Predicting Lynch Syndrome Propensity to Cancer

Two new models help sort out which patients need extensive genetic testing for the hereditary mutation.

BY MARY ANN MOON Contributing Writer

TWO new prediction models help clinicians identify which patients are at highest risk for Lynch syndrome, a genetic condition associated with an increased risk of colorectal, endometrial, ovarian, and other cancers. Lynch syndrome can be diagnosed by genetic testing of the MMR genes for inherited mutations, but the test is not always accurate or available. Instead, clinicians can use the new models to estimate a patient’s risk of having Lynch syndrome.

The PREMM1,2 model, published in April in the Journal of the National Cancer Institute, and the MMRpro model, published in June in the Journal of the American Medical Association, are based on statistical analysis of mutations in DNA repair genes. Each model assigns an individual a score from ‘high risk’ to ‘low risk’ based on the number of lifetime colorectal, endometrial, ovarian, or gastrointestinal lesions and the age of diagnosis.

The PREMM1,2 model thus is more sensitive and specific than clinical criteria in determining which patients should undergo genetic testing. It also helps decide which approach to genetic testing will be most useful. The PREMM1,2 model is available through the Dana-Farber Web site (www.dana-farber.org/premm).

The MMRpro (Mutations of Mismatch Repair) model also is more sensitive and specific than existing clinical guidelines for identifying patients who may benefit from genetic testing, reported Sining Chen, Ph.D., of Johns Hopkins Bloomberg School of Public Health, Baltimore, and associates.

In particular, this statistical model estimates the likelihood that a patient carries deleterious mutations of the MLH1, MSH2, or MSH6 genes in cases in which tumor tissue is not available for analysis or in which commercial germline testing techniques have been insufficiently sensitive to detect a mutation. The MMRpro model was developed using a meta-analysis of studies that provided risk estimates for colorectal and endometrial cancers. It was then validated in a cohort of 279 patients who had undergone germline testing and who were from 226 families believed to be affected by Lynch syndrome. The MMRpro model incorporates both a mutation-prediction algorithm and a cancer-risk prediction algorithm. The latter allows clinicians to estimate the likelihood that cancer will develop in patients who have strong evidence of Lynch syndrome but in whom no mutation has been found. “This feature is also valuable for [patients] who do not wish to be genotyped but would like to consider preventive measures,” Dr. Chen and associates said (JAMA 2006;296:1479-87).

Software for performing MMRpro calculations is open source and available free of charge via either the mendelian risk prediction package Bayes Mendel at www.astor.som.jhmi.edu/BayesMendel or the genetic counseling package CancerGene at www.utsouthwestern.edu/breasthealth/cagenet,” they added.

In an editorial comment accompanying these reports, Dr. James M. Ford and Dr. Alice S. Whitemore of Stanford (Calif.) University’s clinical cancer genetics program said that both prediction models should prove to be “very useful tools for clinicians and their patients, as well as for epidemiologists.” These models should improve clinicians’ ability to identify patients at risk for Lynch syndrome “and hopefully to prevent cancer from occurring using intensive surveillance techniques and prevention schemes,” Dr. Ford and Dr. Whitemore said (JAMA 2006;296:1521-3).

Avastin Label Changed After Reports of Rare Neurologic Disorder

Genentech Inc. has changed the labeling information for Avastin (bevacizumab) to warn physicians about reported cases of a rare brain-capsillary leak syndrome and nasal septum deviation. Avastin, in combination with irinotecan and fluorouracil-based chemotherapy, is indicated for first- or second-line treatment of patients with metastatic colorectal cancer.

Cases of confirmed or possible reversible posterior leukoencephalopathy syndrome have been reported in patients receiving Avastin at a rate of less than 0.1% in clinical trials. The rare disorder is associated with hypertension, fluid retention, and the cytotoxic effects of immunosuppressive drugs on vascular endothelium.

The syndrome can present as headache, seizures, visual disturbance, and altered mental function. If patients develop the disorder, discontinue Avastin and initiate treatment of hypertension.

Resolution of improvement usually occurs in a few days. It is unknown whether it is safe to reinitiate Avastin treatment in patients who have experienced this disorder.

Prescribing information has also been changed to reflect seven cases of nasal septum deviation, reported as postmarketing events.

For more information, contact Genentech Inc. by calling 800-821-8590. To report any serious adverse events suspected to be associated with the use of Avastin, contact the company by calling 888-835-2872 and visit the Food and Drug Administration’s MedWatch reporting system by visiting www.accessdata.fda.gov/scripts/medwatch.

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Ethnicity Matters in Gastrointestinal Lesions With Iron-Deficiency Anemia

BY DOUG BRUNK San Diego Bureau

LOS ANGELES — Among patients with iron-deficiency anemia, significant ethnic differences were found in the frequency, type, and distribution of clinically important gastrointestinal lesions, Dr. Bani Chander reported during a poster session at the annual Digestive Disease Week.

Specifically, whites with iron deficiency had lower rates of clinically important lesions in the lower GI tract, compared with blacks, Hispanics, and other ethnic groups.

Iron deficiency was defined as a transferrin saturation below 15% and a ferritin level below 20 µg/L. Anemia was defined as a hemoglobin level below 13 g/dL in men and below 12 g/dL in women. All patients had a same-day esophagogastroduodenoscopy (EGD) and colonoscopy.

The researchers identified one or more clinically important GI lesions in 54% of whites, 65% of blacks, 63% of Hispanics, and 69% of patients from other ethnic groups.

About 33% of whites had clinically important lesions in the upper GI tract, compared with 32% of blacks, 43% of Hispanics, and 54% of patients from other ethnic groups.

About 33% of whites had clinically important lesions in the lower GI tract, compared with 48% of blacks, 43% of Hispanics, and 42% of patients from other ethnic groups.

Both upper and lower GI lesions were identified in 11% of whites, 15% of blacks, 23% of Hispanics, and 26% of patients from other ethnic groups.

In addition, Dr. Chander and her associates observed that the frequency of clinically important lesions that were proximal to the splenic flexure was significantly higher in blacks (38%) and Hispanics (27%), compared with whites (13%) and patients from other ethnic groups (8%).

Of the patients who had colorectal cancer, the prevalence of advanced lesions was significantly higher in blacks (86%) and Hispanics (100%) than in whites (63%) and in patients from other ethnic groups (7%).

“Most likely Hispanics are seeking less health care than the other groups,” Dr. Chander hypothesized. “But on top of that, I’m sure that diet and other lifestyle choices have probably played a role.”

However, she noted certain limitations of the study, including the fact that it was a single-center study in which most of the subjects were older men. “We do not generalize observations about women in this study, nor can we about a younger population,” she said.

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