

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 identify which patients suspected of having Lynch syndrome should undergo extensive genetic testing for the mutations associated with colorectal cancer.

Lynch syndrome, also known as hereditary nonpolyposis colorectal cancer, is characterized by the predisposition to develop early-onset colorectal cancer as well as cancers of the endometrium, gastrointestinal tract, ovary, hepatobiliary system, urinary tract, brain, and other sites. It is almost always associated with underlying mutations in the mismatch DNA repair system, most often in the MLH1 and MSH2 genes.

Currently, screening for Lynch syndrome is fraught with challenges. Clinical criteria for identifying which patients are likely to have the syndrome are restrictive and don't take into account several variants of the disease. They also rely on detailed family histories or on tumor samples, which often are not available. Further genetic testing is not very sensitive or specific and is expensive.

Two research groups have developed

different models to predict the likelihood that patients have Lynch syndrome and should undergo genetic testing, much like the models that are widely used by health care professionals to predict mutations in the BRCA1 and BRCA2 genes in assessing patients' breast cancer risk.

The PREMM1,2 (Prediction of Mutations in MLH1 and MSH2) model was developed using a cohort of 898 probands and 1,618 first- or second-degree relatives who submitted blood samples for sequencing of the two genes, then validated in another cohort of 1,016 probands. This genetic testing had been ordered by the probands' health care providers—chiefly geneticists, oncologists, gastroenterologists, and gynecologists—who suspected Lynch syndrome because the patients' personal or family histories were suggestive, according to Dr. Judith Balmana of Dana-Farber Cancer Institute, Boston, and her associates.

These large, diverse, national cohorts allowed the investigators to incorporate great detail into their prediction model, including the age at diagnosis of probands and their relatives, the presence of colonic adenomas, and the different degrees of risk for different cancers.

The PREMM1,2 model thus is more sensitive and specific than clinical criteria in determining which patients should undergo extensive genetic testing. It also helps decide which approach to genetic testing will be most useful (JAMA 2006;296:1469-78). The PREMM1,2 model is available through the Dana-Farber Web site (www.dfc.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 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 still like to consider preventative 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/cagene," they added.

In an editorial comment accompanying these reports, Dr. James M. Ford and Dr. Alice S. Whittemore 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. Whittemore 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-capillary leak syndrome and nasal septum deviation.

Avastin, in combination with intravenous 5-fluorouracil-based chemotherapy, is indicated for first- or second-line treatment of patients with metastatic carcinoma of the colon or rectum.

Cases of confirmed and 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 reinstate Avastin therapy 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 888-835-2555 or contact the Food and Drug Administration's MedWatch reporting system by visiting www.accessdata.fda.gov/scripts/medwatch.

—Kerri Wachter

Ethnicity Matters in Gastrointestinal Lesions With Iron-Deficiency Anemia

BY DOUG BRUNK
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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, results from a study of Veterans Affairs patients showed.

"We might have to be more aggressive in terms of colorectal screenings in blacks and Hispanics," Dr. Chander, a recent graduate of New York University, said in an interview. "Not only do they have more advanced lesions, but their lesions also tend to be proximal. So instead of doing a flexible sigmoidoscopy every 3-5 years in blacks and Hispanics, we might have to advocate that we should only do colonoscopy, so we can get to the proximal colon as well."

She and her associates evaluated demographic and clinical data from 1,081 consecutive patients referred to

the VA New York Harbor Healthcare System for evaluation of iron-deficiency anemia. Of the 1,081 patients, 406 were white, 442 were black, 168 were Hispanic, and 65 were from 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 esophagogastro-

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duodenoscopy 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.

In addition, 32% 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 (35%) 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 (75%).

"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 can't make generalizations about women in this study, nor can we about a younger population," she said. ■