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Germline Mismatch Repair Variant Detection and Surveillance Outcomes in Patients with Lynch Syndrome: A Review

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Abstract

Lynch syndrome is the commonest inherited cause of colorectal cancer, and carriers are enrolled in colonoscopic surveillance on the assumption that removing adenomas prevents cancer. Prospective data show cancers continuing to occur at high rates despite that surveillance, and no advantage from shortening the interval.

Objectives: *To review the published evidence on germline mismatch repair variant detection and surveillance outcomes in Lynch syndrome: how carriers are identified, what cancer risk each gene confers, what colonoscopic surveillance achieves, and why shorter intervals have not delivered what was expected.*

Material and Methods: *Narrative review of prospective cohort reports, registry analyses, comparative surveillance studies and society guidelines indexed in PubMed and the major gastroenterology and genetics journals. Studies were eligible if they reported gene-specific cancer risk in variant carriers, the yield or performance of detection strategies, or outcomes of colonoscopic surveillance. No new patient data were generated; every estimate quoted is one published by the original investigators.*

Results: *Among 8,500 carriers under colonoscopic surveillance, cumulative colon cancer risk by age 65 was 48.4, 41.5, 12.7 and 9.5 per cent in men and 36.3, 29.8, 10.1 and 2.8 per cent in women for path_MLH1, path_MSH2, path_MSH6 and path_PMS2 respectively. Rectal cancer followed a different ordering, highest in path_MSH2 at 12.6 per cent in men. In 6,350 carriers, no significantly increased cancer risk was demonstrated for path_PMS2, and path_MSH6 behaved as a sex-limited trait with high endometrial but only modestly raised colorectal risk. Among 218 cancers diagnosed during surveillance, the proportion presenting at stage III or IV did not differ by time since the previous colonoscopy, at 16.7, 19.4, 9.9 and 15.1 per cent across intervals of under 1.5, 1.5 to 2.5, 2.5 to 3.5 and over 3.5 years (p = 0.34).*

Conclusion: *Gene-specific risk differs enough that a single surveillance protocol for all carriers is not defensible, and current guidelines have moved accordingly. The absence of any stage or incidence benefit from shorter intervals suggests that colorectal cancer in this syndrome does not always arise through a slow adenoma sequence, which is the premise surveillance was built on.*

Abbreviations: *LS – Lynch Syndrome, MMR – Mismatch Repair, path_MMR – Pathogenic Mismatch Repair Variant, CRC – Colorectal Cancer, MSI – Microsatellite Instability, dMMR – Deficient Mismatch Repair, IHC – Immunohistochemistry, EPCAM – Epithelial Cell Adhesion Molecule, PLSD – Prospective Lynch Syndrome Database, EHTG – European Hereditary Tumour Group, ESCP – European Society of Coloproctology, AJCC – American Joint Committee on Cancer.*

Keywords: *Lynch Syndrome; Mismatch Repair; Colonoscopic Surveillance; Gene-Specific Risk; Colorectal Cancer*

Introduction

Lynch syndrome is an autosomal dominant cancer predisposition caused by a pathogenic germline variant in one of the mismatch repair genes MLH1, MSH2, MSH6 or PMS2, or by epigenetic silencing of MSH2 through deletion in EPCAM [1,2]. It affects roughly one person in 300 in Western populations [3] and accounts for a few per cent of all colorectal cancer, though most carriers remain undiagnosed [4].

The syndrome was described from family clustering [5,6,7], and detection now rests on tumour features rather than family history. Cancers arising in carriers show mismatch repair deficiency and microsatellite instability, so universal tumour testing by immunohistochemistry or instability analysis, with reflex testing to exclude sporadic MLH1 silencing, is recommended for newly diagnosed colorectal and endometrial cancers [4,8]. Universal testing

of consecutive colorectal cancers identified carriers who would have been missed by family-history criteria, which is the finding that moved practice toward testing everyone [25].

Once identified, carriers enter colonoscopic surveillance. The rationale is the adenoma-carcinoma sequence [9]: if precursor lesions are removed before they progress, cancer should be prevented. Early family studies supported this, with three-yearly colonoscopy reported to reduce incidence and mortality substantially [10], and guidelines subsequently shortened the interval to one or two years on the assumption that more frequent examination would do better [2,11].

Prospective data have not borne that out. This review sets out what gene-specific risk actually is under surveillance, what shortening the interval has achieved, and what the discrepancy implies about how these cancers arise.

Material and Methods

Search strategy: PubMed and the archives of the major gastroenterology, genetics and surgical journals were searched for studies of variant detection and surveillance in Lynch syndrome. Search terms combined Lynch syndrome and hereditary non-polyposis colorectal cancer with mismatch repair, MLH1, MSH2, MSH6, PMS2, EPCAM, universal tumour screening, colonoscopy interval, surveillance and cancer risk. Reference lists of retrieved registry reports and guidelines were screened by hand.

Eligibility: Studies were included if they reported gene-specific cancer risk in defined carrier populations, the yield or accuracy of detection strategies, or clinical outcomes of colonoscopic surveillance. Prospective registry reports were preferred over retrospective series where both addressed the same question, and the design is identified in every case.

Data extraction and handling: Design, cohort size, follow-up duration, variant classification criteria and reported risk or outcome estimates were extracted as published. Gene and sex are reported alongside every risk figure, because pooled estimates across genes conceal differences large enough to change management. No pooling or re-analysis was performed and no patient-level data were obtained. Figures 1 to 4 and Tables 1 to 3 reproduce published values only. This is a narrative synthesis and was not registered as a systematic review.

Results

The four genes are four different diseases: Prospective follow-up of 8,500 carriers across 25 countries, providing 76,289 observation years, produced gene-specific and sex-specific risk estimates under active surveillance. Cumulative colon cancer risk by age 65 was 48.4 per cent in men and 36.3 per cent in women for path_MLH1, 41.5 and 29.8 per cent for path_MSH2, 12.7 and 10.1 per cent for path_MSH6, and 9.5 and 2.8 per cent for path_PMS2 (Figure 1) [12].

Rectal cancer followed a different ordering, with path_MSH2 carrying the highest risk at 12.6 per cent in men and 7.6 per cent in women, against 6.0 and 4.6 per cent for path_MLH1 (Figure 4) [12]. In the earlier report of 6,350 carriers, path_MLH1 and path_MSH2 shared similar colorectal, endometrial and ovarian risks, but older path_MSH2 carriers had higher risks of upper urinary tract, upper gastrointestinal, brain and particularly prostate cancer. Pathogenic MSH6 variants behaved as a sex-limited trait, with high endometrial cancer risk but only modestly raised colorectal risk, and no significantly increased cancer risk was demonstrated for path_PMS2 carriers at all [13].

That last finding matters for how variants are classified. Criteria for identifying Lynch syndrome were developed assuming uniformly high penetrance, which holds for neither MSH6 in men nor PMS2 in either sex [13,14]. Carriers are ascertained unevenly as a result: path_MLH1 and path_MSH2 together accounted for 80.4 per cent of the 6,350-carrier cohort and path_PMS2 for 6.4 per cent (Figure 3) [13].

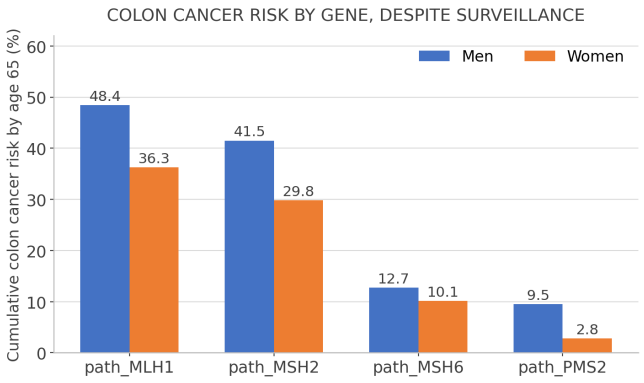

Figure 1: Cumulative colon cancer risk by age 65 by gene and sex among carriers under colonoscopic surveillance [12]

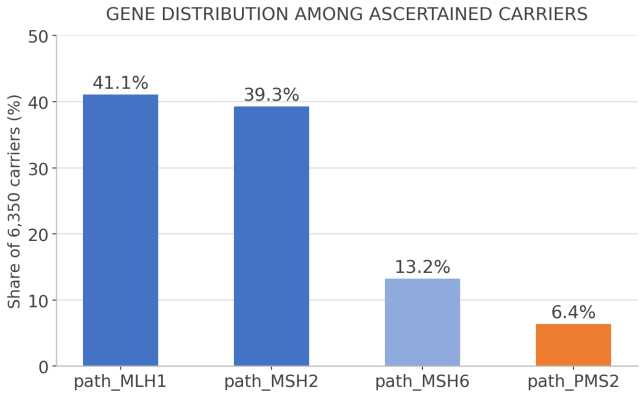

Figure 3: Distribution of pathogenic variants among 6,350 ascertained carriers [13]

Study	n	Design	Principal reported finding
Järvinen et al. [10]	—	Controlled	Three-yearly colonoscopy reduces incidence and mortality
Seppälä et al. 2017 [15]	—	Registry	Incidence similar across follow-up protocols in MLH1
Engel et al. 2018 [16]	—	Three countries	No difference in incidence or stage by national policy
ten Broeke et al. 2018 [14]	—	Registry	PMS2-associated risks lower than assumed
Seppälä et al. 2019 [17]	218	Registry	Stage independent of interval since last colonoscopy
Dominguez-Valentin 2020 [13]	6,350	Prospective	Gene-specific risks; no excess risk shown for PMS2

Table 1: Principal studies reviewed, with design and the finding as reported by the original investigators

Shorter intervals have not helped: The expectation that more frequent colonoscopy would reduce cancer has been tested repeatedly and not confirmed. A comparison across three countries operating different national surveillance policies found no difference in colorectal cancer incidence or stage at detection [16], and within a

single registry, path_MLH1 carriers followed under different protocols showed similar incidence [15].

The stage analysis is the most pointed. Among 218 cancers diagnosed during prospective surveillance in 209 patients, the numbers detected within under 1.5, 1.5 to 2.5, 2.5 to 3.5 and more than 3.5 years of the previous colonoscopy were 36, 93, 56 and 33. The proportions presenting at stage III or IV were 16.7, 19.4, 9.9 and 15.1 per cent respectively, with no significant difference across intervals (p = 0.34), and cancers found more than 2.5 years after the last examination were not more advanced than those found earlier (p = 0.14) (Figure 2) [17].

If a longer gap does not produce later-stage disease, the cancers being found are not straightforwardly the product of missed or slowly progressing precursor lesions. The investigators raised the possibility of over-diagnosis, drawing an explicit parallel with mammographic screening [17,18], and suggested that some lesions in carriers may regress under host immune pressure [17].

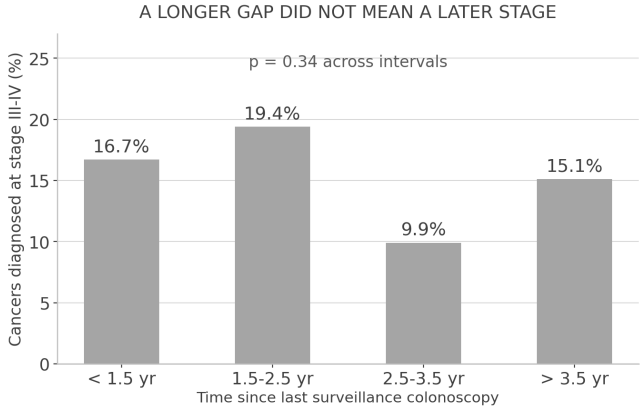

Figure 2: Proportion of cancers presenting at stage III or IV by time since the previous surveillance colonoscopy [17]

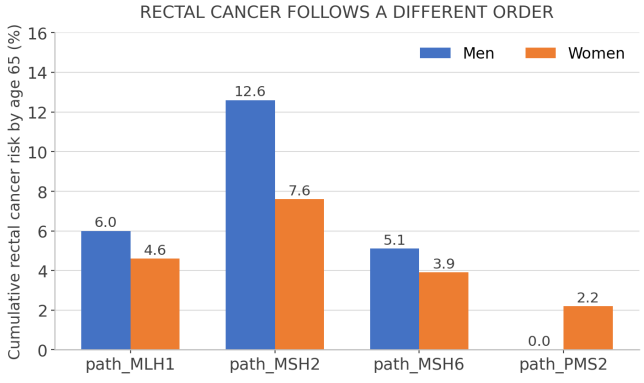

Figure 4: Cumulative rectal cancer risk by age 65, showing a different gene ordering from colon cancer [12]

An alternative model of tumour development: The conventional adenoma-carcinoma sequence [9] predicts that surveillance frequency should determine outcome, and it does not. Analysis of adenoma and cancer incidences under surveillance has been interpreted as indicating an accelerated pathway in three of the four Lynch syndromes, in which cancers arise without passing through a durable, detectable adenoma stage [19]. Work relating variants in MLH1, MSH2 and MSH6 to adenoma and tumour risk and to somatic mutation supports gene-dependent differences in that pathway [20].

Colonoscopy quality is a competing explanation and has been examined directly. Interval cancer risk in this population has been related to colonoscopy quality [21], and performance standards exist against which practice can be measured [22]. But quality alone does not account for findings reproduced across expert centres in multiple countries [15,16].

Gene	Colon cancer risk to 65	Surveillance implication
path_MLH1	48.4% men, 36.3% women [12]	Earliest start, shortest interval [2,12]
path_MSH2	41.5% men, 29.8% women [12]	As MLH1; highest rectal and extracolonic risk [12,13]
path_MSH6	12.7% men, 10.1% women [12]	Sex-limited; endometrial risk dominates [13]
path_PMS2	9.5% men, 2.8% women [12]	No excess risk demonstrated; later start [13,14]

Table 2: Gene-specific colon cancer risk under surveillance and what follows for management

How guidelines have responded: European guidance from the hereditary tumour and coloproctology societies now stratifies by gene and sex rather than treating all carriers alike [2]. The practical yield of surveillance in variant carriers has been quantified directly [23], and the wider management of hereditary colorectal cancer syndromes has been reviewed against the same evidence [24]. Where cancer occurs, the extent of resection is itself gene-dependent, since metachronous risk differs between carriers [1,2].

Discussion

Two conclusions follow, and the second is uncomfortable. The first is that gene-specific risk differs by a factor of five between path_MLH1 and path_PMS2 in men, and by more than tenfold in women [12]. A protocol applied uniformly to all carriers necessarily over-treats one group and under-treats another, and current guidance has moved to stratify accordingly [2,13].

The second is that colonoscopic surveillance is not delivering what its rationale predicts. Cumulative colon cancer risk approaching 50 per cent by age 65 in path_MLH1 men occurs in a population under active surveillance [12], shorter intervals do not reduce incidence [15,16], and stage at diagnosis is independent of the gap since the last examination [17]. Each finding individually could be explained away; together they point at the model rather than the execution.

What the stage data imply

The absence of a stage gradient across intervals is the observation that most constrains interpretation. If cancers arose from adenomas that took years to progress, lengthening the interval would allow more time for progression and produce later-stage disease at diagnosis. It does not [17]. Either these cancers progress too fast for any feasible interval to catch them as adenomas, consistent with the accelerated pathway proposed for three of the four syndromes [19], or some detected lesions would never have progressed, which is the over-diagnosis reading the investigators themselves raised [17,18].

Neither interpretation argues for abandoning surveillance, which reduces mortality against no surveillance [10,23]. Both argue against the assumption that further shortening the interval will help, and that assumption has driven a decade of guideline change [11].

Study limitations

The limitations belong to the underlying literature. Registry cohorts are ascertained through families identified because cancer occurred, which inflates apparent penetrance, and the effect is largest for the lower-penetrance genes where few carriers are identified at all [13,14]. Variant classification differed across contributing centres

before standardised criteria were applied, and inclusion restricted to clinically actionable variants may itself select higher-penetrance MSH6 and PMS2 alleles [13]. Colonoscopy quality varies between centres and is inconsistently reported [21,22]. The comparisons of surveillance interval are observational rather than randomised, so interval was not assigned independently of patient characteristics [15,16,17]. And follow-up in the prospective database, while substantial, remains short relative to a lifetime risk [12].

Two gaps deserve naming. No randomised comparison of surveillance intervals has been conducted in this population, so the observational finding of no benefit from shorter intervals cannot exclude confounding [16,17]. And no study reviewed here reports outcomes for carriers of variants of uncertain significance, who are numerous and currently managed without an evidence base [13].

Conclusion

Lynch syndrome is better understood as four related conditions than as one. Cumulative colon cancer risk by age 65 under surveillance ranges from 48.4 per cent in path_MLH1 men to 2.8 per cent in path_PMS2 women, rectal cancer risk follows a different gene ordering, and no significant excess cancer risk has been demonstrated for path_PMS2 at all. Surveillance reduces mortality but has not prevented cancer to the degree its rationale predicts: incidence is not lower with shorter intervals, and stage at diagnosis is unrelated to the gap since the last colonoscopy. That pattern is difficult to reconcile with a slow adenoma-carcinoma sequence, and points either to accelerated tumour development or to over-diagnosis of lesions that would not have progressed. Stratifying by gene and sex is the change the evidence supports; shortening intervals further is not.

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Conflict of Interest

There is nothing any author needs to declare as a competing interest.

Ethics Statement

Every study drawn on here was published beforehand. Since nobody was recruited and no patient data were obtained afresh, no ethical approval was sought for the work.

References

1. Møller P, Haupt S, Ahadova A, Kloor M, Sampson JR, Sunde L, et al. "Incidences of colorectal adenomas and cancers under colonoscopy surveillance suggest an accelerated Big Bang pathway to CRC in three of the four Lynch syndromes". Hered Cancer Clin Pract 22(2024):6.
2. Seppälä TT, Latchford A, Negoi I, Sampaio Soares A, Jimenez-Rodriguez R, Sanchez-Guillen L, et al. "European guidelines from the EHTG and ESCP for Lynch syndrome: an updated third edition of the Mallorca guidelines based on gene and gender". Br J Surg 108(2021):484-498.
3. Vasen HFA. "Progress report: new insights into the prevention of CRC by colonoscopic surveillance in Lynch syndrome". Fam Cancer 21(2022):49-56.
4. Vasen HF, Tomlinson I, Castells A. "Clinical management of hereditary colorectal cancer syndromes". Nat Rev Gastroenterol Hepatol 12(2015):88-97.
5. Mecklin JP. "Frequency of hereditary colorectal carcinoma". Gastroenterology 93(1987):1021-1025.
6. Jass JR, Stewart SM. "Evolution of hereditary non-polyposis colorectal cancer". Gut 33(1992):783-786.
7. Lynch HT, de la Chapelle A. "Hereditary colorectal cancer". N Engl J Med 348(2003):919-932.
8. Pearlman R, Frankel WL, Swanson B, Zhao W, Yilmaz A, Miller K, et al. "Prevalence and spectrum of germline cancer susceptibility gene mutations among patients with early-onset colorectal cancer". JAMA Oncol 3(2017):464-471.
9. Hill MJ, Morson BC, Bussey HJ. "Aetiology of adenoma-carcinoma sequence in large bowel". Lancet 1(1978):245-247.
10. Järvinen HJ, Aarnio M, Mustonen H, Aktan-Collan K, Aaltonen LA, Peltomäki P, et al. "Controlled 15-year trial on screening for colorectal cancer in families with hereditary nonpolyposis colorectal cancer". Gastroenterology 118(2000):829-834.
11. 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". Gastroenterology 147(2014):502-526.
12. Seppälä TT, Dominguez-Valentin M, Møller P, et al. "Metachronous colorectal cancer risks after extended or segmental resection in MLH1, MSH2 and MSH6 Lynch syndrome: multicentre study from the Prospective Lynch Syndrome Database". Br J Surg 112(2025):znaf061.
13. Dominguez-Valentin M, Sampson JR, Seppälä TT, ten Broeke SW, Plazzer JP, Nakken S, et al. "Cancer risks by gene, age, and gender in 6350 carriers of pathogenic mismatch repair variants: findings from the Prospective Lynch Syndrome Database". Genet Med 22(2020):15-25.
14. ten Broeke SW, van der Klift HM, Tops CMJ, Aretz S, Bernstein I, Buchanan DD, et al. "Cancer risks for PMS2-associated Lynch syndrome". J Clin Oncol 36(2018):2961-2968.
15. Seppälä T, Pylvänäinen K, Evans DG, Järvinen H, Renkonen-Sinisalo L, Bernstein I, et al. "Colorectal cancer incidence in path_MLH1 carriers subjected to different follow-up protocols: a Prospective Lynch Syndrome Database report". Hered Cancer Clin Pract 15(2017):18.
16. Engel C, Vasen HF, Seppälä T, Aretz S, Bigirwamungu-Bargeman M, de Boer SY, et al. "No difference in colorectal cancer incidence or stage at detection by colonoscopy among 3 countries with different Lynch syndrome surveillance policies". Gastroenterology 155(2018):1400-1409.
17. Seppälä TT, Ahadova A, Dominguez-Valentin M, Macrae F, Evans DG, Therkildsen C, et al. "Lack of association between screening interval and cancer stage in Lynch syndrome may be accounted for by over-diagnosis; a prospective Lynch syndrome database report". Hered Cancer Clin Pract 17(2019):8.
18. Gøtzsche PC, Jørgensen KJ. "Screening for breast cancer with mammography". Cochrane Database Syst Rev (2013):CD001877.
19. Møller P, Seppälä T, Bernstein I, Holinski-Feder E, Sala P, Evans DG, et al. "Cancer incidence and survival in Lynch syndrome patients receiving colonoscopic and gynaecological surveillance: first report from the Prospective Lynch Syndrome Database". Gut 66(2017):464-472.
20. Engel C, Ahadova A, Seppälä TT, Aretz S, Bigirwamungu-Bargeman M, Bläker H, et al. "Associations of pathogenic variants in MLH1, MSH2, and MSH6 with risk of colorectal adenomas and tumors and with somatic mutations in patients with Lynch syndrome". Gastroenterology 158(2020):1326-1333.
21. Haanstra JF, Vasen HFA, Sanduleanu S, van der Wouden EJ, Koornstra JJ, Kleibeuker JH, et al. "Quality colonoscopy and risk of

interval cancer in Lynch syndrome". Int J Colorectal Dis 28(2013):1643-1649.

22. Rees CJ, Thomas Gibson S, Rutter MD, Baragwanath P, Pullan R, Feeney M, et al. "UK key performance indicators and quality assurance standards for colonoscopy". Gut 65(2016):1923-1929.
23. Goverde A, Eikenboom E, Viskil E, Bruno M, Dubbink HJ, Dinjens WNM, et al. "Yield of Lynch syndrome surveillance for patients with pathogenic variants in DNA mismatch repair genes". Clin Gastroenterol Hepatol 18(2020):1112-1120.
24. Boland CR, Goel A. "Microsatellite instability in colorectal cancer". Gastroenterology 138(2010):2073-2087.
25. 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 352(2005):1851-1860.

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