographic response rates, and disease control rates in metastatic CRC with MMR deficiency and MSI that had progressed on prior cytotoxic chemotherapy. Pembrolizumab has shown similar benefit in other noncolorectal cancers with MMR deficiency and MSI, but not in tumors that are microsatellite stable.

* **Psychosocial and Behavioral Issues**

[Psychosocial factors](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#_189) influence decisions about genetic testing for inherited cancer risk and risk-management strategies. Uptake of genetic counseling and genetic testing for [Lynch syndrome](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#_2924) and [FAP](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#_2942) varies widely across studies. Factors that have been associated with genetic counseling and testing uptake in Lynch syndrome families include having children, the number of affected relatives, perceived risk of developing CRC, and frequency of thoughts about CRC. Psychological studies have shown [low levels of distress](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#_2925), particularly in the long term, after genetic testing for Lynch syndrome in both carriers and noncarriers. However, other studies have demonstrated the possibility of increased distress following genetic testing for FAP. Colon and gynecologic cancer screening rates have been shown to increase or be maintained among carriers of MMR pathogenic variants within the year after disclosure of results, while screening rates decrease among noncarriers. The latter is expected as the screening recommendations for unaffected individuals are those that apply to the general population. Studies measuring quality-of-life variables in FAP patients show normal-range results; however, these studies suggest that risk-reducing surgery for FAP may have negative quality-of-life effects for at least some proportion of those affected. Patients' communication with their family members about an inherited risk of CRC is complex; gender, age, and the degree of relatedness are some elements that affect disclosure of this information. Research is ongoing to better understand and address psychosocial and behavioral issues in high-risk families.

**Introduction**

*[Note: Many of the medical and scientific terms used in this summary are found in the* [*NCI Dictionary of Genetics Terms*](https://www.cancer.gov/publications/dictionaries/genetics-dictionary)*. When a linked term is clicked, the definition will appear in a separate window.]*

*[Note: Many of the genes described in this summary are found in the Online Mendelian Inheritance in Man (OMIM) database. When OMIM appears after a gene name or the name of a condition, click on OMIM for a link to more information.]*

*[Note: A concerted effort is being made within the genetics community to shift terminology used to describe genetic variation. The shift is to use the term “variant” rather than the term “mutation” to describe a genetic difference that exists between the person or group being studied and the reference sequence. Variants can then be further classified as benign (harmless), likely benign, of uncertain significance, likely pathogenic, or pathogenic (disease causing). Throughout this summary, we will use the term pathogenic variant to describe a disease-causing mutation. Refer to the* [*Cancer Genetics Overview*](https://cdr.cancer.gov/cgi-bin/cdr/QcReport.py?DocId=CDR0000517309&Session=guest#_2676) *summary for more information about variant classification.]*

Colorectal cancer (CRC) is the third most commonly diagnosed cancer in both men and women.

Estimated new cases and deaths from CRC in 2018 in the United States:[[1](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_1_1)]

* New cases: 140,250.
* Deaths: 50,630.

About 75% of patients with CRC have [sporadic disease](https://cdr.cancer.gov/cgi-bin/cdr/Filter.py?DocId=CDR0000339347&Filter=set:QC+GlossaryTermName+with+Concept+Set) with no apparent evidence of having inherited the disorder. The remaining 10% to 30% of patients have a [family history](https://cdr.cancer.gov/cgi-bin/cdr/Filter.py?DocId=CDR0000302456&Filter=set:QC+GlossaryTermName+with+Concept+Set) of CRC that suggests a hereditary contribution, common exposures or shared risk factors among family members, or a combination of both.[[2](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_1_2)] [Pathogenic variants](https://cdr.cancer.gov/cgi-bin/cdr/Filter.py?DocId=CDR0000783960&Filter=set:QC+GlossaryTermName+with+Concept+Set) in high-[penetrance](https://cdr.cancer.gov/cgi-bin/cdr/Filter.py?DocId=CDR0000339344&Filter=set:QC+GlossaryTermName+with+Concept+Set) [genes](https://cdr.cancer.gov/cgi-bin/cdr/Filter.py?DocId=CDR0000045693&Filter=set:QC+GlossaryTermName+with+Concept+Set) have been identified as the cause of inherited cancer risk in some colon cancer–prone families; these are estimated to account for only 5% to 6% of CRC cases overall.[[3](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_1_3), [4](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_1_4)]

In addition, pathogenic variants in lower penetrance genes may contribute to [familial](https://cdr.cancer.gov/cgi-bin/cdr/Filter.py?DocId=CDR0000460148&Filter=set:QC+GlossaryTermName+with+Concept+Set) colon cancer risk. In such cases, gene-gene and gene-environment interactions may contribute to the development of CRC.

(Refer to the PDQ summaries on [Colorectal Cancer Screening](https://cdr.cancer.gov/cgi-bin/cdr/QcReport.py?DocId=CDR0000062753&Session=guest); [Colorectal Cancer Prevention](https://cdr.cancer.gov/cgi-bin/cdr/QcReport.py?DocId=CDR0000062763&Session=guest); [Colon Cancer Treatment](https://cdr.cancer.gov/cgi-bin/cdr/QcReport.py?DocId=CDR0000062687&Session=guest); and [Rectal Cancer Treatment](https://cdr.cancer.gov/cgi-bin/cdr/QcReport.py?DocId=CDR0000062726&Session=guest) for more information about sporadic CRC.)

**Colorectal Polyps as Precursors to Colorectal Cancer (CRC)**

Colorectal tumors present with a broad spectrum of neoplasms, ranging from benign growths to invasive cancer, and are predominantly epithelial-derived tumors (i.e., adenomas or adenocarcinomas).

Transformation of any polyp into cancer goes through the adenoma-carcinoma sequence. Polyps that have traditionally been considered nonneoplastic include those of the hyperplastic, juvenile, hamartomatous, inflammatory, and lymphoid types. However, in certain circumstances, hamartomatous and juvenile polyps can progress into cancer.

Research, however, does suggest a substantial risk of colon cancer in individuals with juvenile polyposis syndrome and Peutz-Jeghers syndrome, although the nonadenomatous polyps associated with these syndromes have historically been viewed as nonneoplastic.[[5](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_1_5), [6](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_1_6), [7](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_1_7)]

Epidemiologic studies have shown that a personal history of colon adenomas places one at an increased risk of developing colon cancer.[[8](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_1_8)]

Two complementary interpretations of this observation are as follows:

1. The adenoma may reflect an innate or acquired tendency of the colon to form tumors.
2. Adenomas are the primary precursor lesion of colon cancer.

More than 95% of CRCs are carcinomas, and about 95% of these are adenocarcinomas. It is well recognized that adenomatous polyps are benign tumors that may undergo malignant transformation. They have been classified into three histologic types, with increasing malignant potential: tubular, tubulovillous, and villous. Adenocarcinomas are generally considered to arise from adenomas,[[9](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_1_9), [10](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_1_10), [11](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_1_11), [12](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_1_12), [13](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_1_13)] based upon the following important observations:

1. Benign and malignant tissue occur within colorectal tumors.[[14](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_1_14)]
2. When patients with adenomas were followed for 20 years, the risk of cancer at the site of the adenoma was 25%, a rate much higher than that expected in the normal population.[[15](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_1_15)]

The following three characteristics of adenomas are highly correlated with the potential to transform into cancer:[[14](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_1_14)]

1. Larger size.
2. Villous pathology.
3. The degree of dysplasia within the adenoma.

In addition, removal of adenomatous polyps is associated with reduced CRC incidence.[[16](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_1_16), [17](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_1_17)] While most adenomas are polypoid, flat and depressed lesions may be more prevalent than previously recognized. Large, flat, and depressed lesions may be more likely to be severely dysplastic, although this remains to be clearly proven.[[18](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_1_18), [19](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_1_19)] Specialized techniques may be needed to identify, biopsy, and remove such lesions.[[20](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_1_20)]

**Family History as a Risk Factor for CRC**

Some of the earliest studies of family history of CRC were those of Utah families that reported a higher percentage of deaths from CRC (3.9%) among the [first-degree relatives](https://cdr.cancer.gov/cgi-bin/cdr/Filter.py?DocId=CDR0000460150&Filter=set:QC+GlossaryTermName+with+Concept+Set) (FDRs) of patients who had died from CRC than among sex-matched and age-matched controls (1.2%).[[21](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_1_21)] This difference has since been replicated in numerous studies that have consistently found that FDRs of affected cases are themselves at a twofold to threefold increased risk of CRC. Despite the various study designs (case-control, cohort), sampling frames, sample sizes, methods of data verification, analytic methods, and countries where the studies originated, the magnitude of risk is consistent.[[22](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_1_22), [23](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_1_23), [24](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_1_24), [25](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_1_25), [26](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_1_26), [27](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_1_27)]

A systematic review and meta-analysis of familial CRC risk has been reported.[[28](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_1_28)] Of 24 studies included in the analysis, all but one reported an increased risk of CRC if there was an affected FDR. The relative risk (RR) for CRC in the pooled study was 2.25 (95% confidence interval [CI], 2.00–2.53) if there was an affected FDR. In 8 of 11 studies, if the index cancer arose in the colon, the risk was slightly higher than if it arose in the rectum. The pooled analysis revealed an RR in relatives of colon and rectal cancer patients of 2.42 (95% CI, 2.20–2.65) and 1.89 (95% CI, 1.62–2.21), respectively. The analysis did not reveal a difference in RR for colon cancer based on location of the tumor (right side vs. left side).

The number of affected family members and age at cancer diagnosis correlated with the CRC risk. In studies reporting more than one FDR with CRC, the RR was 3.76 (95% CI, 2.56–5.51). The highest RR was observed when the index case was diagnosed in individuals younger than 45 years (RR, 3.87; 95% CI, 2.40–6.22) compared with family members of index cases diagnosed at ages 45 to 59 years (RR, 2.25; 95% CI, 1.85–2.72), and to family members of index cases diagnosed at age 60 years or older (RR, 1.82; 95% CI, 1.47–2.25). In this meta-analysis, the familial risk of CRC associated with adenoma in an FDR was analyzed. The pooled analysis demonstrated an RR for CRC of 1.99 (95% CI, 1.55–2.55) in individuals who had an FDR with an adenoma.[[28](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_1_28)] This finding has been corroborated.[[29](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_1_29)] Other studies have reported that age at diagnosis of the adenoma influences the CRC risk, with younger age at adenoma diagnosis associated with higher RR.[[30](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_1_30), [31](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_1_31)] As with any meta-analysis, there could be potential biases that might affect the results of the analysis, including incomplete and nonrandom ascertainment of studies included; publication bias; and heterogeneity between studies relative to design, target populations, and control selection. This study is reinforcement that there are significant associations between familial CRC risk, age at diagnosis of both CRC and adenomas, and multiplicity of affected family members.

|  |
| --- |
| **Table 1. Estimated Relative and Absolute Risk of Developing Colorectal Cancer (CRC)** |
| **Family History**  | **Relative Risk of CRC [**[**28**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_1_28)**]**  | **Absolute Risk (%) of CRC by Age 79 ya**  |
| No family history  | 1  | 4a  |
| One FDR with CRC  | 2.3 (95% CI, 2.0–2.5)  | 9b  |
| More than one FDR with CRC  | 4.3 (95% CI, 3.0–6.1)  | 16b  |
| One affected FDR diagnosed with CRC before age 45 y  | 3.9 (95% CI, 2.4–6.2)  | 15b  |
| One FDR with colorectal adenoma  | 2.0 (95% CI, 1.6–2.6)  | 8b  |

|  |
| --- |
| CI = confidence interval; FDR = first-degree relative. |
| aData from the Surveillance, Epidemiology, and End Results database. |
| bThe absolute risks of CRC for individuals with affected relatives was calculated using the relative risks for CRC [[28](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_1_28)] and the absolute risk of CRC by age 79 yearsa. |

When the family history includes two or more relatives with CRC, the possibility of a genetic syndrome is increased substantially. The first step in this evaluation is a detailed review of the family history to determine the number of relatives affected, their relationship to each other, the age at which the CRC was diagnosed, the presence of multiple primary CRCs, and the presence of any other cancers (e.g., endometrial) consistent with an [inherited CRC syndrome](https://cdr.cancer.gov/cgi-bin/cdr/Filter.py?DocId=CDR0000339343&Filter=set:QC+GlossaryTermName+with+Concept+Set). (Refer to the [Major Genetic Syndromes](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#_89) section of this summary for more information.) Computer models are now available to estimate the probability of developing CRC.[[32](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_1_32)] These models can be helpful in providing [genetic counseling](https://cdr.cancer.gov/cgi-bin/cdr/Filter.py?DocId=CDR0000044961&Filter=set:QC+GlossaryTermName+with+Concept+Set) to individuals at average risk and high risk of developing cancer. In addition, at least three validated models are also available for predicting the probability of carrying a pathogenic variant in a mismatch repair (MMR) gene.[[33](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_1_33), [34](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_1_34), [35](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_1_35)]

[Figure 1](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#_1397) shows the proportion of CRC cases that arise in various family risk settings.[[36](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_1_36)]

**Image:** Colon Cancer Cases Arising in Various Family Risk Settings

*Figure 1. The fractions of colon cancer cases that arise in various family risk settings. Reprinted from Gastroenterology, Vol. 119, No. 3, Randall W. Burt, Colon Cancer Screening, Pages 837-853, Copyright (2000), with permission from Elsevier.*

**Inheritance of CRC Predisposition**

Several genes associated with CRC risk have been identified; these are described in detail in the [Colon Cancer Genes](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#_72) section of this summary. Almost all pathogenic variants known to cause a [predisposition](https://cdr.cancer.gov/cgi-bin/cdr/Filter.py?DocId=CDR0000460153&Filter=set:QC+GlossaryTermName+with+Concept+Set) to CRC are inherited in an [autosomal dominant](https://cdr.cancer.gov/cgi-bin/cdr/Filter.py?DocId=CDR0000339338&Filter=set:QC+GlossaryTermName+with+Concept+Set) fashion.[[37](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_1_37)] One example of [autosomal recessive](https://cdr.cancer.gov/cgi-bin/cdr/Filter.py?DocId=CDR0000339339&Filter=set:QC+GlossaryTermName+with+Concept+Set) inheritance, *MUTYH*-associated polyposis (MAP), has been identified. (Refer to the [MUTYH-Associated Polyposis [MAP]](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#_433) section of this summary for more information.) Thus, the family characteristics that suggest autosomal dominant inheritance of cancer predisposition are important indicators of high risk and of the possible presence of a cancer-predisposing pathogenic variant. These include the following:

1. Vertical transmission of cancer predisposition in autosomal dominant conditions. (Vertical transmission refers to the presence of a [genetic predisposition](https://cdr.cancer.gov/cgi-bin/cdr/Filter.py?DocId=CDR0000460153&Filter=set:QC+GlossaryTermName+with+Concept+Set) in sequential generations.)
2. Inheritance risk of 50% for both male and female children. When a parent carries an autosomal dominant genetic predisposition, each child has a 50% chance of inheriting the predisposition. The risk is the same for both male and female children.
3. Other clinical characteristics also suggest the presence of a hereditary CRC syndrome:
	* Cancers in people with a hereditary predisposition typically occur at an earlier age than in sporadic cases.[[38](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_1_38)]
	* A predisposition to CRC may include a predisposition to other cancers, such as endometrial cancer, as detailed in the [Major Genetic Syndromes](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#_89) section of this summary.
	* In addition, two or more primary cancers may occur in a single individual. These could be multiple primary cancers of the same type (e.g., two separate primary CRCs) or primary cancer of different types (e.g., colorectal and endometrial cancer in the same individual).
	* The presence of non-neoplastic extracolonic features may suggest a hereditary colon cancer predisposition syndrome (e.g., congenital hypertrophy of the retinal pigment epithelium and desmoid tumors in familial adenomatous polyposis [FAP]).
	* An uncommon tumor (e.g., adrenocortical carcinoma, sebaceous adenoma or carcinoma, and trichilemmoma) may serve as a clue to the presence of a hereditary cancer syndrome.
	* The presence of multiple polyps may suggest a hereditary colon cancer predisposition syndrome. As susceptibility to oligopolyposis (as few as 10–15 polyps) has become apparent, clinicians, and gastrointestinal endoscopists in particular, may consider [multigene (panel) testing](https://cdr.cancer.gov/cgi-bin/cdr/Filter.py?DocId=CDR0000775581&Filter=set:QC+GlossaryTermName+with+Concept+Set) of an ever-expanding list of genes associated with CRC. (Refer to [Table 2](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#_686), Genes Associated with a High Susceptibility of Colorectal Cancer, for more information.) Because oligopolyposis also involves diverse pathology (including hamartomas, sessile serrated polyps, and sessile serrated adenomas), careful attention to polyp count and polyp histologies helps to determine whether genetic testing and/or further clinical evaluation is appropriate.

The two most common causes of hereditary CRC are FAP (including AFAP), due to [germline](https://cdr.cancer.gov/cgi-bin/cdr/Filter.py?DocId=CDR0000460154&Filter=set:QC+GlossaryTermName+with+Concept+Set) pathogenic variants in the *APC* gene,[[39](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_1_39), [40](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_1_40), [41](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_1_41), [42](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_1_42), [43](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_1_43), [44](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_1_44), [45](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_1_45), [46](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_1_46)] and Lynch syndrome (previously called hereditary nonpolyposis colorectal cancer [HNPCC]), which is caused by [germline pathogenic variants](https://cdr.cancer.gov/cgi-bin/cdr/Filter.py?DocId=CDR0000781852&Filter=set:QC+GlossaryTermName+with+Concept+Set) in DNA MMR genes.[[47](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_1_47), [48](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_1_48), [49](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_1_49), [50](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_1_50)] ([Figure 2](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#_2756) depicts a classic family with Lynch syndrome, highlighting some of the indicators of hereditary CRC that are described above.) Many other families exhibit aggregation of CRC and/or adenomas, but with no apparent association with an identifiable hereditary syndrome, and are known collectively as familial CRC.[[37](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_1_37)]

**Image:** Lynch syndrome pedigree

*Figure 2. Lynch syndrome pedigree. This pedigree shows some of the classic features of a family with Lynch syndrome, including affected family members with colon cancer or endometrial cancer, a young age at onset in some individuals, and incomplete penetrance. Lynch syndrome families may exhibit some or all of these features. Lynch syndrome families may also include individuals with other gastrointestinal, gynecologic, and genitourinary cancers, or other extracolonic cancers. As an autosomal dominant syndrome, Lynch syndrome can be transmitted through maternal or paternal lineages, as depicted in the figure. Because the cancer risk is not 100%, individuals who have Lynch syndrome may not develop cancer, such as the mother of the female with colon cancer diagnosed at age 37 years in this pedigree (called incomplete penetrance).*

**Identification of Persons at High Genetic Risk of CRC**

Guidelines have been developed by the American College of Medical Genetics and the National Society of Genetic Counselors to aid in the identification of patients appropriate for referral to a cancer genetic counseling service.[[51](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_1_51)]

When such persons are identified, options tailored to the patient situation are considered. (Refer to the [Major Genetic Syndromes](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#_89) section of this summary for information on specific interventions for individual syndromes.)

At this time, the use of pathogenic variant testing to identify [genetic susceptibility](https://cdr.cancer.gov/cgi-bin/cdr/Filter.py?DocId=CDR0000256553&Filter=set:QC+GlossaryTermName+with+Concept+Set) to CRC is not recommended as a screening measure in the general population. The rarity of pathogenic variants in CRC-associated genes and the limited sensitivity of current testing strategies render general population testing potentially misleading and not cost-effective.

Rather detailed recommendations for [surveillance](https://cdr.cancer.gov/cgi-bin/cdr/Filter.py?DocId=CDR0000496506&Filter=set:QC+GlossaryTermName+with+Concept+Set) in FAP and Lynch syndrome have been provided by several organizations representing various medical specialties and societies. These organizations include the following:

* American Cancer Society.[[52](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_1_52)]
* United States Multisociety (American Gastroenterological Association and American Society for Gastrointestinal Endoscopy) Task Force on Colorectal Cancer.[[53](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_1_53)]
* American Society of Colon and Rectal Surgeons.[[54](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_1_54)]
* National Comprehensive Cancer Network.[[55](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_1_55)]
* [Gene Reviews](https://www.ncbi.nlm.nih.gov/gtr/).
* American College of Gastroenterology.[[56](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_1_56)]
* [Society of Gynecologic Oncology and American College of Obstetrics & Gynecology](https://www.sgo.org/wp-content/uploads/2012/09/2014-ACOG-bulletin.pdf).

The evidence bases for recommendations are generally included within the statements or guidelines. In many instances, these guidelines reflect expert opinion resting on studies that are rarely randomized prospective trials.

**Difficulties in Identifying a Family History of CRC Risk**

The accuracy and completeness of family history data must be taken into account in using family history to assess individual risk in clinical practice, and in identifying families appropriate for cancer research. A reported family history may be erroneous, or a person may be unaware of relatives with cancer.[[57](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_1_57)] Increased use of colonoscopy may result in fewer CRCs and more precancerous colon polyps in a family history. Individuals are much less likely to know about their family history of polyps (i.e., type of polyps and total number of polyps in their relatives) than they are to know about their family history of cancer. In addition, small family sizes and premature deaths may limit how informative a family history may be. Also, due to [incomplete penetrance](https://cdr.cancer.gov/cgi-bin/cdr/Filter.py?DocId=CDR0000792352&Filter=set:QC+GlossaryTermName+with+Concept+Set), some persons may carry a genetic predisposition to CRC but do not develop cancer, giving the impression of skipped generations in a family tree.

Accuracy of patient-reported family history of colon cancer has been shown to be good, but it is not optimal. Patient report should be verified by obtaining medical records whenever possible, especially for reproductive tract cancers that may be relevant in identifying risk of Lynch syndrome and less reliably reported by some patients. (Refer to the [Accuracy of the Family History](https://cdr.cancer.gov/cgi-bin/cdr/QcReport.py?DocId=CDR0000062865&Session=guest#_340) section in the PDQ summary on [Cancer Genetics Risk Assessment and Counseling](https://cdr.cancer.gov/cgi-bin/cdr/QcReport.py?DocId=CDR0000062865&Session=guest) for more information.)

Several approaches are available to evaluate a patient with newly diagnosed CRC who may or may not be suspected of having a cancer genetics syndrome. The clinician may suspect a potential inherited disposition based on the family history and physical exam, and genetic tests are available to confirm these suspicions. The American College of Medical Genetics and Genomics has published guidelines for evaluating patients with suspected colon cancer susceptibility syndromes.[[51](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_1_51)] The guidelines aim to identify individuals whose clinical features warrant referral for genetics consultation. If an individual has multiple polyps (>20), depending on the histology, specific gene-directed testing can be a useful diagnostic tool. Similarly, if a patient’s clinical presentation is suspicious for Lynch syndrome, germline genetic testing can be directed towards this syndrome. However, diagnosis is more challenging when the clinical picture is less clear. Currently, tumor screening for Lynch syndrome is the most commonly accepted approach. However, increasingly, panels characterizing somatic variants in tumors are being utilized for a variety of clinical decisions.

A priori risk-assessment testing (which models risk based on a variety of factors, such as age at cancer onset and the spectrum of tumors in the family) may be an appropriate alternative in many cases. Application of such risk models does anticipate the use of multigene (panel) testing; however, their exact role remains to be established.

**Molecular Events Associated With Colon Carcinogenesis**

Much of our initial understanding of the molecular pathogenesis of CRC derived from rare hereditary CRC syndromes and revealed heterogeneity of CRC both molecularly and clinically. It is well accepted that most CRCs develop from adenomas. The transition from normal epithelium to adenoma to carcinoma is associated with acquired molecular events.[[58](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_1_58), [59](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_1_59), [60](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_1_60)] Presently, CRC can be separated into three categories based on similar molecular genetic features, suggesting divergent pathways of tumorigenesis: chromosomal instability (CIN), microsatellite instability (MSI), and CpG island methylator phenotype (CIMP). The understanding of the molecular genetic pathways of colorectal tumorigenesis is still evolving, and each new level of understanding has occurred in the context of the preceding level of knowledge. In addition, these pathways emerged from important clinical and histological heterogeneity of colorectal polyps and cancers. Thus, the introduction below captures the chronological evolution of our current understanding of colorectal tumorigenesis.

**Chromosomal instability (CIN) pathway**

The majority of CRCs develop through the CIN pathway. Key changes in CIN cancers include widespread alterations in [chromosome](https://cdr.cancer.gov/cgi-bin/cdr/Filter.py?DocId=CDR0000046470&Filter=set:QC+GlossaryTermName+with+Concept+Set) number ([aneuploidy](https://cdr.cancer.gov/cgi-bin/cdr/Filter.py?DocId=CDR0000460126&Filter=set:QC+GlossaryTermName+with+Concept+Set)) and frequent detectable losses at the molecular level of portions of chromosomes ([loss of heterozygosity](https://cdr.cancer.gov/cgi-bin/cdr/Filter.py?DocId=CDR0000464169&Filter=set:QC+GlossaryTermName+with+Concept+Set)), such as 5q, 18q, and 17p; and pathogenic variants of the *KRAS* oncogene. The important genes involved in these chromosome losses are *APC* (5q), *DCC*/*MADH2*/*MADH4* (18q), and *TP53* (17p).[[59](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_1_59), [61](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_1_61)] These chromosomal losses are indicative of genetic instability at the molecular and chromosomal levels.[[60](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_1_60)] Among the earliest and most common events in the colorectal tumor progression pathway is loss or pathogenic variant–inactivation of the *APC* gene. Pathogenic variant–inactivation of *APC* was first shown to be important to CRC in FAP, a hereditary CRC syndrome in which affected individuals harbor germline *APC* alterations, resulting in its loss of function and a dramatically increased incidence of colorectal polyps and cancers. Acquired or inherited pathogenic variants of DNA damage-repair genes, for example, base excision repair, nucleotide excision repair, double stranded repair, and MMR, also play a role in predisposing colorectal epithelial cells to pathogenic variants.

**Microsatellite instability (MSI) pathway**

Soon thereafter, a subset (10%–15%) of CRCs was identified that lacked evidence of chromosomal instability but exhibited aberrations in microsatellite repeat sequences,[[62](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_1_62), [63](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_1_63)] a characteristic of tumors in patients with Lynch syndrome.[[64](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_1_64)] It was later found that hypermethylation of the *MLH1* promoter is responsible for sporadic CRCs with MSI. Germline variants in DNA MMR genes were discovered in Lynch syndrome patients, whose CRCs frequently displayed MSI. Thus, the *microsatellite instability pathway* (MSI, sometimes referred to as MIN) was proposed.

The key characteristics of MSI cancers are that they have a largely intact chromosome complement and, as a result of defects in the DNA MMR system, more readily acquire pathogenic variants in important and often unique cancer-associated genes. These types of cancers are detectable at the molecular level by alterations in repeating units of DNA that occur normally throughout the genome, known as DNA microsatellites.

The rate of adenoma-to-carcinoma progression appears to be faster in microsatellite-unstable tumors than in microsatellite-stable tumors.[[65](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_1_65)] The foundation for this is the repeated reports of interval cancers in patients with recent, normal colonoscopy. Further support for this is seen in the serrated pathway (see below), in which high rates of interval cancer have also been observed.[[66](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_1_66), [67](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_1_67)] Characteristic histologic changes, such as increased mucin production, can be seen in tumors that demonstrate MSI, intratumoral T lymphocyte infiltration/[Crohn-like reaction](https://cdr.cancer.gov/cgi-bin/cdr/Filter.py?DocId=CDR0000681114&Filter=set:QC+GlossaryTermName+with+Concept+Set), etc., distinguishing the colorectal tumors in this pathway.

The knowledge derived from the study of inherited CRC syndromes has provided important clues regarding the molecular events that mediate tumor initiation and tumor progression in people without germline abnormalities. Among the earliest events in the colorectal tumor progression pathway (both MSI and CIN) is loss of function of the *APC* gene product.

**CpG island methylator phenotype (CIMP) and the serrated polyposis pathway**

Beginning in the 1980s, studies began reporting an increased risk of CRC in patients with hyperplastic polyposis syndrome (HPS), now referred to as serrated polyposis syndrome (SPS).[[6](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_1_6), [7](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_1_7), [68](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_1_68), [69](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_1_69), [70](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_1_70), [71](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_1_71), [72](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_1_72), [73](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_1_73)] Only a minority of SPS appear to be familial, but no common germline variant has been identified in these families to date. A comparison of the hyperplastic polyps (HPs) found in SPS patients and controls revealed that SPS polyps are histologically distinct and are similar to previously described serrated adenomas, polyps with features of HPs and adenomatous polyps (APs).[[74](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_1_74)] This led to observations that these sessile serrated adenomas (SSA) tend to occur in the right colon, where they are frequently large and sessile, and exhibit increased proliferation, dilation and serration of the crypt bases, decreased endocrine cells, and lack of dysplasia.[[75](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_1_75)]

Further histological characterization of serrated polyps led to subtypes: traditional serrated adenomas (TSA), mixed serrated polyps (MP), and more recently, sessile serrated adenoma/sessile serrated polyp (SSA/SSP).[[76](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_1_76)] TSAs are characterized by a protuberant morphology, ectopic crypt formation (suggestive of deficient bone morphogenetic protein signaling), and villiform and dysplastic histopathology.[[75](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_1_75), [77](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_1_77)] TSAs are not simply SSAs with dysplasia, and evidence that SSAs are precursors of TSAs is lacking. MPs have overlapping features of HPs, SSAs, and TSAs.

In colonoscopy screening studies, large serrated polyps were strongly and independently associated with the development of advanced colorectal neoplasms, while left-sided HPs were not. The term SSA has been a concern to clinicians as these characteristically lack nuclear atypia, the traditional hallmark of adenomas, but rather are termed adenomas due to other architectural features. The classification of SSA is supported by the knowledge that the molecular characteristics denote an increased cancer risk.[[74](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_1_74), [78](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_1_78), [79](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_1_79)]

While APs in Lynch syndrome patients can exhibit MSI, sporadic adenomas rarely do. However, serrated polyps with dysplasia can exhibit MSI with hypermethylation of the *MLH1* promoter. Large (>1 cm) serrated polyps carry greater cancer risk than do conventional hyperplastic polyps and, when developing into cancers, characteristically exhibit MSI.[[77](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_1_77), [80](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_1_80), [81](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_1_81), [82](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_1_82)] In a review of resected serrated polyps with a malignant focus, all of the polyps originated in the right colon and were SSAs.[[80](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_1_80)] The malignant foci were MSI and demonstrated loss of MLH1 immunoreactivity, suggesting an association between SSAs and sporadic MSI colon cancers.

The MSI seen in sporadic CRCs is due to hypermethylation of the promoter of *MLH1*, which abrogates its expression. As promoter regions of other [tumor suppressor genes](https://cdr.cancer.gov/cgi-bin/cdr/Filter.py?DocId=CDR0000046657&Filter=set:QC+GlossaryTermName+with+Concept+Set) were “silenced” through hypermethylation, cancer genome studies of CRC ensued. These showed a consistent pattern of hypermethylation in the evaluated genes in approximately 50% of CRCs.[[83](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_1_83)] Studies of larger numbers of unselected CRC patients show that a minority of CRCs (20%–30%) demonstrate CIMP, defined as hypermethylation of two or more of the CpG islands in *Methylated In Tumors 1* (*MINT1*) *MINT2*, *MINT31*, *CDKN2A* (*p16*), and *MLH1*.[[84](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_1_84), [85](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_1_85)] The term *CIMP* was coined to classify these cancers, which shared clinical features. Early attempts to differentiate CIMP-positive and CIMP-negative CRCs were unsuccessful.[[86](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_1_86)] However, subsequent studies using unbiased hierarchical cluster analysis of heavily methylated genes in CRCs and a population-based study design successfully identified unique clinical and molecular characteristics supporting a CIMP pathway.[[83](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_1_83), [87](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_1_87)]

CIMP-high CRCs were much more likely (82.1%; *P* < .0001) to express MSI than were microsatellite-stable CRCs (24.4%; *P* < .0001).[[83](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_1_83)] In one study, microsatellite-stable, CIMP-high (>2 CIMP markers mentioned [above](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#_1342)) colorectal tumors were significantly more associated with *BRAF* V600E variants, *KRAS2* variants, proximal site, higher American Joint Committee on Cancer stage, older patient age, poor differentiation, and mucinous histology than were CIMP-low (<2 CIMP markers mentioned above) colorectal tumors.[[83](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_1_83)] Microsatellite-unstable, CIMP-high colorectal tumors were significantly more associated with *BRAF* V600E pathogenic variants, proximal site, older patient age, and absence of *KRAS2* pathogenic variants than were microsatellite unstable, CIMP-low tumors.[[83](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_1_83)] There was a significantly greater presence of *BRAF* V600E pathogenic variants in CIMP-high colorectal tumors regardless of MSI.[[83](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_1_83)] Thus, unlike a previous study that questioned the biological significance of CIMP once unstable colorectal tumors were excluded,[[86](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_1_86)] this study demonstrated several clinicopathologic variables were indeed associated with CIMP in microsatellite-stable and microsatellite-unstable colorectal tumors.[[83](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_1_83)]

Studies of polyps revealed CIMP-positive polyps in HPS patients and most frequently in right-sided SSAs.[[67](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_1_67), [88](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_1_88), [89](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_1_89), [90](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_1_90), [91](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_1_91)] More recently, a hotspot *BRAF* pathogenic variant (V600E) was found to be common in MSI colon cancers and serrated polyps.[[92](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_1_92), [93](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_1_93), [94](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_1_94)] A *BRAF* pathogenic variant is absent in CRCs from Lynch syndrome patients and is rare in sporadic adenomatous colorectal polyps, but it is present in the vast majority of serrated polyps, especially SSAs.[[89](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_1_89), [91](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_1_91), [95](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_1_95), [96](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_1_96), [97](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_1_97)] CIMP positivity is commonly found in microvesicular hyperplastic polyps (MVHP), suggesting progression of MVHP to SSA and then to colon cancer.[[89](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_1_89)]

**Conclusion**

The characterization of CIMP CRCs and evidence that MSI occurs later in the adenoma-carcinoma sequence leads to modification of the previous colorectal tumorigenesis model, which was comprised of two pathways: MSI (MIN) and CIN. There is much overlap between the MSI and CIMP pathways. At the heart of the CIMP pathway are serrated polyps harboring *BRAF* pathogenic variants. The CIN pathway is characterized by AP precursors of which the vast majority harbor *APC* pathogenic variants that occur early in the pathway.

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**Colon Cancer Genes**

**Major Genes**

Major [genes](https://cdr.cancer.gov/cgi-bin/cdr/Filter.py?DocId=CDR0000045693&Filter=set:QC+GlossaryTermName+with+Concept+Set) are defined as those that are necessary and sufficient for disease causation, with important [pathogenic variants](https://cdr.cancer.gov/cgi-bin/cdr/Filter.py?DocId=CDR0000783960&Filter=set:QC+GlossaryTermName+with+Concept+Set) (e.g., [nonsense](https://cdr.cancer.gov/cgi-bin/cdr/Filter.py?DocId=CDR0000783965&Filter=set:QC+GlossaryTermName+with+Concept+Set), [missense](https://cdr.cancer.gov/cgi-bin/cdr/Filter.py?DocId=CDR0000783964&Filter=set:QC+GlossaryTermName+with+Concept+Set), [frameshift](https://cdr.cancer.gov/cgi-bin/cdr/Filter.py?DocId=CDR0000783963&Filter=set:QC+GlossaryTermName+with+Concept+Set)) of the gene as causal mechanisms. Major genes are typically considered those that are involved in single-gene disorders, and the diseases caused by major genes are often relatively rare. Most pathogenic variants in major genes lead to a very high risk of disease, and environmental contributions are often difficult to recognize.[[1](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_72_1)] Historically, most major colon cancer [susceptibility genes](https://cdr.cancer.gov/cgi-bin/cdr/Filter.py?DocId=CDR0000460209&Filter=set:QC+GlossaryTermName+with+Concept+Set) have been identified by [linkage analysis](https://cdr.cancer.gov/cgi-bin/cdr/Filter.py?DocId=CDR0000425374&Filter=set:QC+GlossaryTermName+with+Concept+Set) using high-risk families; thus, these criteria were fulfilled by definition, as a consequence of the study design.

The functions of the major colon cancer genes have been reasonably well characterized over the past decade. *~~Three proposed classes of colon cancer genes are~~* [*~~tumor suppressor genes~~*](https://cdr.cancer.gov/cgi-bin/cdr/Filter.py?DocId=CDR0000046657&Filter=set:QC+GlossaryTermName+with+Concept+Set)*~~, oncogenes, and~~* [*~~DNA~~*](https://cdr.cancer.gov/cgi-bin/cdr/Filter.py?DocId=CDR0000045671&Filter=set:QC+GlossaryTermName+with+Concept+Set) *~~repair genes.~~*[[2](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_72_2)] ***[AB-Comment: (Hampel) Maybe this is semantics but I have always considered DNA repair genes to be tumor suppressor genes. Perhaps reword as Colon cancer genes can be tumor suppressor genes (including DNA repair genes) or oncogenes. On second thought, since we don’t have any examples, why not cut this sentence all together.]*** Tumor suppressor genes constitute the most important class of genes responsible for hereditary cancer [syndromes](https://cdr.cancer.gov/cgi-bin/cdr/Filter.py?DocId=CDR0000339343&Filter=set:QC+GlossaryTermName+with+Concept+Set) and represent the class of genes responsible for both [familial](https://cdr.cancer.gov/cgi-bin/cdr/Filter.py?DocId=CDR0000460148&Filter=set:QC+GlossaryTermName+with+Concept+Set) adenomatous polyposis (FAP) and juvenile polyposis syndrome (JPS), among others. [*~~Germline~~*](https://cdr.cancer.gov/cgi-bin/cdr/Filter.py?DocId=CDR0000460154&Filter=set:QC+GlossaryTermName+with+Concept+Set) *~~pathogenic variants in oncogenes are not an important cause of inherited susceptibility to colorectal cancer (CRC), even though somatic variants in oncogenes are ubiquitous in virtually all forms of gastrointestinal cancers.~~* ***~~[AB-Comment: (Boland) Suggested edits to change stability to "DNA stability".]~~*** *~~S~~****DNA s****~~tability~~* **Repair** genes ***(which also fall under the category of tumor suppressor genes) [AB-Comment: (Hampel) Suggested revision to remain stability genes repair genes.]*** , especially the mismatch repair (MMR) genes responsible for Lynch syndrome (*~~also~~****previously*** called hereditary nonpolyposis colorectal cancer [HNPCC]), account for a substantial fraction of hereditary CRC, as noted below. (Refer to the [Lynch Syndrome](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#_2986) section in the [Major Genetic Syndromes](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#_89) section of this summary for more information). *MUTYH* is another important example of a *~~stability~~****repair*** gene that confers risk of CRC based on defective base excision repair. ***[AB-Comment: (Amos) Also POLE and POLD are stability genes…] Germline variants of oncogenes are not an important cause of inherited susceptibility to colorectal cancer (CRC), even though somatic pathogenic variants in oncogenes are ubiquitous in virtually all forms of gastrointestinal cancers. [AB-Comment: (Hampel) Suggested text.]*** [Table 2](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#_686) summarizes the genes that confer a substantial risk of CRC, with their corresponding diseases.

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| **Table 2. Genes Associated with a High Susceptibility of Colorectal Cancer** |
| **Gene**  | **Syndrome**  | **Hereditary Pattern**  | **Predominant Cancer**  |
| **Tumor suppressor genes**  |   |   |   |
| *APC* ([OMIM](https://www.ncbi.nlm.nih.gov/omim/611731))  | [FAP](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#_90)   | Dominant  | Colon, intestine, etc.  |
| *TP53* (*p53*) ([OMIM](https://www.ncbi.nlm.nih.gov/omim/191170))  | Li-Fraumeni   | Dominant  | Multiple (including colon)  |
| *STK11* (*LKB1*) ([OMIM](https://www.ncbi.nlm.nih.gov/omim/602216))  | [PJS](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#_2606)  | Dominant  | Multiple (including intestine)  |
| *PTEN* ([OMIM](https://www.ncbi.nlm.nih.gov/omim/601728))  | [Cowden](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#_2559)   | Dominant  | Multiple (including intestine)  |
| *BMPR1A* ([OMIM](https://www.ncbi.nlm.nih.gov/omim/601299))  | [JPS](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#_647)   | Dominant  | Gastrointestinal  |
| *SMAD4* (*MADH/DPC4*) ([OMIM](https://www.ncbi.nlm.nih.gov/omim/600993))  | [JPS](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#_647)   | Dominant  | Gastrointestinal  |
| ***DNA* Repair*~~/stability~~* genes**  |   |   |   |
| *MLH1* ([OMIM](https://www.ncbi.nlm.nih.gov/omim/120436)), *MSH2* ([OMIM](https://www.ncbi.nlm.nih.gov/omim/609309)), *MSH6* ([OMIM](https://www.ncbi.nlm.nih.gov/omim/600678)), *PMS2* ([OMIM](https://www.ncbi.nlm.nih.gov/omim/600259))  | [Lynch syndrome](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#_2986)   | Dominant  | Multiple (including colon, uterus, and others)  |
| *EPCAM (TACSTD1*) ([OMIM](https://www.ncbi.nlm.nih.gov/omim/185535))  | [Lynch syndrome](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#_2986)   | Dominant  | Multiple (including colon, uterus, and others)  |
| *MUTYH* (*MYH*) ([OMIM](https://www.ncbi.nlm.nih.gov/omim/604933))  | [MUTYH-associated polyposis](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#_433)  | Recessive  | Colon  |
| *POLD1* ([OMIM](https://www.ncbi.nlm.nih.gov/omim/174761)), *POLE* ([OMIM](https://www.ncbi.nlm.nih.gov/omim/174762))  | [Oligopolyposis](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#_2642)  | Dominant  | Colon, endometrial  |

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| *FAP = familial adenomatous polyposis; JPS = juvenile polyposis syndrome; OMIM = Online Mendelian Inheritance in Man database; PJS = Peutz-Jeghers syndrome.* |

**De Novo Pathogenic Variant Rate**

Until the 1990s, the diagnosis of genetically inherited polyposis syndromes was based on clinical manifestations and family history. Now that some of the genes involved in these syndromes have been identified, a few studies have attempted to estimate the spontaneous pathogenic variant rate ([de novo pathogenic variant](https://cdr.cancer.gov/cgi-bin/cdr/Filter.py?DocId=CDR0000783882&Filter=set:QC+GlossaryTermName+with+Concept+Set) rate) in these populations. Interestingly, FAP, JPS, Peutz-Jeghers syndrome, Cowden syndrome, and Bannayan-Riley-Ruvalcaba syndrome are all thought to have high rates of spontaneous pathogenic variants, in the 25% to 30% range,[[3](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_72_3), [4](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_72_4), [5](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_72_5)] while estimates of de novo pathogenic variants in the MMR genes associated with Lynch syndrome are thought to be low, in the 0.9% to 5% range.[[6](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_72_6), [7](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_72_7), [8](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_72_8)] These estimates of spontaneous pathogenic variant rates in Lynch syndrome seem to overlap with the estimates of nonpaternity rates in various populations (0.6% to 3.3%),[[9](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_72_9), [10](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_72_10), [11](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_72_11)] making the de novo pathogenic variant rate for Lynch syndrome seem quite low in contrast to the relatively high rates in the other polyposis syndromes.

**Next-Generation Sequencing and Novel CRC Susceptibility Genes**

[Next-generation sequencing](https://cdr.cancer.gov/cgi-bin/cdr/Filter.py?DocId=CDR0000763024&Filter=set:QC+GlossaryTermName+with+Concept+Set) (NGS) involves technological advances over the traditional capillary-based [Sanger DNA sequencing](https://cdr.cancer.gov/cgi-bin/cdr/Filter.py?DocId=CDR0000763028&Filter=set:QC+GlossaryTermName+with+Concept+Set) that was used in the Human Genome Project to sequence the human genome. NGS dramatically decreases the time required for genomic sequencing by utilizing massively parallel multiplexing techniques. Comparisons of genomic sequencing results between individuals with and without CRC affords yet another method to identify CRC susceptibility genes.

[Whole-genome sequencing](https://cdr.cancer.gov/cgi-bin/cdr/Filter.py?DocId=CDR0000740456&Filter=set:QC+GlossaryTermName+with+Concept+Set) (WGS) and [whole-exome sequencing](https://cdr.cancer.gov/cgi-bin/cdr/Filter.py?DocId=CDR0000740459&Filter=set:QC+GlossaryTermName+with+Concept+Set) (WES) are currently being used to assess somatic alterations in tumors to inform prognosis and/or targeted therapeutics and to assess the germline to identify cancer risk alleles. (Refer to the [Clinical Sequencing](https://cdr.cancer.gov/cgi-bin/cdr/QcReport.py?DocId=CDR0000517309&Session=guest#_2594) section in the PDQ [Cancer Genetics Overview](https://cdr.cancer.gov/cgi-bin/cdr/QcReport.py?DocId=CDR0000517309&Session=guest) summary for more information.)

An example of the success of NGS in identifying CRC susceptibility genes is the discovery of *POLE*/*POLD1* germline pathogenic variants in patients with adenomatous polyposis but no germline variants in ***the*** known *~~CRC~~****polyposis*** genes ***APC or MUTYH***. ***[AB-Comment: (Hampel) Suggested edits.]*** (Refer to the [Oligopolyposis](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#_2642) section in the [Major Genetic Syndromes](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#_89) section of this summary for more information about *POLE/POLD1*.)

WES has also been used to identify new potential CRC predisposition [variants](https://cdr.cancer.gov/cgi-bin/cdr/Filter.py?DocId=CDR0000776887&Filter=set:QC+GlossaryTermName+with+Concept+Set). In one 2016 study, exome sequencing data on 1,006 early-onset familial CRC cases and 1,609 healthy controls were analyzed.[[12](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_72_12)] Highly penetrant rare pathogenic variants were identified in 16% of familial CRC cases, of which the majority were known colon cancer genes while *POT1*, *POLE2*, and *MRE11* were identified as candidate CRC genes. The authors concluded that these findings probably discount the existence of further major high-penetrance susceptibility CRC genes.

**Genetic Polymorphisms and CRC Risk**

It is widely acknowledged that the familial clustering of colon cancer also occurs outside of the setting of well-characterized colon cancer family syndromes.[[13](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_72_13)] Based on epidemiological studies, the risk of colon cancer in a [first-degree relative](https://cdr.cancer.gov/cgi-bin/cdr/Filter.py?DocId=CDR0000460150&Filter=set:QC+GlossaryTermName+with+Concept+Set) of an [affected](https://cdr.cancer.gov/cgi-bin/cdr/Filter.py?DocId=CDR0000460124&Filter=set:QC+GlossaryTermName+with+Concept+Set) individual can increase an individual’s lifetime risk of colon cancer 2-fold to 4.3-fold.[[14](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_72_14)] The relative risk (RR) and absolute risk of CRC for different family history categories is estimated in [Table 1](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#_326). In addition, the lifetime risk of colon cancer also increases in first-degree relatives of individuals with colon adenomas.[[15](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_72_15)] The magnitude of risk depends on the age at diagnosis of the index case, the degree of relatedness of the index case to the at-risk case, and the number of affected relatives. It is currently believed that many of the moderate- and low-risk cases are influenced by alterations in single low-penetrance genes or combinations of low-penetrance genes. ***[AB-Comment: (Boland) [you might cite Wei C et al, Familial Cancer 14(2)297, 2015 here]]*** Given the public health impact of identifying the etiology of this increased risk, an intense search for the responsible genes is under way.

Each [locus](https://cdr.cancer.gov/cgi-bin/cdr/Filter.py?DocId=CDR0000460162&Filter=set:QC+GlossaryTermName+with+Concept+Set) would be expected to have a relatively small effect on CRC risk and would not produce the dramatic familial aggregation seen in Lynch syndrome or FAP. However, in combination with other common genetic loci and/or environmental factors, variants of this kind might significantly alter CRC risk. These types of genetic variations are often referred to as [polymorphisms](https://cdr.cancer.gov/cgi-bin/cdr/Filter.py?DocId=CDR0000044805&Filter=set:QC+GlossaryTermName+with+Concept+Set). Most loci that are polymorphic have no influence on disease risk or human traits (benign polymorphisms), while those that are associated with a difference in risk of disease or a human trait (however subtle) are sometimes termed disease-associated polymorphisms or functionally relevant polymorphisms. When such variation involves changes in single nucleotides of DNA they are referred to as [single nucleotide polymorphisms (SNPs)](https://cdr.cancer.gov/cgi-bin/cdr/Filter.py?DocId=CDR0000458046&Filter=set:QC+GlossaryTermName+with+Concept+Set).

Polymorphisms underlying polygenic susceptibility to CRC are considered low penetrance, a term often applied to sequence variants associated with a minimal to moderate risk. This is in contrast to high-penetrance variants or alleles that are typically associated with more severe [phenotypes](https://cdr.cancer.gov/cgi-bin/cdr/Filter.py?DocId=CDR0000460203&Filter=set:QC+GlossaryTermName+with+Concept+Set), for example those *APC* or MMR gene pathogenic variants leading to an [autosomal dominant](https://cdr.cancer.gov/cgi-bin/cdr/Filter.py?DocId=CDR0000339338&Filter=set:QC+GlossaryTermName+with+Concept+Set) inheritance pattern in a family. The definition of a moderate risk of cancer is arbitrary, but it is usually considered to be in the range of an RR of 1.5 to 2.0. Because these types of sequence variants are relatively common in the population, their contribution to total cancer risk is estimated to be much higher than the [attributable risk](https://cdr.cancer.gov/cgi-bin/cdr/Filter.py?DocId=CDR0000485393&Filter=set:QC+GlossaryTermName+with+Concept+Set) in the population from the relatively rare syndromes such as FAP or Lynch syndrome. Additionally, polymorphisms in genes distinct from the MMR genes can modify phenotype (e.g., average age of CRC) in individuals with Lynch syndrome.

Low-penetrance variants have been identified in a number of strategies. Earlier studies focused on candidates genes chosen because of biologic relevance to cancer pathogenesis. More recently, [genome-wide association studies](https://cdr.cancer.gov/cgi-bin/cdr/Filter.py?DocId=CDR0000636779&Filter=set:QC+GlossaryTermName+with+Concept+Set) (GWAS) have been used much more extensively to identify potential CRC susceptibility genes. (Refer to the [GWAS](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#_2583) section of this summary for more information.) Another approach is to use meta-analyses of existing GWAS datasets to discover additional novel CRC susceptibility genes.

**Polymorphism-modifying risk in average-risk populations**

**Low-penetrance candidate genes**

Several candidate genes have been identified and their potential use for clinical genetic testing is being determined. Candidate alleles that have been shown to associate with modest increased frequencies of colon cancer include heterozygous *BLMAsh* (the allele that is a [founder pathogenic variant](https://cdr.cancer.gov/cgi-bin/cdr/Filter.py?DocId=CDR0000783962&Filter=set:QC+GlossaryTermName+with+Concept+Set) in Ashkenazi Jewish individuals with Bloom syndrome), the *GH1* 1663 T→A polymorphism (a polymorphism of the growth hormone gene associated with low levels of growth hormone and IGF-1), and the *APC* I1307K polymorphism.[[16](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_72_16), [17](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_72_17), [18](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_72_18)]

Of these, the variant that has been most extensively studied is *APC* I1307K. Yet, neither it nor any of the other variants mentioned above are routinely used in clinical practice. (Refer to the [APC I1307K](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#_2599) section of this summary for more information.)

**GWAS**

Although the major genes for polyposis and nonpolyposis inherited CRC syndromes have been identified, between 20% and 50% of cases from any given series of suspected FAP or Lynch syndrome cases fail to have a pathogenic variant detected by currently available technologies. It is estimated that heredity is responsible for approximately one-third of the susceptibility to CRC,[[19](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_72_19)] and causative germline pathogenic variants account for less than 6% of all CRC cases.[[20](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_72_20)] This suggests that there may be other major genes with pathogenic variants that may predispose to ***a high risk of [AB-Comment: (Amos) Suggested edit.]*** CRC with or without polyposis. A few such genes have been detected (e.g., *MUTYH*, *EPCAM*) but the probability for discovery of other such genes is fairly low. More recent measures for new gene discovery have taken a genome-wide approach. Several GWAS have been conducted with relatively large, unselected series of CRC patients that have been evaluated for patterns of polymorphisms in candidate and anonymous genes throughout the genome. These SNPs are chosen to capture a large portion of common variation within the genome, based on the International HapMap Project.[[21](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_72_21), [22](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_72_22)] The goal is to identify alleles that, while not pathogenic variants, may confer an increase (or potential decrease) in CRC risk. Identification of yet unknown aberrant CRC alleles would permit further stratification of at-risk individuals on a genetic basis. Such risk stratification would potentially enhance CRC screening. The use of genome-wide scans in thousands of CRC cases and controls has led to the discovery of multiple common low-risk CRC SNPs, which can be found in the [National Human Genome Research Institute GWAS catalog](http://www.ebi.ac.uk/gwas/). A thorough discussion of GWAS can be found in the [Cancer Genetics Overview](https://cdr.cancer.gov/cgi-bin/cdr/QcReport.py?DocId=CDR0000517309&Session=guest#_147) PDQ summary. GWAS are conducted under the assumption that the genetic underpinnings of complex phenotypes are governed by many alleles, each conferring modest risk. It is very unlikely that an allele with high frequency in the population by itself contributes substantially to cancer risk. This, coupled with the polygenic nature of tumorigenesis, means that the contribution by any single variant identified by GWAS to date is quite small, generally with an odds ratio (OR) for disease risk of less than 1.5.

Meta-analysis of GWAS has allowed for the identification of novel CRC-associated SNPs by combining data from previous GWAS.[[23](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_72_23), [23](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_72_23), [24](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_72_24), [25](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_72_25), [26](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_72_26)] These SNPs are provided in the [GWAS catalog](http://www.ebi.ac.uk/gwas/) referenced above. The same considerations for GWAS mentioned above apply to the meta-analysis approach.

**Genetic variation in 8q24 and *SMAD7***

Three separate studies showed that genetic variation at 8q24.21 is associated with increased risk of colon cancer, with RR ranging from 1.17 to 1.27.[[27](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_72_27), [28](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_72_28), [29](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_72_29)] Although the RR is modest for the risk alleles in 8q24, the prevalence (and population-attributable fraction) of these risk alleles is high. The genes responsible for this association have not yet been identified. In addition, common alleles of *SMAD7* have also been shown to be associated with an approximately 35% increase in risk of colon cancer ***[AB-Comment: (Hampel) This sounds worse than a RR of 1.35 – suggest keeping with RR’s throughout this section.]*** .[[30](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_72_30)]

Other candidate alleles that have been identified on multiple (>3) genetic association studies include the *GSTM1* [null allele](https://cdr.cancer.gov/cgi-bin/cdr/Filter.py?DocId=CDR0000460202&Filter=set:QC+GlossaryTermName+with+Concept+Set) and the *NAT2* G/G allele.[[31](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_72_31)] None of these alleles has been characterized enough to currently support its routine use in a clinical setting. Family history remains the most valuable tool for establishing risk of colon cancer in these families. Similar to what has been reported in prostate cancer, a combination of susceptibility loci may yet hold promise in profiling individual risk.[[32](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_72_32), [33](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_72_33)]

**Variants of uncertain significance in major cancer susceptibility genes**

***[Comment: From WG: This section needs updating. Mention InSiGHT effort on reclassifying variants.]***

***APC* I1307K**

Polymorphisms in *APC* are the most extensively studied polymorphisms with regard to cancer association. The *APC* I1307K polymorphism is associated with an increased risk of colon cancer but does not cause colonic polyposis. The I1307K polymorphism occurs almost exclusively in people of Ashkenazi Jewish descent and results in a twofold increased risk of colonic adenomas and adenocarcinomas compared with the general population.[[18](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_72_18), [34](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_72_34)] ***[AB-Comment: (Amos) Should cite the increased risk associated with this allele – about 2? (Note from RJ: the previous sentence says twofold, so I think this is covered.)]*** The I1307K polymorphism results from a transition from T to A at nucleotide 3920 in the *APC* gene and appears to create a region of hypermutability ***by virtue of the fact that this results in an A8 microsatellite coding sequence [AB-Comment: (Boland) Suggested text.]*** .[[18](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_72_18)] Although clinical assays to assess for the *APC* I1307K polymorphism are currently available, the associated colon cancer risk is not high enough to support routine use. On the basis of currently available data, it is not yet known whether the I1307K carrier state should guide decisions regarding the age to initiate screening, the frequency of screening, or the choice of screening strategy.

***[AB-Comment: (Hampel) Cite new paper suggesting that I1307K does not have a place in the cancer genetics clinic (where screening can usually be based on family history), it may be useful in the GI clinic for management decisions for Ashkenazi Jewish individuals without a family history of cancer. If they have I1307K, they should be screened as if they had an FDR with CRC <60. Thought-provoking.]***

**Clinical implications of low-penetrance alleles**

Although the statistical evidence for an association between genetic variation at these loci and CRC risk is convincing, the biologically relevant variants and the mechanisms by which they lead to increased risk are unknown and will require further genetic and functional characterization. Additionally, these loci are associated with very modest risk, with ORs for developing CRC in heterozygous carriers usually from 1.1 to 1.3. More risk variants will likely be identified. Risks in this range do not appear to confer enough increase in age-specific risk as to warrant modification of otherwise clinically prudent screening. Until their collective influence is prospectively evaluated, their use cannot be recommended in clinical practice.

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**Major Genetic Syndromes**

**Introduction**

***[Comment: This Introduction could include the table of Major Genes (from above).]***

Originally described in the 1800s and 1900s by their clinical findings, the colon cancer susceptibility syndrome names often reflected the physician or patient and family associated with the syndrome (e.g., Gardner syndrome, Turcot syndrome, Muir-Torre syndrome, Lynch syndrome, Peutz-Jeghers syndrome [PJS], Bannayan-Riley-Ruvalcaba syndrome, and Cowden syndrome). These syndromes were associated with an increased lifetime risk of colorectal adenocarcinoma. They were mostly thought to have [autosomal dominant](https://cdr.cancer.gov/cgi-bin/cdr/Filter.py?DocId=CDR0000339338&Filter=set:QC+GlossaryTermName+with+Concept+Set) inheritance patterns. Adenomatous colonic polyps were characteristic of the first four, while hamartomas were found to be characteristic in the last three.

With the development of the Human Genome Project and the identification in 1990 of the *adenomatous polyposis coli* (*APC*) [gene](https://cdr.cancer.gov/cgi-bin/cdr/Filter.py?DocId=CDR0000045693&Filter=set:QC+GlossaryTermName+with+Concept+Set) on [chromosome](https://cdr.cancer.gov/cgi-bin/cdr/Filter.py?DocId=CDR0000046470&Filter=set:QC+GlossaryTermName+with+Concept+Set) 5q, overlap and differences between these [familial](https://cdr.cancer.gov/cgi-bin/cdr/Filter.py?DocId=CDR0000460148&Filter=set:QC+GlossaryTermName+with+Concept+Set) syndromes became apparent. Gardner syndrome and familial adenomatous polyposis (FAP) were shown to be synonymous, both caused by [pathogenic variants](https://cdr.cancer.gov/cgi-bin/cdr/Filter.py?DocId=CDR0000783960&Filter=set:QC+GlossaryTermName+with+Concept+Set) in the *APC* gene. Attenuated FAP (AFAP) was recognized as a syndrome with less adenomas and extraintestinal manifestations due to an *APC* pathogenic variant at the 3’ or 5’ ends of the gene. *MUTYH*-associated polyposis (MAP) was recognized as a separate adenomatous polyp syndrome with [autosomal recessive](https://cdr.cancer.gov/cgi-bin/cdr/Filter.py?DocId=CDR0000339339&Filter=set:QC+GlossaryTermName+with+Concept+Set) inheritance. Once the pathogenic variants were identified, the absolute risk of colorectal cancer (CRC) could be better assessed for [carriers](https://cdr.cancer.gov/cgi-bin/cdr/Filter.py?DocId=CDR0000460132&Filter=set:QC+GlossaryTermName+with+Concept+Set) of pathogenic variants (refer to [Table 3](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#_417)).

***[Comment: From Full Board 5/1: Consider adding TP53 and PTEN to table below. Discuss in WG.]***

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| **Table 3. Absolute Risks of Colorectal Cancer (CRC) for Carriers of Pathogenic Variants in Hereditary CRC Syndromes** |
| **Syndrome**  | **Absolute Risk of CRC in Carriers of a Pathogenic Variant**  |
| FAPa  | 90% by age 45 y [[1](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_1)]  |
| Attenuated FAP  | 69% by age 80 y [[2](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_2)]   |
| Lynch syndrome   | 10% to 56% by age 75 y, depending on the gene involvedb [[3](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_3), [4](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_4), [5](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_5), [6](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_6)]  |
| *MUTYH*-associated polyposis  | 35% to 53% [[7](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_7)]  |
| PJS   | 39% by age 70 y [[8](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_8)]  |
| JPS   | 17% to 68% by age 60 y [[9](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_9), [10](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_10)]  |

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| *FAP = familial adenomatous polyposis; JPS = juvenile polyposis syndrome; PJS = Peutz-Jeghers syndrome.* |
| *aCancer risk estimates quoted here predate the widespread use of* [*surveillance*](https://cdr.cancer.gov/cgi-bin/cdr/Filter.py?DocId=CDR0000496506&Filter=set:QC+GlossaryTermName+with+Concept+Set) *and prophylactic surgery.* |
| *bRefer to the* [*Lynch Syndrome*](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#_2986) *section of this summary for a full discussion of risk.* |

With these discoveries genetic testing and risk management became possible. Genetic testing refers to searching for variants in known cancer [susceptibility genes](https://cdr.cancer.gov/cgi-bin/cdr/Filter.py?DocId=CDR0000460209&Filter=set:QC+GlossaryTermName+with+Concept+Set) using a variety of techniques. Comprehensive genetic testing includes sequencing the entire coding region of a gene, the [intron](https://cdr.cancer.gov/cgi-bin/cdr/Filter.py?DocId=CDR0000660737&Filter=set:QC+GlossaryTermName+with+Concept+Set)-[exon](https://cdr.cancer.gov/cgi-bin/cdr/Filter.py?DocId=CDR0000460146&Filter=set:QC+GlossaryTermName+with+Concept+Set) boundaries (splice sites), and assessment of rearrangements, [deletions](https://cdr.cancer.gov/cgi-bin/cdr/Filter.py?DocId=CDR0000460141&Filter=set:QC+GlossaryTermName+with+Concept+Set), or other changes in copy number (with techniques such as [multiplex ligation-dependent probe amplification](https://cdr.cancer.gov/cgi-bin/cdr/Filter.py?DocId=CDR0000687002&Filter=set:QC+GlossaryTermName+with+Concept+Set) [MLPA] or [Southern blot](https://cdr.cancer.gov/cgi-bin/cdr/Filter.py?DocId=CDR0000460219&Filter=set:QC+GlossaryTermName+with+Concept+Set)). Despite extensive accumulated experience that helps distinguish pathogenic variants from benign variants and [polymorphisms](https://cdr.cancer.gov/cgi-bin/cdr/Filter.py?DocId=CDR0000044805&Filter=set:QC+GlossaryTermName+with+Concept+Set), genetic testing sometimes identifies [variants of uncertain significance](https://cdr.cancer.gov/cgi-bin/cdr/Filter.py?DocId=CDR0000556495&Filter=set:QC+GlossaryTermName+with+Concept+Set) (VUS) that cannot be used for predictive purposes.

**Familial Adenomatous Polyposis (FAP)**

**Introduction**

**By 1900, several reports had demonstrated that patients with a large number of polyps (later subclassified as adenomas) were at very high risk of CRC and that the pattern of transmission in families was autosomal dominant. In the 20th century, the adenoma-to-carcinoma progression was confirmed, and FAP was recognized as the prototypical model for this progression.[**[**11**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_11)**] Various extracolonic manifestations of FAP came to be described, including upper gastrointestinal (GI) tract adenomas and adenocarcinomas; fundic gland stomach polyps; nonepithelial benign tumors (osteomas, epidermal cysts, dental abnormalities); desmoid tumors; congenital hypertrophy of retinal pigment epithelium (CHRPE); and malignant tumors (thyroid and brain tumors, hepatoblastoma). Refer to Table 4 for the risks of these extracolonic manifestations in FAP.**

**FAP is one of the most clearly defined and well understood of the inherited colon cancer syndromes.[**[**1**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_1)**,** [**12**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_12)**,** [**13**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_13)**] It is an autosomal dominant condition, and the reported incidence varies from 1 in 7,000 to 1 in 22,000 live births.[**[**14**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_14)**] The presence of ethnic differences in the prevalence of FAP has been suggested [**[**14**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_14)**] but a recent large study did not find significant differences in ethnic variation in over 6,169 individuals with a personal and/or family history of colorectal cancer (CRC) and polyps who were referred for genetic testing at a large reference laboratory.[**[**15**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_15)**]**

**Classical FAP is characterized by numerous (hundreds to thousands) adenomatous polyps in the colon and rectum developing after the first decade of life (refer to** [**Figure** 3](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#_2801)**).**

**Image:** FAP polyps - endoscopic and surgically resected

***Figure*** *3.* ***Multiple polyps in the colon of a patient with familial adenomatous polyposis shown endoscopically (left panel) and upon surgical resection (right panel).***

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| **Table 4. Extracolonic Tumor Risks in Familial Adenomatous Polyposis** |
| **Malignancy**  | **Relative Risk**  | **Absolute Lifetime Risk (%)**  |
| **Desmoid *tumor***  | **852.0**  | **15.0**  |
| **Duoden*al tumors and cancer****~~um~~*  | **330.8**  | **5.0–12.0**  |
| **Thyroid *cancer***  | **7.6**  | **2.0**  |
| **Brain *cancer***  | **7.0**  | **2.0**  |
| **Ampullary *cancer***  | **123.7**  | **1.7**  |
| **Pancrea*tic cancer****~~s~~*  | **4.5**  | **1.7**  |
| **Hepatoblastoma**  | **847.0**  | **1.6**  |
| **Gastric *cancer***  | **—**  | **0.6a**  |

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| ***Adapted from Giardiello et al.,[***[***16***](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_16)***] Jagelman et al.,[***[***17***](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_17)***] Sturt et al.,[***[***18***](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_18)***] Lynch et al.,[***[***19***](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_19)***] Bülow et al.,[***[***20***](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_20)***] Burt et al.,[***[***21***](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_21)***] and Galiatsatos et al.[***[***22***](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_22)***]*** |
| ***aThe Leeds Castle Polyposis Group.*** |

**FAP has also been known as familial polyposis coli or adenomatous polyposis coli (APC). Gardner syndrome (colorectal polyposis, osteomas, and soft tissue tumors). Gardner syndrome was previously used to designate FAP patients who manifested with these extracolonic features. However, Gardner syndrome has been shown genetically to be a variant of FAP, and thus the term Gardner syndrome is essentially obsolete in clinical practice.[**[**23**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_23)**]**

**Most cases of FAP result from pathogenic variants in the *APC* gene on chromosome 5q21. Individuals who inherit a pathogenic variant in the *APC* gene have a very high likelihood of developing colonic adenomas; the risk has been estimated to be more than 90%.[**[**1**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_1)**,** [**12**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_12)**,** [**13**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_13)**] The age at onset of adenomas in the colon is variable, and the median age for the appearance of colorectal adenomas is 16 years.[**[**24**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_24)**] By age 10 years, only 15% of carriers of the *APC*** [germline variant](https://cdr.cancer.gov/cgi-bin/cdr/Filter.py?DocId=CDR0000781852&Filter=set:QC+GlossaryTermName+with+Concept+Set) **manifest adenomas; by age 20 years, the probability rises to 75%; and by age 30 years, 90% will have presented with FAP.[**[**1**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_1)**,** [**12**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_12)**,** [**13**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_13)**,** [**24**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_24)**,** [**25**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_25)**] The exception is attenuated FAP (AFAP), in which affected individuals typically have fewer colon polyps and later onset of CRC. (Refer to the AFAP section for more information.) Without any intervention, the vast majority of individuals with FAP will develop colon or rectal cancer by the fourth decade of life.[**[**1**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_1)**,** [**12**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_12)**,** [**13**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_13)**] Thus, surveillance and intervention for carriers of an *APC* gene pathogenic variant and at-risk persons have conventionally consisted of annual colonoscopy beginning around puberty for early detection of colonic polyps and to help plan when to perform colectomy.[**[**26**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_26)**,** [**27**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_27)**]**

**The early appearance of clinical features of FAP and the subsequent recommendations for surveillance beginning at puberty raise special considerations relating to the genetic testing of children for** [susceptibility genes](https://cdr.cancer.gov/cgi-bin/cdr/Filter.py?DocId=CDR0000460209&Filter=set:QC+GlossaryTermName+with+Concept+Set)**.[**[**28**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_28)**] Most proponents feel that the genetic testing of children for FAP presents an example in which possible medical benefit justifies genetic testing of minors, especially for the anticipated 50% of at-risk children who will be found not to be carriers of pathogenic variants and who can thus be spared surveillance. In addition, testing infants for FAP can allow for hepatoblastoma surveillance until age 5. *[Comment: Run this past pediatric expert.]* The psychological impact of such testing is currently under investigation and is addressed in the** [**Psychosocial Issues in Hereditary Colon Cancer Syndromes**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#_189) **section of this summary.**

**The adenomatous polyposis coli (APC) gene**

**The *APC* gene on chromosome 5q21 encodes a 2,843-amino acid protein that is important in cell adhesion and signal transduction; the main function of the APC protein is to regulate intracellular concentrations of beta-catenin, a major mediator of the Wnt signal transduction pathway. *APC* is a** [tumor suppressor gene](https://cdr.cancer.gov/cgi-bin/cdr/Filter.py?DocId=CDR0000046657&Filter=set:QC+GlossaryTermName+with+Concept+Set)**, and the loss of *APC* is among the earliest events in the chromosomal instability colorectal tumor pathway. *[AB-Comment: (Hampel) I think in the first section we say that APC mutations are among the earliest events in both CIN and MIN CRC.]* FAP and AFAP can be diagnosed genetically by testing for germline pathogenic variants in the *APC* gene in** [DNA](https://cdr.cancer.gov/cgi-bin/cdr/Filter.py?DocId=CDR0000045671&Filter=set:QC+GlossaryTermName+with+Concept+Set) **from peripheral blood leukocytes. More than 300 different disease-associated pathogenic variants of the *APC* gene have been reported.[**[**29**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_29)**] The vast majority of these changes are insertions, deletions, and** [nonsense variants](https://cdr.cancer.gov/cgi-bin/cdr/Filter.py?DocId=CDR0000783965&Filter=set:QC+GlossaryTermName+with+Concept+Set) **that lead to frameshifts and/or premature stop** [codons](https://cdr.cancer.gov/cgi-bin/cdr/Filter.py?DocId=CDR0000460135&Filter=set:QC+GlossaryTermName+with+Concept+Set) **in the resulting transcript of the gene. The most common *APC* pathogenic variant (10% of FAP patients) is a deletion of AAAAG in codon 1309; no other pathogenic variants appear to predominate. Variants that reduce rather than eliminate production of the APC protein may also lead to FAP.[**[**30**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_30)**]**

**Genetic testing for FAP**

***APC* gene testing is now commercially available and has led to changes in management guidelines, particularly for those whose tests indicate they are not carriers of pathogenic variants. Presymptomatic genetic diagnosis of FAP in at-risk individuals has been feasible with** [linkage](https://cdr.cancer.gov/cgi-bin/cdr/Filter.py?DocId=CDR0000460161&Filter=set:QC+GlossaryTermName+with+Concept+Set) **[**[**24**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_24)**] and direct detection [**[**31**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_31)**] of *APC* pathogenic variants. These tests require a small sample (<10 cc) of blood in which the lymphocyte DNA is tested. If one were to use** [linkage analysis](https://cdr.cancer.gov/cgi-bin/cdr/Filter.py?DocId=CDR0000425374&Filter=set:QC+GlossaryTermName+with+Concept+Set) **to identify gene carriers, ancillary family members, including more than one affected individual, would need to be studied. This approach is almost never used currently because of the success of direct gene analysis. With direct detection, fewer family members’ blood samples are required than for linkage analysis, but the specific pathogenic variant must be identified in at least one affected person by DNA variant analysis or sequencing. The detection rate is approximately 80% using sequencing alone.[**[**32**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_32)**] *[AB-Comment: (Boland) old data, probably higher now]]* In a large cross-sectional study, APC mutations were found in 80% (95% CI 71%–87%) of individuals with more than 1,000 adenomas, 56% (95% CI 54%–59%) in those with 100–999 adenomas, 10% (95% CI 9%–11%) in those with 20–99 adenomas, and 5% (95% CI 4%–7%) in those with 10–19 adenomas.[**[**33**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_33)**]**

**Studies have reported whole exon deletions in 12% of FAP patients with previously negative *APC* testing.[**[**34**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_34)**,** [**35**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_35)**] *[AB-Comment: (Hampel) Add data about the APC promoter deletion and suggest that testing should include this as well. APC promoter 1B deletion in familial polyposis--implications for mutation-negative families. Kadiyska TK, Todorov TP, Bichev SN, Vazharova RV, Nossikoff AV, Savov AS, Mitev VI. Clin Genet. 2014 May;85(5):452-7. PMID:23725351 ]* For this reason, deletion testing is always added to sequencing of *APC*. Furthermore, pathogenic variant detection assays that use MLPA have been developed and are accurate for detecting intragenic deletions.[**[**36**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_36)**] *[Comment: From Scott: Is MLPA now unnecessary with nextgen sequencing?] MUTYH* gene testing may be considered in *APC* pathogenic variant–negative affected individuals.[**[**37**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_37)**] *POLE*/*POLD1* gene testing may be considered in *APC* and *MUTYH* pathogenic variant–negative affected individuals.[**[**38**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_38)**,** [**39**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_39)**] Alternatively, NGS panels are available that include all of these polyposis genes and this can simplify and lower the cost of testing by screening all of these genes at the same time. (Refer to the** [***Adenomatous polyposis coli [APC]***](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#_2551) **section of this summary for more information.)**

***[AB-Comment: (Hampel) I’d consider combining this paragraph and the one above to discuss the Differential diagnosis for adenomatous polyposis – since most people would just order a polyposis panel for either indication now.]* Patients who develop fewer than 100 colorectal adenomatous polyps are a diagnostic challenge. The differential diagnosis includes AFAP, *MUTYH*-associated polyposis (MAP), and polymerase proofreading-associated polyposis (PPAP).[**[**40**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_40)**] AFAP can be diagnosed by testing for germline *APC* gene pathogenic variants. (Refer to the** [**Attenuated Familial Adenomatous Polyposis [AFAP]**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#_118) **section in the** [**Major Genetic Syndromes**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#_89) **section of this summary for more information.) *MUTYH*-associated neoplasia is caused by biallelic germline pathogenic variants in the *MUTYH* gene.[**[**41**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_41)**] PPAP is caused by pathogenic variants in *POLE* and *POLD1*.[**[**38**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_38)**,** [**39**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_39)**] NGS panels are available that include all of these polyposis genes and this can simplify testing by screening all of these genes at the same time.**

[Presymptomatic genetic testing](https://cdr.cancer.gov/cgi-bin/cdr/Filter.py?DocId=CDR0000460210&Filter=set:QC+GlossaryTermName+with+Concept+Set) **removes the necessity of annual screening of at-risk individuals who do not have the familial gene pathogenic variant. For at-risk individuals who have been found to be definitively pathogenic variant–negative by genetic testing, there is no clear consensus on the need for or frequency of colon screening,[**[**25**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_25)**] although all experts agree that at least one flexible sigmoidoscopy or colonoscopy examination should be performed in early adulthood (by age 18–25 y**~~ears~~**). *[AB-Comment: (Hampel) Really? I thought this had gone by the wayside. Is this in the rare case that there was an error in the testing?]* [**[**24**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_24)**,** [**25**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_25)**] Colon adenomas will develop in nearly 100% of persons who are *APC* pathogenic variant–positive; risk-reducing surgery comprises the standard of care to prevent colon cancer after polyps have appeared and are too numerous or histologically advanced to monitor safely using endoscopic resection.**

**Clinical phenotype**

***[Comment: Need text here about colorectal manifestations.]***

**Extracolonic manifestations**

**Desmoid tumors**

**Desmoid tumors are proliferative, locally invasive, nonmetastasizing, fibromatous tumors in a collagen matrix. Although they do not metastasize, they can grow very aggressively and be life threatening.[**[**42**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_42)**] Desmoids may occur** [sporadically](https://cdr.cancer.gov/cgi-bin/cdr/Filter.py?DocId=CDR0000339347&Filter=set:QC+GlossaryTermName+with+Concept+Set)**, as part of classical FAP, or in a hereditary manner without the colon findings of FAP.[**[**19**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_19)**,** [**43**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_43)**] Desmoids have been associated with hereditary *APC* gene pathogenic variants even when not associated with typical adenomatous polyposis of the colon.[**[**43**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_43)**,** [**44**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_44)**]**

**Most studies have found that 10% of FAP patients develop desmoids, with reported ranges of 8% to 38%. The incidence varies with the means of ascertainment and the location of the pathogenic variant in the *APC* gene.[**[**43**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_43)**,** [**45**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_45)**,** [**46**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_46)**] *APC* pathogenic variants occurring between codons 1445 and 1578 have been associated with an increased incidence of desmoid tumors in FAP patients.[**[**44**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_44)**,** [**47**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_47)**,** [**48**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_48)**,** [**49**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_49)**] Desmoid tumors with a late onset and a milder intestinal polyposis phenotype (hereditary desmoid disease) have been described in patients with pathogenic variants at codon 1924.[**[**43**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_43)**]**

**A desmoid risk factor scale has been described in an attempt to identify patients who are likely to develop desmoid tumors.[**[**50**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_50)**] The desmoid risk factor scale was based on gender, presence or absence of extracolonic manifestations,** [family history](https://cdr.cancer.gov/cgi-bin/cdr/Filter.py?DocId=CDR0000302456&Filter=set:QC+GlossaryTermName+with+Concept+Set) **of desmoids, and** [genotype](https://cdr.cancer.gov/cgi-bin/cdr/Filter.py?DocId=CDR0000660739&Filter=set:QC+GlossaryTermName+with+Concept+Set)**, if available. By utilizing this scale, it was possible to stratify FAP patients into low-, medium-, and high-risk groups for developing desmoid tumors. The authors concluded that the desmoid risk factor scale could be used for surgical planning. Validation of the risk factors comprising this scale were supported by a large, multiregistry, retrospective study from Europe.[**[**51**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_51)**]**

**The natural history of desmoids is variable. Some authors have proposed a model for desmoid tumor formation whereby abnormal fibroblast function leads to mesenteric plaque-like desmoid precursor lesions, which in some cases occur before surgery and progress to mesenteric fibromatosis after surgical trauma, ultimately giving rise to desmoid tumors.[**[**52**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_52)**] It is estimated that 10% of desmoids resolve, 50% remain stable for prolonged periods, 30% fluctuate, and 10% grow rapidly.[**[**53**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_53)**] Desmoids often occur after surgical or physiological trauma, and both endocrine and genetic factors have been implicated. Approximately 80% of intra-abdominal desmoids in FAP occur after surgical trauma.[**[**54**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_54)**,** [**55**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_55)**]**

**The desmoids in FAP are often intra-abdominal, may present early, and can lead to intestinal obstruction or infarction and/or obstruction of the ureters.[**[**46**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_46)**] In some series, desmoids are the second most common cause of death after CRC in FAP patients.[**[**56**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_56)**,** [**57**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_57)**] A staging system has been proposed to facilitate the stratification of intra-abdominal desmoids by disease severity.[**[**58**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_58)**] The proposed staging system for intra-abdominal desmoids is as follows: stage I for asymptomatic, nongrowing desmoids; stage II for symptomatic, nongrowing desmoids of 10 cm or less in maximum diameter; stage III for symptomatic desmoids of 11 to 20 cm or for asymptomatic, slow-growing desmoids; and stage IV for desmoids larger than 20 cm, or rapidly growing, or with life-threatening complications.[**[**58**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_58)**]**

**These data suggest that genetic testing could be of value in the medical management of patients with FAP and/or multiple desmoid tumors. Those with *APC* genotypes predisposing to desmoid formation (e.g., at the 3’ end of *APC* codon 1445 *[AB-Comment: (Hampel) I think you might mean “at the 3’ end of APC or codon 1445”? You don’t usually see someone refer to the 3’ end of a codon.]* ), appear to be at high risk of developing desmoids after any surgery, including risk-reducing colectomy and surgical surveillance procedures such as laparoscopy.[**[**45**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_45)**,** [**53**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_53)**,** [**59**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_59)**]**

**The management of desmoids in FAP can be challenging and can complicate prevention efforts. Currently, there is no accepted standard treatment for desmoid tumors. Multiple medical treatments have generally been unsuccessful in the management of desmoids. Treatments have included antiestrogens, nonsteroidal anti-inflammatory drugs (NSAIDs), chemotherapy, and radiation therapy, among others. Studies have evaluated the use of raloxifene alone, tamoxifen or raloxifene combined with sulindac, and pirfenidone alone.[**[**60**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_60)**,** [**61**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_61)**,** [**62**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_62)**]**

**Thirteen patients with intra-abdominal desmoids and/or unfavorable response to other medical treatments, who had expression of estrogen alpha receptors in their desmoid tissues, were included in a prospective study of raloxifene, given in doses of 120 mg daily.[**[**60**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_60)**] Six of the patients had been on tamoxifen or sulindac before treatment with raloxifene, and seven patients were previously untreated. All 13 patients with intra-abdominal desmoid disease had either a partial or a complete response 7 months to 35 months after starting treatment, and most desmoids decreased in size at 4.7 ± 1.8 months after treatment. Response occurred in patients with desmoid plaques and with distinct lesions. Study limitations include small sample size, and the clinical evaluation of response was not consistent in all patients. Several questions remain concerning patients with desmoid tumors not expressing estrogen alpha receptors who have received raloxifene and their outcome and which patients may benefit from this potential treatment.**

**A second study of 13 patients with FAP-associated desmoids, who were treated with tamoxifen 120 mg/day or raloxifene 120 mg/day in combination with sulindac 300 mg/day, reported that ten patients had either stable disease (n = 6) or a partial or complete response (n = 4) for more than 6 months and that three patients had stable disease for more than 30 months.[**[**61**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_61)**] These results suggest that the combination of these agents may be effective in at least slowing the growth of desmoid tumors. However, the natural history of desmoids is variable, with both spontaneous regression and variable growth rates.**

**A third study reported mixed results in 14 patients with FAP-associated desmoid tumors treated with pirfenidone for 2 years.[**[**62**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_62)**] In this study, some patients had regression, some patients had progression, and some patients had stable disease.**

**There are reports of using imatinib mesylate to treat desmoid tumors in FAP patients with some success.[**[**63**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_63)**,** [**64**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_64)**] Nilotinib had the potential to stabilise desmoid tumour growth after treatment failure with imatinib in patients with desmoid tumors.[**[**65**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_65)**]**

[Level of evidence: 4](https://cdr.cancer.gov/cgi-bin/cdr/QcReport.py?DocId=CDR0000531845&Session=guest)

**Because of the high rates of morbidity and recurrence, in general, surgical resection is not recommended in the treatment of intra-abdominal desmoid tumors. A review of one hospital's experience suggested that surgical outcomes with intra-abdominal desmoids may be better than previously believed.[**[**66**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_66)**,** [**67**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_67)**] Issues of subject selection are critical in evaluating surgical outcome data.[**[**66**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_66)**] Abdominal wall desmoids can be treated with surgical resection, but the recurrence rate is high.**

**Stomach tumors**

**The most common FAP-related gastric polyps are fundic gland polyps (FGPs). FGPs are often diffuse and not amenable to endoscopic removal. The incidence of FGPs has been estimated to be as high as 60% in patients with FAP, compared with 0.8% to 1.9% in the general population.[**[**20**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_20)**,** [**22**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_22)**,** [**68**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_68)**,** [**69**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_69)**,** [**70**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_70)**,** [**71**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_71)**,** [**72**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_72)**] These polyps consist of distorted fundic glands containing microcysts lined with fundic-type epithelial cells or foveolar mucous cells.[**[**73**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_73)**,** [**74**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_74)**]**

**The hyperplastic surface epithelium is, by definition, nonneoplastic. Accordingly, FGPs have not been considered precancerous; in Western FAP patients the risk of stomach cancer is minimally increased, if at all. However, case reports of stomach cancer appearing to arise from FGPs have led to a reexamination of this issue.[**[**22**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_22)**,** [**75**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_75)**] In one FAP series, focal dysplasia was evident in the surface epithelium of FGPs in 25% of patients versus 1% of sporadic FGPs.[**[**74**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_74)**] In a prospective study of patients with FAP undergoing surveillance with esophagogastroduodenoscopy, FGPs were detected in 88% of the patients. Low-grade dysplasia was detected in 38% of these patients, whereas high-grade dysplasia was detected in 3% of these patients. In the author's view, if a polyp with high-grade dysplasia is identified, polypectomy can be considered with repeat endoscopic surveillance in 3 to 6 months. Consideration for treatment with daily proton-pump inhibitors (PPIs) also may be given. *[AB-Comment: (Hampel) Given that PPIs cause FGP (see below) I find it surprising that anyone would recommend PPIs for the treatment of FGPs in FAP.]* [**[**76**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_76)**]**

**Complicating the issue of differential diagnosis, FGPs have been increasingly recognized in non-FAP patients consuming PPIs.[**[**74**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_74)**,** [**77**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_77)**] FGPs in this setting commonly show a “PPI effect” consisting of congestion of secretory granules in parietal cells, leading to irregular bulging of individual cells into the lumen of glands. To the trained eye, the presence of dysplasia and the concomitant absence of a characteristic PPI effect can be considered highly suggestive of the presence of underlying FAP. The number of FGPs tends to be greater in FAP than that seen in patients consuming PPIs, although there is some overlap.**

**Gastric adenomas also occur in FAP patients. The incidence of gastric adenomas in Western patients has been reported to be between 2% and 12%, whereas in Japan, it has been reported to be between 39% and 50%.[**[**78**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_78)**,** [**79**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_79)**,** [**80**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_80)**,** [**81**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_81)**] These adenomas can progress to carcinoma. FAP patients in Korea and Japan are reported to have a threefold to fourfold increased gastric cancer risk compared with their general population, a finding not observed in Western populations.[**[**82**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_82)**,** [**83**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_83)**,** [**84**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_84)**,** [**85**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_85)**] The recommended management for gastric adenomas is endoscopic polypectomy. The management of adenomas in the stomach is usually individualized based on the size of the adenoma and the degree of dysplasia. *[AB-Comment: (Hampel) The last two sentences of this para seem contradictory.]***

[Level of evidence: 5](https://cdr.cancer.gov/cgi-bin/cdr/QcReport.py?DocId=CDR0000531846&Session=guest) ***[AB-Comment: (Amos) This is a little confusing as its not really clear what is being evaluated: I guess in general its all management of gastric tumors in FAP – but perhaps a more specific recommendation about surgical resection of gastric adenomas could be addressed with a higher level of evidence. ]***

**Duodenum/small bowel tumors**

**Whereas the incidence of duodenal adenomas is only 0.4% in patients undergoing upper GI endoscopy,[**[**86**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_86)**] duodenal adenomas are found in 80% to 100% of FAP patients. The vast majority are located in the first and second portions of the duodenum, especially in the periampullary region.[**[**68**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_68)**,** [**69**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_69)**,** [**87**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_87)**] There is a 4% to 12% lifetime incidence of duodenal adenocarcinoma in FAP patients.[**[**17**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_17)**,** [**84**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_84)**,** [**88**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_88)**,** [**89**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_89)**] In a prospective multicenter surveillance study of duodenal adenomas in 368 northern Europeans with FAP, 65% had adenomas at baseline evaluation (mean age, 38 y), with cumulative prevalence reaching 90% by age 70 years. In contrast to earlier beliefs regarding an indolent clinical course, the adenomas increased in size and degree of dysplasia during the 8 years of average surveillance, although only 4.5% developed cancer while under prospective surveillance.[**[**20**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_20)**] While this study is the largest to date, it is limited by the use of forward-viewing rather than side-viewing endoscopy and the large number of investigators involved in the study. Intestinal polyps can also be assessed in FAP patients using capsule endoscopy.[**[**90**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_90)**,** [**91**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_91)**,** [**92**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_92)**] One study of computed tomography (CT) duodenography found that larger adenoma size could be accurately measured but smaller, flatter adenomas could not be accurately counted.[**[**93**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_93)**]**

**A retrospective review of FAP patients suggested that the adenoma-carcinoma sequence occurred in a temporal fashion for periampullary adenocarcinomas with a diagnosis of adenoma at a mean age of 39 years, high-grade dysplasia at a mean age of 47 years, and adenocarcinoma at a mean age of 54 years.[**[**94**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_94)**] A decision analysis of 601 FAP patients suggested that the benefit of periodic surveillance starting at age 30 years led to an increased life expectancy of 7 months.[**[**88**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_88)**] Although polyps in the duodenum can be difficult to treat, small series suggest that they can be managed successfully with endoscopy but with potential morbidity—primarily from pancreatitis, bleeding, and duodenal perforation.[**[**95**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_95)**,** [**96**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_96)**]**

**FAP patients with particularly severe duodenal polyposis, sometimes called dense polyposis, or with histologically advanced duodenal adenomas appear to be at the highest risk of developing duodenal adenocarcinoma.[**[**20**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_20)**,** [**89**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_89)**,** [**97**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_97)**,** [**98**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_98)**] Because the risk of duodenal adenocarcinoma is correlated with the number and size of polyps, and the severity of dysplasia of the polyps, a stratification system based on these features was developed to attempt to identify those individuals with FAP at highest risk of developing duodenal adenocarcinoma.[**[**98**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_98)**] According to this system, known as the Spigelman Classification (refer to** [**Table** 5](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#_1120)**), 36% of patients with the most advanced stage will develop carcinoma.[**[**89**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_89)**]**

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| **Table 5. Spigelman Classification** |
| **Points**  | **Polyp Number**  | **Polyp Size (mm)**  | **Histology**  | **Dysplasia**  |
| **1**  | **1–4**  | **1–4**  | **Tubular**  | **Mild**  |
| **2**  | **5–20**  | **4–10**  | **Tubulovillous**  | **Moderate**  |
| **3**  | **>20**  | **>10**  | **Villous**  | **Severe**  |

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| ***Stage I, 1–4 points; Stage II, 5–6 points; Stage III, 7–8 points; Stage IV, 9–12 points [***[***98***](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_98)***]*** |

**A baseline upper endoscopy, including side-viewing duodenoscopy, is typically performed between ages 25 and 30 years in FAP patients.[**[**85**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_85)**] The subsequent intervals between endoscopy vary according to the findings of the previous endoscopy, often, based on Spigelman stage. Recommended intervals are based on expert opinion although the relatively liberal intervals for stage 0-II disease are based in part on the natural history data generated by the Dutch/Scandinavian duodenal surveillance trial (refer to** [**Table** 6](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#_1254)**).[**[**20**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_20)**]**

**The main advantages of the Spigelman Classification are its long-standing familiarity to and usage by those in the field, which allows reasonable standardization of outcome comparisons across studies.[**[**81**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_81)**,** [**99**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_99)**] However, the following are limitations on attempted application of the Spigelman Classification:**

* **Most pathologists do not currently employ the term moderate dysplasia, preferring a simpler low- versus high-grade dysplasia system.**
* **Because of the villous nature of normal duodenal epithelium, pathologists commonly disagree over the classification of “tubular,” “tubulovillous,” and “villous.”**
* **Spigelman staging requires biopsy, which is not always essential when only a few small plaques are present; conversely, for larger adenomas, sampling variation leads to understaging.[**[**100**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_100)**,** [**101**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_101)**]**

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| **Table 6. Recommended Screening Intervals by Spigelman Stage** |
| **Spigelman Stage**   | **NCCN (2017) [**[**102**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_102)**]**  | **Groves et al. (2002) [**[**89**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_89)**]**  |
| **0 (no polyps)**   | **Endoscopy every 4 y**   | **Endoscopy every 5 y**  |
| **I**  | **Endoscopy every 2–3 y**   | **Endoscopy every 5 y**  |
| **II**  | **Endoscopy every 1–3 y**   | **Endoscopy every 3 y**   |
| **CP + ET**   |
| **III**  | **Endoscopy every 6–12 mo**   | **Endoscopy every 1–2 y**   |
| **CP + ET (+/- GA)**  |
| **IV**  | **Surgical evaluation**  | **Surgical resection**  |
| **Complete mucosectomy or duodenectomy, or Whipple procedure if duodenal papilla is involved**  |
| **OR**  |
| **Expert endoscopic surveillance every 3–6 mo**   | **Endoscopy every 1–2 y**  |
| **CP + ET (+/- GA)**  |

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| ***CP = chemoprevention; ET = endoscopic therapy; GA = general anesthetic; NCCN = National Comprehensive Cancer Network.*** |
| ***Refer to the*** [***Interventions for FAP***](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#_260) ***section in the*** [***Major Genetic Syndromes***](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#_89) ***section of this summary for more information about chemoprevention.*** |
| ***See*** [***below***](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#_1241) ***for additional information about the use of surgical resection in Spigelman stage IV disease.*** |

**The results of long-term duodenal adenoma surveillance of FAP patients in Nordic countries and the Netherlands revealed significant duodenal cancer risk in FAP patients.[**[**103**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_103)**] Per protocol, biennial frontal-viewing endoscopy was performed from 1990 through 2000. Subsequently, patients were followed up with surveillance according to international guidelines. The 261 of 304 patients (86%) who had more than one endoscopy comprised the study group. Median follow-up was 14 years (range, 9–17 y). The lifetime risk of duodenal adenomatosis was 88%. Forty-four percent of patients had worsening Spigelman stage over time, whereas 12% improved and 34% remained unchanged. Twenty patients (7%) developed duodenal cancer at a median age of 56 years (range, 44–82 y). The cumulative cancer incidence was 18% at age 75 years (95% CI, 8%–28%). Survival in patients with symptomatic cancers was worse than those diagnosed at surveillance endoscopy.**

[Level of evidence (screening for duodenum/small bowel tumors): 3](https://cdr.cancer.gov/cgi-bin/cdr/QcReport.py?DocId=CDR0000531825&Session=guest)

**Many factors, including severity of polyposis, comorbidities of the patient, patient preferences, and availability of adequately trained physicians, determine whether surgical or endoscopic therapy is selected for polyp management. Endoscopic resection or ablation of large or histologically advanced adenomas appears to be safe and effective in reducing the short-term risk of developing duodenal adenocarcinoma;[**[**95**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_95)**,** [**96**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_96)**,** [**104**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_104)**] however, patients managed with endoscopic resection of adenomas remain at substantial risk of developing recurrent adenomas in the duodenum.[**[**100**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_100)**] The most definitive procedure for reducing the risk of adenocarcinoma is surgical resection of the ampulla and duodenum, although these procedures also have higher morbidity and mortality associated with them than do endoscopic treatments. Duodenotomy and local resection of duodenal polyps or mucosectomy have been reported, but invariably, the polyps recur after these procedures.[**[**105**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_105)**] In a series of 47 patients with FAP and Spigelman stage III or stage IV disease who underwent definitive radical surgery, the local recurrence rate was reported to be 9% at a mean follow-up of 44 months. This local recurrence rate is dramatically lower than any local endoscopic or surgical approach from the same study.[**[**100**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_100)**] Pancreaticoduodenectomy and pancreas-sparing duodenectomy are appropriate surgical therapies that are believed to substantially reduce the risk of developing periampullary adenocarcinoma.[**[**101**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_101)**,** [**105**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_105)**,** [**106**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_106)**,** [**107**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_107)**] If such surgical options are considered, preservation of the pylorus is of particular benefit in this group of patients because most will have undergone a subtotal colectomy with ileorectal anastomosis or total colectomy with ileal pouch–anal anastomosis (IPAA). As noted in a Northern European study,[**[**20**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_20)**] and others,[**[**108**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_108)**,** [**109**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_109)**] the vast majority of patients with duodenal adenomas will not develop cancer and can be followed with endoscopy. However, individuals with advanced adenomas (Spigelman stage III or stage IV disease) generally require endoscopic or surgical treatment of the polyps. Chemoprevention studies for duodenal adenomas in FAP patients are currently under way and may offer an alternate strategy in the future.**

**The endoscopic approach to larger and/or flatter adenomas of the duodenum depends on whether the ampulla is involved. Endoscopic mucosal resection (EMR) after submucosal injection of saline, with or without epinephrine and/or dye, such as indigo carmine, can be employed for nonampullary lesions. Ampullary lesions require even greater care including endoscopic ultrasound evaluation for evidence of bile or pancreatic duct involvement. Stenting of the pancreatic duct is commonly performed to prevent stricturing and pancreatitis. The stents require endoscopic removal at an interval of 1 to 4 weeks. Because the ampulla is tethered at the ductal orifices, it typically does not uniformly “lift” with injection, so injection is commonly not used. Any consideration of EMR or ampullectomy requires great experience and judgment, with careful consideration of the natural history of untreated lesions and an appreciation of the high rate of adenoma recurrence despite aggressive endoscopic intervention.[**[**96**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_96)**,** [**100**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_100)**,** [**101**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_101)**,** [**106**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_106)**,** [**110**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_110)**,** [**111**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_111)**,** [**112**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_112)**,** [**113**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_113)**] The literature uniformly supports duodenectomy for Spigelman stage IV disease. For Spigelman stage II and III disease, there is a role for endoscopic treatment invariably focusing on the one or two worst lesions that are present.**

**Reluctance to consider surgical resection has to do with short-term morbidity and mortality and long-term complications related to surgery. Although these concerns are likely overstated,[**[**100**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_100)**,** [**101**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_101)**,** [**107**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_107)**,** [**110**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_110)**,** [**114**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_114)**,** [**115**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_115)**,** [**116**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_116)**,** [**117**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_117)**,** [**118**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_118)**,** [**119**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_119)**,** [**120**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_120)**] fear of surgical intervention can lead to aggressive and somewhat ill-advised endoscopic interventions. In some circumstances, endoscopic resection of ampullary and/or other duodenal adenomas cannot be accomplished completely or safely by endoscopic means, and duodenectomy cannot be accomplished without risking a short-gut syndrome or cannot be done at all because of mesenteric fibrosis. In such cases, surgical transduodenal ampullectomy/polypectomy can be performed. This is, however, associated with a high risk of local recurrence similar to that of endoscopic treatment.**

[Level of evidence (treatment of duodenum/small bowel tumors): 4](https://cdr.cancer.gov/cgi-bin/cdr/QcReport.py?DocId=CDR0000531845&Session=guest)

**Other tumors**

**The spectrum of tumors arising in FAP is summarized in** [**Table** 4](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#_723)**.**

**Papillary thyroid cancer *(cribriform morular type) [AB-Comment: (Hampel) Suggested addition.]* has been reported to affect 1% to 2% of patients with FAP.[**[**121**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_121)**] However, a recent study [**[**122**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_122)**] of papillary thyroid cancers in six females with FAP failed to demonstrate** [loss of heterozygosity](https://cdr.cancer.gov/cgi-bin/cdr/Filter.py?DocId=CDR0000486444&Filter=set:QC+GlossaryTermName+with+Concept+Set) **(LOH) or pathogenic variants of the wild-type** [allele](https://cdr.cancer.gov/cgi-bin/cdr/Filter.py?DocId=CDR0000339337&Filter=set:QC+GlossaryTermName+with+Concept+Set) **in codons 545 and 1061 to 1678 of the six tumors. In addition, four of five of these patients had detectable somatic *RET/PTC* chimeric genes. This pathogenic variant is generally restricted to sporadic papillary thyroid carcinomas, suggesting the involvement of genetic factors other than *APC* pathogenic variants. Further studies are needed to show whether other genetic factors such as the *RET/PTC* chimeric gene are independently responsible for or cooperative with *APC* variants in causing papillary thyroid cancers in FAP patients. Although** [level 1 evidence](https://cdr.cancer.gov/cgi-bin/cdr/QcReport.py?DocId=CDR0000531823&Session=guest) **is lacking, a consensus opinion recommends annual thyroid examinations beginning in the late teenage years to screen for papillary thyroid cancer in patients with FAP. The same panel suggests clinicians could consider the addition of annual thyroid ultrasounds to this screening routine.[**[**102**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_102)**,** [**123**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_123)**,** [**124**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_124)**]**

[Level of evidence (thyroid cancer ultrasound screening): 4](https://cdr.cancer.gov/cgi-bin/cdr/QcReport.py?DocId=CDR0000531827&Session=guest) ***[AB-Comment: (Amos) Suggested edit.]***

**Adrenal tumors have been reported in FAP patients, and one study demonstrated LOH *at the APC locus [AB-Comment: (Boland) Suggested revision.]* in an adrenocortical carcinoma (ACC) in an FAP patient.[**[**125**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_125)**] In a study of 162 FAP patients who underwent abdominal CT for evaluation of intra-abdominal desmoid tumors, 15 patients (11 females) were found to have adrenal tumors.[**[**126**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_126)**] Of these, two had symptoms attributable to cortisol hypersecretion. Three of these patients underwent subsequent surgery and were found to have ACC, bilateral nodular hyperplasia, or adrenocortical adenoma. The prevalence of an unexpected adrenal neoplasia in this cohort was 7.4%, which compares with a prevalence of 0.6% to 3.4% (*P* < .001) in non-FAP patients.[**[**126**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_126)**] No molecular genetic analyses were provided for the tumors resected in this series. A subsequent study identified adrenal lesions in 26% (23 of 90) of patients with FAP, 18% (2 of 11) of patients with AFAP, and** ~~21%~~**24% (5 of 21) of patients with *MUTYH*-associated polyposis. Most lesions in this series followed a benign and slowly progressive course; no cases of ACC were reported.[**[**127**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_127)**]**

**Hepatoblastoma is a rare, rapidly progressive, and usually fatal childhood malignancy that, if confined to the liver, can be cured by radical surgical resection. Multiple cases of hepatoblastoma have been described in children with an *APC* pathogenic variant.[**[**128**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_128)**,** [**129**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_129)**,** [**130**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_130)**,** [**131**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_131)**,** [**132**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_132)**,** [**133**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_133)**,** [**134**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_134)**,** [**135**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_135)**,** [**136**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_136)**,** [**137**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_137)**] Some series have also demonstrated LOH of *APC* in these tumors.[**[**129**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_129)**,** [**131**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_131)**,** [**138**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_138)**] No specific genotype-phenotype correlations have been identified in FAP patients with hepatoblastoma.[**[**139**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_139)**] Although lacking** [level 1 evidence](https://cdr.cancer.gov/cgi-bin/cdr/QcReport.py?DocId=CDR0000531823&Session=guest)**, a consensus panel has suggested that abdominal examination, abdominal ultrasound, and measurement of serum alpha fetoprotein every 3 to 6 months for the first 5 years of life in children with a predisposition to FAP be considered.[**[**102**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_102)**,** [**140**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_140)**] *It is not necessary to continue screening after age 5. [AB-Comment: (Boland) Suggested text.]***

[Level of evidence (hepatoblastoma or adrenal cancer screening): 5](https://cdr.cancer.gov/cgi-bin/cdr/QcReport.py?DocId=CDR0000526280&Session=guest) ***[AB-Comment: (Amos) Suggested edit.]***

**The constellation of CRC and brain tumors has been referred to as Turcot syndrome; however, Turcot syndrome is molecularly heterogeneous. Molecular studies have demonstrated that colon polyposis and medulloblastoma are associated with pathogenic variants in *APC (thus representing FAP)*, while colon cancer and glioblastoma are associated with pathogenic variants in mismatch repair (MMR) genes *(thus representing Lynch syndrome) [AB-Comment: (Hampel) Suggested additions.]* .[**[**141**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_141)**]**

**There are several reports of other extracolonic tumors *[AB-Comment: (Hampel) I’d list the tumors or delete this paragraph.]* associated with FAP, but whether these are simply coincidence or actually share a common molecular genetic origin with the colonic tumors is not always evident. Some of these reports have demonstrated LOH or a variant of the wild-type *APC* allele in extracolonic tumors in FAP patients, which strengthens the argument for their inclusion in the FAP** *~~syndrome~~****phenotype [AB-Comment: (Boland) Suggested revision.]* .**

**Genotype-phenotype correlations**

**Most *APC* pathogenic variants that occur between codon 169 and codon 1249 result in the classic FAP** [phenotype](https://cdr.cancer.gov/cgi-bin/cdr/Filter.py?DocId=CDR0000460203&Filter=set:QC+GlossaryTermName+with+Concept+Set)**.[**[**142**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_142)**,** [**143**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_143)**,** [**144**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_144)**] There has been much interest in correlating the location of the pathogenic variant within the gene with the clinical phenotype:**

***[Comment: Need to track down refs for this list.]***

* **Researchers have found that dense carpeting of colonic polyps, a feature of classic FAP, is seen in most patients with *APC* pathogenic variants, particularly those variants that occur between codons 1250 and 1464. AFAP is associated with pathogenic variants that occur in or upstream of exon 4 and in the latter two-thirds of exon 15 as well as missense variants in other sites of the APC gene.[28,29,30,31] Refer to the AFAP section of this summary for more information.**
* **CHRPE are rarely associated with pathogenic variants that occur before exon 9.[30,33] Individuals with exon 9 variants tend not to have duodenal adenomas.[34, [**[**145**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_145)**]**
* **Recently it was discovered that families with gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS), who express numerous, predominantly fundic gland, gastric polyps restricted to the body and fundus with regions of dysplasia or gastric adenocarcinoma, and no evidence of colorectal or duodenal polyposis, possessed mutations in the promoter (1B) of APC. These mutations segregrated with the gastric phenotype in multiple GAPPS families. Although penetrance of the gastric polyposis phenotype is high, the phenotype can vary ranging from asymptomatic adults to teenagers presenting with massive symptomatic gastric polyposis as well as unaffected carriers who had clean endoscopies at ages ranging from 42 to 77. However, the penetrance for gastric cancer is less clear. Promoter 1B APC rarely occure in FAP families with gastric fundic gland polyps and colonic polyposis. *[Comment: Scott will send a reference for this bullet.]***
* **APC pathogenic variants occurring between codons 1445 and 1578 have been associated with an increased incidence of desmoid tumors in FAP patients.[33, 37, 40, 41]**

**Interventions for FAP**

**Individuals at risk of FAP, because of a known *APC* pathogenic variant in either the family or themselves, are evaluated for onset of polyposis by flexible sigmoidoscopy or colonoscopy. Once an FAP family member is found to manifest polyps, the only effective management to prevent CRC is** *~~eventual~~* **colectomy *[AB-Comment: (Boland) Suggested edit.]* . Prophylactic surgery has been shown to improve survival in patients with FAP.[**[**146**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_146)**] If feasible, the patient and his/her family members should be included in a registry because it has been shown retrospectively that registration and surveillance reduce CRC incidence and mortality.[**[**147**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_147)**] In patients with classic FAP identified very early in their course, the surgeon, endoscopist, and family may choose to delay surgery for several years in the interest of achieving social milestones. In addition, in carefully selected patients with AFAP (those with minimal polyp burden and advanced age), deferring a decision about colectomy may be reasonable with surgery performed only in the face of advancing polyp burden or dysplasia.**

**A Finnish nationwide population-based retrospective study evaluating whether surveillance of family members with FAP reduced overall mortality and improved survival demonstrated that call-up patients (family members of a** [proband](https://cdr.cancer.gov/cgi-bin/cdr/Filter.py?DocId=CDR0000460211&Filter=set:QC+GlossaryTermName+with+Concept+Set) **who were recruited to the screening program) had equivalent survival to the general population up to 20 years after diagnosis of FAP.[**[**148**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_148)**] The study included 154 families with at least one family member clinically diagnosed with FAP from 1963 to 2015. There were 194 probands and 225 call-ups (83 diagnosed by genetic testing and 142 by endoscopy) with a median time of follow-up of 11.8 years. In this study, the survival analysis of members of FAP families was calculated using the relative survival estimate.[**[**149**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_149)**] This estimation compares survival among FAP probands and call-ups with the survival expected in the absence of FAP among individuals of the same gender and age in each calendar year. The relative survival after 10 and 20 years of follow-up for probands was 67% (95% confidence interval [CI], 60%–75%) and 66% (95% CI, 58%–76%), respectively. For call-ups, the 10- and 20-year relative survival was 98% (95% CI, 95%–101%) and 94% (95% CI, 88%–100%), respectively. At 25 years of follow-up, the relative survival for call-ups was lower than the general population at 87% (95% CI, 79%–96%). The relative survival for probands was significantly lower than for call-ups (*P* < .001). In terms of mortality, the standardized mortality ratio was elevated in probands in both the 0- to 5-year and 5- to 10-year periods of follow-up whereas it remained stable for call-ups until 20 years of follow-up. This difference was more marked in the beginning of follow-up for probands taking into account the fact that probably most were symptomatic, and most likely had CRC at the diagnosis. The authors pointed out that if the CRC was treated successfully without recurrence, the survival of the probands approached that of the call-ups.**

**The recommended age at which surveillance for polyposis should begin involves a trade-off. Someone who waits until the late teens to begin surveillance faces a remote possibility that a cancer will have developed at an earlier age. Although it is rare, CRC can develop in a teenager who carries an *APC* pathogenic variant. However, it is preferable to allow people at risk to develop emotionally before they are faced with a major surgical decision regarding the timing of colectomy. Therefore, surveillance usually begins early (age 10–15 y). Surveillance has consisted of either flexible sigmoidoscopy or colonoscopy every year.[**[**102**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_102)**,** [**150**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_150)**,** [**151**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_151)**] If flexible sigmoidoscopy is utilized and polyps are found, colonoscopy is performed. Historically, sigmoidoscopy may have been a reasonable approach in identifying early adenomas in most patients. However, colonoscopy is the tool of choice in light of (a) improved instrumentation for full colonoscopy; (b) sedation; (c) recognition of AFAP, in which the disease is typically most manifest in the right colon; and (d) the growing tendency to defer surgery for a number of years. Individuals who have tested negative for an otherwise known family pathogenic variant do not need FAP-oriented *endoscopic* surveillance at all. *[AB-Comment: (Boland) Suggested edit.]* They are recommended to undergo average-risk population screening. *[AB-Comment: (Hampel) I agree with this but it’s discrepant with above where it said to have a baseline in the 20s if negative for a known mutation.]* In the case of families in which no family variant has been identified in an affected person, clinical surveillance is warranted. Colon surveillance is not stopped in persons who are known to carry an *APC* pathogenic variant but who do not yet manifest polyps, because adenomas occasionally are not manifest until the fourth and fifth decades of life. (Refer to the** [**Attenuated Familial Adenomatous Polyposis [AFAP]**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#_118) **section of this summary for more information.) (Refer to the PDQ summary on** [**Colorectal Cancer Screening**](https://cdr.cancer.gov/cgi-bin/cdr/QcReport.py?DocId=CDR0000062753&Session=guest) **for more information on these methods.)**

***[AB-Comment: (Hampel) This contradicts the last paragraph which said that colonoscopy is now the tool of choice.]***

*~~In some circumstances, full colonoscopy may be preferred over the more limited sigmoidoscopy. Among pediatric gastroenterologists, tolerability of endoscopic procedures in general has been regarded as improved with the use of deeper intravenous sedation.~~*

***[AB-Comment: (Hampel) Check the newest NCCN but I anticipate that they will also mention POLE and POLD1 testing if APC and MUTYH are negative.]***

**Table** 7 **summarizes the clinical practice guidelines from different professional societies regarding diagnosis and surveillance of FAP.**

|  |
| --- |
| **Table 7. Clinical Practice Guidelines for Diagnosis and Colon Surveillance of Familial Adenomatous Polyposis (FAP)** |
| **Organization**  | ***APC* Gene Test Recommended**   | **Age Screening Initiated**   | **Frequency**  | **Method**  | **Comment**  |
| **American Society of Colon and Rectal Surgeons (2001, 2003) [**[**152**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_152)**,** [**153**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_153)**,** [**154**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_154)**]**  | **Yes**  | **NA**  | **NA**  | **NA**  |   |
| **American Cancer Society (2002) [**[**155**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_155)**]**  | **NA**  | **Puberty**  | **NA**  | **Endoscopy**  | **Referral to a center specializing in FAP screening suggested.**  |
| **GI Societies (2003)a [**[**150**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_150)**]**  | **Yes**   | **10–12 y**   | **Annual**   | **FS**   |   |
| **NCCN (2017) [**[**102**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_102)**]**  | **Yes**   | **10–15 y**   | **Annual**  | **FS or C**  | **If an at-risk individual is found to not carry the *APC* gene pathogenic variant responsible for familial polyposis in the family, screening as an average-risk individual is recommended.**  |

|  |
| --- |
| ***C = colonoscopy; FS = flexible sigmoidoscopy; GI = gastrointestinal; NA = not addressed; NCCN = National Comprehensive Cancer Network.*** |
| ***aGI Societies – American Academy of Family Practice, American College of Gastroenterology, American College of Physicians-American Society of Internal Medicine, American College of Radiology, American Gastroenterological Association, American Society of Colorectal Surgeons, and American Society for Gastrointestinal Endoscopy.*** |

**FAP patients and their doctors should have an individualized discussion to decide when surgery will be performed. It is useful to incorporate into the discussion the risk of developing desmoid tumors after surgery. Timing of risk-reducing surgery usually depends on the number of polyps, their size, histology, and symptomatology.[**[**156**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_156)**] Once numerous polyps have developed, surveillance colonoscopy is no longer useful in timing the colectomy because polyps are so numerous that it is not possible to biopsy or remove all of them. At this time, it is appropriate for patients to consult with a surgeon who is experienced with available options, including total colectomy and postcolectomy reconstruction techniques.[**[**157**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_157)**] Rectum-sparing surgery, with sigmoidoscopic surveillance of the remaining rectum, is a reasonable alternative to total colectomy in those compliant individuals *with relative rectal sparing of polyps and [AB-Comment: (Boland) Suggested text.]* who understand the consequences and make an informed decision to accept the residual risk of rectal cancer occurring despite periodic surveillance.[**[**158**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_158)**]**

***[AB-Comment: (Amos) Should levels of evidence be provided for differing surgical treatments?]***

**Surgical options include restorative proctocolectomy with IPAA, subtotal colectomy with ileorectal anastomosis (IRA), or total proctocolectomy with ileostomy (TPC). TPC is reserved for patients with low rectal cancer in which the sphincter cannot be spared or for patients on whom an IPAA cannot be performed because of technical problems. There is no risk of developing rectal cancer after TPC because the whole mucosa at risk is removed. Whether a colectomy and an IRA or a restorative proctocolectomy is performed, most experts suggest that periodic and lifelong surveillance of the rectum or the ileal pouch be performed to remove or ablate any polyps. This is necessitated by case series of rectal cancers arising in the rectum of FAP patients who had subtotal colectomies with an IRA in which there was an approximately 25% cumulative risk of rectal adenocarcinoma 20 years after IRA and by case reports of adenocarcinoma in the ileoanal pouch and anal canal after restorative proctocolectomy.[**[**159**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_159)**,** [**160**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_160)**,** [**161**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_161)**,** [**162**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_162)**] The cumulative risk of rectal cancer after IRA may be lower than that reported in the literature, in part because of better selection of patients for this procedure, such as those with minimal polyp burden in the rectum.[**[**157**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_157)**] Other factors that have been reported to increase the rectal cancer risk after IRA include the presence of colon cancer at the time of IRA, the length of the rectal stump, and the duration of follow-up after IRA.[**[**163**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_163)**,** [**164**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_164)**,** [**165**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_165)**,** [**166**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_166)**,** [**167**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_167)**,** [**168**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_168)**,** [**169**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_169)**] An abdominal colectomy with IRA as the primary surgery for FAP does not preclude later conversion to an IPAA for uncontrolled rectal polyps and/or rectal cancer. In the Danish Polyposis Registry, the morbidity and functional results of a secondary IPAA (after a previous IRA) in 24 patients were reported to be similar to those of 59 patients who underwent primary IPAA.[**[**170**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_170)**]**

**In most cases, the clinical polyp burden in the rectum at the time of surgery dictates the type of surgical intervention, namely restorative proctocolectomy with IPAA versus IRA. Patients with a mild phenotype (<1,000 colonic adenomas) and fewer than 20 rectal polyps may be candidates for IRA at the time of prophylactic surgery.[**[**171**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_171)**] In some cases, however, the polyp burden is equivocal, and in such cases, investigators have considered the role of genotype in predicting subsequent outcomes with respect to the rectum.[**[**172**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_172)**] Pathogenic variants reported to increase the rectal cancer risk and eventual completion proctectomy after IRA include variants in exon 15 codon 1250, exon 15 codons 1309 and 1328, and exon 15 variants between codons 1250 and 1464.[**[**159**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_159)**,** [**168**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_168)**,** [**169**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_169)**,** [**173**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_173)**] In patients who have undergone IPAA, it is important to continue annual surveillance of the ileal pouch because the cumulative risk of developing adenomas in the pouch has been reported to be up to 75% at 15 years.[**[**174**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_174)**,** [**175**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_175)**] Although they are rare, carcinomas have been reported in the ileal pouch and anal transition zone after restorative proctocolectomy in FAP patients.[**[**176**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_176)**] A meta-analysis of quality of life after restorative proctocolectomy and IPAA has suggested that FAP patients do marginally better than inflammatory bowel disease patients in terms of fistula formation, pouchitis, stool frequency, and seepage.[**[**177**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_177)**]**

**Celecoxib, a specific cyclooxygenase II (COX-2) inhibitor, and nonspecific COX-2 inhibitors, such as sulindac, have been associated with a decrease in polyp size and number in FAP patients, suggesting a role for chemopreventive agents in the treatment of this disorder.[**[**178**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_178)**,** [**179**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_179)**] Although celecoxib had been approved by the U.S. Food and Drug Administration (FDA), its license was voluntarily withdrawn by the manufacturer. Currently, there are no FDA-approved drugs for chemoprevention in FAP. Nevertheless, agents such as celecoxib and sulindac are in sufficiently widespread use that chemopreventive clinical trials typically utilize one of these agents as the control arm. A randomized trial showed possible marginal improvement in polyp burden with the combination of celecoxib and difluoromethylornithine, compared with celecoxib alone.[**[**180**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_180)**]**

**A small, randomized, placebo-controlled, dose-escalation trial of celecoxib in a pediatric population (aged 10–14 y) demonstrated the safety of celecoxib at all dosing levels when administered over a 3-month period.[**[**181**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_181)**] This study found a dose-dependent reduction in adenomatous polyp burden. At a dose of 16 mg/kg/day, which approximates the approved dose of 400 mg twice daily in adults, the reduction in polyp burden paralleled that demonstrated with celecoxib in adults.**

**Omega-3-polyunsaturated fatty acid eicosapentaenoic acid in the free fatty acid form has been shown to reduce rectal polyp number and size in a small study of patients with FAP post subtotal colectomy.[**[**182**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_182)**] Although not directly compared in a randomized trial, the effect appeared to be similar in magnitude to that previously observed with celecoxib.**

**It is unclear at present how to incorporate COX-2 inhibitors into the management of FAP patients who have not yet undergone risk-reducing surgery. A double-blind, placebo-controlled trial in 41 child and young adult carriers of *APC* pathogenic variants who had not yet manifested polyposis demonstrated that sulindac may not be effective as a primary treatment in FAP. There were no statistically significant differences between the sulindac and placebo groups over 4 years of treatment in incidence, number, or size of polyps.[**[**179**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_179)**]**

**Consistent with the effects of COX-2 inhibitors on colonic polyps, in a randomized, prospective, double-blind, placebo-controlled trial, celecoxib (400 mg, administered orally twice daily) reduced, but did not eliminate, the number of duodenal polyps in 32 patients with FAP after a 6-month course of treatment. Of importance, a statistically significant effect was seen only in individuals who had more than 5% of the duodenum involved with polyps at baseline and with an oral dose of 400 mg, given twice daily.[**[**183**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_183)**] A previous randomized study of 24 FAP patients treated with sulindac for 6 months showed a nonsignificant trend in the reduction of duodenal polyps.[**[**184**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_184)**] The same issues surrounding the use of COX-2 inhibitors for the treatment of colonic polyps apply to their use for the treatment of duodenal polyps (e.g., only partial elimination of the polyps, complications secondary to the COX-2 inhibitors, and loss of effect after the medication is discontinued).[**[**183**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_183)**]**

**Because of the common clustering of adenomatous polyps around the duodenal papilla (where bile enters the intestine) and preclinical data suggesting that ursodeoxycholate inhibits intestinal adenomas in mice that harbor an *Apc* germline variant,[**[**185**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_185)**] two trials that employ ursodeoxycholate have been performed.[**[**186**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_186)**,** [**187**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_187)**] In both studies, ursodeoxycholate did not have a significant chemopreventive effect on duodenal polyps; paradoxically, in one study, ursodeoxycholate in combination with celecoxib appeared to promote polyp density in patients with FAP.**

**Because of reports demonstrating an increase in cardiac-related events in patients taking rofecoxib and celecoxib,[**[**188**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_188)**,** [**189**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_189)**,** [**190**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_190)**] it is unclear whether this class of agents will be safe for long-term use for patients with FAP and in the general population. Also, because of the short-term (6 months) nature of these trials, there is currently no clinical information about cardiac events in FAP patients taking COX-2 inhibitors on a long-term basis.**

[Level of evidence (celecoxib): 1b](https://cdr.cancer.gov/cgi-bin/cdr/QcReport.py?DocId=CDR0000538265&Session=guest)

**One cohort study has demonstrated regression of colonic and rectal adenomas with sulindac (an NSAID) treatment in FAP. The reported outcome of this trial was the number and size of polyps, a surrogate for the clinical outcome of main interest, CRC incidence.[**[**191**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_191)**]**

[Level of evidence (sulindac): 1b](https://cdr.cancer.gov/cgi-bin/cdr/QcReport.py?DocId=CDR0000538265&Session=guest)

**Preclinical studies of a small-molecule epidermal growth factor receptor (EGFR) inhibitor and low-dose sulindac in the Apcmin/+ mouse diminished intestinal adenoma development by 87% [**[**192**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_192)**] suggesting that EGFR inhibitors had the potential to inhibit duodenal polyps in FAP patients. A 6-month double-blind, randomized, placebo-controlled trial tested the efficacy of sulindac, 150 mg twice daily, and erlotinib, 75 mg daily, versus placebo in FAP or AFAP patients with duodenal polyps.[**[**193**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_193)**] Ninety-two patients with FAP or AFAP were randomly assigned to receive study drugs or placebo and underwent pretreatment and posttreatment upper endoscopies to determine the changes in the sum diameter of the polyps and number of polyps in a 10 cm segment of proximal duodenum. The trial was terminated prematurely because the primary endpoint was met. The intent-to-treat analysis demonstrated a median decrease in duodenal polyp burden (sum of diameters) of 8.5 mm in the sulindac/erlotinib arm while there was an 8 mm increase in the placebo arm (*P* < .001). Significantly higher rates of grade 1 and grade 2 adverse events occurred in the treatment arm than in the placebo arm: in the treatment arm, 60.9% developed an acneiform rash and 32.6% developed oral mucositis; in the placebo arm, 19.6% developed an acneiform rash and 10.9% developed oral mucositis. Based on the previously modest effects of sulindac and celecoxib on duodenal polyps in FAP patients [**[**179**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_179)**,** [**191**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_191)**] and the dramatic effect of genetic EGFR inhibition on intestinal adenoma development in the Apcmin/+ mouse,[**[**194**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_194)**] it is likely that erlotinib was responsible for the success of this trial. An ongoing clinical trial is determining whether lower doses of erlotinib alone are sufficient for significantly reducing duodenal polyp burden in FAP and AFAP patients.**

[Level of evidence (sulindac + erlotinib): 1b](https://cdr.cancer.gov/cgi-bin/cdr/QcReport.py?DocId=CDR0000538265&Session=guest)

**Patients who carry *APC* germline pathogenic variants are at increased risk of other types of malignancies, including thyroid cancer, small bowel cancer, hepatoblastoma, and brain tumors. The risk of these tumors, however, is much lower than that for colon cancer, and the only surveillance recommendation by experts in the field is upper endoscopy of the gastric and duodenal mucosa.[**[**12**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_12)**,** [**26**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_26)**] *[AB-Comment: (Hampel) Not true. NCCN recommends annual thyroid exam starting in the late teenage years and says annual thyroid ultrasound may be considered. Also suggests liver palpation, abdominal US and AFP every 3-6 mos from 0-5 for hepatoblastoma surveillance (mentioned earlier in this document). Annual abdominal palpation to screen for desmoids plus abdominal MRI or CT 1-3 y post-collection and then every 5-10 years for those with a family history of symptomatic desmoids. Small bowel polyps and cancer – consider adding small bowel visualization to the CT or MRI for desmoids esp if duodenal polyposis is advanced. CNS cancer – annual physical examination.]* The severity of duodenal polyposis detected appears to correlate with risk of duodenal adenocarcinoma.[**[**89**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_89)**] (Refer to the** [**Duodenum/small bowel tumors**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#_613) **section and the** [**Other tumors**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#_618) **section in the** [**Major Genetic Syndromes**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#_89) **section of this summary for more information about screening for extracolonic malignancies in patients with FAP.)**

**~~Familial Adenomatous Polyposis (FAP)~~**

~~By 1900, several reports had demonstrated that patients with multiple polyps (only later subclassified as adenomas and other histologies) were at very high risk of CRC and that the pattern of occurrence in families was autosomal dominant. In the 20th century, the adenoma-to-carcinoma progression was confirmed, and FAP was recognized as one human model for this progression.[~~[~~11~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_11)~~] Various complications of FAP came to be described, including upper gastrointestinal (GI) tract adenomas; fundic gland stomach polyps; nonepithelial benign tumors (osteomas, epidermal cysts, dental abnormalities [this triad is known collectively as Gardner syndrome]); desmoid tumors; congenital hypertrophy of retinal pigment epithelium (CHRPE); and malignant tumors (thyroid and brain tumors, hepatoblastoma).~~

~~FAP is one of the most clearly defined and well understood of the inherited colon cancer syndromes.[~~[~~1~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_1)~~,~~ [~~12~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_12)~~,~~ [~~13~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_13)~~] It is an autosomal dominant condition, and the reported incidence varies from 1 in 7,000 to 1 in 22,000 live births, with the syndrome being more common in Western countries.[~~[~~14~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_14)~~] Autosomal dominant inheritance means that~~ [*~~affected~~*](https://cdr.cancer.gov/cgi-bin/cdr/Filter.py?DocId=CDR0000460124&Filter=set:QC+GlossaryTermName+with+Concept+Set) *~~persons are genetically~~* [*~~heterozygous~~*](https://cdr.cancer.gov/cgi-bin/cdr/Filter.py?DocId=CDR0000339341&Filter=set:QC+GlossaryTermName+with+Concept+Set)*~~, such that~~* ***~~[AB-Comment: (Hampel) Suggested revision. ]~~*** ~~each offspring of a patient with FAP has a 50% chance of inheriting the disease gene. Males and females are equally likely to be affected.~~

~~Classically, FAP is characterized by multiple (>100) adenomatous polyps in the colon and rectum developing after the first decade of life (refer to~~ [~~Figure~~ 3](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#_2801)~~).~~

**Image:** FAP polyps - endoscopic and surgically resected

*~~Figure~~ 4. ~~Multiple polyps in the colon of a patient with familial adenomatous polyposis shown endoscopically (left panel) and upon surgical resection (right panel).~~*

~~FAP features in addition to the colonic polyps may include polyps in the upper GI tract, extraintestinal manifestations such as CHRPE, osteomas and epidermoid cysts, supernumerary teeth, desmoid tumor formation, and other malignant changes such as thyroid tumors, small bowel cancer, hepatoblastoma, and brain tumors, particularly medulloblastoma (refer to Table~~ 4~~).~~

***~~[AB-Comment: (Amos) Suggested edits to table below.]~~***

|  |
| --- |
| **~~Table~~ 8. ~~Extracolonic Tumor Risks in Familial Adenomatous Polyposis~~~~a~~** |
| **~~Malignancy~~**  | **~~Relative Risk~~**  | **~~Absolute Lifetime Risk (%)~~**  |
| ~~Desmoid~~ ***tumor***  | ~~852.0~~  | ~~15.0~~  |
| ~~Duoden~~***al tumors and cancer****~~um~~*  | ~~330.8~~  | ~~5.0–12.0~~  |
| ~~Thyroid~~ ***cancer***  | ~~7.6~~  | ~~2.0~~  |
| ~~Brain~~ ***cancer***  | ~~7.0~~  | ~~2.0~~  |
| ~~Ampullary~~ ***cancer***  | ~~123.7~~  | ~~1.7~~  |
| ~~Pancrea~~***tic cancer****~~s~~*  | ~~4.5~~  | ~~1.7~~  |
| ~~Hepatoblastoma~~  | ~~847.0~~  | ~~1.6~~  |
| ~~Gastric~~ ***cancer***  | ~~—~~  | ~~0.6~~~~b~~  |

|  |
| --- |
| *~~a~~~~Adapted from Giardiello et al.,[~~*[*~~16~~*](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_16)*~~] Jagelman et al.,[~~*[*~~17~~*](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_17)*~~] Sturt et al.,[~~*[*~~18~~*](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_18)*~~] Lynch et al.,[~~*[*~~19~~*](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_19)*~~] Bülow et al.,[~~*[*~~20~~*](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_20)*~~] Burt et al.,[~~*[*~~21~~*](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_21)*~~] and Galiatsatos et al.[~~*[*~~22~~*](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_22)*~~]~~* |
| *~~b~~~~The Leeds Castle Polyposis Group.~~* |

~~FAP~~ *~~is also~~* ***has also been*** ~~known as familial polyposis coli, adenomatous polyposis coli (APC), or Gardner syndrome (colorectal polyposis, osteomas, and soft tissue tumors). Gardner syndrome~~ *~~has sometimes been~~* ***was previously*** ~~used to designate FAP patients who manifest these extracolonic features. However, Gardner syndrome has been shown~~ *~~molecularly~~* ***genetically ~~[AB-Comment: (Boland) Suggested edit.]~~*** ~~to be a variant of FAP, and thus the term Gardner syndrome is essentially obsolete in clinical practice.[~~[~~23~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_23)~~]~~

~~Most cases of FAP result from pathogenic variants in the~~ *~~APC~~* ~~gene on chromosome 5q21. Individuals who inherit a pathogenic variant in the~~ *~~APC~~* ~~gene have a very high likelihood of developing colonic adenomas; the risk has been estimated to be more than 90%.[~~[~~1~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_1)~~,~~ [~~12~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_12)~~,~~ [~~13~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_13)~~] The age at onset of adenomas in the colon is variable~~***, and the median age for first adenomas is 16 [***[***24***](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_24)***] ~~[AB-Comment: (Boland) Suggested text.]~~*** ~~: By age 10 years, only 15% of carriers of the~~ *~~APC~~*[~~germline variant~~](https://cdr.cancer.gov/cgi-bin/cdr/Filter.py?DocId=CDR0000781852&Filter=set:QC+GlossaryTermName+with+Concept+Set) ~~manifest adenomas; by age 20 years, the probability rises to 75%; and by age 30 years, 90% will have presented with FAP.[~~[~~1~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_1)~~,~~ [~~12~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_12)~~,~~ [~~13~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_13)~~,~~ [~~24~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_24)~~,~~ [~~25~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_25)~~] Without any intervention, most persons with FAP will develop colon or rectal cancer by the fourth decade of life.[~~[~~1~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_1)~~,~~ [~~12~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_12)~~,~~ [~~13~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_13)~~] Thus, surveillance and intervention for carriers of an~~ *~~APC~~* ~~gene pathogenic variant and at-risk persons have conventionally consisted of annual sigmoidoscopy beginning around puberty. The objective of this regimen is early detection of colonic polyps in those who have FAP, leading to preventive colectomy.[~~[~~26~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_26)~~,~~ [~~27~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_27)~~]~~

~~The early appearance of clinical features of FAP and the subsequent recommendations for surveillance beginning at puberty raise special considerations relating to the genetic testing of children for~~ [~~susceptibility genes~~](https://cdr.cancer.gov/cgi-bin/cdr/Filter.py?DocId=CDR0000460209&Filter=set:QC+GlossaryTermName+with+Concept+Set)~~.[~~[~~28~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_28)~~]~~ *~~Some~~* ***Most*** ~~proponents feel that the genetic testing of children for FAP presents an example in which possible medical benefit justifies genetic testing of minors, especially for the anticipated 50% of~~ ***at-risk ~~[AB-Comment: (Boland) Suggested edit.]~~*** ~~children who will be found not to be carriers of pathogenic variants and who can thus be spared the necessity of unpleasant and costly annual sigmoidoscopy.~~ ***In addition, testing infants for FAP can allow for hepatoblastoma surveillance until age 5. ~~[AB-Comment: (Hampel) Suggested text.]~~*** ~~The psychological impact of such testing is currently under investigation and is addressed in the~~ [~~Psychosocial Issues in Hereditary Colon Cancer Syndromes~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#_189) ~~section of this summary.~~

***~~[AB-Comment: (Hampel) I think this paragraph could be deleted since everything it mentions is located in the next section.]~~***

*~~A number of different APC pathogenic variants have been described in a series of FAP patients. The clinical features of FAP appear to be generally associated with the location of the variant in the APC gene and the type of variant (i.e.,~~* [*~~frameshift variant~~*](https://cdr.cancer.gov/cgi-bin/cdr/Filter.py?DocId=CDR0000783963&Filter=set:QC+GlossaryTermName+with+Concept+Set) *~~vs.~~* [*~~missense variant~~*](https://cdr.cancer.gov/cgi-bin/cdr/Filter.py?DocId=CDR0000783964&Filter=set:QC+GlossaryTermName+with+Concept+Set)*~~). Two features of particular clinical interest that are apparently associated with APC variants are (1) the density of colonic polyposis and (2) the development of extracolonic tumors.~~*

***The ~~Adenomatous polyposis coli (APC)~~ gene***

~~The~~ *~~APC~~* ~~gene on chromosome 5q21 encodes a 2,843-amino acid protein that is important in cell adhesion and signal transduction;~~ ***the main function of the APC protein is to regulate intracellular concentrations of***~~beta-catenin~~ *~~is its major downstream target~~* ***~~[AB-Comment: (Boland) Suggested revisions.]~~*** ~~.~~ *~~APC~~* ~~is a~~ [~~tumor suppressor gene~~](https://cdr.cancer.gov/cgi-bin/cdr/Filter.py?DocId=CDR0000046657&Filter=set:QC+GlossaryTermName+with+Concept+Set)~~, and the loss of~~ *~~APC~~* ~~is among the earliest events in the chromosomal instability colorectal tumor pathway.~~ ***~~[AB-Comment: (Hampel) I think in the first section we say that APC mutations are among the earliest events in both CIN and MIN CRC.]~~*** ~~The important role of~~ *~~APC~~* ~~in predisposition to colorectal tumors is supported by the association of~~ *~~APC~~*[~~germline~~](https://cdr.cancer.gov/cgi-bin/cdr/Filter.py?DocId=CDR0000460154&Filter=set:QC+GlossaryTermName+with+Concept+Set) ~~pathogenic variants with FAP and AFAP. Both conditions can be diagnosed genetically by testing for germline pathogenic variants in the~~ *~~APC~~* ~~gene in~~ [~~DNA~~](https://cdr.cancer.gov/cgi-bin/cdr/Filter.py?DocId=CDR0000045671&Filter=set:QC+GlossaryTermName+with+Concept+Set) ~~from peripheral blood leukocytes. Most FAP~~ [~~pedigrees~~](https://cdr.cancer.gov/cgi-bin/cdr/Filter.py?DocId=CDR0000044868&Filter=set:QC+GlossaryTermName+with+Concept+Set) ~~have~~ *~~APC~~* ~~alterations that produce truncating pathogenic variants, primarily in the first half of the gene.[~~[~~29~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_29)~~,~~ [~~195~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_195)~~] AFAP is associated with truncating pathogenic variants primarily in the 5’ and 3’ ends of the gene and possibly missense variants elsewhere.[~~[~~142~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_142)~~,~~ [~~143~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_143)~~,~~ [~~144~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_144)~~,~~ [~~196~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_196)~~]~~

~~More than 300 different disease-associated pathogenic variants of the~~ *~~APC~~* ~~gene have been reported.[~~[~~29~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_29)~~] The vast majority of these changes are insertions, deletions, and~~ [~~nonsense variants~~](https://cdr.cancer.gov/cgi-bin/cdr/Filter.py?DocId=CDR0000783965&Filter=set:QC+GlossaryTermName+with+Concept+Set) ~~that lead to frameshifts and/or premature stop~~ [~~codons~~](https://cdr.cancer.gov/cgi-bin/cdr/Filter.py?DocId=CDR0000460135&Filter=set:QC+GlossaryTermName+with+Concept+Set) ~~in the resulting transcript of the gene. The most common~~ *~~APC~~* ~~pathogenic variant (10% of FAP patients) is a deletion of AAAAG in codon 1309; no other pathogenic variants appear to predominate. Variants that reduce rather than eliminate production of the APC protein may also lead to FAP.[~~[~~30~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_30)~~]~~

***~~[AB-Comment: (Boland) Suggested revision.]~~*** ~~Most~~ *~~APC~~* ~~pathogenic variants that occur between codon 169 and codon~~ *~~1393~~* ***1249*** ~~result in the classic FAP~~ [~~phenotype~~](https://cdr.cancer.gov/cgi-bin/cdr/Filter.py?DocId=CDR0000460203&Filter=set:QC+GlossaryTermName+with+Concept+Set)~~.[~~[~~142~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_142)~~,~~ [~~143~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_143)~~,~~ [~~144~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_144)~~] There has been much interest in correlating the location of the pathogenic variant within the gene with the clinical phenotype, including the distribution of extracolonic tumors, polyposis severity, and congenital hypertrophy of the retinal pigment epithelium. The most consistent observations are that attenuated polyposis and the less classic forms of FAP are associated with pathogenic variants that occur in or before exon 4 and in the latter two-thirds of exon 15,[~~[~~143~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_143)~~] and that retinal lesions are rarely associated with pathogenic variants that occur before exon 9.[~~[~~49~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_49)~~,~~ [~~144~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_144)~~] Exon 9 pathogenic variants have also been associated with attenuated polyposis. Additionally, individuals with exon 9 variants tend not to have duodenal adenomas.[~~[~~197~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_197)~~]~~

**~~Density of colonic polyposis~~**

***~~[AB-Comment: (Boland) Suggested revisions. [note: I took the genotype-phenotype data from a paper by Nieuwenhuis et al, Clin Gast Hep 2007;5:374-8, but there were others – from Japan - and the profuse phenotype was nested very tightly between codons 1250 and 1464.]]~~*** ~~Researchers have found that dense carpeting of colonic polyps, a feature of classic FAP, is seen in most patients with~~ *~~APC~~* ~~pathogenic variants, particularly those variants that occur between codons~~ *~~169~~* ***1250*** ~~and~~ *~~1393~~****1464***~~. At the other end of the spectrum, sparse polyps are features of patients with pathogenic variants occurring at the extreme ends of the~~ *~~APC~~* ~~gene or in exon 9. (Refer to the~~ [~~Attenuated Familial Adenomatous Polyposis [AFAP]~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#_118) ~~section of this summary for more information.)~~

**~~Extracolonic tumors~~**

**~~Desmoid tumors~~**

~~Desmoid tumors are proliferative, locally invasive, nonmetastasizing, fibromatous tumors in a collagen matrix. Although they do not metastasize, they can grow very aggressively and be life threatening.[~~[~~42~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_42)~~] Desmoids may occur~~ [~~sporadically~~](https://cdr.cancer.gov/cgi-bin/cdr/Filter.py?DocId=CDR0000339347&Filter=set:QC+GlossaryTermName+with+Concept+Set)~~, as part of classical FAP, or in a hereditary manner without the colon findings of FAP.[~~[~~19~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_19)~~,~~ [~~43~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_43)~~] Desmoids have been associated with hereditary~~ *~~APC~~* ~~gene pathogenic variants even when not associated with typical adenomatous polyposis of the colon.[~~[~~43~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_43)~~,~~ [~~44~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_44)~~]~~

~~Most studies have found that 10% of FAP patients develop desmoids, with reported ranges of 8% to 38%. The incidence varies with the means of ascertainment and the location of the pathogenic variant in the~~ *~~APC~~* ~~gene.[~~[~~43~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_43)~~,~~ [~~45~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_45)~~,~~ [~~46~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_46)~~]~~ *~~APC~~* ~~pathogenic variants occurring between codons 1445 and 1578 have been associated with an increased incidence of desmoid tumors in FAP patients.[~~[~~44~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_44)~~,~~ [~~47~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_47)~~,~~ [~~48~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_48)~~,~~ [~~49~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_49)~~] Desmoid tumors with a late onset and a milder intestinal polyposis phenotype (hereditary desmoid disease) have been described in patients with pathogenic variants at codon 1924.[~~[~~43~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_43)~~]~~

~~A desmoid risk factor scale has been described in an attempt to identify patients who are likely to develop desmoid tumors.[~~[~~50~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_50)~~] The desmoid risk factor scale was based on gender, presence or absence of extracolonic manifestations,~~ [~~family history~~](https://cdr.cancer.gov/cgi-bin/cdr/Filter.py?DocId=CDR0000302456&Filter=set:QC+GlossaryTermName+with+Concept+Set) ~~of desmoids, and~~ [~~genotype~~](https://cdr.cancer.gov/cgi-bin/cdr/Filter.py?DocId=CDR0000660739&Filter=set:QC+GlossaryTermName+with+Concept+Set)~~, if available. By utilizing this scale, it was possible to stratify FAP patients into low-, medium-, and high-risk groups for developing desmoid tumors. The authors concluded that the desmoid risk factor scale could be used for surgical planning. Validation of the risk factors comprising this scale were supported by a large, multiregistry, retrospective study from Europe.[~~[~~51~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_51)~~]~~

~~The natural history of desmoids is variable. Some authors have proposed a model for desmoid tumor formation whereby abnormal fibroblast function leads to mesenteric plaque-like desmoid precursor lesions, which in some cases occur before surgery and progress to mesenteric fibromatosis after surgical trauma, ultimately giving rise to desmoid tumors.[~~[~~52~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_52)~~] It is estimated that 10% of desmoids resolve, 50% remain stable for prolonged periods, 30% fluctuate, and 10% grow rapidly.[~~[~~53~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_53)~~] Desmoids often occur after surgical or physiological trauma, and both endocrine and genetic factors have been implicated. Approximately 80% of intra-abdominal desmoids in FAP occur after surgical trauma.[~~[~~54~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_54)~~,~~ [~~55~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_55)~~]~~

~~The desmoids in FAP are often intra-abdominal, may present early, and can lead to intestinal obstruction or infarction and/or obstruction of the ureters.[~~[~~46~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_46)~~] In some series, desmoids are the second most common cause of death after CRC in FAP patients.[~~[~~56~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_56)~~,~~ [~~57~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_57)~~] A staging system has been proposed to facilitate the stratification of intra-abdominal desmoids by disease severity.[~~[~~58~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_58)~~] The proposed staging system for intra-abdominal desmoids is as follows: stage I for asymptomatic, nongrowing desmoids; stage II for symptomatic, nongrowing desmoids of 10 cm or less in maximum diameter; stage III for symptomatic desmoids of 11 to 20 cm or for asymptomatic, slow-growing desmoids; and stage IV for desmoids larger than 20 cm, or rapidly growing, or with life-threatening complications.[~~[~~58~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_58)~~]~~

~~These data suggest that genetic testing could be of value in the medical management of patients with FAP and/or multiple desmoid tumors. Those with~~ *~~APC~~* ~~genotypes, especially those predisposing to desmoid formation (e.g., at the 3’ end of~~ *~~APC~~* ~~codon 1445~~ ***~~[AB-Comment: (Hampel) I think you might mean “at the 3’ end of APC or codon 1445”? You don’t usually see someone refer to the 3’ end of a codon.]~~*** ~~), appear to be at high risk of developing desmoids after any surgery, including risk-reducing colectomy and surgical surveillance procedures such as laparoscopy.[~~[~~45~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_45)~~,~~ [~~53~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_53)~~,~~ [~~59~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_59)~~]~~

~~The management of desmoids in FAP can be challenging and can complicate prevention efforts. Currently, there is no accepted standard treatment for desmoid tumors. Multiple medical treatments have generally been unsuccessful in the management of desmoids. Treatments have included antiestrogens, nonsteroidal anti-inflammatory drugs (NSAIDs), chemotherapy, and radiation therapy, among others. Studies have evaluated the use of raloxifene alone, tamoxifen or raloxifene combined with sulindac, and pirfenidone alone.[~~[~~60~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_60)~~,~~ [~~61~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_61)~~,~~ [~~62~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_62)~~] There are anecdotal reports of using imatinib mesylate to treat desmoid tumors in FAP patients; however, further studies are needed.[~~[~~63~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_63)~~] Significant desmoid tumor regression was reported in seven patients who had symptomatic, unresectable, intra-abdominal desmoid tumors and failed hormonal therapy when treated with chemotherapy (doxorubicin and dacarbazine) followed by meloxicam.[~~[~~198~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_198)~~]~~

~~Thirteen patients with intra-abdominal desmoids and/or unfavorable response to other medical treatments, who had expression of estrogen alpha receptors in their desmoid tissues, were included in a prospective study of raloxifene, given in doses of 120 mg daily.[~~[~~60~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_60)~~] Six of the patients had been on tamoxifen or sulindac before treatment with raloxifene, and seven patients were previously untreated. All 13 patients with intra-abdominal desmoid disease had either a partial or a complete response 7 months to 35 months after starting treatment, and most desmoids decreased in size at 4.7 ± 1.8 months after treatment. Response occurred in patients with desmoid plaques and with distinct lesions. Study limitations include small sample size, and the clinical evaluation of response was not consistent in all patients. Several questions remain concerning patients with desmoid tumors not expressing estrogen alpha receptors who have received raloxifene and their outcome and which patients may benefit from this potential treatment.~~

~~A second study of 13 patients with FAP-associated desmoids, who were treated with tamoxifen 120 mg/day or raloxifene 120 mg/day in combination with sulindac 300 mg/day, reported that ten patients had either stable disease (n = 6) or a partial or complete response (n = 4) for more than 6 months and that three patients had stable disease for more than 30 months.[~~[~~61~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_61)~~] These results suggest that the combination of these agents may be effective in at least slowing the growth of desmoid tumors. However, the natural history of desmoids is variable, with both spontaneous regression and variable growth rates.~~

~~A third study reported mixed results in 14 patients with FAP-associated desmoid tumors treated with pirfenidone for 2 years.[~~[~~62~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_62)~~] In this study, some patients had regression, some patients had progression, and some patients had stable disease.~~

~~These three studies illustrate some of the problems encountered in the study of desmoid disease in FAP patients:~~

* ~~The definition of desmoid disease is used inconsistently.~~
* ~~In some patients, desmoid tumors do not progress or are very slow growing and may not need therapy.~~
* ~~There is no consistent, systematic way to evaluate the response to therapy.~~
* ~~There is no single institution that will enroll enough patients to perform a randomized trial.~~

~~No randomized clinical trials using these agents have been performed and their use in clinical practice is based on anecdotal experience only.~~

[~~Level of evidence: 4~~](https://cdr.cancer.gov/cgi-bin/cdr/QcReport.py?DocId=CDR0000531845&Session=guest)

~~Because of the high rates of morbidity and recurrence, in general, surgical resection is not recommended in the treatment of intra-abdominal desmoid tumors. However, some have advocated a role for surgery given the ineffectiveness of medical therapy, even when the potential hazards of surgery are considered, and recognizing that not all desmoids are resectable.[~~[~~67~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_67)~~] A recent review of one hospital's experience suggested that surgical outcomes with intra-abdominal desmoids may be better than previously believed.[~~[~~66~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_66)~~,~~ [~~67~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_67)~~] Issues of subject selection are critical in evaluating surgical outcome data.[~~[~~66~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_66)~~] Abdominal wall desmoids can be treated with surgical resection, but the recurrence rate is high.~~

**~~Stomach tumors~~**

~~The most common FAP-related gastric polyps are fundic gland polyps (FGPs). FGPs are often diffuse and not amenable to endoscopic removal. The incidence of FGPs has been estimated to be as high as 60% in patients with FAP, compared with 0.8% to 1.9% in the general population.[~~[~~20~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_20)~~,~~ [~~22~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_22)~~,~~ [~~68~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_68)~~,~~ [~~69~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_69)~~,~~ [~~70~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_70)~~,~~ [~~71~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_71)~~,~~ [~~72~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_72)~~] These polyps consist of distorted fundic glands containing microcysts lined with fundic-type epithelial cells or foveolar mucous cells.[~~[~~73~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_73)~~,~~ [~~74~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_74)~~]~~

~~The hyperplastic surface epithelium is, by definition, nonneoplastic. Accordingly, FGPs have not been considered precancerous; in Western FAP patients the risk of stomach cancer is minimally increased, if at all. However, case reports of stomach cancer appearing to arise from FGPs have led to a reexamination of this issue.[~~[~~22~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_22)~~,~~ [~~75~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_75)~~] In one FAP series, focal dysplasia was evident in the surface epithelium of FGPs in 25% of patients versus 1% of sporadic FGPs.[~~[~~74~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_74)~~] In a prospective study of patients with FAP undergoing surveillance with esophagogastroduodenoscopy, FGPs were detected in 88% of the patients. Low-grade dysplasia was detected in 38% of these patients, whereas high-grade dysplasia was detected in 3% of these patients. In the author's view, if a polyp with high-grade dysplasia is identified, polypectomy can be considered with repeat endoscopic surveillance in 3 to 6 months. Consideration for treatment with daily proton-pump inhibitors (PPIs) also may be given.~~ ***~~[AB-Comment: (Hampel) Given that PPIs cause FGP (see below) I find it surprising that anyone would recommend PPIs for the treatment of FGPs in FAP.]~~*** ~~[~~[~~76~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_76)~~]~~

~~Complicating the issue of differential diagnosis, FGPs have been increasingly recognized in non-FAP patients consuming PPIs.[~~[~~74~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_74)~~,~~ [~~77~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_77)~~] FGPs in this setting commonly show a “PPI effect” consisting of congestion of secretory granules in parietal cells, leading to irregular bulging of individual cells into the lumen of glands. To the trained eye, the presence of dysplasia and the concomitant absence of a characteristic PPI effect can be considered highly suggestive of the presence of underlying FAP. The number of FGPs tends to be greater in FAP than that seen in patients consuming PPIs, although there is some overlap.~~

~~Gastric adenomas also occur in FAP patients. The incidence of gastric adenomas in Western patients has been reported to be between 2% and 12%, whereas in Japan, it has been reported to be between 39% and 50%.[~~[~~78~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_78)~~,~~ [~~79~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_79)~~,~~ [~~80~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_80)~~,~~ [~~81~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_81)~~] These adenomas can progress to carcinoma. FAP patients in Korea and Japan are reported to have a threefold to fourfold increased gastric cancer risk compared with their general population, a finding not observed in Western populations.[~~[~~82~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_82)~~,~~ [~~83~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_83)~~,~~ [~~84~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_84)~~,~~ [~~85~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_85)~~] The recommended management for gastric adenomas is endoscopic polypectomy. The management of adenomas in the stomach is usually individualized based on the size of the adenoma and the degree of dysplasia.~~ ***~~[AB-Comment: (Hampel) The last two sentences of this para seem contradictory.]~~***

[~~Level of evidence: 5~~](https://cdr.cancer.gov/cgi-bin/cdr/QcReport.py?DocId=CDR0000531846&Session=guest) ***~~[AB-Comment: (Amos) This is a little confusing as its not really clear what is being evaluated: I guess in general its all management of gastric tumors in FAP – but perhaps a more specific recommendation about surgical resection of gastric adenomas could be addressed with a higher level of evidence. ]~~***

**~~Duodenum/small bowel tumors~~**

~~Whereas the incidence of duodenal adenomas is only 0.4% in patients undergoing upper GI endoscopy,[~~[~~86~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_86)~~] duodenal adenomas are found in 80% to 100% of FAP patients. The vast majority are located in the first and second portions of the duodenum, especially in the periampullary region.[~~[~~68~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_68)~~,~~ [~~69~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_69)~~,~~ [~~87~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_87)~~] There is a 4% to 12% lifetime incidence of duodenal adenocarcinoma in FAP patients.[~~[~~17~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_17)~~,~~ [~~84~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_84)~~,~~ [~~88~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_88)~~,~~ [~~89~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_89)~~] In a prospective multicenter surveillance study of duodenal adenomas in 368 northern Europeans with FAP, 65% had adenomas at baseline evaluation (mean age, 38 y), with cumulative prevalence reaching 90% by age 70 years. In contrast to earlier beliefs regarding an indolent clinical course, the adenomas increased in size and degree of dysplasia during the 8 years of average surveillance, although only 4.5% developed cancer while under prospective surveillance.[~~[~~20~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_20)~~] While this study is the largest to date, it is limited by the use of forward-viewing rather than side-viewing endoscopy and the large number of investigators involved in the study. Intestinal polyps can also be assessed in FAP patients using capsule endoscopy.[~~[~~90~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_90)~~,~~ [~~91~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_91)~~,~~ [~~92~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_92)~~] One study of computed tomography (CT) duodenography found that larger adenoma size could be accurately measured but smaller, flatter adenomas could not be accurately counted.[~~[~~93~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_93)~~]~~

~~A retrospective review of FAP patients suggested that the adenoma-carcinoma sequence occurred in a temporal fashion for periampullary adenocarcinomas with a diagnosis of adenoma at a mean age of 39 years, high-grade dysplasia at a mean age of 47 years, and adenocarcinoma at a mean age of 54 years.[~~[~~94~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_94)~~] A decision analysis of 601 FAP patients suggested that the benefit of periodic surveillance starting at age 30 years led to an increased life expectancy of 7 months.[~~[~~88~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_88)~~] Although polyps in the duodenum can be difficult to treat, small series suggest that they can be managed successfully with endoscopy but with potential morbidity—primarily from pancreatitis, bleeding, and duodenal perforation.[~~[~~95~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_95)~~,~~ [~~96~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_96)~~]~~

~~FAP patients with particularly severe duodenal polyposis, sometimes called dense polyposis, or with histologically advanced duodenal adenomas appear to be at the highest risk of developing duodenal adenocarcinoma.[~~[~~20~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_20)~~,~~ [~~89~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_89)~~,~~ [~~97~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_97)~~,~~ [~~98~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_98)~~] Because the risk of duodenal adenocarcinoma is correlated with the number and size of polyps, and the severity of dysplasia of the polyps, a stratification system based on these features was developed to attempt to identify those individuals with FAP at highest risk of developing duodenal adenocarcinoma.[~~[~~98~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_98)~~] According to this system, known as the Spigelman Classification (refer to~~ [~~Table~~ 5](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#_1120)~~), 36% of patients with the most advanced stage will develop carcinoma.[~~[~~89~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_89)~~]~~

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| **~~Table~~ 9. ~~Spigelman Classification~~** |
| **~~Points~~**  | **~~Polyp Number~~**  | **~~Polyp Size (mm)~~**  | **~~Histology~~**  | **~~Dysplasia~~**  |
| ~~1~~  | ~~1–4~~  | ~~1–4~~  | ~~Tubular~~  | ~~Mild~~  |
| ~~2~~  | ~~5–20~~  | ~~4–10~~  | ~~Tubulovillous~~  | ~~Moderate~~  |
| ~~3~~  | ~~>20~~  | ~~>10~~  | ~~Villous~~  | ~~Severe~~  |

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| *~~Stage I, 1–4 points; Stage II, 5–6 points; Stage III, 7–8 points; Stage IV, 9–12 points.[~~*[*~~98~~*](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_98)*~~]~~* |

~~A baseline upper endoscopy, including side-viewing duodenoscopy, is typically performed between ages 25 and 30 years in FAP patients.[~~[~~85~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_85)~~] The subsequent intervals between endoscopy vary according to the findings of the previous endoscopy, often, based on Spigelman stage. Recommended intervals are based on expert opinion although the relatively liberal intervals for stage 0-II disease are based in part on the natural history data generated by the Dutch/Scandinavian duodenal surveillance trial (refer to~~ [~~Table~~ 6](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#_1254)~~).[~~[~~20~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_20)~~]~~

~~The main advantages of the Spigelman Classification are its long-standing familiarity to and usage by those in the field, which allows reasonable standardization of outcome comparisons across studies.[~~[~~81~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_81)~~,~~ [~~99~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_99)~~] However, the following are limitations on attempted application of the Spigelman Classification:~~

* ~~Most pathologists do not currently employ the term moderate dysplasia, preferring a simpler low- versus high-grade dysplasia system.~~
* ~~Because of the villous nature of normal duodenal epithelium, pathologists commonly disagree over the classification of “tubular,” “tubulovillous,” and “villous.”~~
* ~~Spigelman staging requires biopsy, which is not always essential when only a few small plaques are present; conversely, for larger adenomas, sampling variation leads to understaging.[~~[~~100~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_100)~~,~~ [~~101~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_101)~~]~~

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| **~~Table~~ 10. ~~Recommended Screening Intervals by Spigelman Stage~~** |
| **~~Spigelman Stage~~**   | **~~NCCN (2017) [~~**[**~~102~~**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_102)**~~]~~**  | **~~Groves et al. (2002) [~~**[**~~89~~**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_89)**~~]~~**  |
| ~~0 (no polyps)~~   | ~~Endoscopy every 4 y~~   | ~~Endoscopy every 5 y~~  |
| ~~I~~  | ~~Endoscopy every 2–3 y~~   | ~~Endoscopy every 5 y~~  |
| ~~II~~  | ~~Endoscopy every 1–3 y~~   | ~~Endoscopy every 3 y~~   |
| ~~CP + ET~~   |
| ~~III~~  | ~~Endoscopy every 6–12 mo~~   | ~~Endoscopy every 1–2 y~~   |
| ~~CP + ET (+/- GA)~~  |
| ~~IV~~  | ~~Surgical evaluation~~  | ~~Surgical resection~~  |
| ~~Complete mucosectomy or duodenectomy, or Whipple procedure if duodenal papilla is involved~~  |
| ~~OR~~  |
| ~~Expert endoscopic surveillance every 3–6 mo~~   | ~~Endoscopy every 1–2 y~~  |
| ~~CP + ET (+/- GA)~~  |

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| *~~CP = chemoprevention; ET = endoscopic therapy; GA = general anesthetic; NCCN = National Comprehensive Cancer Network.~~* |
| *~~Refer to the~~* [*~~Interventions for FAP~~*](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#_260) *~~section in the~~* [*~~Major Genetic Syndromes~~*](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#_89) *~~section of this summary for more information about chemoprevention.~~* |
| *~~See~~* [*~~below~~*](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#_1241) *~~for additional information about the use of surgical resection in Spigelman stage IV disease.~~* |

~~The results of long-term duodenal adenoma surveillance of FAP patients in Nordic countries and the Netherlands revealed significant duodenal cancer risk in FAP patients.[~~[~~103~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_103)~~] Per protocol, biennial frontal-viewing endoscopy was performed from 1990 through 2000. Subsequently, patients were followed up with surveillance according to international guidelines. The 261 of 304 patients (86%) who had more than one endoscopy comprised the study group. Median follow-up was 14 years (range, 9–17 y). The lifetime risk of duodenal adenomatosis was 88%. Forty-four percent of patients had worsening Spigelman stage over time, whereas 12% improved and 34% remained unchanged. Twenty patients (7%) developed duodenal cancer at a median age of 56 years (range, 44–82 y). The cumulative cancer incidence was 18% at age 75 years (95% confidence interval [CI], 8%–28%). Survival in patients with symptomatic cancers was worse than those diagnosed at surveillance endoscopy.~~

[~~Level of evidence (screening for duodenum/small bowel tumors): 3~~](https://cdr.cancer.gov/cgi-bin/cdr/QcReport.py?DocId=CDR0000531825&Session=guest)

~~Many factors, including severity of polyposis, comorbidities of the patient, patient preferences, and availability of adequately trained physicians, determine whether surgical or endoscopic therapy is selected for polyp management. Endoscopic resection or ablation of large or histologically advanced adenomas appears to be safe and effective in reducing the short-term risk of developing duodenal adenocarcinoma;[~~[~~95~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_95)~~,~~ [~~96~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_96)~~,~~ [~~104~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_104)~~] however, patients managed with endoscopic resection of adenomas remain at substantial risk of developing recurrent adenomas in the duodenum.[~~[~~100~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_100)~~] The most definitive procedure for reducing the risk of adenocarcinoma is surgical resection of the ampulla and duodenum, although these procedures also have higher morbidity and mortality associated with them than do endoscopic treatments. Duodenotomy and local resection of duodenal polyps or mucosectomy have been reported, but invariably, the polyps recur after these procedures.[~~[~~105~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_105)~~] In a series of 47 patients with FAP and Spigelman stage III or stage IV disease who underwent definitive radical surgery, the local recurrence rate was reported to be 9% at a mean follow-up of 44 months. This local recurrence rate is dramatically lower than any local endoscopic or surgical approach from the same study.[~~[~~100~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_100)~~] Pancreaticoduodenectomy and pancreas-sparing duodenectomy are appropriate surgical therapies that are believed to substantially reduce the risk of developing periampullary adenocarcinoma.[~~[~~101~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_101)~~,~~ [~~105~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_105)~~,~~ [~~106~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_106)~~,~~ [~~107~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_107)~~] If such surgical options are considered, preservation of the pylorus is of particular benefit in this group of patients because most will have undergone a subtotal colectomy with ileorectal anastomosis or total colectomy with ileal pouch–anal anastomosis (IPAA). As noted in a Northern European study,[~~[~~20~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_20)~~] and others,[~~[~~108~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_108)~~,~~ [~~109~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_109)~~] the vast majority of patients with duodenal adenomas will not develop cancer and can be followed with endoscopy. However, individuals with advanced adenomas (Spigelman stage III or stage IV disease) generally require endoscopic or surgical treatment of the polyps. Chemoprevention studies for duodenal adenomas in FAP patients are currently under way and may offer an alternate strategy in the future.~~

~~The endoscopic approach to larger and/or flatter adenomas of the duodenum depends on whether the ampulla is involved. Endoscopic mucosal resection (EMR) after submucosal injection of saline, with or without epinephrine and/or dye, such as indigo carmine, can be employed for nonampullary lesions. Ampullary lesions require even greater care including endoscopic ultrasound evaluation for evidence of bile or pancreatic duct involvement. Stenting of the pancreatic duct is commonly performed to prevent stricturing and pancreatitis. The stents require endoscopic removal at an interval of 1 to 4 weeks. Because the ampulla is tethered at the ductal orifices, it typically does not uniformly “lift” with injection, so injection is commonly not used. Any consideration of EMR or ampullectomy requires great experience and judgment, with careful consideration of the natural history of untreated lesions and an appreciation of the high rate of adenoma recurrence despite aggressive endoscopic intervention.[~~[~~96~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_96)~~,~~ [~~100~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_100)~~,~~ [~~101~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_101)~~,~~ [~~106~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_106)~~,~~ [~~110~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_110)~~,~~ [~~111~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_111)~~,~~ [~~112~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_112)~~,~~ [~~113~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_113)~~] The literature uniformly supports duodenectomy for Spigelman stage IV disease. For Spigelman stage II and III disease, there is a role for endoscopic treatment invariably focusing on the one or two worst lesions that are present.~~

~~Reluctance to consider surgical resection has to do with short-term morbidity and mortality and long-term complications related to surgery. Although these concerns are likely overstated,[~~[~~100~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_100)~~,~~ [~~101~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_101)~~,~~ [~~107~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_107)~~,~~ [~~110~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_110)~~,~~ [~~114~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_114)~~,~~ [~~115~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_115)~~,~~ [~~116~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_116)~~,~~ [~~117~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_117)~~,~~ [~~118~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_118)~~,~~ [~~119~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_119)~~,~~ [~~120~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_120)~~] fear of surgical intervention can lead to aggressive and somewhat ill-advised endoscopic interventions. In some circumstances, endoscopic resection of ampullary and/or other duodenal adenomas cannot be accomplished completely or safely by endoscopic means, and duodenectomy cannot be accomplished without risking a short-gut syndrome or cannot be done at all because of mesenteric fibrosis. In such cases, surgical transduodenal ampullectomy/polypectomy can be performed. This is, however, associated with a high risk of local recurrence similar to that of endoscopic treatment.~~

[~~Level of evidence (treatment of duodenum/small bowel tumors): 4~~](https://cdr.cancer.gov/cgi-bin/cdr/QcReport.py?DocId=CDR0000531845&Session=guest)

**~~Other tumors~~**

~~The spectrum of tumors arising in FAP is summarized in~~ [~~Table~~ 4](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#_723)~~.~~

~~Papillary thyroid cancer~~ ***(cribriform morular type) ~~[AB-Comment: (Hampel) Suggested addition.]~~*** ~~has been reported to affect 1% to 2% of patients with FAP.[~~[~~121~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_121)~~] However, a recent study [~~[~~122~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_122)~~] of papillary thyroid cancers in six females with FAP failed to demonstrate~~ [~~loss of heterozygosity~~](https://cdr.cancer.gov/cgi-bin/cdr/Filter.py?DocId=CDR0000486444&Filter=set:QC+GlossaryTermName+with+Concept+Set) ~~(LOH) or pathogenic variants of the wild-type~~ [~~allele~~](https://cdr.cancer.gov/cgi-bin/cdr/Filter.py?DocId=CDR0000339337&Filter=set:QC+GlossaryTermName+with+Concept+Set) ~~in codons 545 and 1061 to 1678 of the six tumors. In addition, four of five of these patients had detectable somatic~~ *~~RET/PTC~~* ~~chimeric genes. This pathogenic variant is generally restricted to sporadic papillary thyroid carcinomas, suggesting the involvement of genetic factors other than~~ *~~APC~~* ~~pathogenic variants. Further studies are needed to show whether other genetic factors such as the~~ *~~RET/PTC~~* ~~chimeric gene are independently responsible for or cooperative with~~ *~~APC~~* ~~variants in causing papillary thyroid cancers in FAP patients. Although~~ [~~level 1 evidence~~](https://cdr.cancer.gov/cgi-bin/cdr/QcReport.py?DocId=CDR0000531823&Session=guest) ~~is lacking, a consensus opinion recommends annual thyroid examinations beginning in the late teenage years to screen for papillary thyroid cancer in patients with FAP. The same panel suggests clinicians could consider the addition of annual thyroid ultrasounds to this screening routine.[~~[~~102~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_102)~~,~~ [~~123~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_123)~~,~~ [~~124~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_124)~~]~~

[~~Level of evidence (thyroid cancer ultrasound screening): 4~~](https://cdr.cancer.gov/cgi-bin/cdr/QcReport.py?DocId=CDR0000531827&Session=guest) ***~~[AB-Comment: (Amos) Suggested edit.]~~***

~~Adrenal tumors have been reported in FAP patients, and one study demonstrated LOH~~ ***at the APC locus ~~[AB-Comment: (Boland) Suggested revision.]~~*** ~~in an adrenocortical carcinoma (ACC) in an FAP patient.[~~[~~125~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_125)~~] In a study of 162 FAP patients who underwent abdominal CT for evaluation of intra-abdominal desmoid tumors, 15 patients (11 females) were found to have adrenal tumors.[~~[~~126~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_126)~~] Of these, two had symptoms attributable to cortisol hypersecretion. Three of these patients underwent subsequent surgery and were found to have ACC, bilateral nodular hyperplasia, or adrenocortical adenoma. The prevalence of an unexpected adrenal neoplasia in this cohort was 7.4%, which compares with a prevalence of 0.6% to 3.4% (~~*~~P~~* ~~< .001) in non-FAP patients.[~~[~~126~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_126)~~] No molecular genetic analyses were provided for the tumors resected in this series. A subsequent study identified adrenal lesions in 26% (23 of 90) of patients with FAP, 18% (2 of 11) of patients with AFAP, and 24% (5 of 21) of patients with~~ *~~MUTYH~~*~~-associated polyposis. Most lesions in this series followed a benign and slowly progressive course; no cases of ACC were reported.[~~[~~127~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_127)~~]~~

~~Hepatoblastoma is a rare, rapidly progressive, and usually fatal childhood malignancy that, if confined to the liver, can be cured by radical surgical resection. Multiple cases of hepatoblastoma have been described in children with an~~ *~~APC~~* ~~pathogenic variant.[~~[~~128~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_128)~~,~~ [~~129~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_129)~~,~~ [~~130~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_130)~~,~~ [~~131~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_131)~~,~~ [~~132~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_132)~~,~~ [~~133~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_133)~~,~~ [~~134~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_134)~~,~~ [~~135~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_135)~~,~~ [~~136~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_136)~~,~~ [~~137~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_137)~~] Some series have also demonstrated LOH of~~ *~~APC~~* ~~in these tumors.[~~[~~129~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_129)~~,~~ [~~131~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_131)~~,~~ [~~138~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_138)~~] No specific genotype-phenotype correlations have been identified in FAP patients with hepatoblastoma.[~~[~~139~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_139)~~] Although lacking~~ [~~level 1 evidence~~](https://cdr.cancer.gov/cgi-bin/cdr/QcReport.py?DocId=CDR0000531823&Session=guest)~~, a consensus panel has suggested that abdominal examination, abdominal ultrasound, and measurement of serum alpha fetoprotein every 3 to 6 months for the first 5 years of life in children with a predisposition to FAP be considered.[~~[~~102~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_102)~~,~~ [~~140~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_140)~~]~~ ***It is not necessary to continue screening after age 5. ~~[AB-Comment: (Boland) Suggested text.]~~***

[~~Level of evidence (hepatoblastoma or adrenal cancer screening): 5~~](https://cdr.cancer.gov/cgi-bin/cdr/QcReport.py?DocId=CDR0000526280&Session=guest) ***~~[AB-Comment: (Amos) Suggested edit.]~~***

~~The constellation of CRC and brain tumors has been referred to as Turcot syndrome; however, Turcot syndrome is molecularly heterogeneous. Molecular studies have demonstrated that colon polyposis and medulloblastoma are associated with pathogenic variants in~~ *~~APC~~* ***(thus representing FAP)***~~, while colon cancer and glioblastoma are associated with pathogenic variants in mismatch repair (MMR) genes~~ ***(thus representing Lynch syndrome) ~~[AB-Comment: (Hampel) Suggested additions.]~~*** ~~.[~~[~~141~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_141)~~]~~

~~There are several reports of other extracolonic tumors~~ ***~~[AB-Comment: (Hampel) I’d list the tumors or delete this paragraph.]~~*** ~~associated with FAP, but whether these are simply coincidence or actually share a common molecular genetic origin with the colonic tumors is not always evident. Some of these reports have demonstrated LOH or a variant of the wild-type~~ *~~APC~~* ~~allele in extracolonic tumors in FAP patients, which strengthens the argument for their inclusion in the FAP~~ *~~syndrome~~****phenotype ~~[AB-Comment: (Boland) Suggested revision.]~~*** ~~.~~

**~~Genetic testing for FAP~~**

*~~APC~~* ~~gene testing is now commercially available and has led to changes in management guidelines, particularly for those whose tests indicate they are not carriers of pathogenic variants. Presymptomatic genetic diagnosis of FAP in at-risk individuals has been feasible with~~ [~~linkage~~](https://cdr.cancer.gov/cgi-bin/cdr/Filter.py?DocId=CDR0000460161&Filter=set:QC+GlossaryTermName+with+Concept+Set) ~~[~~[~~24~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_24)~~] and direct detection [~~[~~31~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_31)~~] of~~ *~~APC~~* ~~pathogenic variants. These tests require a small sample (<10 cc) of blood in which the lymphocyte DNA is tested. If one were to use~~ [~~linkage analysis~~](https://cdr.cancer.gov/cgi-bin/cdr/Filter.py?DocId=CDR0000425374&Filter=set:QC+GlossaryTermName+with+Concept+Set) ~~to identify gene carriers, ancillary family members, including more than one affected individual, would need to be studied.~~ ***~~[AB-Comment: (Boland) Suggested text.]~~ This approach is almost never used currently because of the success of direct gene analysis.*** ~~With direct detection, fewer family members’ blood samples are required than for linkage analysis, but the specific pathogenic variant must be identified in at least one affected person by DNA variant analysis or sequencing. The detection rate is approximately 80% using sequencing alone.[~~[~~32~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_32)~~]~~ ***~~[AB-Comment: (Boland) old data, probably higher now]]~~***

~~Studies have reported whole exon deletions in 12% of FAP patients with previously negative~~ *~~APC~~* ~~testing.[~~[~~34~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_34)~~,~~ [~~35~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_35)~~]~~ ***~~[AB-Comment: (Hampel) Add data about the APC promoter deletion and suggest that testing should include this as well. APC promoter 1B deletion in familial polyposis--implications for mutation-negative families. Kadiyska TK, Todorov TP, Bichev SN, Vazharova RV, Nossikoff AV, Savov AS, Mitev VI. Clin Genet. 2014 May;85(5):452-7. PMID:23725351 ] [AB-Comment: (Boland) Suggested revisions.]~~*** ~~For this reason, deletion testing~~ ***is always added****~~has been added as an optional adjunct~~* ~~to sequencing of~~ *~~APC~~*~~. Furthermore, pathogenic variant detection assays that use MLPA~~ *~~are being~~* ***have been*** ~~developed and~~ *~~appear to be~~* **are** ~~accurate for detecting intragenic deletions.[~~[~~36~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_36)~~]~~ *~~MUTYH~~* ~~gene testing may be considered in~~ *~~APC~~* ~~pathogenic variant–negative affected individuals.[~~[~~37~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_37)~~]~~ ***POLE/POLD1 gene testing may be considered in APC and MUTYH pathogenic variant–negative affected individuals.[***[***38***](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_38)***,*** [***39***](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_39)***] Alternatively, NGS panels are available that include all of these polyposis genes and this can simplify testing by screening all of these genes at the same time. ~~[AB-Comment: (Hampel) Proposed text.]~~*** ~~(Refer to the~~ [*~~Adenomatous polyposis coli [APC]~~*](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#_2551) ~~section of this summary for more information.)~~ ***~~[AB-Comment: (Boland) [much of this paragraph is based on old, outdated information]]~~***

***~~[AB-Comment: (Hampel) I’d consider combining this paragraph and the one above to discuss the Differential diagnosis for adenomatous polyposis – since most people would just order a polyposis panel for either indication now.]~~*** ~~Patients who develop fewer than 100 colorectal adenomatous polyps are a diagnostic challenge. The differential diagnosis includes AFAP~~***,****~~and MUTYH~~*~~-associated~~ *~~colorectal neoplasia (also reported as MUTYH-associated~~* ~~polyposis~~ *~~or~~* ***(***~~MAP)~~***, and polymerase proofreading-associated polyposis (PPAP)***~~.[~~[~~40~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_40)~~] AFAP can be diagnosed by testing for germline~~ *~~APC~~* ~~gene pathogenic variants. (Refer to the~~ [~~Attenuated Familial Adenomatous Polyposis [AFAP]~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#_118) ~~section in the~~ [~~Major Genetic Syndromes~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#_89) ~~section of this summary for more information.)~~ *~~MUTYH~~*~~-associated neoplasia is caused by~~ *~~germline~~* [*~~homozygous~~*](https://cdr.cancer.gov/cgi-bin/cdr/Filter.py?DocId=CDR0000339342&Filter=set:QC+GlossaryTermName+with+Concept+Set)***biallelic germline ~~[AB-Comment: (Boland and Hampel) Suggested edits.]~~*** *~~recessive~~* ~~pathogenic variants in the~~ *~~MUTYH~~* ~~gene.[~~[~~41~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_41)~~]~~ ***PPAP is caused by pathogenic variants in POLE and POLD1.[***[***38***](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_38)***,*** [***39***](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_39)***] NGS panels are available that include all of these polyposis genes and this can simplify testing by screening all of these genes at the same time.***

[~~Presymptomatic genetic testing~~](https://cdr.cancer.gov/cgi-bin/cdr/Filter.py?DocId=CDR0000460210&Filter=set:QC+GlossaryTermName+with+Concept+Set) ~~removes the necessity of annual screening of at-risk individuals who do not have the familial gene pathogenic variant. For at-risk individuals who have been found to be definitively pathogenic variant–negative by genetic testing, there is no clear consensus on the need for or frequency of colon screening,[~~[~~25~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_25)~~] although all experts agree that at least one flexible sigmoidoscopy or colonoscopy examination should be performed in early adulthood (by age 18–25 y).~~ ***~~[AB-Comment: (Hampel) Really? I thought this had gone by the wayside. Is this in the rare case that there was an error in the testing?]~~*** ~~[~~[~~24~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_24)~~,~~ [~~25~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_25)~~] Colon adenomas will develop in nearly 100% of persons who are~~ *~~APC~~* ~~pathogenic variant–positive; risk-reducing surgery comprises the standard of care to prevent colon cancer after polyps have appeared and are too numerous or histologically advanced to monitor safely using endoscopic resection.~~

**~~Interventions for FAP~~**

~~Individuals at risk of FAP, because of a known~~ *~~APC~~* ~~pathogenic variant in either the family or themselves, are evaluated for onset of polyposis by flexible sigmoidoscopy or colonoscopy. Once an FAP family member is found to manifest polyps, the only effective management to prevent CRC is~~ *~~eventual~~* ~~colectomy~~ ***~~[AB-Comment: (Boland) Suggested edit.]~~*** ~~. Prophylactic surgery has been shown to improve survival in patients with FAP.[~~[~~146~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_146)~~] If feasible, the patient and his/her family members should be included in a registry because it has been shown retrospectively that registration and surveillance reduce CRC incidence and mortality.[~~[~~147~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_147)~~] In patients with classic FAP identified very early in their course, the surgeon, endoscopist, and family may choose to delay surgery for several years in the interest of achieving social milestones. In addition, in carefully selected patients with AFAP (those with minimal polyp burden and advanced age), deferring a decision about colectomy may be reasonable with surgery performed only in the face of advancing polyp burden or dysplasia.~~

~~A Finnish nationwide population-based retrospective study evaluating whether surveillance of family members with FAP reduced overall mortality and improved survival demonstrated that call-up patients (family members of a~~ [~~proband~~](https://cdr.cancer.gov/cgi-bin/cdr/Filter.py?DocId=CDR0000460211&Filter=set:QC+GlossaryTermName+with+Concept+Set) ~~who were recruited to the screening program) had equivalent survival to the general population up to 20 years after diagnosis of FAP.[~~[~~148~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_148)~~] The study included 154 families with at least one family member clinically diagnosed with FAP from 1963 to 2015. There were 194 probands and 225 call-ups (83 diagnosed by genetic testing and 142 by endoscopy) with a median time of follow-up of 11.8 years. In this study, the survival analysis of members of FAP families was calculated using the relative survival estimate.[~~[~~149~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_149)~~] This estimation compares survival among FAP probands and call-ups with the survival expected in the absence of FAP among individuals of the same gender and age in each calendar year. The relative survival after 10 and 20 years of follow-up for probands was 67% (95% CI, 60%–75%) and 66% (95% CI, 58%–76%), respectively. For call-ups, the 10- and 20-year relative survival was 98% (95% CI, 95%–101%) and 94% (95% CI, 88%–100%), respectively. At 25 years of follow-up, the relative survival for call-ups was lower than the general population at 87% (95% CI, 79%–96%). The relative survival for probands was significantly lower than for call-ups (~~*~~P~~* ~~< .001). In terms of mortality, the standardized mortality ratio was elevated in probands in both the 0- to 5-year and 5- to 10-year periods of follow-up whereas it remained stable for call-ups until 20 years of follow-up. This difference was more marked in the beginning of follow-up for probands taking into account the fact that probably most were symptomatic, and most likely had CRC at the diagnosis. The authors pointed out that if the CRC was treated successfully without recurrence, the survival of the probands approached that of the call-ups.~~

~~The recommended age at which surveillance for polyposis should begin involves a trade-off. Someone who waits until the late teens to begin surveillance faces a remote possibility that a cancer will have developed at an earlier age. Although it is rare, CRC can develop in a teenager who carries an~~ *~~APC~~* ~~pathogenic variant. However, it is preferable to allow people at risk to develop emotionally before they are faced with a major surgical decision regarding the timing of colectomy. Therefore, surveillance usually begins early (age 10–15 y). Surveillance has consisted of either flexible sigmoidoscopy or colonoscopy every year.[~~[~~102~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_102)~~,~~ [~~150~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_150)~~,~~ [~~151~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_151)~~] If flexible sigmoidoscopy is utilized and polyps are found, colonoscopy is performed. Historically, sigmoidoscopy may have been a reasonable approach in identifying early adenomas in most patients. However, colonoscopy is the tool of choice in light of (a) improved instrumentation for full colonoscopy; (b) sedation; (c) recognition of AFAP, in which the disease is typically most manifest in the right colon; and (d) the growing tendency to defer surgery for a number of years. Individuals who have tested negative for an otherwise known family pathogenic variant do not need FAP-oriented~~ ***endoscopic*** ~~surveillance at all.~~ ***~~[AB-Comment: (Boland) Suggested edit.]~~*** ~~They are recommended to undergo average-risk population screening.~~ ***~~[AB-Comment: (Hampel) I agree with this but it’s discrepant with above where it said to have a baseline in the 20s if negative for a known mutation.]~~*** ~~In the case of families in which no family variant has been identified in an affected person, clinical surveillance is warranted. Colon surveillance is not stopped in persons who are known to carry an~~ *~~APC~~* ~~pathogenic variant but who do not yet manifest polyps, because adenomas occasionally are not manifest until the fourth and fifth decades of life. (Refer to the~~ [~~Attenuated Familial Adenomatous Polyposis [AFAP]~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#_118) ~~section of this summary for more information.) (Refer to the PDQ summary on~~ [~~Colorectal Cancer Screening~~](https://cdr.cancer.gov/cgi-bin/cdr/QcReport.py?DocId=CDR0000062753&Session=guest) ~~for more information on these methods.)~~

***~~[AB-Comment: (Hampel) This contradicts the last paragraph which said that colonoscopy is now the tool of choice.]~~***

*~~In some circumstances, full colonoscopy may be preferred over the more limited sigmoidoscopy. Among pediatric gastroenterologists, tolerability of endoscopic procedures in general has been regarded as improved with the use of deeper intravenous sedation.~~*

***~~[AB-Comment: (Hampel) Check the newest NCCN but I anticipate that they will also mention POLE and POLD1 testing if APC and MUTYH are negative.]~~***

~~Table~~ 7 ~~summarizes the clinical practice guidelines from different professional societies regarding diagnosis and surveillance of FAP.~~

|  |
| --- |
| **~~Table~~ 11. ~~Clinical Practice Guidelines for Diagnosis and Colon Surveillance of Familial Adenomatous Polyposis (FAP)~~** |
| **~~Organization~~**  | ***~~APC~~* ~~Gene Test Recommended~~**   | **~~Age Screening Initiated~~**   | **~~Frequency~~**  | **~~Method~~**  | **~~Comment~~**  |
| ~~American Society of Colon and Rectal Surgeons (2001, 2003) [~~[~~152~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_152)~~,~~ [~~153~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_153)~~,~~ [~~154~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_154)~~]~~  | ~~Yes~~  | ~~NA~~  | ~~NA~~  | ~~NA~~  |   |
| ~~American Cancer Society (2002) [~~[~~155~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_155)~~]~~  | ~~NA~~  | ~~Puberty~~  | ~~NA~~  | ~~Endoscopy~~  | ~~Referral to a center specializing in FAP screening suggested.~~  |
| ~~GI Societies (2003)~~~~a~~ ~~[~~[~~150~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_150)~~]~~  | ~~Yes~~   | ~~10–12 y~~   | ~~Annual~~   | ~~FS~~   |   |
| ~~NCCN (2017) [~~[~~102~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_102)~~]~~  | ~~Yes~~   | ~~10–15 y~~   | ~~Annual~~  | ~~FS or C~~  | ~~If an at-risk individual is found to not carry the~~ *~~APC~~* ~~gene pathogenic variant responsible for familial polyposis in the family, screening as an average-risk individual is recommended.~~  |

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| --- |
| *~~C = colonoscopy; FS = flexible sigmoidoscopy; GI = gastrointestinal; NA = not addressed; NCCN = National Comprehensive Cancer Network.~~* |
| *~~a~~~~GI Societies – American Academy of Family Practice, American College of Gastroenterology, American College of Physicians-American Society of Internal Medicine, American College of Radiology, American Gastroenterological Association, American Society of Colorectal Surgeons, and American Society for Gastrointestinal Endoscopy.~~* |

~~FAP patients and their doctors should have an individualized discussion to decide when surgery will be performed. It is useful to incorporate into the discussion the risk of developing desmoid tumors after surgery. Timing of risk-reducing surgery usually depends on the number of polyps, their size, histology, and symptomatology.[~~[~~156~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_156)~~] Once numerous polyps have developed, surveillance colonoscopy is no longer useful in timing the colectomy because polyps are so numerous that it is not possible to biopsy or remove all of them. At this time, it is appropriate for patients to consult with a surgeon who is experienced with available options, including total colectomy and postcolectomy reconstruction techniques.[~~[~~157~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_157)~~] Rectum-sparing surgery, with sigmoidoscopic surveillance of the remaining rectum, is a reasonable alternative to total colectomy in those compliant individuals~~ ***with relative rectal sparing of polyps and ~~[AB-Comment: (Boland) Suggested text.]~~*** ~~who understand the consequences and make an informed decision to accept the residual risk of rectal cancer occurring despite periodic surveillance.[~~[~~158~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_158)~~]~~

***~~[AB-Comment: (Amos) Should levels of evidence be provided for differing surgical treatments?]~~***

~~Surgical options include restorative proctocolectomy with IPAA, subtotal colectomy with ileorectal anastomosis (IRA), or total proctocolectomy with ileostomy (TPC). TPC is reserved for patients with low rectal cancer in which the sphincter cannot be spared or for patients on whom an IPAA cannot be performed because of technical problems. There is no risk of developing rectal cancer after TPC because the whole mucosa at risk is removed. Whether a colectomy and an IRA or a restorative proctocolectomy is performed, most experts suggest that periodic and lifelong surveillance of the rectum or the ileal pouch be performed to remove or ablate any polyps. This is necessitated by case series of rectal cancers arising in the rectum of FAP patients who had subtotal colectomies with an IRA in which there was an approximately 25% cumulative risk of rectal adenocarcinoma 20 years after IRA and by case reports of adenocarcinoma in the ileoanal pouch and anal canal after restorative proctocolectomy.[~~[~~159~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_159)~~,~~ [~~160~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_160)~~,~~ [~~161~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_161)~~,~~ [~~162~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_162)~~] The cumulative risk of rectal cancer after IRA may be lower than that reported in the literature, in part because of better selection of patients for this procedure, such as those with minimal polyp burden in the rectum.[~~[~~157~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_157)~~] Other factors that have been reported to increase the rectal cancer risk after IRA include the presence of colon cancer at the time of IRA, the length of the rectal stump, and the duration of follow-up after IRA.[~~[~~163~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_163)~~,~~ [~~164~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_164)~~,~~ [~~165~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_165)~~,~~ [~~166~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_166)~~,~~ [~~167~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_167)~~,~~ [~~168~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_168)~~,~~ [~~169~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_169)~~] An abdominal colectomy with IRA as the primary surgery for FAP does not preclude later conversion to an IPAA for uncontrolled rectal polyps and/or rectal cancer. In the Danish Polyposis Registry, the morbidity and functional results of a secondary IPAA (after a previous IRA) in 24 patients were reported to be similar to those of 59 patients who underwent primary IPAA.[~~[~~170~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_170)~~]~~

***~~[Comment: From WG 4/28: Make sure we describe study from St. Mark’s (1993) that looked at colectomy. This would be level 3ai (prevention).]~~***

~~In most cases, the clinical polyp burden in the rectum at the time of surgery dictates the type of surgical intervention, namely restorative proctocolectomy with IPAA versus IRA. Patients with a mild phenotype (<1,000 colonic adenomas) and fewer than 20 rectal polyps may be candidates for IRA at the time of prophylactic surgery.[~~[~~171~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_171)~~] In some cases, however, the polyp burden is equivocal, and in such cases, investigators have considered the role of genotype in predicting subsequent outcomes with respect to the rectum.[~~[~~172~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_172)~~] Pathogenic variants reported to increase the rectal cancer risk and eventual completion proctectomy after IRA include variants in exon 15 codon 1250, exon 15 codons 1309 and 1328, and exon 15 variants between codons 1250 and 1464.[~~[~~159~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_159)~~,~~ [~~168~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_168)~~,~~ [~~169~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_169)~~,~~ [~~173~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_173)~~] In patients who have undergone IPAA, it is important to continue annual surveillance of the ileal pouch because the cumulative risk of developing adenomas in the pouch has been reported to be up to 75% at 15 years.[~~[~~174~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_174)~~,~~ [~~175~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_175)~~] Although they are rare, carcinomas have been reported in the ileal pouch and anal transition zone after restorative proctocolectomy in FAP patients.[~~[~~176~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_176)~~] A meta-analysis of quality of life after restorative proctocolectomy and IPAA has suggested that FAP patients do marginally better than inflammatory bowel disease patients in terms of fistula formation, pouchitis, stool frequency, and seepage.[~~[~~177~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_177)~~]~~

~~Celecoxib, a specific cyclooxygenase II (COX-2) inhibitor, and nonspecific COX-2 inhibitors, such as sulindac, have been associated with a decrease in polyp size and number in FAP patients, suggesting a role for chemopreventive agents in the treatment of this disorder.[~~[~~178~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_178)~~,~~ [~~179~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_179)~~] Although celecoxib had been approved by the U.S. Food and Drug Administration (FDA), its license was voluntarily withdrawn by the manufacturer. Currently, there are no FDA-approved drugs for chemoprevention in FAP. Nevertheless, agents such as celecoxib and sulindac are in sufficiently widespread use that chemopreventive clinical trials typically utilize one of these agents as the control arm. A randomized trial showed possible marginal improvement in polyp burden with the combination of celecoxib and difluoromethylornithine, compared with celecoxib alone.[~~[~~180~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_180)~~]~~

~~A small, randomized, placebo-controlled, dose-escalation trial of celecoxib in a pediatric population (aged 10–14 y) demonstrated the safety of celecoxib at all dosing levels when administered over a 3-month period.[~~[~~181~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_181)~~] This study found a dose-dependent reduction in adenomatous polyp burden. At a dose of 16 mg/kg/day, which approximates the approved dose of 400 mg twice daily in adults, the reduction in polyp burden paralleled that demonstrated with celecoxib in adults.~~

~~Omega-3-polyunsaturated fatty acid eicosapentaenoic acid in the free fatty acid form has been shown to reduce rectal polyp number and size in a small study of patients with FAP post subtotal colectomy.[~~[~~182~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_182)~~] Although not directly compared in a randomized trial, the effect appeared to be similar in magnitude to that previously observed with celecoxib.~~

~~It is unclear at present how to incorporate COX-2 inhibitors into the management of FAP patients who have not yet undergone risk-reducing surgery. A double-blind, placebo-controlled trial in 41 child and young adult carriers of~~ *~~APC~~* ~~pathogenic variants who had not yet manifested polyposis demonstrated that sulindac may not be effective as a primary treatment in FAP. There were no statistically significant differences between the sulindac and placebo groups over 4 years of treatment in incidence, number, or size of polyps.[~~[~~179~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_179)~~]~~

~~Consistent with the effects of COX-2 inhibitors on colonic polyps, in a randomized, prospective, double-blind, placebo-controlled trial, celecoxib (400 mg, administered orally twice daily) reduced, but did not eliminate, the number of duodenal polyps in 32 patients with FAP after a 6-month course of treatment. Of importance, a statistically significant effect was seen only in individuals who had more than 5% of the duodenum involved with polyps at baseline and with an oral dose of 400 mg, given twice daily.[~~[~~183~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_183)~~] A previous randomized study of 24 FAP patients treated with sulindac for 6 months showed a nonsignificant trend in the reduction of duodenal polyps.[~~[~~184~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_184)~~] The same issues surrounding the use of COX-2 inhibitors for the treatment of colonic polyps apply to their use for the treatment of duodenal polyps (e.g., only partial elimination of the polyps, complications secondary to the COX-2 inhibitors, and loss of effect after the medication is discontinued).[~~[~~183~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_183)~~]~~

~~Because of the common clustering of adenomatous polyps around the duodenal papilla (where bile enters the intestine) and preclinical data suggesting that ursodeoxycholate inhibits intestinal adenomas in mice that harbor an~~ *~~Apc~~* ~~germline variant,[~~[~~185~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_185)~~] two trials that employ ursodeoxycholate have been performed.[~~[~~186~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_186)~~,~~ [~~187~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_187)~~] In both studies, ursodeoxycholate did not have a significant chemopreventive effect on duodenal polyps; paradoxically, in one study, ursodeoxycholate in combination with celecoxib appeared to promote polyp density in patients with FAP.~~

~~Because of reports demonstrating an increase in cardiac-related events in patients taking rofecoxib and celecoxib,[~~[~~188~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_188)~~,~~ [~~189~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_189)~~,~~ [~~190~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_190)~~] it is unclear whether this class of agents will be safe for long-term use for patients with FAP and in the general population. Also, because of the short-term (6 months) nature of these trials, there is currently no clinical information about cardiac events in FAP patients taking COX-2 inhibitors on a long-term basis.~~

[~~Level of evidence (celecoxib): 1b~~](https://cdr.cancer.gov/cgi-bin/cdr/QcReport.py?DocId=CDR0000538265&Session=guest)

~~One cohort study has demonstrated regression of colonic and rectal adenomas with sulindac (an NSAID) treatment in FAP. The reported outcome of this trial was the number and size of polyps, a surrogate for the clinical outcome of main interest, CRC incidence.[~~[~~191~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_191)~~]~~

[~~Level of evidence (sulindac): 1b~~](https://cdr.cancer.gov/cgi-bin/cdr/QcReport.py?DocId=CDR0000538265&Session=guest)

~~Preclinical studies of a small-molecule epidermal growth factor receptor (EGFR) inhibitor and low-dose sulindac in the Apc~~~~min/+~~ ~~mouse diminished intestinal adenoma development by 87% [~~[~~192~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_192)~~] suggesting that EGFR inhibitors had the potential to inhibit duodenal polyps in FAP patients. A 6-month double-blind, randomized, placebo-controlled trial tested the efficacy of sulindac, 150 mg twice daily, and erlotinib, 75 mg daily, versus placebo in FAP or AFAP patients with duodenal polyps.[~~[~~193~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_193)~~] Ninety-two patients with FAP or AFAP were randomly assigned to receive study drugs or placebo and underwent pretreatment and posttreatment upper endoscopies to determine the changes in the sum diameter of the polyps and number of polyps in a 10 cm segment of proximal duodenum. The trial was terminated prematurely because the primary endpoint was met. The intent-to-treat analysis demonstrated a median decrease in duodenal polyp burden (sum of diameters) of 8.5 mm in the sulindac/erlotinib arm while there was an 8 mm increase in the placebo arm (~~*~~P~~* ~~< .001). Significantly higher rates of grade 1 and grade 2 adverse events occurred in the treatment arm than in the placebo arm: in the treatment arm, 60.9% developed an acneiform rash and 32.6% developed oral mucositis; in the placebo arm, 19.6% developed an acneiform rash and 10.9% developed oral mucositis. Based on the previously modest effects of sulindac and celecoxib on duodenal polyps in FAP patients [~~[~~179~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_179)~~,~~ [~~191~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_191)~~] and the dramatic effect of genetic EGFR inhibition on intestinal adenoma development in the Apc~~~~min/+~~ ~~mouse,[~~[~~194~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_194)~~] it is likely that erlotinib was responsible for the success of this trial. An ongoing clinical trial is determining whether lower doses of erlotinib alone are sufficient for significantly reducing duodenal polyp burden in FAP and AFAP patients.~~

[~~Level of evidence (sulindac + erlotinib): 1b~~](https://cdr.cancer.gov/cgi-bin/cdr/QcReport.py?DocId=CDR0000538265&Session=guest)

~~Patients who carry~~ *~~APC~~* ~~germline pathogenic variants are at increased risk of other types of malignancies, including thyroid cancer, small bowel cancer, hepatoblastoma, and brain tumors. The risk of these tumors, however, is much lower than that for colon cancer, and the only surveillance recommendation by experts in the field is upper endoscopy of the gastric and duodenal mucosa.[~~[~~12~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_12)~~,~~ [~~26~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_26)~~]~~ ***~~[AB-Comment: (Hampel) Not true. NCCN recommends annual thyroid exam starting in the late teenage years and says annual thyroid ultrasound may be considered. Also suggests liver palpation, abdominal US and AFP every 3-6 mos from 0-5 for hepatoblastoma surveillance (mentioned earlier in this document). Annual abdominal palpation to screen for desmoids plus abdominal MRI or CT 1-3 y post-collection and then every 5-10 years for those with a family history of symptomatic desmoids. Small bowel polyps and cancer – consider adding small bowel visualization to the CT or MRI for desmoids esp if duodenal polyposis is advanced. CNS cancer – annual physical examination.]~~*** ~~The severity of duodenal polyposis detected appears to correlate with risk of duodenal adenocarcinoma.[~~[~~89~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_89)~~] (Refer to the~~ [~~Duodenum/small bowel tumors~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#_613) ~~section and the~~ [~~Other tumors~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#_618) ~~section in the~~ [~~Major Genetic Syndromes~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#_89) ~~section of this summary for more information about screening for extracolonic malignancies in patients with FAP.)~~

**Attenuated Familial Adenomatous Polyposis (AFAP)**

AFAP is a heterogeneous clinical entity characterized by fewer adenomatous polyps in the colon and rectum than in classic FAP. It was first described clinically in 1990 in a large [kindred](https://cdr.cancer.gov/cgi-bin/cdr/Filter.py?DocId=CDR0000460158&Filter=set:QC+GlossaryTermName+with+Concept+Set) with a variable number of adenomas. The average number of adenomas in this kindred was 30, though they ranged in number from a few to hundreds.[[199](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_199)] Adenomas in AFAP are believed to form in the mid-twenties to late twenties.[[75](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_75)] Similar to classic FAP, the risk of CRC is higher in individuals with AFAP; the average age at diagnosis, however, is older than classic FAP at 56 years.[[142](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_142), [143](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_143), [200](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_200)] Extracolonic manifestations similar to those in classic FAP also occur in AFAP. These manifestations include upper GI polyps (FGPs, duodenal adenomas, and duodenal adenocarcinoma), osteomas, epidermoid cysts, and desmoid tumors.[[75](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_75)]

AFAP is associated with particular subsets of *APC* pathogenic variants*~~, including missense changes~~* ***[AB-Comment: (Boland) [I do not believe this is true, and this misstates the finding in ref 286 (Wijnen NEJM 1998), as the abnormality is not confined to the missense issue]. ]*** . Three groups of site-specific *APC* pathogenic variants causing AFAP have been characterized:[[142](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_142), [143](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_143), [144](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_144), [196](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_196), [201](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_201), [202](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_202)]

***[AB-Comment: (Boland) Suggested text (second bullet below).]***

* Pathogenic variants associated with the 5’ end of *APC* and exon 4 in which patients can manifest 2 to more than 500 adenomas, including the classic FAP phenotype and upper GI polyps.
* ***Any pathogenic variant in the first 4 exons,[***[***142***](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_142)***] as there is an internal ribosomal entry site in exon 4 that permits the ribosome to skip premature truncation pathogenic variants.[***[***203***](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_203)***]***
* Exon 9–associated phenotypes in which patients may have 1 to 150 adenomas but no upper GI manifestations.
* 3’ region pathogenic variants in which patients have very few adenomas (<50).

*APC* gene testing is an important component of the evaluation of patients suspected of having AFAP.[[204](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_204)] It has been recommended that the management of AFAP patients include colonoscopy rather than flexible sigmoidoscopy because the adenomas can be predominantly right-sided.[[204](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_204)] The role for and timing of risk-reducing colectomy in AFAP is controversial.[[205](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_205)] If germline *APC* pathogenic variant testing is negative in suspected AFAP individuals, genetic testing for *MUTYH****, POLE, and POLD1*** pathogenic variants may be warranted.[[34](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_34)]

Patients found to have an unusually or unacceptably high adenoma count at an age-appropriate colonoscopy pose a differential diagnostic challenge.[[206](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_206), [207](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_207)] In the absence of family history of similarly affected relatives, the differential diagnosis may include AFAP (including MAP), Lynch syndrome, ***biallelic mismatch repair deficiency (BMMRD), germline variants in the DNA polymerase proofreading subunits (POLD1 or POLE), [AB-Comment: (Boland) Suggested text.]*** or an otherwise unclassified sporadic or genetic problem. A careful family history may implicate AFAP or Lynch syndrome.

[Table 12](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#_2699) summarizes the clinical practice guidelines from different professional societies regarding surveillance of AFAP.

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| **Table 12. Clinical Practice Guidelines for Colon Surveillance of Attenuated Familial Adenomatous Polyposis (AFAP)** |
| **Organization**  | **Condition**  | **Screening Method**  | **Screening Frequency**  | **Age Screening Initiated**  | **Comment**  |
| Europe Mallorca Group (2008) [[208](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_208)]  | AFAP  | Colonoscopy  | Every 2 y; every 1 y if adenomas are detected  | 18–20 y  |   |
| NCCN (2017) [[102](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_102)]  | Personal history of AFAP with small adenoma burdena  | Colonoscopy   | Every 1–2 y  |   | If patient had colectomy with IRA, endoscopic evaluation every 6–12 mo depending on polyp burden.   |
| Colectomy and IRA may be considered in patients aged ≥21 y  |
| NCCN (2017) [[102](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_102)]  | Personal history of AFAP with adenoma burden that cannot be handled endoscopically  | Not applicable  | Not applicable  | Not applicable  | Colectomy with IRA preferred. Consider proctocolectomy with IPAA if dense rectal polyposis.  |
| NCCN (2017) [[102](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_102)]  | [Unaffected](https://cdr.cancer.gov/cgi-bin/cdr/Filter.py?DocId=CDR0000460224&Filter=set:QC+GlossaryTermName+with+Concept+Set) at-risk family member; family pathogenic variant known; *APC* pathogenic variant status unknown or positive  | Colonoscopy  | Every 2–3 y  | Late teens  | If *APC* pathogenic variant status not tested, consider genetic testing.  |

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| *IPAA = ileal pouch–anal anastomosis; IRA = ileorectal anastomosis; NCCN = National Comprehensive Cancer Network.* |
| *aFewer than 20 adenomas that are each <1 cm in diameter and without advanced histology so that colonoscopy with polypectomy can be used to effectively eliminate the polyps.* |

***MUTYH*-Associated Polyposis (MAP)**

***[Comment: Revisions to this section approved by WG 5/1/18.]***

***MUTYH*-associated polyposis (MAP) is an autosomal recessively inherited polyposis syndrome caused by pathogenic variants in the *Mut Y homolog* gene. The *Mut Y homolog* gene, which is known as *MUTYH* was initially called *MYH*, but subsequently corrected because the myosin heavy chain gene already had that designation, is located on chromosome 1p34.3-32.1.[**[**209**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_209)**] The protein encoded by *MUTYH* is a base excision repair glycosylase. It repairs one of the most common forms of oxidative damage. Over 100 unique sequence variants of *MUTYH* have been reported (**[**Leiden Open Variation Database**](http://proteomics.bio21.unimelb.edu.au/lovd/genes/MUTYH)**). A** [founder pathogenic variant](https://cdr.cancer.gov/cgi-bin/cdr/Filter.py?DocId=CDR0000783962&Filter=set:QC+GlossaryTermName+with+Concept+Set) **with ethnic differentiation is assumed for *MUTYH* pathogenic variants. In Caucasian populations of northern European descent, two major variants, Y179C and G396D (formerly known as Y165C and G382D), account for 70% of biallelic pathogenic variants in MAP patients, and 90% of these patients carry at least one of these pathogenic variants.[**[**210**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_210)**] Other causative variants that have been found include P405L (formerly known as P391L) (Netherlands),[**[**211**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_211)**,** [**212**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_212)**] E480X (India),[**[**213**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_213)**] Y104X (Pakistan),[**[**214**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_214)**] 1395delGGA (Italy),[**[**215**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_215)**,** [**216**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_216)**] *[Comment: Need to update variant nomenclature in this section.]* 1186-1187insGG (Portugal),[**[**217**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_217)**] and p.A359V (Japan, Korea).[**[**218**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_218)**,** [**219**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_219)**,** [**220**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_220)**]**

~~MAP is an autosomal recessive inherited polyposis syndrome.~~ The *MUTYH* gene~~, which is sometimes referred to as~~ *~~MYH~~* ~~(not to be confused with the~~ *~~myosin heavy chain~~* ~~gene),~~ was first ~~identified~~**linked to polposis** in 2002 in three siblings with multiple colonic adenomas and CRC but no *APC* pathogenic variant.[[41](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_41)] MAP has a broad clinical spectrum. Most often it resembles the clinical picture of AFAP, but it has been reported in individuals with phenotypic resemblance to classical FAP and Lynch syndrome.[[221](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_221)] MAP patients tend to develop fewer adenomas at a later age than patients with *APC* pathogenic variants [[37](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_37), [222](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_222)] ~~and also~~ **but still** carry a high risk of CRC (35%–~~63~~**75**%).[[7](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_7), [223](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_223), [**224**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_224)**]** A 2012 study of colorectal adenoma burden in 7,225 individuals reported a prevalence of [biallelic](https://cdr.cancer.gov/cgi-bin/cdr/Filter.py?DocId=CDR0000775789&Filter=set:QC+GlossaryTermName+with+Concept+Set) *MUTYH* pathogenic variants of 4% (95% CI, 3%–5%) among those with 10 to 19 adenomas, 7% (95% CI, 6%–8%) among those with 20 to 99 adenomas, and 7% (95% CI, 6%–8%) among those with 100 to 999 adenomas.[[225](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_225)] This broad clinical presentation results from the *MUTYH* gene's ability to cause disease in its homozygous or [compound heterozygous](https://cdr.cancer.gov/cgi-bin/cdr/Filter.py?DocId=CDR0000766214&Filter=set:QC+GlossaryTermName+with+Concept+Set) forms. Based on studies from multiple FAP registries, approximately 7% to 19% of patients with a FAP phenotype and without a detectable *APC* germline pathogenic variant carry biallelic variants in the *MUTYH* gene.[[7](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_7), [37](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_37), [213](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_213), [226](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_226)]

Adenomas, serrated adenomas, and hyperplastic polyps can be seen in MAP patients.**[**[**227**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_227)**]** The CRCs tend to be right-sided and synchronous at presentation and seem to carry a better prognosis than sporadic CRC.[[209](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_209)] Clinical management guidelines for ~~biallelic~~ MAP range between once a year to every 3 years for colonoscopic surveillance beginning at age 18 to 30 years,[[102](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_102)][[208](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_208)][[223](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_223)] with upper endoscopic surveillance beginning at age 25 to 30 years.[[208](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_208)] (Refer to [Table 13](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#_2700) for more information about available clinical practice guidelines for colon surveillance in ~~biallelic~~ MAP patients.) The recommended upper endoscopic surveillance interval can be based on the burden of involvement according to Spigelman criteria.[[208](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_208)] Total colectomy with ileorectal anastomosis or subtotal colectomy may be **necessary** ~~appropriate~~ for patients with *MUTYH*-associated polyposis **depending on overall polyp burden**~~, provided that they have no rectal cancer or severe rectal polyposis at presentation and that they undergo yearly endoscopic surveillance thereafter~~.[[223](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_223), [228](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_228)]

**Although MAP is the only known biallelic (recessive) adenoma cancer predisposition described to date, there are examples of biallelic cases presenting with childhood tumors in which MMR genes are involved. Refer to the BMMRD section in the Lynch syndrome section of this summary.**

[Table 13](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#_2700) summarizes the clinical practice guidelines from different professional societies regarding colon surveillance of biallelic MAP.

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| **Table 13. Clinical Practice Guidelines for Colon Surveillance of ~~Biallelic~~ *MUTYH*-Associated Polyposis (MAP)** |
| **Organization**  | **Condition**  | **Screening Method**  | **Screening Frequency**  | **Age Screening Initiated**  | **Comment**  |
| Europe Mallorca Group (2008) [[208](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_208)]  | Carrier of ~~biallelic~~ *MUTYH* pathogenic variants  | Colonoscopy  | Every 2 y  | 18–20 y  |   |
| Nieuwenhuis et al. (2012) [[223](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_223)]  | Carrier of ~~biallelic~~ *MUTYH* pathogenic variants  | Colonoscopy  | Every 1–2 y  |   |   |
| NCCN (2017) [[102](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_102)]  | Personal history of MAP, small adenoma burdena  | Colonoscopy   | Every 1–2 y  |   | If patient had colectomy with IRA, endoscopic evaluation every 6–12 mo depending on polyp burden.  |
| Colectomy and IRA may be considered in patients aged ≥21 y  |
| NCCN (2017) [[102](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_102)]  | Personal history of MAP with adenoma burden that cannot be handled endoscopically   | Not applicable  | Not applicable  | Not applicable  | Colectomy with IRA preferred. Consider proctocolectomy with IPAA if dense rectal polyposis. If patient had colectomy with IRA, then endoscopic evaluation of rectum every 6–12 mo depending on polyp burden.   |
| NCCN (2017) [[102](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_102)]  | Unaffected, at-risk family member; family pathogenic variant known; *MUTYH* pathogenic variant status unknown or positive (biallelic)  | Colonoscopy  | Every 2–3 y  | 25–30 y  | If positive for a single *MUTYH* pathogenic variant, colonoscopy every 5 y beginning at age 40 y or 10 y before age of [FDR](https://cdr.cancer.gov/cgi-bin/cdr/Filter.py?DocId=CDR0000460150&Filter=set:QC+GlossaryTermName+with+Concept+Set) at CRC diagnosis, if applicable.  |

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| *CRC = colorectal cancer; FDR = first-degree relative; IPAA = ileal pouch–anal anastomosis; IRA = ileorectal anastomosis; NCCN = National Comprehensive Cancer Network.* |
| *aFewer than 20 adenomas that are each <1 cm in diameter and without advanced histology so that colonoscopy with polypectomy can be used to effectively eliminate the polyps.* |

Many extracolonic cancers have been reported in patients with MAP including gastric, small intestinal, endometrial, liver, ovarian, bladder, thyroid, and skin cancers (melanoma, squamous epithelial, and basal cell carcinomas).[[229](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_229), [230](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_230)] Additionally, noncancerous extracolonic manifestations have been reported in a few MAP patients including lipomas, congenital hypertrophy of the retinal pigment epithelium, osteomas, and desmoid tumors.[[37](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_37), [215](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_215), [230](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_230), [231](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_231)] Female MAP patients have an increased risk of breast cancer.[[232](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_232)] These extracolonic manifestations seem to occur less frequently in MAP than in FAP, AFAP, or Lynch syndrome.[[233](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_233), [234](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_234)]

Because MAP has an autosomal recessive inheritance pattern, siblings of an affected patient have a 25% chance of also carrying biallelic *MUTYH* pathogenic variants and should be offered genetic testing. Similarly, testing can be offered to the partner of an affected patient so that the risk in their children can be assessed.

The clinical phenotype of monoallelic *MUTYH* pathogenic variants is less well characterized with respect to incidence and associated clinical phenotypes, and its role in **susceptibility to** ~~pathogenesis of polyposis coli~~**polyposis** and colorectal carcinoma remains **unclear**~~in dispute~~. Approximately 1% to 2% of the general population carry a pathogenic variant in *MUTYH*.[[7](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_7), [37](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_37), [41](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_41)] A 2011 meta-analysis found that carriers of monoallelic *MUTYH* pathogenic variants are at modestly increased risk of CRC (odds ratio [OR], 1.15; 95% CI, 0.98–1.36); however, given the rarity of carriers of monoallelic pathogenic variants, they account for only a trivial proportion of all CRC cases.[[235](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_235)] **A large study of 2332 heterozygotes among 9504 relatives of 264 CRC cases with a MUTYH pathogenic variant found that the CRC risk to age 70 irrespective of family history was 7.2% for males and 5.6% for females. Among those with a FDR with a CRC diagnosis <50, the risk to 70 was 12.5% for males and 10% for females.[**[**224**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_224)**] Caution should be exercised in the interpretation of this study as the vast majority of carrier status from this study was imputed and not based on genotype. The authors felt the risk for MUTYH heterozygotes with a FDR with CRC are sufficiently high to warrant more intensive surveillance than the general population (but the same as for anyone with a FDR with CRC dx <50).** ~~Some studies have suggested screening these individuals on the basis of this modest increase in risk.~~[[222](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_222), [224](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_224)]

MMR genes may interact with MUTYH and increase the risk of CRC. An association between MUTYH and MSH6 has been reported. Both proteins interact together in base excision repair processes. A study reported a significant increase of *MSH6* pathogenic variants in carriers of monoallelic *MUTYH* pathogenic variants with CRC compared with noncarriers **with CRC** (11.5% vs. 0%; *P* = .037).[[236](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_236)] **However, a German study failed to duplicate these findings.[**[**237**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_237)**] *[Comment: Need to confirm ref with Kevin.]* Additionally, a larger study found no increased cancer risk for carriers of MMR pathogenic variants with an *MUTYH* variant compared with those with a MMR pathogenic variant alone.[**[**238**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_238)**]**

***~~Mut Y homolog~~***

***~~[AB-Comment: (Boland) [shouldn’t this section be at the beginning of the section on MAP?]]~~***

~~The~~ *~~Mut Y homolog~~* ~~gene, which is also known as~~ *~~MUTYH~~* ~~and~~ *~~MYH~~*~~,~~ ***~~[AB-Comment: (Boland) Suggested revisions. Again, suggest changing MYH to MutYH throughout document.]~~*** ~~is located on chromosome 1p34.3-32.1.[~~[~~209~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_209)~~] The protein encoded by~~ *~~MUTYH~~* ~~is a base excision repair glycosylase. It repairs one of the most common forms of oxidative damage. Over 100 unique sequence variants of~~ *~~MUTYH~~* ~~have been reported (~~[~~Leiden Open Variation Database~~](http://proteomics.bio21.unimelb.edu.au/lovd/genes/MUTYH)~~). A~~ [~~founder pathogenic variant~~](https://cdr.cancer.gov/cgi-bin/cdr/Filter.py?DocId=CDR0000783962&Filter=set:QC+GlossaryTermName+with+Concept+Set) ~~with ethnic differentiation is assumed for~~ *~~MUTYH~~* ~~pathogenic variants. In Caucasian populations of northern European descent, two major variants, Y179C and G396D (formerly known as Y165C and G382D), account for 70% of biallelic pathogenic variants in MAP patients, and 90% of these patients carry at least one of these pathogenic variants.[~~[~~210~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_210)~~] Other causative variants that have been found include P405L (formerly known as P391L) (Netherlands),[~~[~~211~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_211)~~,~~ [~~212~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_212)~~] E480X (India),[~~[~~213~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_213)~~] Y104X (Pakistan),[~~[~~214~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_214)~~] 1395delGGA (Italy),[~~[~~215~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_215)~~,~~ [~~216~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_216)~~]~~ ***~~[Comment: Need to update variant nomenclature in this section.]~~*** ~~1186-1187insGG (Portugal),[~~[~~217~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_217)~~] and p.A359V (Japan, Korea).[~~[~~218~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_218)~~,~~ [~~219~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_219)~~,~~ [~~220~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_220)~~]~~ ***~~[AB-Comment: (Hampel) The following sentence is out of place here and should be moved to where MAP cancer risks are described.]~~*** ~~Biallelic~~ *~~MUTYH~~* ~~pathogenic variants are associated with a 93-fold excess risk of CRC, with near complete~~ [~~penetrance~~](https://cdr.cancer.gov/cgi-bin/cdr/Filter.py?DocId=CDR0000339344&Filter=set:QC+GlossaryTermName+with+Concept+Set) ~~by age 60 years.[~~[~~239~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_239)~~]~~

***NTHL1***

A study utilizing [whole-exome sequencing](https://cdr.cancer.gov/cgi-bin/cdr/Filter.py?DocId=CDR0000740459&Filter=set:QC+GlossaryTermName+with+Concept+Set) in 51 individuals with multiple colonic adenomas from 48 families identified a homozygous germline nonsense pathogenic variant in seven affected individuals from three unrelated families in the base-excision repair gene *NTHL1*.[[240](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_240)] These individuals had CRC, multiple adenomas (8–50), none of which were either hyperplastic or serrated, and in three affected females, there was either endometrial cancer or endometrial complex hyperplasia. There were two other individuals who developed duodenal adenomas and duodenal cancer. All pedigrees were consistent with autosomal recessive inheritance. Upon examining three cancers and five adenomas from different affected individuals, none showed [microsatellite instability](https://cdr.cancer.gov/cgi-bin/cdr/Filter.py?DocId=CDR0000285933&Filter=set:QC+GlossaryTermName+with+Concept+Set) (MSI). These neoplasms did show enrichment of cytosine to thymine transitions. Additional studies are needed to further define the phenotype. A subsequent study of 863 families with CRC and 1,600 families without CRC confirmed an association between *NTHL1* pathogenic variants and inherited CRC risk.[[241](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_241)]

**Oligopolyposis**

Oligopolyposis is a popular term used to describe the clinical presentation of a polyp count or burden that is greater than anticipated in the course of screening in average-risk patients but that falls short of the requirement for a diagnosis of FAP. Thus, *oligo-*, Greek for few, can mean different things to different observers. While conceding a lack of consensus on the matter, the National Comprehensive Cancer Network (NCCN) committee on CRC screening suggests an AFAP diagnosis is worth considering when 10 to less than 100 adenomas are present.[[102](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_102)] It will be used here to describe the circumstance in which the polyp count (generally adenoma) is large enough, with or without any attendant family history, to raise in the mind of the endoscopist the possibility of an inherited susceptibility.

***[AB-Comment: (Hampel) I’m not sure the next two paras go here – maybe move to the LS section in a section about polyps in LS]***

In the setting of known or suspected Lynch syndrome, the detection of one to ten adenomas is still in keeping with the diagnosis. A similar adenoma count in a young patient undergoing colonoscopy for symptoms or in a screening patient over age 50 years could raise the question of Lynch syndrome. In the appropriate clinical setting—early onset and positive family history—the detection of any number of adenomas may support the testing and diagnosis of a patient for underlying Lynch syndrome pathogenic variants, consistent with guidelines such as those offered by the NCCN. Some controversy exists over the utility of testing adenoma tissue for MSI, as the yield is lower than in invasive cancer.[[242](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_242)] In general, and subject to the above caveats, Lynch syndrome is not routinely considered in a discussion of oligopolyposis.

One study considered a series of polyps (37 adenomas) from 21 patients with known MMR pathogenic variants, performing MSI and immunohistochemistry (IHC) for MMR protein expression.[[243](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_243)] Overall, MSI-high (MSI-H) was seen in 41% and in 100% of adenomas larger than 1 cm. Adenomas measuring smaller than 1 cm yielded MSI about 30% of the time. Correlation between MSI and loss of staining on IHC was fairly high, although the discordance rate (17%) was higher than in other series that evaluated invasive cancers from known carriers of MMR pathogenic variants. A higher MSI likelihood was observed in subjects older than 50 years. IHC staining in relation to gene showed 8 of 12 *MLH1* adenomas to have lost protein expression, with 10 of 20 adenomas from *MSH2* patients to have loss of expression. In contrast, none (0 of 6) of the adenomas from carriers of *MSH6* pathogenic variants had loss of associated protein expression. The authors concluded that while normal MSI/IHC was simply not [informative](https://cdr.cancer.gov/cgi-bin/cdr/Filter.py?DocId=CDR0000460156&Filter=set:QC+GlossaryTermName+with+Concept+Set), abnormal MSI/IHC was as likely in larger (>8 mm) polyps as in cancers and thus a reasonable test to consider.

AFAP is *~~found at the other end of the oligopolyposis spectrum~~****the most common cause of oligopolyposis***. ***[AB-Comment: (Hampel) Suggested revision.]*** Most cases will have more than 100 adenomas, albeit at a later age and often with a predominance of microadenomas of the right colon and with fewer, larger polyps in the left colon. Cases with a positive family history and an *APC* pathogenic variant are clearly variant cases of FAP, as the term AFAP implies.[[244](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_244)] However, patients with no immediate family history and a lesser adenoma burden may not be found to have an *APC* pathogenic variant. The lower the polyp count the lower the probability of having an *APC* pathogenic variant. Some of these cases are now known to carry biallelic *MUTYH* pathogenic variants, although even here, the lower the adenoma count the lower the variant likelihood.[[245](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_245)]

***[AB-Comment: (Hampel) Suggest deletion. Also - re: the insurance statement - I don’t think this is true – most insurance companies require 10 adenomas based on NCCN guidelines. Medicare requires 20. I don’t know of any policies that require 15. I would delete this entire paragraph. Reference 196 is the largest study providing the likelihood of APC and biallelic MUTYH mutations based on adenoma counts and should possibly be moved here (so far, I’ve only seen it in the MUTYH section). ]***

*~~Another study evaluated 152 patients with 3 to 100 adenomas and another 107 APC pathogenic variant–negative patients with a “classic” FAP polyp burden for evidence of MUTYH pathogenic variants.[~~*[*~~37~~*](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_37)*~~] Six patients with multiple adenomas and eight with a classic FAP burden had biallelic MUTYH pathogenic variants. The authors concluded that a cut-point of about 15 adenomas was a threshold above which MUTYH testing was reasonable, and many insurance companies in the United States have adopted a policy based on this cumulative adenoma count. Similar rates for MUTYH biallelic pathogenic variants were found by others using 20 adenomas as the threshold for considering testing.[~~*[*~~245~~*](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_245)*~~]~~*

Pathogenic variants in related DNA polymerase genes *POLE* and *POLD1* have been described in families with oligopolyposis and endometrial cancer.[[246](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_246), [247](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_247)] An elegant approach was employed using whole-genome sequencing in 15 selected patients with more than ten adenomas before age 60 years. Several had a close relative with at least five adenomas who could also have whole-genome sequencing performed. All tested patients had CRC or a first-degree relative (FDR) with CRC. All had negative *APC*, *MUTYH*, and MMR gene pathogenic variant test results. No variants were found to be in common among the evaluated families. In one family, however, linkage had established shared regions, in which one shared variant was found (*POLE* p.Leu424Val; c.1270C>G), with a predicted major derangement in protein structure and function. In a validation phase, nearly 4,000 affected cases enriched for the presence of multiple adenomas were tested for this variant and compared with nearly 7,000 controls. In this exercise, 12 additional unrelated cases were found to have the L424V variant, with none of the controls having the variant. In the affected families, inheritance of multiple-adenoma risk appeared to be autosomal dominant. [Somatic variants](https://cdr.cancer.gov/cgi-bin/cdr/Filter.py?DocId=CDR0000781854&Filter=set:QC+GlossaryTermName+with+Concept+Set) in tumors were generally consistent with the otherwise typical chromosome instability pathway, as opposed to MSI or CpG island methylator phenotype (CIMP). No extracolonic manifestations were seen.

A similar approach, whole-genome testing for shared variants, with further “filtering” by linkage analysis identified a variant in the *POLD1* gene (p.Ser478Asn; c.1433G>A). This S478N variant was identified in two of the originally evaluated families, suggesting evidence of common ancestry. The validation exercise showed one patient with polyps with the variant but no controls with the variant. Somatic variant patterns were similar to the *POLE* variant. Several cases of early-onset endometrial cancer were seen. The mechanism underlying adenoma and carcinoma formation resulting from the *POLE* L424V variant appeared to be a decrease in the fidelity of replication-associated polymerase proofreading. This in turn appeared to lead to variants related to base substitution. ***Thus, this condition is referred to as Polymerase Proofreading-Associated Polyposis (PPAP).*** A subsequent study confirmed that *POLE* pathogenic variants are a rare cause of oligopolyposis and early-onset CRC.[[248](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_248)] All individuals in this study were negative for germline pathogenic variants in *APC*, *MUTYH*, and the MMR genes. The *POLE* variant L424V was found in 3 of 485 [index cases](https://cdr.cancer.gov/cgi-bin/cdr/Filter.py?DocId=CDR0000460155&Filter=set:QC+GlossaryTermName+with+Concept+Set) with colorectal polyposis and early-onset CRC. Tumors were MSI and deficient of one or more MMR proteins in two of three index cases. Somatic variants in MMR genes, possibly the result of hypermutability secondary to POLE deficiency, were detected in these two cases. ***[Comment: If approved, this text may need updating to change "hypermutated" and "greater mutational burden" to use variant terminology.] The Cancer Genome Atlas Network performed extensive sequencing analysis of 276 colorectal cancers, and found that the presence of somatic variants in the POLE gene was associated with a hypermutated phenotype with a substantially greater mutational burden than present in colorectal cancers with MSI. Thus, polymerase variants appear to generate a hyper-hypermutated genotype in the tumor.[***[***249***](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_249)***]). [AB-Comment: (Boland) Suggested text.]***

***[AB-Comment: (Boland) Suggested edits.]*** The study authors recommend consideration of *POLE* and *POLD1* testing in patients with multiple or large adenomas in whom *~~alternative~~* ***usual*** pathogenic variant testing is uninformative ***[AB-Comment: (Hampel) OR "in whom APC and MUTYH mutation testing is uninformative..."]*** and ***recommend*** surveillance akin to that afforded patients with Lynch syndrome or MAP.[[246](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_246), [247](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_247)] *POLE* and *POLD1* pathogenic variant testing is being incorporated into the new [multiple-gene (panel) tests](https://cdr.cancer.gov/cgi-bin/cdr/Filter.py?DocId=CDR0000763019&Filter=set:QC+GlossaryTermName+with+Concept+Set) for CRC susceptibility offered commercially ***along with APC and MUTYH so that a polyposis panel can be ordered up front for the patients with oligopolyposis***. ***[AB-Comment: (Hampel) Suggested text.]***

A majority of patients with oligopolyposis involving adenomas are currently not found to have an underlying predisposition when evaluated for pathogenic variants in known predisposition genes. Such cases are generally managed as if they are at an increased risk of recurrent adenomas even when the colon can be “cleared” of polyps endoscopically.

Oligopolyposis caused by juvenile polyposis syndrome (JPS) or PJS can be distinguished from adenomatous polyposis on simple endoscopic and histologic grounds. Serrated polyposis can present in highly variable fashion. ***Additionally, hamartomatous polyps are also typically observed in these conditions. [AB-Comment: (Amos) Suggested text and suggest adding a paragraph break here.]*** The World Health Organization (WHO) criteria for serrated polyposis (*~~=~~****≥***5 serrated polyps proximal to sigmoid with 2 *~~=~~****≥***1 cm, or any number of polyps proximal to sigmoid if there is a relative with serrated polyposis, or *~~>~~****≥***20 serrated polyps ***[AB-Comment: (Boland) Suggested edits.]*** anywhere in the colon) have never been validated. Furthermore, no genetic basis has been established, even in the uncommon familial cases. But cases of oligopolyposis of the serrated variety can initially be challenging to distinguish from oligoadenomatosis, particularly when there is an admixture of adenomas***, which occurs commonly.[***[***250***](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_250)***]***. Consequently, such patients are increasingly being referred for [genetic counseling](https://cdr.cancer.gov/cgi-bin/cdr/Filter.py?DocId=CDR0000044961&Filter=set:QC+GlossaryTermName+with+Concept+Set) and for consideration of genetic testing. Occasional cases of *MUTYH* biallelic pathogenic variants have been found in patients with at least some features of serrated polyposis and serrated polyps can be seen in Lynch syndrome. Generally though, the genetic workup of serrated polyposis is unrewarding.[[251](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_251), [252](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_252), [253](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_253), [254](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_254), [255](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_255)]

Hereditary mixed polyposis, characterized by histology that often includes adenomatous and hyperplastic polyps, has been associated with *GREM1* pathogenic variants in a small number of [Ashkenazi Jewish](https://cdr.cancer.gov/cgi-bin/cdr/Filter.py?DocId=CDR0000460127&Filter=set:QC+GlossaryTermName+with+Concept+Set) families. Polyp number in this syndrome is highly variable but is often in the spectrum consistent with oligopolyposis. (Refer to the [Hereditary mixed polyposis syndrome](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#_649) section of this summary for more information.)

**Lynch Syndrome**

**Introduction**

Lynch syndrome is the most common inherited CRC syndrome and accounts for approximately 3% of all newly diagnosed cases of CRC. It is an autosomal dominant condition caused by pathogenic variants in the MMR genes *MLH1* (*mutL homolog 1*), *MSH2* (*mutS homolog 2*), *MSH6* (*mutS homolog 6*), and *PMS2* (*postmeiotic segregation 2*), as well as the gene *EPCAM* (*epithelial cellular adhesion molecule*, formerly known as *TACSTD1*), in which deletions in *EPCAM* cause [epigenetic](https://cdr.cancer.gov/cgi-bin/cdr/Filter.py?DocId=CDR0000717443&Filter=set:QC+GlossaryTermName+with+Concept+Set) silencing of *MSH2*. Lynch syndrome is also associated with a predisposition for developing several extracolonic manifestations, including sebaceous adenomas and cancers of the endometrium and ovaries, stomach, small intestine, transitional cell carcinoma of the ureters and renal pelvis, hepatobiliary system, pancreas, and brain. Lynch syndrome–associated cancers exhibit MSI; therefore, tumor testing is a key component in the diagnosis of Lynch syndrome, in addition to family history. Universal tumor testing of all CRCs is now recommended as a strategy to screen for Lynch syndrome and identify those individuals who may subsequently benefit from germline genetic testing. Intensive cancer screening and surveillance strategies, including frequent colonoscopy, along with risk-reducing surgeries, are mainstays in patients with Lynch syndrome.

**History of Lynch syndrome**

Between 1913 and 1993, numerous case reports of families with apparent increases in CRC were reported. As series of such reports accumulated, certain characteristic clinical features emerged: early age at onset of CRC; high risk of synchronous (and metachronous) colorectal tumors; preferential involvement of the right colon; improved clinical outcome; and a range of associated extracolonic sites including the endometrium, ovaries, other sites in the GI tract, uroepithelium, brain, and skin (sebaceous tumors). Terms such as **cancer family syndrome**, and **hereditary nonpolyposis colorectal cancer** (**HNPCC**) were used to describe this entity.[[256](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_256)]

The term **Lynch syndrome** replaced HNPCC and is applied to cases in which the genetic basis can be confidently linked to a germline pathogenic variant in a DNA MMR gene. Moreover, HNPCC is misleading as many patients have polyps and many have tumors other than CRC.

With the increased recognition of families that were considered to have a [genetic predisposition](https://cdr.cancer.gov/cgi-bin/cdr/Filter.py?DocId=CDR0000460153&Filter=set:QC+GlossaryTermName+with+Concept+Set) to the development of CRC, research for a causative etiology led to the development of the [Amsterdam criteria](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#_1124) in 1990.[[257](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_257)] The Amsterdam criteria were originally used for the identification of high-risk families and included fulfillment of all of the following: three or more cases of CRC over two or more generations, with at least one diagnosed before age 50 years, and no evidence of FAP.

In 1987, a chromosomal deletion of a small segment of 5q led to the detection of a genetic linkage between FAP and this genomic region,[[258](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_258)] from which the *APC* gene was eventually cloned in 1991.[[259](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_259)] This led to searches for similar linkage in families suspected of having Lynch syndrome who had multiple cases of CRC inherited in an autosomal dominant fashion and young onset of cancer development. The *APC* gene was one of several genes (along with *DCC* and *MCC*) evaluated in families that fulfilled Amsterdam criteria, but no linkage was found among the Lynch kindreds. In 1993, an extended genome-wide search resulted in the recognition of a candidate chromosome 2 susceptibility [locus](https://cdr.cancer.gov/cgi-bin/cdr/Filter.py?DocId=CDR0000460162&Filter=set:QC+GlossaryTermName+with+Concept+Set) in large families. Once *MSH2*, the first Lynch syndrome–associated gene, was sequenced, it was evident from the somatic variant patterns in the CRC tumors that the MMR family of genes was likely involved. Additional MMR genes were subsequently linked to Lynch syndrome, including *MLH1*, *MSH6*, and *PMS2*. Lynch syndrome now refers to the genetic disorder caused by a germline variant in one of these DNA MMR genes, distinguishing it from other familial clusters of CRC.

In 2009, a germline deletion in the *EPCAM* gene was identified as another cause of *MSH2* inactivation in the absence of a germline pathogenic variant in *MSH2*. The variant in *EPCAM* led to hypermethylation of the *MSH2* promoter. Thus, *EPCAM*, which is not a DNA MMR gene, is also implicated in Lynch syndrome and is now routinely tested in at-risk patients along with the DNA MMR genes listed above.

**Defining Lynch syndrome families**

Families with a preponderance of CRC and a possible genetic predisposition were initially categorized as having Lynch syndrome based on family history criteria, as well as personal history of young-onset CRC. With the advent of molecular tumor diagnostic testing and the discovery of the germline alterations associated with Lynch syndrome, the clinical criteria have currently fallen out of favor due to their underperformance. However, their use, or the risk estimates provided by the Lynch syndrome prediction models, may be applicable among individuals without personal history of cancer but with a family history suggestive of Lynch syndrome, or for those individuals with CRC but without available tumor for molecular diagnostic testing. (Refer to the [Universal tumor testing to screen for Lynch syndrome](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#_1110) and the [Clinical risk assessment models that predict the likelihood of an MMR gene pathogenic variant](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#_1101) sections of this summary for more information.)

The first criteria for defining Lynch syndrome families were established by the International Collaborative Group meeting in Amsterdam in 1990 and are known as the Amsterdam criteria.[[257](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_257)] These research criteria were limited to diagnoses of familial CRC. In 1999, the Amsterdam criteria were revised to include some extracolonic cancers, predominantly endometrial cancer.[[260](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_260)] These criteria provide a general approach to identifying Lynch syndrome families, but they are not considered comprehensive; nearly half of families meeting the Amsterdam criteria do not have detectable pathogenic variants.[[261](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_261)]

***Amsterdam criteria I (1990):***

1. One family member diagnosed with CRC before age 50 years.
2. Two affected generations.
3. Three affected relatives, one of them an FDR of the other two.
4. FAP should be excluded.
5. Tumors should be verified by pathological examination.

***Amsterdam criteria II (1999):***

* Same as Amsterdam criteria I, but tumors of the endometrium, small bowel, ureter, or renal pelvis can be used to substitute an otherwise qualifying CRC.

These criteria were subsequently used beyond research purposes to identify potential candidates for [microsatellite](https://cdr.cancer.gov/cgi-bin/cdr/Filter.py?DocId=CDR0000285938&Filter=set:QC+GlossaryTermName+with+Concept+Set) and germline testing. However, the Amsterdam criteria failed to identify a substantial proportion of Lynch syndrome kindreds; families that fulfilled Amsterdam criteria I but did not have evidence of MSI and were without a pathogenic germline variant in a DNA MMR gene, were referred to as familial colorectal cancer type X (FCCX). (Refer to the [FCCX](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#_3006) section of this summary for more information.)

With the hallmark feature of MSI associated with Lynch syndrome tumors, and the limitations of the Amsterdam criteria related to low [sensitivity](https://cdr.cancer.gov/cgi-bin/cdr/Filter.py?DocId=CDR0000322883&Filter=set:QC+GlossaryTermName+with+Concept+Set), the Bethesda guidelines were introduced in 1997. The Bethesda guidelines are a combination of clinical, histopathologic, and family cancer history features that identify cases of CRC that warrant MSI tumor screening. The Bethesda guidelines (with a subsequent revision in 2004) were formulated to target patients in whom evaluation of CRC tumors for MMR deficiency should be considered, and to improve the sensitivity of clinical criteria used to identify individuals who are candidates for [mutational DNA analysis](https://cdr.cancer.gov/cgi-bin/cdr/Filter.py?DocId=CDR0000460195&Filter=set:QC+GlossaryTermName+with+Concept+Set).[[262](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_262), [263](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_263)] (Refer to the [Genetic and molecular testing for Lynch syndrome](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#_1103) section of this summary for more information about testing for MSI and IHC.)

***Bethesda guidelines (1997):***

1. Cancer in families that meet the Amsterdam criteria.
2. The presence of two Lynch syndrome–related cancers, including synchronous and metachronous CRCs or associated extracolonic cancers. *[Note: Endometrial, ovarian, gastric, hepatobiliary, or small-bowel cancer or transitional cell carcinoma of the renal pelvis or ureter.]*
3. The presence of CRC and a FDR with CRC and/or Lynch syndrome–related extracolonic cancer and/or a colorectal adenoma; one of the cancers diagnosed before age 45 years, and the adenoma diagnosed before age 40 years.
4. CRC or endometrial cancer diagnosed before age 45 years.
5. Right-sided CRC with an undifferentiated pattern (solid/cribriform) on histopathology diagnosed before age 45 years. *[Note: Solid/cribriform defined as poorly differentiated or undifferentiated carcinoma composed of irregular, solid sheets of large eosinophilic cells and containing small gland-like spaces.]*
6. Signet-ring–cell CRC diagnosed before age 45 years. *[Note: Composed of more than 50% signet ring cells.]*
7. Adenomas diagnosed before age 40 years.

***Revised Bethesda guidelines (2004)\*:***

1. CRC diagnosed in an individual younger than 50 years.
2. Presence of synchronous, metachronous colorectal, or other Lynch syndrome–associated tumors.\*\*
3. CRC with MSI-H pathologic associated features diagnosed in an individual younger than 60 years. *[Note: Presence of tumor-infiltrating lymphocytes,* [*Crohn-like lymphocytic reaction*](https://cdr.cancer.gov/cgi-bin/cdr/Filter.py?DocId=CDR0000681114&Filter=set:QC+GlossaryTermName+with+Concept+Set)*, mucinous/signet-ring differentiation, or medullary growth pattern.]*
4. CRC or Lynch syndrome–associated tumor\*\* diagnosed in at least one FDR younger than 50 years.
5. CRC or Lynch syndrome–associated tumor\*\* diagnosed at any age in two FDRs or [second-degree relatives](https://cdr.cancer.gov/cgi-bin/cdr/Filter.py?DocId=CDR0000485395&Filter=set:QC+GlossaryTermName+with+Concept+Set).

\*One criterion must be met for the tumor to be considered for MSI testing.

\*\*Lynch syndrome–associated tumors include colorectal, endometrial, stomach, ovarian, pancreatic, ureter and renal pelvis, biliary tract, and brain tumors; sebaceous gland adenomas and keratoacanthomas in Muir-Torre syndrome; and carcinoma of the small bowel.[[263](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_263), [264](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_264)]

Although the Bethesda guidelines were able to identify a higher proportion of Lynch syndrome carriers than the Amsterdam criteria, they still missed approximately 30% of Lynch syndrome families.[[265](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_265)] Furthermore, the Bethesda guidelines were not consistently used in clinical practice to identify the subset of individuals with CRC who should have MSI tumor testing; the guidelines were deemed cumbersome and difficult to remember by health care providers and the opportunity to refer for genetic evaluation was missed.[[266](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_266)]

With the advent of alternative approaches, including universal testing of all newly diagnosed cases of CRC for MSI (regardless of age at diagnosis or family history of cancer), clinical criteria for Lynch syndrome have been rendered obsolete. While the Bethesda guidelines were intended for individuals with cancer, their performance in individuals unaffected by cancer may still be of use. Given the limited modalities available to assess unaffected individuals for Lynch syndrome, family history and the use of clinical criteria may be appropriate in identifying those who warrant further genetic evaluation and testing.

**Clinical risk assessment models that predict the likelihood of an MMR gene pathogenic variant**

Because health care providers ineffectively use clinical criteria to select individuals with CRC for genetic referral and evaluation for Lynch syndrome, computer-based clinical prediction models were developed and introduced in 2006 as alternative modalities to provide systematic genetic [risk assessment](https://cdr.cancer.gov/cgi-bin/cdr/Filter.py?DocId=CDR0000460214&Filter=set:QC+GlossaryTermName+with+Concept+Set) for Lynch syndrome. The risk models include the [PREMM (PREdiction Model for gene Mutations) models](http://premm.dfci.harvard.edu/), [MMRpredict](http://hnpccpredict.hgu.mrc.ac.uk/), and [MMRpro](https://projects.iq.harvard.edu/bayesmendel/mmrpro).[[267](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_267), [268](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_268), [269](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_269), [270](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_270)]

Three models (PREMM[1,2,6], MMRpredict, and MMRpro) quantify an individual’s probability of carrying an MMR gene variant in *MLH1*, *MSH2*, and *MSH6*. The PREMM(1,2,6) model was subsequently extended to include prediction of pathogenic *PMS2* and *EPCAM* variants and is the only model to provide prediction of all five genes associated with Lynch syndrome (PREMM5).[[270](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_270)]

While the models were all created for the same purpose, they differ in the way they were developed and the variables used to predict risk. In addition, the populations in which they were validated reveal each model’s specific characteristics that may impact accuracy.[[271](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_271), [272](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_272), [273](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_273), [274](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_274), [275](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_275), [276](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_276), [277](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_277), [278](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_278), [279](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_279), [280](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_280)] Deciding on which model to use in the risk assessment process depends on both the clinical setting in which it is applied and the patient population that is being evaluated. MMRpro’s predictions account for family size and unaffected relatives, the possibility of including molecular tumor data in the risk analysis, and the option of predicting pathogenic variant carrier status following germline testing. The major limitation in the widespread use of MMRpro in routine practice is the need to input data from the entire pedigree (including individuals without cancer), which is relatively time-consuming. Its best use is likely to be as a genetic counseling tool in a specialized high-risk clinic or research setting, as its accessibility is also limited. PREMM’s major advantage is that it is easy to use, available as a web-based online tool, and has been extensively validated. It includes risk prediction based on personal and family cancer history up to second-degree relatives for a broad spectrum of extracolonic cancers. However, the model does not take into account family size and may overestimate the likelihood of a pathogenic variant in a pedigree that includes multiple elderly family members who are unaffected by CRC or endometrial cancer. Given the ease with which one can use the PREMM model (it has been deemed less time-consuming than MMRpro in validation studies),[[276](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_276)] it may be used by diverse health care providers whose primary aim is to identify patients who should be referred for genetic evaluation, and is likely to be most useful in the pretesting decision-making process. Lastly, MMRpredict’s use may be limited overall because of its less accurate risk estimates [[281](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_281)] when used to evaluate families with Lynch syndrome–associated cancers and older individuals affected by CRC; the model was developed using data from young-onset CRC cases (patients diagnosed at age <55 y) and did not include extracolonic malignancies. Furthermore, the model does not incorporate tumor testing results or provide post-hoc risk estimates based on gene sequencing results.

Overall, there is ample evidence that each of the models has superior performance characteristics of sensitivity, [specificity](https://cdr.cancer.gov/cgi-bin/cdr/Filter.py?DocId=CDR0000322884&Filter=set:QC+GlossaryTermName+with+Concept+Set), and [positive](https://cdr.cancer.gov/cgi-bin/cdr/Filter.py?DocId=CDR0000460206&Filter=set:QC+GlossaryTermName+with+Concept+Set) and [negative predictive values](https://cdr.cancer.gov/cgi-bin/cdr/Filter.py?DocId=CDR0000460198&Filter=set:QC+GlossaryTermName+with+Concept+Set) that support their use when compared with the existing clinical guidelines for diagnosis and evaluation of Lynch syndrome. Because of the diverse clinical settings in which a health care provider has the opportunity to assess an individual for Lynch syndrome, prediction models offer a potentially feasible and useful strategy to systematically identify at-risk individuals, whether or not they are affected with CRC.

**Summary**

In conclusion, the presence of tumor MSI in CRCs, along with a compelling personal and family history of cancer, warrants germline genetic testing for Lynch syndrome, and most clinical practice guidelines provide for such an approach. These guidelines combine genetic counseling and testing strategies with clinical screening and treatment measures. Providers and patients alike can use these guidelines to better understand available options and key decisions. (Refer to [Table 18](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#_3025) for more information about practice guidelines for diagnosis and colon surveillance in Lynch syndrome.)

**Genetics of Lynch syndrome**

The genetics of both the tumor and the germline have an important role in the development and diagnosis of Lynch syndrome. Tumor DNA in Lynch syndrome–associated tumors exhibits characteristic MSI, and in these cases, there is typically loss of IHC expression for one or more of the proteins associated with the MMR genes. Molecular testing with MSI and/or IHC has been adopted as a universal screen for diagnosis of Lynch syndrome in newly diagnosed patients with CRC and endometrial cancer. IHC testing results can potentially direct gene-specific germline testing. Many genetic testing laboratories offer multigene (panel) tests that simultaneously test for pathogenic variants in all of the Lynch syndrome–associated genes (and often additional genes associated with inherited cancer susceptibility).

**Genetic and molecular testing for Lynch syndrome**

**MSI**

The presence of MSI in colorectal tumor specimens is a hallmark feature of Lynch syndrome and can be cause for suspicion of a germline pathogenic MMR gene variant. Microsatellites are short, repetitive sequences of DNA (mononucleotides, dinucleotides, trinucleotides, or tetranucleotides) located throughout the genome, primarily in intronic or intergenic sequences.[[282](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_282), [283](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_283)] The term MSI is used when colorectal, endometrial, or metastatic tumor DNA [[284](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_284)] shows insertions or deletions in microsatellite regions when compared with normal tissue. MSI indicates probable defects in MMR genes, which may be due to somatic variants, germline variants, or [epigenetic alterations](https://cdr.cancer.gov/cgi-bin/cdr/Filter.py?DocId=CDR0000717446&Filter=set:QC+GlossaryTermName+with+Concept+Set).[[285](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_285)] In most instances, MSI is associated with absence of protein expression of one or more of the MMR proteins (MSH2, MLH1, MSH6, and PMS2). However, loss of protein expression may not be seen in all tumors with MSI and not all tumors with loss of protein expression on IHC will be microsatellite unstable.

Certain histopathologic features are strongly suggestive of MSI phenotype, including the presence of tumor-infiltrating lymphocytes (refer to [Figure 5](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#_3123)), Crohn-like reaction, mucinous histology, absence of [dirty necrosis](https://cdr.cancer.gov/cgi-bin/cdr/Filter.py?DocId=CDR0000580966&Filter=set:QC+GlossaryTermName+with+Concept+Set), and histologic heterogeneity.[[286](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_286)]

**Image:** tumor-infiltrating lymphocytes

*Figure 5. Tumor-infiltrating lymphocytes are a histopathologic feature suggestive of microsatellite instability.*

Initial designation of a colorectal adenocarcinoma as microsatellite unstable was based on the detection of a specified percentage of unstable loci from a panel of three dinucleotide and two mononucleotide repeats that were selected at a National Institutes of Health (NIH) Consensus Conference and referred to as the Bethesda panel. If more than 30% of a tumor's [markers](https://cdr.cancer.gov/cgi-bin/cdr/Filter.py?DocId=CDR0000046129&Filter=set:QC+GlossaryTermName+with+Concept+Set) were unstable, it was scored as MSI-H; if at least one, but fewer than 30% of markers were unstable, the tumor was designated MSI-low (MSI-L). If no loci were unstable, the tumor was designated microsatellite stable (MSS). Most tumors arising in the setting of Lynch syndrome will be MSI-H.[[287](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_287)] The clinical relevance of MSI-L tumors remains controversial; the probability is very small that these tumors are associated with a germline pathogenic variant in an MMR gene.

The original Bethesda panel has been replaced by a pentaplex panel of five mononucleotide repeats,[[287](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_287)] which has improved the detection of MSI-H tumors.

(Refer to the [Prognostic and therapeutic implications of MSI](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#_3065) section of this summary for more information about the treatment implications of MSI testing.)

(Refer to the [Universal tumor testing to screen for Lynch syndrome](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#_1110) section of this summary for information about the utilization of MSI status in the diagnostic workup of a patient with suspected Lynch syndrome.)

**IHC**

IHC methods are cheaper, easier to understand, and more widely available as a surrogate for MSI and, for these reasons, have replaced [polymerase chain reaction](https://cdr.cancer.gov/cgi-bin/cdr/Filter.py?DocId=CDR0000044798&Filter=set:QC+GlossaryTermName+with+Concept+Set) (PCR)–based MSI testing in most institutions. IHC is performed in the colorectal or endometrial tumor (or metastatic sites) [[284](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_284)] for protein expression using monoclonal antibodies for the MLH1, MSH2, MSH6, and PMS2 proteins. Isolated loss of expression of any one of these proteins may suggest which specific MMR gene is altered in a particular patient.[[288](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_288), [289](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_289), [290](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_290), [291](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_291)] However, certain proteins can form heterodimers (or have other binding partners) and yield loss of two proteins expressed on IHC.

MSI can lead to nucleotide-pairing slippage (looping) in which single nucleotide mispairs are introduced. Heterodimers of MMR proteins are formed to identify the errors and bind the DNA at these sites.[[285](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_285), [292](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_292)] For example, MSH2 protein complexes with MSH6 protein to form MutSα, which has the main ability to repair single [base pair](https://cdr.cancer.gov/cgi-bin/cdr/Filter.py?DocId=CDR0000460130&Filter=set:QC+GlossaryTermName+with+Concept+Set) mismatches and single base pair loop-out lesions that can occur during the replication of a mononucleotide repeat sequence. In the absence of MSH6 protein, the MSH2 protein will dimerize with the MSH3 protein forming the MutSβ complex, which has the ability to trigger repair of larger loop-out DNA mismatches, but also has some overlapping activity to repair lesions usually repaired by MutSα.

**Image:** immunohistochemical tumor testing for MMR proteins

*Figure 6. Immunohistochemical tumor testing for protein expression of the mismatch repair genes associated with Lynch syndrome, depicted for a single patient with colorectal cancer. Protein expression is preserved for MSH2 and MSH6 (inset) and absent for MLH1 and PMS2 (inset). Absence of MMR protein expression is suggestive of Lynch syndrome and warrants additional evaluation.*

As a result, when the germline pathogenic variant is in the *MSH2* gene, the tumor IHC may not express both MSH2 and MSH6, as the latter protein requires binding to MSH2 for stability. In this case, if no pathogenic variant is found in either gene, germline pathogenic variant testing for *EPCAM* should be considered if it was not already included. Approximately 20% of patients with absence of MSH2 and MSH6 protein expression by IHC and no *MSH2* or *MSH6* pathogenic variant identified will have germline deletions in *EPCAM*.[[293](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_293)] The latter mechanism accounts for approximately 5% of all Lynch syndrome cases.[[293](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_293)] A deletion in one allele of exon 9 of the *EPCAM* (*TACSTD1*) gene, which is immediately upstream of the start site of *MSH2* and in the same orientation, can lead to [transcriptional](https://cdr.cancer.gov/cgi-bin/cdr/Filter.py?DocId=CDR0000390290&Filter=set:QC+GlossaryTermName+with+Concept+Set) read-through and methylation of the *MSH2* promoter, and subsequent silencing of *MSH2* in any tissue that expresses *EPCAM*. The presence of *EPCAM* pathogenic variants showing similar methylation-mediated MSH2 loss has been reported in numerous families.[[294](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_294)] On the strength of these observations, germline *EPCAM* testing is performed in patients with loss of MSH2 protein expression on IHC testing of their CRCs but who lack a detectable *MSH2* germline pathogenic variant and is included with *MSH2* testing in all colon cancer gene panels.

In patients with no variants in any of these genes, tumor sequencing may reveal double somatic *MSH2* variants. (Refer to the [*EPCAM*](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#_1130) and [Lynch-like or HNPCC-like syndrome](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#_3007) sections of this summary for more information.)

Similarly, the loss of *MLH1* (either by germline pathogenic variant or hypermethylation of the *MLH1* promoter) results in the absence of expression of both MLH1 and PMS2 proteins in the tumor. The most common abnormal IHC pattern for DNA MMR proteins in colorectal adenocarcinomas is loss of expression of MLH1 and PMS2. PMS2 and MLH1 function as a stable heterodimer known as MutLα. MutLα binds to MutSβ and guides excision repair of the newly synthesized DNA strand.[[285](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_285)] A functional defect in *MLH1* results in degradation of both MLH1 and PMS2, while a defect in *PMS2* negatively affects only PMS2 expression. Thus, a loss of MLH1 and PMS2 indicates an alteration in *MLH1* (promoter hypermethylation or germline variant), while loss of PMS2 expression indicates a germline *PMS2* variant. However, among 88 individuals with PMS2-deficient CRC, *PMS2* germline pathogenic variant testing followed by *MLH1* germline pathogenic variant testing revealed pathogenic *PMS2* variants in 49 individuals (74%) and *MLH1* pathogenic variants in 8 individuals (12%).[[295](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_295)] Eighty-three percent of the alterations in *MLH1* were missense variants, but two relatives carried identical *MLH1* variants, and one individual, who developed two tumors with retained MLH1 expression, carried an intronic variant that led to skipping of exon 8.[[295](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_295)] Therefore, in CRCs with solitary loss of PMS2 expression, an *MLH1* germline pathogenic variant should be sought if no *PMS2* germline variant is found. Tumors with MSI and loss of MSH2 and MSH6 protein expression are generally indicative of an underlying *MSH2* germline variant (inferred *MSH2* pathogenic variant). Unlike the case with *MLH1*, MSI with MSH2 loss is rarely associated with somatic hypermethylation of the promoter.

Unlike MLH1 and MSH2 (which both dimerize with other proteins or have other binding partners), germline pathogenic variants in *MSH6* and *PMS2* result in the isolated loss of those specific proteins by IHC. However, tumors from *MSH6* pathogenic variant carriers may not display the MSI phenotype at a frequency as high as *MLH1* and *MSH2* carriers (despite an inactive DNA MMR system), as there are pathogenic missense variants that do not completely abrogate protein expression yielding false negative results by IHC testing.[[275](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_275), [296](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_296)] In a study that reported tumor testing results among MMR germline carriers enrolled through the Colon Cancer Family Registry, 7 of 24 carriers (28%) with *MSH6* pathogenic variants had tumors that displayed normal protein expression on IHC staining. IHC tumor testing was more informative for *MLH1* and *MSH2* pathogenic variant carriers in which 93% of *MLH1* carriers had correlating loss of MLH1 protein expression and 96% of *MSH2* carriers had loss of MSH2 protein expression.[[275](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_275)]

In some cases, tumors manifest MSI and/or IHC shows loss of DNA MMR protein expression, but no germline pathogenic variant is identified. This condition is known as *Lynch-like* (or *HNPCC-like*) syndrome and the tumor phenotype is predominantly due to biallelic somatic inactivation of DNA MMR genes and not a pathogenic germline alteration. (Refer to the [Lynch syndrome–related syndromes](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#_1135) section of this summary for more information.)

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| **Table 14. Protein Loss and Potential Germline Defect(s)** |
| **Loss of Protein Expression**  | **Germline MMR Defect Predicted by IHC Protein Expression Loss**  |
|   | ***MLH1***  | ***MSH2***  | ***MSH6***  | ***PMS2***  | ***EPCAM***  |
| MLH1/PMS2  | X  |   |   |   |   |
| MSH2/MSH6  |   | X  |   |   | X  |
| MSH6  |   |   | X  |   |   |
| PMS2  | X  |   |   | X  |   |
| MLH1  | X  |   |   |   |   |
| MSH2  |   | X  |   |   |   |

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| *IHC = immunohistochemistry; MMR = mismatch repair.* |

**Somatic *MLH1* hypermethylation**

It is important to recognize that hypermethylation of the *MLH1* promoter, a somatic event confined to the tumor, can lead to abnormal protein expression of MLH1 on IHC. Approximately 10% to 15% of sporadic CRC cases have a microsatellite unstable tumor phenotype due to *MLH1* hypermethylation and are not heritable. These sporadic MSI colon cancers [[297](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_297)] have a generalized excess of DNA methylation referred to as CIMP.[[298](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_298)] (Refer to the [CIMP and the serrated polyposis pathway](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#_1337) section in the [Introduction](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#_1) section of this summary for more information.) Because loss of MLH1 protein expression on IHC occurs in both Lynch syndrome and sporadic tumors, its specificity for predicting germline MMR gene variants is lower than for the other MMR proteins, and additional molecular testing is often necessary to clarify the etiology of MLH1 absence.

*BRAF* pathogenic variants have been detected in 68% of CRC tumors with *MLH1* promoter hypermethylation and very rarely, if ever, in CRC from patients with Lynch syndrome.[[299](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_299), [300](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_300), [301](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_301), [302](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_302)] This suggests that detection of somatic *BRAF* V600E pathogenic variant detection in CRC may be useful in excluding individuals from germline variant testing. As a result, *BRAF* V600 testing and/or *MLH1* hypermethylation assays are increasingly utilized in universal Lynch syndrome–testing algorithms in an attempt to distinguish between an absence of MLH1 protein expression caused by hypermethylation and germline *MLH1* pathogenic variants. Making such a distinction is also a more cost-effective approach in excluding individuals from germline testing.

**Biallelic mismatch repair deficiency (BMMRD)**

***[Comment: Revisions to this section approved by WG 5/1/18.]***

Rarely, patients with MMR gene variants carry such variants in both parental alleles. When two variant alleles are identified, whether homozygous ~~(implicating consanguinity)~~ or compound heterozygous, this is termed *biallelic mismatch repair deficiency* (BMMRD) or *constitutional mismatch repair deficiency* (CMMRD). **The likelihood of BMMRD involving homozygous MMR gene pathogenic variants will inevitably be higher among consanguineous unions. The incidence of consanguinity may be higher in rural and otherwise geographically and/or culturally isolated populations.[**[**303**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_303)**]**

Tumor studies yield characteristic abnormalities. In a series of 28 patients with BMMRD,[[304](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_304)] 17 brain tumors showed loss of staining for the MMR protein **in the normal stromal cells in addition to neoplastic cells, in**~~. In notable~~ contradistinction from tumors in patients with Lynch syndrome in which normal staining is retained in nontumor cells~~, all tumors from this series showed loss of staining in the normal stromal tissues as well~~. In contrast to this characteristic feature seen with IHC, PCR-based MSI analysis was not reliable, as 20 of 28 tumors were MSS. Of the tumors that were MSI-H, essentially all were colon cancers.

The *PMS2* gene is markedly overrepresented in cases of BMMRD. It has been suggested that the presence of homozygosity of variants in the other MMR genes is a prenatally lethal state, while the otherwise milder expression of *PMS2* is consistent with survival when present in both parental alleles.

(Refer to the [BMMRD](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#_3105) section in the [Prevalence, clinical manifestations, and cancer risks associated with Lynch syndrome](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#_1113) section for more information about the clinical phenotype of BMMRD.)

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| **Table 15. Hereditary Colorectal Cancer (CRC) Syndromes and Associated Tumor Phenotypea** |
| **Clinical Phenotype**  | **Pathogenic Germline Variant in DNA MMR**  | **Somatic Inactivation of DNA MMR**  | **Tumor Phenotype**  |
| Lynch syndrome  | Present in one allele  | Present in one allele  | MSI  |
| Sporadic CRC with hypermethylation of *MLH1* promoter  | Absent  | +*BRAF*  | MSI  |
| BMMRD   | Present in two alleles  | Absent  | MSI (tumor and normal tissue)  |
| Lynch-like  | Absent  | Present in two alleles  | MSI  |
| FCCX  | Absent  | Absent  | MSS  |

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| *BMMRD = biallelic mismatch repair deficiency; FCCX = familial colorectal cancer type X; MMR = mismatch repair; MSI = microsatellite instability; MSS = microsatellite stable.*  |
| *aAdapted from Carethers et al.[*[*305*](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_305)*]* |

**Constitutional epimutation**

***[Comment: This is an exception - we will use the term "constitutional epimutation" (rather than constitutional epivariant) in this section since that is how it is referred to in the literature.]***

While somatic hypermethylation of the *MLH1* promoter is acquired and not uncommon, examples of *MLH1* promoter hypermethylation have been described in the germline and are generally not associated with a stable Mendelian inheritance. This constitutional methylation of MMR genes occurs most often in *MLH1* and, to a lesser extent, *MSH2* and is termed *constitutional* [*epimutation*](https://cdr.cancer.gov/cgi-bin/cdr/Filter.py?DocId=CDR0000717445&Filter=set:QC+GlossaryTermName+with+Concept+Set).[[306](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_306)] A constitutional epimutation (also referred to as a primary epimutation) is an acquired alteration in normal tissue that silences an active gene or activates an inactive gene.[[307](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_307)] Such epimutations occur most often in maternal alleles. In some cases all somatic cells appear involved, while in others there is evidence of [mosaicism](https://cdr.cancer.gov/cgi-bin/cdr/Filter.py?DocId=CDR0000460197&Filter=set:QC+GlossaryTermName+with+Concept+Set). Tumors in patients with primary epimutations are generally indistinguishable from those otherwise typical of Lynch syndrome germline variant carriers, including age at onset, tumor spectrum, and presence of abnormal MSI and IHC. Since these are not inherited in a Mendelian fashion, antecedent family history of tumors is minimal, and risk to offspring somewhat unpredictable. Epimutations present in a [de novo](https://cdr.cancer.gov/cgi-bin/cdr/Filter.py?DocId=CDR0000783882&Filter=set:QC+GlossaryTermName+with+Concept+Set) case seem to typically be "erased" in the process of gametogenesis and to not be passed to the next generation. Very rare cases of inherited *MLH1* epimutations have been reported.[[308](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_308), [309](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_309)]

Interpreting molecular alterations in tumors and distinguishing the likely primary epimutation cases from those of sporadic MSI poses significant challenges. Most instances of absence of MLH1 expression are caused by the sporadic hypermethylation of the *MLH1* promoter. Rare instances of a de novo constitutional epimutation in *MLH1* [[310](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_310)] or an inherited germline *MLH1* methylation [[311](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_311)] add some complexity to the interpretation of MSI associated with absence of MLH1 expression. Akin to sporadic MSI, primary epimutation tumors show methylation of the *MLH1* promotor and may show *BRAF* variants as well. As noted above, family history of cancer in such cases tends to be minimal or absent, as in true sporadic MSI. Distinguishing such cases from sporadic cases may call for assaying normal tissue (e.g., blood or normal colon mucosa) for evidence of *MLH1* methylation, which will be absent from true sporadic cases and absent from carriers of conventional Lynch syndrome MMR pathogenic variants.

Such *MLH1*-predominant primary epimutations are to be distinguished from secondary epimutations such as those occurring when *MSH2* is methylated as a consequence of inherited variants in the upstream *EPCAM* gene. (Refer to the [*EPCAM*](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#_1130) section of this summary for more information.)

**Molecular diagnostic tumor testing to screen for Lynch syndrome in clinical practice**

While many molecular pathology laboratories can assess both MSI and IHC, an approach that uses IHC testing as the initial screen for defective MMR activity has been favored because it is less labor intensive and more cost-effective.[[312](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_312), [313](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_313)] Part of this rationale is that the information provided by IHC may target germline genetic testing toward one specific MMR gene (with the exception of loss of MLH1 expression) as opposed to a comprehensive testing strategy of all Lynch syndrome–related MMR genes that would be directed by the use of MSI alone.[[265](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_265), [312](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_312), [314](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_314), [315](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_315), [316](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_316), [317](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_317)] While MSI testing was originally favored in the oncologic evaluation of individuals with CRC for its prognostic and therapeutic implications, screening for Lynch syndrome can be more effectively directed by IHC testing.

**Universal tumor testing to screen for Lynch syndrome**

Use of MSI and/or IHC testing in all newly diagnosed cases of CRC, regardless of the age at diagnosis or family history of cancer, increases the sensitivity of the initial screen for Lynch syndrome, especially for carriers of *MSH6* and *PMS2* pathogenic variants. This approach is more sensitive than existing clinical criteria, as many individuals with Lynch syndrome are diagnosed at older ages (>50 y) and have less striking family histories of CRC than previously appreciated. This universal testing of colorectal (and [endometrial](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#_1322)) tumors using either MSI or IHC testing has been recommended by many professional organizations and is being widely adopted.[[102](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_102), [318](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_318), [319](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_319), [320](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_320), [321](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_321)]

Genetic risk assessment and MMR gene variant testing in individuals with newly diagnosed CRC can lead to improved outcomes for the patient and at-risk family members. Dating back to 2009, the Evaluation of Genomic Applications in Practice and Prevention (EGAPP), a project developed by the Office of Public Health Genomics at the Centers for Disease Control and Prevention (CDC), reported that there was sufficient evidence to recommend offering tumor screening for Lynch syndrome to individuals with newly diagnosed CRC to reduce morbidity and mortality in relatives.[[322](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_322), [323](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_323)] At that time, there was insufficient evidence to recommend a specific testing strategy between MSI and IHC.

Several studies have demonstrated the feasibility of universal screening for Lynch syndrome. Initial experience from one institution found that among 1,566 patients screened using MSI and IHC, 44 patients (2.8%) had Lynch syndrome. For each proband, an average of three additional family members were subsequently diagnosed with Lynch syndrome.[[265](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_265)] A subsequent pooled analysis of 10,206 incident CRC patients tested with MSI/IHC as part of four large studies revealed a pathogenic variant detection rate of 3.1%.[[324](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_324)] This study compared four strategies for tumor testing for the diagnosis of Lynch syndrome: (1) testing all individuals meeting at least one criterion of the Bethesda guidelines; (2) testing all individuals meeting Jerusalem recommendations;[[325](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_325)] (3) testing all individuals with CRC aged 70 years or younger, or older than 70 and meeting at least one criterion of the Bethesda guidelines; and (4) universal testing of all individuals with CRC.[[324](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_324)] Tumor testing with MSI involved panels individualized at each institution and IHC involved testing all four of the DNA MMR genes involved with Lynch syndrome, across all institutions. The strategy of tumor testing in all individuals diagnosed with CRC at age 70 years or younger and testing individuals over age 70 who met one of the revised Bethesda guidelines yielded a sensitivity of 95.1%, a specificity of 95.5%, and a diagnostic yield of 2.1%. This strategy missed 4.9% of Lynch syndrome cases, but 34.8% fewer cases required IHC/MSI testing, and 28.6% fewer cases underwent germline testing than in the universal approach.

The consideration to further stratify the recommendation for molecular tumor testing by age (i.e., 70 y) warrants attention as it influences the cost-effectiveness of universal screening strategy.

Loss of MLH1 and PMS2 due to somatic hypermethylation is not uncommon, and is more frequently detected with increasing age at CRC diagnosis.[[326](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_326)] Therefore, additional molecular tumor testing including *BRAF* and *MLH1* hypermethylation testing is recommended in cases in which there is loss of MLH1 and PMS2 expression on IHC, thereby decreasing the number of individuals referred for unnecessary germline genetic testing. A testing strategy including *MLH1* hypermethylation analyses in individuals aged 70 years or younger with CRC who had loss of MLH1 on IHC was shown to be cost-effective in a population-based study of 1,117 individuals.[[327](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_327)]

Screening individuals with CRC for Lynch syndrome is most often performed in a stepwise fashion based on IHC tumor testing results that evaluate protein expression for the four MMR genes related to Lynch syndrome. One proposed strategy is summarized in [Figure 7](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#_3125). This framework does not incorporate a germline testing approach that simultaneously evaluates multiple cancer susceptibility genes (multigene [panel] testing), which may be useful in select patient populations. (Refer to the [Multigene [panel] testing](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#_1112) section of this summary for more information.)

**Image:** CRC testing strategy

*Figure 7. A proposed strategy to evaluate individuals with colorectal cancer for Lynch syndrome based on immunohistochemical tumor testing results. Adapted from Geiersbach KB, Samowitz WS. Microsatellite instability and cancer. Arch Pathol Lab Med 135(10):1269-77, 2011.*

**Cost-effectiveness of universal tumor screening for Lynch syndrome**

Results are available from a Markov model that incorporated the risks of colorectal, endometrial, and ovarian cancers to estimate the effectiveness and cost-effectiveness of strategies to identify Lynch syndrome among persons aged 70 years or younger with newly diagnosed CRC .[[313](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_313)] The strategies incorporated in the model were based on clinical criteria, prediction algorithms, and tumor testing or up-front germline pathogenic variant testing followed by directed screening and risk-reducing surgery. IHC followed by *BRAF* pathogenic variant testing was the preferred strategy in this study. An incremental cost-effectiveness ratio of $36,200 per life-year gained resulted from this strategy. In this model, the number of relatives tested (3–4) per proband was a critical determinant of both effectiveness and cost-effectiveness. These results were similar to earlier analyses conducted by EGAPP which found that the most cost-effective approach was to test all tumors for absence of protein expression of MSH2, MLH1, MSH6, and PMS2 followed by targeted germline testing of *MSH2*, *MLH1*, or *MSH6* offered depending on which protein was absent. If there was absence of MLH1, testing was offered for *BRAF* variant-negative tumors.[[323](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_323)]

Currently, NCCN 2017 guidelines support either (1) IHC or MSI testing of all CRCs; or (2) IHC or MSI testing of CRCs in patients diagnosed before age 70 years, and in patients aged 70 years or older who meet Bethesda guidelines.[[102](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_102)] Universal screening in all individuals irrespective of age was associated with a doubling of incremental cost per life-year saved compared with screening only those younger than 70 years.[[313](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_313)] The authors of this analysis conclude that screening individuals younger than 70 years appears reasonable, while screening all individuals regardless of age might also be acceptable, depending on willingness to pay.

However, it is important to note that the conclusions from this study were contingent upon the number of at-risk relatives who underwent germline testing (through a process known as [*cascade screening*](https://cdr.cancer.gov/cgi-bin/cdr/Filter.py?DocId=CDR0000791164&Filter=set:QC+GlossaryTermName+with+Concept+Set)) based on the identification of a germline MMR gene variant in the index case of CRC in the family. In their model, to meet the accepted $50,000 cost-effective threshold, testing a minimum of three to four relatives was necessary.[[313](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_313)] This emphasizes the importance of provider-to-patient communication, family communication, and the need to ensure improved uptake of germline testing in Lynch syndrome families with a known causative gene. (Refer to the [Psychosocial Issues in Hereditary Colon Cancer Syndromes](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#_189) section of this summary for more information about family communication and uptake of genetic testing in families with Lynch syndrome.)

Another study addressed the cost-effectiveness of testing for pathogenic variants in the Lynch syndrome–associated genes and evaluated 21 screening strategies, including clinical criteria, use of clinical Lynch syndrome prediction models, and molecular tumor testing.[[328](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_328)] The model included two steps: (1) measurement of the newly identified number of Lynch syndrome diagnoses; and (2) measurement of the life-years gained as a result of confirming Lynch syndrome in a healthy carrier. Among all of the strategies modeled, screening the proband with a predictive model such as PREMM(1,2,6) followed by IHC for MMR protein expression and germline genetic testing was the best approach, with an incremental cost-effectiveness ratio of $35,143 per life-year gained. Germline genetic testing on all probands was the most effective approach, but at a cost of $996,878 per life-year gained. The authors concluded that the initial step of Lynch syndrome screening should utilize a predictive model in the proband, and that both universal testing and general population screening strategies were not cost-effective screening strategies for Lynch syndrome.

Establishment of an upper age limit for universal tumor testing remains controversial. Some experts have endorsed testing only individuals with CRC who are younger than 70 years (reserving testing in individuals ≥70 y for only those meeting the revised Bethesda criteria; with this strategy, 5% of carriers would be missed).[[102](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_102), [329](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_329)] However, others have advocated against an upper age limit for testing given the potential benefit to younger generations via cascade screening and the opportunity for increased surveillance and other prophylactic interventions in individuals found to carry a known familial pathogenic variant.

Another cost-effectiveness analysis was performed using data from 179 consecutive endometrial cancer patients diagnosed at or before age 70 years and screened with MMR IHC and reflex *MLH1* promoter hypermethylation, among whom seven Lynch syndrome carriers (3.9%) were identified.[[330](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_330)] Only one of the seven Lynch syndrome probands was age 50 years or younger at endometrial cancer diagnosis. The authors calculated that screening women diagnosed with endometrial cancer at age 51 to 70 years resulted in an additional 29.3 life-years gained (on top of the 45.4 life-years gained by screening women diagnosed at age ≤50 y), and the incremental cost-effectiveness ratio for screening all diagnoses at age 70 years or younger versus diagnoses at age 50 years or younger was 5,252 euro per life-year gained. Universal tumor-based screening of all women age 70 years or younger was also cost-effective, compared with strategies using the Bethesda guidelines to guide MMR and MSI testing with an incremental cost-effectiveness ratio of 6,668 euro per life-year gained.

The cost-effectiveness of universal tumor testing in both CRC and endometrial cancer is largely driven by the assumption of cascade screening through which other at-risk family members will be identified, tested, and subsequently pursue their own cancer risk reduction.[[313](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_313)]

The cost of germline genetic testing continues to decrease with advancements in DNA mutational analyses, including simultaneous testing of multiple germline variants associated with malignancy, through multigene (panel) tests. As a result, additional cost-effective analyses using more updated data related to germline testing will need to be conducted. Multigene (panel) testing may become a more favorable and cost-effective approach in the future.

**Considerations and limitations related to universal tumor testing for Lynch syndrome**

While universal screening continues to be adopted nationally, there is significant variability in the uptake and approach to molecular testing. A 2011 survey of the National Society of Genetic Counselors revealed that more than 25% of respondents had some form of universal screening implemented at their center. Tumor screening methods varied; 34 (64.2%) of 53 centers started with IHC, 11 (20.8%) of 53 centers started with MSI testing, and 8 (15.1%) of 53 centers performed both tests on newly diagnosed colorectal tumors.[[331](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_331)] A 2012 survey suggested that some form of universal screening was being routinely performed at 71% of the National Cancer Institute (NCI) Comprehensive Cancer Centers, but utilization dropped to 15% among a random sample of community hospital cancer programs.[[332](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_332)]

Because adherence to universal screening for Lynch syndrome may be poor (many patients are not referred for genetic evaluation and testing), a prospective quality improvement study utilizing the Six Sigma conceptual framework was conducted to improve the implementation of universal genetic screening among young patients with CRC.[[333](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_333)] The main aim of the study was to increase the proportion of tumor studies for deficient MMR among patients with early-onset CRC (aged 18–50 y). The intervention involved patient and provider education, in addition to visual cues provided at point of care. The study demonstrated an improvement of 21.5% in the rate of IHC testing in young adults with CRC over the 12-month postintervention period compared with the preintervention period.

Studies reporting uptake of genetic testing for Lynch syndrome have largely focused on individuals and families who were selected for potential risk of Lynch syndrome based on family history or clinical characteristics. While universal tumor screening is increasingly being adopted to identify newly diagnosed patients who may have a germline variant, few studies have examined the uptake of genetic testing after universal tumor testing. An important implication of universal screening for Lynch syndrome is that it does not result in automatic germline testing in appropriate individuals. In the clinical setting, more follow-up by health care teams to facilitate referral to genetic counseling for patients with abnormal tumor screening results may improve completion of genetic testing.[[334](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_334)] Higher levels of patient completion of genetic testing after abnormal tumor screening may be associated with having genetic counselors involved in this process to disclose screen-positive results, provide counseling after tumor testing, or facilitate referrals.[[335](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_335)]

Subsequent genetic counseling requires coordination between the pathologist, the referring surgeon or oncologist, and a cancer genetics service. As an illustration, a population-based screening study found that only 54% of patients with an IHC-deficient tumor (that was *BRAF* pathogenic variant–negative) ultimately consented to and proceeded with germline MMR testing.[[336](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_336)] One institution found 21 pathogenic variants among 1,100 patients who underwent routine MSI and IHC testing after a diagnosis of CRC. This study found markedly increased uptake of genetic counseling and germline MMR gene testing when both the surgeon and a genetic counselor received a copy of abnormal MSI/IHC results, especially when the genetic counselor played an active role in patient follow-up.[[334](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_334)]

In contrast to tumor testing, which is commonly performed without a patient's prior knowledge, germline genetic testing, such as germline testing for MMR pathogenic variants, generally includes genetic counseling and requires patient permission before it is performed. A cross-sectional survey of U.S. cancer programs (20 NCI–designated Comprehensive Cancer Centers and 49 community hospital cancer programs) found that, of those that performed MSI and/or IHC testing as part of standard pathologic evaluation at the time of colon cancer diagnosis in all or select cases, none required written [informed consent](https://cdr.cancer.gov/cgi-bin/cdr/Filter.py?DocId=CDR0000044677&Filter=set:QC+GlossaryTermName+with+Concept+Set) before tumor testing.[[332](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_332)]

**Diagnostic strategies for all individuals diagnosed with endometrial cancer**

Given the increased prevalence of endometrial cancer among carriers of MMR pathogenic variants, there is a growing consensus to screen patients with endometrial cancer for Lynch syndrome.

In a study that examined the feasibility and desirability of performing tumor screening of all endometrial cancers, regardless of age at diagnosis or family history of cancer, at least 2.3% (95% CI, 1.3%–4.0%) of newly diagnosed patients had Lynch syndrome.[[337](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_337), [338](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_338)] Eight of thirteen cases diagnosed with Lynch syndrome were aged 50 years or older, eight did not meet published family history criteria for Lynch syndrome, and two would have been missed by MSI testing. Because of the increased prevalence of endometrial cancer and the results of this study, the authors support universal screening of endometrial cancers for Lynch syndrome. (Refer to the [IHC](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#_1105) section of this summary for more information about performing IHC for MMR protein expression.)

Another smaller study of 242 consecutive endometrial cases demonstrated a 4.5% (11/242) prevalence of MMR-deficient cases lacking somatic *MLH1* promoter hypermethylation, including four cases (1.7%) with germline MMR mutations, four cases (1.7%) with two somatic MMR alterations on next-generation sequencing, and two cases (0.8%) with otherwise unexplained MMR-deficiency.[[339](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_339)] Such findings demonstrate that universal MMR tumor screening of endometrial cancers will identify individuals with underlying Lynch syndrome and a spectrum of non-Lynch syndrome cases with various forms of MMR-deficiency.

The cost-effectiveness of tumor testing of women diagnosed with endometrial cancer was examined in a model-based simulation study and included IHC testing in the following scenarios: (1) diagnosis before age 50 years; (2) diagnosis before age 60 years; (3) any age at diagnosis with the presence of an FDR with any Lynch syndrome–associated cancer; and (4) all cases irrespective of diagnosis age and family history. Women fulfilling Amsterdam II criteria or those diagnosed before age 50 years with at least one FDR with any Lynch syndrome–associated cancer were directly referred for genetic counseling and genetic testing without IHC testing. A strategy of IHC testing for MMR protein expression in all patients with endometrial cancer and an FDR with any Lynch syndrome–associated cancer was reported to be cost-effective in the detection of Lynch syndrome.[[340](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_340)] This strategy had an incremental cost ratio of $9,126 per life-year gained relative to the least-costly strategy, which was genetic testing on all women diagnosed with endometrial cancer before age 50 years with at least one FDR with a Lynch syndrome–related cancer. Life expectancy was highest with the most inclusive testing strategy of IHC testing of all women with endometrial cancer irrespective of age at diagnosis or family history, but had the least favorable incremental cost ratio of $648,494 per life-year gained. NCCN recommends tumor testing with IHC and/or MSI, Lynch syndrome–specific genetic testing for MMR genes and *EPCAM*, or multigene (panel) testing of all endometrial cancers diagnosed before age 50 years.[[102](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_102)] Despite these recommendations, the uptake of universal screening in women newly diagnosed with endometrial cancer is unclear.

(Refer to the PDQ summary on [Genetics of Breast and Gynecologic Cancers](https://cdr.cancer.gov/cgi-bin/cdr/QcReport.py?DocId=CDR0000062855&Session=guest) for more information about endometrial cancer as a component of Lynch syndrome.)

**Germline genetic testing**

Genetic testing for germline pathogenic variants in *MLH1*, *MSH2*, *MSH6*, *PMS2*, and *EPCAM* can help formulate appropriate intervention strategies for the affected variant-positive individual and at-risk family members, many of whom may be unaffected by cancer.

If a pathogenic variant is identified in an affected person, then testing for that same pathogenic variant should be offered to all at-risk family members. At-risk relatives who test negative for the identified pathogenic variant in the family are not at increased risk of CRC or other Lynch syndrome–associated malignancies and can follow surveillance recommendations applicable to the general population. Family members who carry the familial pathogenic variant are referred to surveillance and management guidelines for Lynch syndrome. (Refer to the [Management of Lynch syndrome](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#_1142) section of this summary for more information.)

If no pathogenic variant is identified in the affected family member, then testing is considered negative for Lynch syndrome in that individual. With advances made in DNA sequencing technologies, it is unlikely that current gene testing is not sensitive enough to detect a pathogenic variant in the genes tested. Advances in testing, including the common use of [next-generation sequencing](https://cdr.cancer.gov/cgi-bin/cdr/Filter.py?DocId=CDR0000763024&Filter=set:QC+GlossaryTermName+with+Concept+Set) (NGS) by most commercial testing laboratories have improved upon the detection of certain alterations such as large deletions or genomic rearrangements as well as the presence of a [pseudogene](https://cdr.cancer.gov/cgi-bin/cdr/Filter.py?DocId=CDR0000775793&Filter=set:QC+GlossaryTermName+with+Concept+Set) *PMSCL* in *PMS2*.

Possible reasons why a pathogenic variant may not be detected include the following:

* The family could have a variant in a yet-unidentified gene that causes Lynch syndrome or a predisposition to colon cancer.
* The individual tested in the family may have developed colon cancer through a nongenetic mechanism (i.e., it is a sporadic case also known as a [phenocopy](https://cdr.cancer.gov/cgi-bin/cdr/Filter.py?DocId=CDR0000538227&Filter=set:QC+GlossaryTermName+with+Concept+Set)), while the other cases in the family are really the result of a germline variant. If this scenario is suspected, testing another affected individual who has had a Lynch syndrome–associated cancer is recommended.
* In cases in which a CRC tumor displayed MSI and/or abnormal IHC but no germline pathogenic variant was detected, biallelic somatic variants may be the etiology. These cases have been coined *Lynch-like* and are not considered familial.

Failure to detect a pathogenic variant could mean that the family truly is not at genetic risk despite a clinical presentation that suggests a genetic basis (e.g., the patient may have double somatic variants in an MMR gene). If no variant can be identified in an affected family member, testing should not be offered to at-risk members because results would be uninformative for the relatives. They would remain at increased risk of CRC by virtue of their family history and should continue with recommended intensive screening.

(Refer to the [Management of Lynch syndrome](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#_1142) section of this summary for more information.)

**Multigene (panel) testing**

Germline mutation analysis of *MLH1*, *MSH2* (including *EPCAM*), *MSH6*, and *PMS2* may be considered in instances in which tumor tissue is not available from individuals to test for MSI and/or MMR protein IHC. This approach has become less expensive with the advent of multigene (panel) testing, which is now offered by several clinical laboratories at a cost that may be comparable to single-gene testing. The cost of multigene testing may also approach the cost of tumor screening and may prove to be a cost-effective approach in individuals affected by CRC. At present, multigene tests are not routinely recommended for universal screening for Lynch syndrome among all newly diagnosed CRC patients, but they may be very useful in select populations, such as those with early-onset CRC [[341](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_341)] or from familial, high-risk clinic-based populations. It is also important to note that pathogenic variants may be detected in other cancer-associated genes beyond Lynch syndrome. In a study of 1,112 individuals who met NCCN criteria for Lynch syndrome testing and who underwent multigene testing with a 25-gene panel, as expected, 114 individuals (9.0%) were found to have pathogenic variants in MMR genes; however, 71 individuals (5.6%) were found to have a pathogenic variant in non-Lynch syndrome cancer predisposition genes, such as *BRCA1*, *BRCA2*, *APC*, *MUTYH* (biallelic), and *STK11*. Lastly, multigene tests yield a high proportion of VUS. In the aforementioned study, a total of 479 patients (38%) had one or more VUS.[[342](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_342)]

Individuals with early-onset CRC have been shown to have a high frequency and wide spectrum of germline pathogenic variants, indicating that panel testing in this population may be beneficial. In a study of 450 patients with early-onset CRC (mean age at diagnosis, 42.5 y) and a family history including at least one FDR with colon, endometrial, breast, ovarian, and/or pancreatic cancer, 75 germline pathogenic or likely pathogenic variants were identified in 72 patients (16%).[[341](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_341)] The spectrum of variants identified included Lynch syndrome and non-Lynch syndrome–associated genes, including several genes that have not traditionally been associated with CRC (e.g., *BRCA1*/*BRCA2*, *ATM*, *CHEK2*, *PALB2*, and *CDKN2A*). Given the high frequency and variety of hereditary cancer syndromes identified, the authors suggested that multigene testing in this population may be warranted.

Multigene testing has also been examined in a larger study of 1,058 individuals with CRC who were unselected for age at diagnosis, personal or family history, or MSI/MMR test results.[[343](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_343)] Germline pathogenic variants in cancer susceptibility genes were identified in 105 individuals (9.9%). While 33 individuals (3.1%) carried pathogenic variants in Lynch syndrome genes, 74 (7.0%) had pathogenic variants in non-Lynch syndrome–associated genes, including *APC*, *MUTYH*, *BRCA1/BRCA2*, *PALB2*, *CDKN2A*, *TP53*, and *CHEK2*. These data illustrate the breadth of variants that may be identified in unselected CRC patients; thus, use of a comprehensive multigene test may be warranted.

A 2017 study examined the frequency of pathogenic Lynch syndrome–associated gene variants in individuals undergoing multigene testing at a single commercial United States laboratory between 2012 and 2015, and reported on the characteristics of those carriers identified with Lynch syndrome.[[344](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_344)] The study reports on the largest cohort of individuals tested through multigene testing to date; data was reported on 34,980 individuals who had undergone various multigene panel tests that included the MMR and *EPCAM* genes, where the indication for testing was not limited to Lynch syndrome. A total of 618 pathogenic variants were identified in 612 individuals (1.7%) and analyses were conducted on 579 subjects (after exclusion of 33 individuals who had a Lynch syndrome–associated variant and a second MMR variant or other pathogenic alteration in another cancer predisposition gene). The majority of carriers were affected by cancer, including non-Lynch syndrome–associated malignancies, where breast cancer was most frequently reported (124/423, 23.5%). *MSH6* variants were most prevalent (29.3%), followed by *PMS2* (24.2%), *MSH2* (23.7%), *MLH1* (21.6%), and *EPCAM* (1.2%). This finding differs from previous data where *MSH2* and *MLH1* variants were more prevalent, as individuals were more often selected for Lynch syndrome–specific testing due to a personal and/or family history of CRC.

The study reports on genotype-phenotype correlations on 528 Lynch syndrome carriers, the majority of whom had CRC (186, 35.2%) and endometrial cancer (136, 25.8%), followed by breast cancer (124, 23.5%) and ovarian cancer (74, 14%).[[344](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_344)] One hundred forty-five carriers presented with breast or ovarian cancer as their sentinel tumor and did not carry a prior diagnosis of CRC or endometrial cancer prior to the time of multigene testing. When examining MMR gene variant distribution among tumor-specific subgroups, a higher frequency of *MSH6* and *PMS2* variants were detected in carriers with breast cancer only than *MLH1* and *MSH2*, where the latter pathogenic variants were more frequent in subjects with CRC only. For patients with breast cancer only, the frequency of *PMS2* gene variants was significantly higher than population estimates, which was not the case for *MLH1*, *MSH2*, or *MSH6*. A comparable retrospective study reported similar findings. Standardized incidence ratios (SIRs) of breast cancer were calculated by comparing observed breast cancer frequencies in a population of 423 women with pathogenic or likely pathogenic variants in MMR genes with those in the general population. The authors reported a statistically significant age-standardized risk of breast cancer for *MSH6* carriers (SIR = 2.11; 95% CI, 1.56–2.86) and *PMS2* carriers (SIR = 2.92; 95% CI, 2.17–3.92).[[345](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_345)] A critical limitation of both of these studies was the excess of breast cancer cases in the overall referral population as well as the known high background population prevalence of *MSH6* and *PMS2* germline pathogenic variants.

Clinical criteria for the identification of Lynch syndrome, including the Amsterdam criteria, revised Bethesda guidelines, or the PREMM(1,2,6) risk prediction model, would have failed to identify 27.3% of Lynch syndrome carriers in this study.[[344](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_344)] Given the increased prevalence of breast and ovarian cancers, 58.9% met the NCCN guidelines for *BRCA1/BRCA2* testing and of these, 36.7% also met NCCN guidelines for Lynch syndrome testing. Lastly, there were limited data on tumor testing results, available only on 18.8% of pathogenic variant carriers, where results were often discordant with the altered gene, which was most often reported in *MSH6* and *PMS2* carriers. Results of this study support the use of multigene testing for Lynch syndrome and further study of the respective cancer risks, as current testing strategies limit identification of Lynch syndrome carriers and associated malignancies.

Lastly, germline MMR genes have been detected unexpectedly among individuals undergoing multigene testing for cancers not commonly associated with Lynch syndrome, such as breast and prostate cancer. As a result, the cancer spectrum associated with Lynch syndrome may be wider than previously appreciated. (Refer to the [Breast cancer](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#_2989) and [Prostate cancer](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#_2990) sections of this summary and the [Genetics of Prostate Cancer](https://cdr.cancer.gov/cgi-bin/cdr/QcReport.py?DocId=CDR0000299612&Session=guest) summary for more information.)

(Refer to the [Multigene [panel] testing](https://cdr.cancer.gov/cgi-bin/cdr/QcReport.py?DocId=CDR0000062865&Session=guest#_1320) section in the PDQ summary on [Cancer Genetics Risk Assessment and Counseling](https://cdr.cancer.gov/cgi-bin/cdr/QcReport.py?DocId=CDR0000062865&Session=guest) for more information about multigene testing, including genetic education and counseling considerations, and research examining the use of multigene testing.)

**Cost-effectiveness of multigene (panel) testing**

As genetic testing becomes routine rather than the exception, questions regarding the cost of testing are inevitable. Historically, a cost-effectiveness ratio of $50,000 per quality-adjusted life-year (QALY) has been utilized as the benchmark for good value for care.[[346](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_346)] Over time it has been suggested that this threshold is too low and that other thresholds such as $100,000 or $150,000 be utilized.[[346](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_346)]

A 2015 study evaluated the cost-effectiveness of multigene testing for CRC and polyposis syndromes in patients referred to a cancer genetics clinic.[[347](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_347)] These authors developed a decision model to estimate the immediate and downstream costs for patients referred for evaluation and of CRC surveillance in family members identified as carriers of pathogenic variants. The costs were estimated on the basis of published models from the CDC and from an academic molecular genetics laboratory. They classified the syndromes on the basis of inheritance pattern and penetrance of CRC. Four custom panels were compared with the standard of care. The four panels tested for (1) Lynch syndrome–associated genes only (*MLH1*, *MSH2*, *MSH6*, *PMS2*, and *EPCAM*); (2) genes in panel 1 and additional genes associated with autosomal dominant inheritance and high CRC penetrance (*APC*, *BMPR1A*, *SMAD4*, and *STK11*); (3) genes in panels 1 and 2 and those associated with autosomal recessive inheritance with high CRC penetrance (*MUTYH*); or (4) all genes in the first three panels and those associated with autosomal dominant conditions with low penetrance (*PTEN*, *TP53*, *CDH1*, *GALNT12*, *POLE*, *POLD1*, *GREM1*, *AKT1*, and *PIK3CA*). The respective costs were as follows: panel 1, $144,235 per QALY; panel 2, $37,467 per QALY; panel 3, $36,500 per QALY; and panel 4, $77,300 per QALY when compared with panel 3. The authors concluded that the use of an NGS multigene test that includes highly penetrant CRC and polyposis syndromes and Lynch syndrome cancer genes was the approach most likely to provide clinically meaningful results in a cost-effective fashion.

The cost of germline genetic testing continues to decrease with advancements in technology since the time this model analysis was conducted; additional studies are needed to continue to assess the cost-effectiveness of this testing approach.

**Prevalence, clinical manifestations, and cancer risks associated with Lynch syndrome**

Lynch syndrome is an autosomal dominant syndrome characterized by an early age of onset of CRC, excess synchronous and metachronous colorectal neoplasms, right-sided predominance, and extracolonic tumors, notably endometrial cancer. Lynch syndrome is caused by pathogenic variants in the DNA MMR genes, namely *MLH1* (*mutL homolog 1*) on chromosome 3p21;[[348](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_348), [349](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_349)] *MSH2* (*mutS homolog 2*) on chromosome 2p22-21;[[350](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_350), [351](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_351)] *MSH6* on chromosome 2p16;[[352](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_352)] and *PMS2* (*postmeiotic segregation 2*) on chromosome 7p22.[[348](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_348), [349](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_349), [350](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_350), [351](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_351), [353](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_353), [354](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_354), [355](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_355), [356](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_356)] The function of these genes is to maintain the fidelity of DNA during replication. Lynch syndrome is also associated with pathogenic variants of the *EPCAM* (*epithelial cellular adhesion molecule*, formerly known as *TACSTD1*) gene on chromosome 2p21, which causes epigenetic silencing of *MSH2*, located immediately downstream of this gene.[[357](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_357), [358](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_358)]

Lynch syndrome accounts for about 3% of all newly diagnosed cases of CRC.[[312](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_312)] In earlier studies, the average age at CRC diagnosis in carriers of Lynch syndrome pathogenic variants was reported as young as 44 to 52 years [[265](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_265), [312](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_312), [359](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_359)] versus 71 years in sporadic CRC.[[360](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_360)] In subsequent studies that corrected for ascertainment bias to determine cancer-related risk estimates and genotype-phenotype correlations, the average age at diagnosis of CRC was reported to be 61 years among carriers of Lynch syndrome–associated pathogenic variants.[[361](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_361)]

Original reports related to overall and gene-specific prevalence estimates in Lynch syndrome relied heavily on retrospective data from familial cancer registries worldwide. Earlier risk estimates of CRC (and endometrial cancer) reported in Lynch syndrome were subject to ascertainment bias and overestimation, given that data were derived largely from familial cancer registries and cases were often ascertained based on young-onset CRC or an increased number of CRC cases among relatives. Correction of these cancer risk estimates has been made possible through modified [segregation analyses](https://cdr.cancer.gov/cgi-bin/cdr/Filter.py?DocId=CDR0000712689&Filter=set:QC+GlossaryTermName+with+Concept+Set), where statistical methodology provides more accurate estimates and adjusts for ascertainment bias. Conversely, risk estimates related to extracolonic malignancies, with the exception of endometrial cancer, may be prone to underestimation because many families may have underreported these cancers in relatives, and Lynch syndrome–related tumors may have occurred later in life.

In a large population-based study of 5,744 CRC cases who were recruited irrespective of family cancer history from the United States, Australia, and Canada, it was estimated that 1 in 279 individuals in the population carry an MMR pathogenic variant associated with Lynch syndrome.[[362](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_362)]

In another population-based study of 450 individuals with CRC but limited to young onset with diagnoses occurring before age 50 years, germline pathogenic variants were identified in 72 of 450 individuals (16%), as detected by multigene (panel) testing for inherited cancer susceptibility genes. As expected, the majority of identified variants were in genes known to be associated with CRC, predominantly Lynch syndrome (37 of 72 patients, 51.4%). However, 13 of 72 patients (18.1%) had pathogenic variants in genes not traditionally associated with CRC, including but not limited to *BRCA1*/*BRCA2*, which accounted for 8% of the identified variants. Because of the high frequency and wide variety of pathogenic variants identified, the authors suggested consideration of multigene testing for all individuals with early-onset CRC.[[341](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_341)]

**Gene-specific considerations and associated CRC risk**

The *MLH1* and *MSH2* genes were originally thought to account for most pathogenic variants of the MMR genes found in Lynch syndrome. However, the prevalence of *MSH6* and *PMS2* pathogenic variants has been increasing with improved DNA mutational analyses and universal tumor screening of all CRCs.[[362](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_362)] *MSH6* and *PMS2* variants may be more common in unselected cases of CRC (and endometrial cancer),[[362](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_362)] compared with *MLH1* and *MSH2* variants which were more commonly identified in individuals from high-risk CRC clinics.[[363](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_363), [364](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_364)]

***MLH1***

In early studies, the prevalence of *MLH1* pathogenic variants in individuals with Lynch syndrome was reported to be between 41.7% [[365](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_365)] and 50%,[[366](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_366)] making *MLH1* the most commonly altered MMR gene in Lynch syndrome families. It was not until a report on the population-based prevalence of Lynch syndrome that the *MLH1* pathogenic variant was estimated to be 1 in 1,946, ranking third after *PMS2* (1 in 714) and *MSH6* (1 in 758), as estimated in a large international study of 5,744 CRC cases.[[362](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_362)]

*MLH1* pathogenic variants are associated with the entire spectrum of malignancies associated with Lynch syndrome [[366](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_366)] The lifetime risk of any Lynch syndrome–associated cancer by age 70 years has been found to range between 59% and 65% in *MLH1* pathogenic variant carriers.[[292](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_292)] The highest risk among carriers of pathogenic *MLH1* variants is for CRC, which is estimated to be between 41% and 68%,[[3](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_3), [4](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_4), [361](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_361)] and the mean age at diagnosis of CRC was 42.8 years (range, 16–81 y) in one study that included 137 affected individuals.[[367](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_367)] In a more recent prospective study using pooled European registry data of 944 *MLH1* carriers without cancer, the cumulative CRC incidence was 46% at age 70 years, despite colonoscopic surveillance (albeit at various intervals).[[5](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_5)]

***MSH2***

The prevalence of *MSH2* pathogenic variants in individuals or families with Lynch syndrome has varied across studies. *MSH2* pathogenic variants were reported in 38% to 54% of Lynch syndrome families in studies including large cancer registries and among cohorts of early-onset CRC (younger than age 55 y).[[267](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_267), [368](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_368)] The reported prevalence of *MSH2* pathogenic variants was 32.8% in 2012 in the database of the International Society for Gastrointestinal Hereditary Tumors (InSiGHT), a large professional organization devoted to the collaborative study of familial GI cancer,[[365](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_365)] with families readily ascertained based on the presence of extracolonic cancers in *MSH2*-associated Lynch syndrome. However, the prevalence of *MSH2* pathogenic variants was estimated to be 1 in 2,841 in a population-based cohort of 5,744 CRC cases recruited from the United States, Australia, and Canada;[[362](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_362)] *MSH2* was the least prevalent of the MMR gene variants associated with Lynch syndrome.

The risk of any Lynch syndrome–associated cancer by age 70 years has been found to range between 57% to nearly 80% in *MSH2* pathogenic variant carriers.[[292](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_292)] The lifetime risk of colon cancer associated with *MSH2* pathogenic variants is estimated to be between 48% and 68%.[[3](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_3), [4](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_4), [361](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_361)] In a case series of Lynch syndrome patients, those carrying germline *MSH2* pathogenic variants (49 individuals, 45% women) had a lifetime (cutoff age, 60 y) risk of extracolonic cancers of 48% compared with 11% for *MLH1* carriers (56 individuals, 50% women).[[369](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_369)] In a more recent prospective study using pooled European registry data of 616 *MSH2* carriers without cancer, the cumulative CRC incidence was 35% at age 70 years, despite colonoscopic surveillance.[[5](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_5)]

The mean age at diagnosis of CRC in *MSH2* carriers has been comparable to *MLH1* carriers. One study that included 143 affected individuals with *MSH2* pathogenic variants found a mean age at CRC diagnosis of 43.9 years (range, 16–90 y). The same study reported a mean age at CRC diagnosis of 42.8 years (range, 16–81 y) in 137 *MLH1* pathogenic variant carriers.[[367](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_367)]

***MSH6***

Most series have reported a prevalence of germline *MSH6* pathogenic variants in approximately 10% of Lynch syndrome families from high-risk clinics and a higher proportion of unselected CRC patients, at approximately 50%.[[352](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_352), [370](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_370), [371](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_371), [372](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_372), [373](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_373), [374](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_374), [375](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_375)] The reported prevalence of *MSH6* pathogenic variants in the InSiGHT database was 18% in 2012.[[365](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_365)] The wide range of prevalence estimates for pathogenic *MSH6* variants was a result of small sample sizes, ascertainment bias, and the later age of CRC onset and less striking family histories in *MSH6*-associated Lynch syndrome families compared with *MLH1-* and *MSH2*-associated Lynch syndrome families.[[370](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_370)] This is in line with findings from a population-based study of 42 carriers of [deleterious](https://cdr.cancer.gov/cgi-bin/cdr/Filter.py?DocId=CDR0000556486&Filter=set:QC+GlossaryTermName+with+Concept+Set) *MSH6* germline pathogenic variants, 30 (71%) of whom had a family cancer history that did not meet the Amsterdam II criteria.[[6](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_6)] In a recent, international, population-based study of 5,744 CRC cases, the prevalence of *MSH6* pathogenic variants was estimated to be 1 in 758, ranking as the second most prevalent of the MMR genes following *PMS2*.[[362](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_362)]

The lifetime risk of any Lynch syndrome–associated cancer among *MSH6* pathogenic variant carriers is approximately 25% [[292](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_292)] with CRC lifetime risk estimated to be between 12% and 22% [[4](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_4), [6](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_6)] with *MSH6* carriers diagnosed with CRC at a later age than *MLH1* and *MSH2* carriers. In an earlier study of 146 *MSH6* carriers (59 men and 87 women) from 20 families, all of whom had truncating pathogenic variants in *MSH6*, there was a similar prevalence of CRC by age 70 years among *MLH1*, *MSH2*, and *MSH6* carriers (*P* = .0854). However, the mean age at diagnosis for colorectal carcinoma was (a) 55 years for male *MSH6* carriers (n = 21; range, 26–84 y) versus 43 years and 44 years in carriers of *MLH1* and *MSH2* pathogenic variants, respectively; and (b) 57 years for female *MSH6* carriers (n = 15; range, 41–81 y) versus 43 years and 44 years in carriers of *MLH1* and *MSH2* pathogenic variants, respectively.[[376](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_376)]

The largest series of carriers of *MSH6* pathogenic variants reported to date includes 113 families from five countries who were ascertained through family cancer clinics and population-based cancer registries.[[6](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_6)] Compared with the incidence for the general population, *MSH6* pathogenic variant carriers had an eightfold increased incidence of CRC (hazard ratio [HR], 7.6; 95% CI, 5.4–10.8), which was independent of sex and age. By age 70 years, 22% (95% CI, 14%–32%) of male carriers of *MSH6* pathogenic variants developed CRC compared with 10% (95% CI, 5%–17%) of female carriers. By age 80 years, the CRC prevalence doubled to 44% (95% CI, 28%–62%) of male carriers of *MSH6* pathogenic variants diagnosed with CRC compared with 20% (95% CI, 11%–35%) among female carriers.

In a more recent prospective study using pooled European registry data of 305 *MSH6* carriers without cancer, the cumulative CRC incidence was 20% at age 70 years despite colonoscopic surveillance.[[5](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_5)]

***PMS2***

*PMS2* was the last of the genes in the MMR family of genes to be identified. This was because lower penetrance among families made it more difficult to identify [[377](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_377)] using clinical criteria, and also because of limitations of DNA mutational analysis that result from pseudogene interference.

In earlier studies of individuals with CRC and suspected Lynch syndrome, the prevalence of *PMS2* pathogenic variants was variable from 2.2% to 5%,[[265](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_265), [378](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_378)] with an increase to 7.5% as reported in the InSiGHT database in 2012.[[365](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_365)] From a study examining universal tumor testing results from unselected cases of CRC in Switzerland, IHC evaluation of 1,000 consecutive cases found isolated absence of PMS2 expression in 1.5% of all tumors. If this frequency of PMS2-deficient CRCs were representative of all *PMS2*-associated Lynch syndrome, *PMS2* would be the most common gene associated with Lynch syndrome.[[379](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_379)] Results from a large, population-based CRC cohort found that the prevalence of *PMS2* pathogenic variants was the highest among all MMR variants, in which 1 person in 714 carried a pathogenic *PMS2* gene variant.[[362](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_362)]

***[Comment: Paper for review: https://www.ncbi.nlm.nih.gov/pubmed/26110232 ]***

The lifetime risk of any cancer has been found to range between 25% and 32% for heterozygous *PMS2* pathogenic variant carriers.[[292](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_292)] A meta-analysis of three population-based studies and one clinic-based study estimated that for carriers of *PMS2* pathogenic variants, the risk of CRC to age 70 years was 20% among men and 15% among women, and the risk of endometrial cancer was 15%.[[380](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_380)] Similarly, a European consortium of clinic-based registries, taking care to correct for ascertainment bias, found a cumulative lifetime (to age 70 y) CRC risk of only 19% in men and 11% in women with *PMS2* pathogenic variants.[[381](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_381)] In addition, patients with *PMS2* pathogenic variants presented with CRC 7 to 8 years later than did those with *MLH1* and *MSH2* pathogenic variants.[[378](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_378)] In a prospective study using pooled European registry data of 77 *PMS2* carriers without cancer, the cumulative CRC incidence was 10% at age 70 years despite colonoscopic surveillance.[[5](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_5)]

It is important to note that a more severe phenotype is seen among carriers of biallelic *PMS2* pathogenic variants. (Refer to the [BMMRD](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#_3012) section in the [Genetics of Lynch syndrome](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#_1102) section of this summary for more information.)

The lifetime risk of CRC and endometrial cancer in carriers of these pathogenic variants is summarized in [Table 16](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#_3023).

|  |
| --- |
| **Table 16. Lifetime Risk of Colorectal and Endometrial Cancers in Carriers of Lynch Syndrome–Associated Pathogenic Variants** |
| **Gene**  | **Lifetime Risk of Colorectal Cancer (%)**  | **Lifetime Risk of Endometrial Cancer (%)**  | **References**  |
| *MLH1*  | 41–50  | 34–54  | [[3](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_3), [4](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_4), [5](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_5)]  |
| *MSH2*  | 35–56  | 21–51  | [[3](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_3), [4](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_4), [5](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_5)]  |
| *MSH6*  | 10–22  | 16–49  | [[4](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_4), [5](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_5), [6](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_6)]  |
| *PMS2*  | 10  | 24  | [[5](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_5)]  |

***EPCAM***

A subset of individuals with Lynch syndrome (approximately 1%) have a pathogenic variant in *EPCAM*, which leads to hypermethylation and inactivation of the *MSH2* promoter.[[382](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_382)] In a European study of 194 *EPCAM* deletion carriers, the cumulative risk of CRC up to age 70 years was 75% with the average age at onset of 43 years. This is comparable to the risk in *MSH2* carriers (up to 68% by age 70 y). However, the risk of endometrial cancer among women with an *EPCAM* deletion was only 12% in this study, compared with a risk of up to 71% in *MSH2* carriers.[[383](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_383)] The associated phenotype is dependent on the location of the deletion variant in the 3’ end of the *EPCAM* gene; if the deletion is large and includes parts of the promoter of *MSH2*, the phenotype will be similar to other *MSH2*-associated Lynch syndrome families.[[383](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_383)] When the deletion involves the termination signal of *EPCAM* but spares all of the *MSH2* gene and promoter, the phenotype is mainly confined to CRC.[[384](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_384)]

One study of two families with the same *EPCAM* deletion limited to the 3’ end of the gene and not extending into the promoter of *MSH2* found few extracolonic cancers and no endometrial cancers.[[384](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_384)] However, a subsequent study demonstrated that women with MSH2 protein expression loss caused by *EPCAM* variants are also at risk of endometrial cancer.[[383](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_383)]

**BMMRD**

As described above, patients may carry MMR gene variants in both parental alleles, in a condition known as BMMRD. (Refer to the [BMMRD](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#_3012) section in the [Genetics of Lynch syndrome](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#_1102) section of this summary for more information.)

The occurrence of such biallelic variants is associated with a characteristic but not diagnostic clinical phenotype. Clinical features include hematologic malignancies and brain tumors in children. When GI tumors occur, the age of onset is strikingly low, sometimes before age 20 years. Café au lait spots and features otherwise suggesting neurofibromatosis are characteristic. Occasionally, patients present with multiple adenomas.

**Ethnic variation and founder pathogenic variants in Lynch syndrome**

**The frequency of MMR variants does not differ markedly from population to population, with similar frequencies identified in a host of different countries. As with hereditary breast and ovarian cancer (HBOC), there are certain mutations that occur at higher frequencies within a particular ethnic group. Notable in HBOC are the commonly recurring Ashkenazi Jewish mutations, so common that direct-to-consumer testing is offered for these common variants. (Refer to the Population estimates of the likelihood of having a BRCA1 or BRCA2 pathogenic variant section of the Genetics of Breast and Gynecologic Cancers summary and the DTC Testing section of the CGRAC summary for more information.) The ancientness of apparent founder mutations is generally established by haplotype analysis. In some instances what may appear to be a founder mutation is simply a frequently recurring de novo mutation.[**[**385**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_385)**]**

**Among the first population findings regarding the MMR genes of LS was the recognition of 2 very common MLH1 variants in Finland, accounting for a majority of cases of LS in Finland.[**[**386**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_386)**,** [**387**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_387)**] Since that time, founder mutations have been identified in most populations in which relatively unselected series of colorectal cancer patients have undergone mutation testing. Many of the reports originate in Europe. As in Finland, these may be straightforward to identify in the setting of fairly homogeneous ethnicity with low in-migration. Founder mutations in Europe have been found in the UK, Sweden, Switzerland, Italy,[**[**388**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_388)**] Portugal, France, Spain, Hungary, and likely are present in all ethnic groups. Fewer such reports have come from Asia,[**[**389**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_389)**] Latin America, the Middle East, and Africa.**

**In the US, a deletion in Exons 1-6 of the MSH2 gene has been estimated to account for as much as 20% of mutations in that gene. This so-called American Founder Mutation has been determined by haplotype analysis to date back about 500 years.[**[**390**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_390)**]**

**A South American study combining data from Uruguay, Colombia, Brazil, Argentina, and Chile, also selected cases of interest according to Amsterdam and Bethesda features, yielding a 60% frequency of MLH1 and 40% MSH2. MSH6 and PMS2 were not evaluated. Selection bias likely influenced the frequency of mutations and perhaps the relative contributions by MLH1 and MSH2. A possible founder mutation in Colombia was noted.[**[**391**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_391)**]**

**Although testing for commonly recurring founder mutations in a given ethnic/geographic area has been considered to be a cost effective first step when a step-wise strategy is employed, it is likely not necessary when the increasingly commonly approach of broad panel testing is undertaken as a basic strategy.**

**One consideration having to do with ethnicity is that of increased rates of consanguinity within certain populations and the subsequent risk of BMMRD. (see BMMRD section for further details).**

**Ethnic variation in the United States**

**In the section below, the data exploring the distribution of MMR gene mutation amongst differing ethnic groups in the US is presented. The interpretation of these studies is challenging given the presence of selection and ascertainment bias. In addition, even population based studies are limited by small sample sizes for many ethnic groups and self-reporting of ethnicity/race.**

**There are few data suggesting the presence of much variation in LS frequency according to geography or ethnicity. Within a small and/or homogeneous ethnic group the presence of founder mutations may seem to increase the prevalence of mutations in that particular gene. Slight differences in the proportion of MLH1 and MSH2 variants exist from one population to another. MSH6 and PMS2 have been insufficiently studied at the population as to enable inferences about their relative frequencies.**

**The most representative population studies in the US, such as that in Columbus, Ohio, have been overrepresented by whites, in accordance with their greater overall numbers. Consequently, data on minorities such as Hispanics and African Americans suffer from smaller and less rigorously representative samples.**

**A study conducted in Puerto Rico considered mutations in 89 Caribbean Hispanic patients with LS suspected on the grounds of Amsterdam Criteria or Bethesda Guidelines.[**[**392**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_392)**] They underwent either immediate germline testing or step-wise evaluation beginning with tumor MSI/IHC. Frequencies of mutations by gene were 67% MSH2, 25% MLH1, and 8% MSH6. No definite founder mutations were evident. Clearly the selection of subjects according to clinical FH criteria would have led to an underreporting of the less penetrant MSH6 and PMS2 genes.**

**Clinic-based series from California, Texas, and Puerto Rico yielded an overall mutation prevalence similar to those described, with somewhat more MLH1 than MSH2, but also including MSH6 and PMS2. Presence of potential founder mutations, traceable back to Spain and Europe were noted.[**[**393**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_393)**]**

**The most nearly population-based information on LS in Hispanics is a Southern California study based on the California Tumor Registry, in which 265 patients were identified.[**[**394**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_394)**] Of those with MSI-H tumors, 13 (62%) had MMR mutations. Frequencies of MMR mutations were MLH1-6 (46%), MSH2-4 (31%), MSH6-2 (15%) and PMS2-1(8%).**

**The problem of small numbers is highlighted by the findings from the more truly population studies that have been done in the US. In a study from Columbus, Ohio, only 8% of the consecutive series were African American and the proportion of Hispanics as a subset of whites was not stated.[**[**341**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_341)**] *[Comment: Question for WG: Is this the right reference?]* In another study involving panel testing of nearly all CRC patients treated at Dana Farber Cancer Center, less than 5% were black and less than 3% Hispanic, underscoring the challenge of extracting meaningful data from small subsets.[**[**342**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_342)**]**

**Lynch syndrome in African Americans**

**The issues in evaluating prevalence of LS and cancer risks associated with MMR mutations in African Americans are similar to those in Hispanics: a heterogeneous population that has been understudied. A study of clinic-based data from 13 US referral centers yielded 51 LS families distributed across the MMR genes as follows: 61% MLH1, 21% MSH2, 6% MSH6, and 12% PMS2. Age of cancer onset distributions curves were very similar to those seen in white populations.[**[**395**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_395)**] As with most of the studies in Hispanics, cases were not identified according to any consistent, programmatic evaluation such as universal tumor testing.**

**Risk of metachronous CRC**

A hallmark feature of Lynch syndrome is that carriers of pathogenic MMR gene variants have an increased risk of development of synchronous and metachronous colorectal neoplasms. In one study of 382 individuals with Lynch syndrome from the Colon Cancer Family Registry, the incidence of metachronous CRCs was 16% at 10 years, 41% at 20 years, and 63% at 30 years after segmental colectomy.[[396](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_396)] The risk of metachronous CRC decreased in a stepwise fashion by 31% for every 10 cm of the colon that was removed, with none of the 50 individuals who had extensive colectomies diagnosed with metachronous CRC. Another prospective study of 1,273 patients with Lynch syndrome who had prior cancer reported a cumulative incidence of subsequent CRC of 46% for *MLH1* carriers, 48% for *MSH2* carriers, and 23% for *MSH6* carriers. This represents only a slightly greater risk of new cancers than pathogenic variant carriers with no previous cancer diagnosis. Excellent survival was again seen and was regarded as a combination of favorable tumor pathology and the effect of surveillance.[[397](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_397)]

**Risk of extracolonic malignancies associated with Lynch syndrome**

Patients with Lynch syndrome are at an increased risk of other cancers, especially those of the endometrium. The cumulative risk of extracolonic cancer has been estimated to be 20% by age 70 years in 1,018 women in 86 families, compared with 3% in the general population.[[398](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_398)] There is some evidence that the rate of individual cancers varies from kindred to kindred.[[399](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_399), [400](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_400), [401](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_401)]

**Endometrial cancer**

The most common extracolonic malignancy in Lynch syndrome is endometrial adenocarcinoma, which affects at least one female member in about 50% of Lynch syndrome families. In addition, 50% of women with an MMR gene pathogenic variant will present with endometrial cancer as her first malignancy.[[402](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_402)]

The lifetime risk of endometrial cancer has been estimated to be from 44% in carriers of *MLH1* pathogenic variants to 71% in carriers of *MSH2* pathogenic variants, although some earlier studies may have overestimated risk due to ascertainment bias.[[6](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_6), [269](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_269), [361](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_361), [368](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_368), [403](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_403)] Lifetime risk of endometrial cancer in carriers of *MSH6* pathogenic variants in 113 families was estimated to be 26% at age 70 years and 44% at age 80 years;[[6](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_6)] overall, female carriers of *MSH6* pathogenic variants had an endometrial cancer risk that was 25 times higher than women in the general population (HR, 25.5; 95% CI, 16.8–38.7; *P* < .001).[[6](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_6)] In another study, the cumulative lifetime risk of uterine cancer was higher in *MSH6* carriers (71%) than in carriers of *MLH1* (27%) and *MSH2* (40%) pathogenic variants (*P* = .02), with an older mean age at diagnosis of 54 years in carriers of *MSH6* pathogenic variants (n = 29; range, 43–65 y) versus 48 years in carriers of *MLH1* and 49 years in carriers of *MSH2* pathogenic variants.[[376](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_376)] In carriers of *PMS2* pathogenic variants, the endometrial cancer risk at age 70 years has been reported to be 15%.[[380](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_380)] Prospective data collected in the Colon Cancer Family Registry program yielded 5-year endometrial cancer risks of about 3% and 10-year endometrial cancer risks of about 10% among women with MMR gene pathogenic variants.[[404](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_404)] A prospective study using pooled European registry data of 1,942 MMR carriers without prior cancer reported a cumulative incidence of endometrial cancer of 34% in *MLH1* carriers, 51% in *MSH2* carriers, 49% in *MSH6* carriers, and 24% in *PMS2* carriers.[[5](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_5)] Women with loss of MSH2 protein expression caused by an *EPCAM* pathogenic variant are also at risk of endometrial cancer depending upon the location of the variant in *EPCAM*. One study found a 12% (95% CI, 0%–27%) cumulative risk of endometrial cancer in *EPCAM* deletion carriers.[[383](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_383)]

A study of 127 women with Lynch syndrome who had endometrial cancer as their index cancer were found to be at significantly increased risk of other cancers. The following elevated risks were reported: CRC, 48% (95% CI, 27.2%–58.3%); kidney, renal pelvis, and ureter cancer, 28% (95% CI, 11.9%–48.6%); urinary bladder cancer, 24.3% (95% CI, 8.56%–42.9%; and breast cancer, 2.51% (95% CI, 1.17%–4.14%).[[405](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_405)]

In a study of 113 families that carried *MSH6* pathogenic variants from the Colon Cancer Family Registry, female *MSH6* carriers had a 26-fold increased incidence of endometrial cancer (HR, 25.5; 95% CI, 16.8–38.7) compared with the general population. A sixfold increased incidence of other cancers associated with Lynch syndrome (HR, 6.0; 95% CI, 3.4–10.7) was observed compared with the general population, but not among male *MSH6* carriers.[[6](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_6)]

Lynch syndrome–associated endometrial cancer is not limited to the endometrioid subtype, and the spectrum of uterine tumors in Lynch syndrome may include clear cell carcinoma, uterine papillary serous carcinoma, and malignant mixed Müllerian tumors.[[406](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_406)] Also, endometrial cancer most commonly arises from the lower uterine segment. (Refer to the [Endometrial cancer screening in Lynch syndrome](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#_3112) section of this summary for information about screening methods.)

**Cancer risk in Lynch syndrome beyond CRC and endometrial cancer**

Multiple studies demonstrate an increased risk of additional malignancies associated with Lynch syndrome, including cancers of the stomach, pancreas, ovary, small intestine, and brain, transitional cell carcinoma of the bladder, ureters, and renal pelvis, and sebaceous adenomas of the skin.[[398](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_398), [399](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_399), [407](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_407), [408](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_408), [409](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_409), [410](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_410)] In addition, some studies have suggested an association with breast, prostate, and adrenal cortex cancers.[[404](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_404), [408](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_408), [411](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_411), [412](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_412), [413](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_413)] The strength of the association for many of these malignancies is limited by the majority of studies having a small sample size (and consequently, wide CIs associated with relative risk [RR]), the retrospective nature of the analyses, and referral or ascertainment bias.

The largest prospective study to date is of 446 unaffected carriers of pathogenic variants from the Colon Cancer Family Registry.[[404](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_404)] The Colon Cancer Family Registry is an international cohort with both population-based and clinic-based recruitment from six centers in North America and Australia. Control subjects were noncarriers from families with a known MMR pathogenic variant. Three subcohorts were used to analyze the risk of CRC (365 carriers, 903 noncarriers), endometrial cancer (215 carriers, 523 noncarriers), and other cancers (446 carriers, 1,029 noncarriers). Participants who were followed for up to 10 years demonstrated an increased SIR for CRC (SIR, 20.48; 95% CI, 11.71–33.27; *P* < .01), endometrial cancer (SIR, 30.62; 95% CI, 11.24–66.64; *P* < .001), ovarian cancer (SIR, 18.81; 95% CI, 3.88–54.95; *P* < .001), gastric cancer (SIR, 9.78; 95% CI, 1.18–35.30; *P* = .009), renal cancer (SIR, 11.22; 95% CI, 2.31–32.79; *P* < .001), bladder cancer (SIR, 9.51; 95% CI, 1.15–34.37; *P* = .009), pancreatic cancer (SIR, 10.68; 95% CI, 2.68–47.70; *P* = .001), and female breast cancer (SIR, 3.95; 95% CI, 1.59–8.13; *P* = .001).[[404](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_404)]

A well-described variant of Lynch syndrome whose phenotype includes multiple cutaneous neoplasms (including sebaceous adenomas, sebaceous carcinomas, and keratoacanthomas) and CRC is Muir-Torre syndrome.[[414](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_414), [415](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_415)] Pathogenic variants in the *MLH1*, *MSH2*, and *MSH6* genes have been found in Muir-Torre families with an increased prevalence described among *MSH2* carriers.[[416](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_416), [417](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_417), [418](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_418), [419](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_419), [420](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_420), [421](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_421), [422](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_422), [423](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_423)] A study of 1,914 unrelated *MLH1* and *MSH2* probands found *MSH2* to be more common in individuals with the Muir-Torre syndrome phenotype. Of 15 individuals with sebaceous skin tumors, 13 (87%) had *MSH2* pathogenic variants compared with two individuals who had *MLH1* pathogenic variants (*P* = .05).[[424](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_424)] Evidence of defective DNA MMR activity using IHC or MSI testing was reported in 69 of 163 randomly collected sebaceous neoplasms (42%), suggesting that this is a common mechanism for the development of these lesions, and that testing for defective MMR in sebaceous neoplasms would be an ineffective means to screen for Lynch syndrome or Muir-Torre syndrome.[[425](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_425)] (Refer to the [Sebaceous Carcinoma](https://cdr.cancer.gov/cgi-bin/cdr/QcReport.py?DocId=CDR0000552637&Session=guest#_439) section in the PDQ summary on [Genetics of Skin Cancer](https://cdr.cancer.gov/cgi-bin/cdr/QcReport.py?DocId=CDR0000552637&Session=guest) for more information about cutaneous neoplasms in Muir-Torre syndrome.)

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| **Table 17. Lynch Syndrome–Associated Cancers and Cumulative Risk Up to Age 70 Yearsa** |
| **Cancer Siteb**  | **General Population Risk (%)c**  | **Risk in Individuals With Lynch Syndrome (%)d**  | **References**  |
| Stomach  | <1  | 0.2–13  | [[4](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_4), [6](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_6), [367](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_367), [428](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_428), [429](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_429), [430](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_430), [431](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_431), [432](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_432), [433](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_433)]  |
| Ovary  | 1.3  | 3.4–22  | [[4](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_4), [6](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_6), [361](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_361), [367](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_367), [376](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_376), [380](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_380), [429](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_429), [430](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_430), [431](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_431), [433](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_433), [434](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_434)]  |
| Hepatobiliary tract  | <1  | 0.02–4  | [[4](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_4), [431](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_431), [433](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_433), [434](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_434)]  |
| Urinary tract  | <1  | 0.2–25.5  | [[4](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_4), [367](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_367), [380](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_380), [429](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_429), [430](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_430), [431](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_431), [433](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_433), [434](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_434), [435](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_435)]  |
| Small bowel  | <1  | 0.4–12  | [[4](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_4), [367](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_367), [428](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_428), [429](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_429), [430](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_430), [431](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_431)]  |
| Brain/CNS  | <1  | 1.2–3.7  | [[367](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_367), [429](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_429), [431](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_431), [433](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_433)]  |
| Sebaceous neoplasms  | <1  | 9.0  | [[418](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_418), [436](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_436), [437](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_437)]  |
| Pancreas  | 1.6  | 0.4–3.7  | [[429](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_429), [438](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_438), [439](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_439)]  |

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| *CNS = central nervous system.* |
| *aAdapted from Syngal et al.[*[*426*](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_426)*]* |
| *bEvolving data suggest a potential association between Lynch syndrome and breast and prostate cancers. (Refer to the* [*Additional cancers potentially associated with Lynch syndrome*](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#_2963) *section of this summary for more information about these cancers.)* |
| *cHowlader et al.[*[*427*](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_427)*]* |
| *dRange of cancer risk estimates vary based on study sample size, subject ascertainment, and statistical methods.* |

**Additional cancers potentially associated with Lynch syndrome**

Additional tumors are being considered as part of the spectrum of Lynch syndrome, but this is controversial. Breast and prostate cancers have been raised as possible Lynch syndrome–associated tumors such that MMR genes are now included on multigene (panel) tests for these cancers.

**Breast cancer**

***[Comment: Note: The following paragraph appears in both the CRC and Breast/Ovarian summaries.]***

The issue of breast cancer risk in Lynch syndrome has been controversial. Retrospective studies have been inconsistent, but several have demonstrated microsatellite instability in a proportion of breast cancers from individuals with Lynch syndrome;[[440](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_440), [441](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_441), [442](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_442), [443](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_443)] one of these studies evaluated breast cancer risk in individuals with Lynch syndrome and found that it is not elevated.[[443](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_443)] However, the largest prospective study to date of 446 unaffected carriers of pathogenic variants from the Colon Cancer Family Registry [[404](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_404)] who were followed for up to 10 years reported an elevated SIR of 3.95 for breast cancer (95% CI, 1.59–8.13; *P* = .001).[[404](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_404)] The same group subsequently analyzed data on 764 carriers of MMR gene pathogenic variants with a prior diagnosis of colorectal cancer. Results showed that the 10-year risk of breast cancer following colorectal cancer was 2% (95% CI, 1%–4%) and that the SIR was 1.76 (95% CI, 1.07–2.59).[[444](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_444)] A series from the United Kingdom composed of clinically referred Lynch syndrome kindreds, with efforts to correct for ascertainment, showed a twofold increased risk of breast cancer in 157 *MLH1* carriers but not in carriers of other MMR variants.[[445](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_445)] Results from a meta-analysis of breast cancer risk in Lynch syndrome among 15 studies with molecular tumor testing results revealed that 62 of 122 breast cancers (51%; 95% CI, 42%–60%) in MMR pathogenic variant carriers were MMR-deficient. In addition, breast cancer risk estimates among a total of 21 studies showed an increased risk of twofold to 18-fold in eight studies that compared MMR variant carriers with noncarriers, while 13 studies did not observe statistical evidence for an association of breast cancer risk with Lynch syndrome.[[446](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_446)] However, further studies are needed to define absolute risks and age distribution before surveillance guidelines for breast cancer can be developed for carriers of MMR pathogenic variants.

**Prostate cancer**

Prostate cancer was found to be associated with Lynch syndrome in a study of 198 families from two U.S. Lynch syndrome registries in which prostate cancer had not originally been part of the family selection criteria. Prostate cancer risk in relatives of carriers of MMR gene pathogenic variants was 6.3% at age 60 years and 30% at age 80 years, versus a population risk of 2.6% at age 60 years and 18% at age 80 years, with an overall HR of 1.99 (95% CI, 1.31–3.03).[[411](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_411)] A 2014 meta-analysis supports this association, finding an estimated RR of 3.67 (95% CI, 2.32–6.67) for prostate cancer in men with a known MMR pathogenic variant.[[447](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_447)] This risk is possibly increased in those with *MSH2* pathogenic variants.[[413](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_413), [447](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_447)] Notwithstanding prevalent controversy surrounding routine prostate-specific antigen (PSA) screening, the authors suggested that screening by means of PSA and digital rectal exam beginning at age 40 years in male MMR gene carriers would be “reasonable to consider.”[[411](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_411)] A study of 692 men with metastatic prostate cancer unselected for family history of cancer or age at diagnosis identified germline MMR pathogenic variants in four men (0.5%).[[448](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_448)] Currently, molecular and epidemiologic evidence supports prostate cancer as one of the Lynch syndrome cancers. As with breast cancer,[[447](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_447)] additional studies are needed to define absolute risks and age distribution before surveillance guidelines for prostate cancer can be developed for carriers of MMR pathogenic variants. (Refer to the [MMR Genes](https://cdr.cancer.gov/cgi-bin/cdr/QcReport.py?DocId=CDR0000299612&Session=guest#_947) section in the PDQ summary on [Genetics of Prostate Cancer](https://cdr.cancer.gov/cgi-bin/cdr/QcReport.py?DocId=CDR0000299612&Session=guest) for more information about prostate cancer and Lynch syndrome.)

**Adrenocortical cancer**

In a series of 114 ACC cases, of which 94 patients had a detailed family history assessment and Li-Fraumeni syndrome was excluded, three patients had family histories that were suggestive of Lynch syndrome. The prevalence of MMR gene pathogenic variants in 94 families was 3.2%, similar to the proportion of Lynch syndrome among unselected colorectal and endometrial cancer patients. In a retrospective review of 135 MMR gene pathogenic variant–positive Lynch syndrome families from the same program, two probands were found to have had a history of ACC. Of the four ACCs in which MSI testing could be performed, all were MSS. These data suggest that if Lynch syndrome is otherwise suspected in an ACC index case, an initial evaluation of the ACC using MSI or IHC testing may be misleading.[[412](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_412)]

**Other cancers**

Several additional cancers have been found to be associated with Lynch syndrome in some studies, but further investigation is warranted. [Table 17](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#_3024) compares the risk of these cancers in the general population with that of individuals with Lynch syndrome.

**Management of Lynch syndrome**

**Screening and surveillance in Lynch syndrome**

**Colon cancer screening and surveillance in Lynch syndrome**

Several aspects of the biologic behavior of CRC and its precursor lesion, the adenomatous polyp, in individuals with Lynch syndrome support a different approach to CRC screening in this population as compared with those recommendations for average-risk people in the general population. At present, the recommendations for cancer screening and surveillance in Lynch syndrome take into account the differences in cancer risks as compared with those in the general population due to the causative germline deficiency in the MMR system. The following biological differences form the basis of the currently implemented screening strategies in Lynch syndrome:

* **CRC and adenomas present at a younger age.**

CRCs in Lynch syndrome occur earlier in life than do sporadic cancers; however the age of onset varies based on which of the MMR genes is altered. (Refer to the [Prevalence, clinical manifestations, and cancer risks associated with Lynch syndrome](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#_1113) section of this summary for more information about gene-specific age of onset of CRC.)

Carriers of Lynch syndrome pathogenic variants have an increased risk of developing colon adenomas and the onset of adenomas appears to occur at a younger age than in pathogenic variant–negative individuals from the same families.[[449](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_449)] The risk of a carrier of MMR pathogenic variants developing adenomas has been reported to be 3.6 times higher than the risk in noncarriers.[[449](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_449)] By age 60 years, 70% of the carriers developed adenomas, compared with 20% of noncarriers. Most of the adenomas in carriers had absence of MMR protein expression and were more likely to have dysplastic features, compared with adenomas from control subjects.[[449](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_449)]

In one study, the mean age at diagnosis of adenoma in carriers was 43.3 years (range, 23–63.2 y), and the mean age at diagnosis of carcinoma was 45.8 years (range, 25.2–57.6 y).[[449](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_449)]

* **There is a right-sided predominance of colon cancer.**

A larger proportion of Lynch syndrome CRCs (60%–70%) occur in the right colon, suggesting that sigmoidoscopy alone is not an appropriate screening strategy and that a colonoscopy provides a more complete structural examination of the colon. Evidence-based reviews of surveillance colonoscopy in Lynch syndrome have been reported.[[147](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_147), [450](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_450), [451](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_451)] The incidence of CRC throughout life is substantially higher in patients with Lynch syndrome, suggesting that the most-sensitive test available should be used. (Refer to [Table 18](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#_3025) for available colon surveillance recommendations.)

* **The adenoma-carcinoma sequence is accelerated.**

The progression from normal mucosa to adenoma to cancer is accelerated,[[452](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_452), [453](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_453)] suggesting that screening should be performed at shorter intervals (every 1–2 years) and with colonoscopy.[[453](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_453), [454](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_454), [455](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_455), [456](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_456)] It has been demonstrated that carriers of MMR gene pathogenic variants develop detectable adenomas at an earlier age than do noncarriers.[[449](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_449), [449](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_449)] It is not known whether this reflects a greater prevalence of adenomas or the presence of larger adenomas with better detection in Lynch syndrome.

**Evidence for the use of colonoscopy for CRC screening and surveillance in Lynch syndrome**

The risk of CRC in Lynch syndrome has been studied and updated in a Finnish screening trial, which spans from the early 1980s to present.[[453](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_453), [457](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_457)] Over the course of this trial, the design of the longitudinal study has evolved. In the earliest period, information about each individual's variant status was unknown and study participants were eligible based on fulfillment of clinical criteria; the study consisted of some people with a previous cancer or adenoma diagnosis and others without such history who were undergoing asymptomatic screening while the comparison group was composed of individuals from those same families who refused screening. Many of these people (68%) had screening with x-ray contrast/barium enema. Colonoscopy was the approach used for carriers of MMR pathogenic variants when this information was obtainable and the interval between exams was shortened from 5 years to 3 years to 2 years, based on results from the study over time.

A 15-year controlled screening trial conducted in this series demonstrated a reduction in the incidence of CRC, CRC-specific mortality, and overall mortality with colonoscopy in individuals from Lynch syndrome families.[[453](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_453)] Colonic screening was provided at 3-year intervals in 133 individuals from Lynch syndrome families and 119 controls from these families had no screening. Among those screened, 8 individuals (6%) developed CRC compared with 19 control subjects (16%), for a risk reduction of 62% with screening. Furthermore, all CRCs in the screened group were local, causing no deaths, while there were 9 deaths caused by CRC in the control group. There was also a benefit in overall mortality in the screened group with 10 deaths in the screened group and 26 deaths in the control group (*P* = .003).

The series subsequently limited its attention to subjects without prior diagnosis of adenoma or cancer. The eligible 420 carriers of pathogenic variants had a mean age of 36 years and underwent an average of 2.1 colonoscopies, with a median follow-up of 6.7 years. Adenomas were detected in 28% of subjects. Cumulative risk of one or more adenomas by age 60 years was 68.5% in men and 48.3% in women. Notably, risk of detecting cancer in those free of cancer at baseline exam, and thus regarded as interval cancers, by age 60 years was 34.6% in men and 22.1% in women. The combined cumulative risk of adenoma or cancer by age 60 years was 81.8% in men and 62.9% in women. For both adenomas and carcinomas, about one-half were located proximal to the splenic flexure. While the rates for CRC despite colonoscopy surveillance appear high, the recommended short intervals were not regularly adhered to in this nonrandomized series. These authors recommended surveillance at 2-year intervals. This is in line with most consensus guidelines (refer to [Table 18](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#_3025)), in which the appropriate colonoscopy screening interval remains every 1 to 2 years. Analysis of colonoscopic surveillance data in 242 carriers of pathogenic variants 10 years after testing shows 95% compliance in surveillance procedures for CRC and endometrial cancer. Although not all CRCs were prevented, mortality was comparable with variant-negative relatives. However, this may be attributable to the modest sample size of the study.[[457](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_457)]

Given that colonoscopy is the accepted measure for colon cancer surveillance, preliminary data suggest that the use of chromoendoscopy, such as with indigo carmine, may increase the detection of diminutive, histologically advanced adenomas.[[458](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_458), [459](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_459)]

When an adenoma is detected, the question of whether to test the adenoma for MSI/IHC is raised. One study of patients with prior CRC and known MMR pathogenic variants found eight of 12 adenomas to have both MSI and IHC protein loss.[[460](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_460)] However, the study authors emphasized that normal MSI/IHC testing in an adenoma does not exclude Lynch syndrome. Abnormal MSI/IHC are uncommon in the smallest adenomas, and more prevalent in adenomas larger than 8 mm, which also suggests that the MMR defect is acquired in the growing adenoma.[[243](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_243)]

[Level of evidence (colon surveillance): 2ai](https://cdr.cancer.gov/cgi-bin/cdr/QcReport.py?DocId=CDR0000531811&Session=guest)

**Special considerations: The impact of gene-specific variability in cancer risk on CRC screening recommendations in Lynch syndrome**

Because of the variability of gene-specific CRC risks, experts in the field have proposed gene-specific screening and surveillance recommendations. For example, a European consortium [[381](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_381)] made a clinical recommendation for delaying the onset of colorectal and endometrial cancer screening to age 30 years, in line with their recommendation for later initiation of screening for carriers of *MSH6* pathogenic variants. Note that the NCCN guideline developers considered but did not adopt these more-liberal guidelines.[[102](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_102)] Additionally, a 2015 review by an ad hoc American virtual workgroup involved in the care of Lynch syndrome patients and families concluded that despite multiple studies indicating reduced penetrance in monoallelic *PMS2* carriers, they could not recommend any changes to Lynch syndrome cancer surveillance guidelines for this group.[[377](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_377)]

While initial data may support different strategies for the initiation and surveillance of CRC and other extracolonic cancers by specific MMR gene alteration,[[404](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_404)] concerns related to (a) the adherence of recommendations overall by the medical community and by affected individuals [[461](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_461)] and (b) limitations related to specific screening modalities [[462](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_462)] have prevented the implementation of gene-specific guidelines until additional data are available.[[102](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_102)]

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| **Table 18. Practice Guidelines for Diagnosis and Colon Surveillance of Lynch Syndromea** |
| **Organization**  | **Age Screening Initiated**   | **Screening Interval**  | **Recommended Screening Modality**   | **Comments**  |
| NCCN (2017) [[102](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_102)]  | 20–25 y *or* 2–5 y before youngest case of CRC in family if before age 25 y  | 1–2 y   | Colonoscopy  |   |
| U.S. Multi-Society Task Force on Colorectal Cancer (2014)b [[319](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_319)]  | 20–25 y *or* 2–5 y before youngest case of CRC in family if before age 25 y   | 1–2 y (annual for carriers of MMR pathogenic variants)  | Colonoscopy   | For *MSH6* and *PMS2* carriers, consider starting screening at ages 30 y and 35 y, respectively, unless an early-onset cancer occurs in the family. Recommendations for individuals with BMMRD are also available.[[465](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_465)]  |
| Mallorca group (2013) [[466](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_466)]  | 20–25 y  | 1–2 y  | Colonoscopy  |   |
| ESMO (2013)c[[464](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_464)]  | 20–25 y *or* 5 y before youngest case of CRC in family; no upper limit established  | 1–2 y   | Colonoscopy   |   |

|  |
| --- |
| *BMMRD = biallelic mismatch repair deficiency; CRC = colorectal cancer; ESMO = European Society for Medical Oncology; IHC = immunohistochemistry; MMR = mismatch repair; MSI = microsatellite instability; NA = not addressed; NCCN = National Comprehensive Cancer Network.* |
| *aThis table summarizes available guidelines from 2010 and later. Other organizations, including the American Cancer Society, have published guidelines before 2010.[*[*463*](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_463)*]* |
| *bU.S. Multi-Society Task Force on Colorectal Cancer includes the following organizations: American Academy of Family Practice, American College of Gastroenterology, American College of Physicians-American Society of Internal Medicine, American College of Radiology, American Gastroenterological Association, American Society of Colorectal Surgeons, and American Society for Gastrointestinal Endoscopy.* |
| *cThe American Society of Clinical Oncology and the Japanese Society of Medical Oncology have endorsed the ESMO guidelines as presented in the table.[*[*329*](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_329)*,* [*464*](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_464)*]* |

**Extracolonic cancer screening in Lynch syndrome**

**Gynecologic cancer screening in Lynch syndrome**

**Endometrial cancer screening in Lynch syndrome**

Note: A separate PDQ summary on [Endometrial Cancer Screening](https://cdr.cancer.gov/cgi-bin/cdr/QcReport.py?DocId=CDR0000062819&Session=guest) in the general population is also available.

Cancer of the endometrium is the most common extracolonic cancer observed in Lynch syndrome families, affecting at least one female in about 50% of Lynch syndrome families. (Refer to the [Endometrial cancer](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#_2950) section of this summary for more information about gene-specific risks of endometrial cancer in carriers of MMR pathogenic variants.)

In the general population, the diagnosis of endometrial cancer is generally made when women present with symptoms including abnormal or postmenopausal bleeding. Endometrial sampling is performed to provide a histologic specimen for diagnosis. Eighty percent of women with endometrial cancer present with stage I disease and there are no data to suggest that the clinical presentation in women with Lynch syndrome differs from that in the general population.

Given their substantial increased risk of endometrial cancer, endometrial screening for women with Lynch syndrome has been suggested. Proposed modalities for screening include transvaginal ultrasound (TVUS) and/or endometrial biopsy. TVUS continues to be widely recommended without data to support its use; current NCCN guidelines suggest that there is no clear evidence to support endometrial cancer screening for Lynch syndrome.[[102](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_102)] Two studies have examined the use of TVUS in endometrial screening for women with Lynch syndrome.[[467](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_467), [468](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_468)] In one study of 292 women from Lynch syndrome families or "Lynch syndrome-like/HNPCC-like" families, no cases of endometrial cancer were detected by TVUS. In addition, two interval cancers developed in symptomatic women.[[467](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_467)] In a second study, 41 women with Lynch syndrome were enrolled in a TVUS screening program. Of 179 TVUS procedures performed, there were 17 abnormal scans. Three of the 17 women had complex atypical hyperplasia on endometrial sampling, while 14 had normal endometrial sampling. However, TVUS failed to identify one patient who presented 8 months after a normal TVUS with abnormal vaginal bleeding, and was found to have stage IB endometrial cancer.[[468](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_468)] Both of these studies concluded that TVUS is neither sensitive nor specific.

A study of 175 women with Lynch syndrome, which included both endometrial sampling and TVUS, showed that endometrial sampling improved sensitivity compared with TVUS. Endometrial sampling found 11 of the 14 cases of endometrial cancer. Two of the three other cases were interval cancers that developed in symptomatic women and one case was an occult endometrial cancer found at the time of hysterectomy. Endometrial sampling also identified 14 additional cases of endometrial hyperplasia. Among the group of 14 women with endometrial cancer, ten also had TVUS screening with endometrial sampling. Four of the ten had abnormal TVUS, but six had normal TVUS.[[469](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_469)] While this cohort study demonstrated that endometrial sampling may have benefits over TVUS for endometrial screening, there are no data that predict that screening with any other modality has benefits for endometrial cancer survival in women with Lynch syndrome.

Some studies suggest that women with a clinical or genetic diagnosis of Lynch syndrome do not universally adopt intensive gynecologic screening.[[470](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_470), [471](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_471)] (Refer to the [Gynecologic cancer screening in Lynch syndrome](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#_558) section in the [Psychosocial Issues in Hereditary Colon Cancer Syndromes](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#_189) section of this summary for more information.)

[Level of evidence: 5](https://cdr.cancer.gov/cgi-bin/cdr/QcReport.py?DocId=CDR0000526280&Session=guest)

**Ovarian cancer screening in Lynch syndrome**

Estimates of the cumulative lifetime risk of ovarian cancer in Lynch syndrome patients range from 3.4% to 22%.[[4](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_4), [361](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_361), [429](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_429), [430](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_430), [431](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_431)] However, no studies on the effectiveness of ovarian screening are currently available for women in Lynch syndrome families. TVUS used for endometrial cancer screening has been extended to include ovarian cancer screening in clinical practice for those women who do not undergo risk-reducing surgery for gynecological cancer prevention. However, NCCN asserts that data do not support routine ovarian cancer screening for Lynch syndrome due to a lack of sensitivity and specificity of available screening modalities.[[102](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_102)]

Level of evidence: None assigned

**Risk-reducing surgeries for the prevention of gynecologic cancers in Lynch syndrome**

An effective strategy for the prevention of endometrial and ovarian cancers in Lynch syndrome families is risk-reducing surgery. A retrospective study of 315 women with pathogenic MMR gene variants compared the rate of endometrial and ovarian cancer among the women who did and did not have hysterectomy and oophorectomy. In women followed for endometrial cancer, the mean follow-up periods were 13.3 years in the surgical group and 7.4 years in the nonsurgical group; in women followed for ovarian cancer, the mean follow-up periods were 11.2 years in the surgical group and 10.6 years in the nonsurgical groups. For those women in the surgical group, no cancers were diagnosed, compared with a 33% rate of endometrial cancer and a 5.5% rate of ovarian cancer in the nonsurgical group.[[472](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_472)] Cost-effectiveness–analysis modeling of risk-reducing surgeries (prophylactic hysterectomy and bilateral salpingo-oophorectomy) versus nonsurgical screening in a theoretical population of carriers aged 30 years with MMR gene variants associated with Lynch syndrome revealed that prophylactic surgery was cost-effective with lower cost and yielded higher QALY.[[435](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_435)] A subsequent modeling study evaluated multiple screening and surgical strategies and found that annual screening initiated at age 30 years followed by risk-reducing surgery at age 40 years was the most effective strategy.[[473](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_473)]

[Level of evidence: 3aii](https://cdr.cancer.gov/cgi-bin/cdr/QcReport.py?DocId=CDR0000531815&Session=guest)

**Additional extracolonic cancer screening in Lynch syndrome**

The decision to screen for other Lynch syndrome–associated cancers is done on an individual basis and relies on the cancers reported among FDRs and second-degree relatives with Lynch syndrome.

**Gastric cancer**

The lifetime risk of gastric cancer is approximately 8% for male Lynch syndrome carriers and 5% for female Lynch syndrome carriers.[[432](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_432)] Recent epidemiologic data report a decreasing trend in the diagnosis of gastric cancer than was previously reported, which was as high as 13%. The histologic characterization of most Lynch syndrome–associated gastric cancer is of the intestinal type and may thereby be detected using screening esophagogastroduodenoscopy (EGD).[[432](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_432), [474](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_474)] EGD can be used to screen for gastric and duodenal cancer in individuals with Lynch syndrome with a baseline examination performed between ages 30 to 35 years. Evaluation and treatment of *Helicobacter pylori* infection is recommended when found. Despite limited data on appropriate surveillance intervals, there is general consensus that surveillance be performed every 3 to 5 years, particularly if there is a family history of gastric, duodenal, or small bowel cancer or for those of Asian descent.[[102](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_102)]

[Level of evidence: 5](https://cdr.cancer.gov/cgi-bin/cdr/QcReport.py?DocId=CDR0000526280&Session=guest)

**Small bowel cancer**

There are variable reports on the lifetime risk of small bowel cancer associated with Lynch syndrome, ranging from less than 1% to 12%.[[4](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_4), [367](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_367), [428](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_428), [429](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_429), [430](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_430), [433](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_433)] Most small bowel malignancies are confined to the duodenum and the ileum, which are within endoscopic reach using EGD and colonoscopy (with dedicated ileal intubation), respectively. Other modalities to assess for small bowel lesions include CT enterography and capsule endoscopy but cost-effectiveness analyses do not support use of these evaluations for routine screening in Lynch syndrome.[[431](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_431)]

[Level of evidence: 5](https://cdr.cancer.gov/cgi-bin/cdr/QcReport.py?DocId=CDR0000526280&Session=guest)

**Urinary tract cancer**

Urinary tract malignancies include those of the transitional cell type of the renal pelvis and ureters, and the bladder. The associated lifetime risk of these malignancies is variable, ranging from less than 1% to as high as 25%, with higher estimates related to pooling the cancers found in different locations within the urinary tract and including the bladder.[[4](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_4), [367](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_367), [429](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_429), [430](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_430), [433](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_433), [434](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_434)] Studies that have evaluated urinary cytology as a potential screening modality revealed that it was associated with low sensitivity and a high false-positive rate and ultimately leads to additional evaluation that is often invasive (i.e., cystoscopy). There are currently no effective modalities used for routine screening in asymptomatic individuals with Lynch syndrome.

[Level of evidence: 5](https://cdr.cancer.gov/cgi-bin/cdr/QcReport.py?DocId=CDR0000526280&Session=guest)

**Pancreatic cancer**

An elevated risk of pancreatic cancer among Lynch syndrome carriers has been supported by two cohort studies that adjust for ascertainment bias. One study reported a cumulative risk of pancreatic cancer of 3.7% by age 70 years and an 8.6-fold increase compared with the general population. [[439](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_439)] Another prospective study using data from the Colon Cancer Family Registry reported an SIR of 10.7 with cumulative risk of 0.95%.[[404](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_404)] Results of these studies have supported an expert consensus that recommended screening for pancreatic cancer in individuals with Lynch syndrome and an FDR with pancreatic cancer, similar to other high-risk populations with comparable risk.[[475](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_475)]

Of note, screening for cancers of the urinary tract, bladder, hepatobiliary system, and pancreas is not recommended beyond that for the general population, unless there is a family history of the specific cancers for which screening is initiated approximately 10 years before the age of diagnosis in the relative with Lynch syndrome.**[**[**102**](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_102)**,** [~~476~~](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_476)~~]~~

[Level of evidence: 5](https://cdr.cancer.gov/cgi-bin/cdr/QcReport.py?DocId=CDR0000526280&Session=guest)

**Chemoprevention in Lynch syndrome**

The Colorectal Adenoma/Carcinoma Prevention Programme (CAPP2) was a double-blind, placebo-controlled, randomized trial to determine the role of aspirin in preventing CRC in patients with Lynch syndrome who were in surveillance programs at a number of international centers.[[477](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_477)] The study randomly assigned 861 participants to receive aspirin (600 mg/day), aspirin placebo, resistant starch (30 g/day), or starch placebo for up to 4 years. At a mean follow-up of 55.7 months (range, 1–128 months), 53 primary CRCs developed in 48 participants (18 of 427 in the aspirin group and 30 of 434 in the aspirin placebo group). Seventy-six patients who refused randomization to the aspirin groups (because of an aspirin sensitivity or a history of peptic ulcer disease) were randomly assigned to receive resistant starch or resistant starch placebo. The intent-to-treat analysis yielded an HR for CRC of 0.63 (95% CI, 0.35–1.13; *P* = .12). However, five of the patients who developed CRC developed two primary colon cancers. A Poisson regression was performed to account for the effect of the multiple primary CRCs and yielded a protective effect for aspirin (incidence rate ratio [IRR], 0.56; 95% CI, 0.32–0.99; *P* = .05). For participants who completed at least 2 years of treatment, the per-protocol analysis yielded an HR of 0.41 (95% CI, 0.19–0.86; *P* = .02) and an IRR of 0.37 (0.18–0.78; *P* = .008). An analysis of all Lynch syndrome cancers (endometrial, ovarian, pancreatic, small bowel, gallbladder, ureter, stomach, kidney, and brain) revealed a protective effect of aspirin versus placebo (HR, 0.65; 95% CI, 0.42–1.00; *P* = .05). There were no significant differences in adverse events between the aspirin and placebo groups, and no serious adverse effects were noted with any treatment. The authors concluded that 600 mg of aspirin per day for a mean of 25 months substantially reduced cancer incidence in Lynch syndrome patients. CAPP2 failed to show any effect from daily resistant starch intake. A limitation of the trial is that the frequency of surveillance studies at the various centers was not reported as being standardized. Earlier CAPP2 trial results for 746 Lynch syndrome patients enrolled in the study were published in 2008 [[478](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_478)] and failed to show a significant preventive effect on incident colonic adenomas or carcinomas (relative risk, 1.0; 95% CI, 0.7–1.4) with a shorter mean follow-up of 29 months (range, 7–74 months). A 2015 survey of 1,858 participants in the Colon Cancer Family Registry suggested that aspirin and ibuprofen might be chemopreventive for carriers of MMR gene pathogenic variants.[[479](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_479)] The [CAPP3](http://www.capp3.org/) trial, which is evaluating the effect of lower doses of aspirin (blinded 100 mg, 300 mg, and 600 mg enteric-coated aspirin), began in 2013 and is expected to enroll approximately 3,000 carriers of pathogenic variants by about 2021.[[480](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_480)]

Despite level 1 evidence, experts believe that the evidence regarding aspirin use for the chemoprevention of Lynch syndrome is not sufficiently robust or mature to recommend its standard use.[[426](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_426)]

[Level of evidence: 1aii](https://cdr.cancer.gov/cgi-bin/cdr/QcReport.py?DocId=CDR0000526277&Session=guest)

**Management of Lynch syndrome-associated CRC**

**Surgical management of CRC in Lynch syndrome**

One of the hallmark features of Lynch syndrome is the presence of synchronous and metachronous CRCs. The incidence of metachronous CRCs has been reported to be 16% at 10 years, 41% at 20 years, and 63% at 30 years after segmental colectomy.[[396](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_396)] Because of the increased incidence of synchronous and metachronous neoplasms, the recommended surgical treatment for a patient with Lynch syndrome with neoplastic colonic lesions is generally an extended colectomy (total or subtotal). Nevertheless, treatment has to be individualized and has often included segmental colectomy. Mathematical models suggest that there are minimal benefits of extended procedures in individuals older than 67 years, compared with the benefits seen in younger individuals with early-onset cancer. In one Markov decision analysis model, the survival advantage for a young individual with early-onset CRC undergoing an extended procedure could be up to 4 years longer than that seen in the same individual undergoing a segmental resection.[[481](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_481)] The recommendation for an extended procedure must be balanced with the comorbidities of the patient, the clinical stage of the disease, the wishes of the patient, and surgical expertise. No prospective or retrospective study has shown a survival advantage for patients with Lynch syndrome who underwent an extended resection versus a segmental procedure.

Two studies have shown that patients who undergo extended procedures have fewer metachronous CRCs and additional surgical procedures related to CRC than do patients who undergo segmental resections.[[396](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_396), [482](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_482)] Balancing functional results of an extended procedure versus a segmental procedure is of paramount importance. Although the majority of patients adapt well after an abdominal colectomy, some patients will require antidiarrheal medication. A decision model compared QALYs for a patient aged 30 years undergoing an abdominal colectomy versus a segmental colectomy.[[483](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_483)] In this model, there was not much difference between the extended and segmental procedure, with QALYs being 0.3 years more in patients undergoing a segmental procedure than in those undergoing an extended procedure.[[483](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_483)]

When considering surgical options, it is important to recognize that a subtotal or total colectomy will not eliminate the rectal cancer risk. The lifetime risk of developing cancer in the rectal remnant after an abdominal colectomy has been reported to be 12% at 12 years post-colectomy.[[484](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_484)] In addition to the general complications of surgery are the potential risks of urinary and sexual dysfunction and diarrhea after an extended colectomy; these risks increase as the anastomosis becomes more distal. Therefore, the choice of surgery must be made on an individual basis by the surgeon and the patient.

In patients with Lynch syndrome and rectal cancer, similar surgical options (extended vs. segmental resection) and considerations must be given. Extended procedures include restorative proctocolectomy and IPAA if the sphincter can be saved, or proctocolectomy with loop ileostomy if the sphincter cannot be saved. The risk of metachronous colon cancer after segmental resection for an index rectal cancer has been reported to be between 15% and 27%.[[444](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_444), [485](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_485)] Two retrospectives studies reported a 15% and 18% incidence of metachronous colon cancer after segmental rectal cancer–resection in patients with Lynch syndrome.[[486](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_486), [487](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_487)] In one of the studies, the combined risk of metachronous high-risk adenomas and cancers was 51% at a median follow-up of 101.7 months after proctectomy.[[487](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_487)]

There are no data about fertility after surgery in Lynch syndrome patients. In female FAP patients, no difference in fecundity after abdominal colectomy and IRA has been reported, whereas there is a 54% decrease in fecundity in patients who undergo restorative proctocolectomy with IPAA compared with the general population.[[488](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_488)] Another study in which a questionnaire was sent to FAP patients reported a similar prevalence of fertility problems among patients who had undergone IRA, IPAA, and proctocolectomy with end ileostomy. In that study, it was reported that earlier age at the time of surgery was associated with more fertility problems.[[489](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_489)]

Most clinicians who treat patients with Lynch syndrome will favor an extended procedure at the time of CRC diagnosis. However, as stated above, the choice of surgery must be made on an individual basis by the surgeon and the patient.[[466](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_466), [490](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_490), [491](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_491)]

[Level of Evidence: 4](https://cdr.cancer.gov/cgi-bin/cdr/QcReport.py?DocId=CDR0000531845&Session=guest)

**Prognostic and therapeutic implications of MSI**

As discussed in previous sections, MSI is not only a molecular feature of Lynch syndrome, but is also present in 10% to 15% of sporadic cases of CRC (largely due to *MLH1* hypermethylation or biallelic somatic pathogenic variants in an MMR gene). Although MSI testing was initially utilized to screen patients who might harbor pathogenic MMR gene variants, it has been increasingly recognized that MSI has important prognostic and therapeutic implications. The utility of MSI testing beyond identifying Lynch syndrome has made the case for universal MSI screening more compelling, and has contributed to its widespread adoption. Several studies have suggested that stage-specific survival is better for MSI-H CRC compared with MSS cancers. Additionally, the chemotherapeutic agent 5-fluorouracil (5-FU) appears ineffective in the adjuvant treatment of resected MSI-H CRC, in contrast to MSS CRC in which this agent is widely utilized for this purpose. Finally, immunomodulation with agents such as checkpoint inhibitors appears effective in the treatment of advanced MSI-H CRC based on early phase 1 and phase 2 studies, while these agents, at least when utilized as monotherapy, show little activity in MSS CRC.

**Prognosis of MSI**

Although MSI-H tumors account for 15% of all sporadic CRC, they appear to be more frequent in stage II compared with stage III CRC,[[492](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_492)] and are even less common in metastatic disease, being present in only 3% to 4% of metastatic cases.[[493](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_493)] This stage distinction alludes to the possibility of a better prognosis associated with underlying MSI-H status.

Several studies subsequently confirmed the improved survival of stage II MSI-H CRC compared with MSS cases. A meta-analysis of 32 studies of 7,642 cases, including 1,277 with MSI-H, showed a combined HR estimate for overall survival (OS) associated with MSI of 0.65 (95% CI, 0.59–0.71; heterogeneity *P* = .16; I2 [a measure of the percentage of variation across studies that is due to heterogeneity rather than chance] = 20%).[[494](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_494)] However, while data were limited, tumors with MSI derived no benefit from adjuvant 5-FU (HR, 1.24; 95% CI, 0.72–2.14). Subsequent data from several large randomized clinical trials confirmed the favorable prognosis associated with MSI-H. These included the QUick And Simple And Reliable (QUASAR) trial, which explored the benefit of adjuvant 5-FU–based chemotherapy compared with surgery alone in 1,900 patients with resected stage II CRC. In this study, MSI-H tumors were associated with a recurrence risk of half that of MSS tumors (risk ratio [RR], 0.53; 95% CI, 0.40–0.70).[[495](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_495)] Similar results were seen in the Pan European Trial Adjuvant Colon Cancer (PETACC)-3 trial, a randomized trial of 5-FU with or without irinotecan in resected stage II or stage III CRC.[[496](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_496)] MSI-H status was associated with an OS odds ratio (OR) of 0.39 (95% CI, 0.24–0.65) and this advantage was seen in both stage II and stage III disease.

Given the predilection for MSI-H tumors to involve the right side of the colon, there is a paucity of data on the outcome and prognosis of MSI-H tumors involving the rectum. One study suggested only 2% of rectal cancers are MSI-H.[[495](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_495)] A study of 62 patients with MSI-H rectal cancers from a single institution were followed for a median of 6.8 years. The 5-year rectal cancer–specific survival was 100% for stage I and stage II, 85.1% for stage III, and 60.0% for stage IV disease, suggesting the favorable prognosis associated with MSI-H may also apply to cancers involving the rectum.[[485](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_485)] The authors additionally reported a favorable 26% pathologic complete response (pCR) rate with 5-FU combined with radiation therapy, suggesting that 5-FU given with radiation for the locoregional treatment of rectal cancer may still be effective in the setting of MSI-H tumors. The substantial rate of pCRs demonstrated in this study also reinforces the need for adequate biopsies to assess MSI status prior to commencing treatment.

**The use of adjuvant chemotherapy after surgery for CRC in Lynch syndrome**

The finding of MSI in a CRC has been shown in several studies to predict the lack of benefit of adjuvant chemotherapy with 5-FU in resected stage II or stage III colon cancer.[[497](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_497)] This has been a controversial area historically. It was known that loss of DNA MMR activity in cultured colon cancer cells conferred resistance to DNA-damaging agents (the common mechanism of cytotoxic chemotherapy) through loss of the signal to arrest the cell cycle in response to DNA damage that cannot be repaired.[[498](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_498)] This led to the prediction that DNA MMR-deficient (dMMR) tumors may not be fully sensitive to alkylating agents, 5-FU, and platinum-containing drugs.[[499](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_499), [500](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_500), [501](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_501)] Unexpectedly, in 2000, a paper was published suggesting that patients with Dukes C (stage III) CRC with MSI had a substantial survival benefit when given 5-FU–based adjuvant chemotherapy.[[502](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_502)] However, the patients in this analysis had not been randomized to therapy; they were selected for adjuvant chemotherapy based upon clinical status, and inadvertently, the median age in the treatment group was 13 years younger than the controls.

In 2003, however, the outcomes in a randomized controlled prospective trial of adjuvant chemotherapy in 570 colon cancer patients demonstrated no benefit from adjuvant 5-FU in the group with MSI. Moreover, there were nonsignificant trends towards increased mortality when colon cancers with MSI were treated: twofold for stage III cancers and threefold for stage II cancers.[[503](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_503)] Subsequently, ten studies confirmed this, as all failed to show benefit when CRC patients were given 5-FU–based chemotherapy.[[497](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_497)] In contrast, a meta-analysis of randomized trials of 5-FU versus observation suggested a potential benefit of 5-FU in patients with MSI stage III disease. An exploratory subset analysis suggested benefit only in those patients with Lynch syndrome–related MSI. An analysis of stage II patients was not undertaken in this study.[[504](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_504)]

Preclinical data suggests the addition of oxaliplatin to 5-FU can overcome the resistance to 5-FU monotherapy seen in MSI-H tumors.[[505](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_505)] A retrospective analysis of 433 MSI-H stage II and stage III CRC cases (both sporadic and secondary to Lynch syndrome) suggested a benefit in disease-free survival (DFS) with FOLFOX (5-FU and oxaliplatin) compared with surgery alone.[[506](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_506)] There was a trend towards improved DFS utilizing FOLFOX in the subset of patients with MSI due to Lynch syndrome, however, the result was not statistically significant. Additional studies have demonstrated similar survival outcomes irrespective of MSI status with adjuvant chemotherapy including FOLFOX.[[507](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_507), [508](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_508)]

[Level of evidence (against the use of adjuvant therapy): 1ai](https://cdr.cancer.gov/cgi-bin/cdr/QcReport.py?DocId=CDR0000531810&Session=guest)

**Immunotherapy**

Tumors that develop via the MSI pathway have more somatic variants than tumors that develop via other pathways. This could imply that dMMR tumors may have more potential antigens (termed *neoantigens*) and may be more responsive to immune system manipulation than proficient MMR (pMMR) tumors. Microscopically, MSI-H tumors often exhibit abundant tumor-infiltrating lymphocytes, sometimes resulting in a Crohn-like reaction. This histologic feature has long suggested the possibility of increased tumor immune surveillance in MSI-H cancers, and is one of the main hypotheses for the better stage-specific survival seen in MSI-H compared with MSS cancers.

To test the hypothesis of efficacy of immunomodulation in MSI-H tumors, a phase 2 trial of programmed cell death-1 (PD-1) inhibition was carried out in a small cohort of patients with MSI-H or MSS cancers. Patients with metastatic disease that had failed various chemotherapy regimens were treated with pembrolizumab, an anti–PD-1 immune checkpoint inhibitor.[[509](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_509)] In this small phase 2 study, 32 patients with CRC (11 were dMMR, 21 were pMMR, and 9 others had noncolorectal dMMR tumors) were treated with intravenous pembrolizumab every 14 days. The immune-related response among evaluable patients was 40% (4 of 10) for dMMR CRC tumors, 0% (0 of 18) for pMMR CRC tumors, and 71% (5 of 7) for non-CRC dMMR tumors. The immune-related 20-week progression-free survival (PFS) was 78% (7 of 9) in patients with dMMR CRC tumors, 11% (2 of 18) in patients with pMMR CRC tumors, and 67% (4 of 6) in patients with non-CRC dMMR tumors. dMMR tumors had a mean of 24-fold more somatic variants than pMMR tumors. Additionally, in this study somatic variant load was associated with prolonged PFS. The authors concluded that MMR status predicted clinical benefit to immune checkpoint blockade with pembrolizumab.

A single-arm phase 2 study of another PD-1 inhibitor, nivolumab, was performed in 74 patients with MSI-H/dMMR CRC that had progressed on prior cytotoxic chemotherapy (including 5-FU, irinotecan, and oxaliplatin).[[510](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_510)] Overall, 31% of patients (23 of 74) experienced an objective response to therapy, and 69% (51 of 74) had disease control for at least 12 weeks. Among patients who responded to nivolumab, the median duration of response was not reached at the time of study analysis (median follow up of 12 months). There was no significant difference in the response rates among individuals with Lynch syndrome–associated metastatic MSI-H/dMMR CRC versus non-Lynch metastatic MSI-H/dMMR CRC in this study. Twenty percent of study participants experienced grade 3 or greater toxicities, most commonly elevations in amylase and/or lipase, and there were no deaths that were attributed to nivolumab.

Based on these data, pembrolizumab 200 mg given intravenously every 3 weeks was approved by the FDA in May 2017 for the treatment of any MSI-H/dMMR metastatic cancer that is refractory to standard therapy and nivolumab 240 mg given intravenously every 2 weeks was granted accelerated approval by the FDA in August 2017 for the treatment of MSI-H/dMMR CRC that is refractory to cytotoxic chemotherapy.

[Level of evidence: 3b](https://cdr.cancer.gov/cgi-bin/cdr/QcReport.py?DocId=CDR0000531837&Session=guest)

**Vaccines in the treatment or prevention of MSI-related CRC**

An alternative approach to immunotherapy in MSI-H CRC involves the use of tumor-directed vaccines. The most promising approaches thus far involve the use of tumor-related neoantigens as epitopes to increase tumor-specific T-cell immunity. Studies are currently under way in the adjuvant treatment of resected stage III CRC ([NCT01461148](https://clinicaltrials.gov/ct2/show/NCT01461148?term=NCT01461148&rank=1)), in patients with metastatic disease ([NCT01885702](https://clinicaltrials.gov/ct2/show/NCT01885702?term=NCT01885702&rank=1)), and in the prevention of CRC in patients with Lynch syndrome [(NCT01885702)](https://clinicaltrials.gov/ct2/show/NCT01885702?term=NCT01885702&rank=1).

**Lifestyle modifications for Lynch syndrome**

***[Comment: Possible new section at a later time.]***

**Lynch syndrome–related syndromes**

**Lynch-like or HNPCC-like syndrome**

Lynch-like syndrome may account for up to 70% of cases in which Lynch syndrome is suspected but germline testing fails to identify a pathogenic MMR gene variant.[[305](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_305)] Similar to the tumor phenotype seen in Lynch syndrome, CRCs manifest MSI and IHC loss of a DNA MMR protein. However, the MMR-deficient CRCs are due to biallelic somatic inactivation of DNA MMR genes,[[511](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_511), [512](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_512), [513](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_513)] in which a somatic variant in one allele of the MMR gene along with loss of heterozygosity of the other allele is most probable versus the presence of two somatic sequence variants. (Refer to [Table 15](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#_3022) for more information about the tumor phenotype of Lynch-like syndrome.)

Possible explanations for the cause of Lynch-like syndrome include the following: (1) the possibility that some germline DNA variants are not detected by current testing; (2) affected individuals may have germline pathogenic variants in genes other than DNA MMR genes currently known to be associated with Lynch syndrome; or (3) there are other mechanisms that inactivate DNA MMR beyond those related to alterations in the germline.

There is growing evidence that the CRC risk among probands and families with Lynch-like syndrome are lower, with an SIR of 2.12, than in Lynch syndrome, with an SIR of 6.04.[[305](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_305)] Preliminary estimates reveal a lower risk of extracolonic cancers with a SIR of 1.69 in Lynch-like syndrome versus 2.81 in Lynch syndrome. In the absence of large-scale studies with longitudinal follow-up, in addition to data pertaining to the rates of neoplastic progression in Lynch-like syndrome, intensive cancer screening recommendations are currently similar to those in Lynch syndrome guidelines.

**Familial colorectal cancer type X**

The term *familial colorectal cancer type X* or *FCCX* was coined to refer to families who meet Amsterdam criteria but lack MSI/IHC abnormalities.[[261](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_261)] Approximately 50% of families that fulfill Amsterdam criteria, lack pathogenic MMR gene variants and thereby are characterized as FCCX families. Research is ongoing to determine a genetic etiology for FCCX, but for the most part it remains unknown and is thought to be a heterogeneous condition. However, differentiating between Lynch syndrome and FCCX has important implications regarding cancer risk assessment and screening recommendations for affected individuals and at-risk relatives. While the risk of CRC is increased to twice that in the general population, it is less than that in Lynch syndrome (>sixfold increase) and there is no significant risk of extracolonic malignancy. Cancer screening recommendations are therefore modified and CRC surveillance is recommended every 5 years.[[261](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_261)]

**Special considerations: Young-onset CRC**

The epidemiology of CRC with regard to age at diagnosis is shifting with individuals increasingly being diagnosed before age 50 years.[[514](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_514)] (Refer to the PDQ summary on [Colorectal Cancer Prevention](https://cdr.cancer.gov/cgi-bin/cdr/QcReport.py?DocId=CDR0000062763&Session=guest) for more information about CRC incidence trends in the general population.) One study that examined the prevalence of highly penetrant pathogenic variants in 450 individuals with young-onset CRC (mean age at diagnosis, 42.5 y) and a family history including at least one FDR with colon, endometrial, breast, ovarian, and/or pancreatic cancer identified 75 germline pathogenic or likely pathogenic variants in 72 patients (16%).[[341](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_341)] The spectrum of variants identified included Lynch syndrome and non-Lynch syndrome–associated genes, including several genes that have not traditionally been associated with CRC (e.g., *BRCA1*/*BRCA2*, *ATM*, *CHEK2*, *PALB2*, and *CDKN2A*). Given the high frequency and variety of hereditary cancer syndromes identified, the authors suggest that multigene (panel) testing in this population may be warranted.

In the absence of additional family or personal history suggestive of Lynch syndrome, isolated cases of CRC diagnosed before age 36 years are uncommonly associated with MMR gene pathogenic variants. One study found MMR pathogenic variants in only 6.5% of such individuals,[[515](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_515)] whereas another study of CRC patients younger than 50 years with no more than one FDR with CRC found abnormal MSI in 21% of tumors and overrepresentation of defects in the *PMS2* and *MSH6* genes.[[516](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_516)] Therefore, isolated cases of very early-onset CRC should be offered tumor screening with MSI/IHC rather than proceeding directly to germline pathogenic variant analysis.

**Advances in Endoscopic Imaging in Hereditary CRC**

Performance of endoscopic therapies for adenomas in FAP and Lynch syndrome, and decision-making regarding surgical referral and planning, require accurate estimates of the presence of adenomas. In both AFAP and Lynch syndrome the presence of very subtle adenomas poses special challenges—microadenomas in the case of AFAP and flat, though sometimes large, adenomas in Lynch syndrome.

**Chromoendoscopy**

The need for sensitive means to endoscopically detect subtle polyps has increased with the recognition of flat adenomas and sessile serrated polyps in otherwise average-risk subjects, very attenuated adenoma phenotypes in AFAP, and subtle flat adenomas in Lynch syndrome. Modern high-resolution endoscopes improve adenoma detection yield, but the use of various vital dyes, especially indigo carmine dye-spray, has further improved detection. Several studies have shown that the improved mucosal contrast achieved with the use of indigo carmine can improve the adenoma detection rate. Whether family history is significant or not, careful clinical evaluation consisting of dye-spray colonoscopy (indigo carmine or methylene blue),[[458](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_458), [517](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_517), [518](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_518), [519](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_519), [520](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_520), [521](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_521), [522](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_522)] with or without magnification, or possibly newer imaging techniques such as narrow-band imaging,[[523](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_523)] may reveal the characteristic right-sided clustering of more numerous microadenomas. Upper GI endoscopy may be informative if duodenal adenomas or fundic gland polyps with surface dysplasia are found. Such findings will increase the likelihood of variant detection if *APC* or *MUTYH* testing is pursued.

In various large series of average-risk populations, subtle flat lesions were detected in about 5% to 10% of cases, including adenomas with high-grade dysplasia and invasive adenocarcinoma.[[524](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_524)] Some of these studies involved tandem procedures—white-light exam followed by randomization to “intensive” (> 20-minute pull-back from cecum) inspection versus chromoendoscopy—with significantly more adenomas detected in the chromoendoscopy group.[[525](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_525)] However, in several randomized trials, no significant difference in yield was seen.[[526](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_526), [527](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_527)]

In a randomized trial of subjects with Lynch syndrome,[[528](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_528)] standard colonoscopy, with polypectomy as indicated, was followed by either indigo carmine chromoendoscopy or repeat “intensive” white-light colonoscopy (a design very nearly identical to the average-risk screening group noted above). In this series, no significant difference in adenoma yield between the chromoendoscopy and intensive white-light groups was detected. However, these patients were younger and in many cases had undergone several previous exams that might have resulted in polyp clearing.

In a German study,[[529](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_529)] one series of Lynch syndrome patients underwent white-light exam followed by chromoendoscopy, while a second series underwent colonoscopy with narrow-band imaging followed by chromoendoscopy. Significant differences in flat polyp detection favored chromoendoscopy in both series, although some of the detected lesions were hyperplastic. In a French series of Lynch syndrome subjects that also employed white-light exam followed by chromoendoscopy, significantly more adenomas were detected with chromoendoscopy.[[459](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_459)]

Fewer evaluations of chromoendoscopy have been performed in AFAP than in Lynch syndrome. One study examined four patients with presumed AFAP and fewer than 20 adenomas upon white-light examination.[[530](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_530)] All had more than 1,000 diminutive adenomas found on chromoendoscopy, in agreement with pathology evaluation after colectomy.

A similar role for chromoendoscopy has been suggested to evaluate the duodenum in FAP. One study from Holland that used indigo carmine dye-spray to detect duodenal adenomas showed an increase in the number and size of adenomas, including some large ones. Overall Spigelman score was not significantly affected.[[531](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_531)]

**Small bowel imaging**

Patients with PJS and JPS are at greater risk of disease-related complications in the small bowel (e.g., bleeding, obstruction, intussusception, or cancer) ***[AB-Comment: (Amos) PJS and JPS should have been described before this point since the reader would have little idea why they are discussed here. ]*** . FAP patients, although at great risk of duodenal neoplasia, have a relatively low risk of jejunoileal involvement. The RR of small bowel malignancy is very high in Lynch syndrome, but absolute risk is less than 10%. Although the risks of small bowel neoplasia are high enough to warrant consideration of surveillance in each disease, the technical challenges of doing so have been daunting. Because of the technical challenges and relatively low prevalences, there is virtually no evidence base for small-bowel screening in Lynch syndrome.

***[AB-Comment: (Boland) Suggested revisions to the next few paras.]***

Historically, the relative endoscopic inaccessibility of the mid and distal small bowel required radiographic measures for its evaluation, including the barium small bowel series or a variant called tube enteroclysis, in which a nasogastroduodenal tube is placed so that all of the contrast goes into the small intestine ***intestine quickly and undiluted by gastric juice*** for more precise imaging. None of these measures were sensitive for small lesions. ***Previously , therapeutic removal of lesions required laparotomy and*** *~~Any therapeutic undertaking required laparotomy. This entailed resection in most cases, although~~* intraoperative endoscopy, with or without enterotomy for scope access*~~, has been available for many years~~*. *~~Peroral enteroscopy (aided by stiffening overtubes with two balloons, one balloon, or spiral ribs) has been employed to overcome the technical problem of excessive looping, enabling deep jejunal access with therapeutic (polypectomy) potential.~~****Currently, however, multiple novel endoscopic approaches have been developed to overcome the technical limitations to small bowel endoscopy,which has enabled jejunal and ileal access and therapeutic polypectomy.***

*~~Most data relate that~~* ***For patients with*** PJS***,*** *~~with~~* double-balloon ***endoscopy or other forms of deep*** enteroscopy *~~is~~* ***are*** the preferred method***s for surveillance*** *~~for endoscopy~~* of the small bowel.[[532](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_532)] This may involve *~~only~~* ***either*** peroral enteroscopy ***or*** *~~, although subsequent~~* retrograde enteroscopy *~~has been described for~~* ***to achieve*** more complete evaluation of the *~~total~~* small bowel. Because these procedures are time-consuming and involve *~~some risk~~* ***risks*** of complication, deep enteroscopy is usually preceded by more *~~noninvasive~~* imaging, including *~~traditional~~* barium exams, capsule endoscopy, *~~and~~* CT or magnetic resonance enterography.[[90](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_90)]

In FAP, data from capsule endoscopy [[90](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_90)] show a 50% to 100% prevalence of jejunal and/or ileal polyps in patients with Spigelman stage III or stage IV duodenal involvement but virtually no such polyps in Spigelman stage I or stage II disease. *~~All p~~****P***olyps *~~were~~* smaller than 10 mm and were not biopsied or removed. Consequently, their clinical significance remains uncertain but is likely limited, given the infrequency of jejunoileal cancer reports in FAP.

Capsule endoscopy in the small series of PJS patients described above [[90](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_90)] showed the presence of a similar frequency (50%–100%) of polyps, but the prevalent polyps were much larger than in FAP, were more likely to become symptomatic, and warranted endoscopic or surgical excision. Capsule studies were suggested as an appropriate replacement for radiographic studies because of the sensitivity of capsule endoscopy. ***[AB-Comment: (Amos) What is the level of evidence for capsule endoscopy? 3?]***

***Non-Lynch Syndrome, Non-FAP* Familial CRC**

***[AB-Comment: (Boland) Suggested revisions.]***

An estimated 7% to 10% of people have an FDR with CRC,[[533](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_533), [534](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_534)] and approximately twice that many have either an FDR or a second-degree relative with CRC.[[534](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_534), [535](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_535)] A simple family history of CRC (defined as one or more close relatives with CRC in the absence of a known hereditary colon cancer ***syndrome***) confers a twofold to sixfold increase in risk. The risk associated with family history varies greatly according to the age of onset of CRC in the family members, the number of affected relatives, the closeness of the genetic relationship (e.g., FDRs), and whether cancers have occurred across generations.[[533](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_533), [536](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_536)] A positive family history of CRC appears to increase the risk of CRC earlier in life such that at age 45 years, the annual incidence is more than three times higher than that in average-risk people***. When the relative has CRC****~~;~~* at age 70 years, the ***familial*** risk is similar to that in average-risk individuals.[[533](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_533)] *~~The~~* ***Similarly, the CRC*** incidence in a 35- to 40-year-old is about the same as that of an average-risk person at age 50 years. There is no evidence to suggest that CRC in people with one affected FDR is more likely to be proximal or is more rapidly progressive.

A personal history of adenomatous polyps confers a 15% to 20% risk of subsequently developing polyps [[537](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_537)] and increases the risk of CRC in relatives.[[538](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_538)] The RR of CRC, adjusted for sex and the year of birth, was 1.78 (95% CI, 1.18–2.67) for the parents and siblings of the patients with adenomas as compared with the spouse controls. The RR for siblings of patients in whom adenomas were diagnosed before age 60 years was 2.59 (95% CI, 1.46–4.58), compared with the siblings of patients who were 60 years or older at the time of diagnosis and after adjustment for the sibling's year of birth and sex, with a parental history of CRC.

While familial clusters account for approximately 20% of all CRC cases in developed countries,[[539](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_539)] the rare and highly penetrant Mendelian CRC diseases contribute to only a fraction of familial cases, which suggests that other genes and/or shared environmental factors may contribute to the remainder of the cancers. Two studies attempted to determine the degree to which hereditary factors contribute to familial CRCs.

The first study utilized the Swedish, Danish, and Finnish twin registries that cumulatively provided 44,788 pairs of same-sex twins (for men: 7,231 monozygotic [MZ] and 13,769 dizygotic [DZ] pairs; for women: 8,437 MZ and 15,351 DZ pairs) to study the contribution of heritable and environmental factors involved in 11 different cancers.[[540](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_540)] The twins included in the study all resided in their respective countries of origin into adulthood (>50 y). Cancers were identified through their respective national cancer registries in 10,803 individuals from 9,512 pairs of twins. The premise of the study was based on the fact that MZ twins share 100% and DZ twins share 50% of their genes on average for any individual twin pair. This study calculated that heritable factors accounted for 35%, shared environmental factors for 5%, and nonshared environmental factors for 60% of the risk of CRC. For CRC, the estimated [heritability](https://cdr.cancer.gov/cgi-bin/cdr/Filter.py?DocId=CDR0000781848&Filter=set:QC+GlossaryTermName+with+Concept+Set) was only slightly greater in younger groups than in older groups. This study revealed that although nonshared environmental factors constitute the major risk of familial CRC, heredity plays a larger-than-expected role.

The second study utilized the Swedish Family-Cancer Database, which contained 6,773 CRCs in offspring and 31,100 CRCs in their parents, from 1991 to 2000.[[541](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_541)] The database included 253,467 pairs of spouses, who were married and lived together for at least 30 years, and who were used to control for common environmental effects on cancer risk. In the offspring of an affected parent, the overall SIR for cancer of the colon was 1.81 (95% CI, 1.62–2.02), for cancer of the rectum it was 1.74 (95% CI, 1.53–1.96), and for cancer of the colon-and-rectum combined it was 1.78 ***[AB-Comment: (Hampel) Seems like this risk should be higher than the risks for colon and rectal cancer alone?]*** (95% CI, 1.53–1.96). The risk conferred by affected siblings was also significantly elevated. Because there was no significantly increased risk of CRC conferred between spouses, the authors concluded that heredity plays a significant role in familial CRCs; however, controls for shared environmental effects among siblings were absent in this study.

Ten percent to 15% of persons with CRC and/or colorectal adenomas have other affected family members,[[533](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_533), [534](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_534), [536](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_536), [537](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_537), [538](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_538), [542](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_542), [543](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_543), [544](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_544), [545](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_545), [546](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_546), [547](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_547)] but their findings do not fit the criteria for FAP, and their family histories may or may not meet clinical criteria for Lynch syndrome. Such families are categorized as having familial CRC, which is currently a diagnosis of exclusion (of known hereditary CRC disorders). The presence of CRC in more than one family member may be caused by hereditary factors, shared environmental risk factors, or even chance. Because of this etiologic heterogeneity, understanding the basis of familial CRC remains a research challenge.

Genetic studies have demonstrated a common autosomal dominant inheritance pattern for colon tumors, adenomas, and cancers in familial CRC families,[[548](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_548)] with a gene frequency of 0.19 for adenomas and colorectal adenocarcinomas.[[547](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_547)] A subset of families with MSI-negative familial colorectal neoplasia was found to link to chromosome 9q22.2-31.2.[[549](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_549)] A more recent study has linked three potential loci in familial CRC families on chromosomes 11, 14, and 22.[[550](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_550)] ***Little progress has been made on these putative familial cancer loci for over a decade.***

**Familial colorectal cancer type X (FCCX)**

Families meeting Amsterdam-I criteria for Lynch syndrome who do not show evidence of defective MMR by MSI testing do not appear to have the same risk of colorectal or other cancers as those families with classic Lynch syndrome and clear evidence of defective MMR. These Amsterdam-I criteria families with intact MMR systems have been described as FCCX,[[261](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_261), [551](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_551), [552](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_552), [553](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_553), [554](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_554), [555](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_555)] and it has been suggested that these families be classified as a distinct group.

The genetic etiology of FCCX remains unclear. Utilizing whole-genome linkage analysis and exome sequencing, a truncating variant in *ribosomal protein S20* (*RPS20*), a ribosomal protein gene, was identified in four individuals with CRC from an FCCX family.[[555](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_555)] The variant cosegregated with CRC in the family, with a logarithm of the odds score of 3. Additionally, the variant was not identified in 292 controls. No LOH was observed in tumor samples, and *in vitro* analyses of mature RNA formation confirmed a model of [haploinsufficiency](https://cdr.cancer.gov/cgi-bin/cdr/Filter.py?DocId=CDR0000781846&Filter=set:QC+GlossaryTermName+with+Concept+Set) for *RPS20*. No germline variants in *RPS20* were found in 25 additional FCCX families studied, suggesting *RPS20* variants are an infrequent cause of FCCX. The same group had previously identified variants in the *bone morphogenetic protein receptor type 1A* (*BMPR1A*) gene in affected individuals from 2 of 18 families with FCCX.[[556](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_556)] Additional studies are necessary to definitively confirm or refute a role for *RPS20* or *BMPR1A* in FCCX.

***[AB-Comment: (Hampel) Add new study showing BRCA2 mutations in FCCX families. Clin Genet. 2015 Jun;87(6):582-7. doi: 10.1111/cge.12427. Epub 2014 Jun 18. BRCA2 gene: a candidate for clinical testing in familial colorectal cancer type X. Garre P1, Martín L, Sanz J, Romero A, Tosar A, Bando I, Llovet P, Diaque P, García-Paredes B, Díaz-Rubio E, de la Hoya M, Caldés T. ] [AB-Comment: (Boland) Suggested text.]***

***Subsequent to these initial studies, several other putative FCCX genes have been found in familial, non-Lynch syndrome clusters of CRC including the polypeptide N-acetylgalactosaminyltransferase 12 gene,[***[***557***](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_557)***] BUB1 and BUB3,[***[***558***](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_558)***] the SEMA4A gene,[***[***559***](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_559)***] RINT1,[***[***560***](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_560)***] FAN1,[***[***561***](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_561)***] and combined effects of pathogenic variants in HNRNPA0 and WIF1 in one large kindred.[***[***562***](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_562)***] The list of possible candidate genes will no doubt continue to grow, complicating any facile approach to handling these families.***

Age of CRC onset in Lynch syndrome ranges from 44 years (registry series) to a mean of 52 years (population-based series).[[265](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_265), [312](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_312), [359](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_359)] There are no corresponding population-based data for FCCX because FCCX by definition requires at least one early-onset case***, is almost certainly very heterogeneous,*** and is not likely to lend itself to any population-based figures in the foreseeable future. Studies that have directly compared age of onset between FCCX and Lynch syndrome have suggested that the age of onset is slightly older in FCCX,[[261](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_261), [551](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_551), [553](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_553)] *~~but~~****and*** the lifetime risk of ***colorectal*** cancer is substantially lower. The SIR for CRC among families with intact MMR (FCCX families) was 2.3 (95% CI, 1.7–3.0) in one large study, compared with 6.1 (95% CI, 5.7–7.2) in families with defective MMR (Lynch syndrome families).[[261](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_261)] The risk of extracolonic tumors was also not found to be elevated in the FCCX families, suggesting that enhanced surveillance for CRC *~~was~~****would be*** sufficient. Although further studies are required, tumors arising within FCCX families also appear to have a different pathologic phenotype, with fewer tumor-infiltrating lymphocytes than those in families with Lynch syndrome.[[552](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_552)]

**Interventions for family history of CRC**

There are no controlled comparisons of screening in people with a mild or modest family history of CRC. Most experts who accept that average-risk people should be screened starting at age 50 years suggest that screening should begin earlier in life (e.g., at age *~~35–~~*40 y ***[AB-Comment: (Boland) Suggested edit]*** ) when the magnitude of risk is comparable to that of a 50-year-old. Because the risk increases with the extent of family history, there is room for clinical judgment in favor of even earlier screening, depending on the details of the family history. Some experts suggest shortening the frequency of the screening interval to every 5 years, rather than every 10 years.[[150](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_150)]

A common but unproven clinical practice is to initiate CRC screening 10 years before the age of the youngest CRC case in the family. There is neither direct evidence nor a strong rational argument for using aggressive screening methods simply because of a modest family history of CRC.

These issues were weighed by a panel of experts convened by the American Gastroenterological Association before publishing clinical guidelines for CRC screening, including those for persons with a positive family history of CRC.[[563](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_563)] These guidelines have been endorsed by a number of other organizations.

The American Cancer Society and the United States Multi-Society Task Force on Colorectal Cancer have published guidelines for average-risk individuals.[[150](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_150), [564](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_564), [565](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_565), [566](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_566), [567](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_567)] These guidelines address screening issues related to modest family history of CRC or adenomas. Given the heterogeneity of this group, it is beyond the scope of this more targeted discussion of major gene conditions.

**Rare Colon Cancer Syndromes**

***[AB-Comment: (Amos) This section needs to come before the discussion of endoscopic procedures. ] [AB-Comment: Li-Fraumeni syndrome should be added to this section.]***

***PTEN* hamartoma tumor syndromes (including Cowden syndrome)**

Cowden syndrome and Bannayan-Riley-Ruvalcaba syndrome (BRRS) are part of a spectrum of conditions known collectively as *PTEN* hamartoma tumor syndromes. Approximately 85% of patients diagnosed with Cowden syndrome, and approximately 60% of patients with BRRS have an identifiable *PTEN* pathogenic variant.[[568](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_568)] In addition, *PTEN* pathogenic variants have been identified in patients with very diverse clinical phenotypes.[[569](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_569)] The term *PTEN* hamartoma tumor syndromes refers to any patient with a *PTEN* pathogenic variant, irrespective of clinical presentation.

*PTEN* functions as a dual-specificity phosphatase that removes phosphate groups from tyrosine, serine, and threonine. Pathogenic variants of *PTEN* are diverse, including [nonsense](https://cdr.cancer.gov/cgi-bin/cdr/Filter.py?DocId=CDR0000783965&Filter=set:QC+GlossaryTermName+with+Concept+Set), missense, [frameshift](https://cdr.cancer.gov/cgi-bin/cdr/Filter.py?DocId=CDR0000783963&Filter=set:QC+GlossaryTermName+with+Concept+Set), and [splice-site variants](https://cdr.cancer.gov/cgi-bin/cdr/Filter.py?DocId=CDR0000783968&Filter=set:QC+GlossaryTermName+with+Concept+Set). Approximately 40% of variants are found in exon 5, which encodes the phosphatase core motif, and several recurrent pathogenic variants have been observed.[[570](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_570)] Individuals with variants in the 5’ end or within the phosphatase core of *PTEN* tend to have more organ systems involved.[[571](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_571)]

Operational criteria for the diagnosis of Cowden syndrome have been published and subsequently updated.[[572](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_572), [573](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_573)] These included major, minor, and [pathognomonic](https://cdr.cancer.gov/cgi-bin/cdr/Filter.py?DocId=CDR0000454769&Filter=set:QC+GlossaryTermName+with+Concept+Set) criteria consisting of certain mucocutaneous manifestations and adult-onset dysplastic gangliocytoma of the cerebellum (Lhermitte-Duclos disease). An updated set of criteria based on a systematic literature review has been suggested [[574](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_574)] and is currently utilized in the National Comprehensive Cancer Network (NCCN) guidelines.[[575](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_575)] Contrary to previous criteria, the authors concluded that there was insufficient evidence for any features to be classified as pathognomonic. With increased utilization of genetic testing, especially the use of [multigene panels](https://cdr.cancer.gov/cgi-bin/cdr/Filter.py?DocId=CDR0000763019&Filter=set:QC+GlossaryTermName+with+Concept+Set), clinical criteria for Cowden syndrome will need to be reconciled with the phenotype of individuals with documented germline *PTEN* pathogenic variants who do not meet these criteria. Until then, whether Cowden syndrome and the other *PTEN* hamartoma tumor syndromes will be defined clinically or based on the results of genetic testing remains ambiguous. The American College of Medical Genetics and Genomics (ACMG) suggests that referral for genetics consultation be considered for individuals with a personal history of or a first-degree relative with 1) adult-onset Lhermitte-Duclos disease or 2) any three of the major or minor criteria that have been established for the diagnosis of Cowden syndrome.[[576](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_576)] Detailed recommendations, including [diagnostic criteria](https://www.nature.com/articles/gim2014147/tables/4) for Cowden syndrome, can be found in the NCCN and ACMG guidelines.[[575](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_575), [576](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_576)] Additionally, a predictive [model](http://www.lerner.ccf.org/gmi/ccscore/) that uses clinical criteria to estimate the probability of a *PTEN* pathogenic variant is available; a cost-effectiveness analysis suggests that germline *PTEN* testing is cost effective if the probability of a variant is greater than 10%.[[577](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_577)]

Over a 10-year period, the International Cowden Consortium (ICC) prospectively recruited a consecutive series of adult and pediatric patients meeting relaxed ICC criteria for *PTEN* testing in the United States, Europe, and Asia.[[578](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_578)] Most individuals did not meet the clinical criteria for a diagnosis of Cowden syndrome or BRRS. Of the 3,399 individuals recruited and tested, 295 probands (8.8%) and an additional 73 family members were found to harbor germline *PTEN* pathogenic variants. In addition to breast, thyroid, and endometrial cancers, the authors concluded that on the basis of cancer risk, melanoma, kidney cancer, and colorectal cancers should be considered part of the cancer spectra arising from germline *PTEN* pathogenic variants. A second study of approximately 100 patients with a germline *PTEN* pathogenic variant confirmed these findings and suggested a cumulative cancer risk of 85% by age 70 years.[[579](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_579)]

The age-adjusted risk of CRC was increased in carriers of pathogenic variants in both studies (SIR, 5.7–10.3).[[578](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_578), [579](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_579)] In addition, one study found that 93% of individuals with *PTEN* pathogenic variants who had undergone at least one colonoscopy had polyps. The most common histology was hyperplastic, although adenomas and sessile serrated polyps were also observed. The increased risk of CRC among carriers of *PTEN* pathogenic variants has led to the recommendation of surveillance colonoscopy in these patients.[[579](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_579), [580](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_580)] However, both the age at which to begin (30–40 y) and the subsequent frequency of colonoscopies (biennial to every 3–5 y) vary considerably and are based on expert opinion.

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| **Table 19. Cancer Risk in Individuals with Germline *PTEN* Pathogenic Variantsa** |
| **Cancer**  | **Age-Adjusted SIR (95% CI)**  | **Age-Related Penetrance Estimates**  |
| Breast  | 25.4 (19.8–32.0)  | 85% starting around age 30 yb  |
| Colorectal  | 10.3 (5.6–17.4)   | 9% starting around age 40 y  |
| Endometrial  | 42.9 (28.1–62.8)  | 28% starting around age 25 y  |
| Kidney  | 30.6 (17.8–49.4)  | 34% starting around age 40 y  |
| Melanoma  | 8.5 (4.1–15.6)  | 6% with earliest age of onset at 3 y  |
| Thyroid  | 51.1 (38.1–67.1)  | 35% at birth and throughout life  |

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| *CI = confidence interval; SIR = standardized incidence ratio.* |
| *aAdapted from Tan et al.[*[*578*](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_578)*]* |
| *bOther historical studies have suggested a lower lifetime risk of breast cancer, in the range of 25%–50%.[*[*574*](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_574)*] (Refer to the* [*PTEN hamartoma tumor syndromes [including Cowden syndrome]*](https://cdr.cancer.gov/cgi-bin/cdr/QcReport.py?DocId=CDR0000062855&Session=guest#_148) *section in the PDQ summary on* [*Genetics of Breast and Gynecologic Cancers*](https://cdr.cancer.gov/cgi-bin/cdr/QcReport.py?DocId=CDR0000062855&Session=guest) *for more information.)* |

**Peutz-Jeghers syndrome (PJS)**

***[Comment: Note: This section will be maintained by the CRC WG but appear in both the CRC and Breast/Ovarian summaries. Full Board decision 4/8/11]***

PJS is an early-onset autosomal dominant disorder characterized by melanocytic macules on the lips, the perioral region, and buccal region; and multiple gastrointestinal polyps, both hamartomatous and adenomatous.[[581](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_581), [582](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_582), [583](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_583)] Germline pathogenic variants in the *STK11* gene at chromosome 19p13.3 have been identified in the vast majority of PJS families.[[584](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_584), [585](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_585), [586](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_586), [587](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_587), [588](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_588)] The most common cancers in PJS are gastrointestinal. However, other organs are at increased risk of developing malignancies. For example, the cumulative risks have been estimated to be 32% to 54% for breast cancer [[8](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_8), [589](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_589), [590](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_590)] and 21% for ovarian cancer ***[Comment: From Breast/Ovarian WG - could you specify whether this refers to sex cord tumors?] [Response: CRC WG: No - this refers to adenocarcinoma.]*** .[[589](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_589)] ***Risk for pancreatic cancer was estimated to be about 100-fold higher than the general population.[***[***589***](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_589)***]*** ***[AB-Comment: (Amos) Suggested text.]*** A systematic review found a lifetime cumulative cancer risk, all sites combined, of up to 93% in patients with PJS.[[591](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_591)] [Table 20](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#_sm_CDR0000738176_1250) shows the cumulative risk of these tumors. The high cumulative risk of cancers in PJS has led to the various screening recommendations summarized in the table of [Published Recommendations for Diagnosis and Surveillance of Peutz-Jeghers Syndrome (PJS)](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#_873) in the PDQ summary on [Genetics of Colorectal Cancer](https://cdr.cancer.gov/cgi-bin/cdr/QcReport.py?DocId=CDR0000062863&Session=guest).

Females with PJS are also predisposed to the development of cervical adenoma malignum, a rare and very aggressive adenocarcinoma of the cervix.[[592](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_592)] In addition, females with PJS commonly develop benign ovarian sex-cord tumors with annular tubules, whereas males with PJS are predisposed to development of Sertoli-cell testicular tumors;[[593](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_593)] although neither of these two tumor types is malignant, they can cause symptoms related to increased estrogen production.

Although the risk of malignancy appears to be exceedingly high in individuals with PJS based on the published literature, the possibility that selection and referral biases have resulted in overestimates of these risks should be considered.

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| **Table 20. Cumulative Cancer Risks in Peutz-Jeghers Syndrome Up To Specified Agea** |
| **Site**  | **Age (y)**  | **Cumulative Risk (%)b**  | **Reference(s)**  |
| Any cancer  | 60–70  | 37–93  | [[8](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_8), [588](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_588), [589](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_589), [590](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_590), [594](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_594), [595](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_595)]  |
| GI cancerc,d  | 60–70  | 38–66  | [[8](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_8), [590](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_590), [594](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_594), [595](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_595)]  |
| Gynecological cancer  | 60–70  | 13–18  | [[8](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_8), [590](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_590)]  |
| ***Per origin***  |   |   |   |
| Stomach  | 65  | 29  | [[589](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_589)]  |
| Small bowel  | 65  | 13  | [[589](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_589)]  |
| Colorectum  | 65  | 39  | [[8](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_8), [589](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_589)]  |
| Pancreas  | 65–70  | 11–36  | [[8](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_8), [589](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_589)]  |
| Lung  | 65–70  | 7–17  | [[8](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_8), [589](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_589), [590](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_590)]  |
| Breast  | 60–70  | 32–54  | [[8](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_8), [589](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_589), [590](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_590)]  |
| Uterus  | 65  | 9  | [[589](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_589)]  |
| Ovary  | 65  | 21  | [[589](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_589)]  |
| Cervixe  | 65  | 10  | [[589](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_589)]  |
| Testese  | 65  | 9  | [[589](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_589)]  |

|  |
| --- |
| *GI = gastrointestinal.* |
| *aReprinted with permission from Macmillan Publishers Ltd: Gastroenterology [*[*591*](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_591)*], copyright 2010.* |
| *bAll cumulative risks were increased compared with the general population (P < .05), with the exception of cervix and testes.* |
| *cGI cancers include colorectal, small intestinal, gastric, esophageal, and pancreatic.* |
| *dWesterman et al.: GI cancer does not include pancreatic cancer.[*[*594*](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_594)*]* |
| *eDid not include adenoma malignum of the cervix or Sertoli cell tumors of the testes.* |

**Peutz-Jeghers gene(s)**

PJS is caused by pathogenic variants in the *STK11* (also called *LKB1*) tumor suppressor gene located on chromosome 19p13.[[585](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_585), [586](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_586)] Unlike the adenomas seen in familial adenomatous polyposis, the polyps arising in PJS are hamartomas. Studies of the hamartomatous polyps and cancers of PJS show allelic imbalance (LOH) consistent with the two-hit hypothesis, demonstrating that *STK11* is a tumor suppressor gene.[[596](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_596), [597](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_597)] However, heterozygous *STK11* knockout mice develop hamartomas without inactivation of the remaining wild-type allele, suggesting that [haploinsufficiency](https://cdr.cancer.gov/cgi-bin/cdr/Filter.py?DocId=CDR0000781846&Filter=set:QC+GlossaryTermName+with+Concept+Set) is sufficient for initial tumor development in PJS.[[598](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_598)] Subsequently, the cancers that develop in *STK11* +/- mice do show LOH;[[599](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_599)] indeed, compound mutant mice heterozygous for pathogenic variants in *STK11* +/- and homozygous for pathogenic variants in *TP53* -/- have accelerated development of both hamartomas and cancers.[[600](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_600)]

Germline variants of the *STK11* gene represent a spectrum of nonsense, frameshift, and missense variants, and splice-site variants and large deletions.[[8](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_8), [584](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_584)] Approximately 85% of variants are localized to regions of the kinase domain of the expressed protein, and no germline variants have been reported in exon 9. No strong genotype-phenotype correlations have been identified.[[8](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_8)] ***A substantial proportion of variants comprise deletions of entire exons. [AB-Comment: (Amos) Suggested text.]***

*STK11* has been unequivocally demonstrated to cause PJS. Although earlier estimates using direct DNA sequencing showed a 50% pathogenic variant detection rate in *STK11*, studies adding techniques to detect large deletions have found pathogenic variants in up to 94% of individuals meeting clinical criteria for PJS.[[584](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_584), [591](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_591), [601](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_601)] Given the results of these studies, it is unlikely that other major genes cause PJS.

***[Comment: Note: PJS module will be maintained by the CRC WG but appear in both the CRC and Breast/Ovarian summaries. Full Board decision 4/8/11]***

**Juvenile polyposis syndrome (JPS)**

JPS is a genetically heterogeneous, rare, childhood- to early adult-onset, autosomal dominant disease that presents characteristically as hamartomatous polyposis throughout the GI tract, although colorectal polyps predominate.[[602](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_602)] JPS can present with diarrhea, GI tract hemorrhage, protein-losing enteropathy, and prolapsing polyps.[[602](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_602), [603](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_603), [604](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_604)] JPS is defined by the presence of a specific type of hamartomatous polyp called a juvenile polyp, often in the setting of a [family history](https://cdr.cancer.gov/cgi-bin/cdr/Filter.py?DocId=CDR0000302456&Filter=set:QC+GlossaryTermName+with+Concept+Set) of JPS. The diagnosis of a juvenile polyp is based on its histologic appearance, rather than age at onset. Solitary juvenile polyps of the colon or rectum are seen sporadically in infants and young children and do not imply a diagnosis of JPS. A clinical diagnosis of JPS is met by individuals fulfilling one or more of the following criteria:[[605](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_605)]

1. More than five juvenile polyps of the colon or rectum.
2. Juvenile polyps in other parts of the GI tract.
3. Any number of juvenile polyps and a positive family history of JPS.

JPS is caused by germline pathogenic variants in the *SMAD4* gene, also known as *MADH4/DPC4*, at chromosome 18q21 [[606](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_606)] in approximately 15% to 60% of cases,[[602](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_602)] and by pathogenic variants in the gene encoding the *bone morphogenic protein receptor 1A* (*BMPR1A*) residing on chromosome [band](https://cdr.cancer.gov/cgi-bin/cdr/Filter.py?DocId=CDR0000460129&Filter=set:QC+GlossaryTermName+with+Concept+Set) 10q22 in approximately 25% to 40% of cases.[[607](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_607), [608](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_608)] Because pathogenic variants in *SMAD4* and *BMPR1A* are known to account for juvenile polyposis, clinicians have referred young patients with fewer than five polyps for genetic testing. A study conducted on 77 patients with a total of 84 polyps found that the yield of genetic testing in patients with a limited number of polyps is minimal; of the germline variants detected, none were classified as definitely pathogenic or likely pathogenic.[[609](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_609)]

Genotype/phenotype correlations suggest *SMAD4* variants may be associated with a greater risk of severe gastric polyposis [[610](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_610)] and features of hereditary hemorrhagic telangiectasia (HHT) (refer to the [features of HHT](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#_2604) below).[[602](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_602)] The lifetime risk of CRC in JPS has been reported to be 39%.[[611](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_611)] There appears to be an increased risk of gastric cancer, albeit much lower than the risk of CRC.[[602](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_602)] Cardiac valvular abnormalities were present in 12% of individuals with JPS who were followed through a single-institution–based polyposis registry,[[602](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_602)] and all those with identifiable pathogenic variants had *SMAD4* variants.

JPS patients ***with SMAD4 pathogenic variants*** may also have signs and symptoms of HHT, such as arteriovenous malformations, mucocutaneous telangiectasias, digital clubbing, osteoarthropathy, hepatic arteriovenous malformations, and cerebellar cavernous hemangioma, suggesting that the two syndromes overlap.[[612](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_612)] Most *~~HHT~~* patients ***with isolated HHT [AB-Comment: (Boland) Suggested edit.]*** will have a pathogenic variant in the *activin receptor-like kinase 1* (*ALK1*) gene or in the *endoglin* (*ENG*) gene, but *SMAD4* pathogenic variants have also been reported, although they are quite rare (approximately 1%–2% of patients with HHT).[[613](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_613)] In one series, 3 of 30 patients (10%) with HHT without a clinical diagnosis of JPS were found to have germline variants in *SMAD4*.[[614](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_614)] Conversely, features of HHT were noted in 21% to 22% of carriers of *SMAD4* pathogenic variants in two studies of individuals with a clinical diagnosis of JPS.[[602](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_602), [615](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_615)] In a study of 21 carriers of *SMAD4* pathogenic variants from nine JPS families, 81% (17 of 21) of patients had HHT manifestations.[[616](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_616)] The high prevalence in this study may have been a result of the inclusion of several relatives from a single family and the inclusion of several families with the same pathogenic variant.[[616](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_616)] ***When a patient is found clinically to have features of both JPS and HHT, the pathogenic variant will be in the SMAD4 gene.***

Surveillance for HHT has been suggested in JPS patients with germline *SMAD4* pathogenic variants.[[602](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_602), [616](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_616)] On the other hand, patients with HHT without germline variants in *ALK1* or *ENG* may be considered for *SMAD4* germline genetic testing; the GI tract should be evaluated if a *SMAD4* germline pathogenic variant is confirmed.[[617](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_617)] (Refer to [Table 22](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#_2622), Published Recommendations for Diagnosis and Surveillance of JPS, for more information.)

A severe form of JPS, in which polyposis develops in the first few years of life, is referred to as JPS of infancy. JPS of infancy is often caused by microdeletions of chromosome 10q22-23, a region that includes *BMPR1A* and *PTEN*. (Refer to the [PTEN hamartoma tumor syndromes [including Cowden syndrome]](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#_2559) section of this summary for more information about *PTEN*.) The phenotype often includes features such as macrocephaly and developmental delay, possibly as a result of loss of *PTEN* function.[[618](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_618)] Recurrent GI bleeding, diarrhea, exudative enteropathy, in addition to associated developmental delay, are associated with a very high rate of morbidity and mortality in these infants, thereby limiting the heritability of such cases.[[618](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_618)]

**Juvenile polyposis gene(s)**

JPS is caused by germline pathogenic variants in the *SMAD4* gene in approximately 15% to 60% of cases, and to pathogenic variants in *BMPR1A* in approximately 25% to 40% of cases.[[602](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_602), [607](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_607), [608](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_608)] The large variability in variant frequency likely reflects the relatively small number of patients reported in individual studies. A subset of individuals meeting clinical criteria for JPS will not have an identified pathogenic variant in either *SMAD4* or *BMPR1A*.

*SMAD4* encodes a protein that is a *~~mediator~~****component*** of the transforming growth factor (TGF)-beta signaling pathway, which mediates growth inhibitory signals from the cell surface to the nucleus. Germline pathogenic variants in *SMAD4* predispose individuals to forming juvenile polyps and cancer,[[606](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_606)] and germline variants have been found in 6 of 11 exons. Most variants are unique, but several recurrent pathogenic variants have been identified in multiple independent families.[[615](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_615), [619](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_619)] ***Patients with SMAD4 pathogenic variants are also at high risk for developing extracolonic GI cancers such as gastric cancers. [AB-Comment: (Amos) Suggested text.]***

*BMPR1A* is a serine-threonine kinase type I receptor of the TGF-beta superfamily that, when activated, leads to phosphorylation of SMAD4. The *BMPR1A* gene was first identified by linkage analysis in families with JPS who did not have identifiable pathogenic variants in *SMAD4*. Variants in *BMPR1A* include nonsense, frameshift, missense, and [splice-site variants](https://cdr.cancer.gov/cgi-bin/cdr/Filter.py?DocId=CDR0000783968&Filter=set:QC+GlossaryTermName+with+Concept+Set).[[607](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_607)] Large genomic deletions detected by MLPA have been reported in both *BMPR1A* and *SMAD4* in patients with JPS.[[615](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_615), [619](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_619)] Rare JPS families have demonstrated variants in the *ENG* and *PTEN* genes, but these have not been confirmed in other studies.[[620](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_620), [621](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_621)]

***CHEK2***

Several studies initially suggested that a subset of families with hereditary breast and colon cancers may have a cancer family syndrome caused by a pathogenic variant in the *CHEK2* gene.[[622](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_622), [623](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_623), [624](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_624)] However, subsequent studies have suggested that *CHEK2* variants are associated with only a modest increase in CRC risk (i.e., low penetrance). One large study showed that truncating variants in *CHEK2* were not significantly associated with CRC; however, a specific missense pathogenic variant (I157T) was associated with modest increased risk (OR, 1.5; 95% CI, 1.2–3.0) of CRC.[[625](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_625)]

Similar results were obtained in another study conducted in Poland.[[626](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_626)] In this study, 463 probands from Lynch syndrome and Lynch syndrome–related families and 5,496 controls were genotyped for four *CHEK2* pathogenic variants, including I157T. The missense I157T allele was associated with Lynch syndrome–related cancer only for MMR variant-negative cases (OR, 2.1; 95% CI, 1.4–3.1). There was no association found with the truncating variants. Further studies are needed to confirm this finding and to determine whether they are related to FCCX. On the basis of available data, clinical testing for *CHEK2* variants is not routinely recommended in clinical practice. There are no established guidelines for CRC screening in individuals with *CHEK2* variants. ***[AB-Comment: (Hampel) Because of NGS panels, CHEK2 testing is being done routinely now for families with breast and/or colon cancer. I think NCCN is going recommend increased CRC surveillance for CHEK2 mutation carriers this year.]***

(Refer to the [*CHEK2*](https://cdr.cancer.gov/cgi-bin/cdr/QcReport.py?DocId=CDR0000062855&Session=guest#_1309) section in the PDQ summary on [Genetics of Breast and Gynecologic Cancers](https://cdr.cancer.gov/cgi-bin/cdr/QcReport.py?DocId=CDR0000062855&Session=guest) for more information.)

**Hereditary mixed polyposis syndrome (HMPS)**

HMPS is a rare cancer family syndrome characterized by the development of a variety of colon polyp types, including serrated adenomas, atypical juvenile polyps and adenomas, and colon adenocarcinoma. Although initially mapped to a locus between 6q16-q21, the HMPS locus is now believed to map to 15q13-q14.[[627](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_627), [628](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_628)] While there is considerable phenotypic overlap between JPS and HMPS, one large family has been linked to a locus on chromosome 15, raising the possibility that this may be a distinct disorder. Linkage analysis of Ashkenazi Jewish families with HMPS revealed shared haplotypes on chromosome 15q13.3.[[629](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_629)] An unusual heterozygous 40kb single-copy duplication was discovered upstream of *gremlin 1* (*GREM1*) that segregated perfectly with individuals and family members with HMPS and not with unaffected controls.[[629](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_629)] The presence of this duplication in HMPS individuals was associated with increased expression of *GREM1* transcript levels in the normal intestinal epithelium.[[629](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_629)] *GREM1* is a bone morphogenetic protein (BMP) antagonist and thus theoretically would promote the stem cell phenotype in the intestine. Germline variants leading to defective BMP signaling also underlie JPS, thus drawing a potential link between HMPS and JPS.

Although exceedingly rare, *GREM1* pathogenic variants have been described in several additional families of Ashkenazi Jewish ancestry, with varying clinical presentations. Although polyposis appears to be a unifying feature in most families, there is a high degree of variability with respect to polyp number, histology, and age of onset. In addition, extracolonic malignancies have been described in several pathogenic variant carriers, although the small number of affected individuals limits the ability to definitively demonstrate a causal link to the *GREM1* pathogenic variant. On the basis of relatively limited data, it is reasonable to consider *GREM1*-variant analysis in Ashkenazi Jewish families presenting with unexplained polyposis and/or familial CRC.[[630](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_630)] In such families, comprehensive variant analysis that includes testing for duplications in noncoding regions of *GREM1* is necessary.

**Serrated polyposis syndrome (SPS)/Hyperplastic polyposis syndrome (HPS)**

Isolated and multiple hyperplastic polyps (HPs) (typically white, flat, and small) are common in the general population, and their presence does not suggest an underlying genetic disorder. Historically, the clinical diagnosis of SPS, as defined by WHO, must satisfy one of the following criteria:

* At least five histologically diagnosed HP occurring proximal to the sigmoid colon (of which at least two are >10 mm in diameter).
* One HP occurring proximal to the sigmoid colon in an individual who has at least one FDR with hyperplastic polyposis.
* More than 30 HPs distributed throughout the colon.[[631](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_631)]

*[Note: Other groups have included serrated adenomas as part of the revised clinical criteria for SPS.[*[*632*](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_632)*]]*

Although the vast majority of cases of SPS lack a family history of HPs, approximately half of the SPS cases have a positive family history of CRC.[[633](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_633), [634](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_634)] Several studies show that the prevalence of colorectal adenocarcinoma in patients with formally defined criteria for SPS is 50% or more.[[635](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_635), [636](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_636), [637](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_637), [638](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_638), [639](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_639), [640](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_640), [641](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_641), [642](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_642)] One study, using a variation of the WHO criteria for SPS (SPS was defined as at least five histologically diagnosed HPs and/or sessile serrated adenomas (SSAs) proximal to the sigmoid colon, of which two are greater than 10 mm in diameter, or more than 20 HPs and/or SSAs distributed throughout the colon), found an RR for CRC in 347 FDRs (41% male) from 57 pedigrees of 5.4 (95% CI, 3.7–7.8).[[632](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_632)]

The WHO criteria are based on expert opinion; and, there is no known susceptibility gene or genomic region that has been reproducibly linked to this disorder, so genetic diagnosis is not possible. Two studies have reported potentially causative germline variants in SPS individuals*~~.~~****,***[[633](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_633), [643](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_643)] ***and one study reported variants in five different genes in “oncogene-induced senescence pathways” in patients with multiple sessile serrated adenomas, including: ATM, PIF1, TELO1, XAF1 and RBL1. However, there were no instances of more than one person with any of these variants nor any first-degree relatives of any proband with the variant and multiple serrated polyps, so the association remains descriptive and uncertain at this time.[***[***644***](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_644)***]***

In a study of 38 patients with more than 20 HPs, a large (>1 cm) HP, or HPs in the proximal colon, molecular alterations were sought in the base-excision repair genes *MBD4* and *MUTYH*.[[633](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_633)] One patient was found to have biallelic *MUTYH* pathogenic variants, and thus was diagnosed with *MUTYH*-associated polyposis. No pathogenic variants were detected in *MBD4* among 27 patients tested. However, six patients had single nucleotide polymorphisms of uncertain significance. Only two patients had a known family history of SPS, and ten of the 38 patients developed CRC. This series presumably included patients with sporadic HPs mixed in with other patients who may have SPS.

In a cohort of 40 SPS patients, defined as having more than five HPs or more than three HPs, two of which were larger than 1 cm in diameter, one patient was found to have a germline variant in the *EPHB2* gene (D861N).[[643](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_643)] The patient had serrated adenomas and more than 100 HPs in her colon at age 58 years, and her mother died of colon cancer at age 36 years. *EPHB2* germline variants were not found in 100 additional patients with a personal history of CRC or in 200 population-matched healthy control patients.

Far more is known about the somatic molecular genetic alterations found in the colonic tumors occurring in SPS patients. In a study of patients with either more than 20 HPs per colon, more than four HPs larger than 1 cm in diameter, or multiple (5–10) HPs per colon, a specific somatic *BRAF* variant (V600E) was found in polyp tissue.[[645](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_645)] Fifty percent of HPs (20 of 40) from these patients demonstrated the V600E *BRAF* pathogenic variant. The HPs from these patients also demonstrated significantly higher CpG island methylation phenotypes (CIMP-high), and fewer *KRAS* variants than left-sided sporadic HPs. In a previous study from this group, HPs from patients with SPS showed a loss of chromosome 1p in 21% (16 of 76) versus 0% in HPs from patients with large HPs (>1 cm), or only five to ten HPs.[[636](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_636)]

Many of the genetic and histological alterations found in HPs of patients with SPS are common with the CIMP pathway of colorectal adenocarcinoma. ***It is speculated that sporadic serrated polyps are the precursors to CRCs of the CIMP pathway.*** (Refer to the [CIMP and the serrated polyposis pathway](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#_1337) section in the [Introduction](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#_1) section of this summary for more information.)

**Interventions for rare colon cancer syndromes**

Individuals with PJS and JPS are at increased risk of CRC and extracolonic cancers. Because these syndromes are rare, there have been no evidence-based surveillance recommendations. Because of the markedly increased risk of colorectal and other cancers in these syndromes, a number of guidelines have been published based on retrospective and case series (i.e., based exclusively on expert opinion).[[151](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_151), [646](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_646), [647](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_647), [648](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_648), [649](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_649)] Clinical judgment must be used in making screening recommendations based on published guidelines.

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| **Table 21. Published Recommendations for Diagnosis and Surveillance of Peutz-Jeghers Syndrome (PJS)**  |
| **Organization**   | ***STK11* Gene Testing Recommendeda**  | **Age Colon Screening Initiated**  | **Frequency**  | **Method**  | **Extracolonic Screening Recommendations**  | **Comment**  |
| Johns Hopkins (2006) [[648](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_648)]  | Yes, at age 8 y  | 18 y   | 2–3 y  | C  | Breast, gynecologic (cervix, ovaries, uterus), pancreas, small intestine, stomach, testes  |   |
| Johns Hopkins (2007) [[649](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_649)]  | Yes, age not specified  | Late teens or at onset of symptoms  | 3 y  | C  | Breast, gynecologic (cervix, ovaries, uterus), pancreas, small intestine, stomach, testes  | Genetic testing in the late teens or at onset of symptoms.  |
| [ACPGBI](https://www.acpgbi.org.uk/content/uploads/2007-CC-Management-Guidelines.pdf) (2007)  |   | 18 y  | 3 y  | C or FS + BE  | No mention of extracolonic screening  | No recommendation for genetic testing; need to consider *STK11/LKB1* testing.  |
| Cleveland Clinic (2007) [[650](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_650)]  |   | 18 y   | 3 y  | C  | Breast, gynecologic (cervix, ovaries), pancreas, small intestine, stomach, testes  |   |
| Erasmus University Medical Center (2010) [[591](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_591)]  |   | 25–30 y  |   | C  | Breast, gynecologic (cervix, ovaries, uterus), pancreas, small intestine, stomach  |   |
| NCCN (2017) [[102](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_102)]  | No specific recommendation  | Late teens  | 2–3 y  | C  | Breast, gynecologic (cervix, ovaries, uterus), lungb, pancreas, small intestine, stomach, testes   | Refer to specialized team.  |

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| *ACPGBI = Association of Coloproctology of Great Britain and Ireland; BE = barium enema; C = colonoscopy; FS = flexible sigmoidoscopy; NCCN = National Comprehensive Cancer Network.*  |
| *aSTK11 testing includes sequencing followed by analysis for deletions (e.g., multiplex ligation-dependent probe amplification), if no variant found by sequencing.*  |
| *bLung cancer risk is increased, but there are no recommendations beyond smoking cessation and heightened awareness of symptoms.* |
| *(Refer to the* [*Other High-Penetrance Syndromes Associated With Breast and/or Gynecologic Cancer*](https://cdr.cancer.gov/cgi-bin/cdr/QcReport.py?DocId=CDR0000062855&Session=guest#_1304) *section in the PDQ summary on the* [*Genetics of Breast and Gynecologic Cancers*](https://cdr.cancer.gov/cgi-bin/cdr/QcReport.py?DocId=CDR0000062855&Session=guest) *for more information about PJS and the risk of breast and ovarian cancer.)* |

[Level of evidence: 5](https://cdr.cancer.gov/cgi-bin/cdr/QcReport.py?DocId=CDR0000526280&Session=guest)

***[Comment: Question for WG: Do you want to add extracolonic screening recommendations to the table below? (See NCCN p JPS-1)]***

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| **Table 22. Published Recommendations for Diagnosis and Surveillance of Juvenile Polyposis Syndrome (JPS)** |
| **Organization/ Author**  | ***SMAD4 / BMPR1A* Testing Recommendeda**   | **Age Screening Initiated**  | **Frequency**  | **Method**  | **Comment**  |
| [ACPGBI](https://www.acpgbi.org.uk/content/uploads/2007-CC-Management-Guidelines.pdf) (2007)  |   | 15–18 yb  | 1–2 y  | C or FS + BE  | Surveillance for gene carriers and affected until age 70 y and discussion of prophylactic surgery.  |
| Cleveland Clinic (2007) [[650](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_650)]  |   | 15 y  | 3 y  | C, EGD  | Some families with *SMAD4* pathogenic variant also have HHT; these individuals may need to be screened for HHT.   |
| Johns Hopkins (2007) [[649](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_649)]  | Yes, genetic testing preferred over C  | 15 y or at onset of symptoms  | Yearly until polyp free then every 2–3 y  | C  | Prophylactic surgery if >50–100 polyps, unable to manage endoscopically, severe GI bleeding, JPS with adenomatous changes, strong family history of CRC.  |
| St. Mark's (2012) [[602](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_602)]  | Yes, genetic testing at age 4 y   | 12 y  | 1–3 y based on severity  | C, EGD  | Consider HHT workup.  |
| NCCN (2017) [[102](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_102)]  | Yes  | ~15 y  | 2–3 y or 1 y if polyps are found  | C  | Refer to specialized team. In families without an identified pathogenic variant, consider substituting endoscopy every 5 y beginning at age 20 y and every 10 y beginning at age 40 y in patients in whom no polyps are found.  |

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| *ACPGBI = Association of Coloproctology of Great Britain and Ireland; BE = barium enema; C = colonoscopy; CRC = colorectal cancer; EGD = esophagogastroduodenoscopy; FS = flexible sigmoidoscopy; GI = gastrointestinal; HHT = hereditary hemorrhagic telangiectasia; NCCN = National Comprehensive Cancer Network.*  |
| *aSMAD4/BMPR1A testing includes sequencing followed by analysis for deletions (e.g., multiplex ligation-dependent probe amplification), if no variant found by sequencing.[*[*619*](https://cdr.cancer.gov/cgi-bin/cdr/QCforWord.py?DocId=CDR0000062863&DocType=Summary:bu&DocVersion=None&parmstring=yes&parmid=118559#CL_89_619)*]* |
| *bYounger, if patient has presented with symptoms.* |

[Level of evidence: 5](https://cdr.cancer.gov/cgi-bin/cdr/QcReport.py?DocId=CDR0000526280&Session=guest) ***[AB-Comment: (Amos) I do not agree with this level of evidence and think that 4 is more appropriate.]***

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