Point: Justification for Lynch Syndrome Screening Among All Patients With Newly Diagnosed Colorectal Cancer

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Key Words
Lynch syndrome, mismatch repair, microsatellite instability, immunohistochemistry, screening

Abstract
Either microsatellite instability testing or immunohistochemical staining for the 4 mismatch repair proteins (MLH1, MSH2, MSH6, and PMS2) should be performed on all newly diagnosed colorectal cancers. This testing will identify tumors that are microsatellite unstable, which has implications for patient prognosis and possibly treatment. In addition, it will identify patients who are more likely to have Lynch syndrome. Of every 35 colorectal cancer patients, 1 has Lynch syndrome, the most common hereditary cause of colorectal and endometrial cancers. Diagnosis of Lynch syndrome affects the medical management of the patient and their relatives, with potentially life-saving ramifications. Although screening only a subset of patients with colorectal cancer based on age at diagnosis, family history, or histologic criteria will reduce the number of screening tests necessary, it will miss a significant proportion of patients with microsatellite unstable colorectal cancer and many patients with Lynch syndrome. Given that universal screening of all patients with newly diagnosed colorectal cancer using immunohistochemistry as the initial test was recently shown to be cost-effective and comparable with other widely accepted preventive services, it is not necessary to try to reduce costs by restricting screening to a subset of patients, which leads to a reduction in the efficacy of the screening program. (JNCCN 2010;8:597–601)

The era of personalized health care has arrived. While everyone is focusing on low penetrance single nucleotide polymorphisms that impart relative risks (RRs) for cancer ranging from 1.2 to 2.0, gene mutations that cause high cancer risks (RRs > 5) are being overlooked. Diagnosing an autosomal dominant, highly penetrant cancer-susceptibility syndrome in patients with cancer may provide important information about their prognosis, treatment, and future cancer risks. In addition, this allows their relatives to undergo genetic counseling and testing to learn if they too are at increased risk for cancer and could benefit from intensive cancer surveillance. The costs of screening can be offset by the benefits of cancer prevention in the patient and their relatives. The best example of this is the current movement to screen all patients with newly diagnosed colorectal cancer for Lynch syndrome using microsatellite instability (MSI) testing or immunohistochemistry (IHC) staining for the mismatch repair (MMR) proteins.

Lynch syndrome is the most common cause of inherited colorectal cancer. With an incidence of 2.8% among all patients with newly diagnosed colorectal cancer,1,2 this syndrome will account for 4200 of the 150,000 colorectal cancers diagnosed in 2010. Individuals with Lynch syndrome have significantly increased risks for colorectal, endometrial, gastric, ovarian, urothelial, sebaceous, and biliary cancers. Although the cancer risks are high, intensive cancer surveillance, including the use of frequent colonoscopy, can significantly reduce cancer-related deaths in individuals with Lynch syndrome.3 Although data are limited regarding the efficacy of transvaginal ultrasound and endometrial biopsies for endometrial cancer surveillance,4,6 hysterectomy and bilateral salpingo-oophorectomy seem to

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Submitted December 18, 2009; accepted for publication January 28, 2010.

Ms. Hampel is supported by grants CA67941 and CA16058 from the National Cancer Institute.

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be effective at preventing endometrial and ovarian cancers in women with Lynch syndrome. Lynch syndrome is caused by germline mutations in an MMR gene, such as MLH1, MSH2, MSH6, or PMS2. Tumors from individuals with Lynch syndrome usually exhibit MSI, which is an expansion or contraction of areas of DNA composed of nucleotide repeats. In addition, following Knudson’s 2-hit hypothesis, Lynch syndrome tumors usually exhibit the absence of at least 1 MMR protein, whereas all proteins are present in normal tissue from individuals with Lynch syndrome. This can be identified using IHC staining of the tumors with antibodies to the 4 MMR proteins. Approximately 12% to 20% of all colorectal cancers exhibit MSI and abnormal IHC. These 2 screening tests can be used interchangeably because results show a greater than 94% concordance (tumors with abnormal IHC are MSI-high and vice versa). Approximately 75% of colorectal cancer patients whose tumors exhibit MSI or abnormal IHC do not have Lynch syndrome, but instead have acquired hypermethylation of the MLH1 promoter. Relatives of these patients are not at risk for inheriting Lynch syndrome; however, these patients are subject to the same prognostic and treatment implications that apply to all patients with MSI-high colorectal cancers. Several methods can help distinguish patients with acquired MLH1 promoter methylation from select patients who would benefit from germline MLH1 gene testing. Without introducing another molecular test, one could avoid germline MLH1 gene testing in patients diagnosed with colorectal cancer older than 60 years of age with no family history of colorectal or endometrial cancer, because these patients are highly likely to have acquired MLH1 promoter methylation. MLH1 promoter methylation testing can also be assessed directly in tumor DNA; however, concerns exist that this could occasionally be the “second hit” in a patient with a germline MLH1 mutation, and therefore a positive methylation test does not rule out a germline MLH1 mutation completely.

Finally, tumor DNA can be tested for the somatic BRAF mutation V600E. This mutation is found in the tumors of 69% of patients with acquired MLH1 promoter methylation and has not yet been reported in a patient with a germline MLH1 mutation. Because this testing is easier and less expensive than methylation testing, it has been implemented routinely as a reflex test in many hospitals that are screening all newly diagnosed colorectal cancer patients for Lynch syndrome when IHC results indicate absence of MLH1 and PMS2. It significantly reduces the number of patients needing further germline testing.

All patients with colorectal cancer should be screened with MSI or IHC because it affects prognosis and the treatment of stage II and III disease and, if they have Lynch syndrome, it will affect their and their relatives’ future cancer risks and surveillance.

**Prognostic Implications**

A large body of data indicates that patients with MSI-high colorectal cancers have a better prognosis when compared stage for stage with patients who have microsatellite-stable (MSS) colorectal cancers. Popat et al. pooled data available in 2005 that included 7642 patients with colorectal cancer reported in 32 studies. Among these, 1277 (16.7%) had MSI-high tumors and an overall survival hazard ratio (HR) of 0.65 (95% CI, 0.59–0.71). These patients had a better prognosis even if the data were restricted to clinical trial patients or patients with locally advanced disease. The studies showed no evidence of heterogeneity. In the 8 studies for which these data were available, patients with MSI-high colorectal cancer had an HR of 0.67 (95% CI, 0.53–0.83) for progression-free survival. This meta-analysis only included patients with colorectal cancer and MSI results; none were assumed to be MSI based on abnormal IHC results.

**Treatment Implications**

A recent meta-analysis evaluated whether MSI status affected the efficacy of 5-flourouracil (5-FU)–based adjuvant chemotherapy. This analysis included 3690 patients with stage II and III colorectal cancer from 7 studies. Among these patients, 454 (24%) had MSI-high colorectal tumors (either based on direct assessment of MSI status or inferred from abnormal IHC results). Regardless of whether they underwent chemotherapy, the patients with MSI-high tumors did not have a significant difference in recurrence-free survival (HR, 0.96; 95% CI, 0.62–1.49; P = .86) or overall survival (HR, 0.70; 95% CI, 0.44–1.09; P =
No significant heterogeneity was seen between the studies. The investigators could not evaluate the efficacy of chemotherapy among patients with MSI-high stage II and III colorectal cancer separately because the numbers were too small. However, patients with MSS colorectal cancers did benefit from 5-FU–based chemotherapy. Their HR for recurrence-free survival was 0.77 (95% CI, 0.68–0.87; \( P < .001 \)). Patients with stage II or III MSI-high colorectal cancer do not seem to benefit from 5-FU–based chemotherapy, but what is not known is whether other chemotherapeutic agents may be more effective for these patients.

### Lynch Syndrome Implications

Among every 35 patients with colorectal cancer, 1 will be found to have Lynch syndrome. These individuals have a high risk for developing a second primary colorectal cancer and other Lynch syndrome–related cancers. According to the NCCN guidelines, follow-up for patients with colorectal cancer includes colonoscopy 1 year after diagnosis and, if normal, repeat in 2 to 3 years, and then every 3 to 5 years based on findings. However, the NCCN guidelines recommend that patients with Lynch syndrome have a colonoscopy every 1 to 2 years throughout their life. Therefore, the management of patients with colorectal cancer with Lynch syndrome will differ from that for those who do not have Lynch syndrome, and this is very important given that they have a 16% to 30% chance of developing a second primary colorectal cancer in the 10 years after their first colon cancer diagnosis.

First-degree relatives of patients with colorectal cancer found to have Lynch syndrome each have a 50% risk of having inherited Lynch syndrome. In addition, many of their second- and third-degree relatives will also have Lynch syndrome. Individuals with Lynch syndrome must begin undergoing colonoscopy every 1 to 2 years at age 20 to 25 years, or 10 years younger than the earliest colorectal cancer diagnosis in the family (whichever is earlier). Family members who did not inherit Lynch syndrome can follow average-risk cancer screening according to the NCCN guidelines because they are not at increased risk for cancer.

A recent 10-year follow-up study of 609 Lynch syndrome family members in Finland found excellent compliance with cancer screening among those who inherited Lynch syndrome (95.9% for colorectal cancer surveillance and 97.1% compliance for gynecologic cancer surveillance). Although the overall cancer risk ratio was 5.8 when the relatives who had Lynch syndrome were compared with the relatives who did not, the cancer mortality (RR, 2.28) and overall death rates (RR, 1.26) were not significantly increased. Increased cancer surveillance among individuals with Lynch syndrome seems to be effective in preventing deaths caused by cancer.

As a result, genetic counseling and testing must be offered to the family members of the patients with colon cancer initially discovered to have Lynch syndrome. In the Columbus-area hereditary nonpolyposis colorectal cancer (HNPPC) study, 249 relatives of the initial 44 patients with colorectal cancer found to have Lynch syndrome underwent genetic counseling and elected to pursue genetic testing (6 relatives per proband). Of these, 109 were diagnosed with Lynch syndrome and 140 learned that they did not inherit Lynch syndrome. This study resulted in major cancer surveillance differences for 293 individuals (44 probands with Lynch syndrome and 249 of their relatives) among a total of 1815 who received some type of testing in this study (1566 patients with colorectal cancer who underwent tumor screening for Lynch syndrome and 249 relatives who underwent genetic testing for Lynch syndrome). Therefore, this universal screening program positively impacted 16.1% of those involved.

### Practical Considerations

Experts have argued that tumor screening for Lynch syndrome should be confined to a subset of all patients with newly diagnosed colorectal cancer primarily to reduce costs of the screening program and maximize return on the investment. Subsets that have been considered are all cases diagnosed at younger than age 50; cases meeting certain family history criteria, such as the Bethesda criteria or greater than 5% risk based on the PREMM1,2 model; and those whose tumors have certain histologic features suggesting MSI positivity.

Although this strategy would significantly reduce the numbers of cases requiring MSI or IHC screening, it is not prudent for multiple reasons. First, one can assume that all patients with colorectal cancer

© Journal of the National Comprehensive Cancer Network | Volume 8 Number 5 | May 2010
would benefit from knowing about their tumor-specific prognosis, and that this information would help all patients with stage II and III colorectal cancer make informed decisions about their treatment. If that is the case, identifying only a subset of MSI-high colorectal tumors is not acceptable; the use of age or family history criteria would miss significant numbers of patients with MSI-high tumors.

Second, although the percentage of patients found to have Lynch syndrome is much higher among younger patients (8.4% of those diagnosed at < 50 years vs. 1.7% diagnosed at ≥ 50 years), 56% of the patients with Lynch syndrome will be missed if screening is restricted to only those diagnosed at younger than 50 years.

Using histologic features to select a subset of patients who are more likely to have MSI-high tumors will identify more patients with those tumors than would using age or family history criteria, but this method will still miss many cases. Thirty-four of the patients diagnosed with Lynch syndrome as part of the Columbus-area HNPCC study were evaluated using the histologic criteria; 12 (35.3%) would have been missed using this as the initial screen.

Perhaps most importantly, a recent cost-effectiveness analysis confirmed that a universal screening program using IHC as the primary screening test costs less than $25,000 per life-year saved relative to no testing, and less than $40,000 per life-year saved relative to testing only patients diagnosed at younger than 50 years. Universal testing has an incremental cost-effectiveness ratio comparable to other accepted preventive services (e.g., colonoscopy every 10 years in adults ≥ 50 years has an incremental cost-effectiveness ratio of $25,000 per life-year saved) and will detect twice as many cases of Lynch syndrome.

Finally, any model beginning with MSI testing costs more than models using IHC as the initial screen, because IHC can direct subsequent genetic testing. As a result, IHC is the preferred method for screening all patients with newly diagnosed colorectal cancer for Lynch syndrome.

Discussion

The time of taking a passive approach to genetics is over. The traditional model involves having cancer genetics professionals wait for patients to be referred for a consultation based on their family history. Although this approach is still appropriate, it is not sufficient because many clinicians do not have the time to take an adequate history or make a proper risk assessment given the multiple sets of complicated referral criteria that exist. In addition, smaller family size and the increased use of colonoscopy make these families more difficult to detect by assessing family history alone. Patients with cancer should be screened for these hereditary cancer syndromes when possible at diagnosis. Their life and the lives of their family members may depend on it.

References

Justification for Lynch Syndrome Screening


