MUTYH Polyposis

Synonyms: Multiple Colorectal Adenomas, Autosomal Recessive; *MUTYH*-Associated Polyposis (MAP)

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Summary

Clinical characteristics

MUTYH polyposis (also referred to as *MUTYH*-associated polyposis, or MAP) is characterized by a greatly increased lifetime risk of colorectal cancer (CRC). Although typically associated with ten to a few hundred colonic adenomatous polyps, CRC develops in some individuals in the absence of polyposis. Serrated adenomas, hyperplastic/sessile serrated polyps, and mixed (hyperplastic and adenomatous) polyps can also occur. Duodenal adenomas are common, with an increased risk of duodenal cancer. The risk for malignancies of the ovary and bladder is also increased, and there is some evidence of an increased risk for breast and endometrial cancer. Additional reported features include thyroid nodules, benign adrenal lesions, jawbone cysts, and congenital hypertrophy of the retinal pigment epithelium.

Diagnosis/testing

The diagnosis is established in a proband by identification of biallelic germline pathogenic variants in *MUTYH* on molecular genetic testing.

Management

Treatment of manifestations: Suspicious polyps identified on colonoscopy should be removed until polypectomy alone cannot manage the large size and density of the polyps, at which point either subtotal colectomy or proctocolectomy is performed. Duodenal polyps showing dysplasia or villous changes should be excised during endoscopy. Abnormal findings on thyroid ultrasound examination should be evaluated by a thyroid specialist to determine what combination of monitoring, surgery, and/or fine needle aspiration is appropriate.

Surveillance: Colonoscopy with polypectomy every one to two years beginning at age 25-30 years; upper endoscopy and side viewing duodenoscopy every three months to four years beginning at age 30-35 years with

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subsequent follow up based on initial findings. Consider annual physical examination, thyroid ultrasound, and skin examination by a dermatologist.

Individuals with a heterozygous germline *MUTYH* pathogenic variant: offer average moderate-risk colorectal screening based on family history.

Evaluation of relatives at risk: It is appropriate to clarify the genetic status of apparently asymptomatic older and younger sibs of an individual with MAP by molecular genetic testing for the *MUTYH* pathogenic variants identified in the proband in order to reduce morbidity and mortality in those who would benefit from appropriate surveillance beginning at age 10-15 years and early identification and treatment of polyps.

Genetic counseling

MAP is inherited in an autosomal recessive manner. At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being a carrier with a small increased risk for CRC, and a 25% chance of being unaffected and not a carrier. Carrier testing for at-risk family members and prenatal diagnosis for pregnancies at increased risk are possible if the pathogenic variants in the family have been identified.

Diagnosis

Suggestive Findings

MUTYH polyposis (MAP) **should be suspected** in an individual with the following clinical findings and family history [NCCN 2019].

Clinical findings

- A personal cumulative lifetime history of ten or more colorectal adenomas in an individual age ≤60 years
- A personal cumulative lifetime history of 20 or more colorectal adenomas in an individual of any age
- A personal cumulative lifetime history of any combination of 20 or more colorectal adenomas, hyperplastic polyps, and/or sessile serrated polyps (excluding rectal and sigmoid hyperplastic polyps)
- Sessile serrated polyposis syndrome:
    - At least five serrated polyps proximal to the sigmoid colon, of which two or more are >10 mm; OR
    - >20 serrated polyps of any size distributed throughout the colon (excluding hyperplastic polyps found in the rectum and sigmoid colon)
- Duodenal polyp(s) and/or duodenal cancer
- Colorectal cancer with or without a history of polyps and identification of a somatic *KRAS* pathogenic variant (c.34G>T in codon 12) or identification of specific mutational signature on tumor tissue testing due to a high percentage of somatic G>T transversions (e.g., COSMIC Signature 18; SigProfiler SBS18/SBS36; SignatureAnalyzer SBS18/SBS36) [Viel et al 2017].

Family history of colorectal cancer (± polyps) consistent with autosomal recessive inheritance.

Establishing the Diagnosis

The diagnosis of MAP **is established** in a proband by identification of germline biallelic pathogenic variants in *MUTYH* by molecular genetic testing (see Table 1 and Table 2).

Germline molecular genetic testing approaches can include **gene-targeted testing** (single-gene testing and/or multigene panel). Since the phenotype of MAP (as described in Suggestive Findings) overlaps with a number of other hereditary polyposis and colorectal cancer syndromes (see Differential Diagnosis), many individuals with MAP will likely be diagnosed using a multigene panel.

- **Single-gene testing.** Sequence analysis of *MUTYH* detects small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. Perform sequence analysis first. If only one or no pathogenic variant is found, perform gene-targeted deletion/duplication analysis to detect intragenic deletions or duplications (Table 1).

- **A multigene panel** that includes *MUTYH* and other genes of interest (see Differential Diagnosis) is most likely to identify the genetic cause of the condition at the most reasonable cost while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests. For this disorder a multigene panel that also includes deletion/duplication analysis is recommended (see Table 1).

For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

Table 1. Germline Molecular Genetic Testing Used in *MUTYH* Polyposis

Gene [1]	Method	Proportion of Pathogenic Variants [2] Detectable by Method
MUTYH	Sequence analysis [3]	~99% [4]
	Gene-targeted deletion/duplication analysis [5]	See footnote 6.

1. See Table A. Genes and Databases for chromosome locus and protein.
2. See Molecular Genetics for information on allelic variants detected in this gene.
3. Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.
4. Out et al [2010]
5. Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.
6. A large (>4.2-kb) deletion encompassing exons 4-16 has been reported in three affected individuals from Spain, France, and Brazil, indicating a possible southern European founder variant [Rouleau et al 2011, Torrezan et al 2011, Castillejo et al 2014]. A deletion of exon 15 has also been reported [Ricci et al 2017].

Table 2. Detection Frequency of Biallelic Germline *MUTYH* Pathogenic Variants by Number of Polyps in Individuals with *APC* Mutation-Negative Polyposis

Number of Polyps	Detection Frequency of Biallelic Germline *MUYTH* Pathogenic Variants
1-19	2% (25/1,430)
10-19	2% (58/2,634)
20-49	11% (60/540)
20-99	7% (306/4,425)
50-99	21% (22/107)
100-999	16% (133/809)
>1,000	8% (2/24)

Based on Grover et al [2012], Stanich et al [2019], Terlouw et al [2020]

Tumor tissue testing prior to germline molecular genetic testing of a proband is generally not required; however, it may be required in certain circumstances (e.g., by third-party payer policy). In other instances, review of past tumor testing on a proband may help determine the preferred germline molecular genetic testing approach (i.e., single-gene testing vs use of a multigene panel).

- **Identification of a somatic *KRAS* pathogenic variant.** The *KRAS* pathogenic variant (c.34G>T in codon 12), present in less than 5%-10% of sporadic colorectal cancers (CRCs), is found in 40%-100% of adenomas and 60%-90% of CRCs in persons with MAP [Nielsen et al 2011, Viel et al 2017]. Furthermore, 10%-25% of persons with CRCs with this somatic *KRAS* variant have biallelic germline *MUTYH* pathogenic variants.

  KRAS somatic molecular genetic testing is often routine in advanced CRCs to identify individuals who are eligible for *MUTYH* germline molecular genetic testing, including probands with atypical clinical findings (CRC and no or very few adenomas) [van Puijenbroek et al 2008, Guarinos et al 2014, Aimé et al 2015, Viel et al 2017].

- **Microsatellite instability (MSI)-low** (For information on MSI testing including advantages and disadvantages, click here). Although the majority of CRCs in persons with MAP are microsatellite stable, the MSI-high phenotype is found in a minority (0%-18%, mean: 4%) (see review in Nielsen et al [2011], Castillejo et al [2014]).

Clinical Characteristics

Clinical Description

MUTYH polyposis (*MUTYH*-associated polyposis; MAP) is characterized by a greatly increased lifetime risk for colorectal cancer (CRC) (43%-63% at age 60 years and a lifetime risk of 80%-90% in the absence of timely surveillance). The risk for malignancies of the duodenum, ovary, and bladder is also increased, and there is some evidence of an increased risk for breast and endometrial cancer (Table 3).

Table 3. Cancer Risks in Individuals with *MUTYH* Polyposis Compared to the General Population

Cancer Type	General Population Risk [1]	Risk Associated with MAP [2]	Median Age of Onset
Colorectal	5.5%	43%-63% by age 60 yrs; 80%-90% lifetime risk w/out surveillance	48 yrs
Duodenal	<0.3%	4%	61 yrs
Ovarian	1.3%	6%-14%	51 yrs
Bladder	1%-4%	6%-8% in females; 6%-25% in males	61 yrs
Breast	12%	12%-25%	53 yrs
Endometrial	2.9%	~3%	51 yrs
Gastric	<0.7%-1%	1%	38 yrs
Pancreatic	1.6%	See footnote 3	
Skin	~20% [4]	See footnote 3	
Thyroid	0.6%-1.8%	See footnote 3	

1. US National Cancer Institute's Surveillance Epidemiology and End Results (SEER) Database 2012-2014

2. Nielsen et al [2006], Lubbe et al [2009], Vogt et al [2009], Win et al [2014], Walton et al [2016]

3. Unclear if the risk for this type of cancer is increased in individuals with MAP

4. Including basal cell carcinoma

Colon polyps and cancer. Most individuals with MAP have between ten and a few hundred colonic polyps with a mean age of presentation of approximately 50 years. Persons with MAP can have colonic adenomas as well as serrated adenomas, hyperplastic/sessile serrated polyps, and mixed (hyperplastic and adenomatous) polyps [Sieber et al 2003, Chow et al 2006, Boparai et al 2008, O'Shea et al 2008]. Of note, eight of 17 persons with MAP had one or more hyperplastic colonic polyps and/or sessile serrated adenomas; findings in three of these eight individuals met criteria for the serrated polyposis syndrome (see Differential Diagnosis) [Boparai et al 2008]. A rectal clustering (studding) of a large number (i.e., >20) of hyperplastic polyps was found in ten of 16 persons with MAP [Church & Kravochuck 2016].

Molecular genetic testing of individuals with CRC has revealed that up to one third of persons with biallelic germline *MUTYH* pathogenic variants develop CRC in the absence of colonic polyposis [Croitoru et al 2004, Farrington et al 2005, Balaguer et al 2007, Cleary et al 2009, Pearlman et al 2017]. In a minority (0%-3.7%) of affected individuals, biallelic germline *MUTYH* pathogenic variants have been found in the index case of a family with a phenotype suggestive of Lynch syndrome [Nielsen et al 2011, Castillejo et al 2014].

In the absence of timely surveillance, the lifetime risk for CRC in individuals with MAP was between 80% and 90% [Lubbe et al 2009, Win et al 2014]. Colon cancers were found to be right-sided in 29%-69% of individuals with MAP [Lipton et al 2003, O'Shea et al 2008, Nielsen et al 2009a]. Metachronous or synchronous colon cancers occurred in 23%-27% of individuals with MAP [Lipton et al 2003, Nielsen et al 2009a].

In one report, survival of individuals with *MUTYH* CRC on average was better than survival in individuals with colorectal adenocarcinoma and unknown family history who did not have microsatellite instability testing [Nielsen et al 2010]. Five-year survival for persons with MAP CRC was 78% (which, after adjustment for differences in age, stage, sex, subsite, country, and year of diagnosis, remained better than for controls).

Duodenal polyps and cancer. Duodenal polyps occur in 17%-34% of individuals with MAP. The lifetime risk for duodenal cancer is approximately 4% [Nielsen et al 2006, Vogt et al 2009, Walton et al 2016].

Ovarian cancer. The incidence of ovarian cancer was significantly increased in women with MAP, with a lifetime risk of 6%-14% and median age at diagnosis of 51 years [Vogt et al 2009, Win et al 2016]. Biallelic germline *MUTYH* pathogenic variants were uncommon in a large cohort of women with ovarian cancer (1/7,646) [LaDuca et al 2020].

Bladder cancer. The incidence of bladder cancer was significantly increased, with a lifetime risk of 6%-8% for females and 6%-25% for males with MAP and a median age at diagnosis of 61 years (range 45-67) [Vogt et al 2009, Win et al 2016].

Other cancers

- **Breast cancer.** It is unclear if the risk for breast cancer is increased in women with MAP. The risk was found to be higher in one study, with median age at diagnosis 53 years (range 45-76) [Vogt et al 2009]. However, a second study did not find an increased breast cancer risk [Win et al 2016]. Although biallelic germline *MUTYH* pathogenic variants have not been reported in individuals from large breast cancer cohorts, one male with biallelic germline *MUTYH* pathogenic variants was reported in a cohort of 560 males with breast cancer [Rizzolo et al 2018].
- **Endometrial cancer** was diagnosed in two of 118 women with MAP, with a median age at diagnosis of 51 years and a lifetime risk of approximately 3% [Vogt et al 2009]. Sutcliffe et al [2019] reported endometrial cancer in four of 45 women with MAP.
- **Gastric fundic gland polyps and gastric cancer.** Among 150 individuals with MAP undergoing endoscopic surveillance, 17 (11%) had gastric fundic gland polyps. Although a higher risk for gastric cancer than in the general population was observed, the trend was not significant [Vogt et al 2009].

- **Pancreatic cancer.** Two (2%) of 83 individuals with MAP were diagnosed with pancreatic cancer [Sutcliffe et al 2019]. Two additional studies including 276 individuals with MAP did not report any instances of pancreatic cancer [Vogt et al 2009, Win et al 2016].
- **Skin cancer.** Thirteen of 276 individuals with MAP had a diagnosis of skin cancer including melanomas, squamous epithelial carcinomas, and basal cell cancers [Vogt et al 2009]. In this same cohort, five individuals also had sebaceous gland adenomas or sebaceous gland epitheliomas. Another study reported two melanomas and six other skin cancers in 81 individuals with MAP [Sutcliffe et al 2019].
- **Thyroid cancer.** Three of 24 individuals with MAP evaluated by thyroid ultrasound had papillary thyroid cancer [LaGuardia et al 2011]; a high incidence of thyroid cancer was not reported in other studies and may have reflected selection bias. Vogt et al [2009] reported two instances of thyroid cancer in 276 individuals with MAP.

Other extraintestinal findings in persons with MAP

- Thyroid nodules were identified in 16 of 24 individuals with MAP examined by ultrasound [LaGuardia et al 2011]. A second study reported thyroid nodules in two of 82 individuals with MAP [Sutcliffe et al 2019].
- **Adrenal lesions** (all benign and not hyperfunctioning) were identified in five (18%) of 21 of individuals with MAP in a prospective study [Kallenberg et al 2017].
- **Dental abnormalities.** Jawbone cysts were reported in 11 of 276 persons with MAP [Vogt et al 2009].
- **Congenital hypertrophy of retinal pigment epithelium (CHRPE).** The estimate of CHRPE in individuals with MAP is about 5.5%; however, this figure may also include misdiagnoses since pigment anomalies of the retina are quite frequent in the general population [Vogt et al 2009].

Heterozygotes

The risk for CRC in individuals heterozygous for a germline *MUTYH* pathogenic variant was only marginally increased in large population-based and family-based studies [Jenkins et al 2006, Jones et al 2009, Win et al 2014]. In a prospective study of 62 *MUTYH* heterozygotes, the frequency of colonic and upper GI polyps was not increased [El Hachem et al 2019].

The risk of developing extraintestinal cancer in *MUTYH* heterozygotes is unclear. A slightly increased cumulative risk for *MUTYH* heterozygotes for gastric, hepatobiliary, endometrial, and breast cancer was reported by Win et al [2016]. Other case-control studies did not find an association between *MUTYH* heterozygosity and risk for breast cancer or hepatocellular carcinoma [Baudhuin et al 2006, Beiner et al 2009, Out et al 2012, Fulk et al 2019].

A heterozygous *MUTYH* pathogenic variant was identified in two of 45 individuals with neuroendocrine tumors (NET) of the pancreas and eight of 160 individuals with adrenocortical carcinomas (ACC) [Pilati et al 2017, Scarpa et al 2017]. Two of 15 probands with familial NET of the small intestine and four of 215 individuals with nonfamilial NET of the small intestine were heterozygous for *MUTYH* pathogenic variant p.Gly396Asp [Dumanski et al 2017]. It is unclear if a heterozygous *MUTYH* pathogenic variant is a risk factor for NET or ACC, as the risk of NET or ACC in individuals with biallelic *MUTYH* pathogenic variants appears to be quite low.

Genotype-Phenotype Correlations

Functional studies have shown differences in glycosylase activity between the c.536A>G pathogenic variant and the c.1187G>A pathogenic variant [Banda et al 2017]. Differences were also seen in clinical manifestations: homozygosity for c.536A>G was associated with a more severe phenotype and an approximately eight-year-earlier age of onset compared to homozygosity for c.1187G>A [Lubbe et al 2009, Nielsen et al 2009b, Terdiman 2009, Morak et al 2010].

For other common variants, such as p.Glu324His, which has up to a 50% minor allele frequency in some populations [Banda et al 2017], association with cancer risk has been reported; however, the reported risks are not consistent with mendelian inheritance and are not used to direct patient care.

Nomenclature

An outdated term for *MUTYH* polyposis is "autosomal recessive adenomatous polyposis."

The gene formerly designated *MYH* is now *MUTYH*.

Prevalence

It is estimated that 1%-2% of the general northern European, Australian, and US populations are heterozygous for a germline *MUTYH* pathogenic variant [Al-Tassan et al 2002, Cleary et al 2009, Win et al 2017]. The Genome Aggregation Database (gnomAD) reports a somewhat lower frequency of *MUTYH* pathogenic variants (~0.8%). Using these figures, the prevalence of 1:20,000 to 1:60,000 for persons with biallelic germline *MUTYH* pathogenic variants can be derived.

MAP is estimated to account for 0.7% of all CRC and between 0.5% and 6% of cohorts of familial or early-onset CRC in which affected individuals have a low number of adenomas (<15-20) [Sieber et al 2003, Cleary et al 2009, Lubbe et al 2009, Landon et al 2015, Pearlman et al 2017]. See also Table 4.

Table 4. Percentage of Persons with MAP by Age at Diagnosis of CRC

Persons with Biallelic *MUTYH* Pathogenic Variants		Age at Diagnosis of CRC
% (n)	Range	
1.3% (52/3,976)	0.5%-6.2%	<50 years
0.3% (28/11,150)	0.0%-0.6%	>50 years

Review of literature, Nielsen et al [2011], Landon et al [2015], Pearlman et al [2017]
CRC = colorectal cancer

Genetically Related (Allelic) Disorders

No phenotypes other than those discussed in this *GeneReview* are known to be associated with biallelic germline pathogenic variants in *MUTYH*.

Differential Diagnosis

MUTYH polyposis (MAP) can be distinguished from other inherited polyposis and colon cancer conditions by clinical findings, pathologic findings, mode of inheritance, and molecular genetic testing. Conditions to consider in the differential diagnosis include the disorders summarized in Table 5.

Table 5. Disorders to Consider in the Differential Diagnosis of *MUTYH* Polyposis

Cancer Susceptibility Syndrome	Gene(s) / Genetic Mechanism	MOI	Polyps / Colon Cancer	Associated Malignancies	Other Features / Comments
APC-associated polyposis conditions	*APC*	AD	Attenuated FAP: • 0-100 colonic polyps • CRC risk: 70% FAP: • 100 colonic polyps • Upper GI polyps • CRC risk: 100%	• Small bowel • Pancreatic • Thyroid • Liver • Brain • Bile duct • Gastric	• CHRPE • Osteomas • Supernumerary or missing teeth • Cutaneous lesions • Desmoid tumors
NTHL1-associated polyposis	*NTHL1*	AR	• 8-50 adenomatous colonic polyps • Duodenal adenomas • CRC in 16/29 individuals	Extracolonic cancer in 12/29 individuals: • Uterine • Duodenal • Breast	• Premalignant endometrial lesions • 2nd most common AR form of colon cancer & polyps after MAP [1]
Lynch syndrome (hereditary non-polyposis colon cancer)	*MLH1* *MSH2* *MSH6* *PMS2* *EPCAM*	AD	• 4% develop ≥10 polyps • Colon tumors often MSI+ • CRC risk: 52%-82%	• Uterine • Ovarian • Small bowel • Gastric • Urinary tract • Skin • Brain • Hepatobiliary tract • Pancreas • Prostate	
Peutz-Jeghers syndrome	*STK11*	AD	• GI hamartomatous polyps • Polyps most often in small bowel • Adenomatous colonic polyps can occur. • CRC risk: 39%	• Gastric • Breast • Ovarian • Small bowel • Pancreas • Cervix • Uterine • Lung • Testicular	• Ovarian sex cord tumors w/annular tubules • Dk-brown to dk-blue melanocytic macules (fade w/age)
Juvenile polyposis syndrome	*BMPR1A* *SMAD4*	AD	• Hamartomatous (juvenile) polyps in small bowel, stomach, colon, & rectum • CRC risk: 38.7%	• Gastric • Upper GI tract • Pancreas	Hereditary hemorrhagic telangiectasia (*SMAD4*-related)

Table 5. continued from previous page.

Cancer Susceptibility Syndrome	Gene(s) / Genetic Mechanism	MOI	Polyps / Colon Cancer	Associated Malignancies	Other Features / Comments
PTEN hamartoma tumor syndrome	*PTEN*	AD	• Multiple hamartomatous & mixed polyps in GI tract • CRC risk: 9%	• Breast • Thyroid • Uterine • Renal • Brain • Melanoma	• Thyroid disease/ nodules • Uterine fibroids • Macrocephaly • Lipomas • Mucocutaneous lesions • Pigmented macules of glans penis • Hamartomatous overgrowth of tissues • Connective tissue nevi • Epidermal nevi • Hyperostoses
Hereditary mixed polyposis syndrome (OMIM 610069, 601228)	*BMPR1A* *GREM1* dup 15q13-q14 [2]	AD	• Adenomatous polyps, juvenile polyps, hyperplastic polyps, & polyps containing mixed histology • ↑ CRC risk [3]	Desmoid tumor, prostate cancer, & duodenal adenocarcinoma reported in 1 individual [4]	Rare condition (few families)
Sessile serrated polyposis syndrome (OMIM 617108)	*RNF43*	AD	• Sessile serrated polyps, serrated adenomas, or hyperplastic polyps of GI tract • CRC risk: ≤54%	Unknown (various cancers reported in untested family members)	Rare condition (few individuals)

AD = autosomal dominant; AR = autosomal recessive; CHRPE = congenital hypertrophy of the retinal pigment epithelium; CRC = colorectal cancer; FAP = familial adenomatous polyposis; MAP = *MUTYH* polyposis; MOI = mode of inheritance; MSI = microsatellite instability

1. Weren et al [2015], Grolleman et al [2019]

2. Leads to overexpression of *GREM1*

3. Jaeger et al [2003]

4. Lieberman et al [2017]

Management

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs of an individual diagnosed with *MUTYH* polyposis (MAP), the evaluations summarized in this section (if not performed as part of the evaluation that led to the diagnosis) are recommended:

- Review of personal medical history with emphasis on those features related to MAP or colorectal cancer (CRC): colon polyps (majority are adenomas), rectal bleeding, abdominal pain and discomfort, bloating, diarrhea
- Colonoscopy and review of pathology
- Baseline upper endoscopy including visualization of the major ampulla starting at age 30-35 years
- Baseline thyroid ultrasound examination [LaGuardia et al 2011]
- Consider skin examination by a dermatologist.
- Consultation with a clinical geneticist and/or genetic counselor

Currently, investigations for other extracolonic manifestations of MAP are not recommended at the time of initial diagnosis.

Treatment of Manifestations

Practice parameters, including information on surgery, have been outlined by the following resources:

- National Comprehensive Cancer Network [NCCN 2019]
- American College of Gastroenterology [Syngal et al 2015] (full text)
- American Society of Colon and Rectal Surgeons [Church et al 2003]
- American Society of Clinical Oncology [Stoffel et al 2015] (full text)
- Society of Surgical Oncology [Guillem et al 2006] (full text)

Colon polyps and colon cancer. Surveillance guidelines for individuals with *MUTYH* polyposis are analogous to the guidelines for individuals with attenuated FAP. Colonoscopy and polypectomy is recommended every one to two years until polypectomy alone cannot manage the large size and density of the polyps, at which point colectomy may be necessary [Lipton & Tomlinson 2006, Sampson & Jones 2009]. Absolute indications for colectomy include documented or suspected CRC or significant symptoms (e.g., obstruction, bleeding), although these symptoms are uncommon in the absence of CRC. Relative indications for colectomy include presence of multiple adenomas >6 mm that cannot be reasonably managed by endoscopy, a significant increase in adenoma number between surveillance examinations, presence of adenomas with high-grade dysplasia, or inability to adequately survey the colon (e.g., due to innumerous diminutive adenomas or limited access to/ compliance with colonoscopy) (see Surveillance).

Types of colectomy include the following:

- Proctocolectomy with ileal pouch anal anastomosis (IPAA), which can be performed laparoscopically, laparoscopically assisted, or open
- Total colectomy with ileorectal anastomosis (IRA)
- Total proctocolectomy with permanent ileostomy

The choice of procedure depends on the clinical circumstances.

- An IPAA is generally performed when the rectal polyp burden is high or as a second procedure after IRA when rectal disease burden cannot be managed endoscopically. The advantages of this procedure are near-elimination of risk for rectal cancer and relatively good preservation of bowel function. There may be an increased risk for bladder/sexual dysfunction and functional results can be variable.
- An IRA is generally considered when the rectal polyp burden is low and deemed to be endoscopically manageable. It is a technically straightforward procedure with low complication rates. It is usually associated with good functional outcome and minimizes risk for sexual or urinary dysfunction. This procedure should not be performed if there is severe rectal disease or the individual cannot reliably undergo endoscopic surveillance of the remaining rectum postoperatively.
- A total proctocolectomy with end ileostomy is almost never required unless a proctocolectomy is necessary (due to rectal polyp/cancer burden) and a contraindication to IPAA is present (e.g., a mesenteric desmoid preventing a pouch from reaching pelvic floor, low rectal cancer invading pelvic floor, or individual preference due to poor sphincter control).

Duodenal polyps. Management of polyps is similar to that in individuals with FAP. Endoscopic or surgical removal of duodenal and/or ampullary adenomas is recommended if polyps exhibit villous change or severe dysplasia, exceed 1 cm in diameter, or cause symptoms [Wallace & Phillips 1998, Saurin et al 1999, Kadmon et al 2001]. Surgical options include a pancreas-sparing duodenectomy, which is a good option when the papilla is not involved and there is no suspicion for cancer. Pancreaticoduodenectomy (Whipple procedure) is associated

with significantly higher morbidity; however, it must be considered if the duodenal papilla is involved or cancer is identified or strongly suspected.

Abnormal thyroid findings should be evaluated by a thyroid specialist to determine the combination of monitoring, surgery, and/or fine needle aspiration that is appropriate [LaGuardia et al 2011].

Prevention of Primary Manifestations

For many individuals with MAP, colonic polyps are limited in number and surveillance with periodic colonoscopic polypectomy is sufficient to prevent CRC. Colonoscopy is therefore used for surveillance and prevention of CRC.

To reduce the risk for duodenal/periampullary adenocarcinoma, endoscopic or surgical removal of duodenal and/or ampullary adenomas should be considered if polyps exhibit villous change or severe dysplasia, exceed 1 cm in diameter, or cause symptoms.

Surveillance

Table 6. Recommended Surveillance for Individuals with *MUTYH* Polyposis

System/Concern	Evaluation	Frequency
Colon	Colonoscopy w/polypectomy	Every 1-2 yrs beginning at age 25-30 yrs [1, 2]
Duodenum/Stomach	Upper endoscopy & side viewing duodenoscopy [3]	Every 3 mos to 4 yrs beginning at age 30-35 yrs [1, 4]
Extraintestinal malignancies	Consider annual physical examination [5]; may consider thyroid ultrasound [5]	Annually
	May consider skin exam by dermatologist [5]	One time or annually

1. Based on the US-based National Comprehensive Cancer Network (NCCN) guidelines [NCCN 2019]
2. If only small adenoma burden (<20 adenomas, <1 cm, and none with advanced histology [NCCN 2019]), colonoscopy can be used to effectively eliminate polyps.
3. Consider chromoendoscopy, which showed improved diagnostic yield in a recent study [Hurley et al 2018].
4. Based on findings using Spigelman Criteria [Spigelman et al 1989]
5. Surveillance beyond existing protocols that are offered to the general population in most Western countries are not firmly recommended in the NCCN guidelines due to limited data.

Individuals Heterozygous for a Germline *MUTYH* Pathogenic Variant

One published report on 62 *MUTYH* heterozygous relatives of persons with MAP who were undergoing colonoscopy found that these persons could be at increased risk for neoplastic lesions compared to the general population, but that these results do not support intensive follow up. Therefore, *MUTYH* heterozygotes are expected to benefit from population screening measures but could also be offered average moderate-risk colorectal screening based on their family history.

- NCCN [2019] guidelines propose that *MUTYH* heterozygotes with a first-degree relative with CRC (who does not have MAP) undergo colonoscopy every five years beginning at age 40 years or ten years prior to the age of the first-degree relative's age at CRC diagnosis.
- For *MUTYH* heterozygotes with a second-degree relative with CRC or no family history of CRC, no screening advice is given due to inconclusive data.

Agents/Circumstances to Avoid

Currently, no studies have investigated external factors or lifestyle factors that could affect the severity of the manifestations of *MUTYH* polyposis.

Smoking may affect polyp development based on a case report of monozygotic twins with MAP in which a somewhat more severe phenotype was observed in the sister who smoked compared to her twin sister who did not smoke. While both twins had about 30 smaller low-grade adenomas, the twin sister who smoked also had three larger (6-10 mm) adenomas and one focal high-grade adenoma of 70 mm [Casper et al 2018].

Evaluation of Relatives at Risk

It is appropriate to clarify the genetic status of apparently asymptomatic older and younger sibs of an individual with MAP by molecular genetic testing for the *MUTYH* pathogenic variants identified in the proband in order to reduce morbidity and mortality in those who would benefit from appropriate surveillance (beginning at age 10-15 years) and early identification and treatment of polyps.

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Therapies Under Investigation

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions. Note: There may not be clinical trials for this disorder.

Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

MUTYH polyposis (MAP) is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of an affected individual are obligate heterozygotes (i.e., carriers of one *MUTYH* pathogenic variant).
- Heterozygous relatives of an individual with MAP are at a two- or at most threefold increased risk for late-onset colorectal cancer (CRC) (see Clinical Description, Heterozygotes; Evaluation of Relatives at Risk; and Surveillance, Individuals Heterozygous for a Germline *MUTYH* Pathogenic Variant).

Sibs of a proband

- At conception, each sib of an affected individual has a 25% chance of being affected, a 50% chance of being a carrier, and a 25% chance of being unaffected and not a carrier.
- Heterozygous relatives of individuals with MAP are at a two- or, at most, threefold increased risk for late-onset CRC (see Clinical Description, Heterozygotes; Evaluation of Relatives at Risk; and Surveillance, Individuals Heterozygous for a Germline *MUTYH* Pathogenic Variant).

Offspring of a proband

- Unless the reproductive partner of a proband is heterozygous for a *MUTYH* pathogenic variant (i.e., a carrier), offspring will be obligate heterozygotes for a pathogenic variant in *MUTYH*.

- The carrier (heterozygote) frequency in the general northern European, Australian, and US population for a *MUTYH* pathogenic variant is 1%-2% (see Prevalence). Therefore, the risk to the offspring of an affected individual and a reproductive partner of northern European, Australian, or US origin of having *MUTYH* polyposis is 0.5%-1.0%.

Other family members. Each sib of the proband's parents is at a 50% risk of being a carrier of a *MUTYH* pathogenic variant.

Heterozygote Detection

Carrier testing for at-risk relatives requires prior identification of the *MUTYH* pathogenic variants in the family.

Reproductive partners of individuals with one or two *MUTYH* pathogenic variants can be offered *MUTYH* molecular genetic testing to determine *MUTYH* carrier status in order to clarify the risk for MAP in their offspring.

Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

Family planning

- The optimal time for determination of genetic risk, clarification of carrier status, and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) and molecular genetic testing when this has not been done before, to young adults who are affected, are carriers, or at risk of being carriers and to their reproductive partner to determine the risk of MAP in offspring (see Carrier Detection).

Prenatal Testing and Preimplantation Genetic Testing

Once the *MUTYH* pathogenic variants have been identified in an affected family member, prenatal testing for a pregnancy at increased risk and preimplantation genetic testing for MAP are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **National Cancer Institute (NCI)**

  6116 Executive Boulevard

  Suite 300

  Bethesda MD 20892-8322

  Phone: 800-422-6237 (toll-free)

  Email: cancergovstaff@mail.nih.gov

  Genetics of Colorectal Cancer (PDQ®)

- **American Cancer Society**

  Phone: 800-227-2345

  www.cancer.org

- **Colorectal Cancer Alliance**

  1025 Vermont Avenue Northwest

  Suite 1066

  Washington DC 20005

  Phone: 877-422-2030

  www.ccalliance.org

- **International Society for Gastrointestinal Hereditary Tumours (InSiGHT)**

  www.insight-group.org

- **United Ostomy Associations of America, Inc.**

  Phone: 800-826-0826

  ostomy.org

Molecular Genetics

Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information. —ED.

Table A. MUTYH Polyposis: Genes and Databases

Gene	Chromosome Locus	Protein	Locus-Specific Databases	HGMD	ClinVar
MUTYH	1p34.1	Adenine DNA glycosylase	MUTYH homepage - Colon cancer gene variant databases	MUTYH	MUTYH

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

Table B. OMIM Entries for MUTYH Polyposis (View All in OMIM)

604933	MutY DNA GLYCOSYLASE; MUTYH
608456	FAMILIAL ADENOMATOUS POLYPOSIS 2; FAP2

Molecular Pathogenesis

DNA base excision repair plays a critical role in DNA damage repair caused by ionizing radiation, various chemical oxidants, and reactive oxygen species. In humans, the most mutagenic species from oxidative damage is 8-oxo7,8-dihydro-2'-deoxyguanosine (8-oxo-dG), which tends to mispair with adenine instead of the usual cytosine. This leads to G:C>T:A transversions in the DNA [Isidro et al 2004].

The following enzymes work together in DNA base excision repair to prevent mutagenesis by DNA damage-produced 8-oxo-dG:

- 8-oxo-dGTPase (encoded by *NUDT1*): removes 8-oxo-dGTPs from the nucleotide pool to prevent incorporation into DNA

- N-glycosylase/DNA lyase (encoded by *OGG1*): detects and excises 8-oxo-dG adducts that have been misincorporated into DNA
- Adenine DNA glycosylase (encoded by *MUTYH)*: recognizes and excises misincorporated adenine bases to prevent G:C>T:A transversions from occurring

Mechanism of disease causation. A lack of functional adenine DNA glycosylase leads to accumulation of G:C>T:A transversions in daughter DNA strands post replication. Studies indicate that this transversion is common in colorectal tumor DNA from individuals with MAP. These pathogenic variants result in loss of adenine DNA glycosylase function [Lipton & Tomlinson 2004].

MUTYH-specific laboratory technical considerations. *MUTYH* has multiple transcript variants encoding different isoforms (www.ncbi.nlm.nih.gov/gene/4595). The isoforms differ in their N-terminus, which contains a mitochondrial localization signal (MLS). The putative nuclear localization signals (NLS) are located at both the N-terminus and C-terminus. The functional significance of the MLS and NLS in *MUTYH* is not entirely clear. Possibly they possess different glycosylase activity levels and/or have different expression levels in different tissues [Ma et al 2004].

Following current HGVS recommendations, a DNA reference sequence (NM_001128425.1) that is the longest possible transcript was created. Reported nucleotide and amino acid variants after nucleotide position 157 (amino acid 53) may differ by up to 42 nucleotides (14 amino acids). Care must be taken when searching the published literature for reported variants.

Table 7. Notable *MUTYH* Pathogenic Variants

Reference Sequences	DNA Nucleotide Change	Predicted Protein Change (Alias [1])	Comment [Reference]
NM_001128425.1 NP_001121897.1	c.536A>G	p.Tyr179Cys (p.Tyr165Cys)	Common pathogenic variants carried by ~1%-2% of the general population that account for ≥90% of all *MUTYH* pathogenic variants in northern European populations [Al-Tassan et al 2002, Cleary et al 2009]; ≤70% of persons w/MAP harbor at least 1 of these variants [Nielsen et al 2009b].
	c.1187G>A	p.Gly396Asp (p.Gly382Asp)	
	c.312C>A	p.Tyr104Ter	Common in Pakistani population [Dolwani et al 2007, Khawaja & Payne 2007, Prior & Bridgeman 2010]
	c.857G>A	p.Gly286Glu	Found in Japanese & Korean populations [Kim et al 2007, Yanaru-Fujisawa et al 2008]
	c.1147delC		Common in northern European populations [Nielsen et al 2009b]
	c.1214C>T	p.Pro405Leu	Common in the Dutch population [Nielsen et al 2005]
	c.1227_1228dup		Common in the Spanish, Portuguese, & Tunisian populations [Gómez-Fernández et al 2009, Abdelmaksoud-Dammak et al 2012]
	c.1437_1439del	p.Glu480del	Common in the Italian population [Gismondi et al 2004]
	c.1438G>T	p.Glu480Ter	Founder variant in the British Indian population [Dolwani et al 2007]
	Del exons 4-16		Common in Spanish, Brazilian, & French populations [Rouleau et al 2011, Torrezan et al 2011, Castillejo et al 2014]

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.

GeneReviews follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.

1. Variant designation that does not conform to current naming conventions

Cancer and Benign Tumors

In general, MAP carcinomas somewhat mimic Lynch and sporadic mismatch repair (MMR)-deficient tumors with a frequently proximal location in the colon and a high number of tumor-infiltrating lymphocytes (TILs) [Nielsen et al 2009a]. Loss of HLA class I expression, a common event in Lynch tumors, was also found to be a frequent event in MAP carcinomas [de Miranda et al 2009]. Also comparable to Lynch tumors, the majority of MAP carcinomas appear near-diploid, and chromosome regions of copy-neutral loss of heterozygosity are frequent [Lipton et al 2003, Middeldorp et al 2008].

Recent studies performed whole-exome sequencing in MAP carcinomas and adenomas [Weren et al 2015, Rashid et al 2016, Viel et al 2017]. In general, the combination of the excess G:C>T:A transversion and specific sequence context (transversions occurring preferentially in AGAA or TGAA motifs) led to assigning a novel mutational signature for MAP tumors, termed *signature 36* [Viel et al 2017].

The overall mutation rate in MAP carcinomas was estimated at approximately twofold higher than in microsatellite-stable (MSS) carcinomas – in contrast to MSI CRCs, which are characterized by an almost tenfold increase over MSS carcinomas [Viel et al 2017]. A higher mutation load when comparing MAP with FAP tumors was found in adenomas from colon and duodenum as well [Rashid et al 2016, Hurley et al 2018]. The higher somatic mutation load in MAP tumors could cause a more activated immune system, comparable to that in Lynch/MMR-deficient colorectal tumors, and also indicates that tumors may be sensitive for immune therapies such as PD-1 blockade [Le et al 2015]. However, no such clinical research has been performed in individuals with MAP. Vaccine strategies now being developed could also be effective in MAP, but this also requires further research.

Chapter Notes

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Revision History

- 27 May 2021 (mn) Revision: variant removed from Table 7: c.1118C>T
- 10 October 2019 (sw) Comprehensive update posted live
- 24 September 2015 (me) Comprehensive update posted live
- 4 October 2012 (me) Review posted live
- 21 June 2011 (ei) Original submission

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