The MMRpro model accurately predicted the probability of carrying a cancer-susceptibility gene mutation for the Lynch syndrome

Chen S, Wang W, Lee S, et al. **Prediction of germline mutations and cancer risk in the Lynch syndrome.** JAMA. 2006;296:1479-87.

Clinical impact ratings: Gastroenterology ★★★★★☆☆ Genetics ★★★★★★★ Oncology ★★★★★★☆

QUESTION

How well is the probability of carrying a deleterious mutation in DNA mismatch repair (MMR) genes predicted by the MMRpro model in persons from families at high risk for the Lynch syndrome (hereditary nonpolyposis colorectal cancer)?

METHODS

Design: Development of a model using estimates based on meta-analyses of the penetrance and prevalence of mutations and of the predictive values of tumor characteristics and validation by comparing model predictions with results of highly sensitive germline mutation detection techniques in a cohort of affected or high-risk persons.

Setting: 2 hereditary colorectal cancer registries and 1 cancer center clinical genetics service in the United States, Canada, and Australia.

Patients: 279 patients (52% women) who had colorectal or endometrial cancer before 50 years of age or were at high risk because of colorectal cancer in ≥ 2 first- or second-degree family members, and who had had extensive testing for germline mutations of the MMR genes MLH1, MSH2, and MSH6.

Description of prediction guide: The following information was entered into the MMRpro model for the counselee and each relative: exact relation to the counselee; colorectal and endometrial cancer status and age at diagnosis, if affected; current age, if unaffected; result of microsatellite instability (MSI) testing or immunohistochemical staining of the tumor, if available; and result of previous germline testing of MMR genes. Software for performing the MMRpro calculations is freely available at http://astor.som.jhmi.edu/BayesMendel.

Outcomes: Accuracy of MMRpro in predicting mutation carrier status.

MAIN RESULTS

The MMRpro model calculated an exact probability of carrying a mutation for each person and showed how the probability would change in the presence of a positive or negative MSI test result. Mutations were present in 121 of the 279 patients; the MMRpro model predicted 129 patients would be carriers, giving good calibration, as quantified by the ratio of observed-to-expected positive results (Table). The discriminatory ability of the model, as measured by the concordance index (equivalent to the area under the receiver-operating characteristic curve), and the overall performance, as quantified by the mean squared error of prediction (a measure of the distance between the predicted probability and the actual mutation status), were slightly improved when MSI testing was included in the model (Table). The performance of the Leiden clinical guideline is included in the Table for comparison.

CONCLUSION

The MMRpro model accurately predicted the probability of carrying a mutation in a DNA mismatch repair gene in persons from families at high risk for the Lynch syndrome.

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Ability of the MMRpro model, with or without microsatellite instability (MSI) testing, to predict the probability of genetic mutations in members of families at high risk for the Lynch syndrome*

Predictive model	Concordance index (95% CI)	O/E ratio† (CI)	Mean squared error (CI)
MMRpro + MSI testing	0.83 (0.78 to 0.87)	0.94 (0.84 to 1.05)	0.18 (0.15 to 0.22)
MMRpro	0.79 (0.74 to 0.84)	0.97 (0.86 to 1.08)	0.19 (0.16 to 0.23)
Leiden	0.77 (0.71 to 0.83)	1.54 (1.35 to 1.80)	0.24 (0.20 to 0.28)

*CI defined in Glossary.
†Ratio of observed-to-expected positive results.

COMMENTARY

The Lynch syndrome, the most common form of hereditary colorectal cancer, is caused by germline mutations in MMR genes MSH2, MLH1, and MSH6. Persons who inherit these mutations are at increased risk for colorectal and endometrial cancer. Identifying unaffected persons who are at risk is an important preventive health care strategy.

Chen and colleagues evaluated MMRpro, a new test designed to predict the probability of a person having a deleterious germline mutation in the MSH2, MLH1, or MSH6 genes and to provide an estimate of future cancer risk in unaffected persons, including mutation carriers, untested persons, and those in whom no mutation is found. MMRpro uses an algorithm that applies the Bayes theorem, taking into account the colorectal and endometrial cancer status, including the tumor MSI status, of the proband and first- and second-degree relatives. As shown by Chen and colleagues, MMRpro provided improved discriminatory ability over the Bethesda guidelines and better performance than the Leiden model.

MMRpro is user friendly and shows discriminatory ability similar to that of multivariate logistic regression models (1, 2). Unlike other models, it incorporates mutations in the MSH6 gene. While documenting accurate medical records on multiple family members is still necessary, MMRpro requires only information on colorectal and endometrial cancer, which simplifies the lengthy record retrieval process and shortens the waiting time for risk assessment. MMRpro may be limited by not including information on other types of cancer associated with the Lynch syndrome, colonic adenomas and polyps, lifestyle, and prophylactic surgery.

Similar models for the hereditary breast and ovarian cancer syndrome are widely used in clinical practice, and I expect MMRpro will also be well utilized. The Lynch syndrome is commonly underdiagnosed; thus, any method contributing to the recognition of persons at risk will heighten clinical awareness and encourage colorectal cancer surveillance and appropriate early management of other associated cancers.

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