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Clinical guidelines versus universal molecular testing: are we ready to choose an optimal strategy for Lynch Syndrome identification?

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Abstract

Lynch Syndrome, also known as hereditary non-polyposis colorectal cancer (HNPCC), is the most common form of inherited colorectal cancer, however, its identification still presents a challenge for health care providers. Clinically-based guidelines have been used as the basis for Lynch Syndrome screening in colorectal cancer patient populations. More recently, it has been argued that universal molecular testing strategies should be implemented to increase the selection of patients who should get germline testing for Lynch Syndrome. In this issue of AJG, Julie *et al* compare the performance of clinical guidelines with a molecular strategy based on universal microsatellite instability (MSI) testing for identifying patients with Lynch Syndrome from among 214 unselected, newly diagnosed CRC patients. The study highlights the need for a systematic approach to identify patients with Lynch Syndrome so that they and their relatives can be targeted for appropriate clinical management.

Lynch syndrome is the most common hereditary colorectal cancer syndrome and accounts for 1%–5% of all colorectal cancers (CRC). Also known as hereditary non-polyposis colorectal cancer (HNPCC), Lynch Syndrome is characterized by a marked increase in lifetime risk of early-onset CRC as well as increased risk of other malignancies, including cancers of the endometrium, stomach, ovary, urinary tract and brain (1). Inherited mutations in DNA mismatch repair (MMR) genes, most commonly *MLH1* and *MSH2*, but also *MSH6* and *PMS2*, underlie the genetic basis of Lynch Syndrome (1). Germline mutations in the MMR genes result in the accumulation of mutations during DNA replication, particularly in repetitive sequences known as microsatellites. This microsatellite instability (MSI) is a hallmark of tumors associated with Lynch Syndrome. Loss of expression of the MMR proteins can also be detected by immunohistochemical (IHC) analysis of the four MMR genes. Approximately 15% of sporadic cases also exhibit MSI; inclusion of *BRAF* mutation and *MLH1* promoter analyses on tumor tissue identifies sporadic MSI-positive tumors and thereby may prevent unnecessary genetic evaluations (2).

Although germline genetic testing can identify mutation-positive individuals, sequencing of the MMR genes is currently much too time-consuming, difficult, and expensive to be feasible for all CRC patients. However, it is of critical importance to distinguish CRC due to Lynch Syndrome from sporadic cases (or other hereditary syndromes), because appropriate clinical management and increased surveillance significantly reduces cancer incidence and

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mortality for both the patient and any mutation-positive relatives (3). Asymptomatic individuals with Lynch Syndrome mutations require colonoscopies every 1–2 years starting at age 20–25, screening for gynecologic and other tumors, as well as consideration of prophylactic surgery (4, 5).

Currently, diagnosis of Lynch Syndrome relies on clinical characteristics of personal and family history of cancer. The Amsterdam criteria (6), later revised to Amsterdam II criteria (7) classically defined Lynch Syndrome, but are now well-recognized to be too stringent and insufficiently sensitive. With the availability of molecular diagnostic testing, the Bethesda Guidelines (8), later updated to the Revised Bethesda Guidelines (9), were developed to select patients who should undergo MSI analysis. Recently, several prediction models (10–12) have been published to quantify the risk of being a mutation carrier and increase identification rate of Lynch syndrome patients; however, their usefulness in the general population still needs to be validated.

In an effort to improve the detection rate of Lynch Syndrome individuals, it has been suggested that tumors of all CRC patients be assessed by MSI analysis or IHC instead of relying on clinical guidelines to select patients for germline analysis. In this issue of AJG, the article by Julie et al. (13) addresses the important issue of determining an optimal strategy for identifying Lynch Syndrome patients. The authors compare the performance of the Revised Bethesda Guidelines and a universal molecular strategy for identifying patients with Lynch Syndrome from among 214 newly diagnosed CRC patients. All tumor samples were evaluated by MSI analysis and those that were MSI positive were further analyzed by IHC. Patients with MSI positive tumors received germline testing guided by the IHC assessment. A total of 8 patients were determined to harbor pathogenic mutations in one of the four MMR genes assessed. The authors compared the Revised Bethesda guidelines to the original Bethesda guidelines and the original and revised Amsterdam criteria. The Revised Bethesda Guidelines followed by MSI analysis performed the best and identified 42.1% of patients for MSI testing, of which 4.2% were MSI positive and 6 were MMR mutation-positive. However, this strategy was less sensitive than a molecular strategy of universal MSI testing followed by BRAF mutation analysis and *MLH1* promoter analysis. The molecular strategy identified 9.8% of patients as MSI positive and, after BRAF and *MLH1* promoter methylation analysis to exclude MSI-positive sporadic cancers, 5.1% of patients for germline assessment to detect all 8 MMR mutation positive patients. Thus, the authors conclude that the Revised Bethesda Guidelines do not adequately identify mutation carriers and that the proposed molecular strategy would better detect Lynch Syndrome individuals with minimal additional workload.

Few previous studies have examined the performance of the clinical guidelines or compared their effectiveness of identifying Lynch Syndrome positive patients to that of universal molecular diagnostic testing strategies in an unselected population of CRC patients. Recently, the first evaluation of the Revised Bethesda Guidelines in a population-based cohort of CRC patients from the Spanish EPICOLON study demonstrated that these and the original Bethesda guidelines, as well as universal molecular testing strategies evaluating MSI and loss of MMR protein expression, were 100% effective in identifying patients with Lynch Syndrome mutations (14, 15). However, another recent study of unselected CRC patients in the US suggested that a universal testing strategy based on MSI or IHC testing was more effective than a combined criteria of original and revised Bethesda guidelines for identifying patients who were MMR mutation-positive(16). It must be noted though, that the reported missed detection rate of the Bethesda guidelines in the latter study may be artificially high since these authors were only able to assess first-degree relatives and might have missed relevant cancer history in second-degree relatives that would result in fulfillment of the clinical criteria.

Therefore, the results by Julie et al. are similar to some studies supporting a universal molecular testing strategy for identifying Lynch Syndrome patients (14–16), but conclusions diverge from those made in the EPICOLON study where the clinical criteria also performed as well as the universal molecular strategy. A number of reasons could account for this difference including the number of MMR genes evaluated (2 in the Spanish study compared to 4 in the present study), different number of markers used to evaluate MSI and natural population variation. Another point of interest is that in both the EPICOLON and Julie et al. studies, similar proportions of the patient population fulfilled original Bethesda Guidelines (approximately 18%) but the prevalence of fulfilling the revised criteria in the current study was almost twice that of the EPICOLON study (42.1% compared to 23.5%). It is not clear what contributes to this difference though the EPICOLON study reported only 0.9% MMR mutation-positive patients compared to 3.7% in the present study. It is particularly notable that the two mutation-positive patients undetected by the Revised Bethesda Guidelines in the study by Julie et al. had no (or limited) family histories of cancer and cancer diagnoses in the proband at a much later age than is typical for Lynch Syndrome patients. Although the authors report that they gathered extensive family history on each of these two individuals, the histories are so atypical for Lynch syndrome that one wonders about accuracy of reporting or other issues such as non-paternity that may be playing a role.

Thus, based on the aggregate currently available literature, it is still debatable whether the best strategy for detecting Lynch Syndrome patients is based on clinical guidelines or on a universal molecular diagnostic strategy. When assessing various approaches for identifying Lynch Syndrome patients, it is important to note that comparison of strategies is complicated by methodological issues for measurement of sensitivity and specificity. Regardless of the screening method used to identify patients for germline assessment (either based on clinical criteria or on molecular diagnostic testing), in population-based studies to date, not all study subjects are assessed by the gold standard of DNA analysis for germline mutations. Therefore, the true sensitivity and specificity of various strategies are unknown. Since the prevalence of Lynch Syndrome positive patients in a study are determined by germline evaluation of patients whose tumors were MSI positive (or demonstrated loss of the MMR gene product), by default, the sensitivity of a universal molecular strategy based on the molecular diagnostic test which identified patients for genetic testing will misleadingly be 100%.

Should clinical guidelines continue to be the basis for identification of Lynch Syndrome patients, or should universal molecular diagnostic testing become standard of care? The study by Julie and colleagues (13) provides evidence supporting a universal molecular diagnostic testing strategy based on MSI analysis. However, implementation of this universal molecular strategy is currently not feasible in the US healthcare system where there is limited availability of MSI testing and routine IHC testing is likely to be more practical (17). It is noteworthy that a recent study supports the conclusion of Julie et al. that BRAF analysis should be included in any molecular screening algorithm for Lynch Syndrome (18). Other issues that are frequently raised when discussing routine molecular testing are cost and concerns about whether informed consent is necessary before proceeding to tumor testing. Although one study suggests that universal MSI testing might be affordable (19), updated, rigorous cost-effectiveness analyses evaluating which strategy would be the most valuable use of limited healthcare dollars are needed.

Considering the problems associated with the different strategies discussed above, it may not be surprising, although it is unfortunate, that no strategy is systematically employed. Currently, most CRC patients are not being appropriately evaluated for Lynch Syndrome as clinical guidelines are not being implemented (20, 21) and most pathology labs are not routinely doing MSI and IHC analysis, even for the subset of patients that do fulfill the

Bethesda Guidelines. From the health care provider's point of view, the optimal strategy for identifying Lynch Syndrome patients likely consists of components of both clinical criteria assessment and molecular diagnostic testing. From the perspective of patients and their families who may have Lynch Syndrome, however, what is most urgently needed is a change in the current standard of care to implement some form of systematic screening for the disease (whether by personal and family history assessment or molecular screening) and for us to continue to debate the nuances later.

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