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# Clinical and anamnestic evaluation rôle for the diagnosis and treatment of families affected by Lynch syndrome. Case report and review of the literature

*Bianca Cudia<sup>1</sup>, Raffaella Liccardo<sup>2</sup>, Giovanni Di Carlo<sup>1</sup>, Giuseppe Damiano<sup>1</sup>, Attilio Ignazio Lo Monte<sup>1</sup>, Paola Izzo<sup>2,3</sup>, Francesca Duraturo<sup>2</sup>*

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**Summary.** The Lynch syndrome increases the chances of developing cancer in individuals at risk, so prevention by instrumental screening of the more frequent cancers becomes very important. Genetic testing allows us to diagnose the disease with certainty and to identify individuals at risk. However, there are also reliable clinical and anamnestic criteria by which to diagnose the syndrome. The clinical case reported in our study shows that, in the absence of genetic characterization, clinical criteria alone rapidly suggested the correct approach leading to early treatment of relatives in the case in point.

**Key words:** Lynch Syndrome, HNPCC, clinical management, screening colorectal cancer, clinical criteria, prevention and treatment, genetic testing

«RUOLO DELLA VALUTAZIONE CLINICA E ANAMNESTICA PER LA DIAGNOSI E IL TRATTAMENTO DI FAMIGLIE AFFETTE DA SINDROME DI LYNCH. CASO CLINICO E REVISIONE DELLA LETTERATURA»

**Riassunto.** Nelle famiglie affette da sindrome di Lynch è presente una maggiore probabilità di sviluppare tumori pertanto, è molto importante la prevenzione mediante la sorveglianza endoscopica e strumentale dei tumori più frequenti nei soggetti a rischio. Il test genetico permette di diagnosticare con certezza la malattia e di identificare i soggetti a rischio. Tuttavia, anche i criteri clinici e anamnesticci permettono di diagnosticare la sindrome con buona affidabilità. Il caso clinico riportato nel nostro studio mette in evidenza che, in assenza di una caratterizzazione genetica, i soli criteri clinici hanno permesso di mettere rapidamente a punto, un corretto approccio per il trattamento precoce dei soggetti a rischio presenti nella famiglia del nostro caso clinico.

**Parole chiave:** Sindrome di Lynch, HNPCC, gestione clinica, sorveglianza endoscopica del cancro coloretta-  
le, criteri clinici, prevenzione e trattamento, test genetico

## Introduction

The majority of colorectal cancer (CRC) cases diagnosed annually are due to sporadic events, but up to 6% are attributed to known monogenic disorders that confer a greatly increased risk for the development

of CRC and multiple extra-colonic malignancies (1). Currently, there are 3 hereditary syndromes that have a proven etiological relationship with colorectal cancer: Familial Adenomatous Polyposis (FAP) (2), MYH Associated Polyposis (MAP) (3) and Hereditary Non-polyposis Colorectal Cancer (HNPCC) or Lynch syn-

drome (LS) (4). In the past years the genetic basis of FAP, MAP and LS syndromes has been clarified enabling one, in the majority of cases, to carry out early pre-clinical diagnosis of subjects belonging to families at risk (5). These syndromes present slighter phenotype traits when associated with lower penetrance gene mutations (6). Knowledge of the clinical and pathological features of hereditary CRC makes it possible to outline a well-defined diagnostic and therapeutic protocol for symptomatic subjects (7-9).

LS is an autosomal dominant inherited syndrome with incomplete penetrance characterized by the predisposition to develop colorectal tumors. CRC sets in around 45 years of age rather than the average age of onset with sporadic forms, which is 63 (10). It is important to note that the syndrome implies not only a predisposition to develop colorectal cancer, but also extracolonic tumors involving the uterus, ovaries, stomach, and urinary tract. For this reason, LS is classified in two forms: Lynch I with an early age of occurrence, predilection for the proximal colon and high rates of metachronous colorectal cancer; and Lynch II, which has the same characteristics but including extracolonic tumors, as described above (11).

LS is primarily associated with germline mutations in DNA Mismatch Repair (MMR) genes, MSH2, MLH1, PMS2 and MLH3 (12). Recently, a germline point mutation in MSH3 was found to be associated with the Lynch syndrome phenotype (13). Inactivation of the MMR complex manifests as microsatellite instability (MSI), which is detected in 90-95% of LS tumor tissues (14, 15).

The risk of developing colorectal cancer is as much as 80% in mutation-carrying relatives of sub-

jects with LS and is dependent on sex and the MMR gene mutated (16). In addition, the risk for developing endometrial cancer is up to 70% rather than 2-3% in the general population (16). Increased risk of developing carcinoma of the ureter, renal pelvis and bladder has often been reported, while adenocarcinomas of the ovary, stomach, hepatobiliary tract, small bowel and brain, as well as cutaneous sebaceous neoplasms, also occur in LS families (16). Again, an increased risk of pancreas cancer has been described (17), while, the risk of developing prostate or breast cancer shows a small increase over that of the general population (16).

LS patients can be identified by clinical criteria such as neoplasia onset-age and family history. The Amsterdam criteria were the first diagnostic guidelines devised to identify families prone to develop LS (18) (Table 1).

Because the Amsterdam criteria were judged too stringent and not sufficiently sensitive (19), Bethesda guidelines were developed to identify individuals who deserve investigation for LS by evaluation of MSI and/or immunohistochemistry (IHC) testing (20) of their tumors (21, 22) with a view to undergoing genetic MMR testing (7-9) (Table 2).

To confirm the clinical diagnosis of LS in a patient and/or family one performs germline MMR testing (MLH1, MSH2, MSH6 and PMS2 gene screening). When the pathogenic mutation has been identified in pedigrees, it can determine the carrier status in risk family members. Moreover, it can direct management of affected and unaffected individuals (16).

Unfortunately, the genetic testing of LS has not yet reached the diffusion and speed required, whereas in practice this pathology requires rapid and precise

**Table 1.** Amsterdam Criteria I and II.

- 
- All of the following must apply for a putative diagnosis of HNPCC to be made in a family
  - There are at least three relatives with an HNPCC-associated cancer (large bowel, endometrium, small bowel, ureter, or renal pelvis, although not including stomach, ovary, brain, bladder, or skin)
  - One affected person is a first-degree relative of the other two
  - At least two successive generations are affected
  - At least one person was diagnosed before the age of 50 years
  - Familial adenomatous polyposis has been excluded
  - Tumors have been verified by pathologic examination
-

**Table 2.** Bethesda Guidelines for MSI Testing.

- 
- Tumors from any of the following should be tested for MSI and then positive patients should continue for MMR testing
  - Individuals with cancer in families that meet the Amsterdam Criteria
  - Individuals with two HNPCC-associated cancers, including synchronous and metachronous CRC or associated extracolonic cancers
  - Individuals with CRC and a first-degree relative with CRC and/or HNPCC-related extracolonic cancer and/or a colorectal adenoma diagnosed at age < 40 years
  - Individuals with CRC or endometrial cancer diagnosed at age < 45 years
  - Individuals with right-sided CRC with an undifferentiated pattern (solid or cribriform) on histopathology diagnosed at age < 45 years
  - Individuals with signet-ring-cell-type CRC diagnosed at age < 45 years
  - Individuals with adenomas diagnosed at age < 40 years
- 

diagnosis, which will allow other members of the family, carriers of the disease, to obtain undisputed benefits. In particular in some regions of Southern Italy, such as Sicily, genetic testing for LS is not practiced nor are investigations carried out, such as MSI or IHC testing, to confirm the clinical suspicion of individuals at risk of LS. In such places, therefore, clinical evaluation and familial history of the patient play an important role in any early diagnosis of LS, and thus risk assessment of risk family individuals.

Little is known in the literature about management of families with a clinical diagnosis of LS, but in the absence of genetic testing. Ersig and colleagues (22) reported a clinical case calling for explanation of risk in families without mutations to the genes involved in LS. In our study, we report on a patient who developed early-onset colon carcinoma. Clinical and anamnestic evaluation on their own enabled a clinical diagnosis of LS to be made. This allowed us to identify several young members of the family, apparently in good health, who were actually already suffering from colon carcinoma. Thus, in the temporary absence of an LS genetic marker, we were able to rapidly carry out all the diagnostic and therapeutic steps to improve these patients' quality of life and life expectancy. Only at a later stage was the clinical diagnosis of LS confirmed by a positive result in MMR genetic testing.

Clinical and anamnestic evaluation may hence still be of basic importance for identifying individuals at risk of LS.

### Case report

A 39 year-old Caucasian man, G.R., from Sicily was admitted to our hospital with intestinal subocclusion. On admission he weighed 75 kg to 175 cm of height. His past history included no significant diseases. He has a primary level of education and a job as a labourer. He reported frequent episodes of abdominal pain with fever and weight loss in the last month. His family history was positive for tumoral diseases (the mother and a sister had died of colorectal cancer at 55 and 42 years respectively). In addition, the patient had two other sisters and a brother in apparently good health. Clinical abdominal examination revealed the presence of a sore mass in the left superior quadrant, with a hard consistency, undefined margins, and apparently fixed with respect to the superficial and deep planes. Pancolonoscopy highlighted a stenosing and vegetating mass approximately 75 cm from the anus, with an ulcerated surface, obstructing  $\frac{2}{3}$  of the colonic lumen. This was repeatedly biopsied. Histologic examination showed a "tubulo-villous adenoma, with small fragments of mucinous adenocarcinoma". Abdominal ultrasonography excluded the presence of focal hepatic lesions or other noteworthy alterations. Since the patient's clinical condition worsened, we decided to perform a left colonic resection, without waiting for further examinations. During the course of surgery, several peritumoral abscesses were identified. The resected colon was the site of a neoforma-

tion sized 5 x 4 x 4.5 cm, partly vegetating and partly ulcerated, of a gelatinous appearance. The histologic diagnosis was mucinous adenocarcinoma with full-thickness infiltration of the wall and perivisceral fibrofatty tissue. The margins of resection were free from neoplastic infiltration and the 22 isolated lymph nodes did not show signs of metastatic colonization (Dukes B2 mod. Astler and Coller - pT3N0Mx Stage II). Ever since hospitalization, the patient's youthful age (less than 40 years of age) and closer assessment of his family history led us to suspect the presence of a hereditary predisposition for colorectal cancer. We thus decided to contact the other family members over 25 years of age and invite them to undergo colonoscopy screening and transvaginal ultrasound. Of the three siblings, one sister and one brother decided to adhere to the surveillance protocol. Both underwent pan-colonoscopy: the woman (who also underwent transvaginal ultrasound) had a negative outcome, but the brother, G.G. aged 33 year and asymptomatic, had an endoscopic outcome of a voluminous, vegetating and sub-stenosing lesion, proximally to the hepatic flexure. Biopsies were carried out along its margins. Histopathologic examination revealed the presence of an adenocarcinoma with a medium degree of differentiation. CT scan of the abdomen confirmed the presence of a thickening of the colonic wall at the point of the hepatic flexure, with hyperdensity of the surrounding fat, and millimetric lymph nodes in its vicinity, and excluded the presence of metastases of the liver and peritoneum. The patient, G.G., a 33-year old Caucasian man from Sicily, on admission weighed 80 kg to 175 cm of height. His past history did not include any significant diseases. He also has a brother of primary level education and a job as a labourer. He underwent right hemicolectomy with termino-lateral ileo-colon anastomosis. Histopathological examination showed a plaque neof ormation, 3 x 4 x 1 cm in size, ulcerated, with the microscopic appearance of a mucinous adenocarcinoma with a medium degree of differentiation, presence of Crohn-like reaction, full-thickness infiltration of the wall, and initial involvement of the serosa. The margins of resection were free from neoplastic foci; metastases were present in 2 out of 27 isolated lymph nodes (Dukes C2 mod. Astler and Coller - pT3N1M0, Stage III).

Given the tumoral familial history, early detection of cancer in the apparently healthy subject GG, as well as fulfilment of the Amsterdam criteria, we decided to perform MSI testing. Unfortunately, in Sicily it was not possible to perform either MSI or IHC testing, for financial limitations. We therefore decided to send total genomic DNA extracted from peripheral blood lymphocytes from both patients to Naples University in order for genetics experts to perform germ-line MMR testing; genetic counselling and risk assessment was available for both probands, who had given written informed consent. The Naples laboratory performed detection point mutation analysis and large genomic rearrangement in MLH1 and MSH2 genes. In this manner they found large-scale deletion of the entire exon 6 in the MSH2 gene, particularly loss of the 9655-bp genomic region, in the DNA of both subjects. This deletion c.942+(346-356)\_1077-(5323-5313) del, is named in accordance with the mutation nomenclature instructions provided by the HGVS (<http://www.hgvs.org/>); it creates a premature stop codon and formation of a truncated protein; therefore it is compatible with the Lynch syndrome phenotype (24).

## Discussion

The decision to carry out partial resection of the colon rather than subtotal colectomy with ileo-rectal anastomosis (IRA) in our patients was mainly influenced by the dramatic clinical appearance upon hospital admission. Secondly, the most important factors considered were: the patients' age, the stage of the tumor, the unknown genotype, the expected quality of life after segmental colectomy compared to more extensive resections, and finally the patients' choice.

Subtotal colectomy offers a better life expectancy in very young patients (up to 27 years) with a Dukes A tumor, but the advantage drastically reduces for older ages and more advanced stages of the tumor. Our patients had a locally advanced endoscopic finding, confirmed in one case by abdominal CT images (G.G.), and suspected in the other case (G.R.) owing to clinical manifestations of intestinal subocclusion. We therefore preferred to carry out more conservative

surgery rather than colectomy, with the intention of carrying out a short-interval endoscopic follow-up to assess the residual colon, in agreement with the recommendations of current guidelines about surveillance in patients with hereditary colon cancer (25). On the other hand, improvements in techniques of endoscopic polypectomy and pharmacological prevention by administration of non-steroidal anti-inflammatory drugs suggested the choice of a less aggressive approach, rather than colectomy and proctocolectomy, in these patients as well (26).

Concerning surgical treatment, patients and physicians must have appropriate understanding of the high risk of metachronous neoplasia in the remaining colon if a segmental resection is performed (27). While most authors agree that total abdomen colectomy (TAC) is the favored option for patients with Lynch syndrome (28), most first CRC<sub>s</sub> in HNPCC are still treated by segmental surgery (29).

Identification of early onset colon cancer in the brother of our index case, as well as his familial history, made us suspect a genetic predisposition to this disease. The clinical diagnosis of LS used to be based on application of the Amsterdam Criteria (6). These criteria, although providing a definition of the syndrome, soon appeared too restrictive, since they exclude a fraction of families with alterations of Mismatch Repair genes (presence of false negatives). The Bethesda criteria (20) are now considered the most accurate clinical criteria for identification of patients at risk of HNPCC. These new guidelines are able to identify families prone to LS with a sensitivity and a specificity equal to 82% and 77% respectively (30, 31). However, recently Musulen and colleagues have shown that the Revised Bethesda Guidelines failed to detect 70% of patients at risk of LS. We therefore recommend universal population screening for LS among all patients with newly diagnosed colorectal carcinoma (32).

In our case, the Amsterdam criteria were fully fulfilled. In accordance with the currently adopted guidelines, the relatives of the observed and treated patients were informed that they might take part in a screening study for LS, followed, in the case of a positive finding, by a surveillance program provided for risk cases or those with LS (16). We thus gave the patient identified as our "index case" a psychological consultation,

with subsequent signing of the informed consent for enrolment in the genetic screening program. DNA was extracted from peripheral blood lymphocytes and from surgically removed and deparaffined tumoral tissue. Only in later times, given the persisting local difficulties in performing genetic testing, did we decide to contact Naples University geneticists in order to check for Lynch Syndrome by MMR-mutation and MSI analysis. While awaiting the diagnosis of genetic and molecular alterations in our patients, we proposed endoscopic monitoring for our operated patients and endoscopic screening of their first-degree relatives over 25 years of age. The outcome obtained from genetic testing confirmed our suspicions. By using the multiple ligation dependent probe amplification (MLPA) technique, the geneticist identified a large deletion of the entire exon 6 in the MSH2 gene. Analysis by long-PCR allowed us to identify the loss of 9655-bp in this genomic region. This deletion identified in our two affected brothers, is named MSH2 :c.942+(346-356)\_1077-(5323-5313) del and creates a premature stop codon and the formation of a truncated protein; it is hence compatible with the Lynch syndrome phenotype. The MSI analysis performed on DNA extracted from tumor tissues of both patients showed MSI high status (all markers analyzed); this condition is present in 95% of colon cancer in LS and is compatible with the mutation identified (24).

Over the following five years, both operated patients, after oncologic counseling, were put on instrumental and endoscopic surveillance, as well as suitable cycles of chemotherapy. Abdominal CT, abdominal ultrasonography, urologic follow-up are to date negative. Endoscopic surveillance has been performed, according to the current guidelines (33) every one or two years. As expected, sequential colonoscopy showed several polyps in our patient's residual colon. Endoscopic polypectomy was performed with a histopathological finding of dysplasia from low- to high-grade one. To date, both operated patients are negative for metachronous or residual CRC or carcinomas in other sites. Clinical and instrumental surveillance is still in progress.

Regarding the surveillance of relatives at risk, in addition to a sister who was free of the disease, we identified 6 other subjects over 25 years of age. Unfor-

tunately only one gave his consent to undergo instrumental examinations in order to enter the surveillance program.

The two patients in the present study belong to a very disrupted family group of low socioeconomic condition, and difficulty in understanding the severity of the disease, which may affect them in the future. It is noteworthy that patient G.G. also interrupted the adjuvant chemotherapy. Unfortunately, the attitude of this family is not rare. Even when informed through genetic analysis of their predisposition toward developing the disease, relatives of patients with hereditary colon cancer do not always join screening programs, as has been confirmed by a Dutch study in which more than half of the subjects at risk did not follow the genetic screening program (34). Hopefully, this attitude will improve in the future thanks to easier access to the World Wide Web, which may provide more thorough patients with the necessary information.

## Conclusions

The temporary difficulty in identifying the genetic mutation affecting our patients at disease onset did not prevent their being included in the Lynch family. Indeed, when Amsterdam criteria are satisfied, the diagnosis of Lynch syndrome may be undertaken through clinical and anamnestic evaluations, as subsequent DNA mutation confirmed in our case too.

At the present time, the genetic mutation found in the DNA of our patients allows for early and preventive identification of carriers of the mutation among the other relatives, who should therefore be put on surveillance screening programs, according to the current guidelines. Obviously, when genetic tests are temporarily unable to highlight the mutation in the proband, it is necessary to carry out all clinical and instrumental screening procedures for all subjects belonging to the family, starting 10 years before the youngest case.

When genetic characterization is unavailable, however, one may be up against the problem of patient compliance, as these subjects must undergo multiple and often complex examinations, which do not involve the digestive system alone. These potential limitations increase the risk of not identifying patients already car-

rying neoplastic lesions that need to be treated soon, although they are not yet clinically apparent.

Finally, performing the genetic test offers the chance, as in our case, of occasional finding of genetic mutations that could involve new research scenarios.

Failure to recognize a specific mutation, which is not sufficient to rule out Lynch syndrome, calls for organization of a longer and more complex working plan on the basis of clinical and anamnestic data, in the search for phenotypic manifestations.

## References

1. Bodmer W, Tomlinson I. Rare genetic variants and the risk of cancer. *Curr Opin Genet Dev* 2010; 20(3): 262-7.
2. Patel SG, Ahnen DJ. Familial colon cancer syndromes: an update of a rapidly evolving field. *Curr Gastroenterol Rep* 2012; 14(5): 428-38.
3. De Rosa M, Galatola M, Borriello S, et al. Implication of adenomatous polyposis coli and MUTYH mutations in familial colorectal polyposis. *Dis Colon Rectum* 2009; 52(2): 268-74.
4. Jasperson KW, Tuohy TM, Neklason DW, et al. Hereditary and Familial Colon Cancer. *Gastroenterology* 2010; 138(6): 2044-58.
5. De Rosa M, Dourisboure RJ, Morelli G, et al. First genotype characterization of Argentinean FAP patients: identification of 14 novel APC mutations. *Hum Mutat* 2004; 23(5): 523-4.
6. Weitz J, Koch M, Debus J, et al. Colorectal cancer. *Lancet* 2005; 365(9454): 153-65.
7. Burt R, Neklason D. Genetic testing for inherited colon cancer. *Gastroenterol* 2005; 128: 1696-716.
8. Vasen HFA, Blanco I, Aktan-Collan K, et al. Revised guidelines for the clinical management of Lynch syndrome (HNPCC): recommendations by a group of European experts. *Gut* 2013; 62: 812-23.
9. Ramsoekh D, van Leerdam ME, Tops CM, et al. The use of genetic testing in hereditary colorectal cancer syndromes: genetic testing in HNPCC, (A)FAP and MAP. *Clin Genet* 2007; 72: 562-7.
10. Rijcken FE, Koornstra JJ, van der Sluis T, et al. Early carcinogenic events in HNPCC adenomas: differences with sporadic adenomas. *Dig Dis Sci* 2007; 13: 54-70.
11. Win AK, Lindor NM, Young JP, et al. Risks of primary extracolonic cancers following colorectal cancer in lynch syndrome. *J Natl Cancer Inst* 2012; 104(18): 1363-72.
12. Lynch HT, de la Chapelle A. Genomic medicine: hereditary colon cancer. *N Engl J Med* 2003; 348: 919-32.
13. Duraturo F, Liccardo R, Cavallo A, et al. Association of low-risk MSH3 and MSH2 variant alleles with Lynch syndrome: probability of synergistic effects. *Int J Cancer*. 2011; 129(7): 1643-50.

14. Pedroni M, Sala E, Scarselli A, *et al.* [Microsatellite instability and mismatch repair protein expression in hereditary and sporadic colorectal carcinogenesis. Cancer Res 2001; 61: 896-9.](#)
15. Giardiello FM, Allen JI, Axilbund JE, *et al.* [Guidelines on genetic evaluation and management of Lynch syndrome: a consensus statement by the US Multi-Society Task Force on colorectal cancer. Gastroenterology 2014; 147\(2\): 502-26.](#)
16. Bonadona V, Bonaïti B, Olschwang S, *et al.* [Cancer risks associated with germline mutations in MLH1, MSH2, and MSH6 genes in Lynch syndrome. JAMA 2011; 305\(22\): 2304-10.](#)
17. Kastrinos F, Mukherjee B, Tayob N, *et al.* [Risk of pancreatic cancer in families with Lynch syndrome. JAMA 2009; 302\(16\): 1790-5.](#)
18. Lindor NM, Rabe K, Petersen GM, *et al.* [Lower cancer incidence in Amsterdam-I criteria families without mismatch repair deficiency: familial colorectal cancer type X. JAMA 2005; 293\(16\): 1979-85.](#)
19. Lindor NM, Burgart LJ, Leontovich O, *et al.* [Immunohistochemistry versus microsatellite instability testing in phenotyping colorectal tumors. J Clin Oncol 2002; 20\(4\): 1043-8.](#)
20. Boland CR, Thibodeau SN, Hamilton SR, *et al.* [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\(22\): 5248-57.](#)
21. Heald B, Plesec T, Liu X, *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\(10\): 1336-40.](#)
22. Ersig AL, Williams JK, Hadley DW, *et al.* [Communication, encouragement, and cancer screening in families with and without mutations for hereditary nonpolyposis colorectal cancer: a pilot study. Genet Med 2009; 11\(10\): 728-34.](#)
23. Abdel-Rahman WM, Peltomäki P. [Lynch syndrome and related familial colorectal cancers. Crit Rev Oncog 2008; 14\(1\): 1-22; discussion 23-31.](#)
24. Duraturo F, Cavallo A, Liccardo R, *et al.* [Contribution of large genomic rearrangements in Italian Lynch syndrome patients: characterization of a novel alu-mediated deletion. Biomed Res Int 2013; id 219897.](#)
25. Vasen HF, Watson P, Mecklin JP, *et al.* [New clinical criteria for hereditary nonpolyposis colorectal cancer \(HNPCC, Lynch syndrome\) proposed by the International Collaborative group on HNPCC. Gastroenterol 1999; 116: 1453-6.](#)
26. de Vos tot Nederveen Cappel W H, Buskens E, van Duijvendijk P, *et al.* [Decision analysis in the surgical treatment of colorectal cancer due to a mismatch repair gene defect. Gut 2003; 52: 1752-75.](#)
27. Lynch PM. [Prevention of colorectal cancer in high-risk populations: the increasing role for endoscopy and chemoprevention in FAP and HNPCC. Digestion 2007; 76: 68-76.](#)
28. Baucom RB, Wise PE. [Endoscopic and Surgical Management of Hereditary Nonpolyposis Colorectal Cancer. Clin Colon Rectal Surg 2012; 25: 90-6.](#)
29. Celentano V, Luglio G, Antonelli G, *et al.* [Prophylactic surgery in Lynch syndrome. Tech Coloproctol 2011; 15\(2\): 129-34.](#)
30. Hampel H, Frankel WL, Martin E, *et al.* [Screening for the Lynch syndrome \(hereditary nonpolyposis colorectal cancer\). N Engl J Med 2005; 352\(18\): 1851-60.](#)
31. Piñol V, Castells A, Andreu M, *et al.* [Accuracy of revised Bethesda guidelines, microsatellite instability, and immunohistochemistry for the identification of patients with hereditary nonpolyposis colorectal cancer. JAMA 2005; 293\(16\): 1986-94.](#)
32. Musulén E, Sanz C, Muñoz-Mármol AM, *et al.* [Mismatch repair protein immunohistochemistry: a useful population screening strategy for Lynch syndrome. Hum Pathol 2014; 45\(7\): 1388-96.](#)
33. Lynch PM. [New issues in genetic counseling of hereditary colon cancer. Clin Cancer Res 2007; 15:13\(22 Pt 2\): 6857s-61s.](#)
34. Schneider R, Rümmele P, Dechant S, *et al.* [Familial non-polyposis colorectal carcinoma \(Lynch syndrome\) in Germany - analysis of information, advisory service and family screening. Dtsch Med Wochenschr 2011; 136\(1-2\): 17-22.](#)

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