PMS2 gene

Associated Syndrome Name: Lynch syndrome/Hereditary non-polyposis colorectal cancer (HNPCC)

PMS2 Summary Cancer Risk Table

CANCER	GENETIC CANCER RISK
Colorectal	High Risk
Endometrial	High Risk

PMS2 gene Overview

Lynch syndrome [1, 2, 3, 4, 5, 6, 7, 8, 9]

- Individuals with mutations in *PMS2* 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 *PMS2* 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.
- Women with Lynch syndrome due to mutations in *PMS2* have a high risk for developing endometrial cancer and possibly an elevated risk for ovarian cancer, often at younger ages than typical in the general population.
- There is still some uncertainty as to whether patients with Lynch syndrome due to *PMS2* mutations have significantly increased risks for the wide variety of cancers associated with Lynch syndrome due to mutations in other genes. These cancers include small bowel, urinary tract, hepatobiliary tract, brain (usually glioblastoma), sebaceous gland, gastric, ovarian, prostate, and pancreatic. There are currently no specific medical management guidelines for screening of these cancers in *PMS2* mutation carriers.
- Cancer risks may be more significant in patients with a family history of particular cancers. Therefore, the general screening and management recommendations provided below should be modified based on individualized risk assessment and counseling.
- 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 in patients with Lynch syndrome due to mutations in *PMS2* a possibly elevated risk for other Lynch associated cancers.
- The timing of risk-reducing gynecological surgeries in individuals with Lynch syndrome due to mutations in *PMS2* should be individualized based on whether childbearing is complete, the individual's medical and surgical history, family history, and other relevant factors.
- 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 a *PMS2* 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.

PMS2 gene Cancer Risk Table

CANCER TYPE	AGE RANGE	CANCER RISK	RISK FOR GENERAL POPULATION
Colorectal	To age 70[2, 3, 10, 11, 12]	Up to 20%	1.8%
Endometrial	To age 70[1, 2, 3, 10, 12, 13, 14]	12%-26%	1.9%
Overall cancer risk (Lynch cancers)	Risk for a second Lynch-related cancer after a first cancer diagnosis[15, 16]	Increased risk	NA

PMS2 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[17]	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 3 years
	Consider the use of aspirin as a risk-reduction agent.[17]	Individualized	Individualized
Endometrial	Patient education about the importance of quickly seeking attention for endometrial cancer symptoms, such as abnormal bleeding or menstrual cycle irregularities[17]	Individualized	Individualized
	Consider endometrial biopsy.[17]	30 to 35 years	Every 1 to 2 years
	Consider transvaginal ultrasound.[17]	After menopause	Individualized
	Consider hysterectomy.[17]	50 years	NA
	Consider options for endometrial cancer risk-reduction agents (i.e. oral contraceptives, progestin intrauterine systems).[17]	Individualized	NA
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)[18]	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 PMS2 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 *PMS2* 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 *PMS2* mutation. Screening the other biological parent of any children for *PMS2* mutations may be appropriate.[7, 10]

Parents who are concerned about the possibility of passing on a *PMS2* mutation to a future child may want to discuss options for prenatal testing and assisted reproduction techniques, such as pre-implantation genetic diagnosis (PGD).[17]

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