

## Lynch Syndrome: *EPCAM* Mutation

### Cancer Risks and General Management Recommendations

Lynch syndrome is the most common cause 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 condition is characterized by early onset colorectal cancer, an increased risk for synchronous and metachronous tumors, and extra-intestinal manifestations.

The majority of Lynch syndrome cases are due to germline mutations in one of the DNA mismatch repair (MMR) genes, *MLH1*, *MSH2*, *MSH6* and *PMS2*. An estimated 1-3% of Lynch syndrome cases are due to deletions in the *EPCAM* gene, which cause hypermethylation of the *MSH2* promoter and silencing of the *MSH2* gene. Although exact cancer risks associated with *EPCAM* mutations are unknown, deletions in the *EPCAM* gene are expected to result in similar cancer risks as those seen in *MSH2* mutation carriers.

Cancer Type	<i>EPCAM</i> ( <i>MSH2</i> ) Mutation Carrier Cancer Risks <sup>1</sup>	General Population Lifetime Cancer Risks <sup>1</sup>	Surveillance/Management Recommendations <sup>1,2</sup>
Colorectal	43-52%	4.5%	<p><i>Surveillance</i></p> <ul style="list-style-type: none"> <li>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</li> </ul> <p><i>Surgery</i></p> <ul style="list-style-type: none"> <li>If colon cancer is detected, segmented or extended colectomy depending on clinical scenario should be considered</li> </ul> <p><i>Chemoprevention</i></p> <ul style="list-style-type: none"> <li>Aspirin may decrease the risk of colon cancer in Lynch syndrome, but optimal dose and duration of aspirin therapy are uncertain<sup>3</sup></li> </ul>
Uterine/endometrial	21-57%	2.7%	<p><i>Surveillance</i></p> <ul style="list-style-type: none"> <li>No clear evidence to support screening for uterine cancer</li> <li>Screening via endometrial biopsy every 1-2 years and transvaginal ultrasound may be considered at clinician's discretion</li> </ul> <p><i>Surgery</i></p> <ul style="list-style-type: none"> <li>Hysterectomy is a risk-reducing option that can be considered</li> <li>Timing should be individualized based on whether childbearing is complete, comorbidities, family history and gene mutation</li> <li>Women undergoing prophylactic hysterectomy should have a pre-operative uterine biopsy and the uterus be examined intra-operatively by a pathologist for occult disease</li> </ul> <p><i>Chemoprevention</i></p> <ul style="list-style-type: none"> <li>In the general population, oral contraceptive use has been associated with a decreased risk of uterine cancer by 50%</li> </ul>
Ovarian	10-38%	1.3%	<p><i>Surveillance</i></p> <ul style="list-style-type: none"> <li>Data do not support routine ovarian cancer screening</li> <li>Transvaginal ultrasound for ovarian cancer screening has not been shown to be sufficiently sensitive or specific, but may be considered at clinician's discretion</li> </ul>

			<ul style="list-style-type: none"> <li>Serum CA-125 is an additional ovarian screening test with similar caveats</li> </ul> <p><i>Surgery</i></p> <ul style="list-style-type: none"> <li>Bilateral salpingo-oophorectomy (BSO) may reduce the incidence of ovarian cancer</li> <li>Timing should be individualized based on whether childbearing is complete, menopause status, comorbidities, family history and gene mutation</li> <li>Detailed pathologic examination of ovarian specimens can yield greater detection of ovarian cancer and should be considered in these high risk patients<sup>4</sup></li> </ul> <p><i>Chemoprevention</i></p> <ul style="list-style-type: none"> <li>In the general population, oral contraceptive use has been associated with a decreased risk of ovarian cancer<sup>5</sup></li> </ul>
Gastric	0.2-16%	<1%	<p><i>Surveillance</i></p> <ul style="list-style-type: none"> <li>No clear evidence to support surveillance for gastric, duodenal, and small bowel cancer</li> <li>Selected individuals with a family history of gastric, duodenal, and small bowel cancer may benefit from surveillance</li> <li>Individuals of descent from any country with a high incidence of gastric cancer may have an increased risk and may benefit from increased surveillance</li> <li>If surveillance is performed, may consider upper endoscopy with visualization of the duodenum every 3-5 years beginning at age 40</li> <li>Consider <i>H. pylori</i> testing and treating, if detected</li> </ul>
Small Bowel	1-10%	<1%	
Urothelial	2-18%	<1%	<p><i>Surveillance</i></p> <ul style="list-style-type: none"> <li>No clear evidence to support surveillance for urothelial cancers</li> <li>Surveillance options may include annual urinalysis starting at 30-35 years of age</li> </ul>
Bladder	4-17%	2%	
Prostate	30-32%	11.6%	<p><i>Surveillance</i></p> <ul style="list-style-type: none"> <li>No consensus management guidelines</li> <li>Discuss family history and prostate cancer surveillance options (i.e., PSA, digital rectal exam) with a clinician to determine an appropriate surveillance regimen</li> </ul>
Pancreatic	Not well-established	1.5%	<p><i>Surveillance</i></p> <ul style="list-style-type: none"> <li>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 <math>\geq 1</math> first- or second-degree relative from the same side (or presumed to be from the same side of) the family as the identified mutation</li> <li>Surveillance is not currently recommended for <i>EPCAM</i> mutation carriers in the absence of a close family history of exocrine pancreatic cancer</li> <li>For individuals considering pancreatic cancer surveillance, surveillance is recommended to be performed in experienced high-volume centers, ideally under research conditions</li> </ul>
Brain/Central	Not well-established	<1%	<p><i>Surveillance</i></p> <ul style="list-style-type: none"> <li>Annual physical/neurological examination starting at age 25-30 to assess for CNS tumors</li> </ul>

Nervous System (CNS)			<ul style="list-style-type: none"> <li>No other screening recommendations have been made at this time</li> </ul>
----------------------	--	--	--

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 an *EPCAM* mutation. Additionally, no consensus management guidelines have been established at this time, aside from general population cancer screening.<sup>6</sup>

#### *Implications for Family Members/Reproductive Considerations*

- First-degree relatives (i.e., parents, siblings, and children) have a 50% chance to have the familial *EPCAM* mutation. Second-degree relatives (i.e., nieces/nephews, aunts/uncles, and grandparents) have a 25% chance to have the familial mutation.
- Rarely, individuals inherit two *EPCAM* gene mutations (one from each parent), which causes congenital tufting enteropathy (CTE).
  - CTE is a rare chronic diarrheal disorder presenting in infancy.
  - EPCAM* genetic testing for the partner of an individual with an *EPCAM* mutation may be appropriate to clarify the risk of having children with CTE.
- 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, including reproductive risks. Family members can visit [www.FindAGeneticCounselor.com](http://www.FindAGeneticCounselor.com) to find genetic services near them.

#### **References**

- NCCN Clinical Practice Guidelines in Oncology®: Genetic/Familial High-Risk Assessment: Colorectal. Version 3.2019. 2019.
- NCCN Clinical Practice Guidelines in Oncology®: Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic. Version 1.2020. 2019.
- 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.
- 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.
- Cancer, Steroid Hormone Study of the Centers for Disease C, the National Institute of Child H, Human D. The reduction in risk of ovarian cancer associated with oral-contraceptive use. *N Engl J Med*. 1987;316(11):650-655.
- Gupta S, Provenzale D, Llor X, et al. NCCN Guidelines Insights: Genetic/Familial High-Risk Assessment: Colorectal, Version 3.2019. *J Natl Compr Canc Netw*. 2019;17(9):1032-1041.