To Screen or Not To Screen for Lynch Syndrome

By Judy Peres

More than a year and a half after a U.S. government panel recommended universal screening of newly diagnosed colorectal cancer patients for Lynch syndrome, compliance appears spotty at best.

Screening for Lynch syndrome (also called hereditary nonpolyposis colorectal cancer, or HNPCC) remains a promising idea for reducing morbidity and mortality from colon cancer, experts say. But certain technical, procedural, and ethical issues stand in the way of translating theory into clinical practice.

Worldwide, colorectal cancer is the third most common cancer among men and the second most common in women. Roughly 3% of colorectal cancers occur as a result of Lynch syndrome, an inherited mutation in one of several DNA mismatch repair genes. Individuals with the syndrome have more than a 70% chance of developing colon cancer by age 70 years, compared with 6% for the general population. They are at higher risk of several other cancers as well (see Stat Bite).

Because Lynch syndrome is inherited in an autosomal-dominant fashion, the siblings and children of carriers have a 50% chance of having the syndrome, and more-distant relatives are also at increased risk. But intensive surveillance, such as annual colonoscopy, can substantially reduce mortality in these high-risk individuals.

Traditionally, family history has been the primary means of identifying colon cancer patients at risk for Lynch syndrome. Those at-risk patients' tumors then undergo screening with an immunohistochemistry (IHC) and/or microsatellite instability (MSI) test. Patients with an abnormal screen can then have a diagnostic DNA test for mismatch repair mutations to confirm or rule out Lynch syndrome.

Family history is the basis for two different sets of criteria to determine which patients should be considered at risk for Lynch syndrome: the Amsterdam criteria and the Bethesda guidelines. But family history isn’t always available, and many patients are thus missed, along with the opportunity to identify their at-risk relatives. That’s why the federal Centers for Disease Control and Prevention (CDC) convened its independent panel—the Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group—to consider a broader screening strategy.

The working group released its findings in January 2009. According to the CDC website, the group “found good scientific evidence to recommend that all individuals with a new diagnosis of colorectal cancer (regardless of age or family history) be offered genetic testing for Lynch syndrome, in order to help prevent cancer in their close relatives.” It did not find enough evidence to recommend any specific preliminary screening strategy, e.g., MSI versus IHC.

“We’re still working on a protocol,” said Sonia Kupfer, M.D., a gastroenterologist at the University of Chicago’s Cancer Risk Clinic. “There’s enough evidence to suggest it’s cost effective and should be done. [But] it involves a lot of different specialists. How is it ordered? How is it reported? Who follows up?”

Not everyone agrees that it’s cost effective in the real world. Michael Hall, M.D., of Fox Chase Cancer Center in Philadelphia, argued in a recent “Counterpoint” article in the Journal of the National Comprehensive Cancer Network that “although Lynch screening has been shown to be feasible, its success in this country will be hindered by pervasive societal barriers to DNA testing, risk communication, and access . . . . Cost-effectiveness is also strongly dependent on the uptake and effectiveness of screening.” And, perhaps most important, “if family members do not receive (and act on) risk information, cost-effectiveness could be heavily compromised.”

Another concern that several clinicians interviewed for this article expressed is that family history, which is already a challenge, will fall by the wayside.

“I see many patients with Lynch syndrome,” said Kupfer. “There are cases where parts of the family history have been taken, but no one has put it together. If we get universal testing, we need to continue to have good communication between the pathologist, the oncologist, and the surgeon to ensure...
we’re putting all the information together—including the family history—so we get the right people in for further evaluation.”

**Potential Barriers**

Heather Hampel, a certified genetic counselor and associate director of the Division of Human Genetics at Ohio State, believes that many centers simply don’t have the infrastructure to deal with abnormal screening test results. Smaller hospitals don’t even have genetic counselors. Hampel, a strong advocate of universal screening, said that “the financial people” may resist because of the added cost. “But most insurers cover the gene test if there’s an abnormal screening test,” she said.

At Ohio State, the pathologist informs Hampel when there’s an abnormal screen, and she then contacts the patient and offers to meet and explain the results and their implications for both the patient and his or her family members. But many newly diagnosed patients don’t take her up on the offer. Beth Peshkin, senior genetic counselor at Georgetown, said that’s entirely understandable: “This is a very sensitive time to approach someone, because of all the other issues they’re dealing with—learning about their prognosis, assimilating treatment options, telling their families.”
Peshkin also finds the issue of informed consent worrisome. “How do you consent people on a wide-scale basis?” she asked. “There’s a lot to explain: What is Lynch syndrome? What is the family history? What are the pros and cons of testing? It could easily be a 1- to 2-hour discussion.”

The National Comprehensive Cancer Network (NCCN), in its 2010 practice guidelines, stops short of calling for universal screening of all new colorectal cancer patients. As in previous guidelines, the network states flatly that “family history is the most important risk factor for [colorectal cancer]” and that “IHC/MSI testing on the colon tumor of the youngest affected family member is warranted.”

NCCN also recommends testing for DNA mismatch repair gene mutations in four other groups of patients. One is stage II patients for whom the clinician is considering fluoropyrimidine therapy alone. That recommendation is based on a 2008 study showing that stage II patients whose tumors have high MSI (a marker of mismatch repair protein deficiency) may have a good prognosis and do not benefit from treatment with 5-fluorouracil. Another group recommended for testing is all colon cancer patients younger than 50 years. The NCCN says mismatch repair protein testing (with either IHC or MSI) “should be strongly considered” for these younger patients, on the basis of “an increased likelihood of HNPCC in this population.” Other groups recommended for testing include patients younger than 60 years with certain histologic features and patients with two or more primary Lynch-related cancers.

But in a nod toward the new EGAPP recommendation, the NCCN notes, “Recently, IHC and/or MSI screening of all colorectal cancers and endometrial cancer, regardless of age at diagnosis or family history, has been implemented at some centers to identify individuals at risk for Lynch syndrome.”

Proponents of universal screening cite the EGAPP Working Group recommendation: “With limited benefit of genetic testing to the colorectal cancer patient, the [working group] recommends that informed consent should be obtained before MSI or IHC testing” (italics added).

“We get informed consent before genetic testing,” said Hampel, “but not before the screen.”

Centers that perform screening tests routinely—without obtaining the patient’s consent—point to the fact that the test results can be helpful in making treatment and surveillance decisions. Hall acknowledged in his article that “the usefulness of MSI for guiding adjuvant fluorouracil-based therapy may one day strengthen the case for routine (uninformed) MSI testing. But for now, he added, “IHC has no clinical usefulness beyond Lynch screening.” That’s why clinicians at Mayo don’t order IHC testing without getting informed consent.

In any case, the EGAPP Working Group was explicit that the primary goal of testing all colon cancer patients for Lynch syndrome was to “reduce morbidity and mortality in relatives” (italics added). And that raises another issue: Whose responsibility is it to reach out to unsuspecting family members?

“There’s a potential benefit to relatives,” said Peshkin. “But what if the patient doesn’t want to inform them? Does the clinician have a duty to warn family members? That’s an ethical issue that will need to be addressed.” Peshkin is worried about the cost of universal screening, too, especially about the possibility that underserved populations will not have equal access to DNA testing and genetic counseling.

“That doesn’t mean we shouldn’t do it,” she said. “But we need to make sure we’re doing it appropriately.”

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