Germline diagnosis of Lynch syndrome in mismatch repair-deficient colorectal cancer: A case series from Bach Mai Hospital

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Abstract:

Lynch syndrome (LS) is the most common hereditary cause of colorectal cancer (CRC) but is frequently missed by family-history-based criteria. We report an immunohistochemistry (IHC)-triggered, next-generation sequencing (NGS)-confirmed diagnostic pathway for LS in patients with mismatch repair-deficient (dMMR) CRC at Bach Mai Hospital in 2025. Three *BRAF* V600E wild-type dMMR CRC patients underwent germline NGS, and a molecular diagnosis of Lynch syndrome was established in two. Case L1, a 41-year-old man with a poorly differentiated descending-colon adenocarcinoma, carried a pathogenic *MLH1* frameshift variant (c.793del, p.Arg265ValfsTer3). Case L2, a 33-year-old man with synchronous transverse-colon and splenic-flexure tumours, carried a likely pathogenic *MSH2* missense variant (c.1865C>G, p.Pro622Arg); a preoperative biopsy showed proficient MMR whereas the resection showed *MSH2/MSH6* loss, illustrating clonal MMR heterogeneity. The third patient (Case N1) had *MLH1/PMS2* loss but no detectable germline variant, consistent with a possible Lynch-like syndrome pending methylation testing. In each patient, the IHC loss pattern correctly directed germline testing. These cases support germline testing of all dMMR colorectal cancers independent of family history and highlight the genetic-counselling and cascade-testing implications for probands and at-risk relatives.

Keywords: **colorectal cancer, immunohistochemistry, Lynch syndrome, mismatch repair deficiency, next-generation sequencing.**

Classification numbers: **3.2, 3.6**

1. Introduction

Lynch syndrome (LS) is the most common hereditary cause of colorectal cancer (CRC), accounting for approximately 3% of all cases [1]. It is an autosomal dominant disorder caused by germline pathogenic variants in the DNA MMR genes (*MLH1*, *MSH2*, *MSH6*, and *PMS2*) or by deletions in *EPCAM*. The MMR system corrects base-base mismatches and insertion-deletion loops that arise during DNA replication, so loss of this function causes microsatellite instability (MSI) and a deficient MMR (dMMR) phenotype. Carriers face a high lifetime risk of colorectal, endometrial, and other malignancies; importantly, this risk is markedly reduced when carriers are identified early and entered into risk-adapted surveillance, which makes timely diagnosis of the proband and cascade testing of at-risk relatives a clinical priority [2].

Selection for genetic testing based on personal and family history misses a substantial proportion of carriers, in some analyses more than half [3]. The United States' National Comprehensive Cancer Network (NCCN) and other guidelines therefore recommend universal, tumour-based screening of all colorectal cancers rather than history-based selection [2]: mismatch repair immunohistochemistry (IHC) is applied to colorectal cancer, and germline next-generation sequencing (NGS) confirms the diagnosis in tumours that show dMMR, irrespective of age or family history. We accordingly report three patients with mismatch-repair-deficient colorectal cancer ascertained through this reflex immunohistochemistry-to-NGS pathway at Bach Mai Hospital in 2025: two in whom germline sequencing established a genetic diagnosis of LS (a pathogenic *MLH1* variant and a likely pathogenic *MSH2* variant), and one

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in whom no germline variant was identified despite loss of *MLH1* and *PMS2*.

2. Materials and methods

2.1. Study design and setting

This was a retrospective, single-centre case series conducted at Bach Mai Hospital, Hanoi, Vietnam between January and December 2025. At this centre, mismatch repair IHC is performed on essentially all colorectal cancers; patients whose tumours are mismatch-repair-deficient are counselled about LS and offered germline testing, but uptake of germline sequencing is limited because it is not reimbursed by health insurance; consequently, few patients complete germline testing. Patients with histopathologically confirmed colorectal cancer showing dMMR on immunohistochemistry, in whom the somatic *BRAF* V600E mutation had been excluded, were eligible for germline analysis.

2.2. Case selection

During the study period, three eligible patients underwent germline NGS and constitute this series. Germline pathogenic variants were identified in two (Cases L1 and L2), who are presented in detail; no sequence variant was detected in the third (Case N1), who is summarised for context.

2.3. Molecular workup

Mismatch repair status was assessed by IHC for the four MMR proteins (*MLH1*, *MSH2*, *MSH6*, and *PMS2*) on tumour specimens; loss of expression of one or more proteins defined the dMMR phenotype. Somatic *BRAF* V600E mutation testing was performed by PCR on tumour material from all three patients; all were wild-type. Eligible patients then provided peripheral blood for germline DNA extraction, and germline variants were analysed by targeted NGS using an IVD-marked, multi-gene diagnostic panel (SOLIDaccuTest DNA, NgeneBio, South Korea) that includes the mismatch repair genes (*MLH1*, *MSH2*, *MSH6*, *PMS2*) and *EPCAM*. Variants were reported using the MANE-select transcripts (*MSH2* NM_000251.3; *MLH1* NM_000249.4). Sequencing was performed to a depth adequate for heterozygous variant detection; the two reported variants met the assay's acceptance criteria (read depth ≥30× at the variant position, a variant allele fraction of 30-70%, as expected for a germline heterozygous variant, and passing quality-control metrics); library preparation, alignment, and variant calling followed the manufacturer's validated bioinformatics pipeline. The overall IHC-to-sequencing strategy is consistent with that previously reported by our group, although a different and broader panel was used here [4].

Technical limitations. The sequencing platform employed short-read technology capable of detecting only single-nucleotide variants (SNVs) and small insertions and deletions (indels, up to approximately 10 nucleotides) within the coding regions and the adjacent intronic regions (±10 nucleotides from each exon splice site) of the targeted genes. The panel did not include copy-number variant (CNV) calling and was therefore unable to detect large structural rearrangements, whole-exon deletions or duplications, or 3′ *EPCAM* deletions. MSI testing and *MLH1* promoter hypermethylation analysis were not performed in this study.

2.4. Variant classification

Germline variants were annotated and classified according to the ClinGen InSiGHT Hereditary Colorectal Cancer/Polyposis Variant Curation Expert Panel (VCEP) specifications (version 2.0.0) [5, 6], which define gene-specific evidence-code weights for the MMR genes (*MLH1*, *MSH2*, *MSH6*, *PMS2*) as refinements of the American College of Medical Genetics and Genomics/Association for Molecular Pathology (ACMG/AMP) classification framework.

2.5. Ethical considerations

The study adhered to the ethical principles of the Declaration of Helsinki. The protocol was reviewed and approved by the Institutional Ethics Committee in Biomedical Research of Bach Mai Hospital. Written informed consent was obtained from all participating patients or their legal representatives prior to genetic testing, together with pre- and post-test genetic counselling.

3. Results

3.1. Characteristics and molecular results of the tested patients

During 2025, three patients with dMMR colorectal cancer, all confirmed *BRAF* V600E wild-type, underwent germline NGS and were included in this report. A germline variant was identified in two (Cases L1 and L2); no variant was detected in the third (Case N1). The clinical, pathological, immunohistochemical, and molecular features of all three patients are summarised in Table 1.

Table 1. Clinical, pathological, immunohistochemical, and molecular features of the three dMMR colorectal cancer patients who underwent germline NGS.

Case	Age/sex	Tumour location	Histology/stage	*BRAF* V600E	IHC (MMR loss)	Germline NGS result
L1	41/M	Descending colon	Poorly diff. adenoca; pT3N0M0	Wild-type	*MLH1+PMS2*	*MLH1* c.793del (p.Arg265ValfsTer3), pathogenic
L2	33/M	Transverse colon+splenic flexure (synchronous)	Mod. diff. adenoca (pT4b)+mucinous adenoca (pT2); pT4bN1bM0	Wild-type	*MSH2+MSH6*	*MSH2* c.1865C>G (p.Pro622Arg), Likely pathogenic
N1	58/M	Splenic flexure	Mod. diff. adenoca; pT4a (0/21 nodes); serosal invasion, no LVI/PNI	Wild-type	*MLH1+PMS2*	No variant detected

IHC: immunohistochemistry; MMR: mismatch repair; BRAF: B-Raf proto-oncogene, serine/threonine kinase; LVI: lymphovascular invasion; PNI: perineural invasion.

Case N1 (variant-negative dMMR). A 58-year-old man with a moderately differentiated splenic-flexure adenocarcinoma (pT3N0) showed concurrent *MLH1*/*PMS2* loss with wild-type *BRAF* V600E, but germline sequencing detected no variant. Family history was unremarkable. Because *MLH1* promoter methylation and MSI testing were not performed, this case could not be assigned a definitive sporadic or hereditary aetiology, and a possible Lynch-like syndrome is discussed below.

3.2. Clinical and germline sequencing results of the two variant-carrying index cases

Of the three patients tested, two carried a germline variant and are described in detail; both were younger than 50 years at presentation (Table 2 and Fig. 1).

Case L1. A 41-year-old man with no significant personal or family history underwent computed tomography, which showed irregular wall thickening of the descending colon over a 53-mm segment, and colonoscopy identified a descending-colon tumour with multiple synchronous polyps along the left colon. Postoperative histopathology showed a primary, ulcerated, poorly differentiated adenocarcinoma of the descending colon (approximately 4 cm) invading the subserosa, staged pT3N0M0 (0/52 nodes), with two synchronous tubular adenomas (one high-grade, one low-grade dysplasia). IHC showed concurrent loss of *MLH1* and *PMS2*. Somatic *BRAF* V600E testing returned wild-type. Germline sequencing revealed a heterozygous frameshift variant in *MLH1* (NM_000249.4):c.793del (p.Arg265ValfsTer3), which was classified as pathogenic.

Case L2. A 33-year-old man with no prior history of malignancy presented with synchronous, multifocal colorectal cancer; his family history was notable for a maternal grandfather with colorectal cancer diagnosed at an unknown age. An initial colonoscopic biopsy of a splenic-flexure tumour showed moderately differentiated adenocarcinoma; IHC on this biopsy showed retained expression of all four MMR proteins (proficient MMR). The patient underwent extended right hemicolectomy with wedge gastrectomy. Histopathology of the resected specimen confirmed two synchronous tumours: a moderately differentiated adenocarcinoma of the transverse colon invading the stomach wall (pT4b) and a mucinous adenocarcinoma at the splenic flexure (pT2), with metastasis in 3 of 24 regional lymph nodes (pT4bN1bM0). Repeat IHC on both surgical specimens showed concurrent loss of *MSH2* and *MSH6*, in contrast to the initial biopsy. Somatic *BRAF* V600E testing on the resected tumour returned wild-type. Germline sequencing identified a heterozygous missense variant in *MSH2* (NM_000251.3): c.1865C>G (p.Pro622Arg), classified as likely pathogenic.

Table 2. Detailed pathological, immunohistochemical, and molecular profiles of the two index cases.

Feature	Case L1	Case L2
Age at diagnosis/sex	41/male	33/Male
Family history	None reported	Maternal grandfather with CRC (age unknown)
Tumour location	Descending colon	Synchronous: transverse colon+splenic flexure
Histology	Ulcerated, poorly differentiated adenocarcinoma; 2 synchronous tubular adenomas (high- and low-grade dysplasia)	Mod. diff. adenocarcinoma (pT4b, transverse colon, invading stomach); mucinous adenocarcinoma (pT2, splenic flexure)
Stage	pT3N0M0 (0/52 nodes)	pT4bN1bM0 (3/24 nodes positive)
BRAF V600E	Wild-type	Wild-type
IHC (MMR loss)	*MLH1+PMS2*	Biopsy: all four MMR retained (pMMR); surgical specimen: *MSH2+MSH6* loss
Gene/transcript	*MLH1*/NM_000249.4	*MSH2*/NM_000251.3
cDNA change	c.793del	c.1865C>G
Protein change	p.Arg265ValfsTer3	p.Pro622Arg
Variant type	Frameshift (1-bp deletion)	Missense
Zygosity	Heterozygous	Heterozygous
Classification (ClinGen InSiGHT MMR VCEP v2.0.0)	Pathogenic: PVS1+PM2_Supporting+ PP4_Supporting	Likely pathogenic: PS3+ PM5+PP3+pp4+ PM2_Supporting
ClinVar accession/ classification	VCV000218027; Pathogenic/ Likely pathogenic (5 submitters)	VCV000265573; Pathogenic/Likely pathogenic (5 submitters)

IHC: immunohistochemistry; MMR: mismatch repair; BRAF: B-Raf proto-oncogene, serine/threonine kinase; LVI: lymphovascular invasion; PNI: perineural invasion; VCEP: Variant Curation Expert Panel.

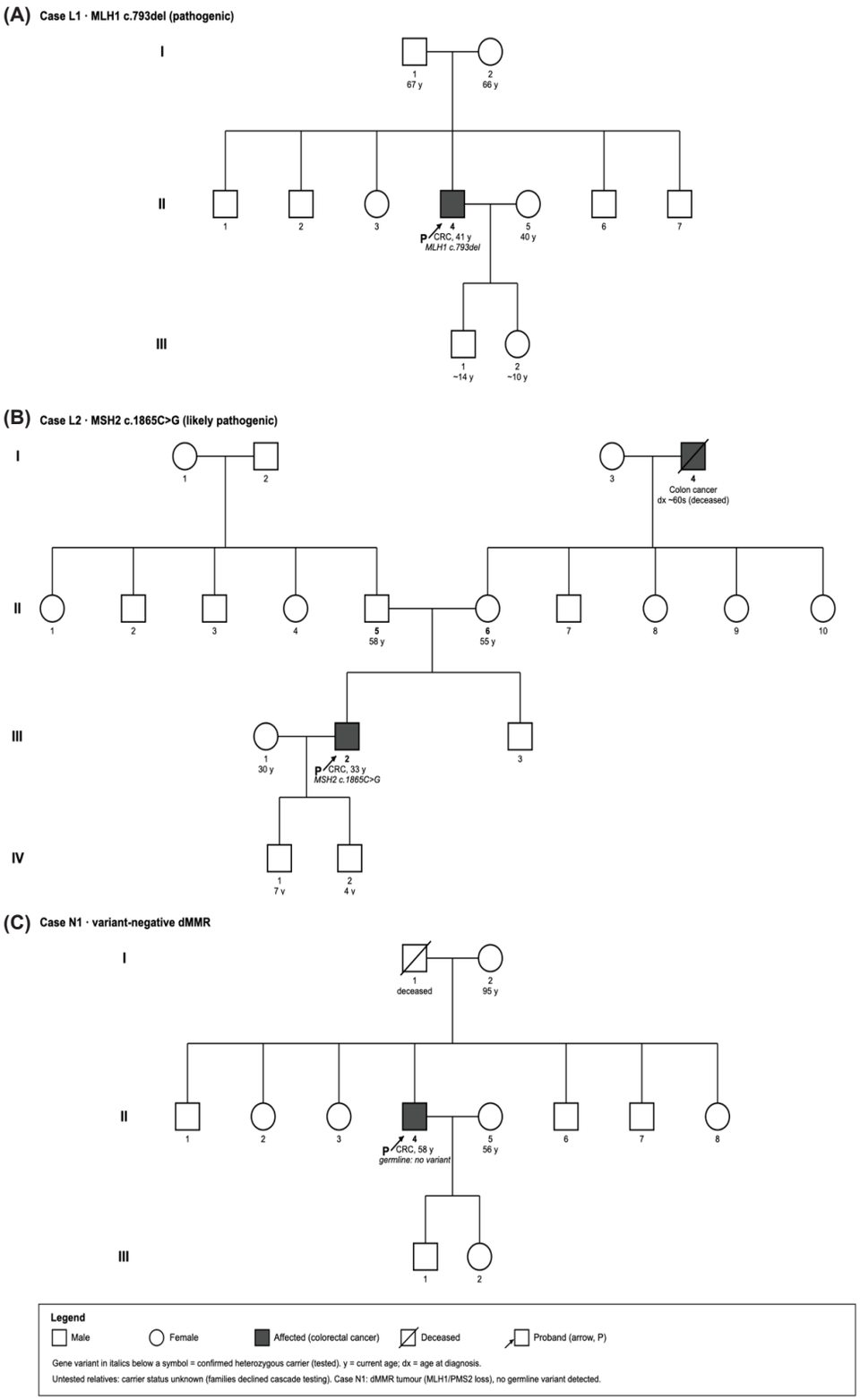

Fig. 1. Pedigrees of the three patients (A, Case L1 - *MLH1*; B, Case L2 - *MSH2*; C, Case N1) drawn to standardised human-genetics nomenclature. Filled symbols=affected (colorectal cancer); diagonal=deceased; arrow=proband; italicised gene variant below a symbol=confirmed heterozygous carrier.

4. Discussion

In this study, targeted germline NGS applied to three patients with *BRAF* V600E wild-type dMMR colorectal cancer established the molecular basis of LS in two: a pathogenic *MLH1* frameshift variant (Case L1) and a likely pathogenic *MSH2* missense variant (Case L2). Both probands were younger than 50 years and were ascertained through the IHC-triggered pathway. The biopsy-versus-resection MMR discordance in Case L2 provides an instructive example of clonal intratumoural MMR heterogeneity in LS, and the variant-negative case N1 illustrates the diagnostic gap left by a sequencing-only panel. These cases support the NCCN-endorsed universal screening pipeline of mismatch-repair IHC for all colorectal cancers and germline testing for dMMR, *BRAF* V600E wild-type tumours. They also highlight the molecular-genetic, counselling, and cascade-testing implications of this approach in a Vietnamese clinical setting.

Variant interpretation followed the ClinGen InSiGHT Hereditary Colorectal Cancer/Polyposis VCEP specifications (version 2.0.0), which refine the ACMG/AMP evidence-code weights for the MMR genes [6]. The *MLH1* variant c.793del (p.Arg265ValfsTer3) is a

single-nucleotide deletion producing a frameshift with a premature termination codon at codon 267, well upstream of the VCEP nonsense-mediated-decay threshold (codon 753), and is therefore predicted to undergo nonsense-mediated decay. As a null variant in a gene where loss of function is the established disease mechanism, it meets PVS1 at the Very Strong level, together with PM2_Supporting (absent or extremely rare in gnomAD v4). The concurrent *MLH1*/*PMS2* loss, which is consistent with the variant location, supports the tumour-phenotype criterion (PP4). This application of PP4 based on tumour phenotype is consistent with expert-panel practice for *MLH1* null variants. The variant is absent from the published literature and the InSiGHT database, but it is recorded as pathogenic/likely pathogenic in ClinVar by five clinical laboratories. The combination of PVS1, PM2_Supporting and PP4 therefore classifies the variant as pathogenic.

The *MSH2* variant c.1865C>G (p.Pro622Arg) is supported under the same framework by one strong and three moderate lines of evidence. The functional evidence is decisive: in a massively parallel assay of mismatch-repair activity, X. Jia, et al. (2021) [7] scored p.Pro622Arg as functionally abnormal (loss-of-function score 1.88, above the abnormal threshold of 0.4); this assay has been approved by the ClinGen InSiGHT MMR VCEP for application at the strong level for the PS3 criterion (PS3) [5]. Three additional criteria apply: PM5, because a different pathogenic missense change at the same residue (p.Pro622Leu) is an InSiGHT class 5 variant; PP3, because the gene-specific HCI-PRIORS meta-predictor returns a prior probability of 0.90; and PP4 with concurrent *MSH2*/*MSH6* loss on IHC, consistent with an *MSH2* variant. Together with PM2_Supporting (rarity in gnomAD), this combination is classified as likely pathogenic, in agreement with the aggregate ClinVar and LOVD classifications. Cascade segregation analysis, if performed, would be expected to support a pathogenic classification.

A notable feature of Case L2 was the discordance between the pre-operative biopsy, which retained all four MMR proteins, and the resection specimens, which showed concurrent loss of *MSH2* and *MSH6*. The most likely explanation is intratumoural clonal heterogeneity arising from the two-hit mechanism: because the somatic second event inactivating the wild-type *MSH2* allele is acquired clonally during tumour evolution, MMR-proficient and MMR-deficient clones may coexist within the same tumour, and a limited biopsy may sample predominantly proficient tissue, as has been reported for several MMR genes [8-10]. An alternative explanation that cannot be fully excluded is that the biopsy sampled a different tumour region, or even a distinct lesion, rather than an MMR-proficient clone of the same tumour; notably, the histological phenotype also differed between the biopsy (moderately differentiated adenocarcinoma) and the resected splenic-flexure specimen (mucinous adenocarcinoma). Regardless of mechanism, this case reinforces the principle that a single MMR-proficient biopsy does not exclude dMMR at the whole-tumour level, and confirmation on the resection specimen (or supplementary MSI analysis) is advisable before germline testing is deferred on the basis of a proficient biopsy alone [9, 10].

The tumours in both cases showed features characteristic of MMR deficiency, such as poor differentiation, a mucinous component, and synchronous adenomas, which should themselves prompt consideration of a hereditary syndrome [8]. Carriers of pathogenic variants in either gene face a substantially elevated lifetime risk of colorectal and other Lynch-spectrum cancers.

These two cases illustrate the gene-IHC concordance that underlies the value of IHC as a directing screen: *MSH2*/*MSH6* loss in Case L2 guided germline testing to *MSH2*, and *MLH1*/*PMS2* loss in Case L1 guided testing to *MLH1*, patterns consistent with the established IHC-genotype correlations for LS [2, 11]. Family-history-based selection, by contrast, would not have flagged either patient for germline referral: Case L1 had no reportable family history, and Case L2 had only a single affected second-degree relative. This highlights the value of tumour-based screening independent of family history [2].

In the third patient (Case N1), who showed loss of *MLH1* and *PMS2* but no detectable germline variant, a definitive sporadic origin cannot be established. Confirmation of *BRAF* V600E wild-type status substantially reduces, but does not exclude, the probability of sporadic *MLH1* promoter hypermethylation; direct methylation testing was not performed and would be required to resolve the

aetiology of the *MLH1/PMS2* loss. In addition, because the sequencing panel detects only SNVs and indels and not copy-number variants or large rearrangements, a germline large rearrangement cannot be excluded. This patient is therefore best regarded as genetically unresolved rather than Lynch-syndrome-excluded, and illustrates a diagnostic gap. By current definitions, Case N1 may represent Lynch-like syndrome; however, this cannot be established without *MLH1* methylation and MSI testing, since a wild-type *BRAF* result does not exclude a methylated sporadic tumour.

The principal downstream value of these diagnoses is genetic. Each proband is an index case for cascade testing, and targeted testing of the family-specific variant is recommended for at-risk relatives, enabling risk-stratified surveillance for carriers and release from intensive screening for non-carriers. Post-test genetic counselling was provided to all three families, and cascade germline testing of at-risk relatives was recommended; however, the families elected clinical surveillance and follow-up rather than predictive germline testing of relatives. The dMMR/MSI-high phenotype additionally predicts potential responsiveness to immune checkpoint inhibitor therapy, providing therapeutic context for the probands.

Two recent Vietnamese studies from a single Ho Chi Minh city centre provide local context. In a cross-sectional series of 190 colorectal cancer patients offered universal germline testing without an IHC gate, C.B. Huynh, et al. (2025a) [12] diagnosed LS in 12 (6.3%), with *PMS2* the most frequent gene (5/12, 41.7%), followed by *MSH2* (3/12, 25%), *MLH1* (2/12, 16.7%) and *MSH6* (2/12, 16.7%); 7 of 12 carriers (58.3%) reported no family history of colorectal cancer. A companion cost-utility analysis by the same group found both an IHC-triggered germline pathway and a germline-first strategy to be cost-effective in the Vietnamese healthcare system [13]. Our cases exemplify the IHC-triggered pathway shown to be cost-effective, while the variant-negative Case N1 illustrates the imperfect specificity of IHC. They also broaden the reported Vietnamese mismatch-repair mutation spectrum, adding a pathogenic *MLH1* frameshift and a likely pathogenic *MSH2* missense variant.

This study also has several limitations. First, Sanger confirmation of the two variants was not performed. However, both were detected with an IVD-marked NGS diagnostic assay and met the assay's acceptance criteria (read depth ≥30×, a variant allele fraction of 30-70%, and passing quality-control metrics), supporting their analytical validity. Both the NCCN and the ClinGen InSiGHT MMR VCEP recommend *MLH1* promoter-methylation testing to increase the specificity of the dMMR phenotype in *MLH1/PMS2*-deficient tumours, because somatic *BRAF* V600E is present in only approximately 69% of *MLH1*-methylated colorectal cancers; thus, a wild-type *BRAF* result does not exclude *MLH1* promoter methylation [2]. The SNV/indel-only panel cannot detect large rearrangements, CNV, or 3′ *EPCAM* deletions, so a negative result does not exclude LS. Additionally, the series is small (n=3), single-centre, and retrospective, which limits generalisability to the broader Vietnamese CRC population. Future directions should include continued genetic counselling and cascade germline testing for at-risk relatives, *MLH1* promoter hypermethylation testing, large-rearrangement detection, and expansion to a prospective, multicentre cohort to characterise the prevalence and spectrum of LS among dMMR colorectal cancers in Vietnam.

5. Conclusions

In two patients with dMMR colorectal cancer, an IHC-triggered germline NGS pathway established a molecular diagnosis of LS, with the IHC loss pattern correctly predicting the affected gene in each case: a pathogenic *MLH1* frameshift variant and a likely pathogenic *MSH2* missense variant. A third patient with *MLH1/PMS2* loss and no detectable germline variant remained genetically unresolved, consistent with a possible Lynch-like syndrome pending methylation testing. These cases support universal mismatch-repair immunohistochemistry screening of all colorectal cancers, with reflex germline sequencing for dMMR, *BRAF* V600E wild-type tumours, regardless of age or family history, supported by structured genetic counselling and cascade testing for probands and at-risk relatives. Closing the principal diagnostic gaps (MSI, *MLH1* promoter methylation, large-rearrangement testing, and *EPCAM* testing) would ensure that LS is neither missed nor left unresolved.

CRediT author statement

Phuc Hong Dinh: Conceptualisation, Investigation, Writing original draft; Phuong Cam Pham, Mai Bich Bui: Investigation, Resources, Data curation; Ha Thi Vu, Phuong Thi Kim Doan: Conceptualisation, Supervision, Writing - Review and Editing.

Declaration of Generative AI and AI-assisted technologies

During the preparation of this article, the authors used Claude (Anthropic) to improve the language, grammar, and readability of the text. After using this tool, the authors reviewed and edited the content as needed and took full responsibility for the content of the publication.

COMPETING INTERESTS

The authors declare that there is no conflict of interest regarding the publication of this article.

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