



Original Article

# Current evidence for universal molecular testing for colorectal cancer patients



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## ARTICLE INFO

### Article history:

Received 6 June 2017

Accepted 26 June 2017

Available online 11 July 2017

### Keywords:

Lynch Syndrome

Genetics

Screening

Colorectal cancer

Testing

## ABSTRACT

**Background:** Risk assessment for Lynch Syndrome may be a complex and challenging task. Demonstration of germline mutations has the benefits of confirming Lynch Syndrome diagnosis and may also provide screening and surgical orientation for affected members and relief for non-affected relatives.

**Objective:** The present paper aimed to critically review the criteria to diagnose Lynch Syndrome, focusing the attention on the new perspective of adopting universal screening for patients diagnosed with colorectal cancer.

**Methods:** We performed a literature review about the rationale and preliminary results of universal testing for Lynch Syndrome.

**Results:** The use of selective eligibility criteria to determine who should undergo Lynch Syndrome testing may fail in a substantial proportion of cases. Moreover, universal strategy is feasible, cost-effective and more sensitive than previous methods. However, there still exist problems regarding clinical practice implementation and compliance either by medical doctors and patients.

**Conclusions:** Standard guidelines for colorectal cancer screening are not ideal to provide early detection of Lynch Syndrome patients. And although universal screening has been associated with an increased identification of Lynch Syndrome patients, a successful implementation of this approach is still limited by the lack of clinical expertise among physicians, and also requires standardization of the existing protocols for routine genetic screening.

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<http://dx.doi.org/10.1016/j.jcol.2017.06.003>

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## Evidências atuais para testes moleculares universais para pacientes com câncer colorretal

### R E S U M O

#### Palavras-chave:

Síndrome de Lynch  
Genética  
Triagem  
Câncer colorretal  
Testes

**Introdução:** A avaliação de risco para síndrome de Lynch (SL) pode ser tarefa complexa e desafiadora. A demonstração de mutações na linha germinal resulta em benefícios, como a confirmação do diagnóstico de SL e também pode proporcionar orientações para a triagem e procedimentos cirúrgicos para os membros afetados, além de trazer alívio para os parentes não afetados.

**Objetivo:** Este artigo teve por objetivo oferecer uma revisão crítica dos critérios para o diagnóstico de SL, com enfoque na atenção sobre a nova perspectiva de adoção da triagem universal para pacientes diagnosticados com câncer colorretal (CCR).

**Métodos:** Procedemos a uma revisão da literatura com ênfase nas justificativas e resultados preliminares de testes universais para SL.

**Resultados:** O uso de critérios seletivos de qualificação, com vistas a determinar quem deveria passar por um teste para SL, pode ser malsucedido em substancial percentual de casos. Foi também constatado que a estratégia universal é exequível, com bom custo-benefício e com maior sensibilidade, em comparação com os métodos previamente utilizados. Contudo, ainda existem problemas concernentes à sua implementação na prática clínica e também na cooperação de médicos e de pacientes.

**Conclusões:** As orientações padronizadas para a triagem de CCR não são ideais, em termos de se obter a imediata detecção de pacientes com SL. Por outro lado, embora a triagem universal tenha sido associada a um aumento na identificação de pacientes com SL, a bem-sucedida implementação dessa abordagem fica ainda limitada pela pouca experiência clínica entre os médicos e, além disso, também há a necessidade de padronização dos protocolos existentes para a triagem genética de rotina.

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## Introduction

The comprehension and interpretation of molecular mechanisms involved in colorectal cancer (CRC) carcinogenesis have improved a lot during the recent decades. In the era of personalized medicine, the translation of all the acquired knowledge into clinical practice represents a major advance and a very important tool in screening and management of the disease.<sup>1</sup> In this setting, stratification of patients at risk through detection of germline mutations implicated in hereditary syndromes is crucial as it may influence clinical decision-making and cancer surveillance for their relatives. This is especially true to Lynch Syndrome (LS) patients, the most common hereditary CRC syndrome (one in 35 patients with CRC), comprising 3–5% of all CRC burdens.<sup>2–4</sup>

Since Aldred Scott Warthin concluded that there was “some influence of heredity on cancer” in his 1895 manuscript,<sup>5</sup> LS has been the object of many investigations and received different nomenclature over time (*cancer family syndrome, hereditary nonpolyposis colorectal cancer*). Nowadays, the eponym LS renders an homage to Dr. Henry Lynch after his 1966 seminal paper that comprehensively described this condition as having an autosomal-dominant inheritance pattern and an early age of onset (average age at onset <45 years) and involving adenocarcinomas of the colon, endometrium, and stomach.<sup>6</sup>

## Main characteristics of Lynch Syndrome

LS is a disorder caused by a germline mutations in a mismatch repair (MMR) gene (MLH1, MSH2, MSH6 and PMS2) or deletion in the epithelial cell adhesion molecule (EPCAM) gene leading to the closely linked MSH2 loss of expression. Proteins related to these genes may recognize nucleotides that have been inadequately incorporated. Thus, the absence (or inactivation) of such proteins are leads to accumulation of cellular mutations and a variable lifetime risk of CRC.<sup>7</sup> Consequently, CRC screening in this population is fundamental, as those patients develop CRC earlier than normal subjects (mean age 44–61 years). In MLH1 and MSH2 mutation carriers, this risk approaches 30–74% of patients, while lower figures were reported among women (30–52%), in patients with MSH6 (10–22%) or PMS2 (15–20%) mutations.<sup>8</sup>

This CRC risk is due to an adenoma–carcinoma progression ratio of 1:1 (estimated adenoma–cancer transformation time 1–3 years), as compared to sporadic cancers that have a ratio of 30:1 (estimated adenoma–cancer transformation time 8–17 years).<sup>9</sup> Consequently, LS patients and those at risk have been advised to undergo colonoscopy every 1–2 years after 20–25 years of age. Other common clinical features in LS colon tumors are proximal location, mucinous differentiation and increased rates of multiple (synchronous or metachronous) lesions.<sup>10</sup>

There also exists a modest increased risk of extracolonic cancers arising in the stomach, ovaries, small bowel, hepatobiliary epithelium, urinary tract and sebaceous glands.<sup>8,11</sup> Particularly, females with LS have a 28–60% lifetime risk for endometrial cancer (EC), so they are advised to perform annual pelvic examination/endometrial sampling after 30–35 years of age.<sup>10,11</sup>

Over the years, many institutions have abandoned traditional screening programs in favor of a universal screening approach. For this reason, it is now necessary to discuss issues about the viability of performing and implementing strategies of universal tumor screening for all CRC patients.

### Problems and limitations to identify Lynch Syndrome patients

The identification of patients carrying MMR gene mutations is of crucial importance for cancer surveillance and preventive measures. Although patients with CRC or EC represent the most effective way to identify LS, specific educational programs directed to the general population and physicians would probably increase their awareness regarding hereditary CRC, with positive effects on LS identification.

Risk assessment for LS may be a complex and challenging task even for physicians specialized in familial cancer, as they believe LS is probably under diagnosed.<sup>12</sup> This perception comes from the recognition that almost 28% of LS patients may be missed due to the low sensitivity and efficiency of the current used strategies.<sup>13–15</sup> Moreover, LS diagnosis presents other limitations regarding terminology, patient acceptance, public health implications and cost of genetic tests. Nevertheless, some of these barriers have been surpassed in different ranges.

First of all, we have to know what we are talking about. Different terminology is used to separate patients with distinct clinical features when compared to LS.<sup>16</sup> Thus, while hereditary non-polyposis colorectal cancer defines patients presenting Amsterdam criteria, LS is reserved only for those exhibiting MMR or EPCAM gene mutations. To add more confusion, patients presenting microsatellite instability (MSI) or immunohistochemistry (IHC) abnormalities but no germline mutations are referred as *Lynch-like syndrome*. And finally, those with Amsterdam criteria without MSI in tumor test are classified as *Familial Colorectal Cancer Type X*.

LS patients may be identifiable with the aid of different approaches such as clinical data, prediction models, tumor testing, germline testing, and universal testing.<sup>10</sup> Traditionally, indications for either tumor or germline testing were based on criteria derived from expert consensus (Amsterdam Criteria or Bethesda Guidelines). The Amsterdam Criteria<sup>17</sup> requires the attainment of a detailed family history and sensitivity is less than 50%, besides being broadened in 1999 to incorporate extracolonic tumors.<sup>4,18</sup> Due to loss of identification of a great number of mutation carriers, Bethesda guidelines were proposed in 1997 and revised in 2004<sup>19</sup> to include family history and specific pathologic features of CRC. They were less restrictive and presented sensitivity greater than 72%.<sup>4</sup>

It is well recognized that some LS families may not meet both criteria and guidelines. Conversely, despite meeting them, some families will not express germline alterations in any MMR genes. Moreover, family history is not always available. Consequently, their use have rendered criticism and limited implementation of these criteria in clinical practice.

The demonstration of germline mutations by tumor testing has the benefits of confirming LS diagnosis and, doing so, it may provide screening and surgical orientation for affected members and relief for non-affected relatives.<sup>7</sup> Tumor testing is made by polymerase chain reaction (PCR) to identify MSI, and/or IHC to detect protein products expressed by MMR genes.

MSI tumors with loss of MLH1 protein are likely secondary to somatic events, while loss of MSH2, MSH6 or PMS2 proteins are likely from a germline mutation.<sup>7</sup> As 10–15% of sporadic CRCs may also exhibit MSI, MSI+ patients with no MLH1 expression are suggested to undergo additional tumor testing (BRAF), as this occurs in 75% of cases as a result of somatic promoter hyper methylation.<sup>20</sup> There is a strong concordance between both tests, with specificity close to 90%.<sup>21</sup> While MSI analysis presents 93% sensitivity in detecting MMR deficiency in MMR mutation carriers, IHC testing allows for target mutation analysis.<sup>10</sup>

### Rationale and perspectives of universal testing

Occasionally, the consequence of an unexpected CRC diagnosis in a young patient in a non-suspected LS family is inappropriate management (partial resection of colon, non-indication of a prophylactic hysterectomy or lack of extracolonic tumors screening). Moreover, relatives at risk would not be advised to undergo genetic testing. This scenario explains why the idea of exploring systematic testing for LS independent of clinical criteria has gained increasing acceptance in the literature.

The strategy of screening all cases of newly diagnosed CRC for LS has been referred to as “universal screening”.<sup>4,22–26</sup> In 2005, Hampel et al.<sup>24</sup> reported that among 2.8% of LS patients diagnosed by universal screening, half of them had more than 50 years of age, and 25% did not meet either Amsterdam or the revised Bethesda criteria. Later in 2009, the Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group (EWG) incorporated the suggestion of the Jerusalem Workshop to perform routine genetic testing for all CRCs in patients younger than 70 years.<sup>27</sup> This independent group (EWG) formed by multidisciplinary experts published an evidence-based recommendation to perform screening for LS on all newly diagnosed CRC by PCR-based MSI testing or IHC, in order to reduce morbidity and mortality among their relatives.<sup>28</sup>

Further studies clearly demonstrate that selective eligibility criteria to determine who should undergo LS testing would fail in a substantial proportion of cases, considering the missed diagnosis of the patient with CRC and relatives at-risk.<sup>8,20,29</sup> The establishment of this approach allowed the identification of a substantial rate of mutation carriers (2.4–3.7%) and led to the perception that 12–28% of these cases would not be diagnosed based only on clinical/pathological selection criteria.<sup>4,13–15,30,31</sup>

Progressively, the 2009 EGAPP proposition received support from many experts who believed that implementation of universal LS screening on a population level is worth pursuing. It has been demonstrated that the benefits outweighs harms,<sup>20,32,33</sup> and that it is highly cost-effective.<sup>22,23</sup> Following this tendency, some leading cancer institutions and public health agencies created the Lynch Syndrome Screening Network (LSSN) in 2011. The main purpose was to implement LS screening for both CRC and ECs. According to this project, the involved entities are encouraged to share resources, protocols and data; moreover, access to experts in LS screening should be facilitated.<sup>34</sup>

The feasibility and effectiveness of such program are well observed in an interesting publication from the Cleveland Clinic, where the Implementation of universal MSI/IHC, along with effective multidisciplinary communication and plans of responsibility for patient contact, resulted in increased identification of patients with LS.<sup>32</sup>

In Europe, the Mallorca group (formed by 35 specialists from 13 countries) recently published the revised guidelines for the clinical management of LS, recommending to perform analysis of all CRC younger than 70 years by IHC of the four MMR proteins (MLH1/MSH2/MSH6/PMS2) or MSI.<sup>35</sup> Tumors that demonstrate loss of MLH1 should undergo BRAF testing or MLH1 promoter hyper methylation analysis. This statement was further incorporated in the updated NCCN guidelines for Genetic/Familial-Risk Assessment.<sup>36</sup>

The US Multi-Society Task Force on CRC has also endorsed this change toward universal LS screening.<sup>10</sup> This group emphasized the need for appropriate infrastructure and the opportunity to perform the tumor testing on preoperative biopsy specimens, in order to facilitate tumor testing. Probably, this level III evidence may help standardize the existing protocols for routine LS genetic screening within US, as a previous evaluation in 2010 showed a variable scenario characterized by the use different combinations of preliminary tumor testing (e.g., MSI only, IHC only, MSI and IHC, and IHC with BRAF), as well as non-uniform patient/family consent and follow-up procedures.<sup>36</sup>

However, it should be acknowledged that a successful implementation of such recommendations might face many challenges. Firstly, the most significant barrier is the general lack of clinical expertise regarding genetic tests among physicians Laura Valle, fact that raises the need for improving the awareness and comprehension of genetic tests among cancer care providers.<sup>37</sup> For this matter, educational material containing updated information should be also developed. Secondly, indication of these tests requires pre- and post-counseling, in order to discuss and explain clinical, psychosocial, financial, and ethical issues that may come up during this process.<sup>10</sup> Thus, cooperation and integration among the involved specialists (gastroenterologist, colorectal surgeon, gynecologists, geneticist, genetic counselor, oncologist, etc.) is essential. Other important issues include population access, costs and protocols standardization.<sup>11,32</sup> Additionally, one should recognize that estimates of benefit might be compromised in families with lower penetrance and later age of onset (such as MSH6 and PMS2 mutation carriers).

In summary, standard guidelines for CRC screening are not safe to provide early detection or prevention for LS

malignancies, mainly because they usually occur at young ages. Otherwise, the universal LS screening strategy is more sensitive than previous methods and may have several potential benefits. Unfortunately, the many difficulties to implement it in clinical practice has made compliance with this idea spotty at best.<sup>25</sup> The scientific community and government institutions should focus their efforts to discuss how universal screening should be performed, rather than if it should be done. The task is to push research and clinical setting feasibility to the population level. For the future, there is also hope for greater availability and decreased costs of panel testing for germline mutations in genes involved in carcinogenesis.

## Conflicts of interest

The authors declare no conflicts of interest.

## REFERENCES

1. Pritchard CC, Grady WM. Colorectal cancer molecular biology moves into clinical practice. *Gut*. 2011;60:116–29.
2. Barnetson RA, Tenesa A, Farrington SM, Nicholl ID, Cetnarskyj R, Porteous ME, et al. Identification and survival of carriers of mutations in DNA mismatch-repair genes in colon cancer. *N Engl J Med*. 2006;354:2751–63.
3. Piñol V, Castells A, Andreu M, Castellví-Bel S, Alenda C, Llor X, et al. Gastrointestinal Oncology Group of the Spanish Gastroenterology Association. Accuracy of immunohistochemistry for the identification of patients with hereditary nonpolyposis colorectal cancer. *JAMA*. 2005;293:1986–94.
4. Hampel H, Frankel WL, Martin E, Arnold M, Khanduja K, Kuebler P, et al. Feasibility of screening for Lynch Syndrome among patients with colorectal cancer. *J Clin Oncol*. 2008;26:5783–8.
5. Warthin AS. Heredity with reference to carcinoma as shown by the study of the cases examined in the pathological laboratory of the University of Michigan, 1895–1913. *Arch Intern Med*. 1913;12:546–55.
6. Lynch HT, Shaw MW, Magnuson CW, Larsen AL, Krush AJ. Hereditary factors in cancer. Study of two large midwestern kindreds. *Arch Intern Med*. 1966;117:206–12.
7. Baiocchi GL, Portolani N, Vermi W, Baronchelli C, Gheza F, Zogno C, et al. Lynch Syndrome from a surgeon perspective: retrospective study of clinical impact of mismatch repair protein expression analysis in colorectal cancer patients less than 50 years old. *BMC Surg*. 2014;14:9.
8. Sehgal R, Sheahan K, O'Connell PR, Hanly AM, Martin ST, Winter DC. Lynch Syndrome: an updated review. *Genes*. 2014;5:497–507.
9. De Jong AE, Morreau H, van Puijenbroek M, Eilers PH, Wijnen J, Nagengast FM, et al. The role of mismatch repair gene defects in the development of adenomas in patients with HNPCC. *Gastroenterology*. 2004;126:42–8.
10. Giardiello FM, Allen JI, Axilbund JE, Boland CR, Burke CA, Burt RW, et al. Guidelines on genetic evaluation and management of Lynch Syndrome: a consensus statement by the US Multi-Society Task Force on colorectal cancer. *Dis Colon Rectum*. 2014;57:1025–48.
11. Bellcross CA, Bedrosian SR, Daniels E, Duquette D, Hampel H, Jasperson K, et al. Implementing screening for Lynch Syndrome among patients with newly diagnosed colorectal

- cancer: summary of a public health/clinical collaborative meeting. *Genet Med.* 2012;14:152–62.
12. Tranø G, Wasmuth HH, Sjørnsen W, Hofslø E, Vatten LJ. Awareness of heredity in colorectal cancer patients is insufficient among clinicians: a Norwegian population-based study. *Colorectal Dis.* 2009;11:456–61.
  13. Julié C, Trésallet C, Brouquet A, Vallot C, Zimmermann U, Mitry E, et al. Identification in daily practice of patients with Lynch Syndrome (hereditary nonpolyposis colorectal cancer): revised Bethesda guidelines-based approach versus molecular screening. *Am J Gastroenterol.* 2008;103:2825–35.
  14. van Lier MG, Leenen CH, Wagner A, Ramsoekh D, Dubbink HJ, van den Ouweland AM, et al., LIMO Study Group. Yield of routine molecular analyses in colorectal cancer patients ≤70 years to detect underlying Lynch Syndrome. *J Pathol.* 2012;226:764–74.
  15. Pérez-Carbonell L, Ruiz-Ponte C, Guarinos C, Alenda C, Payá A, Brea A, et al. Comparison between universal molecular screening for Lynch Syndrome and revised Bethesda guidelines in a large population-based cohort of patients with colorectal cancer. *Gut.* 2012;61:865–72.
  16. Valle L. Genetic predisposition to colorectal cancer: where we stand and future perspectives. *World J Gastroenterol.* 2014;20:9828–49.
  17. Vasen HF, Watson P, Mecklin JP, Lynch HT. New clinical criteria for hereditary nonpolyposis colorectal cancer (HNPCC, Lynch Syndrome) proposed by the International Collaborative group on HNPCC. *Gastroenterology.* 1999;116:1453–6.
  18. Salovaara R, Loukola A, Kristo P, Kääriäinen H, Ahtola H, Eskelinen M, et al. Population-based molecular detection of hereditary nonpolyposis colorectal cancer. *J Clin Oncol.* 2000;18:2193–200.
  19. Umar A, Boland CR, Terdiman JP, Syngal S, de la Chapelle A, Rüschoff J, et al. Revised Bethesda Guidelines for hereditary nonpolyposis colorectal cancer (Lynch Syndrome) and microsatellite instability. *J Natl Cancer Inst.* 2004;96:261–8.
  20. de la Chapelle A, Palomaki G, Hampel H. Identifying Lynch Syndrome. *Int J Cancer.* 2009;125:1492–3.
  21. Palomaki GE, McClain MR, Melillo S, Hampel HL, Thibodeau SN. EGAPP supplementary evidence review: DNA testing strategies aimed at reducing morbidity and mortality from Lynch Syndrome. *Genet Med.* 2009;11:42–65.
  22. Mvundura M, Grosse SD, Hampel H, Palomaki GE. The cost-effectiveness of genetic testing strategies for Lynch Syndrome among newly diagnosed patients with colorectal cancer. *Genet Med.* 2010;12:93–104.
  23. Ladabaum U, Wang G, Terdiman J, Blanco A, Kuppermann M, Boland CR, et al. Strategies to identify the Lynch Syndrome among patients with colorectal cancer: a cost-effectiveness analysis. *Ann Intern Med.* 2011;155:69–79.
  24. Hampel H, Frankel WL, Martin E, Arnold M, Khanduja K, Kuebler P, et al. Screening for the Lynch Syndrome (hereditary nonpolyposis colorectal cancer). *N Engl J Med.* 2005;352:1851–60.
  25. Peres J. To screen or not to screen for Lynch Syndrome. *J Natl Cancer Inst.* 2010;102:1382–4.
  26. Hampel H. Point: justification for Lynch Syndrome screening among all patients with newly diagnosed colorectal cancer. *J Natl Compr Cancer Netw.* 2010;8:597–601.
  27. Boland CR, Shike M. Report from the Jerusalem workshop on Lynch Syndrome-hereditary nonpolyposis colorectal cancer. *Gastroenterology.* 2010;138, 2197.e1–7.
  28. Evaluation of Genomic Applications in Practice Prevention (EGAPP) Working Group. Recommendations from the EGAPP Working Group: genetic testing strategies in newly diagnosed individuals with colorectal cancer aimed at reducing morbidity and mortality from Lynch Syndrome in relatives. *Genet Med.* 2009;11:35–41.
  29. Hampel H. Genetic testing for hereditary colorectal cancer. *Surg Oncol Clin N Am.* 2009;18:687–703.
  30. Canard G, Lefevre JH, Colas C, Coulet F, Svrcek M, Lascols O, et al. Screening for Lynch Syndrome in colorectal cancer: are we doing enough? *Ann Surg Oncol.* 2012;19:809–16.
  31. Moreira L, Balaguer F, Lindor N, de la Chapelle A, Hampel H, Aaltonen LA, et al. EPICOLON Consortium. Identification of Lynch Syndrome among patients with colorectal cancer. *JAMA.* 2012;308:1555–65.
  32. Heald B, Plessek T, Liu X, Pai R, Patil D, Moline J, et al. Implementation of universal microsatellite instability and immunohistochemistry screening for diagnosing Lynch Syndrome in a large academic medical center. *J Clin Oncol.* 2013;31:1336–40.
  33. Ward RL, Hicks S, Hawkins NJ. Population-based molecular screening for Lynch Syndrome: implications for personalized medicine. *J Clin Oncol.* 2013;31:2554–62.
  34. Mange S, Bellcross C, Cragun D, Duquette D, Gorman L, Hampel H, et al. Creation of a network to promote universal screening for Lynch Syndrome: the Lynch Syndrome screening network. *J Genet Couns.* 2015;24:421–7.
  35. Vasen HF, Blanco I, Aktan-Collan K, Gopie JP, Alonso A, Aretz S, et al. Revised guidelines for the clinical management of Lynch Syndrome (HNPCC): recommendations by a group of European experts. *Gut.* 2013;62:812–23.
  36. National Comprehensive Cancer Network NCCN Practice Guidelines in Oncology. Available from: <http://www.nccn.org>.
  37. Rybak C, Hall MJ. Interpretation of genetic testing for Lynch Syndrome in patients with putative familial colorectal cancer. *J Natl Compr Cancer Netw.* 2011;9:1311–20.