# Informed consent and immunohistochemistry screening for Lynch syndrome

*To the Editor:*

We appreciated the thoughtful article by Chubak et al.[1] that discussed informed consent for tumor-based Lynch syndrome (LS) screening by either microsatellite instability (MSI) or immunohistochemistry (IHC). We agree with the authors that the recommendation from the Evaluation of Genomic Applications in Practice and Prevention (EGAPP) working group that consent for MSI or IHC be obtained[2] is overly conservative and not justified by evidence or consistent with the ethical arguments advanced. The authors note that there has been limited ethical analysis of consent in this clinical scenario and no empirical studies on the impact of these screening programs on patients. The authors conclude that, based on their ethical analysis, informed consent is not needed for MSI analysis of tumors but should be done for IHC screening. The key issue that distinguishes IHC from MSI in the authors view is that "… a positive IHC test suggests that not only one of the MMR genes is mutated but also which MMR gene is implicated" (mismatch repair [MMR]). They note that abnormal IHC staining for MLH1 can be due to somatic epigenetic changes, then state, "… loss of any of the other MMR proteins is generally indicative of a germline mutation of the gene for the absent protein." Setting aside the evidence that abnormal staining for MSH6 can be caused by neoadjuvant chemotherapy before resection,[3] the implication is that the abnormal staining confirms a germline mutation. However, the authors later acknowledge that positive screens by either method "… must be followed by DNA sequencing to determine whether germline MMR mutations are present …" What the authors seem to be saying is that if a screening test (of any kind) exceeds some prediction or specificity threshold for a germline mutation that consent should be required because of concerns of harm for the patient and family. This is a provocative assertion that has not been proposed for other genetic testing scenarios. If one considers applying this to the pathology laboratory, standard pathologic evaluation frequently identifies lesions that are highly specific for genetic disorders with germline mutations. Examples include medullary thyroid cancer (familial medullary thyroid cancer or multiple endocrine neoplasia type 2; mutations in *RET*); trichillemoma (Cowden syndrome; mutations in *PTEN*); and facial angiofibromas (tuberous sclerosis; mutations in *TSC1–2*). Although these biopsies may be done after discussion of a suspected genetic disease, the pathologic results frequently raise the question of a genetic disease not previously anticipated. All these patients have expressed disease or manifestations, as do patients with colorectal cancer. Should informed consent be applied in these clinical scenarios? Does a routine tumor-based screening program raise ethical issues not relevant to other patients tested in the context of a manifested disease? What is the threshold of a priori certainty above which consent is required?

Intermountain Healthcare initiated an IHC-based LS screening program in 2009. We were also concerned about the issues of consent and in the fall of 2008 convened a national advisory group that engaged with our local guidance council to discuss this issue. Expertise was from a broad range of disciplines and included nationally recognized experts in medical ethics. Before the meeting, we surveyed institutions that had implemented or were in the process of implementing LS screening programs. The majority, who had considered the consent issue, were not requiring informed consent, although some were using a fully consented approach. The group addressed the same issues raised by the authors but concluded that informed consent was not required for IHC as the screening result by itself was not clinically actionable by either the patient or family unless subsequent mutation analysis confirmed the presence of a germline mutation. The group did recommend that educational materials about the screening program be prepared and given to all patients undergoing resection of a colorectal tumor, that an "opt out" be made available and that a genetic counselor contact and meet with all patients who have a positive screen to discuss the results and provide informed consent about confirmatory testing. All these recommendations have been incorporated. To date, more than 200 patients have been screened, and there have been no concerns raised by any patient who had a positive screen, although given the low prevalence of LS the numbers remain small. It is also important to note that LS represents only one condition that contributes to increased risk of cancer for patients and their families. We are in the process of implementing targeted family history collection for all patients with colorectal cancer to identify those at increased risk for referral for genetic services. This screening program will identify many more at-risk patients compared with tumor-based screening for LS. Informed consent has not been recommended for family history screening, although patients will arguably have more direct control in that they would have to complete the family history implying a certain level of consent. Educational materials will be provided for this screening as well.

Our final point is that any discussion of harms must consider not only the harms that may occur if a program is implemented but also the harms that occur if a program is not implemented. One of the fallacies in the literature is that identification of LS has value for the patient's family but has little impact on management for the patient. The authors note that the presence of MSI in the tumor has implications for the patient's response to fluorouracil-based chemotherapeutic agents.[4] For women with colorectal cancer, LS has significant implications for development of endometrial and ovarian cancers for which enhanced surveillance or prophylactic surgery can be life saving. There is also emerging evidence that LS patients have a better prognosis than patients with sporadic colorectal cancer—information that could be of great importance to patients. When considered against the risk of potential insurance discrimination or psychological disturbance for patients who are already undergoing treatment for cancer, in our view the balance of harms strongly favors universal screening.

In conclusion, we do not think that informed consent is required for tumor-based LS screening irrespective of whether MSI or IHC is used. Given the acknowledged lack of formal study in this area, it is understandable that different groups thoughtfully considering this question can come to different conclusions. We strongly support the authors' recommendation that this question is worthy of additional research, and we are committed to gathering information from our patients about this issue.

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Disclosure: The authors declare no conflict of interest.

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## Folic acid and neural tube defects

***To the Editor:***

The policy statement from the American College of Medical Genetics on folic acid and neural tube defects[1] singles out the 1992 randomized controlled trial by Czeizel and Dudas[2] as the "most definitive." That characterization actually is more appropriate for the Medical Research Council study, which was published the preceding year.[3] The factorial design of the MRC study, coupled with its large number of pregnancies affected by neural tube defects, allowed folic acid to be definitively pinpointed as the active agent and set the stage for governments in various areas of the world to fortify the food supply. The study by Czeizel and Dudas[2] provided useful supplementary evidence, but the intervention group received only a multivitamin preparation. Being confident that folic acid was the active agent, therefore, required knowledge of results from the MRC study.

In making its recommendations for an appropriate intake of folic acid, the Policy and Practice Guidelines Committee did not consider the modeled calculations published by Wald et al.[4] in 2001, showing a dose-response reduction for neural tube defects with folic acid intakes up to 5 mg/day. The authors concluded that all women planning pregnancy would achieve greatest risk reduction at this dose level, rather than limiting folic acid doses in this range to high-risk women. It would be reasonable for the committee to acknowledge this analysis.

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***In Reply:***

We thank Dr. Haddow for his comments on the guideline and acknowledge that the Medical Research Council study did indeed lay the groundwork for folate supplementation and fortification.

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### ERRATUM

MLPA as first screening method for the detection of microduplications and microdeletions in patients with X-linked mental retardation: Erratum

In the article that appeared on page 117 of volume 9, number 2, one author name is misspelled. The seventh author should appear as Miguel Fernández-Burriel, PhD.

### REFERENCE

Madrigal I, Rodríguez-Revenga L, Badenas C, Sánchez A, Martinez F, Fernandez I, et al. MLPA as first screening method for the detection of microduplications and microdeletions in patients with X-linked mental retardation. *Genet Med* 2007;9:117–122.