

Lynch Syndrome: PMS2 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	<i>PMS2</i> Mutation Carrier Cancer Risks ¹	General Population Lifetime Cancer Risks ¹	Surveillance/Management Recommendations ¹
Colorectal	12-20%	4.5%	<p><i>Surveillance</i></p> <ul style="list-style-type: none"> • 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 <p><i>Surgery</i></p> <ul style="list-style-type: none"> • If colon cancer is detected, segmented or extended colectomy depending on clinical scenario should be considered <p><i>Chemoprevention</i></p> <ul style="list-style-type: none"> • Aspirin may decrease the risk of colon cancer in Lynch syndrome, but optimal dose and duration of aspirin therapy are uncertain²
Uterine/endometrial	up to 15%	2.7%	<p><i>Surveillance</i></p> <ul style="list-style-type: none"> • 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 <p><i>Surgery</i></p> <ul style="list-style-type: none"> • 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 be examined intra-operatively by a pathologist for occult disease <p><i>Chemoprevention</i></p> <ul style="list-style-type: none"> • In the general population, oral contraceptive use has been associated with a decreased risk of uterine cancer by 50%
Ovarian	Not well-established	1.3%	<p><i>Surveillance</i></p> <ul style="list-style-type: none"> • 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

			<ul style="list-style-type: none"> • Serum CA-125 is an additional ovarian screening test with similar caveats <p><i>Surgery</i></p> <ul style="list-style-type: none"> • Bilateral salpingo-oophorectomy (BSO) may reduce the incidence of ovarian cancer; currently, insufficient evidence exists to make a specific recommendation for risk-reducing salpingo-oophorectomy in individuals with <i>PMS2</i> mutations • 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 patients³ <p><i>Chemoprevention</i></p> <ul style="list-style-type: none"> • In the general population, oral contraceptive use has been associated with a decreased risk of ovarian cancer⁴
Pancreatic	Not well-established	1.5%	<p><i>Surveillance</i></p> <ul style="list-style-type: none"> • NCCN: No consensus management guidelines • International Cancer of the Pancreas Screening (CAPS) consortium: patients with Lynch syndrome with one first-degree relative (parent, sibling, or child) with pancreatic cancer should be considered for screening⁵ • If screening is performed, it should be considered in high-volume centers with multidisciplinary teams, preferably with research protocols

Other Cancer Risks: Lynch syndrome is associated with other increased cancer risks including bladder, brain, breast, hepatobiliary tract, small bowel, stomach, prostate, ureter and renal pelvis cancers. Exact risks for these cancer types are not well-established individuals with a *PMS2* mutation. Additionally, no consensus management guidelines have been established at this time, aside from general population cancer screening.¹

Implications for Family Members/Reproductive Considerations

- First-degree relatives (i.e., parents, siblings, and children) have a 50% chance to have the familial *PMS2* mutation. Second-degree relatives (i.e., nieces/nephews, aunts/uncles, and grandparents) have a 25% chance to have the familial mutation.
- Rarely, children inherit a *PMS2* gene mutation from both parents. Children with two *PMS2* 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 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. Burn J, Gerdes AM, Macrae F, et al. Long-term effect of aspirin on cancer risk in carriers of hereditary colorectal cancer: an analysis from the CAPP2 randomised controlled trial. *Lancet*. 2011;378(9809):2081-2087.

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.
5. Canto MI, Harinck F, Hruban RH, et al. International Cancer of the Pancreas Screening (CAPS) Consortium summit on the management of patients with increased risk for familial pancreatic cancer. *Gut*. 2013;62(3):339-347.