Identification of Lynch syndrome: How should we proceed in the 21st century?

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Abstract

Lynch syndrome, also known as hereditary non-polyposis colorectal cancer (HNPCC), is the most common form of hereditary colorectal cancer. Although great advances in the understanding of its molecular basis have taken place in the last decade, optimal selection of individuals for HNPCC genetic testing remains controversial. This is especially relevant since colonoscopy has been proven effective for reducing colorectal cancer incidence and mortality in individuals at-risk for this disorder. In this manuscript, we summarize the most significant contributions to this important issue that have appeared in the last few years.

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Key words: Hereditary non-polyposis colorectal cancer; Screening; Prevention; Microsatellite instability; Genetics

INTRODUCTION

Lynch syndrome, also known as hereditary non-polyposis colorectal cancer (HNPCC), is the most common form of hereditary colorectal cancer (CRC), accounting for 2%-5% of all colorectal malignancies[1]. It is characterized by early onset of CRC and other related neoplasms including endometrial, ovarian, gastric and urinary tract cancer. This syndrome is inherited in a non-fully penetrant autosomal dominant pattern, and occurs as a result of germline mutations in mismatch repair genes, predominantly MLH1 and MSH2 (>90% of cases), but also MSH6 and PMS2. The abnormal function of these genes leads to the accumulation of errors during DNA replication, especially in repetitive sequences (microsatellites). As a result, tumors in patients with Lynch syndrome characteristically demonstrate microsatellite instability (MSI), as well as loss of expression of the affected protein[2].

Although great advances in the understanding of its molecular basis have taken place in the last decade, optimal selection of individuals for HNPCC genetic testing remains controversial[3]. This is especially relevant since colonoscopy has been proven effective for reducing CRC incidence and mortality in individuals at-risk for this disorder[4]. In 1991, the International Collaborative Group on HNPCC established clinical criteria, known as the Amsterdam criteria, which provided a pivotal definition of this syndrome and were critical in identifying its molecular basis[5]. In response to criticism that the Amsterdam criteria were too stringent, the extended Amsterdam II criteria were developed to include extracolonic HNPCC-associated cancers[6].

The use of the Amsterdam criteria achieved the original purpose of classifying a family as having HNPCC, but their limited sensitivity hampered decisions about which patients should undergo genetic testing[7]. In 1996, an international workshop on HNPCC hosted by the National Cancer Institute outlined a set of recommendations, known as the Bethesda guidelines, for the identification of individuals with HNPCC who should be tested for MSI and/or genetic testing[8]. More recently, a second HNPCC workshop revised these criteria and proposed a new set of recommendations, the revised Bethesda guidelines[9].

As it was previously mentioned, tumor MSI is a phenotypic indicator of defective DNA mismatch repair[10]. The fact that more than 90% of HNPCC-related cancers exhibit MSI suggests that screening of tumors for MSI may be an efficient way of selecting individuals for HNPCC genetic testing[11-13]. On the other hand, most mutations in either MSH2 or MLH1 genes result in abnormal MSH2 or MLH1 protein expression[14,15]. As a consequence, immunostaining for these two proteins is associated with MSI[16,17], but this association is not without exceptions[18]. Indeed, a mutant protein product can be expressed and detected by immunostaining[19].
whereas germline mutations may occur in patients with MSI-negative tumors\[^{19}\]. These conflicting results have precluded the establishment of a unique method for primary screening of mismatch repair deficiency.

Recently, the Epicolon study, a prospective, multicenter, nation-wide survey aimed at assessing the incidence and characteristics of hereditary and familial CRC in Spain\[^{20}\], has demonstrated that the revised Bethesda guidelines constitute a very useful approach to select patients at risk for HNPCC\[^{21}\]. Moreover, in patients fulfilling these criteria, both MSI testing and protein immunostaining were equivalent and highly cost-effective strategies to further select those patients who should be tested for \(\text{MSH2/MLH1}\) germline mutations. Considering this equivalence and the fact that immunostaining is more available than DNA analysis in a clinical setting, the use of immunohistochemistry may contribute to identify a larger proportion of patients with Lynch syndrome\[^{21,22}\].

The combination of revised Bethesda guidelines with tumor molecular analysis, however, is not fully accepted since some gene mutation carriers do not fulfill these clinical criteria\[^{23}\]. To overcome this limitation, a massive, universal tumor mismatch repair screening by MSI analysis and/or immunostaining in any given CRC patient has been proposed\[^{23,24}\]. Nevertheless, this approach is much less efficient\[^{21}\], a critical issue that could be somehow solved by improving tumor molecular analysis. In that sense, it has been recently demonstrated that the use of two microsatellite markers (combination of \(\text{BAT25 or BAT26 with NR21 or NR24}\) performed as well as the entire pentaplex of mononucleotide repeats (\(\text{BAT26, BAT25, NR21, NR22, and NR24 markers}\) and better than the recommended panel by the National Cancer Institute (\(\text{BAT26, BAT25, DSS346, D2S123, and D17S250 markers}\) in identifying mismatch repair deficient tumors\[^{25}\]). Similarly, the introduction of \(\text{BRAF V600E mutation analysis as a step prior to germline gene testing in patients with mismatch repair deficiency improves the cost-effectiveness of this approach, especially in those with incomplete or unknown family history}\[^{26,27}\].

On the other hand, the revised Bethesda guidelines have also been criticized because of their broad and complex variables, their relatively low specificity, and their inability to establish the likelihood of carrying a mutation in a given patient\[^{24,28}\]. In addition, the need of performing tumor molecular analyses in patients fulfilling these criteria by some means constitutes a restriction since tissue samples are not always available. In that sense, as in hereditary breast-ovarian cancer syndrome in the past, identification of Lynch syndrome is moving toward complex algorithms and multivariable models combining personal and family history\[^{28-31}\].

The first approach to this goal was the Leiden model\[^{29}\], a regression logistic model derived from CRC patients attended in a high-risk clinic and designed to identify \(\text{MLH1/MSH2}\) mutation carriers, which has represented the only predictive model for years. Variables included in this model were fulfillment of the Amsterdam criteria, mean age of CRC diagnoses, and presence of any endometrial cancer in the family. However, it still included rather complex variables, it was developed using a relatively small population in a high-risk setting, and it did not take into account tumor molecular.

More recently, a second model was developed in the United Kingdom in a large population-based cohort of early onset (< 55 years) CRC patients\[^{30}\] and consists of two consecutive stages: stage 1, based exclusively on clinical variables (age, sex, tumor location, presence of synchronous or metachronous CRC, family history of colorectal and endometrial cancer, and age of the youngest relative with CRC) and available on the web\[^{31}\], and stage 2, based on tumor MSI or immunostaining data. The area under the ROC curve of this model, which predicts \(\text{MLH1, MSH2 and MSH6 germline mutations, was 0.82 (95\% CI, 0.72-0.91)}\). However, its applicability to CRC patients older than 55 years or those with other Lynch syndrome-associated tumors has not been assessed yet\[^{32}\].

The third approach is a Mendelian model for determining \(\text{MLH1, MSH2 and MSH6}\) carrier probabilities based on published estimates of mutation frequencies and cancer penetrances in both mutation and non-mutation carriers, and including MSI data\[^{33}\]. This Bayesian model uses the CancerGene software\[^{33}\] and provides the likelihood of finding a mutation in both probands and relatives on the basis of clinical and molecular information (age at diagnosis of colorectal and endometrial cancer, age of healthy relatives, MSI analysis and genetic testing). The area under its ROC curve was 0.83 (95\% CI, 0.78-0.88). The performance of this model on clinical practice and different population settings is still unknown\[^{32}\].

Finally, the PREMM1,2 model (accessible at the Dana-Farber Cancer Institute web site\[^{34}\]) has demonstrated an excellent ability to discriminate between risk groups (area under the ROC curve of 0.80; 95\% CI, 0.76-0.84), categorized by the estimated risk for probability of a mutation\[^{35}\]. This study provides a new model based on a logistic regression analysis from one of the largest cohorts published so far of patients at-risk for hereditary CRC with proved mutation in the \(\text{MSH2/MLH1}\) genes. The authors recommend using their model as an initial assessment for individuals at risk for this disorder, before molecular information is available to the clinician. Based on the risk estimate generated from the model and other factors (accessibility to genetic services, timelines of genetic information, insurance coverage, and availability of tumor block), the clinician may choose whether genetic evaluation should be pursued as well as the approach to testing (MSI analysis and/or immunostaining, versus direct germline testing)\[^{34}\]. The model does not include tumor molecular data to further refine the estimated probability nor takes into account \(\text{MSH6}\) gene mutations, although updates of the model are planned.

In summary, at the beginning of the 21st century, there is no unique, universally accepted strategy for the identification of Lynch syndrome. However, the tremendous advances in recent years allow us to be optimistic. Indeed, besides the fact that ongoing investigations may eventually elucidate the most effective and efficient approach to select individuals for HNPCC gene testing, the attention paid by the whole medical
community to this disease in the last decade will definitely contribute to make Lynch syndrome recognition more widely accessible.

REFERENCES

1. Lynch HT, de la Chapelle A. Hereditary colorectal cancer. N Engl J Med 2003; 348: 919-932
2. Umar A, Risinger JH, Hawk ET, Barrett JC. Testing guidelines for hereditary non-polyposis colorectal cancer. Nat Rev Cancer 2004; 4: 153-158
3. Järvinen HJ, Aarnio M, Mustonen H, Aktan-Collan K, Aktan LA, Peltonäki P, de La Chapelle A, Mecklin JP. Controlled 15-year trial on screening for colorectal cancer in families with hereditary nonpolyposis colorectal cancer. Gastroenterology 2000; 118: 829-834
4. Vassen HF, Mecklin JP, Khan PM, Lynch HT. The International Collaborative Group on Hereditary Non-Polyposis Colorectal Cancer (ICG-HNPC). Dis Colon Rectum 1991; 34: 424-425
5. Vassen HF, Watson P, Mecklin JP, Lynch HT. New clinical criteria for hereditary nonpolyposis colorectal cancer (HNPPC, Lynch syndrome) proposed by the International Collaborative group on HNPCC. Gastroenterology 1999; 116: 1453-1456
6. Rodríguez-Bigas MA, Boland CR, Hamilton SR, Henson DE, Jass JR, Khan PM, Lynch H, Perucchini M, Smyrk T, Sobin L, Srivastava S. A National Cancer Institute Workshop on Hereditary Nonpolyposis Colorectal Cancer Syndrome: meeting highlights and Bethesda guidelines. J Natl Cancer Inst 1997; 89: 1758-1765
7. Umar A, Boland CR, Terdiman JP, Syngal S, de la Chapelle A, Rüschoff J, Fischel R, Lindor NM, Burgart LJ, Hamelin R, Hamilton SR, Hiatt RA, Jass J, Lindblom A, Lynch HT, Peltonäki P, Ramsey SD, Rodriguez-Bigas MA, Vassen HF, Hawk ET, Barrett JC, Freedman AN, Srivastava S. Revised Bethesda Guidelines for hereditary nonpolyposis colorectal cancer (Lynch syndrome) and microsatellite instability. J Natl Cancer Inst 2004; 96: 261-268
8. Boland CR, Thibodeau SN, Hamilton SR, Sidransky D, Eshleman JR, Burt RW, Melter SJ, Rodríguez-Bigas MA, Fodde R, Ranzani GN, Srivastava S. A National Cancer Institute Workshop on Microsatellite Instability for cancer detection and familial predisposition: development of international criteria for the determination of microsatellite instability in colorectal cancer. Cancer Res 1998; 58: 5248-5257
9. Giardìello FM, Bresnigging JD, Petersen GM. AGA technical review on hereditary colorectal cancer and genetic testing. Gastroenterology 2001; 121: 198-213
10. Aaltonen LA, Salovaara R, Kristo P, Canzian F, Emminkhi A, Petolmäki P, Chadwick RB, Kääriäinen H, Eskelinen M, Järvinen H, Mecklin JP, de la Chapelle A. Incidence of hereditary nonpolyposis colorectal cancer and the feasibility of molecular screening for the disease. N Engl J Med 1998; 338: 1481-1487
11. Salovaara R, Loukola A, Kristo P, Kääriäinen H, Ahola H, Eskelinen M, Härkönen N, Julkunen R, Kangas E, Ojala S, Tulikoura J, Valkamo E, Järvinen H, Mecklin JP, Aaltonen LA, de la Chapelle A. Population-based molecular detection of hereditary nonpolyposis colorectal cancer. J Clin Oncol 2000; 18: 2193-2200
12. Samowitz WS, Curtin K, Lin HH, Robertson MA, Schaffer D, Nichols M, Grunenthal K, Leppert MF, Slattery ML. The colon cancer burden of genetically defined hereditary nonpolyposis colon cancer. Gastroenterology 2001; 121: 830-838
13. Thibodeau SN, French AJ, Cunningham JM, Tester D, Burgart LJ, Roche PC, McDonnell SK, Schaid DJ, Vockley CW, Michels VV, Farr GH, O’Connell MJ. Microsatellite instability in colorectal cancer: different mutator phenotypes and the principal involvement of hMLH1. Cancer Res 1998; 58: 1713-1718
14. Cunningham JM, Kim CY, Christensen ER, Tester DJ, Parc Y, Burgart LJ, Halling KC, McDonnell SK, Schaid DJ, Walsh Vockley C, Kubly V, Nelson H, Michels VV, Thibodeau SN. The frequency of hereditary defective mismatch repair in a prospective series of unselected colorectal carcinomas. Am J Hum Genet 2001; 69: 780-790
15. Terdiman JP, Gum JR, Conrad PG, Miller GA, Weinberg V, Crawley SC, Levin TR, Reeves C, Schmitt A, Hepburn M, Siesmenger MH, Kim YS. Efficient detection of hereditary nonpolyposis colorectal cancer genes carriers by screening for tumor microsatellite instability before germine genetic testing. Gastroenterology 2001; 120: 21-30
16. Lindor NM, Burgart LJ, Leontovich O, Goldberg RM, Cunningham JM, Sargent DJ, Walsh-Vockley C, Petersen GM, Walsh MD, Leggett BA, Young JP, Barker MA, Jass JR, Hopper J, Gallinger S, Bapat B, Redston M, Thibodeau SN. Immunohistochemistry versus microsatellite instability testing in phenotyping colorectal tumors. J Clin Oncol 2002; 20: 1043-1048
17. de la Chapelle A. Microsatellite instability phenotype of tumors: genotyping or immunohistochemistry? The jury is still out. J Clin Oncol 2002; 20: 897-899
18. Wahlberg SS, Schmitt J, Thomas G, Loda M, Garber J, Syngal S, Kolodner RD, Fox E. Evaluation of microsatellite instability and immunohistochemistry for the prediction of germline MSH2 and MLH1 mutations in hereditary nonpolyposis colon cancer families. Cancer Res 2002; 62: 3485-3492
19. Scartozzi M, Bianchi F, Rosati S, Galizia E, Antolini A, Loretelli C, Piga A, Bearzi I, Cellerino R, Porfiri E. Mutations of hMLH1 and hMSH2 in patients with suspected hereditary nonpolyposis colorectal cancer: correlation with microsatellite instabilities and abnormalities of mismatch repair protein expression. J Clin Oncol 2002; 20: 1203-1208
20. Piñol V, Andreu M, Castells A, Payá A, Bessa X, Rodríg J. Frequency of hereditary non-polyposis colon cancer and other colorectal cancer familial forms in Spain: a multicentre, prospective, nationwide study. Eur J Gastroenterol Hepatol 2004; 16: 39-45
21. Piñol V, Castells A, Andreu M, Castellvi-Bel S, Alenda C, Llor X, Xicola RM, Rodríguez-Moranta F, Payá A, Jover R, Bessa X. Accuracy of revised Bethesda guidelines, microsatellite instability, and immunohistochemistry for the identification of patients with hereditary nonpolyposis colorectal cancer. JAMA 2005; 293: 1986-1994
22. Rodríguez-Moranta F, Castells A, Andreu M, Piñol V, Castellvi-Bel S, Alenda C, Llor X, Xicola RM, Jover R, Payá A, Bessa X, Balaguer F, Cubiella J, Argüello L, Morillas JD, Bujanda L. Clinical performance of original and revised Bethesda guidelines for the identification of MSH2/MLH1 gene carriers in patients with newly diagnosed colorectal cancer: proposal of a new and simpler set of recommendations. Am J Gastroenterol 2005; 110: 1104-1111
23. Hampel H, Frankel WL, Martin E, Arnold M, Konduku J, Kuebler P, Nakagawa H, Sotamaa K, Prior TW, Westman J, Panescu J, Fix D, Lockman J, Comeras I, de la Chapelle A. Screening for the Lynch syndrome (hereditary nonpolyposis colorectal cancer). N Engl J Med 2003; 352: 1851-1860
24. Vassen HF, Boland CR. Progress in genetic testing, classification, and identification of Lynch syndrome. JAMA 2005; 293: 2028-2030
25. Xicola RM, Llor X, Pons E, Castells A, Alenda C, Piñol V, Andreu M, Castellvi-Bel S, Payá A, Jover R, Bessa X, Girós A, Duque JM, Nicolás-Pérez D, García A, Rigau J, Gassull MA. Performance of different microsatellite marker panels for detection of mismatch repair-deficient colorectal tumors. J Natl Cancer Inst 2007; 99: 244-252
26. Bessa X, Ballesté B, Andreu M. Role of BRAF mutation in HNPC screening strategies. Gastroenterology 2006; 130: 33
27. Beniloch S, Payá A, Alenda C, Bessa X, Andreu M, Jover R, Castells A, Llor X, Aranda FL, Massuti B. Detection of BRAF V600E mutation in colorectal cancer: comparison of automatic sequencing and real-time chemistry methodology. J Mol Diagn 2006; 8: 540-543
28. Balmaña J, Smithwell DH, Steyverberg EW, Stoffel EM, Deffenbaugh AM, Reid JE, Ward B, Scholl T, Hendrickson B, Tazelar A, Burbridge LA, Syngal S. Prediction of MLH1
and MSH2 mutations in Lynch syndrome. JAMA 2006; 296: 1469-1478

29 Wijnen JT, Vasen HF, Khan PM, Zwinderman AH, van der Klift H, Mulder A, Tops C, Møller P, Fodde R. Clinical findings with implications for genetic testing in families with clustering of colorectal cancer. N Engl J Med 1998; 339: 511-518

30 Barnetson RA, Tenesa A, Farrington SM, Nicholl ID, Cetnarskyj R, Porteous ME, Campbell H, Dunlop MG. Identification and survival of carriers of mutations in DNA mismatch-repair genes in colon cancer. N Engl J Med 2006; 354:

31 Chen S, Wang W, Lee S, Nafa K, Lee J, Romans K, Watson P, Gruber SB, Euhus D, Kitzler KW, Jass J, Gallinger S, Lindor NM, Casey G, Ellis N, Giardiello FM, Offit K, Parmigiani G. Prediction of germline mutations and cancer risk in the Lynch syndrome. JAMA 2006; 296: 1479-1487

32 MMRpredict: http://www1.hgu.mrc.ac.uk/softdata/mmrpredict.php

33 CancerGene: http://www3.utsouthwestern.edu/cancergene

34 PREMM12: http://www.dfci.org/premm

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