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Lynch Syndrome Risk Models

What are risk models?

Hereditary cancer risk models are statistical tools used alongside genetic counseling to help assess an individual's likelihood of having or being at risk to develop a hereditary form of cancer. These models help estimate the likelihood that genetic testing will detect a mutation in a cancer-susceptibility gene. The appropriateness and utility of each model is determined by a patient's personal and family history.

The National Comprehensive Cancer Network (NCCN) provides guidelines for a genetic evaluation for Lynch Syndrome (LS). This criteria includes individuals with a ≥5% risk of having a pathogenic mutation in a mismatch repair (MMR) gene based on one of the predictive risk models outlined below. Additionally, these numerical estimations can assist with the patient's understanding of their cancer risks, allowing for more realistic expectations about genetic testing results. In some cases, these risk models can be used as supportive evidence for insurance companies to help cover the cost of genetic testing.

MMRPro

Developed in 2006, this model is used to determine the risk of a patient having a mutation in the *MLH1*, *MSH2*, and *MSH6* genes. It utilizes a personal and family history of colon and/or endometrial cancer within the patient's first- and second-degree relatives. It also utilizes ancestry, location of the cancer in the colon, age of cancer onset, age of unaffected family members, results of microsatellite instability (MSI)/ immunohistochemistry (IHC) testing of the colon tumor, and LS-related mutation carrier status.

Limitations of this model include the mutation risk calculation does not include LS-related cancers outside of colon and endometrial, MSI in a sporadic setting (i.e., *BRAF* and *MLH1* hypermethylation testing of the tumor), colorectal adenomas/polyps, or prophylactic hysterectomy. Additionally, the risk of a *PMS2* gene mutation is not calculated.

MMRPredict

Also developed in 2006, this model is used to determine the overall likelihood of having a LS-related mutation in *MLH1*, *MSH2*, and *MSH6* in patients with colon cancer, but does not provide gene-specific risk estimates like MMRPro. It utilizes the age at which the patient was diagnosed with colon cancer, the presence of multiple primary colon cancers, a family history of colon/endometrial cancer in first-degree relatives.

Its limitations are similar to those of MMRPro. Additionally, this model was validated in a Scottish cohort of affected individuals diagnosed before age 55. This means it is likely to perform best in patients with early-onset colon cancer, and it is unclear if it performs as well for older populations or other ethnicities.

PREMM$_5$

Introduced in 2017, this model replaced the previous PREMM$_{1,2,6}$ model. This model predicts the likelihood of a LS-related mutation in *MLH1*, *MSH2*, *MSH6, PMS2,* and *EPCAM* for a patient. The risk is calculated using the patient's personal history of a LS-related cancer (colon, endometrial, or extra-colonic), the age at diagnosis, and gender. It also uses a family history of LS-related cancers in first- and second-degree relatives, including the ages at diagnosis.

Limitations of this model include the possibility of an inaccurate estimation of a *PMS2* mutation. Reliable prediction of *PMS2* in the study cohort the model is based-upon proved to be difficult due to a weaker phenotype. Additionally, it does not account for family size or unaffected family members, and does not incorporate MSI/IHC data or a patient's history of colorectal adenomas.

How can I learn more?

For information about genetic testing and genetic counseling, visit the UT Southwestern Cancer Genetics for Health Professionals site.

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For additional resources on coordinating genetics counseling and testing for patients, or providing genetics services, visit the Genetic Screening and Navigation Toolkit.

To find a genetic counselor near you, visit the National Society of Genetic Counselors Find a Genetic Counselor Tool.

References

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