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MUTYH-Associated Polyposis (MAP)

Cancer Risks and General Management Recommendations

MUTYH-associated polyposis (MAP) is an adult-onset colorectal cancer predisposition syndrome characterized by the growth of tens to hundreds of adenomatous colorectal polyps.[1,2] Features typically present at approximately 47 years of age.[3] Polyp types can include conventional adenomas, as well as serrated adenomas, hyperplastic polyps, and mixed (hyperplastic and adenomatous) polyps.[4] Occasionally, colon cancer may develop in the absence of polyposis.[5-7]

Cancer Type	MAP Cancer Risks	General Population Lifetime Cancer Risks	Surveillance/Management Recommendations[8]

Colorectal[1,2]	43-100%	4.2%	*Surveillance*
			• For unaffected individuals:
			  ○ Begin colonoscopy at age 25-30 years, and every 1-2 years if negative
			• For individuals with polyps:
			  ○ Age <21 years with a small adenoma burden: Colonoscopy and polypectomy every 1-2 years; surgical evaluation and counseling if appropriate
			  ○ Age ≥21 years with small adenoma burden: Colonoscopy and polypectomy every 1-2 years; colectomy and ileorectal anastomosis (IRA) may be considered; surgical evaluation and counseling if appropriate
			• Small adenoma burden is defined as <20 adenomas, all <1 cm in diameter, and none with advanced histology
			Surgery
			• Colectomy may be indicated if colonoscopy is difficult and polyp control is uncertain. Surgery could be considered when polyp burden is >20 at any individual examination, when polyps have been previously ablated, when polyps have reach a size >1 cm, or when advance histology is encountered in any polyp.
			• Extent of colectomy may be modified based on the burden and distribution of adenomas
			• Colectomy with IRA if adenoma burden cannot be managed endoscopically
			  ○ If individual had colectomy with IRA, endoscopy evaluation of rectum every 6-12 months depending on polyp burden
			• Consider proctocolectomy with ileal pouch-anal anastomosis (IPAA) if dense rectal polyposis not manageable with polypectomy
			Chemoprevention

			• The use of chemoprevention may facilitate management of the remaining rectum post-surgery • There are no known FDA-approved medications for this indication at present • There are data to suggest sulindac is the most potent polyp regression medication; however, it is not known if the decrease in polyp burden decreases the cancer risk

Upper GI tract[2,8]	5%
	
	(Duodenal polyps found in 17-25% of individuals with MAP)
		0.3%	*Surveillance*
			• Annual physical examination
			• For unaffected individuals:
			  ○ Consider upper endoscopy (including complete visualization of the ampulla of Vater) beginning at age 30-35 years
			• For individuals with polyps:
			  ○ Baseline upper endoscopy beginning at age 30-35 years is recommended
			• Frequency of upper endoscopic surveillance should be based on duodenoscopic findings:
			  ○ Stage 0, no polyposis: repeat every 4 years
			  ○ Stage I, minimal polyposis (1-4 tubular adenomas, size 1-4mm): repeat every 2-3 years
			  ○ Stage II, mild polyposis (5-19 tubular adenomas, size 5-9mm): repeat every 1-3 years
			  ○ Stage III, moderate polyposis (>20 lesions, or size >1cm): repeat every 6-12 months
			  ○ Stage IV, dense polyposis or high grade dysplasia: surgical evaluation, expert surveillance every 3-6 months, complete mucosectomy or duodenectomy, or Whipple procedure if duodenal papilla is involved
			• Recommended examination with side-viewing endoscope and use of Spigelman's or other standardized staging
			• More intensive surveillance and/or treatment is required in individuals with large or villous adenomas, and with advancing age >50 years
			Surgery
			• Surgery (as described above) is recommended for invasive carcinoma as well for dense polyposis or high-grade dysplasia that cannot be managed endoscopically

Other Clinical Features and Cancer Risks: Extra-gastrointestinal manifestations are uncommon, but may include jaw-bone cysts and congenital hypertrophy of the retinal pigment epithelium (CHRPE).[9] There may be other cancer extra-intestinal cancer risks associated with MAP for which there is insufficient evidence to warrant intervention, including

ovarian, bladder, endometrial, skin, and thyroid cancers.[2,9,10] Further research is needed to make conclusions about these risks.

Implications for Family Members/Reproductive Considerations

- MAP is an autosomal recessive condition caused by biallelic *MUTYH* mutations (i.e., two pathogenic mutations in *MUTYH*, one in each copy of the gene).
- Individuals with MAP will pass one *MUTYH* mutation to all of their children.
- Individuals with a single (monoallelic) *MUTYH* mutation are considered *carriers* of MAP.
    - If only one parent is a carrier, each of their children has a 50% chance to be a *carrier* of MAP
    - If both parents are carriers, each of their children has a 25% chance of having MAP.
- Individuals with a monoallelic *MUTYH* mutation are not affected with MAP, but may have moderately increased risks for colorectal cancer.[5,11-13]
- Family members should have full *MUTYH* gene analysis rather than single-site testing for the known familial mutation(s), as 1-2% of the general Northern European population is a carrier of a monoallelic *MUTYH* mutation.[5,14,15]
- For carriers of a known mutation, assisted reproduction (with or without egg or sperm donation), pre-implantation genetic testing, and prenatal diagnosis options exist.
- All family members are encouraged to pursue genetic counseling to clarify their risks. Family members can visit www.FindAGeneticCounselor.com to find genetic services near them.

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