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
Gastric	Elevated Risk
Other	Elevated Risk
Ovarian	Elevated Risk
Pancreatic	Elevated Risk
Prostate	Elevated Risk
Skin	Elevated 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, prostate, and pancreatic. In some cases, precise risk estimates are not available because there is less information available for patients with *PMS2* mutations compared with patients who have mutations in other Lynch syndrome genes. However, it is clear that the risks associated with *PMS2* mutations are not nearly as high as the risks seen with other Lynch syndrome genes.
- 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.
- Patients with Lynch syndrome due to mutations in *PMS2* may have an increased risk for gastric cancer. Earlier screening or more frequent intervals may be considered based on family history of upper gastrointestinal cancers or high-risk endoscopic findings. Random biopsy of the proximal and distal stomach should at minimum be performed on the initial upper endoscopy procedure to assess for *Helicobacter pylori*, autoimmune gastritis, and intestinal metaplasia.
- 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 a high risk for other Lynch associated cancers, such as those of the upper gastrointestinal tract, urinary tract, and other sites.
- 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
Lynch-associated Skin Tumors	To age 70[7, 10, 17, 18]	Elevated risk	<1.0%
Prostate	To age 70[2, 3, 12, 14]	Possibly elevated risk	6.2%
Ovarian	To age 70[2, 3, 12, 14]	Possibly elevated risk	0.6%
Gastric	To age 70[3, 12]	Possibly elevated risk	0.3%
Small Bowel	To age 70[3, 12, 13, 14]	Possibly elevated risk	0.1%
Urothelial	To age 70[2, 3, 12]	Possibly elevated risk	0.6%
Pancreatic	To age 70[12, 13]	Possibly elevated risk	0.6%
Brain	To age 70[2, 3, 12, 14]	Possibly elevated risk	0.3%
Hepatobiliary Tract	To age 70[3, 12, 13]	Possibly elevated risk	0.5%

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

CANCER TYPE	PROCEDURE	AGE TO BEGIN	FREQUENCY (UNLESS OTHERWISE INDICATED BY FINDINGS)
Lynch-associated Skin Tumors	Consider skin exams[17]	Individualized	Every 1 to 2 years
Prostate	Incorporating information about increased risk due to gene mutation, consider prostate cancer screening. Discuss potential benefits and harms of baseline digital rectal examination (DRE) and prostate specific antigen (PSA).[17, 19]	40 years	Individualized, consider annually or adjust based on PSA
Ovarian	Consider bilateral salpingo-oophorectomy (BSO).[17]	50 years	NA
	Consider options for ovarian cancer risk-reduction agents (i.e. oral contraceptives, progestin intrauterine systems).[17, 20]	Individualized	NA
Gastric	Consider testing and treating Helicobacter pylori infection.[17]	Individualized	NA
	Consider upper endoscopy, preferably performed in conjunction with colonoscopy. See clinical overview.[17]	30 to 40 years, or earlier if there is a family history of gastric cancer at a young age	Every 2 to 4 years
Small Bowel	Consider upper endoscopy, preferably performed in conjunction with colonoscopy. Push enteroscopy can be considered in place of upper endoscopy to enhance small bowel visualization.[17]	30 to 40 years, or earlier if there is a family history of small bowel cancer at a young age	Every 2 to 4 years
Urothelial	Consider urinalysis.[17]	30 to 35 years	Annually
Pancreatic	Currently there are no specific medical management guidelines for the possibly increased risk for pancreatic cancer in mutation carriers.	NA	NA
Brain	Patient education about the importance of quickly seeking attention for signs and symptoms of neurologic cancer[17]	Individualized	NA
Hepatobiliary Tract	Currently there are no specific medical management guidelines for hepatobiliary cancer risk in mutation carriers.[17]	NA	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)[21]	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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