FH gene

Associated Syndrome Name: Hereditary leiomyomatosis and renal cell carcinoma syndrome (HLRCC)

FH Summary Cancer Risk Table

CANCER	GENETIC CANCER RISK
Other	High Risk
Renal	High Risk
Other	Elevated Risk
Skin	Elevated Risk

FH gene Overview

Hereditary leiomyomatosis and renal cell carcinoma syndrome (HLRCC) [1, 2, 3, 4]

- Individuals with mutations in the *FH* gene have hereditary leiomyomatosis and renal cell carcinoma syndrome (HLRCC).
- Patients with HLRCC have a high risk for an aggressive type of renal cell cancer, known as *FH*-deficient or type 2 papillary. Other types of malignant (cancerous) and non-malignant (benign) renal tumors can also occur.
- Most women with HLRCC will develop uterine leiomyomas (fibroids) at relatively young ages. These may be multiple and large in size, requiring surgery. There may be a small risk for these benign uterine tumors to develop into malignant leiomyosarcomas.
- Patients with HLRCC often develop non-cancerous smooth muscle tumors of the skin (skin leiomyomas). These may be painful and are most commonly found on the trunk, arms, leg and face. When present, they tend to increase in number and size with age. There may be a small risk for these benign skin tumors to develop into malignant leiomyosarcomas.
- Studies have looked at the possibility that patients with HLRCC have an increased risk for other cancers, benign tumors and additional medical problems. In particular, there is some evidence that specific variants in the *FH* gene have an increased risk for paragangliomas and pheochromocytomas. Screening for paragangliomas and pheochromocytomas is only recommended for individuals who have these specific variants. **If this patient's *FH* mutation is known to be associated with an increased risk for paragangliomas and pheochromocytomas, that information and the screening guidelines are provided in the DETAILS ABOUT: *FH* section of the Genetic Result.**
- Although there are high risks for cancer and other medical issues in patients with HLRCC, and there is still uncertainty about all of the associated risks, it may be possible to reduce these risks with appropriate medical management. Guidelines from the National Comprehensive Cancer Network (NCCN), the American Association for Cancer Research (AACR), and the Consensus Meeting of the Second Symposium on HLRCC are provided below. Since HLRCC is a complex condition, patients with *FH* mutations and a diagnosis of HLRCC should be managed by a multidisciplinary team with experience in the surveillance and treatment of the complications associated with this condition.

FH gene Cancer Risk Table

CANCER TYPE	AGE RANGE	CANCER RISK	RISK FOR GENERAL POPULATION
Renal	To age 80[1, 3, 4, 5]	16-21%, with a strong tendency towards young ages of diagnosis, median age of diagnosis is estimated to be 44	1.4%
Uterine Leiomyosarcoma	To age 80[1, 3, 6]	Possibly elevated risk	<0.1%
Skin Leiomyosarcoma	To age 80[1, 3, 6]	Possibly elevated risk	<0.1%
Other - Non-malignant features of HLRCC (women only)	All ages[1, 3, 6]	Most women with HLRCC will develop multiple uterine fibroids at young ages (see Overview)	NA

CANCER TYPE	AGE RANGE	CANCER RISK	RISK FOR GENERAL POPULATION
Other - Non-malignant features of HLRCC	All ages[1, 3, 6]	Individuals with HLRCC are likely to develop skin leiomyomas (see Overview)	NA

FH 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)
Renal	Abdominal (renal) imaging with MRI (preferred) or CT, with and without contrast[7, 8]	8 to 10 years	Annually
	Since mutation carriers are at an increased risk for more aggressive kidney cancer, this information may be considered when choosing management options for individuals with any suspicious renal lesion or a diagnosis of renal cancer[8]	NA	NA
Uterine Leiomyosarcoma	Provide education about the symptoms of uterine leiomyosarcoma, including change in menses and abdominal discomfort.[8]	Teenage years	Individualized
Skin Leiomyosarcoma	Provide education about the symptoms of skin leiomyosarcoma, including new skin lesions and pain.[8]	Teenage years	Individualized
Other - Non-malignant features of HLRCC	Provide education about the symptoms of uterine and skin leiomyoma, including change in menses, abdominal discomfort, and new skin lesions and pain.[8]	Teenage years	Individualized
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. inhibitors of VEGF and EGFR, immunotherapy).[7]	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 FH 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 *FH* gene, leading to the condition fumarase deficiency, or fumaric aciduria. Individuals with this condition have severe neurologic problems during infancy, usually leading to death in childhood. The children of this patient are at risk of inheriting fumarase deficiency only if the other parent is also a carrier of an *FH* mutation. Screening the other biological parent of this patient for *FH* mutations may be appropriate even if they do not have a diagnosis of HLRCC.[3]

Since *FH* mutations have a risk for cancers in children and some screenings may be considered to begin at young ages, mutation testing should be considered in childhood, before beginning MRI screening.[2, 6]

References

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Last Updated on 03-Jun-2025