J COLOPROCTOL (RIO J). 2017;xxx(xx):xxx–xxx

Journal of Coloproctology

www.jcol.org.br

Original Article

Current evidence for universal molecular testing for colorectal cancer patients

Fábio Guilherme Campos[a,*], *Marleny Novaes Figueiredo*[a], *Carlos Augusto Real Martinez*[b,c]

[a] *Universidade de São Paulo (USP), Faculdade de Medicina, Departamento de Gastroenterologia, Divisão de Cirurgia Colorretal, São Paulo, SP, Brazil*

[b] *Universidade São Francisco (USF), Programa de Pós-graduação em Ciências da Saúde, Bragança Paulista, SP, Brazil*

[c] *Universidade Estadual de Campinas (Unicamp), Faculdade de Ciências Médicas, São Paulo, SP, Brazil*

ARTICLE INFO

Article history:
Received 6 June 2017
Accepted 26 June 2017
Available online xxx

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.

* *Corresponding author.*
E-mail: fgmcampos@terra.com.br (F.G. Campos).

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

Please cite this article in press as: Campos FG, et al. Current evidence for universal molecular testing for colorectal cancer patients. J Coloproctol (Rio J). 2017. http://dx.doi.org/10.1016/j.jcol.2017.06.003

Evidências atuais para testes moleculares universais para pacientes com câncer colorretal

Palavras-chave:
Síndrome de Lynch
Genética
Triagem
Câncer colorretal
Testes

RESUMO

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.

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.[1] 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.[2–4]

Since Aldred Scott Warthin concluded that there was "some influence of heredity on cancer" in his 1895 manuscript,[5] 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.[6]

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.[7] 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.[8]

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).[9] 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.[10]

Please cite this article in press as: Campos FG, et al. Current evidence for universal molecular testing for colorectal cancer patients. J Coloproctol (Rio J). 2017. http://dx.doi.org/10.1016/j.jcol.2017.06.003