UpToDate®
Official reprint from UpToDate®
www.uptodate.com © 2023 UpToDate, Inc. and/or its affiliates. All Rights Reserved.

Wolters Kluwer

MUTYH-associated polyposis

AUTHORS: Shilpa Grover, MD, MPH, AGAF, Elena Stoffel, MD, MPH
SECTION EDITOR: J Thomas Lamont, MD
DEPUTY EDITOR: Kristen M Robson, MD, MBA, FACG

All topics are updated as new evidence becomes available and our peer review process is complete.

Literature review current through: **Sep 2023.**
This topic last updated: **Jun 24, 2022.**

INTRODUCTION

MUTYH-associated polyposis is an autosomal recessive polyposis syndrome. Affected patients have multiple colorectal adenomas and an increased risk for developing colorectal cancer. This topic will review the clinical manifestations, diagnosis, and management of *MUTYH*-associated polyposis. The clinical manifestations, diagnosis, and management of familial adenomatous polyposis, Lynch syndrome, and hamartomatous polyposis syndromes are discussed elsewhere. (See "Clinical manifestations and diagnosis of familial adenomatous polyposis" and "Lynch syndrome (hereditary nonpolyposis colorectal cancer): Cancer screening and management" and "Juvenile polyposis syndrome".)

GENETICS

MUTYH-associated polyposis is an autosomal recessive polyposis syndrome caused by biallelic pathogenic germline variants in the *MUTYH* gene [1]. *MUTYH* is a base excision repair gene whose protein repairs oxidative damage to the DNA. Oxidation of guanine leads to the formation of 8-oxo-6, 7, 8-dihydroxy-2 deoxyguanosine. Failure of base excision repair results in mispairing of this nucleotide with adenine and resultant somatic CG–AT transversions in multiple genes, including the *APC* and *KRAS* genes. The target genes that are mutated as a consequence of oxidative damage strongly influence the polyposis phenotype [2].

The two most common *MUTYH* gene pathogenic variants in Western Europeans and North Americans are Y179C and G396D (previously referred to as Y165C and G382D, respectively) [3]. However, pathogenic germline variants have been reported at other loci, and the prevalence of specific variants differs by ethnicity of the population [4-8]. Patients with *MUTYH*-associated polyposis may be homozygous or compound heterozygous for pathogenic germline variants in the *MUTYH* gene.

EPIDEMIOLOGY

Approximately 1 to 2 percent of the general population carry a single (monoallelic) germline *MUTYH* pathogenic variant, with two (biallelic) pathogenic variants identified in <1 percent of individuals diagnosed with colorectal cancer [9]. Among individuals with multiple colorectal adenomas in whom an *APC* mutation has been excluded, biallelic *MUTYH* pathogenic variants are found in 7 to 13 percent of patients with >100 adenomas and in 14 to 40 percent of patients with 10 to 99 adenomas [1,10-13].

CLINICAL MANIFESTATIONS

MUTYH-associated polyposis is typically characterized by the presence of multiple colorectal adenomas; however, the phenotype can vary based on the genotype. In addition, environmental and epigenetic factors may also affect the *MUTYH*-associated polyposis phenotype [14]. A number of extracolonic manifestations have also been associated with *MUTYH*-associated polyposis. (See 'Genotype phenotype correlation' below.)

Colonic manifestations — Individuals with *MUTYH*-associated polyposis usually develop between 10 to 100 colorectal polyps by the fifth or sixth decade [1,15]. However, the clinical presentation can vary, and biallelic *MUTYH* pathogenic variants have been identified in individuals with colorectal cancer (CRC) in the setting of few (<10) or no colorectal polyps [16-18]. Although adenomas are the predominant polyp type in patients with *MUTYH*-associated polyposis, multiple hyperplastic and/or sessile serrated polyps have been reported in some patients. In a study that included 17 patients with *MUTYH*-associated polyposis, eight (47 percent) had at least one hyperplastic and/or sessile serrated polyp [2]. In addition, three (18 percent) met criteria for serrated polyposis syndrome, and of these, one patient had over 100 hyperplastic and sessile serrated polyps. (See "Overview of colon polyps", section on 'Sessile serrated polyps and traditional serrated adenomas'.)

Individuals with biallelic *MUTYH* pathogenic variants and *MUTYH*-associated polyposis are at high risk for developing CRC, and approximately 60 percent of patients have CRC at presentation [19-25]. In contrast, the risk of CRC in monoallelic *MUTYH* carriers appears to be only marginally increased with an estimated lifetime risk of 5 to 7 percent [5,17,20-23,26,27]. In a meta-analysis of eight studies that included 20,565 CRC cases and 15,524 controls, there was no significant increase in CRC risk in individuals with monoallelic G396D variants, while individuals with a monoallelic Y179C variant had a 1.3-fold (95% CI 1.01-1.77) increased risk of CRC [20].

Extracolonic manifestations — Data on the extraintestinal manifestations of *MUTYH*-associated polyposis continue to emerge. Individuals with *MUTYH*-associated polyposis are at increased risk of upper gastrointestinal polyps and appear to have an increased risk for developing cancers of the duodenum [28,29].

However, as compared with patients with familial adenomatous polyposis, patients with *MUTYH*-associated polyposis appear to have a lower burden of adenomas. In a cohort study of 394 patients with *MUTYH*-associated polyposis, 21 percent had duodenal adenomas; median number of adenomas was three (range 1 to 20) and the majority were <10 mm in size [30]. Although Spigelman stage IV duodenal polyposis was rare, four individuals developed duodenal cancers, none of which occurred in the setting of stage IV duodenal polyposis (table 1). High-grade dysplasia was noted in small adenomas and two of the duodenal cancers developed within one year of a prior normal upper endoscopy, reinforcing the importance of upper endoscopic surveillance.

The incidence of extraintestinal malignancies in individuals with *MUTYH*-associated polyposis has not been well-defined. Rare extracolonic features that have been reported in patients with *MUTYH*-associated polyposis include osteomas, congenital hypertrophy of the retinal pigment epithelium, dental cysts, desmoids, sebaceous hyperplasia, and Muir-Torre phenotype with sebaceous gland tumors [27].

The risk for thyroid cancer also appears to be moderately increased [31]. (See 'Management' below.)

The tumor spectrum associated with biallelic *MUTYH* pathogenic variants continues to evolve. An early report suggested overall cancer incidence was almost twice that of the general population (standardized incidence ratio 1.9; 95% CI 1.4-2.5), with risks of cancers of the duodenum, ovaries, bladder, and skin significantly higher as compared with the general population (4, 10, 6, and 17 percent, respectively) [28]. Another study evaluated the risk of extracolonic cancer in 266 probands with *MUTYH* pathogenic germline variants (41 biallelic and 225 monoallelic) and 5158 first- and second-degree relatives from the Colon Cancer Family registry [32] and found the

cumulative risk of bladder cancer by age 70 years was 25 percent for males and 8 percent for females. In that analysis, females with biallelic *MUTYH* pathogenic germline variants had an elevated risk of ovarian cancer; however, this has not been consistently observed. In addition, while some studies have suggested risks of breast cancer and endometrial cancer may be increased in individuals with *MUTYH*-associated polyposis, this has not been consistently demonstrated [33-35]. (See "Muir-Torre syndrome".)

Some reports have suggested that prevalence of Barrett's esophagus may be higher in individuals with *MUTYH*-associated polyposis compared with the general population; however, additional studies are needed to confirm these findings [36].

Genotype phenotype correlation — The clinical phenotype in patients with *MUTYH*-associated polyposis who carry biallelic G396D pathogenic germline variants appears to be less severe than for Y179C homozygotes [19]. In one study that evaluated the phenotype of 257 patients with *MUTYH*-associated polyposis, patients with a homozygous G396D variant or compound heterozygous G396D/Y179C variants presented at a later age and had a lower risk of developing CRC as compared with patients with a homozygous Y179C variant. The mean ages of CRC diagnosis for individuals who were homozygous G396D, compound heterozygous G396D/Y179C, and homozygous Y179C were 58, 52, and 46 years, respectively. However, long-term prospective studies are needed to validate these findings.

DIAGNOSIS

The diagnosis of *MUTYH*-associated polyposis should be suspected in individuals with 10 or more cumulative colorectal adenomas or a history of multiple adenomas in combination with extracolonic features associated with *MUTYH*-associated polyposis (eg, duodenal/ampullary adenomas, desmoid tumors, thyroid cancer, congenital hypertrophy of the retinal pigment epithelium, epidermal cysts, or osteomas). Biallelic pathogenic germline variants in the *MUTYH* gene are required to establish the diagnosis [37-40].

When an individual is diagnosed with biallelic germline variants in *MUTYH* that are classified as pathogenic or likely pathogenic, genetic testing should be offered to at-risk relatives of the index case. Siblings of the index case with biallelic germline *MUTYH* variants have a 25 percent chance of having inherited both *MUTYH* variants and a 50 percent chance of being carriers of a monoallelic *MUTYH* variant. Since *MUTYH* pathogenic germline variants are carried by 1 to 2 percent of individuals in the general population, children of mono- or biallelic *MUTYH* carriers have a 0.5 to 1.0 percent chance of inheriting two *MUTYH* variants because the other parent might also be a *MUTYH* heterozygote. A cost-effectiveness analysis of Dutch *MUTYH*-associated

polyposis patients estimated that *MUTYH* testing in spouses of *MUTYH*-associated polyposis patients, and spouses of *MUTYH* heterozygotes, may be cost-effective [41]. Genetic counseling should be offered prior to genetic testing [42]. (See "Genetic testing".)

DIFFERENTIAL DIAGNOSIS

Familial adenomatous polyposis (FAP) — FAP is an autosomal dominant polyposis syndrome, in which carriers of germline pathogenic variants in the *APC* gene develop multiple (ie, 10 to >1000) colorectal adenomas. Unlike *MUTYH*-associated polyposis (which is associated with autosomal recessive inheritance), most families with FAP exhibit a vertical (parent-to-child) transmission of polyposis. However, approximately one-third of individuals with FAP have de novo *APC* mutation and thus have no family history of FAP [43]. FAP is characterized by germline pathogenic variants in the *APC* gene and can be differentiated from *MUTYH*-associated polyposis by genetic testing. (See "Clinical manifestations and diagnosis of familial adenomatous polyposis", section on 'Clinical manifestations'.)

Lynch syndrome — Lynch syndrome (previously known as hereditary nonpolyposis colorectal cancer) is an autosomal dominant hereditary cancer syndrome characterized by an increased risk for colorectal cancer (CRC), endometrial cancer, and several other malignancies, including cancers of the ovary, renal pelvis, ureter, stomach, small bowel, bile duct, skin (sebaceous neoplasms), and brain (gliomas). Lynch syndrome is caused by a germline pathogenic variant in one of several DNA mismatch repair genes (*MLH1, MSH2, MSH6, PMS2*) or loss of expression of *MSH2* due to deletion in the *EPCAM* gene. While most individuals with monoallelic pathogenic germline variants in DNA mismatch repair genes develop relatively few colorectal adenomas, individuals who harbor biallelic pathogenic germline variants in DNA mismatch repair genes (known as Biallelic/ Constitutional Mismatch Repair Deficiency) often develop multiple colorectal adenomas in childhood [44]. Individuals with *MUTYH*-associated polyposis who have few colorectal adenomas (oligo-polyposis) may be difficult to distinguish clinically from Lynch syndrome, but the diagnosis can be confirmed by genetic testing. (See "Lynch syndrome (hereditary nonpolyposis colorectal cancer): Clinical manifestations and diagnosis", section on 'Clinical features'.)

Polymerase proofreading-associated polyposis — Polymerase proofreading-associated polyposis is an autosomal dominant hereditary cancer syndrome caused by germline pathogenic variants in DNA polymerase ε (*POLE*) and δ (*POLD1*). Affected individuals develop adenomatous polyposis (classic or oligo-polyposis) and are at risk for developing CRC and endometrial cancer at an early age. Polymerase proofreading-associated polyposis appears to be rare compared with the prevalence of *MUTYH*-associated polyposis, FAP, and Lynch

Syndrome, and only a few families have been characterized [45]. In one study of 858 familial/early-onset CRC cases and polyposis patients, one *POLE* germline pathogenic variant and one *POLD1* pathogenic variant were identified [46]. Given the potential overlap among the adenomatous polyposis syndromes, germline genetic testing of patients with multiple (20 or more) adenomatous polyps should include a multigene panel to evaluate for variants in *APC, MUTYH*, and other genes associated with predisposition to polyposis and/or CRC [47].

MANAGEMENT

Colorectal cancer surveillance — For individuals with *MUTYH*-associated polyposis, we suggest colorectal cancer (CRC) screening with a colonoscopy every one to two years, starting at 25 to 30 years of age. Our recommendations are consistent with the American College of Gastroenterology guidelines, which are based on expert consensus [31]. However, other guidelines recommend colonoscopy annually starting at age 18 to 20 for biallelic carriers [48,49].

Surgical resection (eg, partial, subtotal, or total colectomy) is reserved for patients with documented or suspected CRC, or significant polyp burden that cannot be effectively managed with colonoscopic polypectomy. For patients with subtotal colectomy with ileorectal anastomosis, we perform sigmoidoscopy six months after surgery and annually thereafter [31].

Monoallelic *MUTYH* pathogenic variants may be associated with a small increase in risk (1.5 to 2-fold) for CRC; we therefore suggest that these individuals be managed based on their family history. Colonoscopic surveillance at five-year intervals should begin 10 years earlier than the earliest CRC diagnosis in the family or at age 40 years, whichever is earlier [49-51]. (See "Screening for colorectal cancer in patients with a family history of colorectal cancer or advanced polyp".)

Extracolonic surveillance

- We suggest that patients with *MUTYH*-associated polyposis undergo an upper endoscopy with duodenoscopy at baseline or the age of 30 to 35 years [31,49]. Examination of the stomach should include random sampling of fundic gland polyps. It is important to note that low-grade dysplasia is common in fundic gland polyps. Fundic gland polyps >1 cm should be resected for evaluation of high-grade dysplasia and malignant transformation [49]. In addition, polyps in the gastric antrum and duodenum should be endoscopically resected given the high probability of adenomas in this location. Surgery is reserved for high-grade dysplasia or cancer.

If endoscopic evaluation demonstrates an ampulla with mucosal abnormality or enlargement (>10 mm), we obtain biopsies of the ampulla. In patients with duodenal polyps, the surveillance interval should be based on the extent of duodenal polyposis. (See "Familial adenomatous polyposis: Screening and management of patients and families", section on 'Duodenal polyps'.)

While studies suggest that the use of chromoendoscopy may increase the diagnostic yield of upper endoscopy in patients wi*th MUTYH*-associated polyposis, further studies are needed to determine if this improves patient outcomes [52].

- We suggest annual thyroid screening by physical examination and/or ultrasound since individuals with *MUTYH*-associated polyposis appear to have a moderate increase in risk for thyroid cancer [31]; however, data to support the effectiveness of thyroid surveillance in this population are lacking.

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Hereditary colorectal cancer syndromes".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topics (see "Patient education: Colon and rectal cancer screening (The Basics)" and "Patient education: Colonoscopy (The Basics)" and "Patient education: Familial

adenomatous polyposis (The Basics)")

- Beyond the Basics topics (see "Patient education: Screening for colorectal cancer (Beyond the Basics)" and "Patient education: Colonoscopy (Beyond the Basics)" and "Patient education: Flexible sigmoidoscopy (Beyond the Basics)")

SUMMARY AND RECOMMENDATIONS

- **Genetics** – *MUTYH*-associated polyposis is an autosomal recessive polyposis syndrome caused by biallelic pathogenic variants in the base excision repair gene *MUTYH.* (See 'Genetics' above.)

- **Epidemiology** – Among individuals with multiple colorectal adenomas in whom an *APC* pathogenic germline variant has been excluded, biallelic *MUTYH* pathogenic variants are found in 7 to 13 percent of patients with >100 adenomas and in 14 to 40 percent of patients with 10 to 99 adenomas. *MUTYH*-associated polyposis is estimated to account for less than 1 percent of all colorectal cancers (CRCs). Monoallelic *MUTYH* pathogenic variants are found in 1 to 2 percent of the general population. (See 'Epidemiology' above.)

- **Colonic manifestations** – Individuals with *MUTYH*-associated polyposis usually develop between 10 to 100 colorectal polyps. However, the clinical presentation can vary, and biallelic *MUTYH* pathogenic variants have been identified in individuals who develop CRC in the absence of colorectal polyps.

  The lifetime risk of CRC is increased for individuals with biallelic *MUTYH* pathogenic variants; however, the risk for monoallelic carriers of a single pathogenic variant is only marginally increased. (See 'Colonic manifestations' above.)

- **Extracolonic manifestations** – Individuals with *MUTYH*-associated polyposis are at increased risk of gastric and duodenal polyps. Other rare extracolonic features may include osteomas, congenital hypertrophy of the retinal pigment epithelium, dental cysts, desmoids, sebaceous hyperplasia, and Muir-Torre phenotype with sebaceous gland tumors. The risk of developing thyroid cancer is increased, whereas the risk for other extraintestinal cancers such as breast and gynecologic cancers have not been consistently demonstrated. (See 'Extracolonic manifestations' above.)

- **Diagnosis** – The diagnosis of *MUTYH*-associated polyposis should be suspected in individuals with 10 or more cumulative colorectal adenomas or a history of adenomas in combination with extracolonic features associated with *MUTYH*-associated polyposis.

Biallelic germline pathogenic variants in the *MUTYH* gene are required to establish the diagnosis. (See 'Extracolonic manifestations' above and 'Diagnosis' above.)

- **Management** – For patients with *MUTYH*-associated polyposis, we initiate CRC screening with a colonoscopy every one to two years, starting at 25 to 30 years of age. We reserve colectomy for patients with documented or suspected cancer, or significant polyp burden that cannot be effectively managed with colonoscopic polypectomy. (See 'Colorectal cancer surveillance' above.)

  For patients with *MUTYH*-associated polyposis, we perform upper endoscopy with duodenoscopy at baseline or the age of 30 to 35 years. Examination of the stomach should include random sampling of fundic gland polyps. (See 'Extracolonic surveillance' above.)

  As monoallelic *MUTYH* pathogenic germline variants are associated with a small increase in risk for CRC, these individuals are managed based on their family history, with colonoscopic surveillance every five years, beginning 10 years earlier than the earliest CRC diagnosis in the family or at age 40 years, whichever is earlier. (See 'Colorectal cancer surveillance' above.)

Use of UpToDate is subject to the Terms of Use.

REFERENCES

1. Sieber OM, Lipton L, Crabtree M, et al. Multiple colorectal adenomas, classic adenomatous polyposis, and germ-line mutations in MYH. N Engl J Med 2003; 348:791.
2. Boparai KS, Dekker E, Van Eeden S, et al. Hyperplastic polyps and sessile serrated adenomas as a phenotypic expression of MYH-associated polyposis. Gastroenterology 2008; 135:2014.
3. Russell AM, Zhang J, Luz J, et al. Prevalence of MYH germline mutations in Swiss APC mutation-negative polyposis patients. Int J Cancer 2006; 118:1937.
4. Dolwani S, Williams GT, West KP, et al. Analysis of inherited MYH/(MutYH) mutations in British Asian patients with colorectal cancer. Gut 2007; 56:593.
5. Nielsen M, Franken PF, Reinards TH, et al. Multiplicity in polyp count and extracolonic manifestations in 40 Dutch patients with MYH associated polyposis coli (MAP). J Med Genet 2005; 42:e54.
6. Kim DW, Kim IJ, Kang HC, et al. Germline mutations of the MYH gene in Korean patients with multiple colorectal adenomas. Int J Colorectal Dis 2007; 22:1173.

7. Miyaki M, Iijima T, Yamaguchi T, et al. Germline mutations of the MYH gene in Japanese patients with multiple colorectal adenomas. Mutat Res 2005; 578:430.
8. Gómez-Fernández N, Castellví-Bel S, Fernández-Rozadilla C, et al. Molecular analysis of the APC and MUTYH genes in Galician and Catalonian FAP families: a different spectrum of mutations? BMC Med Genet 2009; 10:57.
9. Cleary SP, Cotterchio M, Jenkins MA, et al. Germline MutY human homologue mutations and colorectal cancer: a multisite case-control study. Gastroenterology 2009; 136:1251.
10. Jones S, Emmerson P, Maynard J, et al. Biallelic germline mutations in MYH predispose to multiple colorectal adenoma and somatic G:C-->T:A mutations. Hum Mol Genet 2002; 11:2961.
11. Venesio T, Molatore S, Cattaneo F, et al. High frequency of MYH gene mutations in a subset of patients with familial adenomatous polyposis. Gastroenterology 2004; 126:1681.
12. Knopperts AP, Nielsen M, Niessen RC, et al. Contribution of bi-allelic germline MUTYH mutations to early-onset and familial colorectal cancer and to low number of adenomatous polyps: case-series and literature review. Fam Cancer 2013; 12:43.
13. Jo WS, Bandipalliam P, Shannon KM, et al. Correlation of polyp number and family history of colon cancer with germline MYH mutations. Clin Gastroenterol Hepatol 2005; 3:1022.
14. Casper M, Spier I, Holz R, et al. Phenotypic Variability of MUTYH-Associated Polyposis in Monozygotic Twins and Endoscopic Resection of A Giant Polyp in Pregnancy. Am J Gastroenterol 2018; 113:625.
15. Grover S, Kastrinos F, Steyerberg EW, et al. Prevalence and phenotypes of APC and MUTYH mutations in patients with multiple colorectal adenomas. JAMA 2012; 308:485.
16. Wang L, Baudhuin LM, Boardman LA, et al. MYH mutations in patients with attenuated and classic polyposis and with young-onset colorectal cancer without polyps. Gastroenterology 2004; 127:9.
17. Balaguer F, Castellví-Bel S, Castells A, et al. Identification of MYH mutation carriers in colorectal cancer: a multicenter, case-control, population-based study. Clin Gastroenterol Hepatol 2007; 5:379.
18. Terdiman JP. MYH-associated disease: attenuated adenomatous polyposis of the colon is only part of the story. Gastroenterology 2009; 137:1883.
19. Nielsen M, Joerink-van de Beld MC, Jones N, et al. Analysis of MUTYH genotypes and colorectal phenotypes in patients With MUTYH-associated polyposis. Gastroenterology 2009; 136:471.

20. Theodoratou E, Campbell H, Tenesa A, et al. A large-scale meta-analysis to refine colorectal cancer risk estimates associated with MUTYH variants. Br J Cancer 2010; 103:1875.
21. Jones N, Vogt S, Nielsen M, et al. Increased colorectal cancer incidence in obligate carriers of heterozygous mutations in MUTYH. Gastroenterology 2009; 137:489.
22. Win AK, Cleary SP, Dowty JG, et al. Cancer risks for monoallelic MUTYH mutation carriers with a family history of colorectal cancer. Int J Cancer 2011; 129:2256.
23. Win AK, Dowty JG, Cleary SP, et al. Risk of colorectal cancer for carriers of mutations in MUTYH, with and without a family history of cancer. Gastroenterology 2014; 146:1208.
24. Jenkins MA, Croitoru ME, Monga N, et al. Risk of colorectal cancer in monoallelic and biallelic carriers of MYH mutations: a population-based case-family study. Cancer Epidemiol Biomarkers Prev 2006; 15:312.
25. Lubbe SJ, Di Bernardo MC, Chandler IP, Houlston RS. Clinical implications of the colorectal cancer risk associated with MUTYH mutation. J Clin Oncol 2009; 27:3975.
26. Kanter-Smoler G, Björk J, Fritzell K, et al. Novel findings in Swedish patients with MYH-associated polyposis: mutation detection and clinical characterization. Clin Gastroenterol Hepatol 2006; 4:499.
27. Aretz S, Uhlhaas S, Goergens H, et al. MUTYH-associated polyposis: 70 of 71 patients with biallelic mutations present with an attenuated or atypical phenotype. Int J Cancer 2006; 119:807.
28. Vogt S, Jones N, Christian D, et al. Expanded extracolonic tumor spectrum in MUTYH-associated polyposis. Gastroenterology 2009; 137:1976.
29. Walton SJ, Kallenberg FG, Clark SK, et al. Frequency and Features of Duodenal Adenomas in Patients With MUTYH-Associated Polyposis. Clin Gastroenterol Hepatol 2016; 14:986.
30. Collaborative Group on Duodenal Polyposis in MAP, Thomas LE, Hurley JJ, et al. Duodenal Adenomas and Cancer in MUTYH-associated Polyposis: An International Cohort Study. Gastroenterology 2021; 160:952.
31. Syngal S, Brand RE, Church JM, et al. ACG clinical guideline: Genetic testing and management of hereditary gastrointestinal cancer syndromes. Am J Gastroenterol 2015; 110:223.
32. Win AK, Reece JC, Dowty JG, et al. Risk of extracolonic cancers for people with biallelic and monoallelic mutations in MUTYH. Int J Cancer 2016; 139:1557.
33. Zhang Y, Newcomb PA, Egan KM, et al. Genetic polymorphisms in base-excision repair pathway genes and risk of breast cancer. Cancer Epidemiol Biomarkers Prev 2006; 15:353.

34. Beiner ME, Zhang WW, Zhang S, et al. Mutations of the MYH gene do not substantially contribute to the risk of breast cancer. Breast Cancer Res Treat 2009; 114:575.
35. Villy MC, Masliah-Planchon J, Buecher B, et al. Endometrial cancer may be part of the MUTYH-associated polyposis cancer spectrum. Eur J Med Genet 2022; 65:104385.
36. Daans CG, Ghorbanoghli Z, Velthuizen ME, et al. Increased prevalence of Barrett's esophagus in patients with MUTYH-associated polyposis (MAP). Fam Cancer 2020; 19:183.
37. American Gastroenterological Association. American Gastroenterological Association medical position statement: hereditary colorectal cancer and genetic testing. Gastroenterology 2001; 121:195.
38. Burt R, Neklason DW. Genetic testing for inherited colon cancer. Gastroenterology 2005; 128:1696.
39. Mao R, Krautscheid P, Graham RP, et al. Genetic testing for inherited colorectal cancer and polyposis, 2021 revision: a technical standard of the American College of Medical Genetics and Genomics (ACMG). Genet Med 2021; 23:1807.
40. NCCN colorectal cancer screening practice guidelines. National Comprehensive Cancer Network. Oncology (Williston Park) 1999; 13:152.
41. Nielsen M, Hes FJ, Vasen HF, van den Hout WB. Cost-utility analysis of genetic screening in families of patients with germline MUTYH mutations. BMC Med Genet 2007; 8:42.
42. Robson ME, Bradbury AR, Arun B, et al. American Society of Clinical Oncology Policy Statement Update: Genetic and Genomic Testing for Cancer Susceptibility. J Clin Oncol 2015; 33:3660.
43. Bisgaard ML, Fenger K, Bülow S, et al. Familial adenomatous polyposis (FAP): frequency, penetrance, and mutation rate. Hum Mutat 1994; 3:121.
44. Durno C, Boland CR, Cohen S, et al. Recommendations on Surveillance and Management of Biallelic Mismatch Repair Deficiency (BMMRD) Syndrome: A Consensus Statement by the US Multi-Society Task Force on Colorectal Cancer. Gastroenterology 2017; 152:1605.
45. Palles C, Cazier JB, Howarth KM, et al. Germline mutations affecting the proofreading domains of POLE and POLD1 predispose to colorectal adenomas and carcinomas. Nat Genet 2013; 45:136.
46. Valle L, Hernández-Illán E, Bellido F, et al. New insights into POLE and POLD1 germline mutations in familial colorectal cancer and polyposis. Hum Mol Genet 2014; 23:3506.
47. Gupta S, Provenzale D, Llor X, et al. NCCN Guidelines Insights: Genetic/Familial High-Risk Assessment: Colorectal, Version 2.2019. J Natl Compr Canc Netw 2019; 17:1032.

48. Monahan KJ, Bradshaw N, Dolwani S, et al. Guidelines for the management of hereditary colorectal cancer from the British Society of Gastroenterology (BSG)/Association of Coloproctology of Great Britain and Ireland (ACPGBI)/United Kingdom Cancer Genetics Group (UKCGG). Gut 2020; 69:411.
49. Yang J, Gurudu SR, Koptiuch C, et al. American Society for Gastrointestinal Endoscopy guideline on the role of endoscopy in familial adenomatous polyposis syndromes. Gastrointest Endosc 2020; 91:963.
50. Provenzale D, Gupta S, Ahnen DJ, et al. Genetic/Familial High-Risk Assessment: Colorectal Version 1.2016, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw 2016; 14:1010.
51. Patel R, McGinty P, Cuthill V, et al. Risk of colorectal adenomas and cancer in monoallelic carriers of MUTYH pathogenic variants: a single-centre experience. Int J Colorectal Dis 2021; 36:2199.
52. Hurley JJ, Thomas LE, Walton SJ, et al. The impact of chromoendoscopy for surveillance of the duodenum in patients with MUTYH-associated polyposis and familial adenomatous polyposis. Gastrointest Endosc 2018; 88:665.

Topic 86140 Version 16.0

GRAPHICS

Modified Spigelman score and classification of duodenal polyposis

Factor	Score		
	1 point	2 points	3 points
Number of polyps	1-4	5-20	>20
Polyp size, mm	1-4	5-10	>10
Histology	Tubulous	Tubulovillous	Villous
Dysplasia	Low grade	--	High grade

Classification: no polyp: stage 0; 1 to 4 points: stage I; 5 to 6 points: stage II; 7 to 8 points: stage III; 9 to 12 points: stage IV.

Reproduced with permission from: Saurin J, Gutknecht C, Napoleon B, et al. Surveillance of duodenal adenomas in familial adenomatous polyposis reveals high cumulative risk of advanced disease. J Clin Oncol 2004; 22:493. Copyright © 2004 American Society of Clinical Oncology (ASCO).

Graphic 71691 Version 5.0

Contributor Disclosures

Shilpa Grover, MD, MPH, AGAF No relevant financial relationship(s) with ineligible companies to disclose. **Elena Stoffel, MD, MPH** No relevant financial relationship(s) with ineligible companies to disclose. **J Thomas Lamont, MD** Equity Ownership/Stock Options: Allurion [Weight loss]. Consultant/Advisory Boards: Teledoc [Gastrointestinal diseases]. All of the relevant financial relationships listed have been mitigated. **Kristen M Robson, MD, MBA, FACG** No relevant financial relationship(s) with ineligible companies to disclose.

Contributor disclosures are reviewed for conflicts of interest by the editorial group. When found, these are addressed by vetting through a multi-level review process, and through requirements for references to be provided to support the content. Appropriately referenced content is required of all authors and must conform to UpToDate standards of evidence.

Conflict of interest policy

→