

MSH6 gene

Associated Syndrome Name: Lynch syndrome/Hereditary Non-Polyposis Colorectal Cancer (HNPCC)

MSH6 Summary Cancer Risk Table

| CANCER | GENETIC CANCER RISK |
|-------------|---------------------|
| Colorectal | High Risk |
| Endometrial | High Risk |
| Other | High Risk |
| Gastric | Elevated Risk |
| Ovarian | Elevated Risk |
| Pancreatic | Elevated Risk |
| Prostate | Elevated Risk |
| Skin | Elevated Risk |

MSH6 gene Overview

Lynch syndrome ^{1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12}

- Individuals with mutations in *MSH6* have Lynch syndrome. This condition is also known as Hereditary Non-Polyposis Colorectal Cancer (HNPCC).
- Men and women with Lynch syndrome due to mutations in *MSH6* have a high risk of developing colorectal cancer, often at younger ages than seen in the general population. Colorectal cancer in patients with Lynch syndrome develops from adenomatous polyps which progress to cancer more quickly than polyps in individuals who do not have Lynch syndrome. Colorectal cancer risk may be somewhat lower in women than in men, but there are no differences in the colorectal cancer screening guidelines for men and women.
- Women with Lynch syndrome due to mutations in *MSH6* have a high risk for developing endometrial cancer and an elevated risk for ovarian cancer, often at younger ages than typical in the general population.
- Patients with Lynch syndrome due to mutations in *MSH6* are also believed to have an increased risk of developing a wide variety of other Lynch syndrome associated cancers, including small bowel, urinary tract, hepatobiliary tract, brain (usually glioblastoma), sebaceous gland, and pancreatic. Precise risk estimates are not available because there is less information available for patients with *MSH6* mutations compared with patients who have mutations in other Lynch syndrome genes. These risks may be more significant in patients with a family history of these cancers. Therefore, the general screening and management recommendations provided below should be modified based on individualized risk assessment and counseling.
- Patients with Lynch syndrome due to mutations in *MSH6* have an increased risk for gastric cancer. Screening may be particularly important for patients with additional risk factors for gastric cancer, such as being male, older age, first-degree relative with gastric cancer, Asian ethnicity, residing in, or immigrating from countries with high background incidence of gastric cancer, chronic autoimmune gastritis, gastric intestinal metaplasia, and gastric adenomas.
- An increased risk for prostate cancer has been documented in multiple studies of men with Lynch syndrome. Estimates range from an approximately 2 to 5-fold increase in risk, or up to 30%, but the exact increase has not yet been established for men with mutations in *MSH6*.
- Studies have investigated the possibility that patients with Lynch syndrome have an increased risk for other cancers, including breast cancer and adrenocortical carcinoma. However, the data are not conclusive at this time and there are currently no medical management guidelines related to these cancers.
- Patients with Lynch syndrome have a high risk for developing second primary cancers following an initial diagnosis of colorectal or endometrial cancer. This includes a high risk for endometrial cancer in women following colorectal cancer and vice versa, a high risk for a second primary colorectal cancer in any portions of the colon or rectum remaining after surgical treatment, and an increased risk for other Lynch associated cancers, such as those of the upper gastrointestinal tract, urinary tract, and other sites.
- Although there are high risks for cancer in patients with Lynch syndrome, many of these risks can be greatly reduced with appropriate medical management. Guidelines for the medical management of patients with Lynch syndrome have been developed by the National Comprehensive Cancer Network (NCCN) and other expert groups. These are listed below. It is recommended that patients with an *MSH6* mutation and a diagnosis of Lynch syndrome be managed by a multidisciplinary team with expertise in medical genetics and the care of patients with this condition.

MSH6 gene Cancer Risk Table

| CANCER TYPE | AGE RANGE | CANCER RISK | RISK FOR GENERAL POPULATION |
|-------------------------------------|---|------------------------|-----------------------------|
| Colorectal (male and female) | To age 70 ^{1, 2, 12, 13, 14, 15, 16} | 10%-36% | 1.8% |
| Endometrial | To age 70 ^{1, 2, 7, 12, 14, 15, 16, 17} | 16%-49% | 1.9% |
| Overall cancer risk (Lynch cancers) | Risk for a second Lynch-related cancer after a first cancer diagnosis ^{18, 19} | Increased risk | NA |
| Prostate | To age 70 ^{2, 15, 16, 17, 20} | Possibly elevated risk | 6.1% |
| Ovarian | To age 70 ^{2, 12, 14, 15, 16, 17} | Up to 13% | 0.6% |
| Urothelial | To age 70 ^{1, 2, 8, 15, 16} | 3%-9% | 0.7% |
| Gastric | To age 70 ^{14, 15, 16, 17} | 1%-10% | 0.3% |
| Small Bowel | To age 70 ^{14, 15, 16, 17} | Possibly elevated risk | 0.1% |
| Pancreatic | To age 70 ^{11, 14, 15, 16} | Possibly elevated risk | 0.6% |
| Brain | To age 70 ^{2, 14, 15, 16, 17} | Up to 2% | 0.4% |
| Hepatobiliary Tract | To age 70 ^{12, 14, 15, 16} | Possibly elevated risk | 0.5% |
| Lynch-associated Skin Tumors | To age 70 ^{6, 7, 9, 10, 12} | Elevated risk | <1.0% |

MSH6 Cancer Risk Management Table

The overview of medical management options provided is a summary of professional society guidelines. The most recent version of each guideline should be consulted for more detailed and up-to-date information before developing a treatment plan for a particular patient.

This overview is provided for informational purposes only and does not constitute a recommendation. While the medical society guidelines summarized herein provide important and useful information, medical management decisions for any particular patient should be made in consultation between that patient and his or her healthcare provider and may differ from society guidelines based on a complete understanding of the patient's personal medical history, surgeries and other treatments.

| CANCER TYPE | PROCEDURE | AGE TO BEGIN | FREQUENCY (UNLESS OTHERWISE INDICATED BY FINDINGS) |
|-------------|--|---|---|
| Colorectal | Colonoscopy ¹⁰ | 30 to 35 years, or 2 to 5 years younger than the earliest colorectal cancer diagnosis in the family if it is under age 30 | Every 1 to 2 years |
| | Consider the use of aspirin as a risk-reduction agent ¹⁰ | Individualized | Individualized |
| Endometrial | Patient education about the importance of quickly seeking attention for endometrial cancer symptoms, such as abnormal bleeding or menstrual cycle irregularities ¹⁰ | Individualized | Individualized |
| | Consider pelvic examination, endometrial sampling and transvaginal ultrasound. ¹⁰ | 30 to 35 years | Every 1 to 2 years |
| | Consider hysterectomy. ¹⁰ | After completion of childbearing | NA |

| CANCER TYPE | PROCEDURE | AGE TO BEGIN | FREQUENCY (UNLESS OTHERWISE INDICATED BY FINDINGS) |
|--------------------------------------|--|--|---|
| Prostate | Incorporating information about increased risk due to gene mutation, start risk and benefit discussion about offering baseline digital rectal examination (DRE) and Prostate Specific Antigen (PSA). ^{10, 21} | Age 40 | Individualized, consider annually |
| Ovarian | Consider bilateral salpingo-oophorectomy. ¹⁰ | After completion of childbearing | NA |
| | Consider transvaginal ultrasound and CA-125 measurement. ¹⁰ | 30 to 35 years | NA |
| | Consider options for ovarian cancer risk-reduction agents (i.e. oral contraceptives). ^{10, 26} | Individualized | NA |
| | Patient education about ovarian cancer symptoms ¹⁰ | Individualized | NA |
| Urothelial | Consider urinalysis. ¹⁰ | 30 to 35 years | Annually |
| Gastric | Consider testing and treating <i>Helicobacter pylori</i> infection. ¹⁰ | Individualized | NA |
| | Consider upper endoscopy, particularly for patients with additional risk factors (see clinical overview). Consider biopsy of the proximal and distal stomach. ^{10, 22} | 40 years | Every 3 to 5 years |
| Small Bowel | Consider upper endoscopy, particularly for patients with additional risk factors for small bowel cancer, such as family history. ¹⁰ | 30 to 40 years | Every 3 to 5 years |
| Pancreatic | For patients with a family history of pancreatic cancer, consider available options for pancreatic cancer screening, including the possibility of endoscopic ultrasonography (EUS) and MRI/magnetic resonance cholangiopancreatography (MRCP). It is recommended that patients who are candidates for pancreatic cancer screening be managed by a multidisciplinary team with experience in screening for pancreatic cancer, preferably within research protocols. ^{10, 23} | 45 to 50 years, or 10 years younger than the earliest diagnosis of pancreatic cancer in the family | Annually |
| | Provide education about ways to reduce pancreatic cancer risk, such as not smoking and losing weight. ²⁵ | Individualized | Individualized |
| Brain | Patient education about the importance of quickly seeking attention for signs and symptoms of neurologic cancer ¹⁰ | Individualized | NA |
| Hepatobiliary Tract | Currently there are no specific medical management guidelines for hepatobiliary cancer risk in mutation carriers. ¹⁰ | NA | NA |
| Lynch-associated Skin Tumors | Consider skin exams ¹⁰ | Individualized | Every 1 to 2 years |
| For Patients With A Cancer Diagnosis | For patients with a gene mutation and a diagnosis of cancer, targeted therapies may be available as a treatment option for certain tumor types (e.g., antibodies to PD-1) ²⁴ | NA | NA |

Information for Family Members

The following information for Family Members will appear as part of the MMT for a patient found to have a mutation in the *MSH6* gene.

This patient's relatives are at risk for carrying the same mutation(s) and associated cancer risks as this patient. Cancer risks for females and males who have this/these mutation(s) are provided below.

Family members should talk to a healthcare provider about genetic testing. Close relatives such as parents, children, brothers and sisters have the highest chance of having the same mutation(s) as this patient. Other more distant relatives such as cousins, aunts, uncles, and grandparents also have a chance of carrying the same mutation(s). Testing of at-risk relatives can identify those family members with the same mutation(s) who may benefit from surveillance and early intervention.

In rare instances, an individual may inherit mutations in both copies of the *MSH6* gene, leading to the condition Constitutional Mismatch

Repair-Deficiency syndrome (CMMR-D). Individuals with CMMR-D often have significant complications in childhood, including colorectal polyposis and a high risk for colorectal, small bowel, brain, and hematologic cancers. Individuals with CMMR-D often have café-au-lait spots. The children of this patient are at risk of inheriting CMMR-D only if the other parent is also a carrier of a *MSH6* mutation. Screening the other biological parent of any children for *MSH6* mutations may be appropriate.⁶

Parents who are concerned about the possibility of passing on an *MSH6* mutation to a future child may want to discuss options for prenatal testing and assisted reproduction techniques, such as pre-implantation genetic diagnosis (PGD).¹⁰

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