Original Article

Yonsei Med J 2025 Dec;66(12):816-825
https://doi.org/10.3349/ymj.2024.0352

Yonsei Medical Journal
YMJ
pISSN: 0513-5796 · eISSN: 1976-2437

Cost-Utility Analysis of Universal Lynch Syndrome Screening among Colorectal Cancer Patients in a Low-Middle-Income Country

Cong Bang Huynh[1], Changsoo Kim[2], Nien Vinh Lam[1,3], and Van Viet Ung[1,4]

[1]Department of Endoscopy, University Medical Center Ho Chi Minh City, Ho Chi Minh City, Vietnam;
[2]Department of Preventive Medicine, Yonsei University College of Medicine, Seoul, Korea;
[3]Department of Biochemistry, Faculty of Medicine, University of Medicine and Pharmacy at Ho Chi Minh City, Ho Chi Minh City, Vietnam;
[4]Department of Surgery, Faculty of Medicine, University of Medicine and Pharmacy at Ho Chi Minh City, Ho Chi Minh City, Vietnam.

Purpose: Lynch syndrome (LS) is the most common hereditary cause of colorectal cancer (CRC). While screening for LS is recommended in Western countries, limited economic evaluations exist in lower-middle-income countries such as Vietnam, where CRC incidence is rapidly increasing. This study assessed the cost-utility of universal LS screening in Vietnam from the healthcare system's perspective.

Materials and Methods: We developed a decision-analytic model integrating decision trees and Markov models to compare the cost-effectiveness of three strategies: no screening, universal immunohistochemistry (IHC) followed by germline testing, and germline testing without prior tumor analysis. Cost data were derived from Vietnamese healthcare sources, and outcomes were measured in quality-adjusted life years (QALYs). To assess parameter uncertainty, we conducted both one-way sensitivity analysis and probabilistic sensitivity analysis.

Results: Universal LS screening was found to be highly cost-effective. Universal germline testing identified the most LS CRC patients (n=742), followed by universal IHC testing (n=646). Compared to no screening, the incremental cost-effectiveness ratios were 47615038 VND/QALY (1904 USD/QALY) for germline testing and 126095537 VND/QALY (5043 USD/QALY) for IHC. Key influential variables included LS prevalence, CRC risk in LS carriers, the proportion of relatives with LS accepting increased surveillance, the acceptance rate of LS testing among relatives, and germline testing cost.

Conclusion: All LS screening strategies for CRC patients are cost-effective within the Vietnamese health system, with germline testing being the most favorable. These findings support the inclusion of LS screening in health policies, even in resource-limited settings such as Vietnam.

Key Words: Colorectal cancer, Lynch syndrome, universal screening, cost-utility analysis, lower-middle-income countries, Vietnam

Received: November 4, 2024 **Revised:** May 22, 2025
Accepted: June 6, 2025 **Published online:** September 30, 2025
Corresponding author: Van Viet Ung, PhD, MD, Department of Surgery, Faculty of Medicine, University of Medicine and Pharmacy at Ho Chi Minh City, 217 Hong Bang Str., District 5, Ward 11, Ho Chi Minh City, 700000, Vietnam.
E-mail: viet.uv@umc.edu.vn

The content of the article was presented as an abstract at the 16th Asian Conference on Pharmacoepidemiology (ACPE) in 2024 in Tokyo, Japan.
•The authors have no potential conflicts of interest to disclose.

INTRODUCTION

With an age-standardized incidence of 13.9 cases per 100000 individuals in 2022, colorectal cancer (CRC) is one of the most frequent cancers in Vietnam.[1] Compared to prior decades, this represents a significant rise in incidence. By 2025, CRC is projected to be the most common cancer in Ho Chi Minh City and the second most common cancer in Hanoi, the two largest healthcare and population centers in Vietnam, for both males and females.[2]

Lynch syndrome (LS) accounts for the majority of hereditary disorders, with approximately 2%–3% of all CRC cases being attributed to its inheritance.[3] The LS condition can be at-

tributed to a mutation in any of the mismatch repair (MMR) genes, namely MLH1, MSH2, MSH6, PMS2, or EPCAM. Early-onset CRC with a high chance of recurrence, endometrial cancer, and other extracolonic malignancies are also characteristics of this syndrome. According to the U.S. guidelines for the genetic evaluation and management of LS, total colectomy was the recommended therapeutic approach for patients diagnosed with LS and presenting with colon cancer or colon neoplasia that cannot be removed through endoscopy.[4] The European Hereditary Tumour Group and the European Society of Coloproctology recommended ileosigmoidal/ileorectal anastomosis for newly diagnosed CRC in path MLH1 or path MSH2 carriers to reduce the risk of metachronous CRC.[5] Detection of LS in CRC patients is necessary, as affected patients and their family members can benefit from LS surveillance programs, which reduce the burden of CRC. The U.S. guidelines, as well as European guidelines, recommend routine LS screening via tumor testing in CRC patients.[4,5] The U.S. guidelines support universal tumor testing for LS, whereas European guidelines have recently recommended universal LS screening or routine screening of CRC patients up to 70 years of age.[4,5] The U.S. Multi-Society Task Force on Colorectal Cancer and European experts also believe that germline testing, rather than tumor testing, may be the most cost-effective universal testing technique in the near future when prices become affordable.[4]

Despite the documented benefits of screening programs for LS in CRC patients and its widespread adoption in many countries worldwide, LS testing remains limited in Vietnam—a lower-middle-income country that has historically prioritized infectious disease control. Currently, LS testing is conducted on a case-by-case basis, guided by physician recommendations. However, with the recent rise in noncommunicable diseases, including CRC, the Vietnamese Ministry of Health has introduced strategies such as the National Strategy for the Prevention and Control of Noncommunicable Diseases, Period 2015–2025, and the plan "Prevention, Early Detection, Management, and Treatment of Cancer, Cardiovascular Diseases, Diabetes, Chronic Obstructive Pulmonary Disease, Asthma, and Mental Health Disorders 2024–2025" (Decision 1651/QĐ-BYT). These efforts lay the groundwork for improving CRC prevention, with LS testing poised to receive greater attention in the near future.

The primary objective of our study was to assess the cost-effectiveness of implementing universal screening for LS among patients with CRC from the perspective of a healthcare system. Additionally, we sought to identify critical parameters that may influence the cost-effectiveness of LS screening and warrant consideration by Vietnamese policymakers and those in other lower-middle-income countries.

MATERIALS AND METHODS

Study plan

This study employed a cost-utility analysis to evaluate the economic value of universal LS screening among CRC patients in Vietnam. The analysis was conducted from the healthcare system's perspective and followed a lifetime horizon to comprehensively assess costs and outcomes. Costs were measured in Vietnamese dong (VND) and converted to USD for international comparison (1 USD=25000 VND). Prices from expert opinions and Vietnam's Public Portal for Healthcare Pricing (VPPHP) were collected in 2023. Prices obtained from other studies were adjusted for inflation using the Consumer Price Index. The primary outcome measure was quality-adjusted life years (QALYs), and results were reported as incremental cost-effectiveness ratios (ICERs). As there is no official cost-effectiveness threshold in Vietnam, we used the World Health Organization's (WHO) threshold of three times the gross domestic product per capita. The threshold was equal to 325950000 VND (13038 USD).[6]

Target population

The target population included CRC patients diagnosed in Vietnam and their first-degree relatives (FDRs). The incidence rate of CRC in Vietnam was estimated at 0.0139%.[1] Based on our local study, the prevalence of LS among Vietnamese CRC patients was 0.0632. The distribution of MMR gene mutations in our study was as follows: 0.25 for MSH2, 0.167 for MLH1, 0.167 for MSH6, and 0.416 for PMS2.

The inclusion of FDRs enabled the evaluation of cascade screening. Each CRC patient was assumed to have an average of 3.83 FDRs, based on Severin, et al.,[7] with an estimated germline mutation carrier rate of 0.44 among FDRs, according to Snowsill, et al.[8] No age restrictions were applied, ensuring the model's inclusivity across all age groups.

Diagnostic strategies

Fig. 1 depicts a flowchart for the two approaches.

In our study, we compared two distinct strategies for LS testing with the no screening approach. The first strategy, designated as Strategy 1, began by offering immunohistochemistry (IHC) testing to all diagnosed CRC patients using antibodies that target the MMR proteins produced by the four MMR genes: MLH1, MSH2, MSH6, and PMS2. An absent protein stain served as an indicator of the likely presence of a pathogenic variant in the corresponding gene, thereby prompting MMR sequencing of the said gene. Alternatively, Strategy 2 entailed the sequencing of all MMR genes using Next Generation Sequencing without prior tumor analysis. In case a causative alteration is identified in a CRC patient, targeted DNA testing for the same variant could be offered to their FDRs. Consequently, relatives who inherited the family-specific variant, which is characteristic of LS mutation carriers, would then be eligible for targeted prevention

programs.

The proportion of CRC patients accepting LS testing was assumed to be 0.85, based on Ramsoekh, et al.,[9] for both screening strategies. The proportion of FDRs agreeing to DNA testing was assumed to be 38.9%, according to Seppälä, et al.[10] The estimates from Palomaki, et al.[11] were used for the sensitivity and specificity of IHC laboratory testing, which were 0.87 and 0.91, respectively. Additionally, it was assumed that the sensitivity and specificity of germline testing in CRC patients and FDRs were both 100%.[11,12]

Model structure

Our study used a combined model that integrates a decision tree (Fig. 1) and a Markov model (Fig. 2) to evaluate the cost-utility of LS screening strategies among CRC patients in Vietnam. This modeling approach allowed us to comprehensively assess both the initial diagnostic process and long-term health and economic outcomes associated with LS screening.

Decision tree

The decision tree component of the model was designed to capture the initial diagnostic process, including the three strategies evaluated:

No screening

Patients receive standard CRC care without systematic LS screening.

Universal IHC testing (Strategy 1)

CRC patients undergo IHC testing to detect MMR protein deficiencies, followed by germline testing for patients with abnormal IHC results.

Universal germline testing (Strategy 2)

All CRC patients are offered germline testing directly, without prior tumor analysis.

The decision tree simulates the diagnostic outcomes for CRC patients and their FDRs, including the detection of LS mutation carriers and the cascade screening of FDRs.

Markov model

The Markov model was used to simulate the long-term progression of health states among CRC patients and their FDRs. The model included the following health states:

- Well: Individuals with no current cancer diagnosis.
- CRC: Patients diagnosed with CRC at various stages.
- Second cancer: Patients who develop an additional cancer following the primary CRC diagnosis.
- Alive after cancer: Individuals who survive treatment and remain cancer-free.
- Death: All-cause mortality or death due to cancer.

The model utilized annual cycles over a lifetime horizon to account for disease progression, preventive measures, and surveillance outcomes.

The probability of CRC for LS carriers was assumed to be 0.009, based on Snowsill, et al.[8] The CRC stage distribution among LS

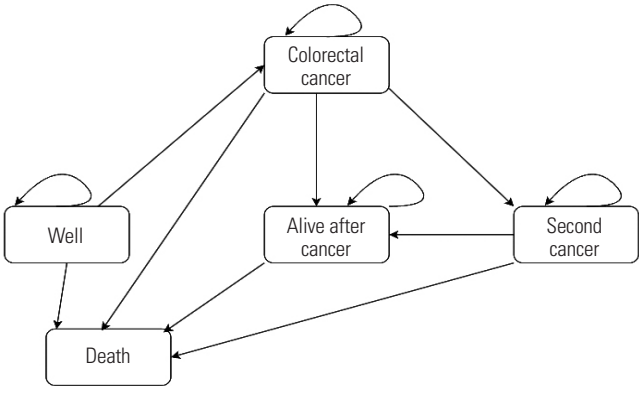

Fig. 2. Markov model.

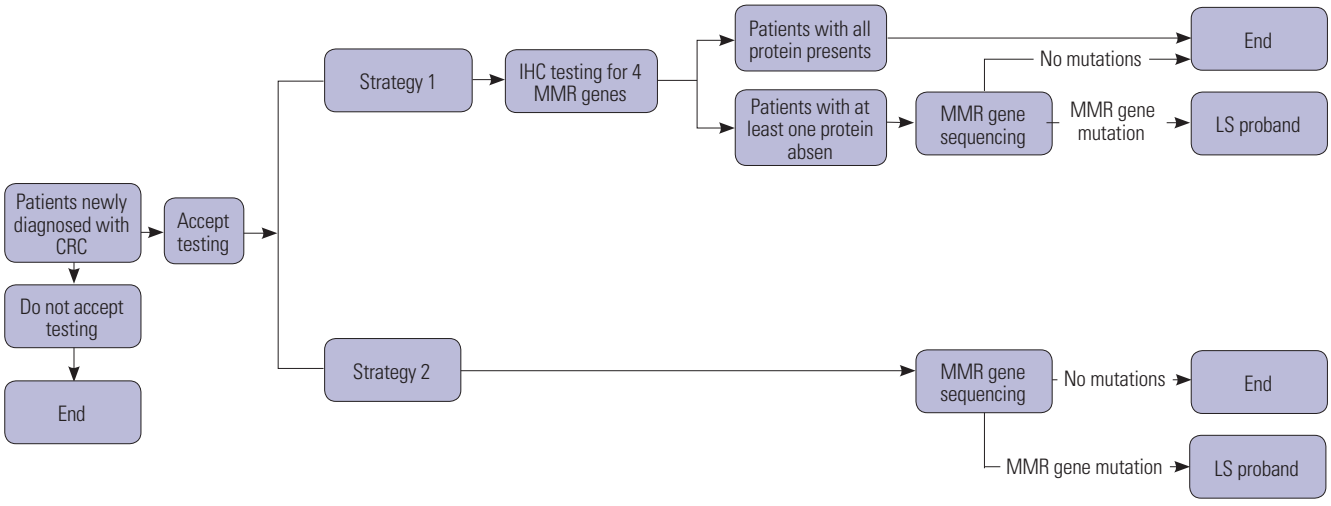

Fig. 1. Flowchart of the two diagnostic strategies for identifying LS. LS, Lynch syndrome; CRC, colorectal cancer; IHC, immunohistochemistry; MMR, mismatch repair.

https://doi.org/10.3349/ymj.2024.0352

carriers with increased surveillance was derived from Engel, et al.[13] For LS carriers not undergoing increased surveillance, the CRC stage distribution was assumed to be similar to that of the general CRC patient population and was based on data from Le, et al.[14] in Vietnam. The probability of developing a second CRC for LS carriers was assumed to be 0.0173, according to Parry, et al.[15] Additionally, the probability of death for CRC patients, stratified by stage and years from diagnosis, was derived from Snowsill, et al.[8]

Prevention program

In our model, the prevention programs for FDRs identified as LS mutation carriers included two main interventions:

Regular colonoscopy surveillance

FDR mutation carriers were assumed to undergo colonoscopy screening every two years starting from the recommended age (typically between 25–30 years or 10 years earlier than the youngest CRC case in the family). The average age at which screening begins was assumed to be 43.2 years, based on Snowsill, et al.[8] Participation in prevention programs was assumed to result in earlier detection of CRC at more favorable stages, leading to improved survival outcomes. The stage distribution for CRC detection among participants was adjusted based on previous studies to reflect the benefits of surveillance.[13,14]

Aspirin prophylaxis

Mutation carriers were assumed to receive low-dose aspirin as part of the prevention program, based on evidence suggesting its role in reducing CRC risk among LS carriers.

Among FDRs identified as mutation carriers, 80% were assumed to participate in regular prevention programs, including colonoscopy surveillance and aspirin prophylaxis. This adherence rate was based on estimates reported in the Severin, et al.[7] and Snowsill, et al.[8]

This combined approach was chosen because it enables a comprehensive evaluation of both short-term decisions (e.g., choice of screening strategy) and long-term outcomes (e.g., QALYs and costs). Decision trees are ideal for capturing immediate diagnostic outcomes, while Markov models are well-suited for simulating the lifetime consequences of those initial decisions, including disease progression and treatment effects.

The decision to use this modeling structure was informed by its successful application in similar studies conducted internationally.[16-19]

The model was reviewed by local experts in oncology and health economics to ensure its applicability to the Vietnamese context. Semi-structured interviews were conducted to validate key assumptions, input parameters, and the overall structure of the model. Although no formal validation study has been conducted for this specific model in Vietnam, its structure and methodology have been extensively tested in international settings, providing robust evidence for its reliability.

Parameters

Supplementary Table 1 (only online) presents the input parameters used in this study, which were derived from a combination of existing literature, semi-structured interviews, and expert opinions.

The model relied on several key assumptions to estimate the costs and health outcomes associated with LS screening strategies and the participation of FDRs in prevention programs. The main assumptions have been detailed in the relevant sections above. Additional assumptions include:

Discount rates

Costs were discounted at 5% per year, and health benefits (QALYs) were discounted at 3.5% per year. The 5% discount rate for costs reflects the financial conditions and inflationary environment in Vietnam. This rate is consistent with economic evaluations conducted in other lower-middle-income countries, where inflation and the time value of money tend to be higher. Using this rate ensures that the present value of future costs is appropriately adjusted for the economic context. The 3.5% discount rate for health outcomes is aligned with recommendations from international guidelines, such as those by the WHO and the UK National Institute for Health and Care Excellence. The use of differing discount rates is common in health economic evaluations and has been applied in several studies evaluating LS screening strategies.[16,17,19]

Costs

The cost of genetic testing was obtained from expert opinions at the University Medical Center of Ho Chi Minh City and data from VPPHP. The cost of colonoscopy was sourced from Tran, et al.[20] at Hue Central Hospital, Vietnam.

The cost of low-dose aspirin was estimated at 20000 VND (0.8 USD) per month, aggregated annually, based on VPPHP.

The cost of hospital treatment for complications from bleeding after colonoscopy was obtained from Tran, et al.[20] at Hue Central Hospital, Vietnam, while the cost of hospital treatment for complications from perforation after colonoscopy was derived from expert opinions at the University Medical Center of Ho Chi Minh City.

The cost of CRC treatment was also sourced from Tran, et al.[21] at Hue Central Hospital, Vietnam.

For cost of annual surveillance post-CRC, this cost includes one colonoscopy, one ultrasound, and one carcinoembryonic antigen test per year. The unit costs were obtained from VPPHP, while the surveillance procedures were determined based on expert opinions from gastroenterologists and oncologists at the University Medical Center of Ho Chi Minh City.

Utility values

The health states modeled included: healthy, cancer, alive af-

ter cancer, second cancer, and death. We assigned a QALY of 1 to the healthy state and 0 to death. Similar to the study by Pastorino, et al.,[19] we assumed that the alive after cancer state (health state for individuals who have been diagnosed with CRC, received treatment, and survived the disease without active recurrence or progression) had a QALY of 0.95.

For cancer, QALYs were assigned based on disease stage (I, II, III, and IV). In line with Pastorino, we referenced QALY values from the systematic review by Snowsill, et al.,[8] which compiled data from Ness. Specifically, the assigned QALYs for CRC patients were:

- Stage I: 0.74
- Stage II: 0.67
- Stage III: 0.50
- Stage IV: 0.25

For second cancer (occurrence of a new CRC in individuals who have previously been diagnosed with CRC), we assumed QALY values similar to those of the initial cancer, corresponding to the respective stage at diagnosis.

Model analysis

In the base-case analysis, we estimated the costs, health outcomes (QALYs), and ICERs for each screening strategy. The analysis was conducted from the Vietnamese healthcare system's perspective using a decision-analytic model that integrates decision trees and Markov models.

The base-case model compared three strategies:

1) No screening (standard CRC care without systematic LS screening).

2) Universal IHC testing (IHC for all CRC patients, followed by germline testing if IHC results are abnormal).

3) Universal germline testing (direct germline testing for all CRC patients without prior IHC).

For each strategy, we calculated:

- Total costs, including screening, surveillance, and treatment costs.
- Total QALYs gained for patients and their FDRs.
- ICERs relative to the no screening strategy.

The model was run using TreeAge Pro, applying a 5% discount rate for costs and 3.5% for health benefits.

To account for the uncertainty of input parameters, we conducted one-way sensitivity analysis and probabilistic sensitivity analyses (PSA). For the PSA, we performed 1000 Monte Carlo simulations, where input values were randomly sampled from the assigned distributions for each iteration. The theoretical distributions for input variables followed those used in previous studies by Ladabaum, et al.[22] and Severin, et al.[7]: beta distributions were assigned to probabilities, gamma distributions to costs, and a Poisson distribution to the number of FDRs undergoing screening. The parameters for these distributions are detailed in Supplementary Table 1 (only online).

Additionally, a one-way sensitivity analysis was conducted, varying each parameter individually within its specified range. The upper and lower bounds for these parameters are also provided in Supplementary Table 1 (only online).

Ethics statement

The protocol of the study was approved by the Institutional Review Board (IRB) of the University of Medicine and Pharmacy at Ho Chi Minh City, Vietnam (No. 618/HĐĐĐ-ĐHYD).

This study was conducted and reported in accordance with the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) guidelines to ensure comprehensive and transparent reporting of health economic evaluations (https://www.equator-network.org/reporting-guidelines/cheers/).

RESULTS

Table 1 showed the numbers of LS probands in patients diagnosed with CRC, the numbers of relatives tested for LS, the numbers of relatives with LS mutations detected, and the costs of screening for different testing strategies. The total number of relatives with LS mutations was 875 in the simulated popula-

Table 1. Numbers of LS Probands and Relatives and Costs for Each Strategy

	No screening	Universal IHC testing	Universal germline testing
No. of LS probands detected	0	646	742
No. of relatives tested for LS	0	964	1106
No. of relatives with LS mutations detected	0	424	487
Cost of detecting LS in CRC patients	0	34517800000 VND (1380712 USD)	29377500000 VND (1175100 USD)
Cost of detecting LS in relatives	0	1156800000 VND (46272 USD)	1327200000 VND (53088 USD)
Cost of surveillance and treatment for CRC in relatives with LS mutations	15696341952 VND (627853 USD)	25163944317 VND (1006557 USD)	4572519010 VND (182900 USD)
Total cost	15696341952 VND (627853 USD)	60838544317 VND (2433541 USD)	35277219010 VND (1411088 USD)

LS, Lynch syndrome; CRC, colorectal cancer; IHC, immunohistochemistry.

https://doi.org/10.3349/ymj.2024.0352

Table 2. Cost-Effectiveness Analysis Results Based on ICER among Different Strategies

Strategy	Cost	QALYs	Incremental costs per QALY gained (relative to no screening)	Incremental costs per QALY gained (relative to the strategy in the previous line)
No screening	15696341952 VND (627853 USD)	1186124		
Universal germline testing	35277219010 VND (1411088 USD)	1186535	47615038 VND/QALY (1904 USD/QALY)	47615038 VND/QALY (1904 USD/QALY)
Universal IHC testing	60838544317 VND (2433541 USD)	1186482	126095537 VND/QALY (5043 USD/QALY)	Dominated

ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years; IHC, immunohistochemistry.

tion. As expected, universal germline testing was the most efficient strategy to identify relatives with LS mutations. Universal germline testing identified 487 relatives with LS mutations, followed by 424 for universal IHC testing. Interestingly, universal germline testing was actually less expensive than universal IHC testing.

Table 2 revealed that universal germline testing was the most cost-effective strategy, offering 1186535 QALYs at a cost of 35277219010 VND (1411088 USD) with an ICER of 47615038 VND (1904 USD) per QALY gained relative to no screening. In contrast, universal IHC testing resulted in 1186482 QALYs at a much higher cost of 60838544317 VND (2433541 USD), leading to an ICER of 126095537 VND (5043 USD) per QALY gained relative to no screening. Considering a threshold of 325950000 VND (13038 USD)/QALY, both universal germline testing and universal IHC testing were cost-effective compared to no screening. Furthermore, the negative ICER when comparing universal IHC testing to universal germline testing indicated that universal IHC testing was both more expensive and less effective, making it an unfavorable option.

The one-way sensitivity analysis results are shown in the tornado diagrams (Supplementary Figs. 1-3, only online).

The first one-way sensitivity analysis (Supplementary Fig. 1, only online) evaluated universal germline testing compared to no screening. The ICER was most sensitive to the prevalence of LS among CRC patients, the probability of CRC among LS carriers, and the proportion of relatives with LS accepting increased surveillance. The acceptance rate of LS testing among relatives and CRC stage distribution without surveillance also had a notable impact, while costs related to complications, IHC characteristics, and the number of FDRs per patient showed minimal influence.

The second one-way sensitivity analysis (Supplementary Fig. 2, only online) compared universal IHC testing with no screening. Similar to the first analysis, the most influential factors were the prevalence of LS, the probability of CRC in LS carriers, and the acceptance of surveillance among relatives. The acceptance rate of LS testing among relatives, germline testing cost, and IHC sensitivity further influenced the ICER. Other parameters, including late-stage treatment costs and complications, were less impactful.

The third analysis (Supplementary Fig. 3, only online) compared universal germline testing with universal IHC testing. The dominant drivers of ICER included the prevalence of LS, the probability of CRC in LS carriers, and surveillance uptake among relatives. The cost of germline testing and the acceptance rate of LS testing among relatives also played important roles. In contrast, factors such as IHC sensitivity, costs of complications, and the number of FDRs per patient had minimal effect.

The cost-effectiveness acceptability curve illustrated the probability that each of the three strategies—universal germline testing, universal IHC testing, and no screening—was cost-effective across a range of willingness-to-pay (WTP) thresholds. Initially, no screening was the most cost-effective option at very low WTP values, but its acceptability quickly diminished as the WTP increased. Universal germline testing rapidly became the most favorable strategy, reaching a peak probability of around 70% at a WTP of approximately 50000000 VND (2000 USD), maintaining a dominant position thereafter. Universal IHC testing gradually increased in cost-effectiveness with higher WTP values, but never surpassed the probability of universal germline testing, indicating that universal germline testing was generally the most cost-effective option across most WTP values, especially in scenarios with higher WTP. No screening remained the least cost-effective as WTP increased, and universal IHC testing was less favored compared to universal germline testing at almost all WTP levels.

As shown in Fig. 3, at the specific WTP threshold of 325950000 VND, the probability of each strategy being cost-effective was: universal germline testing (60%), universal IHC testing (39.7%), and no screening (0.3%). This suggests that at the current WTP level in Vietnam, universal germline testing has the highest probability of being the most cost-effective strategy, followed by universal IHC testing, while no screening remains the least favorable option with a very low probability of cost-effectiveness.

DISCUSSION

LS screening in CRC patients helps personalize the treatment strategy for the patient with LS and allows for follow-up genetic screening for the patient's relatives. The life expectancy

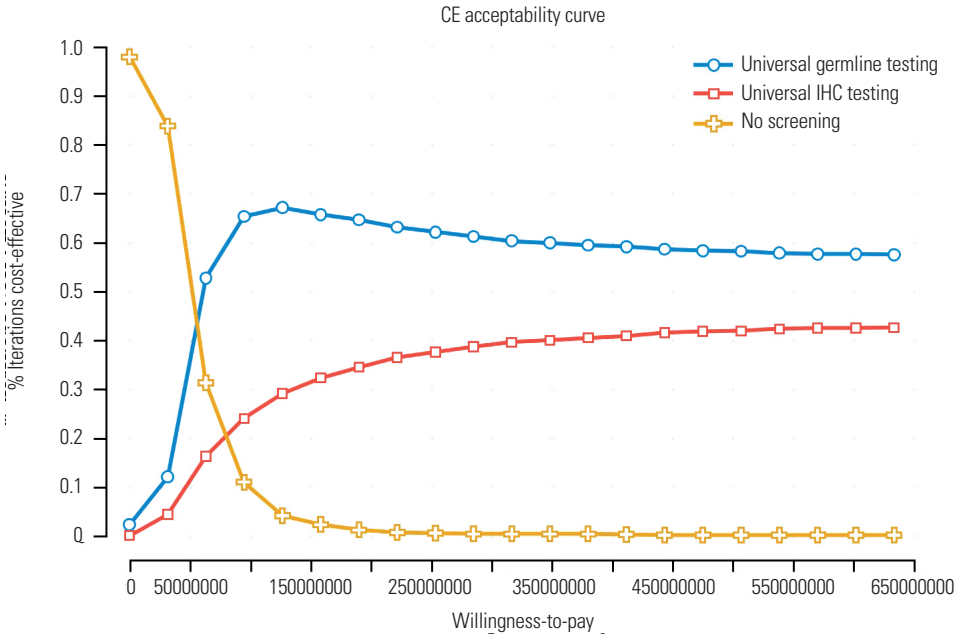

Fig. 3. Cost-effectiveness acceptability curve. IHC, immunohistochemistry.

and quality of life of disease carriers are increased by proactive disease prevention measures. In developed European nations and the United States, comparative cost-effectiveness analyses of LS screening strategies have been performed extensively.[17-19,22] Singapore and Taiwan conducted a cost-effectiveness analysis of LS screening in CRC patients.[16,23] Our study is one of the first to perform a cost-effectiveness analysis of LS screening in patients with CRC in a lower-middle-income country such as Vietnam.

Two typical screening methods for LS in CRC patients worldwide are 1) IHC testing followed by germline testing and 2) germline testing without prior tumor analysis. Usually, the initial option presents higher cost-efficiency compared to the latter.[8,18,19] Our findings indicated that germline testing without prior tumor analysis is more effective in the Vietnamese scenario. This can be explained by the fact that IHC testing is more expensive in Vietnam than in other countries. The price of the IHC test in Vietnam is approximately 2800000 VND (116 USD), whereas the price of an equivalent test in Italy and Taiwan is 64 USD and 62 USD, respectively.[16,19] In the meantime, the cost of germline testing in Vietnam is substantially lower than in other countries. The cost of germline testing in Vietnam is 2500000 VND (100 USD). Meanwhile, a test for reproductive cells in Italy costs 270 USD, in Taiwan it costs 4012 USD, and in Switzerland it costs 3791 USD.[16,18,19] Therefore, screening based on germline testing prior to tumor analysis is a practical and economical option for Vietnam. This intriguing discovery may considerably contribute to the improvement of LS screening in Vietnam.

The technique of screening CRC patients for LS using germline testing without prior tumor testing has long been projected to be the most cost-effective approach.[4,18] IHC testing, followed by genetic sequencing, is the current screening technique for LS.[16,18,19] Having to do sequential testing is inconvenient for patients and their families, resulting in up to 64% of CRC patients missing follow-up appointments.[24] In contrast, germline testing without prior tumor testing is nearly 100% accurate, enabling confirmation of the presence of all cases of LS and eliminating false-negative and false-positive diagnoses. This could lead to more personalized CRC treatments with improved patient results. This technique also helps reduce the number of CRC cases where patients opt out of LS screening due to the complexity of the screening process, detect more cases of non-carrying relatives, and diagnose CRC in these relatives at an earlier stage. Both the 2014 guidelines on genetic evaluation and management of LS (Guidelines on Genetic Evaluation and Management of Lynch Syndrome: A consensus statement by the US Multi-Society Task Force on Colorectal Cancer) and the majority of cost-effectiveness studies have predicted that germline testing without prior tumor testing will replace tumor testing as the most cost-effective approach to LS screening.[4,18] However, this will only be possible if the cost of germline testing is reduced to a reasonable level. From 2014 to 2021, studies showed that the method of germline testing without prior tumor testing is medically cost-effective, but it was not the best-performing technique when compared to other strategies, such as IHC testing.[16,18,19] In 2022, the Salikhanov, et al.[18] in Switzerland assessed the comparative health-economic effectiveness of two screening procedures for LS, namely primary screening by tumor testing (the current strategy) and germline testing without prior tumor testing (alternative strategy). In around 80% of cases, germline and cascade testing for relatives was cost-effective.

https://doi.org/10.3349/ymj.2024.0352

This method saved 17 lives at a cost of CHF 645 per death, with an ICER of CHF 65058 per QALY saved and a cost-effectiveness threshold of 100000 CHF in Switzerland.[18]

In the majority of previous cost-effectiveness studies regarding LS screening in CRC patients, the clinical criteria approach, such as the revised Bethesda criteria, was utilized as one of the comparison arms.[16,19,22] Due to its limited applicability, this strategy is used less frequently over time. Due to its unavailability in the Vietnamese context, this strategy was excluded from our comparative arm. Previously, the application of the Amsterdam II criteria for colorectal and other cancers involved clinical and pedigree evaluation. The clinical criteria used to identify patients at high risk for CRC are complex and difficult to implement in practice. Between 23% and 50% of cases may be missed by the revised Amsterdam II and Bethesda guidelines.[25]

Several population-specific parameters, such as the cost of genetic testing and the prevalence of LS among CRC patients, can result in differences in the analysis results between our study and others.

The cost of genetic testing is an important factor. In the one-way sensitivity analysis, the results of Salikhanov, et al.[18] revealed that the number of invited relatives and the cost of germline DNA sequencing for patients with CRC had a major impact on the outcome. In the deterministic analysis of ICER for universal germline testing compared to universal IHC testing in our study, the cost of germline testing was identified as one of the most influential factors affecting the cost-effectiveness between the two strategies. ICER is not only directly impacted by the cost of genetic testing but also indirectly by the acceptance rate of testing among CRC patients and their relatives. The cost of genetic testing in our study is 2500000 VND (100 USD) for CRC patients and 1200000 VND (48 USD) for their relatives. The cost of these tests is very low compared to those of previous studies, which significantly contributed to lowering the ICER and demonstrating the effectiveness of the LS screening program in Vietnam.[16,18,19] Concerning the indirect influence of ICER through test acceptance, Chieng and Lee[26] report on genetic testing acceptance in Singapore revealed that only 35% of patients and relatives agreed to undertake the test, with price concerns (60%) being the primary reason patients cited for refusing the test. In Singapore, the cost of testing is entirely paid by the patient and is considerably higher than the median household income of 4000 USD in 2012, according to government data.[26] In the 2006 Chieng and Lee[27] conducted in Singapore, acceptance of the BRCA1/2 test increased from 4% prior to 2004 to 44% between 2004 and 2006, when the government agreed to pay for the test. In 2006, after the government subsidy program ceased, the rate of BRCA1/2 testing dropped to 23%. In recent years, patient adoption of the test has increased, despite the fact that cost remains a significant barrier to the decision to perform the test. More than half of respondents cited cost as their reason for declining a test. In fact, among the 69 patients who underwent BRCA1/2 testing in Chieng and Lee,[26] more than 50 percent of these patients were funded by the government, which can be viewed as a contributing factor. Numerous studies have similarly identified cost as a barrier to genetic testing.[28,29] These studies demonstrated that health programs that fund testing for moderate-to-high-risk individuals could improve the delivery of genetic information with the ultimate aim of identifying individuals contain mutations in order to monitor or implement cancer prevention programs that reduce incidence, mortality, and medical costs.

The prevalence of LS among CRC patients is an additional factor that significantly impacted the study design. Taiwan's analysis model demonstrated that this was the most influential factor on the ICER.[16] According to our research, this was also one of the most influential factors on ICER. Vietnam has a 6.32% prevalence rate of LS in CRC patients. When focusing on the key genes MLH1, MSH2, and MSH6, the prevalence was 3.7%. This frequency is comparable to that found in Nadine's 2022 global meta-analysis of the prevalence of LS in CRC patients.[3] Northeast Asia was the location where the first studies on the prevalence of LS in Asia were conducted, and these studies revealed fewer cases than studies conducted in Europe and the United States. In 2003, Jeong, et al.[30] Korean investigation revealed that only 0.4% of patients with CRC had LS. In 2017, Kumamoto, et al.[31] in Japan revealed that 0.7% of CRC patients had LS. The minimal prevalence of LS in Northeast Asia is not, however, representative of Asia as a whole. The prevalence of LS among CRC patients in Beijing in 2020 was 2.7%, which is roughly equivalent to the rate in the United States, which was 3%.[32] The research conducted by Jiang in Guangzhou (South China) revealed that the prevalence of LS in CRC patients was as high as 2.9%.[33] The rate of LS in CRC patients was also 2.3%, according to a study conducted by Chang, et al.[34] in Taiwan, where population characteristics are comparable to those of mainland China. According to studies of Vietnamese genomes, Vietnamese alleles are comparable to those of the Thai and South Chinese populations.[35] This may explain why the prevalence of LS gene mutations in the Vietnamese population is comparable to that of the South Chinese.

Likewise, our study has numerous limitations. First, only direct medical costs were included in our study. The model would be more inclusive and valid if it included indirect medical expenditures. To obtain these data, however, additional health economics evaluation studies are required. Second, our research did not include preventative measures against gastric cancer in its computational model. According to studies conducted in Japan and China, gastric cancer may be the most prevalent non-colon cancer.[36,37] However, due to limited data availability and the absence of a structured gastric cancer screening program in Vietnam, we did not include it in our model. Future research should address this limitation as more data become available. Finally, since there are no studies on some parameters in Vietnam, many parameters in our research model were derived from studies conducted in other countries. In both one-way

sensitivity analyses for the IHC and germline testing strategies, despite significant variations in key parameters, the ICERs for both strategies remained below the WTP threshold of 325950000 VND. Therefore, these parameters do not impact the overall conclusion regarding the cost-effectiveness of LS screening. While some parameters lack Vietnam-specific data and further research is needed to refine these estimates, our findings strongly suggest that universal screening for LS, using either strategy, remains cost-effective in the Vietnamese context.

Our study evaluated the cost-effectiveness of screening for LS in CRC patients in Vietnam. The study results indicated that all the screening strategies for LS are cost-effective compared with no screening in terms of the Vietnamese health system. In particular, screening by germline testing without prior tumor testing was the most cost-effectiveness strategy. Therefore, LS screening in CRC patients should be considered in health policies, even in lower-middle-income countries such as Vietnam.

ACKNOWLEDGEMENTS

This study was supported by an MEF Fellowship conducted as part of the "Education and Research Capacity-Building Project at the University of Medicine and Pharmacy at Ho Chi Minh City," implemented by the Korea International Cooperation Agency (KOICA) during 2021–2026 (No. 2021-00020-4)

AUTHOR CONTRIBUTIONS

Conceptualization: Cong Bang Huynh, Nien Vinh Lam, and Van Viet Ung. Data curation: Cong Bang Huynh and Van Viet Ung. Formal analysis: Cong Bang Huynh, Nien Vinh Lam, and Van Viet Ung. Funding acquisition: Cong Bang Huynh and Changsoo Kim. Investigation: Cong Bang Huynh and Nien Vinh Lam. Methodology: Cong Bang Huynh, Nien Vinh Lam, and Van Viet Ung. Project administration: Nien Vinh Lam and Van Viet Ung. Resources: Van Viet Ung. Software: Changsoo Kim. Supervision: Changsoo Kim, Nien Vinh Lam, and Van Viet Ung. Validation: Nien Vinh Lam and Van Viet Ung. Visualization: Van Viet Ung. Writing—original draft: Huynh Cong Bang. Writing—review & editing: Nien Vinh Lam and Van Viet Ung. Approval of final manuscript: all authors.

ORCID iDs

Cong Bang Huynh https://orcid.org/0000-0002-8816-0812
Changsoo Kim https://orcid.org/0000-0002-5940-5649
Nien Vinh Lam https://orcid.org/0000-0003-2161-8523
Van Viet Ung https://orcid.org/0000-0003-3168-4831

REFERENCES

1. International Agency for Research on Cancer. GLOBOCAN 2022 [accessed on 2025 January 24]. Available at: https://gco.iarc.who.int/media/globocan/factsheets/populations/900-world-fact-sheet.pdf.
2. Nguyen SM, Deppen S, Nguyen GH, Pham DX, Bui TD, Tran TV. Projecting cancer incidence for 2025 in the 2 largest populated cities in Vietnam. Cancer Control 2019;26:1073274819865274.
3. Abu-Ghazaleh N, Kaushik V, Gorelik A, Jenkins M, Macrae F. Worldwide prevalence of Lynch syndrome in patients with colorectal cancer: systematic review and meta-analysis. Genet Med 2022;24:971-85.
4. 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 2014;147:502-26.
5. Seppälä TT, Latchford A, Negoi I, Sampaio Soares A, Jimenez-Rodriguez R, Sánchez-Guillén 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 2021;108:484-98.
6. General Statistics Office of Vietnam. Key indicators on national accounts by items and year 2023 [Internet] [accessed on 2025 January 24]. Available at: https://www.nso.gov.vn/wp-content/uploads/2024/07/NG-TCTK-2023_Final.pdf.
7. Severin F, Stollenwerk B, Holinski-Feder E, Meyer E, Heinemann V, Giessen-Jung C, et al. Economic evaluation of genetic screening for Lynch syndrome in Germany. Genet Med 2015;17:765-73.
8. Snowsill T, Coelho H, Huxley N, Jones-Hughes T, Briscoe S, Frayling IM, et al. Molecular testing for Lynch syndrome in people with colorectal cancer: systematic reviews and economic evaluation. Health Technol Assess 2017;21:1-238.
9. Ramsoekh D, van Leerdam ME, Wagner A, Kuipers EJ, Steyerberg EW. Mutation prediction models in Lynch syndrome: evaluation in a clinical genetic setting. J Med Genet 2009;46:745-51.
10. Seppälä TT, Pylvänäinen K, Mecklin JP. Uptake of genetic testing by the children of Lynch syndrome variant carriers across three generations. Eur J Hum Genet 2017;25:1237-45.
11. 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;11:42-65.
12. Pritchard CC, Smith C, Salipante SJ, Lee MK, Thornton AM, Nord AS, et al. ColoSeq provides comprehensive Lynch and polyposis syndrome mutational analysis using massively parallel sequencing. J Mol Diagn 2012;14:357-66.
13. Engel C, Rahner N, Schulmann K, Holinski-Feder E, Goecke TO, Schackert HK, et al. Efficacy of annual colonoscopic surveillance in individuals with hereditary nonpolyposis colorectal cancer. Clin Gastroenterol Hepatol 2010;8:174-82.
14. Le DD, Vo TV, Sarakarn P. Overall survival rate of Vietnamese patients with colorectal cancer: a hospital-based cohort study in the central region of Vietnam. Asian Pac J Cancer Prev 2021;22:3569-75.
15. Parry S, Win AK, Parry B, Macrae FA, Gurrin LC, Church JM, et al. Metachronous colorectal cancer risk for mismatch repair gene mutation carriers: the advantage of more extensive colon surgery. Gut 2011;60:950-7.
16. Chen YE, Kao SS, Chung RH. Cost-effectiveness analysis of different genetic testing strategies for Lynch syndrome in Taiwan. PLoS One 2016;11:e0160599.
17. Mvundura M, Grosse SD, Hampel H, Palomaki GE. The cost-effectiveness of genetic testing strategies for Lynch syndrome among newly diagnosed patients with colorectal cancer. Genet Med 2010;12:93-104.
18. Salikhanov I, Heinimann K, Chappuis P, Buerki N, Graffeo R, Heinzelmann V, et al. Swiss cost-effectiveness analysis of universal screening for Lynch syndrome of patients with colorectal cancer followed by cascade genetic testing of relatives. J Med Genet 2022;59:924-30.
19. Pastorino R, Basile M, Tognetto A, Di Marco M, Grossi A, Lucci-Cordisco E, et al. Cost-effectiveness analysis of genetic diagnostic

strategies for Lynch syndrome in Italy. PLoS One 2020;15:e0235038.
20. Tran BT, Choi KS, Sohn DK, Kim SY, Suh JK, Tran TH, et al. Estimating cost-effectiveness of screening for colorectal cancer in Vietnam. Expert Rev Pharmacoecon Outcomes Res 2021;21:1211-20.
21. Tran BT, Choi KS, Nguyen TX, Sohn DK, Kim SY, Suh JK, et al. The direct and indirect costs of colorectal cancer in Vietnam: an economic analysis from a social perspective. Int J Environ Res Public Health 2020;18:12.
22. Ladabaum U, Wang G, Terdiman J, Blanco A, Kuppermann M, Boland CR, et al. Strategies to identify the Lynch syndrome among patients with colorectal cancer: a cost-effectiveness analysis. Ann Intern Med 2011;155:69-79.
23. Wang VW, Koh PK, Chow WL, Lim JF. Predictive genetic testing of first degree relatives of mutation carriers is a cost-effective strategy in preventing hereditary non-polyposis colorectal cancer in Singapore. Fam Cancer 2012;11:279-89.
24. Zumstein V, Vinzens F, Zettl A, Heinimann K, Koeberle D, von Flüe M, et al. Systematic immunohistochemical screening for Lynch syndrome in colorectal cancer: a single centre experience of 486 patients. Swiss Med Wkly 2016;146:w14315.
25. Trujillo-Rojas MA, Ayala-Madrigal ML, Gutiérrez-Angulo M, González-Mercado A, Moreno-Ortiz JM. Diagnosis of patients with Lynch syndrome lacking the Amsterdam II or Bethesda criteria. Hered Cancer Clin Pract 2023;21:21.
26. Chieng WS, Lee SC. Discrepancy between initial high expression of interest in clinical cancer genetic testing and actual low uptake in an Asian population. Genet Test Mol Biomarkers 2012;16:785-93.
27. Chieng WS, Lee SC. Establishing a cancer genetics programme in Asia - the Singapore experience. Hered Cancer Clin Pract 2006;4:126-35.
28. Kieran S, Loescher LJ, Lim KH. The role of financial factors in acceptance of clinical BRCA genetic testing. Genet Test 2007;11:101-10.
29. Suther S, Kiros GE. Barriers to the use of genetic testing: a study of racial and ethnic disparities. Genet Med 2009;11:655-62.
30. Jeong SY, Shin KH, Shin JH, Ku JL, Shin YK, Park SY, et al. Microsatellite instability and mutations in DNA mismatch repair genes in sporadic colorectal cancers. Dis Colon Rectum 2003;46:1069-77.
31. Kumamoto K, Ishida H, Suzuki O, Tajima Y, Chika N, Kuwabara K, et al. Lower prevalence of Lynch syndrome in colorectal cancer patients in a Japanese hospital-based population. Surg Today 2016;46:713-20.
32. Dong L, Jin X, Wang W, Ye Q, Li W, Shi S, et al. Distinct clinical phenotype and genetic testing strategy for Lynch syndrome in China based on a large colorectal cancer cohort. Int J Cancer 2020;146:3077-86.
33. Jiang W, Cai MY, Li SY, Bei JX, Wang F, Hampel H, et al. Universal screening for Lynch syndrome in a large consecutive cohort of Chinese colorectal cancer patients: high prevalence and unique molecular features. Int J Cancer 2019;144:2161-8.
34. Chang SC, Lin PC, Yang SH, Wang HS, Liang WY, Lin JK. Taiwan hospital-based detection of Lynch syndrome distinguishes 2 types of microsatellite instabilities in colorectal cancers. Surgery 2010;147:720-8.
35. Tran NH, Vo TB, Nguyen VT, Tran NT, Trinh TN, Pham HT, et al. Genetic profiling of Vietnamese population from large-scale genomic analysis of non-invasive prenatal testing data. Sci Rep 2020;10:19142.
36. Kanaya N, van Schaik TA, Aoki H, Sato Y, Taniguchi F, Shigeyasu K, et al. High risk of multiple gastric cancers in Japanese individuals with Lynch syndrome. Ann Gastroenterol Surg 2024;8:1008-16.
37. Cai SJ, Xu Y, Cai GX, Lian P, Guan ZQ, Mo SJ, et al. Clinical characteristics and diagnosis of patients with hereditary nonpolyposis colorectal cancer. World J Gastroenterol 2003;9:284-7.