

# Lynch Syndrome—It’s Time We Start Detecting It

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## INTRODUCTION

Approximately 5%–10% of all cancers are inherited and approximately 50 inherited cancer syndromes have been recognized till date.<sup>[1]</sup> These inherited cancer syndromes are characterized by an early age of presentation and likelihood of multiple cancers in one individual, several individuals from the same family being the sufferers. Most of the hereditary cancers, with a few exceptions, are transmitted in autosomal-dominant manner with variable penetrance. “Lynch syndrome” and *BRCA* germline mutation-associated “hereditary breast and ovarian cancer syndrome” are two of the most common hereditary cancer syndrome.

Lynch syndrome, also inaccurately known as hereditary nonpolyposis cancer syndrome, is possibly the most common of all hereditary cancer syndromes. It accounts for approximately 5% of all colorectal cancers (CRCs) and equal proportion of endometrial cancers.<sup>[2]</sup> Besides, it also raises the risk of gastric, ovarian, ureteric, renal pelvis, small intestinal, prostate, brain, and sebaceous cancers albeit with relatively low penetrance.

Identifying the patients with Lynch syndrome helps predict prognosis, optimize treatment, plan future surveillance against recurrences, occurrence of second primary, and screen biological relatives to identify mutation carriers who can be counseled to practice risk reduction approaches and live a near-normal life.

Lynch syndrome is divided into two categories: (1) site-specific colonic cancer (Lynch Syndrome I) and (2) extra-colonic cancer (Lynch syndrome II) affecting other sites as mentioned previously.<sup>[3]</sup>

## RISK OF CANCERS IN LYNCH SYNDROME

Lynch syndrome has a high penetrance. Men with Lynch syndrome have a 60%–80% lifetime risk of developing colon cancer. Women have a 40%–60% lifetime risk of developing colon cancer as well as a 40%–60% chance of

developing endometrial cancer.<sup>[4]</sup> The risk of developing cancers of the small bowel, stomach, and ovary is each between 5% and 15%. Hepatobiliary, renal pelvis, urethra, central nervous system, and skin cancers are also observed at a rate of approximately 4% as against less than 1% in general population [Figure 1].<sup>[5]</sup> In addition, there is a 50% risk of having a second cancer within 15 years in the affected patients.<sup>[6]</sup> The high penetrance but fortunately successful means of averting the two most common cancers associated with Lynch syndrome necessitates identifying the carriers. Besides, the high risk of second malignancy in patients of Lynch syndrome, underlines the need to diagnose it and apply appropriate preventive strategies during follow-up.

How can Lynch syndrome be diagnosed depends on clear understanding of its molecular mechanism. It might have been a simple algorithm but for the presence of a sporadic type of CRC associated with an epigenetic phenomenon of CpG island methylation, which shares several mechanistic steps with Lynch syndrome, and the occurrence of MSI, a screening surrogate for both these types of CRC. Let us briefly look at these facts.

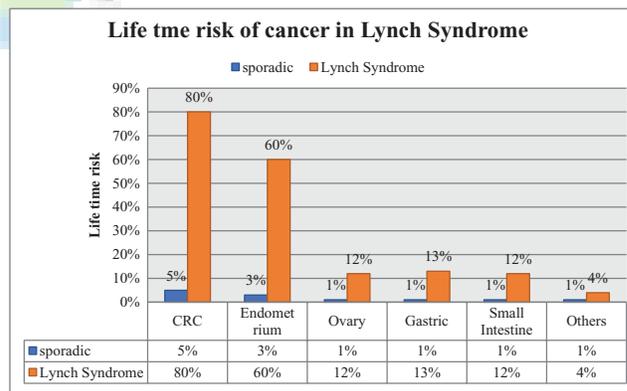


Figure 1: The lifetime risk of different cancer types in Lynch syndrome

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## CRC AND LYNCH SYNDROME I

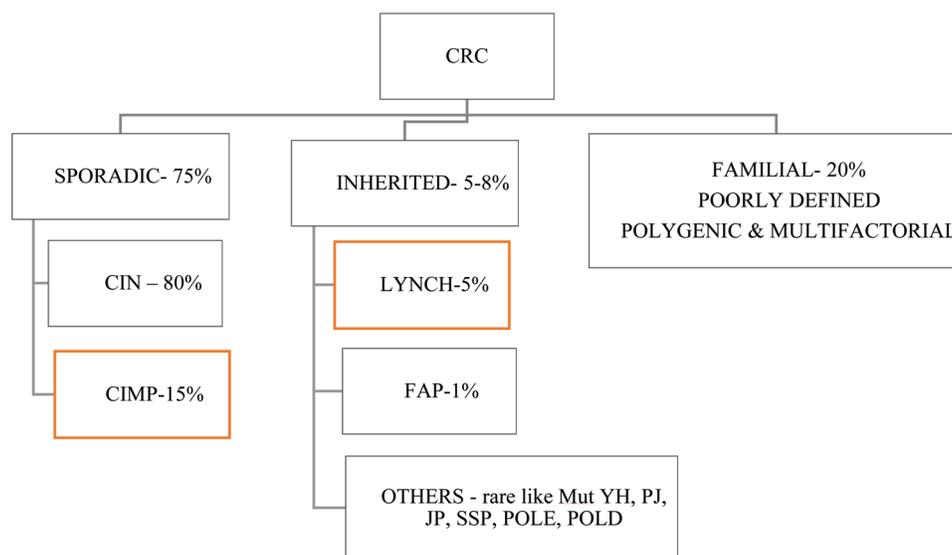
Colorectal carcinoma is the third most common cancer responsible for 10.2% of all newly diagnosed cancers and second worst cause of cancer mortality accounting for 9.2% of all cancer-related deaths as per GLOBOCAN 2018.<sup>[7]</sup>

CRC is divided into three main categories as shown in Figure 2. The CpG island methylator phenotype (CIMP) among sporadic cancers and Lynch syndrome among inherited CRCs are distinctive in being characterized by a genomic alteration, whereby the numbers of microsatellites are altered through the intergenic and intragenic regions of genome. Microsatellites are repeats of 1–6 nucleotides that are polymorphic (variable times the repeats occur) at several sites based on inheritance and are also monomorphic (fixed times the repeats occur) at other sites.<sup>[8]</sup> Their elongation or shortening in tumor tissue beyond a minimum number of additional nucleotide repeats compared to normal tissue is observed in these two types of CRC. This phenomenon of altered microsatellite lengths is called “microsatellite instability” and is the common thread through CIMP-associated CRC and Lynch syndrome. Usually, five microsatellite sites are tested by national cancer institute panel comprising BAT25, BAT26, D2S123, D5S346, and D17S250 or Promega panel comprising BAT-25, BAT-26, NR-21, NR-24, and MONO-27. Instability in a single site is called MSI low (MSI-L) and instability in greater than or equal to two sites is called MSI high (MSI-H). MSI-L is usually a nonspecific change and has rarely been described with *MSH6* germline mutations. Most cases of Lynch syndrome and CIMP CRC are MSI-H. Personal experience with Promega panel has shown that when instability is noted it is observed in most microsatellites.

## GENETICS OF LYNCH SYNDROME

Deoxyribonucleic acid (DNA) is constantly stressed by endogenous and exogenous influences. Maintaining integrity of DNA is one of the prime physiological functions with a third of all genes involved in it. Slippages in incorporation of correct complementary nucleotide during “S” phase of cell cycle often happen. This error is immediately corrected by proofreading ability of DNA polymerase D1, which also has 5’–3’ exonuclease activity with which it removes the wrong nucleotide and replaces it with the appropriate one. Nevertheless, some errors still escape this proofreading. The noncomplementary nucleotides cause a bulge in the helix and invite an additional repair system called “Mismatch Repair (MMR) Pathway.” Essentially, composed of four proteins, MLH1, MSH2, MSH6, and PMS2 and synthesized by the translation of similarly named genes, the mismatch repair system recognizes and repairs these bulges caused by noncomplementarity. A loss of function mutation in any one of these four genes or epigenetic silencing of *MLH1* abrogates the corrective ability of MMR pathway and allows mismatches (mutations) to accumulate a process called “Replication Error Repair (RER)” phenotype. When these mutations affect tumor suppressor genes by deactivating them or involve oncogenes augmenting their functions, transformation and carcinogenesis are initiated.

Germline loss of function mutations in *MLH1*, *MSH2*, *MSH6*, and *PMS2* causes Lynch syndrome. The penetrance and the site affected are different for different genes. More than 90% of Lynch syndrome is caused by *MLH1* and *MSH2* mutations.<sup>[9]</sup> *MSH6* gene mutations have lesser frequency and penetrance, and the cancers have late onset.<sup>[10]</sup> The progression of carcinogenesis in Lynch syndrome is shown in Figure 3.



**Figure 2:** Classification of CRC. CIN = chromosomal instability, FAP = familial adenomatous polyposis, PJ = Peutz–Jegher syndrome, JP = juvenile polyposis, POLE = polymerase E, POLD = Polymerase D, SSP = sessile serrated polyps

## CLINICOPATHOLOGIC PROFILE OF COLONIC CANCER ASSOCIATED WITH LYNCH SYNDROME

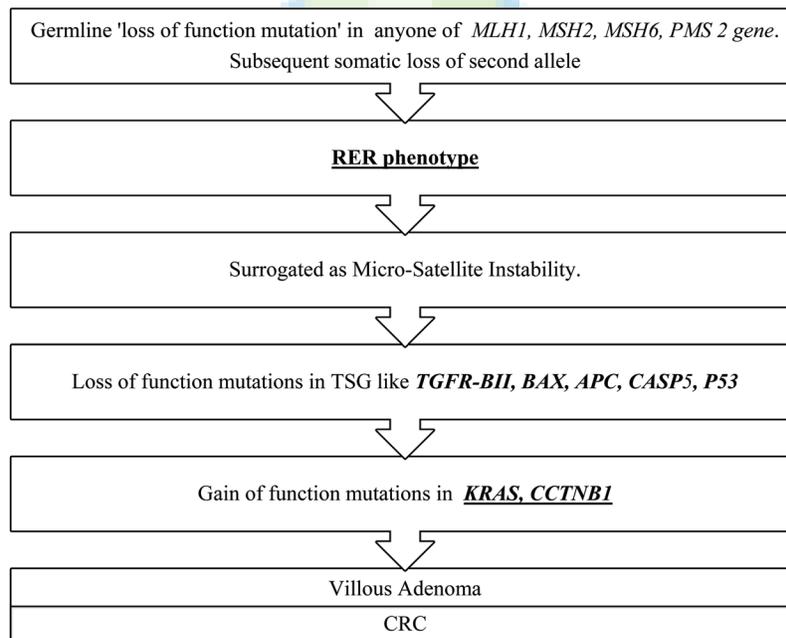
Majority of the CRCs in Lynch syndrome occur on the right side (70%) and are preceded or accompanied with a single or a few villous adenomas.<sup>[11]</sup> The rate of progression from the adenoma to invasive cancer is rapid, usually taking 2–3 years. This knowledge is crucial to decide the interval of follow-up or screening colonoscopy in a patient or a mutation carrier. Despite rapid progression, patients with MSI-H present more often in stage II than in stage III (PETACC-3 trial; 22% vs. 12%).<sup>[12]</sup> In another large study, MSI-H tumors only made up 3.4% of all metastatic CRCs.<sup>[13]</sup> Evidence suggests that stage II disease with MSI-H status is a favorable prognostic marker and possibly also a predictive marker of unlikely benefit from fluoropyrimidine-based treatment.<sup>[14]</sup>

The histomorphology of CRC in Lynch syndrome is mucinous, signet ring cell type, or medullary with tumor infiltrating lymphocytes and a peritumoral rosary bead-like lymphoid infiltrate. The tumor margin is pushing and lacks tumor budding. Classical garland and dirty necrosis pattern is not observed. Lynch CRCs are significantly less positive for CK20 and B catenin. *MUC2*, *MUC5AC*, and *MUC6* expression are more commonly observed.<sup>[15]</sup>

More significantly, these tumors show loss of immunohistochemical staining for one of the four MMR proteins. As MLH1 and PMS2 exist as heterodimer, loss of MLH1 also results in loss of PMS2 immunostaining; however, vice versa is not true and PMS2 loss is noted in isolation. Same phenomenon is observed with MSH2 and MSH6. Loss of MSH2 abolishes the expression of MSH6, whereas MSH6 loss of expression happens in isolation. Table 1 explains the various possible staining patterns and their interpretation.

The deficient MMR (dMMR) protein carries same connotations as MSI [Figure 4]. The sensitivity and specificity of each test to identify RER phenotype are similar and shown in Figure 4.<sup>[16]</sup> Against loss of any one of the MMR protein in Lynch syndrome, only loss of expression of MLH1 happens in CIMP-associated CRC as this gene undergoes epigenetic silencing and manufactures no MLH1 protein. The presence of MSI and dMMR in Lynch as well as in CIMP-associated CRC creates diagnostic complexities and that necessitates understanding the CIMP pathway of CRC.

Although germline mutations are responsible for Lynch syndrome, somatic methylation of CpG island in promoter sequence of MLH1 and consequent silencing of this gene create RER and CIMP types of sporadic CRC.



**Figure 3:** Germline mutations in *MMR* gene initiate a cascade that terminates in CRC. Note that pathway transits through a classical villous adenoma. TSG = tumor suppressor genes

Table 1: Interpretation of IHC results for IHC staining of MMR proteins					
Protein	MLH1	PMS2	MSH2	MSH6	Interpretation
Status	Loss	Loss	Present	Present	Loss of MLH1 protein
	Present	Loss	Present	Present	Loss of PMS2 protein
	Present	Present	Loss	Loss	Loss of MSH2 protein
	Present	Present	Present	Loss	Loss of MSH6 protein

## CIMP PATHWAY OF CRC

CpG island are repeats of C and G nucleotides bound by phosphodiester bond (and hence the intervening p of CpG) and lie upstream of a gene in promoter region. The methylation of these island suppresses the transcription of gene and result in the absence of corresponding protein. Global hypermethylation and hypomethylation characterizes certain cancers with a unique pattern in a specific cancer type. The cause of this methylation is not known but is ascribed to aging, folate deficiency, alcohol abuse, and smoking.<sup>[17]</sup> The sequence of events leading to CRC through CIMP pathway are shown in Figure 5.

An important point to stress here is the presence of BRAF V600E in 75% of CIMP CRCs.<sup>[18]</sup> This genetic alteration is not observed in Lynch syndrome-associated CRCs and is of great value in separating the two conditions.

## DIAGNOSIS OF LYNCH SYNDROME

Despite the numerous available clinical criteria such as Amsterdam criteria, Amsterdam criteria 2, Bethesda guidelines, and revised Bethesda guidelines proposed for Lynch syndrome screening, none has performance characteristics as would be desired of a screening methodology. Many predictive computational models have

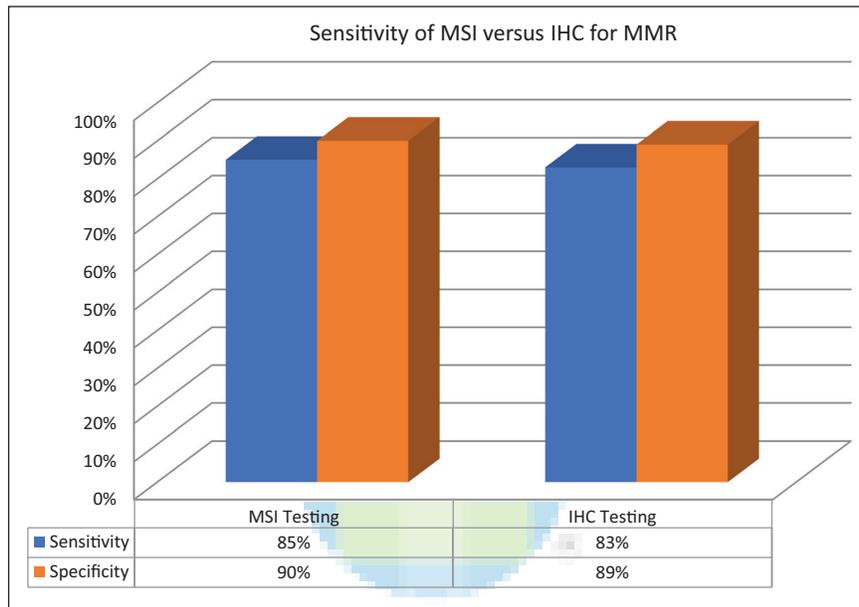


Figure 4: Comparability of sensitivity and specificity of MSI and MMR

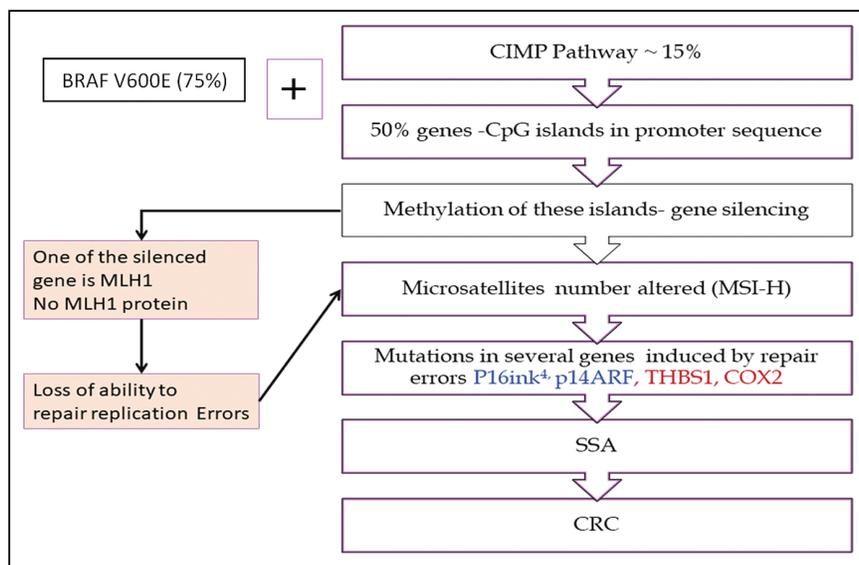


Figure 5: The sequence of events in CIMP pathway of colorectal carcinogenesis. Note the CRC precedes sessile serrated adenoma (SSA). Please also note that nearly 75% of CIMP CRC are associated with BRAF V600E mutation. P16ink4 and P14ARF are tumor suppressor genes and THBS1 and COX2 are oncogenes. While the former undergo loss of function mutations the latter are mutated to overactive state

also been used to select patients with the likelihood of Lynch syndrome but none of these has shown adequate sensitivity. The contemporary practice as enunciated in national comprehensive cancer network guidelines requires universal screening of patients of CRC for Lynch syndrome.<sup>[19]</sup>

Currently, the most cost-effective and best screening strategy is filtering in patients with MSI-H or patients deficient in MMR proteins (dMMR) for further definitive testing. These two screening methods used alone have 100% sensitivity and 93% specificity. The widespread availability of immunohistochemistry (IHC), ease of testing and validation, cost-effectiveness, and identifying the awry gene has made testing for MMR proteins a preferred method in most laboratories.

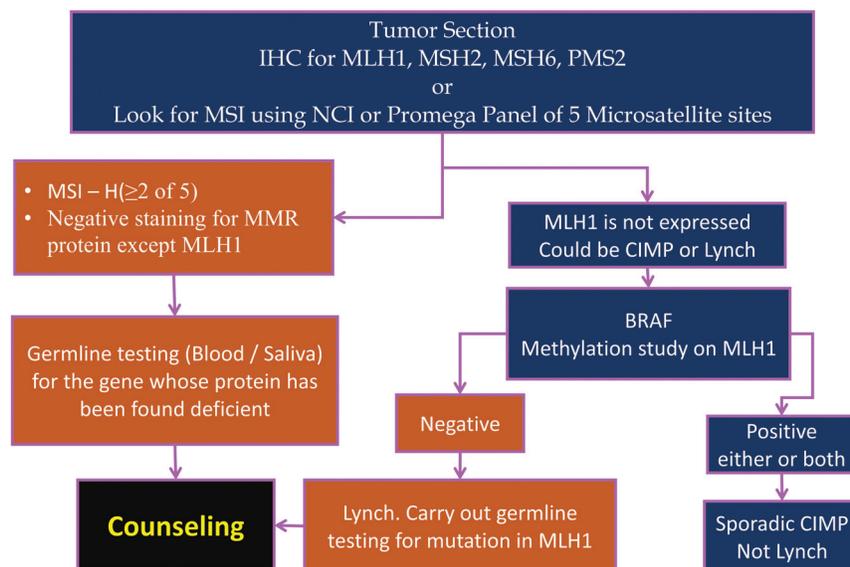
A practical and simple diagnostic algorithm excluding some rare and complex issue of germline epigenetic MLH1 methylation, biallelic somatic mutations in *MMR* gene without a germline mutation and Lynch syndrome-like features, inversion of exon 1–7 in *MSH2* gene in a small geographically defined population, and *EPCAM* gene deletion (all combined are extremely rare) is shown in Figure 6.

It is evident from this schema that all cases found to have MSI-H will need to undergo germline testing for *MLH1*, *MSH2*, *PMS2*, and *MSH6*. Contrarily, the IHC testing for dMMR identifies the likely gene to be mutated and hence, the germline testing can be focused on that single gene.

The germline testing is best conducted on next generation sequencing and deletion/duplication analysis. However, large genomic rearrangements need multiplex ligation probe amplification assay (MLPA). The genetic testing is expensive and requires specialized laboratory proficient in next-generation sequencing and MLPA. This said, there are definite benefits of performing the genetic testing and must

be offered to the patients who screen positive after MSI-H or dMMR. The gains of testing for the patient and relatives are enormous and cannot be overemphasized. It is for these reasons that we must start detecting Lynch syndrome in our clinical practice. These benefits are enumerated as follows:

1. A genetic germline test revealing a pathogenic mutation confirms the Lynch syndrome and defines high risk of recurrence and second primary in a long-term survivor. A careful and detailed surveillance program will need to be followed lifelong.
2. It is important to mention here that only 60% of patients with MSI-H/dMMR tumors without “*BRAF V600E* mutation” and “methylation genotype” reveal germline mutations. For the rest 40% without germline mutation in the MMR gene are eluded as “Lynch-like syndrome.” Two-third of these Lynch-like syndrome reveal biallelic somatic mutations in *MMR* genes. Somatic testing at this point of time is not recommended. Whether intensive lifelong surveillance is necessary for this group of patients is unknown.
3. The group with CIMP-associated CRC need no extra follow-up than other patients of CRC.
4. The specific pathogenic mutation identified in the patient acts as a founder mutation for this family and a simple site-specific testing should be offered to all relatives at risk after due genetic counseling.
5. Vigorous surveillance and management can then be recommended for healthy mutation carriers who test positive for the family-specific pathogenic mutation.
6. Genetic testing needs only a simple blood draw.
7. Most significant reason for germline testing of a patient is to identify the pathogenic mutation and use this mutation as a screen for all relatives at risk. This smaller site-specific, cost-efficient screening test compared to performing the entire germline analysis on all possible



**Figure 6:** The diagnostic algorithm for Lynch syndrome. Germline testing is carried out on blood/saliva

high-risk relatives is a far more cost-effective way to identify mutation carriers, especially in light of high prevalence of Lynch syndrome. This has the potential to save several lives and cost of treating invasive cancers.

## ENDOMETRIAL CARCINOMA AND LYNCH SYNDROME II

Endometrium is the second most common site for Lynch syndrome-associated cancer. Endometrial cancers with *MMR* mutations have aggressive morphology, prominent peritumoral lymphocytes, tumor-infiltrating lymphocytes, and tumor heterogeneity. Lower uterine segment appears to be a preferred site in many studies though not in all.<sup>[20-22]</sup> Survival is better despite higher grade and stage at presentation.

Akin to CRCs, the endometrial cancers with MSI-H and dMMR also have the differential of CIMP-associated endometrial cancer and Lynch syndrome. The diagnostic algorithm is same as for CRC [Figure 6]. One important difference is that CIMP-associated endometrial cancers are not associated with *BRAF V600E* mutation, and methylation genotyping is essential to separate the CIMP-associated MSI-H, MLH1 dMMR tumors.

Given the high incidence of Lynch syndrome-associated endometrial cancers, a universal testing has been recommended.

## CONCLUSION

Prevalence of germline *MMR* mutation is not uncommon. High penetrance of these cancer-causing mutations creates high risk of CRC and endometrial cancers and high-moderate- and low-moderate-risk of several other malignancies. Identification of Lynch syndrome in a patient can greatly improve the oncological outcomes. This patient acting as a proband allows testing of first-degree relatives with 50% probability of identifying pathogenic germline mutations in them. With appropriate surveillance and risk-reduction protocols, these individuals can achieve near normal longevity. Genotypic screening is preferred over phenotypic screening (guidelines and prediction tools) for reasons of much higher sensitivity. Universal genotypic screening with MSI or IHC for *MMR* protein is recommended for patients of CRC and endometrial cancer as nearly 5% of them are Lynch syndrome associated. Though universal testing appears more costly, it is also more effective.

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## Conflicts of interest

There are no conflicts of interest.

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