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Lynch Syndrome: *MSH2* Mutation

Cancer Risks and General Management Recommendations

Lynch syndrome is the most common type of hereditary colon cancer and accounts for 2%-4% of all colon cancers and 3% of endometrial cancers in the general population. Lynch syndrome occurs in 1:300 to 1:500 individuals, making it the most common hereditary cancer predisposition syndrome. This syndrome is a result of a germline mutation in one of the DNA mismatch repair (MMR) genes, *MLH1*, *MSH2*, *MSH6* and *PMS2*. Lynch syndrome is characterized by early onset colorectal cancer, an increased risk for synchronous and metachronous tumors, and extra-intestinal manifestations.

Cancer Type	*MSH2* Mutation Carrier Cancer Risks[1]	General Population Lifetime Cancer Risks[1]	Surveillance/Management Recommendations[1,2]
Colorectal	43-52%	4.5%	*Surveillance* • Colonoscopy every 1-2 years starting at age 20-25, or 2-5 years prior to the earliest colon cancer if it is diagnosed under age 25 *Surgery* • If colon cancer is detected, segmented or extended colectomy depending on clinical scenario should be considered *Chemoprevention* • Aspirin may decrease the risk of colon cancer in Lynch syndrome, but optimal dose and duration of aspirin therapy are uncertain[3]
Uterine/ endometrial	21-57%	2.7%	*Surveillance* • No clear evidence to support screening for uterine cancer • Screening via endometrial biopsy every 1-2 years and transvaginal ultrasound may be considered at clinician's discretion *Surgery* • Hysterectomy is a risk-reducing option that can be considered • Timing should be individualized based on whether childbearing is complete, comorbidities, family history and gene mutation • Women undergoing prophylactic hysterectomy should have a pre-operative uterine biopsy and the uterus examined intra-operatively by a pathologist for occult disease *Chemoprevention* • In the general population, oral contraceptive use has been associated with a decreased risk of uterine cancer by 50%
Ovarian	10-38%	1.3%	*Surveillance* • Data do not support routine ovarian cancer screening • Transvaginal ultrasound for ovarian cancer screening has not been shown to be sufficiently sensitive or specific, but may be considered at clinician's discretion

			• Serum CA-125 is an additional ovarian screening test with similar caveats *Surgery* • Bilateral salpingo-oophorectomy (BSO) may reduce the incidence of ovarian cancer • Timing should be individualized based on whether childbearing is complete, menopause status, comorbidities, family history and gene mutation • Detailed pathologic examination of ovarian specimens can yield greater detection of ovarian cancer and should be considered in these high risk patients [3] *Chemoprevention* • In the general population, oral contraceptive use has been associated with a decreased risk of ovarian cancer[4]
Gastric Small Bowel	0.2-16% 1-10%	<1% <1%	*Surveillance* • No clear evidence to support surveillance for gastric, duodenal, and small bowel cancer • Selected individuals with a family history of gastric, duodenal, and small bowel cancer may benefit from surveillance • Individuals of descent from any country with a high incidence of gastric cancer may have an increased risk and may benefit from increased surveillance • If surveillance is performed, may consider upper endoscopy with visualization of the duodenum every 3-5 years beginning at age 40 • Consider *H. pylori* testing and treating, if detected
Urothelial Bladder	2-18% 4-17%	<1% 2.5%	*Surveillance* • No clear evidence to support surveillance for urothelial cancers • Surveillance options may include annual urinalysis starting at 30-35 years of age
Prostate	30-32%	11.6%	*Surveillance* • No consensus management guidelines • Discuss family history and prostate cancer surveillance options (i.e., PSA, digital rectal exam) with a clinician to determine an appropriate surveillance regimen
Pancreatic	Not well established	1.5%	*Surveillance* • Consider annual contrast-enhanced MRI/MRCP and/or EUS beginning at age 50 years (or 10 years younger than the earliest exocrine pancreatic cancer diagnosis in the family, whichever is earlier) for individuals with ≥1 first- or second-degree relative from the same side (or presumed to be from the same side of) the family as the identified mutation • Surveillance is not currently recommended for *MSH2* mutation carriers in the absence of a close family history of exocrine pancreatic cancer • For individuals considering pancreatic cancer surveillance, surveillance is recommended to be performed in experienced high-volume centers, ideally under research conditions

Brain/ Central Nervous System (CNS)	Not well established	<1%	*Surveillance* • Annual physical/neurological examination starting at age 25-30 to assess for CNS tumors • No other screening recommendations have been made at this time

Other Cancer Risks: Lynch syndrome is associated with other increased cancer risks including breast and hepatobiliary tract cancers. Exact risks for these cancer types are not well-established individuals with a *MSH2* mutation. Additionally, no consensus management guidelines have been established at this time, aside from general population cancer screening.

Implications for Family Members/Reproductive Considerations

- First-degree relatives (i.e., parents, siblings, and children) have a 50% chance to have the familial *MSH2* mutation. Second-degree relatives (i.e., nieces/nephews, aunts/uncles, and grandparents) have a 25% chance to have the familial mutation.
- Rarely, children inherit an *MSH2* gene mutation from both parents. Children with two *MSH2* gene mutations have a condition called Constitutional Mismatch Repair Deficiency (CMMRD) associated with an increased risk for pediatric colon cancer, lymphoma, brain tumors, and café-au-lait spots. We recommend that couples that are concerned about this risk talk with a cancer genetic counselor.
- 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 cancer risks. Family members can visit www.FindAGeneticCounselor.com to find genetic services near them.

References

1. NCCN Clinical Practice Guidelines in Oncology®: Genetic/Familial High-Risk Assessment: Colorectal. Version 3.2019. 2019.
2. NCCN Clinical Practice Guidelines in Oncology®: Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic. Version 1.2020. 2019.
3. Powell CB, Kenley E, Chen LM, et al. Risk-reducing salpingo-oophorectomy in BRCA mutation carriers: role of serial sectioning in the detection of occult malignancy. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* 2005;23(1):127-132.
4. The Reduction in Risk of Ovarian Cancer Associated with Oral-Contraceptive Use. *New England Journal of Medicine.* 1987;316(11):650-655.