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ARTICLE

The predicted effect and cost-effectiveness of tailoring colonoscopic surveillance according to mismatch repair gene in patients with Lynch syndrome

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ABSTRACT

Purpose: Lynch syndrome-related colorectal cancer (CRC) risk substantially varies by mismatch repair (MMR) gene. We evaluated the health impact and cost-effectiveness of MMR gene-tailored colonoscopic surveillance.

Methods: We first estimated sex- and MMR gene-specific cumulative lifetime risk of first CRC without colonoscopic surveillance using an optimization algorithm. Next, we harnessed these risk estimates in a microsimulation model, "*Policy1-Lynch*," and compared 126 colonoscopic surveillance strategies against no surveillance.

Results: The most cost-effective strategy was 3-yearly surveillance from age 25 to 70 years (pathogenic variants [*path_*] in *MLH1* [*path_MLH1*], *path_MSH2*) with delayed surveillance for *path_MSH6* (age 30-70 years) and *path_PMS2* (age 35-70 years) heterozygotes (incremental cost-effectiveness ratio = Australian dollars (A) $8,833/life-year saved). This strategy averted 60 CRC deaths (153 colonoscopies per death averted) over the lifetime of 1000 confirmed patients with Lynch syndrome (vs no surveillance). This also reduced colonoscopies by 5% without substantial change in health outcomes (vs nontailored 3-yearly surveillance from 25-70 years). Generally, starting surveillance at age 25 (vs 20) years was more cost-effective with minimal effect on life-years saved and starting 5 to 10 years later for *path_MSH6* and *path_PMS2* heterozygotes (*vs path_MLH1* and *path_MSH2*) further improved cost-effectiveness. Surveillance end age (70/75/80 years) had a minor effect. Three-yearly surveillance strategies were more cost-effective (vs 1 or 2-yearly) but prevented 3 fewer CRC deaths.

Conclusion: MMR gene-specific colonoscopic surveillance would be effective and cost-effective.

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Introduction

Lynch syndrome (LS) is a genetic disorder that impairs functioning in any of the following 4 DNA mismatch repair (MMR) genes: *MLH1*, *MSH2*, *MSH6*, and *PMS2*.[1] The lifetime risk of colorectal cancer (CRC) in heterozygotes of pathogenic MMR gene variants (herein, "patients with LS") varies based on sex and the impaired MMR gene.[1,2] Regular colonoscopic surveillance can effectively reduce CRC burden in patients with LS.[3] However international consensus is lacking on the most appropriate colonoscopic surveillance strategy for confirmed patients with LS.[4-8] Regular colonoscopic surveillance is generally recommended starting at age 20 to 25 years (or from confirmation of pathogenic MMR gene variants [herein, "LS confirmation"]) with consideration to starting 5 to 10 years later for heterozygotes of pathogenic variants (*path_*) in *MSH6* (*path_MSH6)* and *path_PMS2* than in *path_MLH1* and *path_MSH2* heterozygotes.[4-9] Most clinical recommendations do not specify an upper age limit.[4-7] The recommended surveillance intervals vary from 1 (eg, Germany) to 3 years (eg, Finland).[10] Less frequent surveillance can be considered using a predefined age cut-off (eg, after age 60 years in Australia[4] or until age 40 years in Canada[7]). Currently, the recommended interval does not vary between heterozygotes of pathogenic variants in different MMR genes, because there are no specific data to suggest that the speed of carcinogenesis differs between *path_MSH6* and *path_PMS2* heterozygotes and *path_MLH1* and *path_MSH2* heterozygotes,[8] despite high CRC prevalence in the latter.

A previous evaluation showed that colonoscopies are pivotal in determining cost-effectiveness because they account for up to 40% of total costs associated with systematic LS testing and management (ie, universal tumor testing and cascade testing and subsequent colonoscopic surveillance if LS is confirmed).[11] As such, identifying the most cost-effective colonoscopic surveillance strategy is needed to help maximize health benefits from limited health resources. However, there have been limited empirical data that can be used to inform cost-effectiveness modeling; data requirements include sex- and MMR gene-specific lifetime cumulative risk of first CRC in patients with LS without colonoscopic surveillance and the level of protection (or hazard ratios [HRs]) associated with different colonoscopic surveillance intervals (vs no colonoscopic surveillance) on CRC incidence. To our knowledge, only 1 directly relevant study has been published, which estimated MMR gene-specific cumulative lifetime CRC risk in males and females combined and separately considered surveillance cost-effectiveness for each MMR gene in the United States.[12]

In this analysis, we evaluated detailed colonoscopic surveillance strategies after LS is confirmed, considering compound strategies with alternative options across all MMR genes. This complements our previous analysis on systematic LS testing[11] and harnesses emerging evidence on sex- and MMR gene-specific risks. First, we used an optimization algorithm to estimate the lifetime risk of first CRC in patients with LS by sex and MMR gene without colonoscopic surveillance using a range of real-world data. We then used the aforementioned CRC risk estimates to perform an in-depth analysis of the health impact and cost-effectiveness of colonoscopic surveillance strategies in confirmed patients with LS in a microsimulation model.

Materials and Methods

We performed the analysis in 3 stages. In stage 1, we estimated sex- and MMR gene-specific cumulative risk of first CRC without colonoscopic surveillance and with colonoscopic surveillance at varying intervals using an optimization algorithm[13] on the basis of the available evidence (see Appendix 1; Supplemental Tables 1-3; Supplemental Figure 1).[3,14,15]

In stage 2, we used the first CRC risk estimates obtained from the optimization algorithm as inputs to a microsimulation model, "*Policy1-Lynch*".[11] Using "*Policy1-Lynch*", we investigated the effect of various colonoscopic surveillance strategies in a single Australian cohort of confirmed patients with LS aged 20 years in 2020 with no history of CRC, throughout their lifetime up to age 84 years. We assumed that an individual could develop up to 2 CRCs during their lifetime (ie, up to 1 metachronous CRC)[11] and modeled the site of metachronous CRC depending on the extent of previous surgery (Supplemental Table 4; see Appendix 2 for detailed clinical management pathways; Appendix 3; Supplemental Table 5 for overview of the model specification). We explicitly modeled combinations of colonoscopic surveillance start age, end age, and surveillance interval (see Appendix 4), incorporating observed adherence rates to recommended surveillance intervals (90% initial acceptance rate and 70%-90% subsequent interval-specific adherence rate; see Appendix 5). Health and economic outcomes of various colonoscopic surveillance strategies were estimated compared with that with no surveillance (ie, comparator), which were then presented for 1000 confirmed patients with LS. The model and underlying data sources have been previously described[11] and a summary of parameter inputs is provided in Appendix 6. Australian health economic conventions were used (discount rate 5.0% on both costs and health outcomes, willingness-to-pay [WTP] = Australian dollars (A) $30,000-$50,000/life-year saved [LYS]).[16,17]

In stage 3, we also performed a series of one-way sensitivity analyses to investigate the effects of key parameters on the cost-effectiveness of colonoscopic surveillance strategies as well as uncertainty analysis on the effect of colonoscopic surveillance on CRC incidence.

Stage 1: Sex- and MMR gene-specific risks of first CRC

First CRC risks without colonoscopic surveillance

Appendix 1.1 describes detailed methods and assumptions. For *path_MLH1*, *path_MSH2*, or *path_MSH6*

heterozygotes, we used the baseline and the range of estimates reported in 3 studies to estimate sex- and MMR gene-specific risk of first CRC without colonoscopic surveillance. These included (1) sex- and MMR gene-specific cumulative CRC risks in patients with LS without previous cancer and under 1- to 3-yearly colonoscopic surveillance reported by the Prospective Lynch Syndrome Database (PLSD),[14] (2) HR associated with 3-yearly colonoscopic surveillance on CRC incidence reduction (vs no surveillance) reported by Järvinen et al,[3] and (3) MMR gene-specific cumulative CRC risk in *path_MLH1*, *path_MSH2*, or *path_MSH6* heterozygotes (males and females combined) who were censored at the time of first colonoscopy (ie, CRC risk without colonoscopic surveillance) reported by Bonadona et al.[15] Using an optimization algorithm, we systematically searched for values within the 95% CI provided by the PLSD and SE on the HR, such that the combined MMR gene-specific cumulative lifetime risk for first CRC for males and females under no surveillance lies within the 95% CI provided by Bonadona et al.[15] The compatible estimates were then found for sex- and MMR gene-specific cumulative CRC risk in patients with LS and the corresponding HR (ie, fitted HR associated with 3-yearly colonoscopic surveillance) while satisfying a priori conditions on the basis of the current clinical and biological understanding and the reported literature. For example, we assumed that the cumulative lifetime risk of first CRC up to age 25 years is 0%, that the risk increases with age up to 80 years, there is a 5% point increase from age 70 to 80 years, and then it remains stable.[14,15,18,19] The best fitting parameter set for each MMR gene was defined as the one with the smallest mean squared error when compared with the lifetime risk estimates provided by Bonadona et al,[15] and the compatible sex- and MMR gene-specific risks were used as the baseline inputs.

We used sex-specific first CRC risk in *path_PMS2* heterozygotes from a large international study as a surrogate estimate for first CRC risk without colonoscopic surveillance, which adjusted for the ascertainment bias using a modified segregation analysis.[20]

First CRC risks with colonoscopic surveillance at varying intervals

We compared the cumulative CRC risk in patients with LS under various colonoscopic surveillance intervals[21-25] and found approximately 2% absolute reduction for every 1-year decrement in the surveillance interval, which is equivalent to decrease in HR by 0.05.[11] Therefore, for every 1-year decrement in the surveillance interval, we assumed that the estimated HR for first CRC incidence in patients with LS undergoing regular surveillance decreased by 0.05 from the fitted HR associated with 3-yearly colonoscopic surveillance (vs no surveillance), while also assuming the same HR across all ages that are surveilled (see Appendix 1.2).[11] We made a simplified assumption that the relative effect of colonoscopic surveillance on first CRC incidence in *path_PMS2* heterozygotes is the same as those in *path_MSH6* heterozygotes (ie, the same HR).

Stage 2: Effects of various colonoscopic surveillance strategies in confirmed patients with LS

Colonoscopic surveillance strategies

Colonoscopic surveillance strategies were formulated as per the recommendations in Australia, the United Kingdom, the United States, and Canada (Supplemental Table 6).[4-8] A total of 126 surveillance strategies, which were based on the combinations of surveillance start age, end age, and interval, were compared with a no surveillance strategy. First, surveillance strategies were grouped into 6 scenarios on the basis of the combinations of start age (20 and 25 years) and end age (70, 75, and 80 years). Second, strategies with the same surveillance start age and end age were grouped into 3 subscenarios: (1) uniform (ie, nontailored) surveillance with all patients with LS managed in the same way, (2) delayed surveillance for both *path_MSH6* and *path_PMS2* heterozygotes by 5 years, and (3) delayed surveillance for *path_MSH6* heterozygotes by 5 years and for *path_PMS2* heterozygotes by 10 years. Finally, each subscenario included 7 strategies on the basis of the combinations of surveillance interval (1, 2, and 3 years) and whether or not there was a switch to a longer surveillance interval before age 40 years or after age 60 years. The details of each strategy are shown in Supplemental Table 7.

Assumptions regarding the natural history of CRC in patients with LS

CRC development in patients with LS was modeled as cumulative CRC risk, with and without colonoscopic surveillance, for first CRC (sex- and MMR gene-specific risk) and for metachronous CRC in treated individuals (overall risk based on years since first CRC).[11] We assumed that metachronous CRC risk does not differ by sex, MMR genes, or individual's age at the time of surgery[11,18,19,26,27] and the effect of colonoscopic surveillance on metachronous CRC incidence is the same regardless of surveillance interval (HR = 0.881) (see Appendix 1.3).[21] We modeled the same CRC stage distribution regardless of surveillance interval because strict annual surveillance did not significantly reduce CRC incidence or early-stage diagnosis (vs 2- or 3-yearly).[10]

We made a simplifying assumption that CRC diagnosis is made at the time of regular colonoscopy visit (ie, interval cancers were not modeled). We also assumed that 96% of first CRC will develop in the colon and 4% will develop in the rectum and the site of metachronous CRC depends on the extent of previous surgery (see Appendix 1.4). CRC mortality was assumed to be that of 2015, which was the most recent Australian data at the time of analysis, and all-cause mortality were based on data from 2016-2018.[28]

Assumptions regarding test characteristics of colonoscopy and adherence to interval-specific colonoscopic surveillance

We did not explicitly model colonoscopy test characteristics because the reduction in CRC incidence associated with regular colonoscopic surveillance already captured the sensitivity of colonoscopy as part of the overall effectiveness of surveillance.[11] We assumed that the initial uptake of colonoscopic surveillance (ie, acceptance rate) in confirmed patients with LS was 90%.[11,18,29] The adherence rate to subsequent interval-specific colonoscopic surveillance was assumed to be 70% for 1-yearly, 80% for 2-yearly, and 90% for 3-yearly colonoscopic surveillance (see Appendix 5, Supplemental Table 8).[10]

Assumptions regarding costs, utilities, and health economic parameters

Health and economic outcomes of various colonoscopic surveillance strategies were estimated compared with no surveillance (ie, comparator), which were then presented for 1000 confirmed patients with LS. We conducted the analysis from the perspective of the Australian health care system (Medicare—Australia's publicly-funded universal health insurance scheme). We only used costs for colonoscopic surveillance (with or without complication based on costs weighted for complications) and stage-specific treatment for CRC diagnosed after LS confirmation (2020 prices in Australian dollars) because LS testing pathways are not modeled (Supplemental Table 9). We did not calculate quality-adjusted life-years (QALYs) because to our best knowledge there are no data to inform utility weights for colonoscopic surveillance in patients with LS (eg, utility weights at varying surveillance intervals and colonoscopy results). An incremental cost-effectiveness ratio (ICER) was calculated to determine which strategy was most cost-effective by considering all strategies in a single calculation (ie, all variations on surveillance start age, end age, and surveillance interval are considered in 1 ICER calculation).

Stage 3: Sensitivity and uncertainty analyses

We performed a series of one-way sensitivity analyses to investigate the effects of key parameters on the most cost-effective colonoscopic surveillance strategy identified in stage 2 analysis, providing a range for the cost-effectiveness of this strategy. We also performed a sensitivity analysis on the strategies on the cost-effectiveness frontier curve by using 50 randomly selected fitted sets (identified in stage 1) on the cumulative risk of first CRC in *path_MLH1*, *path_MSH2*, or *path_MSH6* heterozygotes. Uncertainty analysis was performed on all the strategies considered in our baseline analysis assuming reduced effect size of colonoscopic surveillance on CRC incidence (see Appendix 9).

Results

Stage 1: Sex- and MMR gene-specific risks of first CRC

Figure 1 and Supplemental Table 3 show the estimated sex- and MMR gene-specific risk of first CRC in patients with LS without colonoscopic surveillance and with colonoscopic surveillance at varying intervals obtained from the best fitting parameter sets, using optimization algorithms, for *MLH1*, *MSH2*, and *MSH6* and as reported by ten Broeke et al[20] for *PMS2* (also see Supplemental Figure 1). The corresponding first CRC risk without colonoscopic surveillance by age 70 was 48%, 50%, 8%, and 8% in males and 43%, 34%, 15%, and 7% in females. The fitted HR associated with 3-yearly colonoscopic surveillance on first CRC incidence (vs no surveillance) obtained from the best fitting parameter set was 0.587, 0.585, and 0.587 for *path_MLH1, path_MSH2*, and *path_MSH6* heterozygotes, respectively.

Stage 2: Effects of various colonoscopic surveillance strategies in confirmed patients with LS

As seen in Figure 2A, the cost-effectiveness of colonoscopic surveillance strategies largely depended on surveillance start age and surveillance interval, with a relatively minor effect of surveillance end age. Between 52 and 63 CRC deaths were averted through surveillance, with an additional 9177-19,130 colonoscopies over the lifetimes of 1000 confirmed patients with LS (153-303 colonoscopies per CRC death averted) against no surveillance (ie, comparator). At an indicative WTP threshold of A$30,000 to A$50,000/LYS, all the strategies were cost-effective compared with no surveillance with the strategies with a start age of 20 years and 1-yearly surveillance being the least cost-effective (A$32,760-A$38,520/LYS). Detailed outcomes for each of 127 strategies are described in Appendix 7 (Supplemental Figures 2-4; Supplemental Tables 10 and 11).

Incremental cost-effectiveness analysis

As seen in Figure 2B and Table 1, when all variations on surveillance start age, end age, and surveillance interval are considered in 1 ICER calculation, the most cost-effective surveillance strategy was 3-yearly surveillance from age 25 to 70 years (*path_MLH1* and *path_MSH2*) with delayed surveillance in *path_MSH6* (from age 30 to 70 years) and *path_PMS2* (from age 35 to 70 years) heterozygotes (strategy 7.3.5; ICER = A$8,833/LYS). This strategy averted 60 CRC deaths with additional 9206 colonoscopies (ie, 153 colonoscopies to avert 1 CRC death) over the lifetimes of 1000 confirmed patients with LS. Compared with an equivalent nontailored approach—3-yearly surveillance from age 25 to 70 years in all patients with LS—this resulted in about 5% reduction in colonoscopies with no substantial change in health outcomes (Table 2, Supplemental Table 11). Accordingly, the equivalent nontailored strategy was dominated and

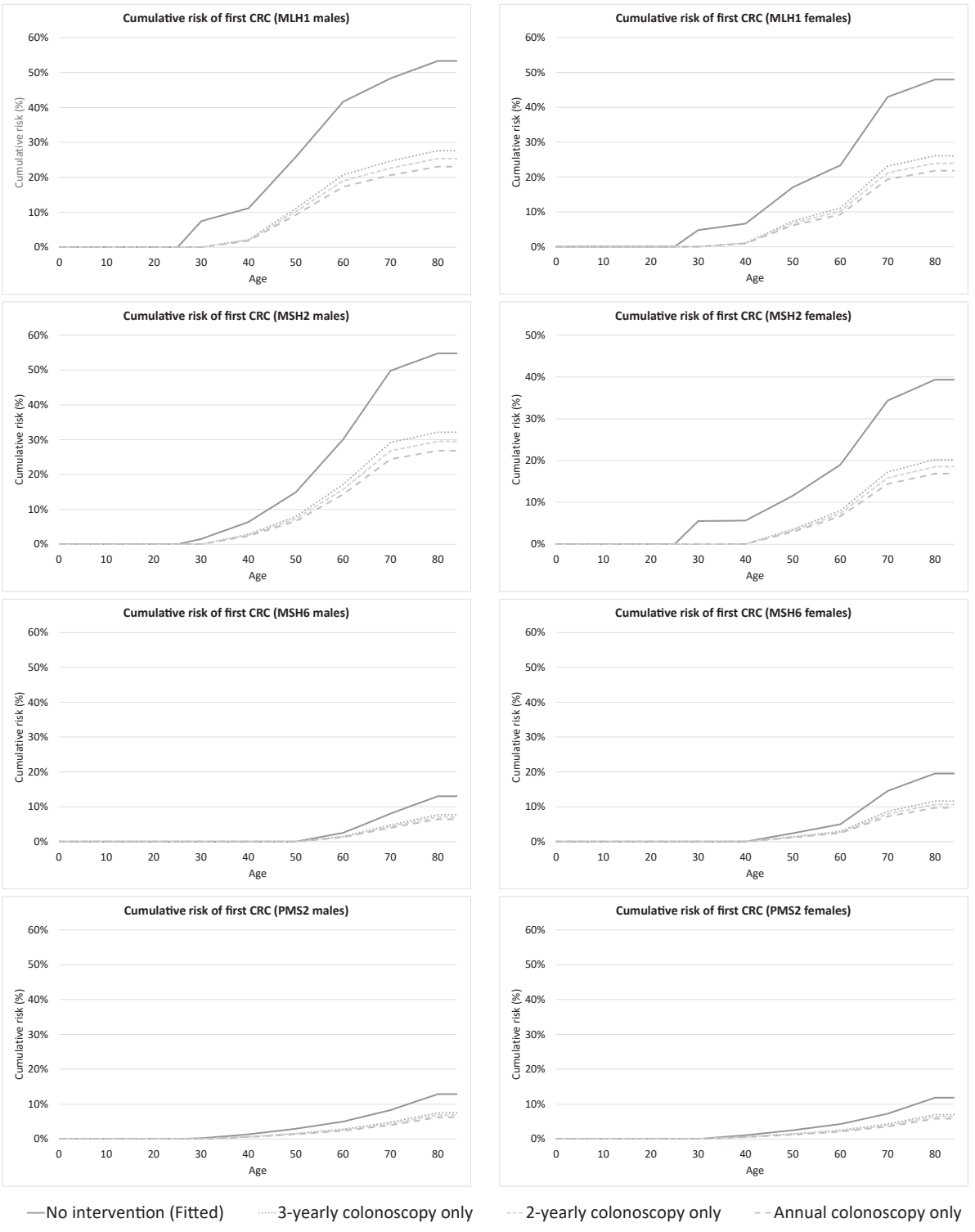

Figure 1 Estimated sex- and MMR gene-specific risk of first CRC in patients with LS considering the effect of colonoscopic surveillance at varying intervals. CRC, colorectal cancer; LS, Lynch syndrome; MMR, mismatch repair.

not on the cost-effectiveness frontier curve. More intensive surveillance strategies (eg, shorter surveillance interval and/or wider age range surveilled) would avert up to 3 more CRC deaths but cost substantially more (ICERs from A$186,822 to A$56,090,129/LYS). Generally, strategies on the cost-effectiveness frontier curve were either MMR gene-tailored or nontailored but adopted reduced surveillance interval after age 60 years.

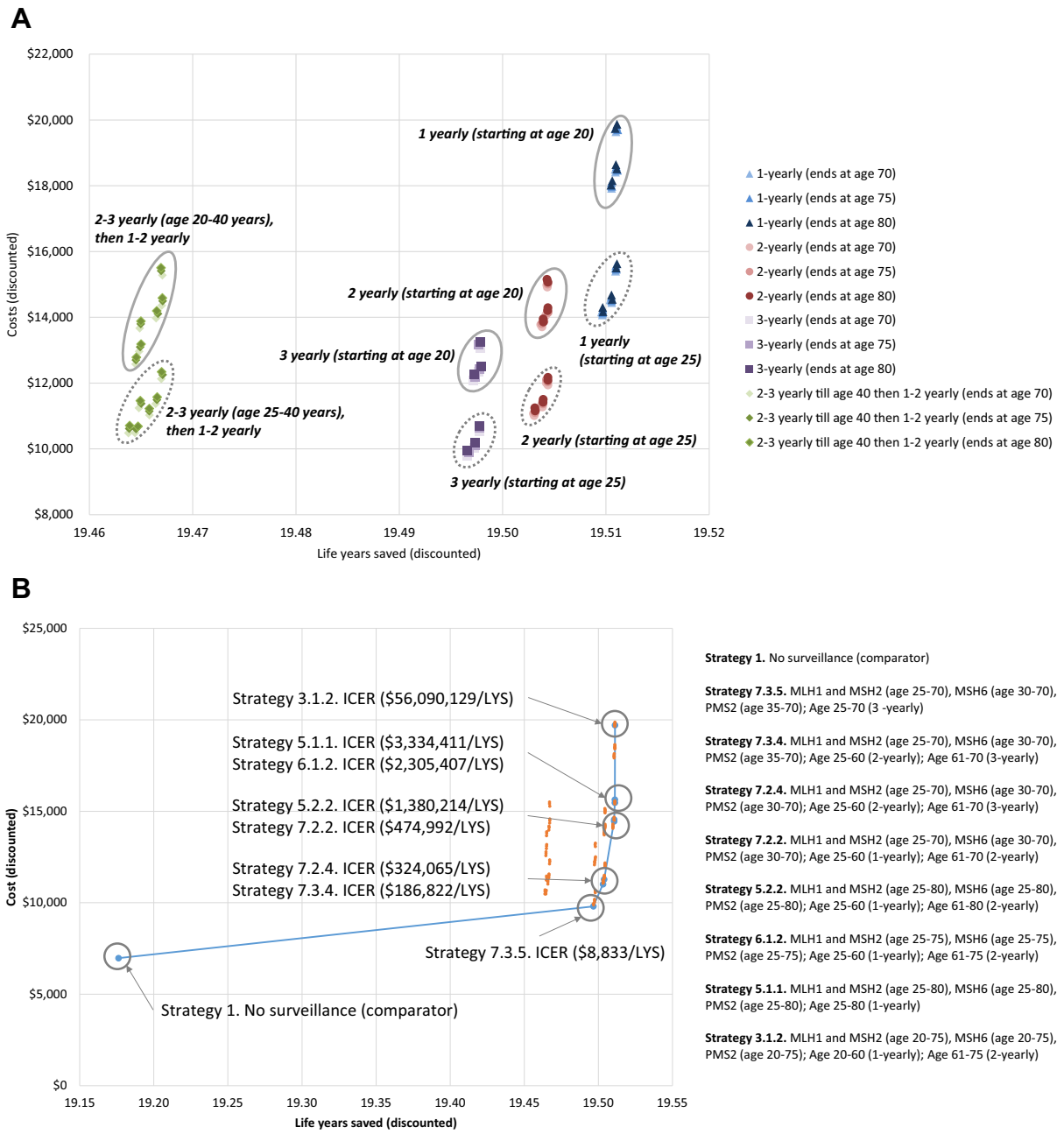

Figure 2 Discounted costs and life years associated with various colonoscopic surveillance strategies in confirmed patients with LS aged 20 years in 2020 in Australia. A. By surveillance interval and surveillance start and end age compared with no surveillance. B. ICER of strategies on the cost-effectiveness frontier curve. Note: In Figure 2A, strategies in solid circles represent colonoscopic surveillance starting at age 20 years and strategies in dotted circles represent colonoscopic surveillance starting at age 25 years. Three distinct points with the same color in each circle represent an option of delaying 5 to 10 years for *path_MSH6* and *path_PMS2* heterozygotes (vs *path_MLH1* and *path_MSH2* heterozygotes; see Supplemental Figure 3 for details). In Figure 2B, strategies not on blue solid line are dominated; ie, they have either higher costs or a higher cost per LYS than a more effective strategy. ICER, incremental cost-effectiveness ratio; LS, Lynch syndrome; LYS, life-year saved.

Surveillance age ranges

Strategies starting surveillance at age 25 years averted a similar number of CRC deaths (52-63 deaths per 1000 patients with LS) with 11% fewer colonoscopies than those starting at age 20 years (153-270 vs 175-303 colonoscopies per CRC death averted). Strategies ending surveillance at age 70 years averted a similar number of CRC deaths (52-63 deaths per 1000 patients with LS) compared with those ending at age 75 or 80 years, requiring up to 6% less colonoscopies for every 5-year increment (153-288 vs 162-296 vs 170-303 colonoscopies per CRC death averted) (Table 2, Supplemental Figure 2).

Table 1 Health economic, health, and resource outcomes associated with the colonoscopic surveillance strategies on the cost-effectiveness frontier curve for confirmed patients with LS aged 20 years in Australia in 2020, compared with no surveillance

Surveillance Strategies		Health Economic Outcomes[a]				Health and Resources Outcomes (per 1000 Confirmed Patients With LS)[a]				
Strategy	Description (Surveillance Start Age-End Age, y; Surveillance Interval)	Discounted Costs	Discounted LYS	CER[b]	ICER[c]	Cancer Cases	Cancer Deaths	No. of Colonoscopies	Cancer Deaths Averted vs No Surveillance	No. of Colonoscopies to Avert 1 CRC Death vs No Surveillance
1	***No surveillance (comparator)***	***$6970***	***19.1762***	–	**–**	406	110	–	–	–
7.3.5	MLH1 and MSH2 (age 25-70), MSH6 (age 30-70), PMS2 (age 35-70); age 25-70 (3-yearly)	$9800	19.4966	$8833/LYS	$8833/LYS	323	49	9206	60	153
7.3.4	MLH1 and MSH2 (age 25-70), MSH6 (age 30-70), PMS2 (age 35-70); age 25-60 (2-yearly); age 61-70 (3-yearly)	$11,011	19.5031	$12,363/LYS	$186,822/LYS	313	48	10,881	62	177
7.2.4	MLH1 and MSH2 (age 25-70), MSH6 (age 30-70), PMS2 (age 30-70); age 25-60 (2-yearly); age 61-70 (3-yearly)	$11,273	19.5039	$13,131/LYS	$324,065/LYS	313	48	11,101	62	180
7.2.2	MLH1 and MSH2 (age 25-70), MSH6 (age 30-70), PMS2 (age 30-70); age 25-60 (1-yearly); age 61-70 (2-yearly)	$14,451	19.5106	$22,371/LYS	$474,992/LYS	303	46	15,070	63	239
5.2.2	MLH1 and MSH2 (age 25-80), MSH6 (age 25-80), PMS2 (age 25-80); age 25-60 (1-yearly); age 61-80 (2-yearly)	$14,548	19.5106	$22,658/LYS	$1,380,214/LYS	301	46	15,757	63	250

(continued)

Table 1 Continued

Surveillance Strategies		Health Economic Outcomes[a]				Health and Resources Outcomes (per 1000 Confirmed Patients With LS)[a]				
Strategy	Description (Surveillance Start Age-End Age, y; Surveillance Interval)	Discounted Costs	Discounted LYS	CER[b]	ICER[c]	Cancer Cases	Cancer Deaths	No. of Colonoscopies	Cancer Deaths Averted vs No Surveillance	No. of Colonoscopies to Avert 1 CRC Death vs No Surveillance
6.1.2	MLH1 and MSH2 (age 25-75), MSH6 (age 25-75), PMS2 (age 25-75); age 25-60 (1-yearly); age 61-75 (2-yearly)	$15,463	19.5110	$25,363/LYS	$2,305,407/LYS	302	46	16,048	63	254
5.1.1	MLH1 and MSH2 (age 25-80), MSH6 (age 25-80), PMS2 (age 25-80); Age 25-80 (1-yearly)	$15,632	19.5111	$25,864/LYS	$3,334,411/LYS	301	46	17,032	63	270
3.1.2	MLH1 and MSH2 (age 20-75), MSH6 (age 20-75), PMS2 (age 20-75); age 20-60 (1-yearly); age 61-75 (2-yearly)	$19,703	19.5111	$38,012/LYS	$56,090,129/LYS	302	46	18,147	63	287

Note: Strategy 1. No surveillance (comparator) was italicized and in bold values as the other strategies are in reference to Strategy 1.
CER, cost-effectiveness ratio; *CRC*, colorectal cancer; *ICER*, incremental cost-effectiveness ratio; *LS*, Lynch syndrome; *LYS*, life-year saved.
[a]Mean outcomes obtained from 20 simulations; costs and life-years are each discounted by 5%.
[b]Difference in mean costs divided by difference in mean LYS for surveillance strategy vs no surveillance.
[c]Relative to the next most cost-effective strategy.

Table 2 Summary results on the ranges of health economic, health, and resource outcomes associated with various colonoscopic surveillance strategies for confirmed patients with LS aged 20 years in Australia in 2020, compared with no surveillance (per 1000 confirmed patients with LS)

Surveillance Strategies		Range of Health Economic Outcomes		Range of Health and Resource Outcomes per 1000 Confirmed Patients With LS[a]				
Category	Subcategory	Discounted Costs[b]	Discounted LYS[b]	CRC Cases (% Change vs No Surveillance)[c]	CRC Deaths (% Change vs No Surveillance)[c]	No. of Colonoscopies	CRC Deaths Averted (% Change vs Ref Within Category)[d]	No. of Colonoscopies to Avert 1 CRC Death (% Change vs Ref Within Category)[d]
Comparator	No colonoscopic surveillance	$6970	19.1762	406	110	–	–	–
Overall	All intervention strategies	$9800-$19,870	19.4638-19.5111	301-383 (–26%, –6%)	46-57 (–58%, –48%)	9177-19,130	52-63 (–58%, –48%)	153-303 (–58%, –48%)
Surveillance start age, y	20	$12,074-$19,870	19.4645-19.5111	301-383 (–26%, –6%)	46-57 (–58%, –48%)	10,343-19,130	52-63 (Ref)	175-303 (Ref)
	25	$9800-$15,632	19.4638-19.5111	301-383 (–26%, –6%)	46-57 (–58%, –48%)	9177-17,032	52-63 (0%, 0%)	153-270 (–11%, –11%)
Surveillance end age, y	70	$9800-$19,729	19.4638-19.5110	302-383 (–26%, –6%)	46-57 (–58%, –48%)	9177-18,141	52-63 (Ref)	153-288 (Ref)
	75	$9886-$19,812	19.4639-19.5111	302-382 (–26%, –6%)	46-57 (–58%, –48%)	9749-18,670	52-63 (0%, 0%)	162-296 (3%, 6%)
	80	$9950-$19,870	19.4639-19.5111	301-382 (–26%, –6%)	46-57 (–58%, –48%)	10,246-19,130	52-63 (0%, 0%)	170-303 (5%, 12%)
Surveillance interval	1-yearly	$14,163-$19,870	19.5096-19.5111	301-303 (–26%, –25%)	46-47 (–58%, –57%)	15,121-19,130	63-63 (Ref)	240-303 (Ref)
	2-yearly	$11,070-$15,156	19.5030-19.5044	311-314 (–23%, –23%)	48-48 (–56%, –56%)	11,144-14,449	62-62 (3%, 3%)	181-234 (–26%, –24%)
	3-yearly	$9800-$13,258	19.4965-19.4980	321-323 (–21%, –20%)	49-49 (–55%, –55%)	9206-12,434	60-60 (6%, 6%)	153-206 (–39%, –35%)
Staggered start (*MLH1/MSH2* starting at age 20 y)	MSH6 (age 20 y)/ PMS2 (age 20 y)	$10,547-$15,632	19.4648-19.5111	301-382 (–26%, –6%)	46-57 (–58%, –48%)	11,090-19,130	52-63 (Ref)	184-303 (Ref)
	MSH6 (age 25 y)/ PMS2 (age 25 y)	$10,025-$14,679	19.4644-19.5106	301-382 (–26%, –6%)	46-57 (–58%, –48%)	10,706-18,521	52-63 (0%, 0%)	177-294 (–3%, –3%)
	MSH6 (age 25 y)/ PMS2 (age 30 y)	$9800-$14,303	19.4638-19.5097	301-383 (–26%, –6%)	46-57 (–58%, –48%)	10,343-18,208	52-63 (0%, 0%)	175-289 (–7%, –5%)

(continued)

Table 2 Continued

Surveillance Strategies		Range of Health Economic Outcomes		Range of Health and Resource Outcomes per 1000 Confirmed Patients With LS[a]				
Category	Subcategory	Discounted Costs[b]	Discounted LYS[b]	CRC Cases (% Change vs No Surveillance)[c]	CRC Deaths (% Change vs No Surveillance)[c]	No. of Colonoscopies	CRC Deaths Averted (% Change vs Ref Within Category)[d]	No. of Colonoscopies to Avert 1 CRC Death (% Change vs Ref Within Category)[d]
Staggered start (MLH1/MSH2 starts at age 25 y)	MSH6 (age 25 y)/ PMS2 (age 25 y)	$13,073-$19,870	19.4649-19.5111	301-382 (–26%, –6%)	46-57 (–58%, –48%)	9653-17,032	52-63 (Ref)	160-270 (Ref)
	MSH6 (age 30 y)/ PMS2 (age 30 y)	$12,339-$18,642	19.4648-19.5111	301-382 (–26%, –6%)	46-57 (–58%, –48%)	9177-16,424	52-63 (0%, 0%)	156-261 (–5%, –4%)
	MSH6 (age 30 y)/ PMS2 (age 35 y)	$12,074-$18,152	19.4645-19.5106	302-383 (–26%, –6%)	47-57 (–58%, –48%)	9206-16,108	52-63 (0%, 0%)	153-256 (–5%, –5%)
Switching interval (at age 60 y)	1-yearly (constant)	$14,163-$19,870	19.5096-19.5111	301-303 (–26%, –25%)	46-47 (–58%, –57%)	15,121-19,130	63-63 (Ref)	240-303 (Ref)
	1-yearly till age 60 y then 2-yearly	$14,075-$19,742	19.5097-19.5111	301-303 (–26%, –25%)	46-47 (–58%, –57%)	14,756-18,465	63-63 (0%, 0%)	234-293 (–3%, –2%)
Switching interval (at age 60 y)	2-yearly (constant)	$11,070-$15,156	19.5030-19.5044	311-314 (–23%, –23%)	48-48 (–56%, –56%)	11,144-14,449	62-62 (Ref)	181-234 (Ref)
	2-yearly till age 60 y then 3-yearly	$11,011-$15,067	19.5031-19.5044	311-313 (–23%, –23%)	48-48 (–56%, –56%)	10,881-13,979	62-62 (0%, 0%)	177-227 (–3%, –2%)

(continued)

Table 2 Continued

Surveillance Strategies		Range of Health Economic Outcomes		Range of Health and Resource Outcomes per 1000 Confirmed Patients With LS[a]				
Category	Subcategory	Discounted Costs[b]	Discounted LYS[b]	CRC Cases (% Change vs No Surveillance)[c]	CRC Deaths (% Change vs No Surveillance)[c]	No. of Colonoscopies	CRC Deaths Averted (% Change vs Ref Within Category)[d]	No. of Colonoscopies to Avert 1 CRC Death (% Change vs Ref Within Category)[d]
Switching interval (at age 40 y)	1-yearly (constant)	$14,163-$19,870	19.5096-19.5111	301-303 (–26%, –25%)	46-47 (–58%, –57%)	15,121-19,130	63-63 (Ref)	240-303 (Ref)
	2-yearly till age 40 y then 1-yearly	$11,027-$15,507	19.4658-19.4671	379-381 (–7%, –6%)	57-57 (–48%, –48%)	9639-14,097	53-53 (22%, 23%)	184-268 (–36%, –26%)
Switching interval (at age 40 y)	2-yearly (constant)	$11,070-$15,156	19.5030-19.5044	311-314 (–23%, –23%)	48-48 (–56%, –56%)	11,144-14,449	62-62 (Ref)	181-234 (Ref)
	3-yearly till age 40 y then 2-yearly	$10,484-$13,882	19.4638-19.4650	381-383 (–6%, –6%)	57-57 (–48%, –48%)	9177-12,575	52-52 (19%, 19%)	175-240 (–18%, –13%)

Note: See Supplemental Tables 9 and 10 for detailed results for all strategies evaluated in the analysis. Incremental cost-effectiveness ratios comparing strategies within the same category were not calculated owing to no noticeable differences in life-years saved with substantially higher cost differences.

CRC, colorectal cancer; *LS*, Lynch syndrome; *LYS*, life-year saved; *Ref*, reference group.

[a]Mean outcomes obtained from 20 simulations were summarized as ranges across comparable surveillance strategies considered on the basis of surveillance start age, end age, surveillance interval, and combinations of these attributes and were presented per 1000 confirmed patients with LS.

[b]Costs and life-years are each discounted by 5%.

[c]Negative values represent a decrease compared with no surveillance.

[d]Negative values represent a decrease compared with the reference group within the category.

Surveillance interval

Although 3-yearly colonoscopic surveillance strategies averted 2 to 3 fewer CRC deaths than 2-yearly or 1-yearly surveillance strategies (~60 vs ~62 vs ~63 deaths per 1000 patients with LS), they appeared to be more cost-effective owing to substantially lower colonoscopy demand (153-206 vs 181-234 vs 240-303 colonoscopies per CRC death averted; Table 2).

Tailored surveillance

Delaying surveillance for *path_MSH6* and *path_PMS2* heterozygotes averted a similar number of CRC deaths (52-63 deaths per 1000 patients with LS) compared with those with uniform surveillance (ie, the equivalent strategy but with the same interval and age range for all patients with LS). For example, compared with uniform surveillance starting at age 25 years, 5% reduction in colonoscopies were predicted when delaying surveillance by 5 years for *path_MSH6* and 10 years for *path_PMS2* heterozygotes (160-270 vs 153-256 colonoscopies per CRC death averted) (Table 2, Supplemental Figure 3).

Switching surveillance interval

Compared with those maintaining the same interval, strategies with reduced colonoscopic surveillance after age 60 years reduced colonoscopy demand without substantial change in health outcomes and strategies with reduced surveillance until age 40 years reduced colonoscopy demand but averted up to 10 fewer CRC deaths. For example, if surveillance interval was reduced to 2-yearly after age 60 years (vs maintaining 1-yearly), similar CRC deaths (~63 deaths per 1000 patients with LS) were averted with approximately 3% less colonoscopies (234-293 vs 240-303 colonoscopies per CRC death averted). If surveillance interval was reduced to 2-yearly until age 40 years (vs maintaining 1-yearly), CRC deaths averted (per 1000 patients with LS) decreased from approximately 63 to approximately 53 with approximately 36% less colonoscopies (184-268 vs 240-303 colonoscopies per CRC death averted) (Table 2, Supplemental Figure 4).

Stage 3: Sensitivity and uncertainty analyses

One-way sensitivity analysis on the most cost-effective colonoscopic surveillance strategy showed that cost of colonoscopy had the greatest influence on cost-effectiveness (Supplemental Figure 5). Neither changing the discount rate (5% vs 3%) nor the cumulative risk of first CRC in *path_MLH1*, *path_MSH2*, or *path_MSH6* heterozygotes (best fitted set vs randomly selected fitted sets) affected the order of the strategies on the cost-effectiveness frontier curve (Supplemental Figures 6 and 7). The findings from the uncertainty analysis agreed very well with the baseline analysis (Supplemental Tables 12 and 13; Supplemental Figures 8 and 9). Most surveillance strategies on the cost-effectiveness frontier curve from the baseline analysis were retained in the uncertainty analysis without the order being changed (Supplemental Table 14). Compared with the baseline analysis, overall, uncertainty analysis assuming the reduced effect size of colonoscopic surveillance showed increased CRC incidence (327-401 vs 301-383 per 1000 patients with LS) and death (48-58 vs 46-57 per 1000 patients with LS) and prevented up to 1 less CRC death (52-62 vs 52-63 CRC death per 1000 patients with LS) requiring the similar colonoscopy demand (154-304 vs 153-303 colonoscopies per CRC death averted; Supplemental Tables 15 and 16).

Discussion

The estimation of cancer risks in patients with LS has been challenging, largely owing to ascertainment bias, and reported cancer risks substantially vary among studies. Although it is well-established that regular colonoscopic surveillance can effectively reduce CRC burden in patients with LS,[3] the magnitude of the protective effect of surveillance has been difficult to estimate from the available data.[14,15,30] To address this problem, for the first time we used the available data and estimated the sex- and MMR gene-specific cumulative lifetime risk of first CRC both without colonoscopic surveillance and with colonoscopic surveillance at varying intervals using an optimization algorithm approach. We estimated that cumulative first CRC risk by age 70 years in *path_MLH1*, *path_MSH2*, *path_MSH6*, and *path_PMS2* heterozygotes without colonoscopic surveillance was 48%, 50%, 8%, and 8%, respectively, in males and 43%, 34%, 15%, and 7%, respectively, in females. These estimates are broadly comparable with calibrated CRC risks independently estimated by Kastrinos et al[12] with their respective estimate of 57%, 47%, 15%, and 9% in males and females combined.

We found that surveillance start age and interval were the 2 main determinants on the cost-effectiveness of colonoscopic surveillance strategies (vs no surveillance). Strategies starting surveillance at age 25 (vs age 20) years were equally effective while requiring 11% fewer colonoscopies, indicating they are substantially more cost-effective. A staggered start across different MMR genes further improved cost-effectiveness compared with the equivalent nontailored strategy. Conversely, surveillance end age had a relatively minor effect. Overall, the estimated optimal colonoscopic surveillance age range was 25 to 70 years, averting 52 to 63 CRC deaths with an additional 9177 to 16,043 colonoscopies per 1000 confirmed patients with LS (153-254 colonoscopies per CRC death averted). This related to our assumption that the cumulative lifetime risk of first CRC up to age 25 years is 0%.[14,15] As seen in Supplemental Table 1, Bonadona et al[15] reported minimum increase in CRC risk from age 20 (0%) to 30 years (0%-2%) and the PLSD reported CRC risk from age 25 years (0% [95% CI = 0%-0%]). The only value satisfying the fitting criteria of the optimization algorithm was 0%, hence this assumption was made, pointing to a need for

future research. Currently, there is a lack of international consensus on the most appropriate colonoscopic surveillance interval in confirmed patients with LS. In our study, 3-yearly colonoscopic surveillance strategies were less effective at averting CRC deaths but required almost 40% less colonoscopies (vs 1- or 2-yearly), indicating they are substantially more cost-effective.

Accordingly, the most cost-effective surveillance strategy was 3-yearly surveillance at age 25 to 70 years (*path_MLH1* and *path_MSH2*) with delayed surveillance for *path_MSH6* (age 30 to 70 years) and *path_PMS2* (age 35 to 70 years) heterozygotes (ICER: A$8,833/LYS), which could avert 60 CRC deaths over the lifetime of 1000 confirmed patients with LS. Up to 3 more CRC deaths (per 1000 confirmed patients with LS) could be averted by targeting a wider age range or by shortening surveillance intervals, but this improved effectiveness came at an additional A$186,000 to A$56 million cost for 1 additional LYS.

Our findings for overall cost-effectiveness were somewhat different from a recent analysis by Kastrinos et al[12] who separately considered strategies for each MMR gene but did not consider the whole-of-population with LS framing. In their analysis, the optimal strategy was 1-yearly surveillance at age 25 to 75 years for *path_MLH1*, 2-yearly surveillance at age 25 to 75 years for *path_MSH2*, 3-yearly surveillance at age 35 to 75 years for *path_MSH6*, and 3-yearly surveillance at age 40 to 75 years for *path_PMS2* heterozygotes (using a WTP threshold of US dollars $100,000/QALY).[12] Our results cannot be directly compared with this, because we considered compound strategies across all heterozygotes of pathogenic variants in MMR genes and the previous study was performed in the United States context with a consequently high WTP threshold, and the results are unlikely to apply in many other countries.

We used estimated sex- and MMR gene-specific first CRC risk and overall metachronous CRC risk to model initial CRC and up to 1 metachronous CRC in a single cohort of confirmed patients with LS with no history of CRC at age 20 years throughout their lifetime up to age 84 years. In our analysis, MMR gene-specific colonoscopic surveillance strategies were considered in the context of cumulative CRC risk (*MLH1* and *MSH2* vs *MSH6* vs *PMS2*). There was no compelling evidence to invalidate the assumption of the same velocity of tumor growth and the available guidelines currently do not recommend varying intervals between heterozygotes of pathogenic variants in different MMR genes.[4-8] Should new evidence emerge suggesting variable velocity, tailored surveillance interval will need to be considered. We considered the entirety of the population with LS and the results were aggregated on the basis of the relative proportion of each MMR gene,[31] as opposed to a compartmentalized single MMR gene perspective, incorporating observed adherence rate to interval-specific colonoscopic surveillance.[10,32-35] There is potential evidence that the relative distribution of each MMR gene in LS changes over time because of the complete mix of screening and detection overlay. However, if *path_MSH6* and *path_PMS2* heterozygotes were more prevalent than previously thought, that will only make our optimal strategy more cost-effective.

Kastrinos et al[12] simulated MMR gene-specific surveillance strategies in a single cohort of CRC-free patients with LS from age 25 to 75 years using MMR gene-specific CRC risk (males and females combined). Surveillance ended either at age 75 years, CRC diagnosis, or death, whichever occurred first, and surveillance after first CRC treatment and metachronous CRC development were not modeled. Surveillance strategies were tested separately for each of 4 MMR genes assuming 100% adherence to colonoscopy and the results were reported separately for each MMR gene. The model incorporated health state utilities associated with colonoscopy and stage-specific CRC and assumed 1- to 2-yearly surveillance resulted in slightly decreased stage III/IV diagnosis compared with 3-yearly surveillance (82% vs 89%). This resulted in larger effect on QALYs compared with life years associated with 3-yearly surveillance given utility values decreases with more advanced stage disease.

Despite the differences in the predicted optimal surveillance for each MMR gene, both analyses support less intensive surveillance in confirmed patients with LS with the relatively lower risk. We found that starting surveillance 5 to 10 years later for *path_MSH6* and *path_PMS2* heterozygotes than for *path_MLH1* and *path_MSH2* heterozygotes did not substantially change the effectiveness (vs uniform surveillance) neither did switching to less frequent surveillance after age 60 years (vs constant surveillance interval). However, switching to less frequent surveillance before age 40 years resulted in 10 additional CRC deaths per 1000 confirmed patients with LS. Therefore, consideration could be given to starting surveillance 5 to 10 years later for *path_MSH6* and *path_PMS2* heterozygotes than for *path_MLH1* and *path_MSH2* heterozygotes, and/or offering less intensive surveillance after age 60 years. Both analyses did not consider the additive effect of aspirin chemoprevention on CRC incidence reduction as reported in the latest Cancer Prevention Programme study findings.[36]

Our findings show a need for further studies to develop and validate tailored and risk-stratified colonoscopic surveillance strategies to provide critical information required for cost-effectiveness analysis of prevention and/or early detection of CRC in patients with LS. This information includes (1) sex- and MMR gene-specific cumulative risk of first CRC without colonoscopic surveillance and with surveillance by time since last colonoscopy and the recommended surveillance interval and (2) HR associated with different colonoscopic surveillance intervals (vs no surveillance) on CRC incidence in patients with LS. The predicted health impact and cost-effectiveness of colonoscopic surveillance strategies considering different risk profiles of each MMR gene could be re-evaluated once such empirical data become available to support cost-effectiveness modeling of risk-stratified testing and surveillance strategies and our microsimulation model "*Policy1-Lynch*" is able to adapt to the new emerging evidence and different cost assumptions.

Conclusion

We performed a comprehensive evaluation of the health impacts and cost-effectiveness of colonoscopic surveillance strategies for confirmed patients with LS that could potentially inform clinical practice guidelines and health services planning. We found that a tailored approach would be effective and cost-effective. At an indicative WTP threshold of A$30,000 to A$50,000/LYS, there were multiple cost-effective colonoscopic surveillance strategies for confirmed patients with LS. We found that cost-effectiveness was improved by starting surveillance 5 to 10 years later for *path_MSH6* and *path_PMS2* heterozygotes than for *path_MLH1* and *path_MSH2* heterozygotes and/or offering less intensive surveillance after age 60 years. As the surveillance interval increases, colonoscopic surveillance becomes more cost-effective, largely because of substantial reduction in colonoscopies, but it becomes less effective and prevents fewer CRC deaths. Ongoing emerging data on sex- and MMR gene-specific CRC risks in patients with LS with or without surveillance will reduce the uncertainty of lifetime risk estimates and inform ongoing discussions around optimal surveillance.

Data Availability

Data supporting the findings of this study are available within the article and the Supplemental methods and results (Appendix 1-9).

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Ethics Declaration

Ethics approval was not required for our modeled simulation based on aggregated data from prior publications. Authors reviewed previously published studies from which data is included in the manuscript to ensure that it was collected in compliance with appropriate principles of research ethics. Each study received Institutional Review Board/Research Ethics Committee approval, waiver, or exemption.

Conflict of Interest

K.C. is co–principle investigator of an investigator-initiated trial of cervical screening, "Compass", run by The Australian Centre for the Prevention of Cervical Cancer (ACPCC), which is a government-funded not-for-profit charity; "Compass" receives infrastructure support from the Australian government and the ACPCC has received equipment and a funding contribution from Roche Molecular Diagnostics, USA. She is also co–principle investigator on a major implementation program Elimination of Cervical Cancer in the Western Pacific which has received support from the Minderoo Foundation and the Frazer Family Foundation, and equipment donations from Cepheid Inc. She also receives support for a range of other Australian and international government projects including support from philanthropic organizations, WHO, and government agencies related to cervical cancer control. K.C. is a Chair or member of a number of government or meetings convened by the World Health Organization (WHO), or philanthropic organizations such as Bill and Melinda Gates Foundation (BMGF).

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Additional Information

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References

1. Lynch HT, de la Chapelle A. Hereditary colorectal cancer. *N Engl J Med*. 2003;348(10):919–932. http://doi.org/10.1056/NEJMra012242.
2. Prospective Lynch Syndrome Database. Prospective Lynch Syndrome Database (PLSD) – cumulative risk for cancer by age, genetic variant, and gender. Accessed August 18, 2019. http://lscarisk.org/.
3. Järvinen HJ, Aarnio M, Mustonen H, et al. Controlled 15-year trial on screening for colorectal cancer in families with hereditary nonpolyposis colorectal cancer. *Gastroenterology*. 2000;118(5):829–834. http://doi.org/10.1016/s0016-5085(00)70168-5.
4. Cancer Institute NSW. eviQ (Cancer Treatments Online): Risk Management for Lynch syndrome (ID: 1410 v.7). Accessed August 18, 2019.
5. National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines): Colon Cancer Version 2. 2019. Accessed May 15, 2019.
6. Syngal S, Brand RE, Church JM, et al. ACG clinical guideline: genetic testing and management of hereditary gastrointestinal cancer syndromes. *Am J Gastroenterol*. 2015;110(2):223–262;quiz 63. http://doi.org/10.1038/ajg.2014.435.
7. BC Cancer Agency, Hereditary Cancer Program. Understanding Lynch syndrome: hereditary nonpolyposis colorectal cancer (HNPCC). BC Cancer Agency. Published July 2004. Updated March 2015. Accessed August 18, 2019. http://www.bccancer.bc.ca/coping-and-support-site/Documents/Hereditary%20Cancer%20Program/HCP_BrochurePromo-Lynch%20SyndromeBooklet.pdf.
8. Monahan KJ, Bradshaw N, Dolwani S, et al. Guidelines for the management of hereditary colorectal cancer from the British Society of Gastroenterology (BSG)/Association of Coloproctology of Great Britain and Ireland (ACPGBI)/United Kingdom Cancer Genetics Group (UKCGG). *Gut*. 2020;69(3):411–444. http://doi.org/10.1136/gutjnl-2019-319915.
9. National Comprehensive Cancer Network (NCCN). NCCN clinical practice guidelines in oncology (NCCN Guidelines): Gnetic/Familial High-Risk Assessment: Colorectal. version 1.2021; May 11, 2021.
10. Engel C, Vasen HF, Seppälä T, et al. No difference in colorectal cancer incidence or stage at detection by colonoscopy among 3 countries with different Lynch syndrome surveillance policies. *Gastroenterology*. 2018;155(5):1400–1409.e2. http://doi.org/10.1053/j.gastro.2018.07.030.
11. Kang YJ, Killen J, Caruana M, et al. The predicted impact and cost-effectiveness of systematic testing of people with incident colorectal cancer for Lynch syndrome. *Med J Aust*. 2020;212(2):72–81. http://doi.org/10.5694/mja2.50356.
12. Kastrinos F, Ingram MA, Silver ER, et al. Gene-specific variation in colorectal cancer surveillance strategies for Lynch syndrome. *Gastroenterology*. 2021;161(2):453–462.e15. http://doi.org/10.1053/j.gastro.2021.04.010.
13. Price KV, Storn RM, Lampinen JA. *Differential Evolution: A Practical Approach to Global Optimization*. Springer; 2005.
14. Møller P, Seppälä TT, Bernstein I, et al. Cancer risk and survival in *path_MMR* carriers by gene and gender up to 75 years of age: a report from the Prospective Lynch Syndrome Database. *Gut*. 2018;67(7):1306–1316. Published correction appears in *Gut*. 2020;69(6):e4. https://doi.org/10.1136/gutjnl-2017-314057.
15. 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):2304–2310. http://doi.org/10.1001/jama.2011.743.
16. Lew J, Simms KT, Smith MA, et al. National Cervical Screening Program renewal: effectiveness modelling and economic evaluation in the Australian setting (assessment report). MSAC Application No. 1276. 2013. https://www.semanticscholar.org/paper/National-Cervical-Screening-Program-Renewal%3A-and-in-Lew-Simms/a94feff09efea3180015b362297ec00d7c0a362e#citing-papers.
17. Australian Government Department of Health. Quadrivalent human papillomavirus (types 6, 11, 16, 18) recombinant vaccine, injection, 0.5 mL, Gardasil November 2006. The pharmaceutical benefits scheme. Updated March 2, 2007. Accessed March 5, 2019. http://www.pbs.gov.au/info/industry/listing/elements/pbac-meetings/psd/2006-11/pbac-psd-gardasil-nov06.
18. Snowsill T, Coelho H, Huxley N, et al. Molecular testing for Lynch syndrome in people with colorectal cancer: systematic reviews and economic evaluation. *Health Technol Assess*. 2017;21(51):1–238. http://doi.org/10.3310/hta21510.
19. Snowsill T, Huxley N, Hoyle M, et al. A systematic review and economic evaluation of diagnostic strategies for Lynch syndrome. *Health Technol Assess*. 2014;18(58):1–406. http://doi.org/10.3310/hta18580.
20. Ten Broeke SW, van der Klift HM, Tops CMJ, et al. Cancer risks for PMS2-associated Lynch syndrome. *J Clin Oncol*. 2018;36(29):2961–2968. Published correction appears in *J Clin Oncol*. 2019;37(9):761. https://doi.org/10.1200/JCO.2018.78.4777.
21. Lindberg LJ, Rasmussen M, Andersen KK, Nilbert M, Therkildsen C. Benefit from extended surveillance interval on colorectal cancer risk in Lynch syndrome. *Colorectal Dis*. 2020;22(5):529–536. http://doi.org/10.1111/codi.14926.
22. de Vos tot Nederveen Cappel WH, Järvinen HJ, Lynch PM, Engel C, Mecklin JP, Vasen HF. Colorectal surveillance in Lynch syndrome families. *Fam Cancer*. 2013;12(2):261–265. http://doi.org/10.1007/s10689-013-9631-1.
23. Engel C, Rahner N, Schulmann K, et al. Efficacy of annual colonoscopic surveillance in individuals with hereditary nonpolyposis colorectal cancer. *Clin Gastroenterol Hepatol*. 2010;8(2):174–182. http://doi.org/10.1016/j.cgh.2009.10.003.
24. Mecklin JP, Aarnio M, Läärä E, et al. Development of colorectal tumors in colonoscopic surveillance in Lynch syndrome. *Gastroenterology*. 2007;133(4):1093–1098. http://doi.org/10.1053/j.gastro.2007.08.019.
25. Vasen HF, Abdirahman M, Brohet R, et al. One to 2-year surveillance intervals reduce risk of colorectal cancer in families with Lynch syndrome. *Gastroenterology*. 2010;138(7):2300–2306. http://doi.org/10.1053/j.gastro.2010.02.053.
26. Cirillo L, Urso ED, Parrinello G, et al. High risk of rectal cancer and of metachronous colorectal cancer in probands of families fulfilling the Amsterdam criteria. *Ann Surg*. 2013;257(5):900–904. http://doi.org/10.1097/SLA.0b013e31826bff79.
27. Parry S, Win AK, Parry B, et al. Metachronous colorectal cancer risk for mismatch repair gene mutation carriers: the advantage of more extensive colon surgery. *Gut*. 2011;60(7):950–957. http://doi.org/10.1136/gut.2010.228056.
28. Australian Bureau of Statistics. Life tables. Published October 30, 2019. Accessed June 19, 2020. https://www.abs.gov.au/statistics/people/population/life-tables/2016-2018.
29. Lew JB, St John DJB, Xu XM, et al. Long-term evaluation of benefits, harms, and cost-effectiveness of the National Bowel Cancer Screening Program in Australia: a modelling study. *Lancet Public Health*. 2017;2(7):e331–e340. http://doi.org/10.1016/S2468-2667(17)30105-6.
30. Dominguez-Valentin M, Sampson JR, Seppälä TT, 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*. 2020;22(1):15–25. Published correction appears in *Genet Med*. 2020;22(9):1569. https://doi.org/10.1038/s41436-019-0596-9.
31. Palomaki GE, McClain MR, Melillo S, Hampel HL, Thibodeau SN. EGAPP supplementary evidence review: DNA testing strategies aimed at reducing morbidity and mortality from Lynch syndrome. *Genet Med*. 2009;11(1):42–65. http://doi.org/10.1097/GIM.0b013e31818fa2db.
32. Newton K, Green K, Lalloo F, Evans DG, Hill J. Colonoscopy screening compliance and outcomes in patients with Lynch syndrome. *Colorectal Dis*. 2015;17(1):38–46. http://doi.org/10.1111/codi.12778.
33. Bleiker EM, Menko FH, Taal BG, et al. Screening behavior of individuals at high risk for colorectal cancer. *Gastroenterology*. 2005;128(2):280–287. http://doi.org/10.1053/j.gastro.2004.11.002.
34. Meiser B, Kaur R, Kirk J, et al. Evaluation of implementation of risk management guidelines for carriers of pathogenic variants in mismatch

repair genes: a nationwide audit of familial cancer clinics. *Fam Cancer*. 2020;19(4):337–346. http://doi.org/10.1007/s10689-020-00183-4.

35. Pylvänäinen K, Kairaluoma M, Mecklin JP. Compliance and satisfaction with long-term surveillance in Finnish HNPCC families. *Fam Cancer*. 2006;5(2):175–178. http://doi.org/10.1007/s10689-005-5442-3.
36. Burn J, Sheth H, Elliott F, et al. Cancer prevention with aspirin in hereditary colorectal cancer (Lynch syndrome), 10-year follow-up and registry-based 20-year data in the CAPP2 study: a double-blind, randomised, placebo-controlled trial. *Lancet*. 2020;395(10240):1855–1863. http://doi.org/10.1016/S0140-6736(20)30366-4.