Original Article

Counterpoint: Implementing Population Genetic Screening for Lynch Syndrome Among Newly Diagnosed Colorectal Cancer Patients—Will the Ends Justify the Means?

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Key Words

Colorectal cancer, mismatch repair, MMR, microsatellite instability, MSI, immunohistochemistry, screening

Abstract

Inherited mutations in 1 of 4 known mismatch repair genes (*MLH1, MSH2, MSH6, PMS2*) are associated with various cancer risks collectively referred to as *Lynch syndrome*. Roughly 3 of every 100 new colorectal cancers (CRCs) have an underlying Lynch mutation. Tumor-based screening for Lynch among all patients with newly diagnosed CRC could theoretically improve the ability to identify Lynch and prevent cancer among at-risk family members, but the patient-level and social implications of this approach must be carefully considered before adopting this strategy. Poorly addressed issues include the role/timing of informed consent for testing, access and cost barriers associated with genetic counseling and DNA testing, psychosocial burdens to the thousands of middle-aged and elderly patients with CRC coping with surgical and chemotherapy treatments and poor prognosis, the need for providers to warn third-party relatives of risk for Lynch syndrome, limited effectiveness of screening, and the cost burden to society when poor DNA testing uptake, test limitations, and modest screening compliance are considered. Diverse barriers to the success of a population-based Lynch screening program in the United States remain (e.g., clinical resource needs, financial limitations, clinical expertise gaps, educational deficits). Data supporting clinical efficacy (feasibility) and effectiveness (real-life performance) are critical before important policy changes are adopted, especially where issues of hereditary cancer risk and genetic privacy are involved. (*JNCCN* 2010;8:606–611)

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Roughly 3% of newly diagnosed colorectal cancer (CRC) occurs as the result of an inherited mutation in a mismatch repair (MMR) gene as part of hereditary nonpolyposis colorectal cancer or Lynch syndrome. Individuals with a mutation in an MMR gene (*MLH1*, *MSH2*, *MSH6*, or *PMS2*) have an elevated lifetime risk for cancer, including CRC (~60%–80%), endometrial (~40%–60%), gastric (~15%–20%), and a smaller increased risk for several other cancers. Mutation carriers are advised to pursue intensive screening.[1] Carriers may also elect to share personal genetic information with family members. For individuals at risk of having a familial mutation, confirmatory testing can diagnose or rule-out Lynch, allowing screening to be targeted appropriately.

Traditionally, family history was the primary way to identify individuals with Lynch.[2–5] When guided by family history–based criteria,[2,3] 2 tumor-based screening tests (microsatellite instability [MSI] and immunohistochemical [IHC] testing) have shown excellent efficacy in facilitating the detection of Lynch.[6] In light of limitations associated with the Amsterdam criteria and revised Bethesda guidelines,[2,3,7,8] 2 groups (Evaluation of Genomic Applications in Practice and Prevention Working Group [EGAPP] and a research team from Ohio State University [OSU]) have proposed that genetic evaluation (screening and/or testing) of all newly diagnosed CRC cases would "reduce morbidity and mortality in relatives"[7] and improve identification of Lynch in the

United States.[7,9] Although EGAPP does not endorse a best strategy, the OSU team has produced prospective evidence for feasibility of population genetic screening with IHC. The OSU team suggests that their approach fits large-scale screening prerequisites (feasibility, desirability, cost-effectiveness).[9]

An enormous volume of research has been devoted to evaluating clinical testing for Lynch.[5–11] Discussion of the entirety of the meta-analyses and primary studies that compose this body of evidence is beyond the scope of this article. Nonetheless, it is the platform of this counterpoint opinion that genetic screening of patients with newly diagnosed CRC remains unproven 1) as a cost-effective means to identify individuals with Lynch in the United States population and, more importantly, 2) to effectively improve health outcomes for patients with CRC and their relatives, because of a paucity of information on real-life access barriers, educational gaps, and patient preferences for managing genetic risk and health care needs. The OSU team and EGAPP embrace feasibility but do not fully account for patient-level and social ramifications of this policy. Among the unaddressed issues, the most important question is whether population screening could harm unsuspecting patients by creating unanticipated personal burdens (e.g., financial, emotional) that are unwanted and unjustified by personal survival and/or quality-of-life benefits.

This article highlights critical barriers to the success of a population genetic screening strategy for Lynch. Figure 1 presents a schematic on how barriers to the effectiveness of genetic risk information affect health-related outcomes. As a supplement to the publications by EGAPP[6–8] and OSU,[8] Ramsey et al.[10] have previously discussed many of the cost and policy issues associated with population genetic screening for Lynch.

Patient: Need for Informed Consent and Consideration of Unanticipated Burdens

The need to obtain pretesting informed consent and the patient burdens created by population-based MSI/IHC testing are the most concerning issues in the proposed screening strategy, and together present the greatest barriers to its success. Obtaining informed consent is standard of care before germline (DNA-based) genetic testing is performed.[12] Tumor-based tests, such as MSI/IHC, do not necessarily warrant informed consent if used to guide treatment and if results lack heritable implications (e.g., HER2/*neu* testing), yet the proposed screening would have no immediate clinical value for patients with newly diagnosed CRC and would be performed primarily to gauge familial risk. EGAPP specifies that informed consent must be obtained before testing,[7] but how, when, and by whom consent would be obtained in a population screening program remain unanswered.[7,9,13]

Low provider knowledge of MSI/IHC and scarce genetic counseling resources[14] would likely leave many patients poorly informed about the implications of MSI/IHC screening results. Supporting the need for adequate consent are also patient data showing low knowledge of MSI/IHC[15] and data showing strong preferences for detailed pretest information when hereditary risk is present.[16]

The usefulness of MSI for guiding adjuvant fluorouracil–based therapy[17] may one day strengthen the case for routine (uninformed) MSI testing, although IHC has no clinical usefulness beyond Lynch screening.

Genetic risk awareness balances the burdens of fear and anxiety about future cancer risk with knowledge of modification strategies. Even with informed consent, information on future risks engenders distress.[18] Patients alerted to hereditary risk through population Lynch screening may be unprepared, even unwilling, to accept these burdens, particularly considering that screening results only suggest a detectable Lynch mutation. More concerning is the fact that the principal beneficiaries of population genetic screening of patients with CRC would be relatives, not the patients themselves.[7,9] Precedent policy for this approach is unclear, although when considering HIV testing in comparison, blood donors unaware of HIV-positive status are shielded from uninformed disclosure of this status despite the enormous personal and public health implications. It would seem that patients unaware of a genetic risk for CRC should at minimum be warned about risk information they may receive, and granted the right of refusal.

The patient burdens created by Lynch screening become clearer when considering the population tested. Because the median age of CRC diagnosis is approximately 70 years, many individuals informed of the possibility of having Lynch will have outlived

much of their Lynch-associated cancer risk (e.g., in the OSU study, 31% of mutation carriers were ≥ 55 years of age and 16% were ≥ 60 years, not to mention the thousands more individuals with MSI/IHC abnormal tumors[9,18]). More importantly, approximately 50% to 60% of all patients with newly diagnosed CRC will undergo multiagent chemotherapy either short-term or lifelong (6 months for stage III [~30%] and some stage II [~20%]; all stage IV [~20%]), and that approximately 30% will die of CRC within 2 to 3 years.[19]

Many patients receiving Lynch screening results will be facing a multitude of physical and psychological demands (e.g., recovery from surgery; ostomy; treatment side-effects; fear of recurrence, stigma, and job loss), including the 20% of patients with stage IV CRC who will be coping with very poor prognosis. Is it acceptable to force incomplete risk information on these individuals? EGAPP and others cite data that risk-related distress is short-lived,[6–8] but these studies do not consider the uncertainties and burdens created by the proposed Lynch screening program. Perhaps most disconcerting, if a Lynch screening program is to be successful, the burden is placed on patients with CRC to take action on behalf of family members (e.g., genetic counseling, additional testing) based on the risk information they receive, including disclosing this information to them. Strikingly little consideration has been given to patients who do not have or know relatives, do not communicate with relatives, or simply do not wish to be responsible for the health risks of their relatives.

Costs incurred in a Lynch screening program represent a last important burden. Because of the low specificity of MSI/IHC testing,[7] many patients with an abnormal screen would require further testing (e.g., all patients undergoing only MSI or any patients with *MLH1* loss on IHC would require additional *BRAF* testing or *MLH1* methylation testing) to determine whether they have sporadic cancers with an *MLH1* gene methylation–related MSI/IHC abnormal result or are, in fact, likely to have Lynch.

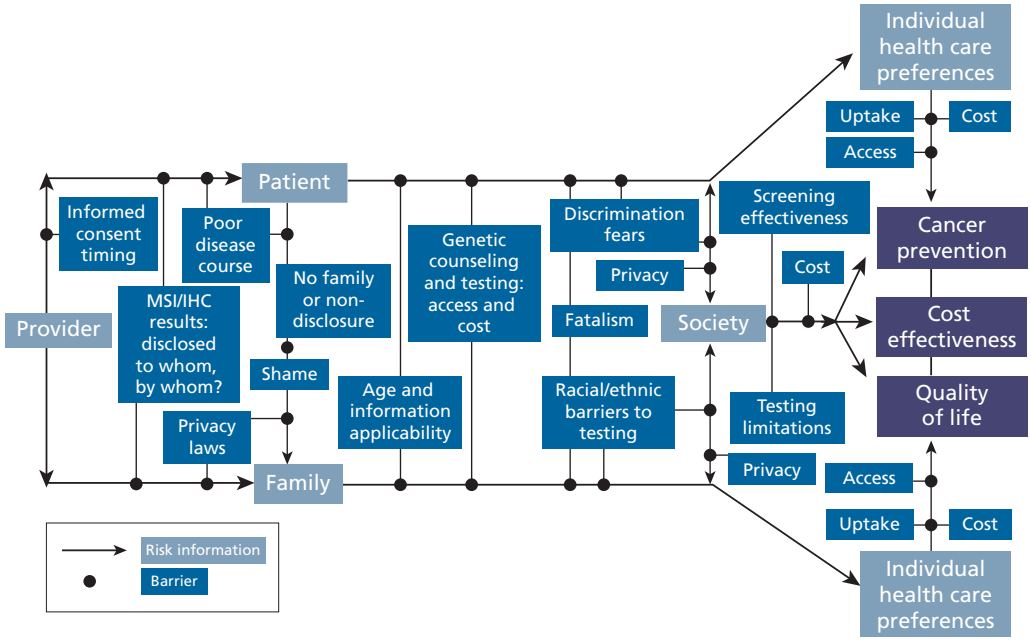

Figure 1 Barriers to the transmission and health impact of hereditary risk information. A hypothetical pathway outlining the transmission of genetic risk information from a provider to an at-risk patient and family (upper and lower paths →) and the anticipated positive health care outcomes for at-risk persons and society (far right center boxes: Cancer prevention, Cost effectiveness, Quality of life). Barriers to transmission and achievement of outcomes are shown in gray boxes (e.g., cost). For Patient → and Family → paths, the ability of risk information to lead to favorable outcomes is mediated by Individual health care preferences (far right top and bottom boxes). For Society (center box), barriers to public health benefits that could be realized by genetic information sharing by at-risk individuals and family members are also shown. Health outcomes for at-risk persons ultimately may not be realized if they are not congruent with personal preferences (Access, Uptake, and Cost barriers along the path from Individual health care preferences to the beneficial outcomes of Cancer prevention, Cost effectiveness, and Quality of life).
Abbreviations: IHC, immunohistochemistry; MSI, microsatellite instability.

For patients in whom germline DNA genetic testing is recommended, additional costs may be incurred. For Medicare-aged individuals undergoing DNA genetic testing for Lynch, costs would include out-of-pocket fees for genetic counseling (~$350) because Medicare does not cover this service. Commercial DNA testing costs can readily exceed $4000 per patient if comprehensive testing is sought to rule out rarer causes of Lynch (Table 1). Finally, even after all testing has been completed (e.g., MSI/IHC → *BRAF*/*MLH1* methylation → germline DNA sequencing), approximately 10% to 15% of patients will receive an inconclusive result.[6–9] Studies have shown that patients frequently misinterpret and are falsely reassured by indeterminate results from DNA genetic testing.[19,20] How risk uncertainty will impact perceived risk, information transmission, and screening practices in surviving patients or family members identified through a Lynch screening program is unknown, but these studies suggest that nondefinitive test results could themselves be highly detrimental to anticipated prevention goals.

Provider: Managing Risk and Maintaining Vigilance

Roughly 13% to 15% of patients with newly diagnosed CRC (~22,500 per year) would have an abnormal MSI/IHC result that would need to be communicated to them and used as a foundation to educate and organize genetic counseling and testing for Lynch. However, currently there is no provision (or working population framework) for how community providers will effectively facilitate the complex management of risk information generated in this program.[7,9] Stitzenberg et al.[21] recently showed that most CRC surgeries performed in New Jersey, New York, and Pennsylvania occur at moderate- to low-volume hospitals. Disproportionate barriers to access to high-volume medical centers experienced by poor, black, rural, and uninsured individuals would almost certainly manifest in reduced access to genetic counseling and testing in underserved populations.[21]

More important for providers, population genetic screening would not obviate the need to collect a family history, but would risk shifting a busy provider's attention to a "family risk test" rather than a complete clinical picture. In downplaying the importance of family history in identifying Lynch among patients with CRC,[7] the EGAPP recommendations risk failure to detect other important risks that can be assessed through family history. For instance, data from the Colon Cancer Family Registry has shown that 15% to 20% of patients meeting Amsterdam criteria (i.e., autosomal dominant CRC inheritance) do not show MSI.[23] Individuals from these families do not have the diversity of cancer risks associated with Lynch, but CRC risk is still 2 to 3 times more than normal (~12%–18% lifetime risk). Hereditary CRC risk in individuals with normal MSI/IHC results (122,250 patients per year) may remain unaddressed, and other less common cancer syndromes (e.g., attenuated familial adenomatous polyposis, MYH, Peutz-Jeghers syndrome, totaling ~2000–3000 patients per year) may be missed if the value of family history is de-emphasized in the community practice setting.

Table 1 Commercial Pricing for Genetic Screening and Testing

Test	List Price
MSI testing	$541
IHC testing	$519
MSI/IHC combined	$910–$955
MLH1/*MSH* sequence/deletion/duplication	$2100
MLH1/*MSH2*/*MSH6* sequencing alone	$3600
MSH6 sequencing/deletion/duplication	$1155
MSH6 deletion/duplication alone	$446
PMS2 sequencing	$1870
TACSTD1 testing	$446

Abbreviations: IHC, immunohistochemistry; MSI, microsatellite instability.
Data from http://www.mayomedicallaboratories.com and http://www.bcm.edu/geneticlabs/cptcodes.html. Accessed December 15, 2009.

Society: Balancing Prevention, Preferences, and Policy

The social benefits and cost-effectiveness anticipated by a population screening program for Lynch hinge on several key components in translating cancer risk information from a patient with CRC to preventive behaviors in unaffected relatives. Although Lynch screening has been shown to be feasible,[9,13] its success in this country will be hindered by pervasive societal barriers to DNA testing, risk communica-

tion, and access. For instance, in the racially diverse United States population where Lynch prevalence is currently unknown, cost-effectiveness could fluctuate 5-fold or more depending on true disease prevalence.[10] Cost-effectiveness is also strongly dependent on the uptake and effectiveness of screening.[9,11] However, only intensive colonoscopy has shown consistent efficacy in Lynch, and this finding is based heavily on data from an observational European cohort with likely far fewer knowledge, socioeconomic, and access barriers than would be encountered in the United States.[10,21,22]

Of greater interest, the United States provider's responsibility to family members under a Lynch screening program remains unclear. Should providers directly inform family members of risks? Who should be informed? The importance of informing relatives of cancer risks is implicit in the recommendation to test patients with CRC for the benefit of relatives,[7,9] yet United States privacy laws generally restrict providers from disclosing medical information to third parties.[10] A legal obligation to warn relatives of genetic risk would represent a substantial deviation from current privacy standards, but has been challenged in court (*Pate v Threlkel*, 661 So.2d 278 [Fla. 1995]; *Safer v Estate of Pack*, 677 A2d 1188 [NJ Supp 1996]). If family members do not receive (and act on) risk information, cost-effectiveness could be heavily compromised.[10,11]

Finally, policy makers should not forget that patients have preferences for health care and management of personal risk. Highlighting the complexity of behavior when genetic risk is concerned are data showing low uptake (< 15%) of *BRCA1/2* testing among women with a strong cancer history, and modest mammographic screening compliance (68% at 1 year posttesting) among proven mutation carriers.[24–26] Would testing/screening uptake be higher among Lynch carriers, considering multi-organ risks and the invasiveness of recommended screening measures? The societal benefits stemming from population-based genetic screening will forever remain only as effective as the preferences of the patient willing to embrace them. Clinical cancer genetics has the unique opportunity to unite the goals of population cancer control and personal cancer risk management. However, for the individual, the greatest promise of genomics will be strategies that integrate public health goals with personal health preferences, so that better methods for identifying and modifying cancer risks may be developed and targeted.

References

1. Burt RW, Barthel JS, Dunn KB, et al. NCCN clinical practice guidelines in oncology: colorectal cancer screening. version 1, 2010. Available at: http://www.nccn.org/professionals/physician_gls/PDF/colorectal_screening.pdf Accessed December 1, 2009.
2. Vasen HF, Mecklin JP, Khan PM, et al. The International Collaborative Group on Hereditary Non-Polyposis Colorectal Cancer (ICG-HNPCC). Dis Colon Rectum 1991;34:424–425.
3. Umar A, Boland CR, Terdiman JP, et al. Revised Bethesda Guidelines for hereditary non-polyposis colorectal cancer (Lynch Syndrome) and microsatellite instability. J Natl Cancer Inst 2004;96:261–268.
4. Guttmacher AE, Collins FS, Carmona RH. The family history—more important than ever. N Engl J Med 2004;351:2333–2336.
5. Newcomb PA, Baron J, Cotterchio M, et al. Colon cancer family registry: an international resource for studies of the genetic epidemiology of colon cancer. Cancer Epidemiol Biomarkers Prev 2007;16:2331–2343.
6. Palomaki GE, McClain MR, Melillo S, et al. EGAPP supplementary evidence review: DNA testing strategies aimed at reducing morbidity and mortality from Lynch syndrome. Genet Med 2009;11:42–65.
7. EGAPP Working Group. Recommendations from the EGAPP working group: genetic testing strategies in newly diagnosis individuals with colorectal cancer aimed at reducing morbidity and mortality from Lynch syndrome in relatives. Genet Med 2009;11:35–41.
8. Agency for Healthcare Research and Quality. Hereditary nonpolyposis colorectal cancer: diagnostic strategies and their implications. Available at: http://www.ahrq.gov/clinic/tp/hnpcctp.htm. Accessed November 20, 2009.
9. Hampel H, Frankel WL, Martin E, et al. Feasibility of screening for Lynch syndrome among patients with colorectal cancer. J Clin Oncol 2008;26:5783–5788.
10. Ramsey SD, Clarke L, Etzioni R, et al. Cost-effectiveness of microsatellite instability screening as a method for detecting hereditary non-polyposis colorectal cancer. Ann Intern Med 2001;135:577–588.
11. Mvundura M, Palomaki GE, McClain MR, et al. Cost effectiveness of genetic testing for Lynch syndrome among newly diagnosed colorectal cancer patients and their first-degree relatives [abstract]. Presented at the 30th Annual Meeting of the Society for Medical Decision Making; October 19, 2008; Philadelphia, PA.
12. American Society of Clinical Oncology Policy Statement Update: genetic testing for cancer susceptibility. J Clin Oncol 2003;21:2397–2406.
13. Hampel H, Frankel WL, Martin E, et al. Screening for the Lynch syndrome (hereditary non-polyposis colorectal cancer). N Engl J Med 2005;352:1851–1860.
14. Parrott S, Del Vecchio M. National Society of Genetic Counselors, Inc.: Professional Status Survey 2006. Available at: http://www.nsgc.org. Accessed April 28, 2009.
15. Manne SL, Chung DC, Weinberg DS, et al. Knowledge and attitudes about microsatellite instability testing among high-risk

individuals diagnosed with colorectal cancer. Cancer Epidemiol Biomarkers Prev 2007;16:2110–2117.

16. Ormand KE, Banuvar S, Daly A, et al. Information preferences of high literacy pregnant women regarding informed consent models for genetic carrier screening. Patient Educ Couns 2009;75:244–250.
17. Sargent DJ, Marsoni S, Thibodeau SN, et al. Confirmation of deficient mismatch repair (dMMR) as a predictive marker for lack of benefit from 5-FU based chemotherapy in stage II and III colon cancer (CC): a pooled molecular reanalysis of randomized chemotherapy trials [abstract]. J Clin Oncol 2009;26(Suppl 1):Abstract 4008.
18. Burgess MM. Beyond consent: ethical and social issues in genetic testing. Nat Rev Genet 2001;2:147–151.
19. Jemal A, Siegel R, Ward E, et al. Cancer Statistics 2009. CA Cancer J Clin 2009;4:225–249.
20. Grover S, Stoffel EM, Mercado RC, et al. Colorectal cancer risk perception on the basis of genetic test results in individuals at risk for Lynch syndrome. J Clin Oncol 2009;27:3981–3986.
21. Stitzenberg KB, Sigurdsen ER, Egleston BL, et al. Centralization of cancer surgery: implications for patient access to optimal care. J Clin Oncol 2009;27:4671–4678.
22. Jarvinen HJ, Aarnio M, Mustonen H, et al. Controlled 15-year trial on screening for colorectal cancer in families with hereditary nonpolyposis colorectal cancer. Gastroenterology 2000;118:829–834.
23. Lindor NM, Rabe K, Petersen GM, et al. Lower cancer incidence in Amsterdam-1 criteria families without mismatch repair deficiency: familial colorectal cancer X. JAMA 2005;293:1979–1985.
24. Peters N, Domchek SM, Rose A, et al. Knowledge, attitudes, and utilization of BRCA1/2 testing among women with early-onset breast cancer. Genet Test 2009;9:48–53.
25. Levy DE, Garber JE, Shields AE. Guidelines for genetic risk assessment of hereditary breast and ovarian cancer: early disagreements and low utilization. J Gen Intern Med 2009;24:822–828.
26. Lerman C, Hughes C, Croyle RT, et al. Prophylactic surgery decisions and surveillance practices one year following BRCA1/2 testing. Prev Med 2000;31:75–80.