Patient preference and cost-effectiveness analysis of colorectal cancer screening and treatment

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A Dissertation Submitted in Partial Fulfillment of the Requirements

for the Degree of Doctor of Philosophy (Economics) in Economics

Common Course

Faculty of Economics

Chulalongkorn University

Academic Year 2019

ความพึงพอใจของผู้ป่วยและการวิเคราะห์ต้นทุนประสิทธิผลของการคัดกรองและรักษามะเร็งลำไส้ใหญ่และทวารหนัก

น.ส.พจมาน พิศาลประภา

วิทยานิพนธ์นี้เป็นส่วนหนึ่งของการศึกษาตามหลักสูตรปริญญาเศรษฐศาสตรดุษฎีบัณฑิต
สาขาวิชาเศรษฐศาสตร์ ไม่สังกัดภาควิชา/เทียบเท่า
คณะเศรษฐศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย
ปีการศึกษา 2562

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พจมาน พิศาลประภา : ความพึงพอใจของผู้ป่วยและการวิเคราะห์ต้นทุนประสิทธิผลของการคัดกรองและรักษามะเร็งลำไส้ใหญ่และทวารหนัก. (Patient preference and cost-effectiveness analysis of colorectal cancer screening and treatment) อ.ที่ปรึกษาหลัก : ศ. ดร.ศิริเพ็ญ ศุภกาญจนกันติ, อ.ที่ปรึกษาร่วม : รศ. ดร.ณธร ชัยญาคุณาพฤกษ์

ภูมิหลัง/วัตถุประสงค์: ประเทศพัฒนาแล้วมีรายงานความคุ้มค่าของการคัดกรองและการรักษามะเร็งลำไส้ใหญ่และทวารหนัก แต่ยังไม่มีการศึกษาในประเทศที่มีรายได้น้อยถึงปานกลาง งานวิจัยนี้มีวัตถุประสงค์เพื่อศึกษาปัจจัยที่มีผลต่อความพึงพอใจของผู้ป่วยและการวิเคราะห์ต้นทุนประสิทธิผลของการคัดกรองและรักษามะเร็งลำไส้ใหญ่และทวารหนัก

วิธีการวิจัย: งานวิจัยนี้แบ่งเป็นสามส่วน ส่วนที่หนึ่งศึกษาปัจจัยที่มีผลต่อความพึงพอใจของผู้ป่วยในการคัดกร อง มะเร็งลำไส้ใหญ่และทวารหนัก โดยใช้การทดลองทางเลือกและวิเคราะห์การถดถอยโลจิสติกพหุกลุ่ม ส่วนที่สองวิเคราะห์ต้นทุนประสิทธิผลและผลกระทบด้านงบประมาณของการคัดกรอง โดยเปรียบเทียบการตรวจอุจจาระทุกปีกับการส่องกล้องลำไส้ใหญ่ทุก 10 ปี ผลลัพธ์จากการศึกษาส่วนแรกจะนำไปสู่การเพิ่มอัตราการเข้าร่วมการคัดกรองซึ่งมีความสำคัญต่อการวิเคราะห์ต้นทุนประสิทธิผลของวิธีที่ใช้คัดกรอง ส่วนที่สามได้วิเคราะห์ต้นทุนประสิทธิผลและผลกระทบด้านงบประมาณของการรักษามะเร็งระยะที่สาม เพื่อหาการรักษาที่คุ้มค่าที่สุดสำหรับประเทศไทย ข้อมูลในแบบจำลองได้จากฐานข้อมูลการคัดกรองและการรักษามะเร็งลำไส้ใหญ่และทวารหนักของโรงพยาบาลศิริราช ฐานข้อมูลของประเทศไทย และการทบทวนวรรณกรรมอย่างเป็นระบบ

ผลการศึกษา: ผู้เข้าร่วมการศึกษาจำนวน 400 คน เลือกการคัดกรองที่สามารถลดอัตราการเสียชีวิตจากมะเร็งลำไส้ใหญ่และทวารหนักได้สูง ไม่มีภาวะแทรกซ้อน ตรวจซ้ำทุก 5 ปี เตรียมลำไส้น้อย และราคาถูก การตรวจอุจจาระทุกปีเป็นทางเลือกที่ผู้เข้าร่วมการศึกษามีความเต็มใจที่จะจ่ายและยินยอมเข้าร่วมการคัดกรองสูงสุด จากผลการวิเคราะห์ต้นทุนประสิทธิผลพบว่าทั้งการตรวจอุจจาระและการส่องกล้องลำไส้ใหญ่มีความคุ้มค่าเมื่อเทียบกับการไม่ตรวจคัดกรอง และการส่องกล้องลำไส้ใหญ่มีความคุ้มค่ามากกว่าเมื่อเทียบกับการตรวจอุจจาระ อย่างไรก็ตาม การส่องกล้องลำไส้ใหญ่มีผลกระทบด้านงบประมาณสูงกว่า 8 เท่าและต้องใช้ทรัพยากรสูงกว่ามาก สำหรับการรักษามะเร็งระยะที่สาม ยาสูตรใหม่ อาทิเช่น capecitabine และ irinotecan จะมีความคุ้มค่าเมื่อราคายาลดลงประมาณร้อยละ 50-80 และผลกระทบด้านงบประมาณของการตรวจคัดกรองตั้งแต่ระยะแรกต่ำกว่าการรักษามะเร็งระยะที่สามเนื่องจากการป้องกันการเสียชีวิตก่อนวัยอันควร

สรุป: งานวิจัยนี้แสดงปัจจัยที่มีผลต่อความพึงพอใจของผู้ป่วยในการคัดกรองมะเร็งลำไส้ใหญ่และทวารหนัก ในชีวิตจริง ร่วมกับการวิเคราะห์ต้นทุนประสิทธิผลของการคัดกรองและรักษามะเร็งลำไส้ใหญ่และทวารหนัก การตรวจอุจจาระทุกปีเป็นทางเลือกที่มีความคุ้มค่าเป็นไปได้จริงในการดำเนินโครงการและได้รับความพึงพอใจสูงสุด ในขณะที่ยาใหม่สำหรับการรักษามะเร็งระยะที่สามไม่มีความคุ้มค่า ผู้กำหนดนโยบายสามารถนำความรู้จากการศึกษานี้มาพัฒนาอัตราการคัดกรองและการเลือกยาที่เหมาะสมสำหรับมะเร็งลำไส้ใหญ่และทวารหนักในประเทศไทยได้

สาขาวิชา	เศรษฐศาสตร์	ลายมือชื่อนิสิต .....
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5885907429 : MAJOR ECONOMICS

KEYWORD: preference, cost-effectiveness analysis, screening, treatment, colorectal cancer, Thailand

Pochamana Phisalprapa : Patient preference and cost-effectiveness analysis of colorectal cancer screening and treatment. Advisor: Prof. SIRIPEN SUPAKANKUNTI, Ph.D. Co-advisor: Assoc. Prof. Nathorn Chaiyakunapruk, Ph.D.

Background/Aims: Colorectal cancer (CRC) screening and treatment have been reported to be cost-effective in many high-income countries. However, there was no such study in low- and middle-income countries (LMICs). This study aimed to assess the factors determine individuals' preferences and cost-effectiveness of CRC screening and treatment.

Methods: This study consists of three parts. The first part focused on the factors determine individuals' preferences for CRC screening using discrete choice experiment and multinomial logit model. The second part investigated the cost-effectiveness and budget impact analyses of CRC screening comparing between annual fecal immunochemical test (FIT) and colonoscopy every 10 years. The results from the first part can be used to improve patients' participation rate which is the key factor for the cost-effectiveness analysis of the screening tests. Finally, the last part evaluated the cost-effectiveness and budget impact analyses of CRC stage III treatment. This part aimed to identify the most cost-effective treatment regimen in Thailand. The input parameters were obtained from Siriraj CRC screening and treatment projects, health care costs and databases of Thailand, and systematic literature review.

Results: A total of 400 respondents preferred screening with high risk reduction of CRC-related mortality, no complication, 5-year interval, less bowel preparation, and lower cost. FIT is the preferred choice of screening with the highest willingness-to-pay and uptake rate. From cost-effectiveness analysis results, both FIT and colonoscopy were cost-effective when compared to no screening. Colonoscopy was cost-effective when compared to FIT. However, colonoscopy required 8-times higher budget and more human resource than FIT. In addition, for CRC stage III, the new regimens of capecitabine and irinotecan will be cost-effective if the prices were reduced about 50-80%. The budget impact of early screening was lower than treatment due to the preventing of premature deaths.

Conclusions: This study provides real-world patients' preference and cost-effectiveness evidence of CRC screening and treatment. Annual FIT was preferred to other screening tests and it could be implemented with no human resource and financial constraint. The new drugs for CRC stage III treatment were not cost-effective. Policy makers can use these findings to improve the success rate of CRC screening and appropriate treatment in Thailand.

Field of Study: Economics Student's Signature .....

Academic Year: 2019 Advisor's Signature .....

Co-advisor's Signature .....

ACKNOWLEDGEMENTS

I would like to thank many persons involved in my thesis. First of all, I would like to express my gratitude to Prof. Siripen Supakankunti, Ph.D. my thesis advisor and Assoc. Prof. Nathorn Chaiyakunapruk, Ph.D. my thesis co-advisor for their guidance, valuable comments, advice, and enthusiastic support during the preparation of this thesis.

I am very grateful to Assoc. Prof. Sothitorn Mallikamas, Ph.D., as the chairperson in my committee, Assist. Prof. Nopphol Witvorapong, Ph.D., Assoc. Prof. Kannika Damrongplasit, Ph.D., Prof. Chitr Sitthi-Amorn, M.D., Ph.D., member of committee for their kindly support and useful suggestion. I also would like to thank Ph.D. program in Economics, Faculty of Economics, Chulalongkorn University for academic supports. I also would like to thank Miss Orawan Thongya, program secretary, for her helpful.

I would like to acknowledge Chayanis Kositamongkol, research assistant, for collecting the data. I would also like to express our gratitude to Associate Professor Surachat Ngorsuraches, Ph.D., Harrison School of Pharmacy, Auburn University, USA. for his careful review and suggestions to improve our reporting of this study.

I would like to take opportunity to thank all lecturers who give me the knowledge and all staffs at Ph.D. program in Economics for their help during my study at Chulalongkorn University. Many thanks to all of my best classmates for their good advice, encouragement, and moral support.

Finally, I would like to offer my immense gratitude to my family for their love, understanding, and encouragement for a successful thesis.

Pochamana Phisalprapa

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LIST OF ABBREVIATIONS

ABBREVIATIONS	FULL NAME
ADR	Adenoma detection rate
AEC	Asian Endoscopy Community
ASMR	Age specific mortality rate
CAD	Coronary artery disease
CBA	Cost-benefit analysis
CCA	Cost-consequence analysis
CEA	Cost-effectiveness analysis
CI	Confidence interval
CMA	Cost-minimization analysis
CPI	Consumer price index
CRC	Colorectal cancer
CSMBS	Civil Servant Medical Benefit Scheme
CTC	Computed tomography colonography
CUA	Cost-utility analysis
DCBE	Double-contrast barium enema
DCE	Discrete choice experiment
DLP	Dyslipidemia
DM	Diabetes mellitus
FOBT	Fecal occult blood test
FIT	Fecal immunochemical test
FS	Flexible sigmoidoscopy
GI	Gastrointestinal
HDI	Human development index
HEDIS	Health plan employer data and information set
HRFQ	High-risk factor questionnaire
HRP	High-risk polyp
HRQoL	Health-related quality of life

ABBREVIATIONS	FULL NAME
HT	Hypertension
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
I-CRC	Interval colorectal cancer
LE	Life expectancy
LMICs	Low- and middle-income countries
LRP	Low-risk polyp
LYG	Life-year gained
LY	Life-year
MOPH	Ministry of Public Health
NMB	Net monetary benefit
OOP	Out-of-pocket
PSA	Probabilistic sensitivity analysis
QALY	Quality-adjusted life year
RCT	Randomized controlled trials
RR	Relative risk
SD	Standard deviation
SSS	Social Security Scheme
TAGE	Thai Association of Gastrointestinal Endoscopy
TC	Total colonoscopy
THB	Thai Baht
UCS	Universal Coverage Scheme
USD	United States Dollar
USPSTF	US Preventive Services Task Force
WTP	Willingness-to-pay

CHAPTER I Patient preference and cost-effectiveness analysis of colorectal cancer screening and treatment

1.1 Literature review

Burden of colorectal cancer

There were more than 14 million new cases of cancer occurred each year. Of these, over 8 million patients were reported death (Ferlay et al., 2015). The worldwide data estimated an increasing trend of number of new cancer cases, 20 million new cases will occur by 2025. They predicted higher number of new cases in low income countries (Ferlay et al., 2015).

Colorectal cancer (CRC) is the third most common cancer and the fourth leading cause of cancer death worldwide. About 1.4 million new CRC cases were diagnosed in 2012. Besides, about 700,000 patients died from CRC (8% of all cancers deaths) (Ferlay et al., 2015). Median age at diagnosis is about 70 years in developed countries (Siegel et al., 2012). The highest incidence is reported in developed countries such as countries in Europe, North America, and Oceania, whereas incidence is found to be lower in some countries of Asia especially southern and central part as well as Africa (Center, Jemal, Smith, & Ward, 2009). The burden of CRC varies in different countries, with more than two-thirds of all cases and 60% of all deaths occurring in high or very high human development index (HDI) countries (Ferlay et al., 2015). The global incidence of CRC is assumed to increase by 60% to more than 2.2 million new cases and 1.1 million deaths by 2030 (Ferlay et al., 2015).

In Thailand, the 2010-2012 data from hospital-based cancer registry; National Cancer Institute showed that CRC was the second and third leading cancer in male and female, respectively (Table 1). The mean annual age-standardized incidence rate per 100,000 populations were 14.4 in male and 11.2 in female. The incidence rate tended to increase as population became older, particularly at the age of 50 and older. More patients were diagnosed at the late stages of cancer. In addition, CRC was also the fifth leading causes of cancer death in Thailand (National Cancer Institute Thailand, 2015a).

Table 1. The prevalence of cancers in Thailand

Ranks	Male	Female
1	Lung and bronchus (18.5%)	Breast (37.0%)
2	**Colon and rectum (14.1%)**	Cervix (14.4%)
3	Liver and bile duct (12.4%)	**Colon and rectum (8.1%)**
4	Oral cavity (8.4%)	Lung and bronchus (6.8%)
5	Prostate gland (5.6%)	Liver and bile duct (4.0%)
6	Esophagus (5.1%)	Ovary (3.7%)
7	Non-Hodgkin lymphoma (4.1%)	Corpus (3.0%)
8	Nasopharynx (3.9%)	Oral cavity (2.9%)
9	Larynx (2.8%)	Non-Hodgkin lymphoma (2.4%)
10	Stomach (2.6%)	Thyroid gland (2.3%)

CRC is an example of the cancer transition which linked to western lifestyles. CRC has replaced infection-related cancers in the altering of society and economy, which are presented in high-income countries (Bray, 2014; Center et al., 2009). CRC is one of the leading causes of cancer mortality worldwide (Ferlay et al., 2015). In many low-and middle-income countries (LMICs), CRC incidence and mortality are rapidly increased. On the other hand, they have been stabilizing or reducing in high-income countries. It might be due to the early detection strategies (Murphy, Harlan, Lund, Lynch, & Geiger, 2015). The benefit of CRC screening not only by reducing cancer-related morbidity and mortality but also saving overall costs (Vekic et al., 2019). The modern chemotherapy and radiotherapy have an important role for the decrease in the mortality rate, especially, in many developed countries (Murphy et al., 2015).

Primary prevention with early detection is necessary to decrease the number of CRC patients in the future. Developments and improvements of treatment strategies as well as accessibility are necessary, particularly in LMICs that encounter an increasing burden of CRC (Arnold et al., 2017). Because capacity for health service provision and monetary resource are limited, prioritization and integration of primary prevention and early detection should be provided incoming health care plans.

Risk factors of colorectal cancer

Age, male sex, family history of CRC (Taylor, Burt, Williams, Haug, & Cannon–Albright, 2010), inflammatory bowel disease (Jess, Rungoe, & Peyrin–Biroulet, 2012), alcohol consumption (Fedirko et al., 2011), low fruits and vegetables consumption and high red/processed meats consumption (Working, 2015), obesity (Renehan, Tyson, Egger, Heller, & Zwahlen, 2008), physical inactivity (Harriss et al., 2009), smoking (Walter, Jansen, Hoffmeister, & Brenner, 2014), and diabetes mellitus (DM) (Jiang et al., 2011) are identified risk factors of CRC.

Some protective factors which could partially explain incidence stabilizing in developed countries include high physical activity (Boyle, Keegel, Bull, Heyworth, & Fritschi, 2012), the regular use of aspirin (Bosetti, Rosato, Gallus, Cuzick, & La Vecchia, 2012), the use of estrogens after menopause (Lin, Cheung, Lai, & Giovannucci, 2012), vitamin D intake (Brenner, Chang-Claude, Seiler, Rickert, & Hoffmeister, 2011), and colonoscopy with precancerous lesion removal (Elmunzer et al., 2012), for which the strongest risk reduction has been reported. Increases in mortality have been reported in many countries in Latin America and Asia (Malvezzi et al., 2004), and these may reflect limited health care structure and lower accessibility of early detection and treatment (CanTreat, 2010).

Colorectal cancer screening

CRC screening has been shown to decrease cancer mortality through retarding disease progression by early detection and removal of precancerous lesions (Hoff, Grotmol, Skovlund, & Bretthauer, 2009; A. G. Zauber et al., 2012).

The US Preventive Services Task Force (USPSTF) recommendation 2016 concludes that screening for CRC in average-risk, asymptomatic adults aged 50 to 75 years yields substantial net benefit (A recommendation) because CRC is most frequently diagnosed among adults aged 65 to 74 years and the median age of CRC mortality is 68 years. The decision to screen for CRC in adults aged older than 76 years should be individual, considering the patient's overall health and prior screening history (C recommendation) (U. S. Preventive Services Task Force et al., 2016).

There are several CRC screening methods such as stool tests, imaging, and endoscopy. The various types of stool tests primarily aiming at the early detection of CRC, whereas endoscopic screening tests are effective at both early detection and treatment (Bernard Levin et al., 2008). Different screening methods are expected to have a different impact on CRC incidence and mortality reduction. Fecal immunochemical test (FIT) and colonoscopy have been available with clear effectiveness on the reduction of CRC incidence and its associated mortality (Zhang et al., 2017). However, currently, evidence-based information to recommend one screening method over another in insufficient. CRC screening methods perceived as the most burdensome (i.e. endoscopy) also have the largest potential for prevention of CRC (Bernard Levin et al., 2008).

FIT is a noninvasive intervention (Sharp et al., 2012) with high sensitivity for CRC and adenomas detection (Brenner & Tao, 2013). Patients with positive FIT tests require colonoscopy for confirmative diagnosis (B. Levin et al., 2008; Sano et al., 2016).

Double-contrast barium enema (DCBE) is an imaging-based screening test. This method can examine the entire colon. It needs bowel preparation by using of laxatives and enemas to optimize the effectiveness. Patients may experience discomfort during and after the test. The complications are relatively lower than colonoscopy (B. Levin et al., 2008).

Computed tomography colonography (CTC) is newer, more effective, and more tolerable than DCBE (D. K. Rex et al., 2017). However, it requires full bowel preparation which has an impact on its accuracy (B. Levin et al., 2008). This method is less invasive (Howard et al., 2011) and it has lower risk of complications than colonoscopy. However, the long-term risk from radiation exposed from repeated use should be concerned (U. S. Preventive Services Task Force et al., 2016).

Flexible sigmoidoscopy (FS) is one of the direct visualization endoscopy tests. It has advantages such as less bowel preparation, lower cost, and less complications when compared to colonoscopy (D. K. Rex et al., 2017; U. S. Preventive Services Task Force et al., 2016). Nonetheless, FS reduces only distal CRC incidence and mortality. It provides poorer effectiveness in the protection of right-sided colon cancer (D. K. Rex et al., 2017).

Colonoscopy can be applied as a primary screening tool as well as effective precancerous lesion removal. It is able to examine entire colon (B. Levin et al., 2008; Pox, 2014). Colonoscopy is recommended in CRC screening guideline for higher adenomas and cancer detection rates comparing with other methods, even though it is not a flawless screening method (B. Levin et al., 2008; D. K. Rex et al., 2017; U. S. Preventive Services Task Force et al., 2016; Wong, Ching, Chan, & Sung, 2015). However, colonoscopy requires bowel preparation and is more invasive and costlier (B. Levin et al., 2008).

The results from a recent network meta-analysis suggested that colonoscopy was the most effective screening strategy for preventing CRC-related deaths (Zhang et al., 2017). FIT, FS, and colonoscopy reduced CRC-related mortality by 59% (relative risk [RR], 0.41; 95% confidence interval [CI], 0.29-0.59), 33% (RR, 0.67; 95% CI, 0.58-0.78), and 61% (RR, 0.39; 95% CI, 0.31-0.50) compared with no screening, respectively (Zhang et al., 2017).

Patients' preference for colorectal cancer screening

Attendance is one of the most important determinants of the effectiveness of CRC screening programs. Uptake is a key factor that determines the effectiveness of such a screening program. It has been established that the reduction of CRC-related mortality would be the most if the uptake of CRC screening is increases, in comparison with other targets (Vogelaar et al., 2006). Attendance rates depend on the intention and preference of individuals to undergo a certain screening test. These may be influenced by perceived advantages and drawbacks of CRC screening tests and moreover, by knowledge and awareness of CRC, CRC risks and CRC screening (Keighley et al., 2004). Individuals may be willing to undergo a screening test despite several disadvantages in order to maximize health benefit or vice versa. To optimize a CRC screening program, it is best to investigate insight in factors that influence population preferences for CRC screening programs, and the trade-offs individuals are willing to make between benefits and burdensome of a CRC screening program. There is an increasing emphasis on involvement of patients in health care decisions (Phillips, Van Bebber, Marshall, Walsh, & Thabane, 2006).

Uptake of CRC screening in many countries has remained suboptimal (Faivre et al., 2004; Hardcastle et al., 1996; Hol, Van Leerdam, et al., 2010; Manfredi et al., 2008). In addition, there is currently no organized CRC screening program in many countries in the world, especially in LMICs. Although the guideline is recommended for CRC screening in average-risk persons, unfortunately, small proportion of the targeted average-risk population underwent CRC screening (Faivre et al., 2004; Hol, Van Leerdam, et al., 2010). Various factors bound targeted population from participating CRC screening such as limited knowledge about the screening, fear of pain, being afraid of the complications, inconvenience, and screening cost. (Jones et al., 2010; Pignone et al., 2014; Xu, Levy, Daly, Bergus, & Dunkelberg, 2015).

Recently, Thailand has adopted a population-based CRC screening policy using FIT as a primary tool (Aniwan et al., 2015) with a pilot program in Lampang province and other provinces (Khuhaprema et al., 2014). The data showed that the acceptance rate of FIT screening was about 63% and the patients with positive FIT did not further perform colonoscopy with a high rate of 28% (Khuhaprema et al., 2014). Thus, it is of particular importance to study preferences in a screening-naïve population, since they may guide the introduction and adjustment of new CRC screening programs in Thailand. The new strategies to enhance the acceptance and preference were essential for the success of the screening policy. In addition, the willingness-to-pay (WTP) is also an important issue that should be considered, in order to improve rate of CRC screening as well as planning for a future policy.

There is an absence of knowledge regarding factors determined individuals' preferences for CRC screening programs including the most preference screening strategy in Thailand. This research aimed to evaluate these factors. The policy makers can use the results to optimize an appropriate CRC screening program in Thailand. Because attendance rates depend on the willingness of individuals to undergo a certain screening test and uptake is a key factor that determines the effectiveness of such a screening program, these results are necessary for improving success rate of CRC screening campaign and can be implemented as a National health policy. The average-risk persons will receive appropriate screening, early diagnosis of the precancerous lesions, and early treatment.

Moreover, there is a lack of knowledge regarding long-term benefits and cost-effectiveness of CRC screening for average-risk group in Thailand. This research aimed to evaluate the cost-effectiveness and budget impact of CRC screening in Thailand comparing annual FIT and colonoscopy every 10 years according to the international guidelines. If the results show which CRC screening is cost-effective and how much of its budget, it will contribute as new knowledge and can be implemented as a policy. The average-risk persons will receive the appropriate screening at a lower cost from a national health policy. They will receive an early diagnosis and receive early appropriate treatments to prevent more serious and costly complications.

For the patients who do not receive CRC screening, they may be diagnosed as the late stages of CRC. These patients have many choices of treatment especially in stage III. Adjuvant chemotherapy is required to prolong disease-free survival (DFS) and overall survival (OS) in stage III CRC, it knowingly recommended as a standard treatment in both international and local CRC treatment guidelines (Bockelman, Engelmann, Kaprio, Hansen, & Glimelius, 2015). Five-year disease-free survival of stage III CRC patients who receive adjuvant chemotherapy is about 64% (95% CI, 59.3-67.9) (Bockelman et al., 2015), compared to 49% (95% CI, 23.2-74.8) in patients without chemotherapy. However, there are various chemotherapy regimens available in Thai market, both orally and intravenously administered agents. The evidence shows that there are differences in efficacy and safety of each chemotherapy regimen. Newer agents such as capecitabine, oxaliplatin, and irinotecan have been concluded that they are able to prolong survival in CRC patients compared to 5-fluorouracil/leucovorin (5-FU/LV) monotherapy (Landre et al., 2015). The preferences of patients and costs of treatment are also distinct (Krol, Koopman, Uyl-de Groot, & Punt, 2007). Nowadays, the generic versions of chemotherapy agents have been launched in Thailand, resulting in lower cost of treatment.

This research aimed to evaluate the cost-effectiveness of chemotherapy regimens for stage III CRC treatment in Thailand. If this study can report the most cost-effective treatment regimen for stage III CRC, it will contribute as new knowledge. Stage III CRC patients will receive the appropriate treatment. It may prolong their survival with good quality of life.

Therefore, this research is divided into 3 parts for 3 aspects of studies. The first part is the factors determine individuals' preferences for colorectal cancer screening using discrete choice experiment (DCE). The second part is a cost-effectiveness analysis of colorectal cancer screening. And, the third part is a cost-effectiveness analysis of colorectal cancer treatment. The last part of this research is conclusions and policy implications which explained the benefits of the study as a part of evidence-based information to the health policy makers to consider as national policy.

CHAPTER II Factors determine individuals' preferences for colorectal cancer screening: A discrete choice experiment

2.1 Introduction

Health technology assessment (HTA) is recognized as a crucial tool for evidence-informed policy decision making under universal health coverage. It has been widely used for health benefit package design in many countries. It is suggested that incorporating patient's preference as part of decision-making process may enhance the likelihood of successful implementation of health interventions in practice. Despite the recognition of the importance of consideration of patient's perspective, the practice of incorporating patients' preference in HTA process remains uncommon especially in LMICs.

In Thailand, CRC screening rate was still lower than standard recommendation. There was no data of factors determine individuals' preferences for CRC screening. Therefore, this study aimed to assess how procedural characteristics of CRC screening tests determine individuals' preferences including their WTP for each screening modality and how individuals weigh these against the perceived benefits from participation in CRC screening using DCE. Health policy makers can use these findings to improve the success rate of CRC screening campaign.

Discrete choice experiment

Discrete choice experiment is a survey methodology. Nowadays, they are increasingly used to evaluate the patients' preferences in health care sectors because DCE is composed of a reasonably straightforward task and one which more closely resembles a real-world decision. DCE approach is able to evaluate the process effects and non-health outcomes additional to traditional quality-adjusted life year (QALY) analysis.

DCE consists of a series of choices between two or more health care interventions or services that have different combinations of attribute levels. Analyzing the responses allows to evaluate of the relative importance of the included attributes for respondents' preferences, and for evaluation of the trade-offs that individuals make between the attributes. Responses of a DCE are modeled within a satisfaction function

which provides information on whether or not the given attributes are important in the perspective of responsder; the relative importance of attributes; the rate at which individuals are willing to trade between attributes; and overall benefit scores for alternatives (Louviere, Hensher, & Swait, 2000; Ryan & Farrar, 2000). If the cost of health interventions is included as an attribute the WTP can also be estimated as well. It is possible to evaluate how much individuals express to be willing to pay to avoid side effects based on responses to the choice set.

The discrete choices observed in a DCE are assumed to reveal an underlying utility function. Thus, an individual will choose alternative A over B, if U (XA, Z) > U (XB, Z), where U is the individual's indirect utility function from certain alternatives, XA the attributes of alternative A, XB the attributes of alternative B, and Z socioeconomic characteristics of the individual that influence his/her utility. The results of a DCE provided information on the relative importance of the attributes and the trade-offs individuals were willing to make between these attributes.

There were some studies of factors determine individuals' preferences for CRC screening by using DCE method. For example, in Netherlands, a DCE was conducted among subjects in the age between 50-75 years, including both screening-naive subjects and subjects who involved with a CRC screening program. Subjects were asked to choose the alternatives CRC screening programs based on their preferences. The alternative scenarios were based on 8 different attributes that represent CRC screening method. The results showed that all aspects proved to significantly influence the respondents' preferences. The positive beta coefficients for shorter screening intervals. The negative value for all other attributes indicate that individuals preferred a screening test of shorter duration of procedure, with no preparation, no pain, and no risk of complications. This study showed that improving awareness on CRC mortality reduction by CRC screening may increase acceptance of screening (van Dam et al., 2010).

Another DCE study from Netherlands, subjects were asked to choose between scenarios on the basis of FIT, FS, and colonoscopy with various screening intervals and mortality reductions, and no screening. The results showed that the type of screening, screening interval, and risk reduction of CRC-related mortality influenced subjects' preferences. Subjects preferred 5-yearly FS and 10-yearly colonoscopy, but favored

both endoscopic strategies to annual FIT screening due to the more favorable risk reduction of CRC-related mortality by endoscopy (Hol, de Bekker-Grob, et al., 2010).

In Australia, there was a DCE of preferences for CTC and colonoscopy for CRC screening using a mixed logit model. The results showed colonoscopy was preferred over CTC, as the likelihood of missing cancers or polyps increased and as CTC test cost increased (Howard et al., 2011).

In the US, screening for CRC is suboptimal. A DCE used to explore about how individuals in North Carolina value different aspects of CRC screening programs. The results showed that individuals preferred programs that required shorter travel time; rewards or small copayments; stool testing; and greater coverage of follow-up costs (Pignone et al., 2014).

There was a labeled DCE in preferences for potential innovations in non-invasive CRC screening e.g. stool-based and blood samples based tests or both that may be a solution to increase CRC screening uptake. Multinomial logit (MNL) model showed that the combi-test is generally preferred over the blood-test and the stool-test alone. Furthermore, it was shown that the preference was varied by participants' socio-demographic background. This new test had the potential to increase CRC screening participation rate (Benning, Dellaert, Dirksen, & Severens, 2014).

Therefore, the inclusion of patient viewpoint as part of HTA should be done to support population-based CRC screening campaign. As CRC is also recognized as a leading cause of death in Thai population, policy makers and clinicians have vast interest in determining the suitable CRC screening program for nation-wide implementation. The evidence on how patient values each of the screening methods will be highly valuable to clinicians and policy makers. We believe that understanding patients' preference in Thailand, which is one of the LMICs, can benefit Thailand and other jurisdictions in designing the population-based CRC screening program in the future.

2.1.1 Research questions

Primary research questions

1. What determines individuals' preferences for CRC screening programs in Thailand?

Secondary research questions

1. What is the most preferred CRC screening method in Thailand?
2. How individuals' weigh the procedural characteristics of various screening methods against the expected health benefits from CRC screening?
3. How individuals' trade-offs between risk reduction and different aspects of a CRC screening program?
4. What are the differences in preference among symptomatic vs. asymptomatic Thai population?

2.1.2 Research objectives

General objectives

1. To evaluate the factors determine individuals' preferences for CRC screening programs in Thailand

Specific objectives

1. To evaluate the individuals' preferences for CRC screening strategies by comparing between FIT, DCBE, CTC, FS, and colonoscopy in Thailand
2. To evaluate the individuals' weigh the procedural characteristics of various screening methods against the expected health benefits from CRC screening
3. To evaluate the individuals' trade-offs between risk reduction and different aspects of a CRC screening program
4. To evaluate the differences in preference among symptomatic vs. asymptomatic Thai population

2.1.3 Hypotheses

There are many significantly influence the respondents' preferences such as pain, risk of complications, screening location, preparation, duration of procedure, screening interval, missing rate of cancers or polyps, type of screening, risk reduction of CRC-related death, and amount of copayment.

These results will show the individuals' trade-offs between risk reduction and different aspects of a CRC screening program and identify the most preference screening strategy and interval of Thai average-risk population.

2.1.4 Scope of the study

The study aims to evaluate the factors determine individuals' preferences for CRC screening programs comparing FIT, DCBE, CTC, FS, and colonoscopy in Thailand using DCE. In addition, this study will analyze the individuals' weigh the procedural characteristics of various screening methods against the expected health benefits from CRC screening and trade-offs between risk reduction and different aspects of a CRC screening program. This study uses primary data from a questionnaire-based study in out-patient department of a university hospital.

2.1.5 Possible benefits of the study

There is a lack of knowledge regarding factors determine individuals' preferences for CRC screening programs in Thailand. If this study can reveal these factors and the trade-offs individuals, the policy makers can organize an appropriate CRC screening program with a high success rate in Thailand. Because attendance rate is a key factor that determines the effectiveness of CRC screening program.

2.2 Methodology

2.2.1 Study design

This research is a questionnaire-based study focused on the factors determine individuals' preferences for CRC screening programs in Thailand by using DCE.

2.2.1.1 Study population

Eligible participants were screening-naïve adults aged between 50-75 years who visited the out-patient department of Faculty of Medicine Siriraj Hospital (a 2,061-bed hospital), Mahidol University, the largest tertiary care and university hospital in Thailand. (Vamvanij & Chuchotirot, 2017).

2.2.1.2 Sample size

This study used multiple approaches, including a good DCE research practice and a published practice guide for achieving the statistical power of 80%, to determine the sample size (de Bekker-Grob, Donkers, Jonker, & Stolk, 2015). There is no optimal method for determining the sample size for DCE. In common practices, sample sizes for DCE studies generally range from about 150 to 1,200 participants. For robust quantitative research, the optimal recommended sample size was at least 300 participants. Since the purpose of the research is to compare groups of participants and detect significant differences between symptomatic and asymptomatic individuals, a sample size of 200 per group was recommended (Orme, 2010). Therefore, we used this method to determine a sample size of 400 participants: subjects with gastrointestinal (GI) symptoms (N=200) such as abdominal pain, lower GI bleeding, bloating, constipation, diarrhea, bowel habit change and subjects without GI symptoms (N=200).

The participants were randomly selected from the patients of out-patient department at Siriraj Hospital representing the population who can access the hospital care. Subjects were informed about general background information of CRC and CRC screening and then they were invited to answer the questionnaire.

2.2.1.3 Questionnaire development

The questionnaire consisted of 2 parts: First, the patient socio-demographic data which included self-rating healthiness 1-10 scoring scale and 5-point scale (i.e. excellent, very good, good, fair, and poor). Second, discrete choice experiment choice sets: 6 CRC screening attributes were extracted from the literature review and patient interviews (Table 2). It was able to generate a total of 432 (i.e. $2^2 \times 3^3 \times 4^1$) possible scenarios. However, to make the questionnaire more eligible, a total of 36 choice sets was generated and divided into six blocks. Each block comprised six choice sets and a

validation choice set. Each choice set contained three unlabeled alternatives, including two hypothetical CRC screening methods and an opt-out alternative. The opt-out alternative was used to resemble a real-world option since patients might not choose any CRC screening test at all. Table 2 summarizes the selected attributes and their levels.

This study conducted a literature review and interviews with gastroenterologists and patients to select CRC screening attributes and levels, which were important to them. We purposively selected 20 patients for in-depth interviews as part of the attribute and level determination process. In the interviews, we asked individuals to point out which of these attributes were important in their decision to participate in a CRC screening program. Finally, we chose a total of six attributes, including pain, risk reduction of CRC-related mortality, risk of complications, screening interval, bowel preparation, and amount of copayment, in our choice sets.

Table 2. Attributes and levels for colorectal cancer screening

Attributes	β-coefficients
Pain	β_1
No pain (reference level)	
Mild pain	
Risk reduction of CRC mortality	β_2
0% (reference level)	
40%	
80%	
Risk of complications	β_3
None (reference level)	
Small	
Screening interval	
None (reference level)	
Annual	β_4
Every 5 years	β_5
Every 10 years	β_6
Bowel preparation	
None (reference level)	
Taking laxative and enema. No fasting	β_7
Drinking 2 liters of fluid and 6-hour fasting	β_8
Out-of-pocket cost	β_9
0 USD	
88 USD	
176 USD	

Five screening programs were evaluated: (1) colonoscopy, every 10 years (2) FS, every 5 years, and (3) DCBE, every 5 years (4) CTC, every 5 years, and (5) FIT, every year. The characteristic of each screening strategy was described in Table 3.

The levels we applied for assessing the uptake of FIT were no pain, no risk of complications, 1-year interval, and no preparation. For DCBE, we applied no pain, a

small risk of complications, 5-year interval, and preparation by laxative and enema. For colonoscopy, we used mild pain, a small risk of complications, 10-year interval, and full preparation by drinking 2 L of fluid.

Table 3. Screening programs' characteristics

Choice	**A (TC)**	**B (FS)**	**C (DCBE)**	**D (CTC)**	**E (FIT)**	**F (No screening)**
Pain	Mild pain	Mild pain	Mild pain	Mild pain	No pain	No pain
RR of CRC-related mortality	50-70% (61%)	22-42% (33%)	40-50% (45%)	40-50% (45%)	40-70% (59%)	0%
Risk of complications	Small	Small	Small	Small	No	No
Screening interval	q 10 years	q 5 years	q 5 years	q 5 years	q 1 year	0
Preparation	Fluid 2 liters & 6-hour fasting	Laxative and enema	Laxative and enema	Fluid 2 liters & 6-hour fasting	No	No
Price (USD)	103-176	59-132	68-118	118-176	0.7-3	0

CTC, computed tomography colonography; DCBE, double-contrast barium enema; FIT, fecal immunochemical test; FS, flexible sigmoidoscopy; TC, total colonoscopy; RR, relative risk

2.2.2 Data collection

A total of 440 participants was randomly selected and individually interviewed during October 2017 to January 2018. The participants were informed about general background information of CRC and CRC screening and then they were invited to answer the questionnaire. One block of six choice sets was presented to the participant. Demographic data were collected. In the DCE part, participants were asked to choose one hypothetical screening alternative in each choice set. All costs were converted and reported in 2017 United States Dollars (USD) (1 USD=34 Thai Baht (THB)) (Bank of Thailand, 2017).

2.2.3 Conceptual framework

This conceptual framework represents an overview of the steps of the research plan and the information needed to be collected and calculated. For this study, the conceptual framework showed 9 main steps of the economic evaluation.

Step 1: A pilot study of 20 average-risk persons is performed to point out which of these attributes they expected to be important or had been important in their decision to participate in a CRC screening program.

Step 2: A pilot study of 30 average-risk persons is performed to examine the intelligibility, acceptability, and validity of the questionnaire.

Step 3: Four hundred average-risk persons (200 symptomatic persons vs. 200 asymptomatic persons) are informed and interviewed.

Step 4: Respondent characteristics are analyzed.

Step 5: The data from DCE are analyzed by MNL model to evaluate the factors determine individuals' preferences for CRC screening programs in Thailand.

Step 6: The individuals' weigh the procedural characteristics of various screening methods against the expected health benefits from CRC screening are evaluated.

Step 7: The individuals' trade-offs between risk reduction and different aspects of a CRC screening program are evaluated.

Step 8: The WTP and uptake rate of screening of each screening method are calculated

Step 9: Subgroup analysis (symptomatic vs. asymptomatic) are performed to evaluate the differences in preference structures among subgroups.

2.2.4 The DCE model

Only data from participants, who correctly chose the right alternative in the validity choice set, were included in the analyses. On this basis, we estimated the following model for the DCE: $U = V + \varepsilon$

$U = \beta 0 + \beta 1$ pain $+ \beta 2$ mortality reduction $+ \beta 3$ complications $+ \beta 4$ interval 1 $+ \beta 5$ interval 5 $+ \beta 6$ interval 10 $+ \beta 7$ prep 1 $+ \beta 8$ prep 2 $+ \beta 9$ copayment $+ \varepsilon$

Utility (U) represents latent utility of a CRC screening alternative in a choice set. It is assumed that an individual will choose the CRC screening alternative which maximizes his/her utility (Hol, de Bekker-Grob, et al., 2010).

V refers to a systemic, explainable, component specific as a function of the attribute of the CRC screening alternatives (van Dam et al., 2010).

ε refers to the random (unexplainable) component representing unmeasured variation in preferences (van Dam et al., 2010).

B0 refers to the specific constant that indicated relative weight individual place on screening programs compared to no screening (van Dam et al., 2010).

β1-9 refer to coefficients of the attributes indicating the relative weight individuals place on a certain attribute (level) (van Dam et al., 2010).

MNL was used to estimate the utility model and determine relative preferences of each attribute. The level of statistical significance was set at 0.05. From the equation, the value of each coefficient represents the importance that respondents assigned to a certain level. However, different attributes utilized different units of measurement. An attribute with a two-sided p-value that is smaller than 0.05 is considered to be important in the decision to participate in CRC screening program.

The trade-offs respondents are willing to make between the attributes are calculated by the ratios of the coefficients of the different attributes with risk reduction as the denominator. To examine the expected uptake of CRC screening based on our results, we applied the model as presented by Gerard and colleagues (Ryan, Gerard, & Amaya-Amaya, 2007) and Hall and colleagues (Hall et al., 2002) to our data.

$$P_{participation} = \frac{1}{(1 + e^{\wedge -V})}$$

The model assumed that a preference score of 0 indicated that the expected participation rate equals 50%. The influence of the different levels on expected uptake was calculated by entering the coefficients of the levels, added to the constant term, into the model. In addition, their WTP for each screening modality and how individuals weigh these against the benefits from participation in CRC screening program were analyzed.

Marginal WTPs of the attributes were calculated by taking the ratio of the mean attribute coefficient to the mean coefficient of cost attribute. Finally, WTPs for CRC screening methods in the real-world were calculated by multiplying the marginal WTP for that screening method with the difference between attribute levels, which were obtained from clinical literature.

As the goal of this work is to understand participant's preference on the acceptability of the screening method, we calculated the uptake rates of each screening test per the following formula:

Probability of screening test A = $\exp^{[(\beta pain*pain\ of\ test\ A) + (\beta cost*cost\ of\ test\ A) + (\beta risk\ reduction*risk\ reduction\ of\ CRC\ mortality\ of\ test\ A) + (\beta complication*risk\ of\ complication\ of\ test\ A) + (\beta interval*interval\ of\ test\ A) + (\beta prep*preparation\ of\ test\ A)]}$/Summation of exponential of every tests and no screening

In addition, we performed subgroup analysis to determine whether the preference differs among participants with and without GI symptoms.

2.2.5 Data analysis

2.2.5.1 Statistical analyses

All data were analyzed using the statistical package SPSS (version 18.0; SPSS Inc., Chicago, IL, USA). The data were presented as mean ± standard deviation (SD) for normality, median [P25, P75] for non-normality, and percent where appropriated. Demographic data were analyzed using descriptive statistical tests. Independent t-test for normality and Mann Whitney U-test for non-normality, and Chi-square test for categorical data were used for comparison between groups. P-value less than 0.05 was accepted as statistically significant.

2.2.5.2 Questionnaire validation

A pilot study of 20 average-risk persons was performed to point out which of these attributes they expected to be important or had been important in their decision to participate in a CRC screening program. Then, a pilot study of 30 average-risk persons is performed to examine the intelligibility, acceptability, and validity of the questionnaire. Only the subjects who chose a hypothetical screening program, that was logically preferable over another or no screening in a validation choice set were included in the analyses.

2.2.6 Ethical issues

The study was ethically approved by Siriraj Institutional Review Board (SIRB) No. 298/2560 (EC1).

2.3 Results

Demographic data

A total of 440 screening-naïve adults were interviewed, 428 of them (97.3%) completed the questionnaire. Of these, there were 28 subjects (6.5%) failed in validation by a rationality test. The data from 400 subjects were analyzed. The average age of subjects was 62.4 ± 6.4 years. Two hundred and forty-six (61.5%) were female. The common comorbidities were hypertension (HT), dyslipidemia (DLP), DM, and coronary artery disease (CAD) (50%, 30%, 23%, and 7%, respectively). The average of education was graduated from secondary school. More than half of them were retired from work. The average regular income was 470 USD. The average of self-rating healthiness was 6.4 ± 1.4 in 1-10 scoring scale and 2.4 ± 0.8 in 5-point scoring scale which referred to fair to good health. Among of them, 6% had first-degree family history of CRC, and 36% know relatives or friends who had CRC. More than half of the subjects know about CRC before the interview, but only 23.5% know that CRC screening was available. Twenty-four percent of subjects terrified about having CRC, 35.5% of them had some fear, and 40.5% of subjects were fearless or unconcerned. The participants preferred colonoscopy over FIT and DCBE, if those screening programs were free of charge (47%, 42%, and 11%, respectively). On the other hand, subjects would prefer FIT over colonoscopy and DCBE, if they had to pay out-of-pocket (62.0%, 25.5%, and 12.5%, respectively). The accepted amounts of copayment were 88, 44, and 3 USD from the full price of 176, 88, and 3 USD for colonoscopy, DCBE, and FIT, respectively, as shown in Table 4. However, 71 subjects (17.8%) denied to undergo CRC screening with various reasons such as no symptom, busy, and afraid to know the results.

Subjects' preferences and willingness-to-pay

All attributes, except pain and less bowel preparation, were statistically significant ($p<0.05$). The respondents preferred screening with high risk reduction of CRC-related mortality, no complication, 5-year interval, less bowel preparation, and lower cost. According to the β-coefficients, the factors that highly influence the individuals' decisions were risk reduction of CRC-related mortality and costs (Table

6). The uptake rates of colonoscopy, FS, DCBE, CTC, FIT, and no screening were 11.4%, 11.4%, 14.6%, 9.2%, 38.2%, and 15.3%, respectively (Table 7). The WTP of participants was 48 USD for CRC screening when compared to no screening. In addition, they were willing to pay 44 USD for 5-year interval, -43 USD for complication, -36 USD for full bowel preparation, and 3 USD in exchange for every 1% increased RR of CRC-related mortality. The WTP for FIT, colonoscopy, DCBE, CTC, and FS were 238, 180, 174, 146, and 135 USD, respectively (Table 8).

Table 4. Patients' demographic data

Parameters	N=400 (%)
Age	62.4 ± 6.4
Female	246 (61.5%)
Comorbidities; DM:HT:DLP:CAD	92:201:121:30 (23%:50%:30%:7%)
Education (grade)	10.5 ± 5.3
Retired	229 (57.3%)
Income (USD)	470 (206-882)
Own money	74.8%
Health rating (0-10)	6.4 ± 1.4
Health rating 5-point scoring scale	2.4 ± 0.8
Health insurance schemes; CSMBS:OOP:UCS:SSS	251:68:57:24 (63%:17%:14%:6%)
Having knowledge about CRC	214 (53.5%)
First-degree family history of CRC	24 (6.0%)
Known relatives/friends had CRC	144 (36.0%)
Fear of CRC 2:1:0	96:142:162 (24%:35.5%:40.5%)
Having knowledge about CRC screening	94 (23.5%)
Colonoscopy:Barium:FIT if free	189:43:168 (47%:11%:42%)
Colonoscopy:Barium:FIT if own pay	102:50:248 (25.5%:12.5%:62%)
Accept to copay for colonoscopy (USD)	88 (44-88)
Accept to copay for DCBE (USD)	44 (29-44)
Accept to copay for FIT (USD)	3 (3-3)
Decision no screening	71 (17.8%)

CAD, coronary artery disease; CSMBS, Civil Servant Medical Benefit Scheme; DCBE, double-contrast barium enema; DLP, dyslipidemia; DM, diabetes mellitus; FIT, fecal immunochemical test; HT, hypertension; OOP, Out-of-Pocket; SSS, Social Security Scheme; UCS, Universal Coverage Scheme

Subgroup analyses

A total of 400 subjects were divided into 2 subgroups; subjects with GI symptoms (N=200) and subjects without GI symptom (N=200). Subgroup analyses were performed to evaluate the differences in preference patterns among two subgroups. The common patients' symptoms were abdominal pain (44.5%), constipation (40.5%), bloating (31.5%), lower GI bleeding (12%), and bowel habit change (2%). The patients' demographic data were shown in Table 5. The asymptomatic subgroup had higher age (63.2 vs. 61.6 years) and health-rating scores (6.6 vs. 6.2) whereas the symptomatic subgroup had better knowledge about CRC screening (29.5% vs. 17.5%). In the asymptomatic subgroup, all attributes, except pain and less bowel preparation, were statistically significant ($p<0.05$), whereas in the symptomatic subgroup, all attributes, except pain, 10-year interval, and less bowel preparation, were statistically significant (Table 6). The reason behind this might be that symptomatic subgroup needs to do screening test more frequency than asymptomatic subgroup. The interval of 10 years might be too long for this subgroup. Moreover, The WTP for FIT, colonoscopy, and DCBE were 252 vs. 223 USD, 163 vs. 200 USD, and 155 vs. 199 USD, in symptomatic vs. asymptomatic subgroup, respectively (Table 8).

Table 5. Patients' demographic data among two subgroups

Parameters	Symptoms (N=200) (%)	No symptom (N=200) (%)	p-value
Age	61.6 ± 6.8	63.2 ± 5.9	0.010
Female	122 (61%)	124 (62%)	0.837
Education (grade)	10.1 ± 5.2	11.0 ± 5.5	0.087
Retired	110 (55%)	119 (59.5%)	0.363
Income (USD)	441 (181-882)	588 (265-882)	0.810
Own money	74.8%	74.8%	0.565
Health rating (0-10)	6.2 ± 1.5	6.6 ± 1.3	0.007
Health rating 5-point scoring scale	2.3 ± 0.8	2.5 ± 0.8	0.016
Health insurance schemes; CSMBS:OOP:UCS:SSS	106:36:36:22 (53%:18%:18%:11%)	145:32:21:2 (73%;16%:20%:1%)	<.001
Having knowledge about CRC	115 (57.5%)	99 (49.5%)	0.109
First-degree family history of CRC	12 (6.0%)	12 (6.0%)	1.000
Known relatives/friends had CRC	76 (38.0%)	68 (34.0%)	0.405
Fear of CRC 2:1:0	76:80:44 (38%:40%:22%)	86:62:52 (43%:31%:26%)	0.899
Having knowledge about CRC screening	59 (29.5%)	35 (17.5%)	0.005
Colonoscopy:DCBE:FIT if free	82:29:89 (41%:14%:45%)	107:14:79 (54%:7%:39%)	0.010
Colonoscopy:DCBE:FIT if own pay	43:27:130 (22%:13%:65%)	59:23:118 (30%:11%:59%)	0.182
Accept to copay for colonoscopy (USD)	88 (29-88)	88 (59-88)	0.032
Accept to copay for DCBE (USD)	44 (15-44)	44 (29-59)	0.178
Accept to copay for FIT (USD)	3 (3-3)	3 (3-3)	0.233
Decision no screening	35 (17.5%)	36 (18.0%)	0.896

CAD, coronary artery disease; CSMBS, Civil Servant Medical Benefit Scheme; DCBE, double-contrast barium enema; DLP, dyslipidemia; DM, diabetes mellitus; FIT, fecal immunochemical test; HT, hypertension; OOP, Out-of-Pocket; SSS, Social Security Scheme; UCS, Universal Coverage Scheme

Table 6. Multinomial logistic regression analysis

Attributes	Total		Symptomatic		Asymptomatic	
	β-coefficients	z	β-coefficients	z	β-coefficients	z
CON	.31296***	3.35	.35368***	2.62	.26209**	2.00
Pain	-.07518	-1.11	-.08993	-0.92	-.04979	-0.53
Risk reduction of CRC mortality	.02069***	19.44	.02171***	14.16	.01963***	13.11
Risk of complications	-.27750***	-3.64	-.26945**	-2.44	-.26604**	-2.50
Interval 1 year	-.28600***	-4.43	-.18926**	-2.04	-.38456***	-4.23
Interval 5 years	.28381***	5.22	.23421***	2.99	.33091***	4.35
Interval 10 years	.16388***	2.94	.07980	0.99	.23067***	2.94
Minimal bowel preparation	-.05585	-1.19	-.09926	-1.47	-.02186	-0.33
Intensive bowel preparation	-.22938***	-4.83	-.24000***	-3.45	-.22451***	-3.39
Cost	-.00019***	-14.13	-.00021***	-10.79	-.00017***	-9.01

CRC, colorectal cancer; ***, **, * Significance at 1%, 5%, 10% level, respectively.

Table 7. Analysis of uptake of screening

Screening tests	β-coefficients	Exponential	Probabilities	% Uptake
Colonoscopy	-0.30	0.74	0.11	11.4
Flexible sigmoidoscopy	-0.30	0.74	0.11	11.4
Double-contrast barium enema	-0.05	0.95	0.15	14.6
CT colonography	-0.51	0.60	0.09	9.2
FIT	0.92	2.50	0.38	38.2
No	0	1	0.15	15.3
Total		6.54	1	100

FIT, fecal immunochemical test

Table 8. Analysis of willingness-to-pay

Willingness-to-pay (USD) (95% CI)	Symptoms (N=200)	No symptom (N=200)	Total (N=400)
Colonoscopy	163 (-12-343)	200 (-14-422)	180 (47-316)
Flexible sigmoidoscopy	119 (-38-276)	157 (-32-352)	135 (16-256)
Double-contrast barium enema	155 (-9-322)	199 (0-404)	174 (49-301)
CT colonography	136 (-29-303)	162 (-39-370)	146 (22-275)
Fecal immunochemical test	252 (192-319)	223 (146-310)	238 (191-289)

2.4 Discussion

Our findings demonstrated that the participants preferred the CRC screening method which provides higher risk reduction of CRC-related mortality, having no risk of complications, having longer screening interval requiring, less bowel preparation, and requiring lower copayment. Only pain and less bowel preparation were not shown the statistically significant in relative preference in our results. The reason behind this might be that pain depends on individual and all screening modalities except FIT caused only mild pain or discomfort.

These results were consistent with other studies which had been conducted in other countries in the world from 2002 to 2016. In the Netherlands, a DCE was conducted among naive subjects and previously screened subjects, aged 50-75 years. The results showed that pain, risk of complications, screening location, preparation, duration of procedure, screening interval, and risk reduction of CRC-related death proved to significantly influence the respondents' preferences same as our study (van Dam et al., 2010). Another study from the Netherlands showed that the type of screening test, screening interval, and risk reduction of CRC-related mortality influenced subjects' preferences. Screening-naive and previously screened subjects equally preferred 5-yearly FS and 10-yearly colonoscopy, but favored both endoscopic strategies to annual FIT screening due to the more favorable risk reduction of CRC-related mortality (Hol, de Bekker-Grob, et al., 2010). In Australia, the results showed

colonoscopy was preferred over CTC. Preferences also varied significantly sociodemographic characteristics (Howard et al., 2011). In the US, the study enrolled 150 adults ages between 50-75 at average risk of CRC from rural North Carolina communities with low rates of CRC screening, targeting those with public or no insurance and low incomes. The results showed that individuals preferred a test that required shorter travel time, rewards or small copayments, includes stool testing as an option, and has greater coverage of follow-up costs (Pignone et al., 2014).

A study in Thailand studied preferences and acceptance of FIT and colonoscopy in the 437 patients aged 50-69 who visited the primary care unit by face-to-face interviews. Subjects were informed about CRC and the screening tests included FIT and colonoscopy. FIT had more acceptance rate of 74.1% compared to 55.6% in colonoscopy. FIT was preferred because of its simplicity and non-invasiveness. The acceptance of colonoscopy was associated with perceived susceptibility to CRC and family history of cancer. No symptoms, unwilling to screen, being healthy, too busy, and anxious about diagnosis were reasons for refusing to undergo screen test (Saengow, Chongsuwiwatvong, Geater, & Birch, 2015), this consisted with our results.

The factors that highly influence the individuals' decisions were risk reduction of CRC-related mortality and costs. If the costs of screening become higher in the future or nation economy declines, the acceptance rate of screening will be lower. From these results, FIT is the highest preference choice of screening because of its lowest cost and second rank of risk reduction of CRC-related mortality. Although colonoscopy yields the highest CRC-related mortality reduction, its cost and other character bring it is lower preference than FIT. Because the cost of screening is very important, the government should support the screening campaign, especially in LMICs like Thailand. Otherwise, Thai people may not join the screening test if they have to pay by themselves. The screening acceptance rate will increase and policy will be more successful.

In this study, FIT had the highest uptake rate of 38.2% and it is only one screening test that the participants accepted more than no screening. The population who denied screening from the survey was 17.8% (Table 4) vs. 15.3% from the DCE results (Table 7) which were similar.

Uptake is a key factor that determines the effectiveness of such a screening program. It has been reported that the increase of CRC screening uptake could produce a large potential for reducing CRC-related mortality (Vogelaar et al., 2006) compared with other goals. Attendance rates mostly depend on the individuals' preference to undergo a certain screening test. This preference may be influenced by perceived advantages and disadvantages of CRC screening tests and furthermore, by knowledge and awareness of CRC as disease itself, risk of CRC, and varieties of CRC screening strategies (Blalock, DeVellis, Afifi, & Sandler, 1990; Keighley et al., 2004; Vernon, 1997). To optimize a CRC screening program, it is important to gain insight into factors that influence population preferences for CRC screening programs, and the trade-offs individuals are willing to make between the benefits and drawbacks of a CRC screening program. This study concluded that patient preferences can have a major impact on their willingness to use services and furthermore, there is an increasing emphasis on the involvement of patients in health care decisions (Phillips et al., 2006).

Lack of knowledge is also an important issue which is a barrier to CRC screening participation. According to the result, only about 20% of the subject knew that CRC screening programs were available in Thai healthcare system. To improve rate of screening, first of all, we should improve knowledge about CRC screening programs among targeted population. As well as reminding them to repeat the test as recommended (U. S. Preventive Services Task Force et al., 2016). After the interviewer gave the information about who should undergo CRC screening program and each CRC screening program characteristic, its process, benefits, and harms, there was about 18% of subjects who decided no participation in the screening program. One of the most given reasons was that they thought that they had no risk of having CRC, this refers to the lack of health awareness in Thai population.

Not only the cost of screening test itself is matter to the decision of subjects, but consequence costs such as cost of treatments, cost of complications, cost of follow-up, and other indirect costs also. We should be thinking of who has responsibility for those payments.

2.5 Strengths and limitations

The strength of this study is that this is the first patients' preferences study of CRC screening program in Thailand as an example of LMICs by using DCE. Using a DCE can capture individual preferences over many aspects of CRC screening beyond the outcome in term of QALY (Ryan, 2004). The results from DCE can be a useful part of the evidence for the preventive health policy making. Second, this study's results were very robust because the uptake of screening of each screening test and no screening were similar among questionnaire survey and the results calculated from DCE results. Third, these findings showed FIT was preferred over other screening tests. It was high feasibility and affordability when compared to colonoscopy in clinical practice. Fourth, this study can reveal the factors that influence population preferences for CRC screening programs and the trade-offs individuals are willing to make between benefits and drawbacks of a CRC screening program, the policy makers can optimize an appropriate CRC screening program in Thailand. Because attendance rates depend on the willingness of individuals to undergo a certain screening test. This study results are useful for improving the success rate of CRC screening and can be implemented as a national health policy. The average-risk persons will receive appropriate screening, early diagnosis of the precancerous lesions, and early treatment.

There are several limitations in this study. First, these results may be appropriate to apply for Thailand only because of the difference in sociodemographic characteristics among countries. Second, interview location is at the hospital that may affect characteristic of the subjects, interviewed subjects might be the persons who concern about their health and can access the hospital service more than those who do not visit the hospital. The results of this study should be interpreted with caution. It may not reflect the whole country's population. Third, in reality, people may not behave as they respond to the questionnaire (Ryan, 2004).

2.6 Conclusion

Risk reduction of CRC-related mortality, complication, screening interval, bowel preparation, and cost influence the CRC screening preferences of Thai adults. FIT was preferred to other screening tests. These results are useful for health policy makers to incorporate in improving the success rate of CRC screening campaign.

CHAPTER III Cost-effectiveness analysis of colorectal cancer screening

3.1 Introduction

Health-related quality of life and quality-adjusted life year

To allocate the decisions by concerning the prioritization of healthcare resources among interventions, the involvement of evaluating the impact on both costs and health outcomes is needed. Healthcare studies use many different measurements to demonstrate the effect of a treatment in term of health outcome. It is difficult to decide where healthcare resources should be most efficiently directed, when the different types of outcome measures arising from many different inevitable utilizable interventions. If only survival is used to decide the best among healthcare interventions, the impact on the health-related quality of life (HRQoL) as a consequence of an intervention is ignored. To be able to compare across different areas of healthcare, a common measure is needed. This measure should ideally consider the impact of a treatment on both a patient's length of life and their health-related quality of life, which is recognized as a key indicator of treatment outcomes.

QALYs are used primarily to adjust someone's life expectancy based on the levels of health-related quality of life they are predicted to experience throughout the course of their entire or part of their life. The number of QALYs lived by an individual in one year can be calculated by a simple equation:

QALYs lived in one year = 1 * Q with $Q \leq 1$; where Q is the health-related quality of life weight attached to the relevant year of life. The number of QALYs gained can be determined as follows:

$$\text{QALYs gained} = \sum_{t=a}^{a+L^i} \frac{Q_t^i}{(1+r)^{t-a}} - \sum_{t=a}^{a+L} \frac{Q_t}{(1+r)^{t-a}}$$

Where Q^i is a vector of health-related quality of life weights predicted for each time period t following the intervention. L should be defined as the duration of the disease, while L^i is the period over which the individual enjoys the benefits of treatment. Normally, the period L^i will be at least as long as L, but it will be longer than L when interested treatment or intervention is capable to prolong the individual's life

expectancy, or when treatment may negatively affect the individual's quality of life for a period longer than L (Sassi, 2006).

QALYs do not depend on person's age. QALY is always the same value, regardless of the age at which it is lived, although this does not imply neutrality over age distributions (Sassi, Archard, & Le Grand, 2000). Utilities are measured on a scale of 0-1, where 0 indicates death or as worse as death and 1 indicates full functional health. The QALY is able to combine 'the effects of health interventions on mortality and morbidity into a single index', (Kind, Lafata, Matuszewski, & Raisch, 2009) thereby providing a 'common currency' to enable comparisons across different disease or health care areas.

The most commonly used method of economic evaluation in health care is CEA. CEA considers only one disease-specific outcome and the outcome is typically measured in clinical units, such as symptom-free days or life years gained. CUA is a subset of CEA that measures patient outcomes in QALYs. In order to assess the cost-effectiveness of an interested intervention, it must be compared to at least one other intervention. CEA helps with this decision by estimating the additional cost per one unit of additional gain which represents the incremental cost-effectiveness ratio (ICER). ICERs can be compared with those of other interventions or with a threshold value representing what is considered cost-effective which depends on each country's policy maker.

Colorectal cancer screening

Several screening modalities, such as FIT and colonoscopy, are effective on the reduction of CRC incidence and mortality (Qaseem et al., 2012; von Karsa et al., 2013; Zhang et al., 2017). CRC screening guideline recommends colonoscopy for higher adenomas and cancer detection rates, as compared to FIT (Burt et al., 2013; Douglas K Rex et al., 2009). However, colonoscopy is more invasive and costlier (B. Levin et al., 2008).

Because CRC naturally develops slowly over many years and the early stage disease is mostly curable if detected. A meta-analysis (Hewitson, Glasziou, Watson, Towler, & Irwig, 2008) of randomized trials inferred that yearly CRC screening with FOBT yielded a 16% reduction in CRC mortality (25% reduction in those who

attended). A meta-analysis of CRC screening could reduce CRC incidence by 18% and 28% and reduce CRC mortality by 32% and 50%, respectively (Elmunzer et al., 2012). As expected, stronger reductions were reported for the distal colon. Previous observational studies suggested even larger reductions in both incidence and mortality by screening colonoscopy (Brenner et al., 2011; A. G. Zauber et al., 2012), but randomized trials have not yet been completely conducted (Kaminski et al., 2012), and results will not be available until the mid-2020s. In the past 30 years, FIT for human hemoglobin in stool has been developed and increasingly used. These tests offer several advantages over gFOBT. FIT provided a higher sensitivity for detection of both CRCs and colorectal adenomas (Brenner & Tao, 2013; Duffy et al., 2011), also higher in acceptance and detects higher yield of colorectal neoplasms in population-based screening than did gFOBT (Vart, Banzi, & Minozzi, 2012). However, a positive gFOBT or FIT has to be followed up by colonoscopy and complete removal of the lesions.

According to the USPSTF recommendation 2016, CRC screening in average-risk, asymptomatic adults aged 50 to 75 years is of substantial benefit. Four strategies yielded a comparable balance of screening burden and benefit: colonoscopy every 10 years; FS every 10 years with annual FIT; CTC every 5 years; and annual FIT (Knudsen et al., 2016).

Thailand data

Although a significant reduction in CRC mortality is associated with CRC screening and surveillance, there is no national consensus on CRC screening and surveillance for Thai population. However, there are 5 CRC screening-related literature in Thailand.

First, a study that aimed to estimate preferences and acceptance of 2 CRC screening modalities i.e. FIT and colonoscopy, explore factors influencing the acceptance, and investigate reasons behind accepting and rejecting to screen before the program was implemented at primary care unit. A total of 437 subjects were included in the study (86.7% response rate). More than 70% of subjects accepted FITand about half accepted colonoscopy. No symptoms, unwilling to screen, being healthy, being too busy and anxious about diagnosis were the reported reasons for refusing to screen. The benefits of FIT over colonoscopy include its simplicity and non-invasiveness. Most

subjects preferred colonoscopy because of its accuracy, but for those who refused, the reasons were due to its procedure and risks of complications (Saengow et al., 2015).

Second, a study that assesses nationwide current practice in CRC screening among Thai general surgeons in 2008, mainly to those who worked in the general hospital and university hospital. Colonoscopy is the most popular investigation used in CRC screening, followed by FIT and DCBE (Lohsiriwat, Lohsiriwat, & Thavichaigarn, 2009).

Third, a study that conducted by the collaboration of Chulalongkorn University and the Thai Association of Gastrointestinal Endoscopy (TAGE) and supported by the Thai Government aimed to validate a practical strategic CRC screening protocol. Due to the limitation of endoscopists in Thailand (<1,000), there is a need for a primary screening test to identify patients at high. By adopting the combination of APCS score (Yeoh et al., 2011) and the results of FIT, the group was able to prioritize subjects for earlier colonoscopy. The authors concluded that positive FIT subjects with high-risk score should undergo colonoscopy as the first priority and that those with either high-risk or FIT positivity alone should undergo colonoscopy later. In 2015, the protocol included cities outside Bangkok and, recently, some cities of neighboring countries had adopted this protocol in including Mandalay and Yangon in Myanmar, and Hanoi in Vietnam (Aniwan et al., 2015).

Fourth, a pilot CRC screening program using the FIT was implemented through the routine Government Health Services in Lampang Province. A target population aged between 50-65 years was informed about CRC screening. Among the 127,301-target population, 62.9% were screened using FIT between April 2011 and November 2012. The participation rate of women (67.8%) was higher than men (57.8%). A total of 627 (72.0%) FIT positive subjects have had colonoscopy and resulted in 3.7% being CRC cases and 30.6% had adenomas. The results of participation and detection rates of colorectal neoplasia in Lampang pilot study are consistent with findings from other pilot and national programs. The participation rate of eligible participants in this Thai study was similar to rates reported in the UK (57%), France (55%), and Finland (71%) (Khuhaprema et al., 2014).

Fifth, a study that aimed to determine polyp and adenoma detection rates among Thai population and to evaluate the incidence of CRC detected during colonoscopy

screening. A total of 1,594 cases were reviewed. Of all included patients, 488 (30.6%) had colonic polyps. Adenomatous polyps were found in 263 cases, accounting for 16.5 % of ADR. Advanced adenomas were detected in 43 cases (2.6%). CRC was diagnosed in 10 cases (0.6%) (Aswakul, Prachayakul, Lohsiriwat, Bunyaarunnate, & Kachintorn, 2012).

Cost-effectiveness analysis of colorectal cancer screening

There were several published model-based studies that have investigated the effectiveness and cost-effectiveness of CRC screening programs (Iris Lansdorp-Vogelaar, Knudsen, & Brenner, 2011). Most studies focused on the screening including annual or biannual screening with gFOBT or FIT, FS every 5 years, or colonoscopy every 10 years with starting at age 50 years in average-risk persons were (Qaseem et al., 2012; von Karsa et al., 2013). Studies have consistently found that each of these screening options was effective and cost-effective (if not cost-saving), but the conclusive results of the most cost-effective screening method were varied because of factors such as incidence of CRC, costs of screening procedures and treatment which vary between countries and with time. Currently, researchers are ongoing towards the development of non-invasive blood or stool-based screening tests, such as blood-based DNA methylation or protein markers or stool DNA tests (de Wit, Fijneman, Verheul, Meijer, & Jimenez, 2013). Extensive research is also exploring the effectiveness of novel imaging technologies, such as CTC or capsule endoscopy for CRC screening. However, so far, their cost-effectiveness have not yet been concluded (Knudsen et al., 2010; Iris Lansdorp-Vogelaar et al., 2011). The restriction in the use of CTC for primary screening should be concerned because of exposure to radiation. Nevertheless, CTC might be the method of choice when complete endoscopic inspection of the large bowel is not possible e.g. in case of patient with a stenosis. However, some of these options are less feasible because of limitation in resource, especially for lower-resource areas. A skilled examiner is required in colonoscopy to provide an optimal sensitivity. Colonoscopy also requires greater cost, is less convenient, and has more risk for the patient compared with other tests (Winawer, 2006). FIT is inexpensive and easy to perform, may be consider a more practical option in many parts of the world (Center et al., 2009).

There is a systematic review of the economic evaluation studies of different CRC screening methods to identify the optimal screening modality. Full economic evaluation studies that focused on assessing CRC screening in average-risk population from 2003 to 2013 were retrieved. Eighteen publications from ten countries with 4 modeling approaches were included in the review. Fifty-six percent of included studies used CUA, whereas the rests were conducted by CEA. The method of gFOBT was the most included option, while FIT-biennial screening was the most reported optimal strategy. It was found that CRC screening was considered as a cost-effective or even cost-saving when compared with no screening (K Kittrongsiri & Chaikledkaew, 2014).

In France, ten-year simulation modeling was used to assess a virtual asymptomatic, average-risk population 50-74 years. CTC was always the most effective but not the most cost-effective. FIT was the least effective but most cost-effective strategy. Colonoscopy was of intermediate efficacy and the least cost-effective strategy in the setting of mass CRC screening in France (Lucidarme et al., 2012).

In Ireland, a CEA of a population-based screening program based on (i) biennial gFOBT at ages 55-74, with reflex FIT; (ii) biennial FIT at ages 55-74; and (iii) once-only FS at age 60. A third-party payer perspective was adopted. All scenarios would be considered highly cost-effective compared with no screening. The lowest ICER was found for FS, followed by FIT and gFOBT. Compared with FS, FIT was associated with greater gains in QALYs and reductions in lifetime cancer incidence and mortality, but was costlier, required considerably more colonoscopies and resulted in more complications (Sharp et al., 2012).

In Japan, a study compared cost-effectiveness of colonoscopy (strategy 1) and FIT (strategy 2) by using the database from February 2004 to August 2010 (n = 15,348) and the Japanese nationwide survey of CRC screening in 2008 (n = 5,267,443). This study showed that the rate of earlier-stage CRC was higher in strategy 1. The cost was higher using colonoscopy as a primary screening procedure. However, the difference was not excessive, and considering the increased rate of detecting earlier CRC, the use of colonoscopy as a primary screening tool may be cost-effective (Sekiguchi et al., 2012).

A systematic review was conducted for cost-effectiveness studies comparing CTC and colonoscopy as a screening tool and providing outcomes in life-years saved,

published between January 2006 and November 2012. Nine studies were included in the review. CTC has the potential to be a cost-effective CRC screening strategy when compared to colonoscopy. There is a strong need for a differential consideration of patient adherence and compliance to CTC and colonoscopy (Kriza, Emmert, Wahlster, Niederländer, & Kolominsky-Rabas, 2013).

A study in 8,484 registered patients. 5,384 were randomized and analyzed. Detection rates were 7.3% (93/1277) for CTC, compared with 5.6% (141/2527) for DCBE ($p = 0.0390$). The difference was due to better detection of large polyps by CT, with no significant difference for cancer. At the 3-year follow-up, the cancer missing rate was 6.7% for CTC and 14.1% for DCBE. In the short term, CTC was significantly more acceptable to patients than DCBE or colonoscopy. Total costs for CTC and colonoscopy were finely balanced, but CTC was associated with higher health-care costs than DCBE (Halligan et al., 2015).

In Hong Kong, a CEA study showed that colonoscopy detected notably more adenomas (23.6% vs. 1.6%) and advanced lesions or cancer (4.2% vs. 1.2%) than FIT. Colonoscopy is considered cost-effective for screening adenoma, advanced neoplasia, and a composite endpoint of advanced neoplasia or stage I CRC (Wong et al., 2015).

CEA can be used to compare the costs and outcomes of alternative treatments, health interventions, as well as policy options. Cost-effectiveness threshold is the value that determines whether the intervention is a good value for money to be identified. In 2001, WHO on Macroeconomics in Health suggested that eligible thresholds should base on multiples of a country's per-capita gross domestic product (GDP). In some contexts, in deciding whether the money should be invested for health interventions, these thresholds have been used as decision rules.

However, the use of thresholds which based on GDP in decision-making processes at country level shows them to lack country specificity and this, in addition to the uncertainty in the modeled cost-effectiveness ratios, can lead to the wrong decision on how to spend health-care resources. WHO suggested that countries should establish a context-specific process for their decision-making that is legalized, has stakeholder buy-in and is consistent, fair, and transparent. While cost-effectiveness ratios are undoubtedly informative in assessing value for money from either the supply

or demand side-they also need to be considered alongside affordability, budget impact, fairness, feasibility and any other criteria considered important in the local context.

For Thailand, in 2007, the subcommittee responsible for the development of Thailand's national list of essential medicines set a threshold of 100,000 THB (0.8 of the per-capita GDP – per QALY gained) (Teerawattananon, Natanant, Kulpeng, Yothasamut, & Werayingyong, 2013). This threshold, which applies specifically to medicines included on the essential medicines list, has been a particularly powerful tool in price negotiations. Decisions on the benefit package are made by the National Health Assembly, using societal values, and cost-effectiveness thresholds are therefore not the only aspect taken into consideration (Youngkong, Baltussen, Tantivess, Mohara, & Teerawattananon, 2012).

In LMICs, health care financing sustainability is to be considered thoroughly in the long-run. The increasing disease burden coupled with aging population are inevitable issues in many countries. The appropriate model of health care financing strategy is important to provide long-term sustainability in healthcare system and to ensure that funding has been invested for the right services at the right time. Cost-effective solutions are needed especially in health promotion and prevention (Vekic et al., 2019).

Despite a large number of studies demonstrating that funding in CRC screenings was worth for the money in many western countries (Iris Lansdorp-Vogelaar et al., 2011), the cost-effectiveness study in LMICs is still limited. Thailand, a member of LMICs situated in Southeast Asia, had reported a high burden of CRC which ranked in one of the leading causes of death in the country. About half of the CRC cases detected at late stages (Leite, Salles, Araujo, Villela-Nogueira, & Cardoso, 2009). Recently, Thailand has launched CRC population-based screening campaigns using either FIT or colonoscopy, indicating policy makers have paid attention in CRC prevention. As Thailand is one of the leading countries advocating the use of HTA evidence to help in decision making as part of Universal Health Coverage policy, there is a strong need to understand which screening intervention is worth for funding. This study aimed to determine the cost-effectiveness of all relevant CRC screening options including FIT and colonoscopy in Thailand.

In Thailand, there is no data in the cost-effectiveness of CRC screening. The sixty-seventh World Health Assembly report 2014: Health intervention and technology assessment in support of universal health coverage recognized that HTA of healthcare interventions is a crucial tool that can be used for evidence-informed policy decision making in order to ensure sustainable healthcare financing under universal health coverage. HTA has been widely used for health benefit package design of universal coverage insurance scheme in many countries including Thailand. The interpretation of the cost-effectiveness of the findings was based on an official WTP of 160,000 THB/QALY (4,706 USD/QALY) adopted by Thai Health Economic Working Group (Teerawattananon, Tritasavit, Suchonwanich, & Kingkaew, 2014). Thus, it is necessary to evaluate CUA in Thailand context for a part of policymakers' decision making. If this study shows cost-effective, the screening program can be implemented in Thai average-risk population as a national welfare.

3.1.1 Research questions

Primary research questions

1. Is CRC screening cost-effective in Thailand?

Secondary research questions

1. Which test of CRC screening is the most cost-effective in Thailand?
2. Which age of start screening is cost-effective in Thailand?
3. How many cases prevented from CRC and death by each method of screening?
4. What is the additional cost per 1 QALY gained by each cancer screening strategy?
5. What are the effects of the parameter uncertainties in the models?

3.1.2 Research objectives

General objectives

1. To evaluate the cost-effectiveness analysis of CRC screening in Thailand

Specific objectives

1. To evaluate the most cost-effective CRC screening test in Thailand
2. To evaluate the most cost-effective age of start screening in Thailand

3. To evaluate the number of cases prevented from CRC and death by each method of screening
4. To evaluate the cost-utility analysis of CRC screening in Thailand in terms of the additional cost per QALY gained
5. To evaluate the effect of uncertainties of the parameters in the models

3.1.3 Hypotheses

CRC screening is cost-effective in Thailand when compared to no screening in terms of

- Cost-saving from decrease progression to cancer and death
- Increase life-years saved
- Increase QALY gained
- Accepted incremental cost-effectiveness ratio

3.1.4 Scope of the study

The study aims to evaluate CRC screening for average-risk persons in terms of CUA. This study uses primary data from a CRC screening project that reports the adenomatous polyp detection rates in Thai people and evaluates the incidence of CRC during screening colonoscopy at Siriraj Hospital, Mahidol University.

A hybrid model consisting of decision tree and Markov models are used to approximate relevant costs and health outcomes of CRC screening for average-risk persons who screened compare to average-risk persons who do not receive screening. Multimodality of CRC screenings is also analyzed to evaluate the most cost-effective strategy of screening in Thailand.

Screening modalities of interest are colonoscopy every 10 years and annual FIT. Due to limitations of screening tests in sensitivity and specificity, this model is classified into 4 sub-categories; true positive, false positive, false negative, and true negative of screening tests to improve the accuracy of the model. Our model is developed to mimic the natural history of CRC and clinical practice. Since average-risk persons can be a life-long condition, the lifetime horizon is chosen in this study. We undertake this study using a social perspective in costing calculation as advised by Thailand's HTA guideline (Thai Working Group on Health Technology Assessment

Guidelines in Thailand, 2013). We perform a CUA expressing findings as incremental cost per QALY gained.

For the input parameters, sensitivity, and specificity of each screening modality, annual transitional probabilities, costs, and utilities are filled in the Markov models. These parameters are obtained from a data set of Siriraj Hospital and systematic literature search from other studies (local and international publications) which are the most applicable to Thai population.

3.1.5 Possible benefits of the study

There is an absence of knowledge regarding long-term benefits and cost-effectiveness of CRC screening with intervention for the average-risk group in Thailand. If this study shows that CRC screening is cost-effective, it will contribute as new knowledge and can be implemented as a policy. The average-risk persons will receive the appropriate screening at a lower cost from national health policy. They will receive an early diagnosis and appropriate treatments to prevent more serious and high costs complications.

3.2 Methodology

3.2.1 Study design

This research is a cost-effectiveness analysis study of CRC screening for average-risk persons in Thailand.

3.2.2 Data collection

A cost-effectiveness analysis was conducted to estimate relevant incremental costs of CRC screening programs and the health outcomes the unit of QALYs gained when compared with no screening The target population of CRC screening is Thai average-risk population. The interested choices of screening in this study included 2 screening strategies: (1) FIT every year (2) Colonoscopy every 10 years. In order to capture outcomes of adenomatous polyps and CRC, the lifetime time horizon was implemented in this study. As based on Thailand's HTA guideline (Thai Health Technology Assessment Guideline Working Group, 2008), the perspective of societal was applied in this study. Our findings were presented in ICERs in USD per QALY

gained. The cost-effectiveness threshold used in the analysis was an official WTP of 4,706 USD/QALY (160,000 THB/QALY) used by the Health Economics Working Group of the National List of Essential Medicines (NLEM) committee (Teerawattananon et al., 2014). As the recommended national guideline, all future costs and health outcomes were annually discounted at the rate of 3% (Permsuwan, Kansinee, & Buddhawongsa, 2014).

This study uses primary data from a CRC screening project that reports the adenomatous polyp detection rates in Thai people and evaluates the incidence of CRC during screening colonoscopy at Siriraj Hospital, Mahidol University. It was conducted by retrospective electronic chart review of asymptomatic Thai adults who underwent screening colonoscopy in Siriraj endoscopic center from June 2007 to October 2010. A total of 1,594 cases were reviewed. A total of 488 patients (30.6%) were reported to have colonic polyps. Two hundred and sixty-three cases had adenomatous polyps, accounting for 16.5 % adenomatous detection rate. Advanced adenomas were detected in 43 cases (2.6%). Ten cases (0.6%) were found to have CRC.

3.2.3 Conceptual framework

This conceptual framework provides an overview of the steps of the research plan and the information needed to be collected and calculated. For this study, the conceptual framework showed 5 main steps of the economic evaluation.

Step 1: A hybrid model consisting of decision tree and Markov models is established. The primary data, secondary data, data from systematic literature review and meta-analysis are filled in the model.

Step 2: Total costs between the patients who receive the screening and intervention versus the controlled group who do not receive the screening are compared.

Step 3: The effectiveness in terms of the number of cases prevented from CRC and death, life-years saved, and QALYs gained are compared between two groups.

Step 4: The incremental cost-effectiveness ratios of each modality of screening are analyzed.

Step 5: The uncertainties of the parameters are tested by using one-way sensitivity analyses with Tornado diagrams and probabilistic sensitivity analyses.

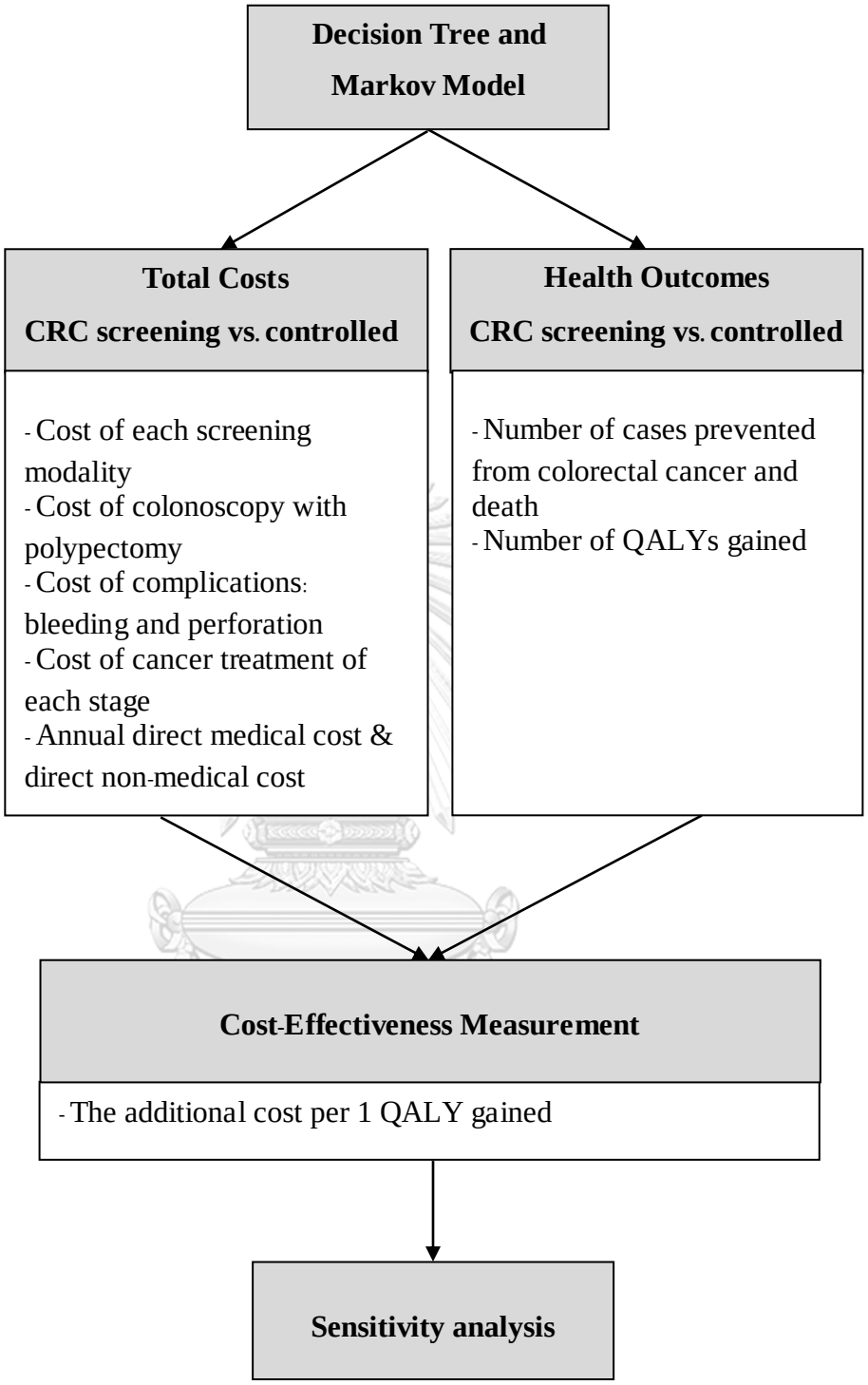

Figure 1. Conceptual framework of colorectal cancer screening

3.2.4 The economic model

A total of 100,000 hypothetical Thai average-risk, asymptomatic persons, following the criteria of the National Cancer Institute of Thailand (National Cancer Institute Thailand, 2015b), was simulated for the study modeling. We assumed the population age at 50 years as the base case analysis of the study according to the USPSTF 2016 (U. S. Preventive Services Task Force et al., 2016) recommendation. The screening test was assumed to repeatedly done with a specific interval, as followed to the national guideline (National Cancer Institute Thailand, 2015b), until the population become 75 years of age.

The economic model used in this study cooperated decision tree with Markov model. A decision tree allowed researchers to classified patients into 2 groups i.e. a screening group with therapeutic interventions in those with abnormal results and a no-screening group. To replicate the natural of screening test accuracy, the screening group subjects were divided into 4 groups, including i.e. true positive, false positive, false negative, and true negative according to sensitivity and specificity from network meta-analysis to the validity of the result from the models.

True positive: In this group, the costs are calculated by summing of costs of screening, cost of intervention, cost of cancer treatment, and cost of complications. The effectiveness is the number of cases prevented from CRC, the number of LY saved and QALYs gained.

False positive: In this group, the costs are calculated the same as true positive group but these patients receive the overdiagnosis. They do not have adenomatous polyp or CRC, thus, no effectiveness is gained.

False negative: In this group, the costs are calculated by summing of costs of screening but it does not include the cost of intervention and cancer treatment. They were considered having adenomatous polyp or CRC, however, these patients do not receive early intervention because of miss diagnosis and no effectiveness is gained in this group.

True negative: In this group, the costs are calculated by summing of costs of screening. The effectiveness is the same as the controlled group (no screening).

Colorectal cancer is naturally a slowly progressive disease and the intervention such screening tests known to provided long-term effects e.g. a decrease in cancer mortality needed a Markov model to capture result in the future. A lifetime horizon with a one-year cycle length Markov model was conducted. The Markov model was designed to compose with 8 principal health stages including normal, low-risk polyp (LRP), high-risk polyp (HRP), CRC stage I-IV, and death followed to the natural progression of CRC which normally starts from the precancerous lesion or adenomatous polyp. The hypothetical cohorts, who have gone through either of the screening test, would receive the treatments if any positive results were found via screening tests. While patients in no screening group would be diagnosed and treated only after CRC suspected symptoms are detected. During each 1-yearly cycle of the Markov model, the patients could either stay in their current state or move to another worse adjacent state including the death state. Patients with normal health or patients without colonic lesions could progress to Low-risk polyp state. According to the natural history of disease, low-risk polyp could progress to high-risk polyp and high-risk polyp could progress to CRC stage I-IV stage by stage. None of the patients in each health state could reverse to a previous better health state, followed to the natural course of CRC, as shown in Figure 2. One of our assumptions is that the stage-specific progression transitional probability of CRC in each cycle of each health was assumed to be constant over time.

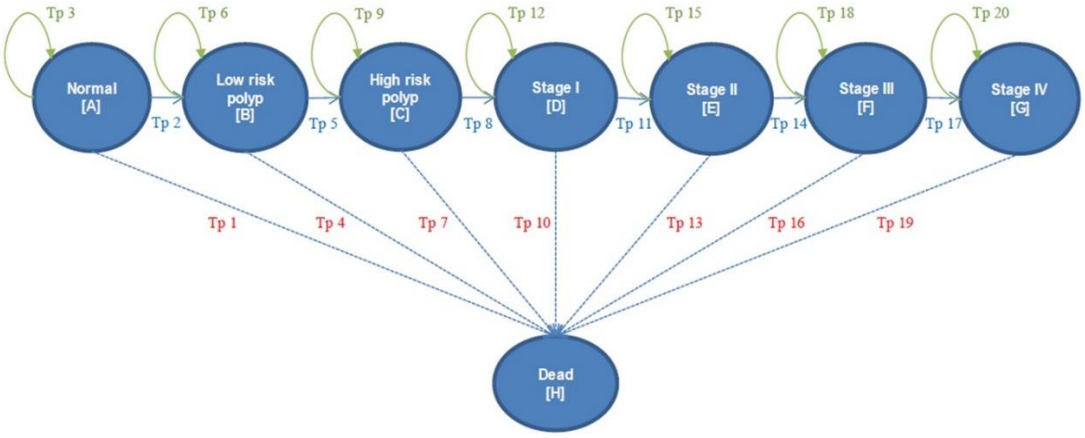

Figure 2. A Markov model shows the natural course of colorectal cancer progression

Input parameters of the model (Table 9)

The model input parameter related to colonoscopy screening included the prevalence of LRP, HRP, and each stage of CRC which were based on primary data from the CRC screening project that had been carried through 1,594 Thai subjects. The rate of adenomatous polyp detection and the CRC incidence from colonoscopy screenings from Jan 2007 to Dec 2010 from the Siriraj endoscopic center (Aswakul et al., 2012) was evaluated. The other secondary data source was gathered from the report of prospective colonoscopy screening project of 1,404 cases at Chulabhorn Hospital, the tertiary care hospital in Thailand (Siripongpreeda et al., 2016). In this study (Siripongpreeda et al., 2016), the colonoscopy for CRC screening was offered to 1,500 healthy volunteers, who were registered in the program from July 2009 to June 2010.

In the model of FIT screening, the prevalence of all health states was derived from the pilot population-based CRC screening program study using annual FIT among the population in Lampang Province, Thailand (Khuhaprema et al., 2014). Other input parameters including test performance (i.e. sensitivity and specificity of FIT and colonoscopy), transition probabilities, utilities, and costs were obtained from locally and internationally published literature, as shown in Table 9.

The effectiveness of each included screening options

The test performance of FIT screening was retrieved from a systematic review and meta-analysis of 19 individual studies including 113,360 participants. (Lee, Liles, Bent, Levin, & Corley, 2014) that indicated pool data of both sensitivity and specificity. The pooled sensitivity and specificity of the FIT screening test for the CRC detection using the values of greater than 50 micrograms of hemoglobin per gram of feces as cutoff points were 67% (95% CI, 59%-74%) and 96% (95% CI, 94%-98%), respectively, as compared to the colonoscopy which is the reference standard of CRC detection. In our model, we cooperated the participation rate of FIT screening as the long-term compliance rate of annual screening and the colonoscopy participation rate after positive FIT was found (Khuhaprema et al., 2014) to ensure not to overestimate the overall benefits of the FIT screening.

The sensitivity of colonoscopy screening was based on a recent systematic review and meta-analysis of 49 studies (11,151 participants) (Pickhardt, Hassan, Halligan, & Marmo, 2011) which reported 94.7% overall sensitivity for the CRC detection (95% CI ,90.4%-97.2%). In addition, the specificity of colonoscopy screening was based on another recent systematic review including 20 individual studies (79,551 participants) (Allameh, Davari, & Emami, 2011). The reported overall specificity of colonoscopy for the CRC detection was 99.8% (95% CI ,99.6%-100%). We also calculated the participation rate of colonoscopy screening and incorporated into the model in order to provide more accurate results. (Khuhaprema et al., 2014; Saengow et al., 2015).

The results from the recent network meta-analysis including 44 individual studies concluded that the most effective screening was colonoscopy that could provide the result of the highest number of cases avoiding CRC-related mortality. Colonoscopy decreased the mortality of CRC by 61% (RR, 0.39; 95% CI, 0.31-0.50) and FIT could reduce 59% (RR, 0.41; 95% CI, 0.29-0.59), when compared with no screening, respectively. Moreover, the colonoscopy could reduce the overall incidence of CRC by 57% (RR, 0.43; 95% CI, 0.30-0.60) whereas FIT provided the overall incidence of CRC reduction of 21% (RR, 0.79; 95% CI, 0.69-0.92) when compared to no screening (Zhang et al., 2017).

Probability data

To represent colorectal polyp progression rates of the model, the yearly incidence of LRP and the transition probabilities among all stages (LRP, HRP, and CRC stage I-IV) were estimated and used in the model (Gopalappa, Aydogan-Cremaschi, Das, & Orcun, 2011; Leshno, Halpern, & Arber, 2003). The age-specific mortality rate (ASMR) of Thai population (World Health organization, 2016.) was transformed to the probability of death among the cohort of average-risk people in the model. The probability of death of patient in each CRC stage was obtained from a meta-analysis of 4 studies in Thailand; 2 from Siriraj Hospital, Mahidol University (including 1,047 cases between January 2003 and December 2007 (Techawathanawanna, Nimmannit, & Akewanlop, 2012) and 2,610 cases during January 2009 to December 2013 (unpublished data)), another one from Rajavithi Hospital including 287 cases

studied during January 1995 to December 2003 (Sudsawat Laohavinij & Maneechavakajorn, 2010), and the other from Songklanagarind Hospital consisted of 1,013 cases between January 2004 and December 2013 (Sermsri, Boonpipattanapong, Prechawittayakul, & Sangkhathat, 2014).

Cost data

Our model focus on only direct medical and direct nonmedical costs. But indirect costs were not included, as we assumed that lost or impaired ability to work or engage in leisure activities due to morbidity would be carried out in the disutility of QALY (Riewpaiboon, 2008). All associated costs were assembled from previously published studies in Thailand. The health care utilization was estimated using a micro-costing technique. We assigned the average-risk people with normal result to undergo either annual FIT screening or 10-yearly colonoscopy screening. The patients with adenomatous polyps, both LRP and HRP, would refer to therapeutic polyp removals followed the colonoscopy screenings and repeat the colonoscopy screenings within a shorter interval of 5 years. We estimated the total cost of colonoscopy which already covered its possible complications based on the reported incidence of post-colonoscopy complications in a recent meta-analysis (Reumkens et al., 2016). The treatment costs of each CRC stage were obtained from a previous study in Thailand (Sermsri et al., 2014). In a follow-up period, we assumed that the patients with CRC would have 4 times per year of outpatient visits and incur costs from follow-up laboratory testing. The standard unit direct costs of FIT screening, colonoscopy screening, laboratory testing, and x-rays and direct nonmedical costs of transportation, meals, accommodation, and facilities were obtained from the previous publish standard cost list for HTA of Thailand (Riewpaiboon, 2011a). All costs were converted and reported in 2017 USD (1 USD=34 THB) and using the consumer price index (CPI) and international exchange rate in 2017 (Bank of Thailand, 2017; "Consumer Price index (CPI) of Thailand, Economic and Trade Indices Database (ETID)," 2017).

Utility data

All utility for each health state were based on previously published literature. The utility values of patients with or without adenomatous polyps were obtained from 2 studies. The first one is population-based values for EQ-5D health states in Thai general population (Tongsiri & Cairns, 2011). The second one is a large cohort study conducted among 4,850 Thai subjects aged older than 45 years using the Thai EQ-5D questionnaire. In 2017, a total of 1,409 respondents were interviewed by 3 methods of utility measurement i.e. the ranking, visual analogue scale, and time trade-off methods (Kimman et al., 2013). The utility values of patients with each CRC stage were obtained using the standard gamble technique from a study involving 81 participants in the US. (Ness, Holmes, Klein, & Dittus, 1999).

Table 9. Model input parameters of colorectal cancer screening

Input parameters	Distri-bution	Mean (SE)	Reference
Baseline parameters			
Annual discount rate (%)		3 (0-6)	(Permsuwan et al., 2014)
Prevalence of polyp and CRC			
Low-risk polyp	Beta	0.113 (0.008)	(Aswakul et al., 2012; Siripongpreeda et al., 2016)
High-risk polyp	Beta	0.070 (0.007)	(Aswakul et al., 2012; Siripongpreeda et al., 2016)
Colorectal cancer	Beta	0.013 (0.003)	(Aswakul et al., 2012; Siripongpreeda et al., 2016)
Positive fecal immunochemical test	Beta	0.011 (0.006)	(Khuhaprema et al., 2014)
Positive colonoscopy	Beta	0.195 (0.028)	(Aswakul et al., 2012; Siripongpreeda et al., 2016)
Effectiveness of FIT			
Overall sensitivity	Beta	0.670 (0.036)	(Lee et al., 2014)
Overall specificity	Beta	0.960 (0.010)	(Lee et al., 2014)
CRC incidence reduction	Beta	0.210 (0.051)	(Zhang et al., 2017)
FIT screening participation rate	Beta	0.629 (0.057)	(Khuhaprema et al., 2014)
Compliance for colonoscopy in positive FIT	Beta	0.718 (0.050)	(Khuhaprema et al., 2014)
Effectiveness of colonoscopy			
Overall sensitivity	Beta	0.947 (0.013)	(Pickhardt et al., 2011)
Overall specificity	Beta	0.998 (0.001)	(Allameh et al., 2011)
CRC incidence reduction	Beta	0.570 (0.066)	(Zhang et al., 2017)
Colonoscopy screening participation rate	Beta	0.472 (0.043)	(Khuhaprema et al., 2014; Saengow et al., 2015)
Annual transition probabilities			
Normal → low-risk polyp	Beta	0.0075 (0.0003)	(Gopalappa et al., 2011; Leshno et al., 2003)
Low-risk polyp → high-risk polyp	Beta	0.0200 (0.0077)	(Gopalappa et al., 2011; Leshno et al., 2003)
High-risk polyp → CRC stage I	Beta	0.0500 (0.0255)	(Gopalappa et al., 2011; Leshno et al., 2003)
CRC stage I → stage II	Beta	0.2800 (0.0357)	(Gopalappa et al., 2011; Leshno et al., 2003)
CRC stage I → death	Beta	0.0230 (0.0092)	(Landre et al., 2015; Sermsri et al., 2014; Sudsawat Laohavinij & Maneechavakajorn, 2010; Techawathanawanna et al., 2012)
CRC stage II → stage III	Beta	0.2800 (0.0357)	(Gopalappa et al., 2011; Leshno et al., 2003)
CRC stage II → death	Beta	0.0389 (0.0123)	(Landre et al., 2015; Sermsri et al., 2014; Sudsawat Laohavinij &

Input parameters	Distri-bution	Mean (SE)	Reference
			Maneechavakajorn, 2010; Techawathanawanna et al., 2012)
CRC stage III → stage IV	Beta	0.6300 (0.0357)	(Gopalappa et al., 2011; Leshno et al., 2003)
CRC stage III → death	Beta	0.0883 (0.0193)	(Landre et al., 2015; Sermsri et al., 2014; Sudsawat Laohavinij & Maneechavakajorn, 2010; Techawathanawanna et al., 2012)
CRC stage IV → death	Beta	0.2483 (0.1157)	(Landre et al., 2015; Sermsri et al., 2014; Sudsawat Laohavinij & Maneechavakajorn, 2010; Techawathanawanna et al., 2012)
Costs (2017 USD)			
Annual direct medical costs			
FIT	Gamma	1.4 (0.2)	(Riewpaiboon, 2011a)
Colonoscopy	Gamma	106.7 (13.6)	(Reumkens et al., 2016; Riewpaiboon, 2011a)
Treatment of polyp	Gamma	87.6 (11.2)	(Riewpaiboon, 2011a)
Treatment of CRC stage I	Gamma	2,498.1 (318.6)	(Sermsri et al., 2014)
Treatment of CRC stage II	Gamma	4,667.5 (595.3)	(Sermsri et al., 2014)
Treatment of CRC stage III	Gamma	5,382.3 (686.5)	(Sermsri et al., 2014)
Treatment of CRC stage IV	Gamma	5,715.3 (729.0)	(Sermsri et al., 2014)
Follow up	Gamma	780.3 (99.5)	(Riewpaiboon, 2011a)
Annual direct nonmedical costs			
Transportation	Gamma	754.0 (96.2)	(Riewpaiboon, 2011a)
Food	Gamma	26.4 (3.4)	(Riewpaiboon, 2011a)
Utilities			
Normal	Beta	0.83 (0.09)	(Kimman et al., 2013; Tongsiri & Cairns, 2011)
Low-risk polyp	Beta	0.83 (0.09)	(Kimman et al., 2013; Tongsiri & Cairns, 2011)
High-risk polyp	Beta	0.83 (0.09)	(Kimman et al., 2013; Tongsiri & Cairns, 2011)
CRC stage I	Beta	0.74 (0.02)	(Ness et al., 1999)
CRC stage II	Beta	0.67 (0.06)	(Ness et al., 1999)
CRC stage III	Beta	0.61 (0.06)	(Ness et al., 1999)
CRC stage IV	Beta	0.25 (0.03)	(Ness et al., 1999)

CRC, colorectal cancer; FIT, fecal immunochemical test; USD, United States Dollars

3.2.5 Data analysis

All data are analyzed by using the CUA. The total costs and the effectiveness of each CRC screening modality with intervention and no screening are compared in terms of ICER.

Cost-effectiveness analysis

Base-case analysis

The first outcomes of interest are clinical outcomes of the number of cases prevented from CRC and death by each CRC screening modality with intervention. And the other outcomes are lifetime costs, QALYs gained, and ICER per QALY gained.

The cost-effectiveness of each CRC screening modality with intervention is assessed by calculating its ICER according to the following formula:

$$\frac{\text{Total costs}_{\text{screening}} - \text{Total costs}_{\text{no screening}}}{\text{Outcomes}_{\text{screening}} - \text{Outcomes}_{\text{no screening}}}$$

The results are presented as ICER of CRC screening for average-risk persons with screening intervention compared to no screening group. Based on the USPSTF 2016 recommendation (U. S. Preventive Services Task Force et al., 2016), the starting age of screenings at 50 years was used as the base case to show the benefits of the screening test. We also reported the numbers of both early and late stages of cancer cases prevented by screening. For the base-case analysis, ICERs were calculated by the expected lifetime costs and outcomes.

To validate the model, the incidence of interval colorectal cancer (I-CRC), a CRC diagnosed within 5 years after a negative result of screening by colonoscopy estimated by the model was compared to the results from other studies.

3.2.6 Sensitivity analysis

We performed a series of one-way sensitivity analyses by varying related parameter values within the 95% CI ranges one by one at a time to review the impact of parameter values on the ICERs. The parameters included in one-way sensitivity analyses were all clinical outcomes, costs, utilities, and discount rates. A tornado

diagram was developed to represent the results of the robustness of the model. Tornado diagrams are used to determine which variables were relatively important or had the most impact on ICERs when compared to the other variables. In tornado diagrams, the first ten bars demonstrate the items that contribute the most impact on the ICER. The decision maker should prioritize these parameters first when consider implementing the result from the model. In addition, the starting ages of the screenings were also varied from 40 to 80 years in order to evaluate the impact of the starting age on the results.

A probabilistic sensitivity analysis (PSA) was conducted using a Monte Carlo simulation performed by Microsoft Excel 2003 (Microsoft Corp, Redmond, WA) to simultaneously examine the effects of all parameter uncertainties at once (Briggs, Sculpher, & Claxton, 2006). The distributions of each probability were assigned. Beta-distributions were assigned for the parameter in which their values ranged between 0 and 1, these included the prevalence, effectiveness of CRC screening with therapeutic interventions, probabilities, and utilities. Gamma distributions were assumed for the costs which valued positively. A Monte Carlo simulation was run for 1,000 iterations to provide a range of values for total costs, outcomes, and ICERs. We plotted cost-effectiveness acceptability curves to represent the results from PSA. The expected net monetary benefit (NMB) was calculated for the WTP threshold in Thailand to show the probability of each screening option being cost-effective for monetary values when compared to no screening that a decision maker might decide to offer the funding.

3.2.7 Budget impact analysis

The 5-year budget impact analysis was conducted to evaluate the financial impact from both 2 screening strategies. The size of the target population was estimated based on national epidemiological data ("Population of Thailand Classified by Age," 2018). The persons eligible for CRC screening included the whole Thai people aged between 50-75 years. Both the ideal and real-life situations which participation rate is not equal to 100% were taken into consideration in this BIA.

3.2.8 Ethical issues

The study was ethically approved by Siriraj Institutional Review Board (SIRB) No. 302/2560 (EC1).

3.3 Results

Base case analysis

The result from base-case analysis of starting age of screening at 50 years showed that the annual FIT coupled with therapeutic interventions could prevent 1,049 (5.7%) cases from the development of early stage of cancer and 1,220 (9.2%) cases from late stage of cancer per 100,000 screening over a lifetime when compared with no screening according to the real-life participation rate. Moreover, when compared to no screening, the colonoscopy screening every 10 years with therapeutic interventions in those with detectable abnormality could prevent 3,288 (17.9%) cases from the development of early stage of cancer and 3,695 (27.8%) cases from late stage of cancer per 100,000 screening over lifetime. Our findings of preventable cases were only a slightly lower than the results of the recent systematic review and network meta-analysis (Zhang et al., 2017) which showed that screening by colonoscopy and FIT could provide the overall reduction of CRC incidence by 8%-31% and 40%-70%, respectively, compared with no screening. These findings may be explained by a lower participation rate in our model.

As compared to no screening, the screenings by either annual FIT or colonoscopy every 10 years was considered cost-effective because the ICERs of 509.84 and 600.20 USD/QALY gained were shown, respectively. However, when compared to the annual FIT screening, the colonoscopy screening every 10 years was also cost-effective with the ICERs of 646.53 USD/QALY gained (Table 10).

Table 10. Estimated lifetime costs and health outcomes of colorectal cancer screening option and no screening

Screening options	Total costs (USD)	LYs	QALYs	Incremental cost (USD)	Incremental QALYs	ICERs (USD/QALY)
No screening	1,186.90	18.102	14.959	-	-	-
Annual fecal immuno-chemical test	1,208.89	18.144	15.002	21.99	0.043	509.84 (Cost-effective)
Colonoscopy every 10 years	1,263.27	18.225	15.086	54.38	0.084	646.53 (Cost-effective)

ICERs, incremental cost-effectiveness ratios; LYs, life-years; QALYs, quality-adjusted life years; USD, US Dollars

For model validation, the estimated I-CRC within 5 years after normal colonoscopy screening was compared to the results of previously published studies. The incidence of I-CRC per 5 years of both early and late stages in our model is about 3.1% (Table 11) which is comparable with the range of 2.6%-3.0% that had been reported in previously published literature (Erichsen et al., 2013; le Clercq et al., 2014; Richter, Campbell, & Chung, 2015).

Table 11. The interval colorectal cancer within 5 years after normal colonoscopy screening

Year	Normal	LRP	HRP	CRC1	CRC2	CRC3	CRC4	Death	SUM	New early CRC after screening	New Late CRC after screening
Y 0	79.42	11.87	7.36	0.90	0.30	0.08	0.08	0.00	100	0.00	0.00
Y 1	78.27	12.15	7.28	0.96	0.41	0.09	0.09	0.75	100	0.45	0.10
Y 2	77.14	12.41	7.21	1.00	0.50	0.13	0.11	1.50	100	0.46	0.13
Y 3	76.03	12.65	7.14	1.03	0.58	0.16	0.14	2.26	100	0.47	0.16
Y 4	74.94	12.88	7.08	1.05	0.65	0.19	0.18	3.04	100	0.47	0.19
Y 5	73.62	13.06	7.01	1.06	0.70	0.22	0.22	4.12	100	0.47	0.22
SUM										2.33	0.80
5-year interval cancer										**3.13**	

CRC, colorectal cancer; HRP, high-risk polyp; LRP, low-risk polyp

Sensitivity analyses

One-way sensitivity analyses

The tornado diagrams demonstrated one-way sensitivity analyses results of the colonoscopy screening compared to no screening shown in Figure 3. Only the results from influencing parameters were showed in the diagram. The transition probability of HRP to CRC stage I had the most impact on ICER between the colonoscopy screening and no screening, followed by the CRC incidence reduction by colonoscopy, the transition probability of LRP to HRP, the cost of colonoscopy, the prevalence of positive colonoscopy, and the participation to colonoscopy. Despite the varying these parameters, the ICER changes as a result of the colonoscopy screening with the starting age at 50 years remained cost-effective. This impact of parameters' value on ICERs was greater when the starting ages of screening were at 40 and 50 years than 60 and 70 years. Moreover, when varied the age of screening covered until 80 years the results showed that screening age after was not cost-effective (Table 12).

Another parameter that had an impact on the cost-effectiveness of the results was the participation rate. The cost-effective result would be shown only if participation in FIT screening and colonoscopy screening were more than 21% and 17%, respectively (Table 13). In addition, we also explored the maximum acceptable costs of FIT and colonoscopy that would still make screening cost-effective. If the cost of FIT was higher than 12 USD and the cost of colonoscopy was more expensive than 310 USD, the screening would no longer consider cost-effective, when compared to no screening. In addition, FIT was cost-effective when compared to colonoscopy if either the participation rate of colonoscopy screening was less than 29% or the cost of colonoscopy was higher than 275 USD (Table 14).

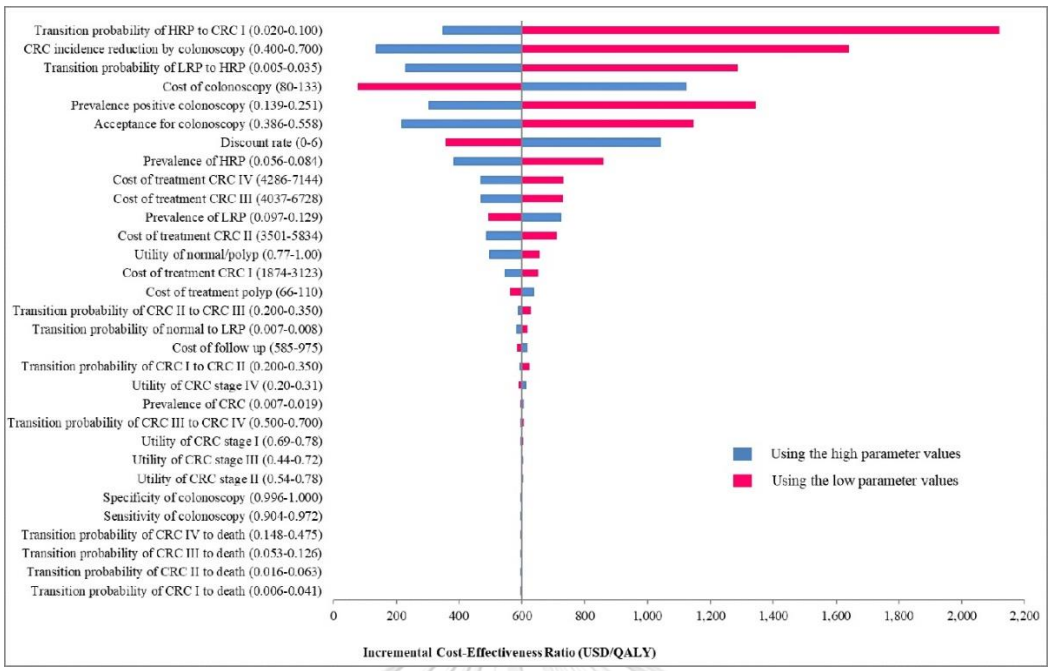

Figure 3. Tornado diagram illustrating the one-way sensitivity analysis results of screening by colonoscopy every 10 years compared to no screening

Table 12. Appropriate ages of start screening

Age of start screening (years)	ICERs (USD/QALY gained)	Interpretation
40	545.59	Cost-effective
45	585.90	Cost-effective
50	646.53	Cost-effective
55	738.80	Cost-effective
60	888.71	Cost-effective
65	1,143.01	Cost-effective
70	1,602.88	Cost-effective
75	2,449.39	Cost-effective
80	4,148.43	Cost-effective
85	7,489.13	Not cost-effective

ICERs, incremental cost-effectiveness ratios; QALYs, quality-adjusted life years; USD, United States Dollars

Table 13. Effects of acceptance of screening on cost-effectiveness results when compared to no screening

Acceptance of FIT (%)	**ICERs (USD/QALY gained)**	**Interpretation**
10	11,980.85	Not cost-effective
20	5,169.78	Not cost-effective
30	2,896.80	Cost-effective
40	1,758.30	Cost-effective
50	1,073.56	Cost-effective
60	615.65	Cost-effective
70	287.34	Cost-effective
80	40.01	Cost-effective
90	-153.37	Cost-saving
100	-309.01	Cost-saving
Acceptance of colonoscopy (%)	**ICERs (USD/QALY gained)**	**Interpretation**
10	9,574.45	Not cost-effective
20	3,902.23	Cost-effective
30	2,001.61	Cost-effective
40	1,043.20	Cost-effective
50	461.07	Cost-effective
60	66.50	Cost-effective
70	-221.44	Cost-saving
80	-443.26	Cost-saving
90	-621.50	Cost-saving
100	-769.74	Cost-saving

FIT, fecal immunochemical test; ICERs, incremental cost-effectiveness ratios; QALYs, quality-adjusted life years; USD, United States Dollars

Table 14. Effects of the cost of screening on cost-effectiveness results when compared to no screening

Cost of FIT (USD)	ICERs (USD/QALY gained)	Interpretation
1	383.40	Cost-effective
2	742.83	Cost-effective
3	1,102.26	Cost-effective
4	1,461.69	Cost-effective
5	1,821.12	Cost-effective
6	2,180.54	Cost-effective
7	2,539.97	Cost-effective
8	2,899.40	Cost-effective
9	3,258.83	Cost-effective
10	3,618.26	Cost-effective
11	3,977.69	Cost-effective
12	4,337.12	Cost-effective
13	4,696.55	Not cost-effective
Cost of colonoscopy (USD)	**ICERs (USD/QALY gained)**	**Interpretation**
100	469.15	Cost-effective
125	959.08	Cost-effective
150	1,449.01	Cost-effective
175	1,938.94	Cost-effective
200	2,428.87	Cost-effective
225	2,918.80	Cost-effective
250	3,408.73	Cost-effective
275	3,898.66	Cost-effective
300	4,388.59	Cost-effective
325	4,878.52	Not cost-effective

FIT, fecal immunochemical test; ICERs, incremental cost-effectiveness ratios; QALYs, quality-adjusted life years; USD, US Dollars

Multivariate probabilistic sensitivity analyses

The PSA results of both screening tests from 1000 Monte Carlo simulations shown in the cost-effectiveness plane (Figure 4) and the acceptability curves (Figure 5). The superiority of the colonoscopy screening every 10 years over the annual FIT for all WTP values was found. The PSA results were illustrated by the cost-effectiveness acceptability curves. At the WTP in Thailand of 4,706 USD per QALY gained, the probability of being cost-effective for colonoscopy every 10 years was 75% and for the probability of annual FIT was 25%.

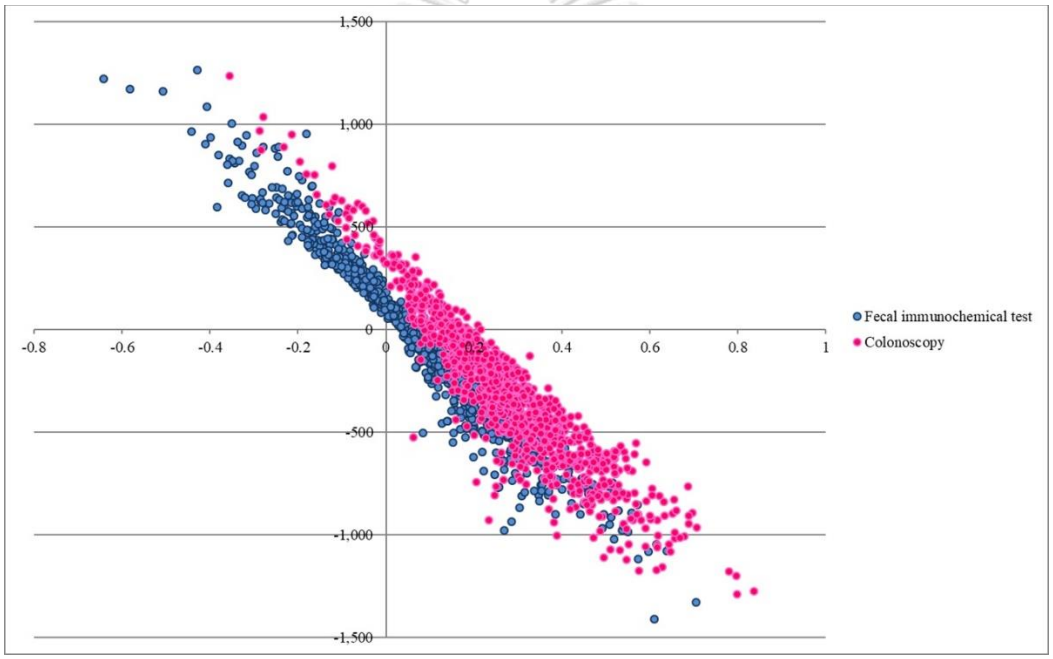

Figure 4. Cost-effectiveness plane of colorectal cancer screening options compared to no screening

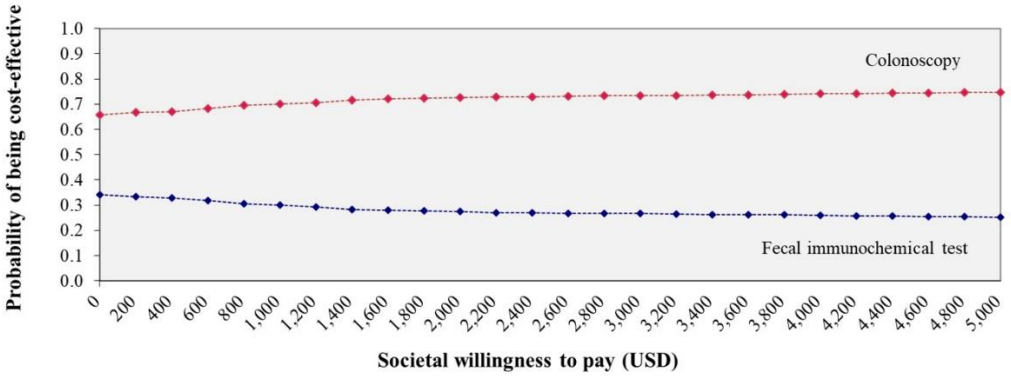

Figure 5. Cost-effectiveness acceptability curves of colorectal cancer screening options

Budget impact analysis

The results of budget impact analysis were estimated based on the target population eligible for CRC screening who were Thai average-risk, asymptomatic adults aged 50 to 75 years. In the ideal scenario of 100% participation rate, the total eligible cases involved with 17.6 million of Thai population. Based on the real-life situation of 62.9% participation rate, the number of annual FIT screening was reduced to about 12 million people per year and about 90 thousand needed for further colonoscopy. The estimated budget impact was 25.5 million USD per year for implementing FIT as CRC screening policy. On the other hand, for colonoscopy screening as a first option, the number of eligible cases for colonoscopy was 1,857,108 per year at the participation rate of 47.2%, and the average budget impact was 198.1 million USD per year. The large impact on the budget for the health plan of CRC screening for prevention was found. The details were shown in Table 15.

Table 15. Budget impact analysis of colorectal cancer screening

Annual FIT as a first choice	Y 1	Y 2	Y 3	Y 4	Y 5	Total 5 years	Per year
FIT ideal scenario (100% participation, cases)	17,564,960	18,091,909	18,618,858	19,145,806	19,672,755	93,094,288	18,618,858
Participation to FIT screening (62.9%)	11,048,360	11,379,811	11,711,261	12,042,712	12,374,163	58,556,307	11,711,261
Positive FIT (1.1%)	121,532	125,178	128,824	132,470	136,116	644,119	128,824
Colonoscopy participation in cases of positive FIT	87,260	89,878	92,496	95,113	97,731	462,478	92,496
FIT screening (exclude the patients who underwent colonoscopy within 10 years)	11,048,360	11,292,551	11,534,124	11,773,079	12,096,676	57,744,790	11,548,958
Budget impact of FIT (USD)	**24,225,049**	**24,834,000**	**25,439,417**	**26,041,299**	**26,757,448**	**127,297,213**	**25,459,443**
Colonoscopy every 10 years as a first choice	**Y 1**	**Y 2**	**Y 3**	**Y 4**	**Y 5**	**Total 5 years**	**Per year**
Colonoscopy ideal scenario (100% participation, cases)	17,564,960	526,949	526,949	526,949	526,949	19,672,755	3,934,551
Participation to colonoscopy screening (47.2%)	8,290,661	248,720	248,720	248,720	248,720	9,285,540	1,857,108
Budget impact of colonoscopy (USD)	**884,530,635**	**26,535,919**	**26,535,919**	**26,535,919**	**26,535,919**	**990,674,311**	**198,134,862**

FIT, fecal immunochemical test; USD, United States Dollars

3.4 Discussion

The preventable development of CRC by applying screening strategies in the health care system was shown in our findings. The CRC screening by annual FIT and 10-yearly colonoscopy among Thai average-risk population could prevent the development of both early and late stages of CRC. This study showed that either annual FIT screening or 10-yearly colonoscopy screening every 10 years was considered cost-effective within the Thai WTP threshold, when compared with no screening. In spite of the relatively higher participation and compliance of the annual FIT screening when compared to colonoscopy screening, mainly due to its noninvasive character, (I. Lansdorp-Vogelaar, Knudsen, & Brenner, 2010; Sano et al., 2016), the colonoscopy screening every 10 years was still consider cost-effective when compared to the annual FIT screening. A reasonable cause of this may associate with the better test performance of colonoscopy screening i.e. higher sensitivity and specificity. The practical interval of FIT screening is shorter than colonoscopy, it has to be repeated more frequently and its positive result has to be inevitably confirmed by the colonoscopy in order to provide the optimal benefit (U. S. Preventive Services Task Force et al., 2016).

Our results were consistent with the results of previously studies in other countries (I. Lansdorp-Vogelaar et al., 2010; Patel & Kilgore, 2015). The reasons behind the more favorable result of colonoscopy may be associated with higher incidence and mortality reduction benefits of colonoscopy screening, nevertheless, we retrieved this data from the report of a recent systematic review and network meta-analysis (Zhang et al., 2017). In addition, our results were also consistent with a recently published literature of large community-based organized CRC screening in the US which showed the better effect of CRC screening on the reduction of incidence and mortality due to greater detection of early stage of cancers (Levin et al., 2018). The rate of CRC screening has been significantly increasing from 38.9% in 2000 to 82.7% in 2015. Therefore, the reduction of CRC incidence and mortality were seen. A total of 25.5% and 52.4% of reduction in CRC incidence and mortality, respectively, were reported between 2000 and 2015.

However, when considered the real-life participation rate, the number of CRC cases prevented by screening strategies of either colonoscopy every 10 years or annual FIT were found to be 1,049 and 3,288 cases of early cancer and 1,220 and 3,695 cases of late cancer, respectively, per 100,000 screening over a lifetime when compared to no screening. The small difference between the early and late stages of CRC incidence prevention may be due to the input data from the first-year pilot population-based CRC screening project in Thailand (Khuhaprema et al., 2014) which leads to the higher detection of both the early and late stages of CRC. The late-stage detection was projected to be decreased in the future after national policy implements the campaign in a long term as the screening could prevent late stage of cancer by early detection and treatment, which expected result should be similar to the results from a recently published study (Vicentini et al., 2019).

Both FIT and colonoscopy screening strategies showed more impact on ICERs when the starting age of screening was 40 to 50 years rather than 60 to 70 years. Moreover, the result showed that the screening policy in the population at more than 80 years of age was not cost-effective. These results were synchronous with the recommendation of USPSTF in 2016 which concluded that the screening should start in the population whose ages were 50 years (U. S. Preventive Services Task Force et al., 2016) and with the Cancer Intervention and Surveillance Modeling Network

(CISNET) that suggested the starting of CRC screening at the age of 45 years would offer a better increase in life expectancy (A. Zauber, Knudsen, Rutter, Lansdorp-Vogelaar, & Kuntz, 2015). In addition, the guideline in 2018 developed by the American Cancer Society suggested the screening should be started at the age of 45 years and the clinicians should not continue the screening in any individuals older than 85 years (Wolf et al., 2018). In other words, the conclusive recommendation from established evidence is that the 50 to 75 years of age is the most optimal range to screen CRC. Otherwise, the detection of CRC might be too late and resulted in less effective treatment.

Although, in the present study, the colonoscopy screening was considered the best-buy option, the results of budget impact analysis showed that a very large amount of budget was required for the colonoscopy screening. About 8-times higher in the budget was required to conduct colonoscopy screening policy among Thai population, as compared to FIT. Moreover, there was also the limitation of resource. Therefore, colonoscopy screening is not an eligible strategy for CRC prevention program for public health insurance, it should be applied only in those who are willing to undergo and pay out-of-pocket. In other words, the more practical option was the annual FIT screening as it was more affordable when compared to colonoscopy. Thereby, FIT is the perfect choice to include in benefit package of the national health insurance in Thailand. Our present study could be another evidence-based information compatible for clinicians and policy makers when deciding the inclusion of CRC screening program into national health benefit package as a part of health policy. However, the holistic approach, aside from economic factors, including socio-cultural values and ethical considerations, should be concerned before the policy implementation (Aggarwal, Ginsburg, & Fojo, 2014).

Other factors that are important not to leave behind are the patients' participation rate to the screen and compliance with the following screening test after a positive result. The suboptimal rate of screening (Sano et al., 2016), patient compliance (I. Lansdorp-Vogelaar et al., 2010), and lack of health awareness (Saengow et al., 2015) are the challenges that have a large impact on the cost-effectiveness of the CRC screenings. The result from Lampang province informed that the participation rate of the FIT screening in Thailand was about 63% and about 28% of patients who had

positive FIT did not further undergo confirmation test by colonoscopy, this resulted in the missed detected CRC cases (Khuhaprema et al., 2014). As shown in the result part, the cost-effectiveness depended on many factors including the participation and compliance rate of the patient as well as the costs of screening tests. According to our results, the higher participation rate resulted in a more cost-effective result. Previous studies also showed the same trend of screening benefits which are increasing along with the higher participation and compliance rate (I. Lansdorp-Vogelaar et al., 2010; Sano et al., 2016). New strategies that could enhance the levels of preference, participation, and compliance are necessary for the successful and cost-effective screening policy.

3.5 Strengths and limitations

As far as we concerned, this is the first economic evaluation of CRC screenings in LMICs. Our study provided highly valid and contextually relevant findings due to 4 main reasons. Firstly, experienced gastroenterologists were involved throughout the process of study conduction since the beginning of literature reviews and model development through result interpretation. Secondly, the local data were used in our analysis as much as it availability. We also adjusted the mortality rates of these patients by incorporating specific ASMR that reflect Thai population context (Landre et al., 2015). The information on the prevalence of LRP, HRP, and each CRC stage was also obtained from previous studies that conduct among Thai subjects which expected to be able to reflect the natural course of disease of Thai patients. The annual transition probabilities of each stage CRC mortality were retrieved from the meta-analysis that we performed using the data of the 4 large studies in Thailand (Sermsri et al., 2014; Sudsawat Laohavinij & Maneechavakajorn, 2010; Techawathanawanna et al., 2012). All related costs were elicited from reliable local published sources (Riewpaiboon, 2011a). Costs of treatments specific to each stage of CRC from previous studies in Thailand were assembled and used for our model inputs. Thirdly, the rest of input parameters, including probabilities, costs, and utilities, such that all estimates in the model incorporated the majority of data, were collected from the most updated systematic reviews, meta-analyses, as well as large randomized controlled trials that currently available in the valid international electronic database which we

comprehensively searched to identify the values. Our study is expected to provide the robust and good quality results in order to make decisions. Lastly, our models gave the results that were consistent with the previous study which also reported that colonoscopy and FIT could prevent the development of both early- and late-stage CRC as compared to no screening (Zhang et al., 2017). Moreover, the I-CRC incidence data from our model is similar to those reported in previous studies. These meant that our model is quite valid (Erichsen et al., 2013; le Clercq et al., 2014; Richter et al., 2015).

There are several limitations in our study. Firstly, not every CRC screening modalities mentioned in the international guidelines were included in this study. As FIT-fecal DNA test, FS and CTC were not considered to be the candidate strategies for usual screening in Thai practice, they were not included in the present study (National Cancer Institute Thailand, 2015b; Patel & Kilgore, 2015; Pox, 2014; D. K. Rex et al., 2017; U. S. Preventive Services Task Force et al., 2016). Although, FS provided some advantages over colonoscopy including less bowel preparation, lower cost, and less risks of complications (D. K. Rex et al., 2017; U. S. Preventive Services Task Force et al., 2016)., it could only reduce the risks of distal colon and rectum cancer incidence and mortality. It provides lower effectiveness in the protection of right-sided colon cancer because this type of endoscopy allows endoscopists to observe only distal colon and rectum (D. K. Rex et al., 2017). The screening involved with radiology such as CTC not only requires an expensive machine and specific software, but patients who would undergo this screening modality are also requested to prepare their bowels by the method in which as complicate as what required in colonoscopy. Secondly, 10-yearly colonoscopy screening, which considered the most cost-effective test in this study, may not be able implemented as the usual screening method in some areas of Thailand due to the limit number of endoscopists despite the large number of needed to be screen population. In this case, annual FIT screening may be more eligible and more practical in the context of Thailand, also it is a simpler test with minimal risk of complication. Lastly, in terms of generalizability of the results from our study when considered to apply as another source of information for national policy decisions of other countries, it is important to concern about the difference in the context of each area. Theoretically and practically, there is no recommendation to directly transfer the results of any cost-effectiveness analysis to other areas where any difference could or

might be found. The mentioned differences included the differences in macro issues, such as economic status, healthcare system, decision-making process or criteria, and micro issues, such as costs of care and difference in patient characteristic associated with ethnicity and choices of treatment availabilities (Drummond et al., 2008). Recently, it has been a study claimed that the model structure that represents a course of interested disease, study design approach, and parameter values, especially those clinical variables related to the natural history of disease are only the potential transferability which readers should mainly focus on, rather than on findings. Our recommendation is that this study provided the latest comprehensive information and ideas on which can be applied in the conduction of other cost-effectiveness analyses of the CRC screenings that would give the most valuable result specific to those countries in need of evidence-based information for policy making.

3.6 Conclusion

This present study showed the both early and late stages of CRC can be prevented by CRC screening including FIT and colonoscopy, especially when applied the policy since starting age of screening before 50 years as they provide an opportunity for early diagnosis and treatments in order to prevent the development of advanced CRC stages resulted in the avoidable higher costs of treatments. In Thailand, 10 yearly colonoscopy screening was a favored but not practical strategy, when compared with either the annual FIT screening or no screening. The annual FIT screening is considered more eligible within the limited monetary and human resources of Thailand. In addition, the transferability and practicability are important to consider for real-world applications of both national and international policies. Health policy makers and practitioners may consider our study results as part of the evidence-based decision for including either the annual FIT or 10-yearly colonoscopy screening in the CRC screening program of Thailand.

CHAPTER IV Cost-effectiveness analysis of colorectal cancer treatment

4.1 Introduction

Colorectal cancer treatment

Pharmacotherapy, also recognized as chemotherapy, is not eligible for every stage of CRC. Patients with stage I CRC should not receive any additional treatment other than surgery because there are evidence showed that the low (about 3%) local recurrence rate is reported among this group of patient, also the benefit of neoadjuvant treatment is very limited, reported number needed to treat (NNT) to prevent a local recurrence of 38 (Van Gijn et al., 2011).

In the patients with stage II CRC, the benefit from additional treatment is less clear when compared with stage III (Hofheinz et al., 2012). Statistically significantly better in disease-free survival and overall survival were observed in stage II CRC patients than stage III CRC. According to the reduction of survival benefit from adjuvant chemotherapy, it is generally only recommended in those high risk of relapse patients (T4 tumors, perforated tumors, bowel obstruction at the time of surgery, and <12 lymph nodes removed). The Quasar trial (Group, 2007) reported that giving patients a chemotherapy regimen involved with 5-FU after curative resection provided a relative risk of death from any cause of 0.82 (95% CI, 0.70-0.95). If 5-year mortality of the patients whom chemotherapy regimens were not given was 20%, these data refer to an absolute improvement in survival of 3.6% (95% CI, 1.0-6.0).

In general, the tumor and corresponding lymph vessels are removed during surgery and adjuvant chemotherapy is administered to the high-risk of relapse patients. Because the patients with stage III CRC or lymph node metastasis have a risk of recurrence ranging between 15% and 50%, adjuvant chemotherapy is recommended for all patients with stage III CRC without contraindications after curative resection.

Adjuvant chemotherapy in stage III CRC is required to prolong disease-free survival and overall survival, it knowingly recommended as a standard treatment in both international and local CRC treatment guidelines (Bockelman et al., 2015; National Cancer Institute Thailand, 2015b). Five-year disease-free survival of Stage III

CRC patients who received adjuvant chemotherapy is about 64% (95% CI, 59.3-67.9) (Bockelman et al., 2015), compared to 49% (95% CI, 23.2-74.8) in the patient without chemotherapy.

Regimens containing 5-FU are able to decrease the recurrence rate at about 17%, thus observed overall survival was increased about 13-15% (Gill et al., 2004). Alternatively, the comparable efficacy in CRC treatment was reported for capecitabine, an oral prodrug of 5-FU (Twelves et al., 2011). There are several large prospective trials that tried to investigate the additional benefit of adding oxaliplatin to usual regimens that contain 5-FU or capecitabine whether it could improve disease-free survival and overall survival of the patient. The addition of oxaliplatin could increase the absolute 5-year disease-free survival about 6.2 - 7.5% and the overall survival about 2.7 - 4.2% in patients suffered from stage III CRC (Haller et al., 2011; Yothers et al., 2011).

However, secondary subset analyses of 2 studies suggest that the advantage of oxaliplatin might be only seen in patients aged less than 65 years (de Gramont et al., 2012) or 70 years (Yothers et al., 2011). In large randomized trials (Alberts et al., 2012; de Gramont et al., 2012), the addition of targeted therapy, such as bevacizumab or cetuximab, to an oxaliplatin-based regimen did not show any additional benefit on disease-free survival. Moreover, the studies investigated the potential benefit from the use of irinotecan combined with 5-FU also failed to a show significant benefit over 5-FU-based regimen alone, meanwhile, the increased toxicity observed (Papadimitriou et al., 2011).

Nowadays, there are various chemotherapies available in the market, both orally and intravenously administered agents. The evidence showed that there was a difference in the efficacy and safety of each regimen. Newer agents such as capecitabine, oxaliplatin, and irinotecan have been concluded that they are able to prolong survival in CRC patients compared to 5-FU/LV monotherapy (Folprecht et al., 2008; Krol et al., 2007; Landre et al., 2015; Pandor, Eggington, Paisley, Tappenden, & Sutcliffe, 2006). The preference of patients and the cost of treatment were also distinct (Krol et al., 2007). Recently, the generic versions of chemotherapy agents have been launched in the market, resulting in the lower cost of treatment.

The stage at diagnosis is the most important prognostic factor that indicated the long-term survivor (Richards, 2009). For example, in the US in 2001-2007, the relative

5-year survival of patients diagnosed with CRC was 90.1%, 69.2%, and 11.7% for patients with localized stage, regional spread, and distant tumor spread, respectively (Siegel et al., 2012).

The slowly but continually improved prognosis of CRC patients is during the past decades was reported in many countries. Currently, relative 5-year survival has been maximized to almost 65% in high-income countries, such as Australia, Canada, the US, and several European countries, but it is still less than 50% in low-income countries (Brenner et al., 2012; Sankaranarayanan et al., 2010; Siegel et al., 2012).

The unfavorable distribution of advanced cancers in LMICs may explain the increases in mortality in these countries. In addition, in low-income settings, surgery is often the only available treatment option and adjunctive therapy often not available (Kingham et al., 2013). In the LMICs, only 3.1% received radiotherapy among all patients with rectal cancer, while the 'optimum' proportion should have been 61% (Barton, Frommer, & Shafiq, 2006). Furthermore, delays in diagnosis, referral and treatment and also cultural beliefs and financial constraints may cause higher mortality in the LMICs (Goss et al., 2013; Kingham et al., 2013).

Cost-effectiveness analysis of colorectal cancer treatment

Several adjuvant chemotherapy regimens exist for the treatment of stage III CRC. Economic evaluation studies have investigated the effectiveness and cost-effectiveness of CRC treatment. The MOSAIC trial demonstrated that the addition of oxaliplatin to 5-FU/LV provided more efficacy in terms of preventing and delaying the recurrence of disease than 5-FU/LV alone as the adjuvant treatment among stage III CRC patients who had undergone complete surgical resection. Evidence from the X-ACT study has proved that treatment with capecitabine at least could provide an equivalent in disease-free survival to the bolus 5-FU/LV regimen in resected stage III CRC patients. Moreover, capecitabine monotherapy showed significantly better in relapse-free survival, as compared to bolus 5-FU/LV. Cost-effectiveness studies based on the assumptions regarding long-term survival, suggested that both capecitabine and FOLFOX4 (5-FU/LV/oxaliplatin) appeared to have favorable outcomes when compared with 5-FU/LV regimens, based on levels of cost-effectiveness which are

currently considered by policymakers to represent acceptable value for money (Pandor et al., 2006).

A study in Japan also showed that capecitabine as adjuvant therapy could improve health outcomes by consuming lowers direct costs of treatments, as compared to bolus FU/LV in stage III CRC patients (Shiroiwa, Fukuda, Shimozuma, Ohashi, & Tsutani, 2009).

In China, XELOX is also expected to dominate FOLFOX4 regimens; Thus, XELOX provides a more cost-effective adjuvant chemotherapy (Wen et al., 2014).

In Taiwan, a study also showed that capecitabine not only saves costs but also improves health outcomes compared with 5-FU/LV in the adjuvant treatment of stage III CRC (Hsu et al., 2011).

In advanced CRC, the combination of 5-FU and irinotecan was more cost-effective than the single agent sequential therapies used in the FOCUS trial, or 5-FU plus oxaliplatin (Manca et al., 2012).

The recent study of adjuvant therapy in stage III CRC, capecitabine and XEROX yield more cost and less effective than other regimens, and FOLFOX, compared to 5-FU/LV, resulted in a cost of 25,997 USD/QALY gained. In a real-world setting, FOLFOX is more effective but also more costly than 5-FU/LV alone (Soni et al., 2015).

However, there were several studies in the economic evaluation of adjuvant chemotherapy. Most of them concluded that capecitabine or FOLFOX were more favorable than compared regimen, i.e. 5-FU/LV alone (Aballéa et al., 2007; Attard, Maroun, Alloul, Grima, & Bernard, 2010; Douillard et al., 2007).

From a study reviewed the outcomes of randomized clinical trials (RCTs) and CEA, capecitabine-based regimens were less costly and more effective than 5-FU-based regimens. The combination of oxaliplatin leads to modestly improved effectiveness and at an acceptable incremental cost (Soni & Chu, 2015) as shown in Table 16.

In Japan, anticancer drug costs and hospital fees accounted for 50 to 77 % and 11 to 25 % of the overall costs, respectively. The costs of irinotecan-based regimens were lower than oxaliplatin-based regimens and molecular targeted agents (Yajima et al., 2016).

Table 16. Cost studies for adjuvant chemotherapy in colorectal cancer

Regimens	Country	Time horizon	Type	Favored
5-FU:Capecitabine	Netherlands	Treatment period	CBA	Capecitabine (cost-saving)
5-FU:Capecitabine	UK	Lifetime	CEA	Capecitabine (dominant)
5-FU:Capecitabine 5-FU:FOLFOX4	UK	Lifetime	CEA	Capecitabine (dominant) FOLFOX
5-FU:FOLFOX4	US	Lifetime	CEA	FOLFOX
5-FU:Capecitabine	France	3 years	CCA	Capecitabine (cost-saving)
XELOX:FOLFOX	Greece	Median > 1 year	CMA	XELOX (cost-saving)
5-FU:Capecitabine	US	Treatment period	CMA	Capecitabine (cost-saving)
5-FU:Capecitabine	Canada	Lifetime	CEA	FOLFOX

5-FU, fluorouracil; CBA, Cost-benefit analysis; CEA, Cost-effectiveness analysis; CCA, Cost-consequence analysis; CMA, Cost-minimization analysis; UK, the United Kingdom; US, the United State

Thailand data

Although the cost studies and CEA of CRC treatment in Thailand were lack, 2 associated literature were reviewed.

First, a study aimed to analyze the cost of CRC care in Thai hospitalized patients. Information of inpatients and casualties was elicited from hospitals nationwide and from hospital withdrawals from the 3 health insurance schemes in 2010 fiscal data. It is reported that CRC founded in 45,692 cases of all admissions. The overall hospital charge of CRC was 1,729,912,359 THB. The average hospital charge per admission of patients with CRC was 41,052 THB. The average hospital charges per admission in 3 insurance schemes groups: government welfare, social welfare, and universal coverage were 64,241, 49,490 and 28,588 THB, respectively. The hospital charges were extensive, especially in those on the government welfare scheme. Besides, there was a

trend toward increasing the cost of advanced disease. The range of cost of treatment among the 3 insurance schemes was wide because of the difference in drug accessibility of each scheme especially in the novel drugs; Oxaliplatin, Irinotecan, Bevacizumab, and Cetuximab (Chindaprasirt et al., 2012).

Second, a CUA study of adjuvant chemotherapy for stage III CRC after resection. The results showed that the adjuvant 5-FU/LV plus capecitabine as the first-line therapy for the metastatic disease would be the most cost-effective chemotherapy. The adjuvant FOLFOX and FOLFIRI as the first-line treatment for metastatic disease would be cost-effective if both prices of FOLFOX and FOLFIRI were decreased by 40% (Lerdkiattikorn et al., 2015). A few years later, after this study showed the good results of oxaliplatin, it became in the NLEM list for stage III CRC treatment with the 69% reduced price.

The data showed an increasing CRC burden in LMICs, whereas stabilizing or decreasing trends were spotted only in highly developed countries. Thus, better management options and more accessibility are needed in those lesser-developed areas (Arnold et al., 2017) such Thailand. The association of health outcomes and health-related quality of life (HRQoL) of the patients as well as country's limited resources should be considered in long-term planning. Resouce-appropriate CRC treatment regimens should be included in the national policy.

According to Thai survey data, patients treated with the orally administered agent had more utility than those treated with IV administered regimens (Lerdkiattikorn et al., 2015). However, capecitabine (an effective orally administered chemotherapy), for the indication of stage III CRC treatment are not available in Thailand NLEM for CRC treatment. In addition, the new expensive agents which have been shown to prolong survival in CRC and currently are a part of the standard treatment guidelines, are also not listed in NLEM. Only some groups of patients are able to access this drug (Chindaprasirt et al., 2012). Policy makers should consider treatment regimens thoroughly specifically cost-effectiveness and social equality aspects and for the development and introduction of new treatment agents to the NLEM list. This study aimed to evaluate cost-utility and budget impact analyses of chemotherapy treatment regimens for stage III CRC treatment in Thailand.

4.1.1 Research questions

Primary research questions

1. Is each treatment regimen cost-effective for stage III CRC in Thailand?

Secondary research questions

1. Which treatment regimen of stage III CRC is the most cost-effective in Thailand?
2. How many cases prevented from disease progression to stage IV CRC and death by each CRC treatment regimen?
3. What is the additional cost per 1 QALY gained by each CRC treatment regimen?
4. What are the effects of the parameter uncertainties in the models?

4.1.2 Research objectives

General objectives

1. To evaluate the cost-effectiveness analysis of stage III CRC treatment in Thailand

Specific objectives

1. To evaluate the most cost-effective treatment regimen for stage III CRC in Thailand
2. To evaluate the number of cases prevented from disease progression to stage IV CRC cancer and death by each treatment regimen
3. To evaluate the cost-utility analysis of each treatment regimen for stage III CRC in Thailand in terms of the additional cost per QALY gained
4. To evaluate the effect of the uncertainties of the parameters in the models

4.1.3 Hypotheses

Some new treatment regimen is cost-effective for stage III CRC in Thailand when compared to the standard treatment regimen in terms of

- Cost-saving from decrease disease progression to stage IV CRC and death
- Increase QALY gained
- Low incremental cost-effectiveness ratio

4.1.4 Scope of the study

The study aims to evaluate each treatment regimen for stage III CRC in Thai patients in terms of CUA. This study uses primary data from a Siriraj CRC registry project, Siriraj Hospital, that reported the stages of disease, treatment regimens, response rate of treatment, and survival.

A hybrid model consisting of decision tree and Markov models are used to approximate relevant costs and health outcomes of stage III CRC treatment the patients who treated with one regimen compare to the patients who receive another regimen or do not receive treatment. The lifetime horizon is chosen in this study. We undertake this study using a social perspective in costing calculation as advised by the Thailand's HTA guideline (Thai Working Group on Health Technology Assessment Guidelines in Thailand, 2013). We perform a CUA expressing findings as incremental cost per QALY gained.

For the input parameters, treatment regimens, response rate of treatment, adverse events, survival rate, annual transitional probabilities, annual CRC-specific mortality rate, costs, and utilities are filled in the Markov models. These parameters are obtained from a data set of Siriraj Hospital and systematic literature search from other studies (local and international publications) which are the most applicable to Thai population.

4.1.5 Possible benefits of the study

There is an absence of knowledge regarding long-term benefits and cost-effectiveness of stage III CRC treatment in Thailand. If this study can report the most cost-effective treatment regimen of stage III CRC, it will contribute as new knowledge and can be implemented as a policy. The patients will receive the appropriate treatment at a lower cost from a national health policy and may prolong their survival with a good quality of life.

4.2 Methodology

4.2.1 Study design

This research is a descriptive study focused on the CUA of treatment for stage III CRC patients in Thailand.

4.2.2 Data collection

A cost-utility analysis was performed to estimate related costs and health outcomes of patients with stage III CRC treated by various regimens of treatment. The regimens which were included in our analyses composed of 2 groups of chemotherapy regimens, the first one was an adjuvant chemotherapy regimen for stage III CRC treatment at the time of diagnosis and the second one was a chemotherapy regimen for those who had recurrence or progression to the metastatic stage (stage IV CRC). Eight regimens of treatment i.e. (1) 5-FU/LV+FOLFOX (oxaliplatin plus 5-FU/LV), (2) 5-FU/LV+XELOX (capecitabine and oxaliplatin), (3) 5-FU/LV+FOLFIRI (irinotecan plus 5-FU/LV), (4) capecitabine+FOLFOX, (5) capecitabine+XELOX, (6) capecitabine+FOLFIRI, (7) FOLFOX+FOLFIRI, and (8) XELOX+FOLFIRI were included in our analysis as shown in Table 17.

Table 17. All interventions of chemotherapy for stage III and stage IV colorectal cancer

Adjuvant chemotherapy for stage III CRC	First-line chemotherapy for metastatic disease (stage IV CRC)
5-FU/LV	FOLFOX
5-FU/LV	XELOX
5-FU/LV	FOLFIRI
Capecitabine	FOLFOX
Capecitabine	XELOX
Capecitabine	FOLFIRI
FOLFOX	FOLFIRI
XELOX	FOLFIRI

5-FU/LV, 5-fluorouracil and leucovorin; FOLFIRI, irinotecan plus 5-FU/LV; FOLFOX, oxaliplatin plus 5-FU/LV; XELOX, Capecitabine and oxaliplatin

As Thai HTA guideline version 2.0 (Thai Working Group on Health Technology Assessment Guidelines in Thailand, 2013) recommended, the lifetime horizon and societal perspective were utilized in this analysis. All future costs and outcomes were discounted at 3% per annum (Thai Working Group on Health Technology Assessment Guidelines in Thailand, 2013). The outcomes were reported in terms of incremental costs per QALY gained. The cost-effectiveness threshold in this study was based on an official WTP of 160,000 THB/QALY (4,706 USD/QALY) (Teerawattananon et al., 2014), as it is the maximum value of Thai social WTP.

This study used primary data from the Siriraj CRC registry project that included the data of the stages of disease, treatment regimens, response rate of treatment, adverse events, and survival rate. It was conducted by retrospective electronic chart review of CRC patients who were treated at Siriraj Hospital from January 2009 to July 2019. A total of 951 cases of stage III CRC from 2,898 cases of all stages were reviewed. In addition, the secondary data from the most recently published systematic review, meta-analysis, or other large RCTs data are filled in the economic model.

4.2.3 Conceptual framework

This conceptual framework provides an overview of the steps of the research plan and the information needed to be collected and calculated. For this study, the conceptual framework showed 5 main steps of the economic evaluation as Figure 6.

Step 1: A hybrid model consisting of decision tree and Markov models is established. The primary data, secondary data, data from systematic literature review and meta-analysis are filled in the model.

Step 2: Total costs of the patients who receive one treatment regimen and another regimen are compared.

Step 3: The effectiveness in terms of the number of cases prevented from disease progression to advanced cancer and death and QALYs gained are compared between 2 groups.

Step 4: The incremental cost-effectiveness ratios of each treatment regimen are analyzed.

Step 5: The uncertainties of the parameters are tested by using one-way sensitivity analyses with Tornado diagrams and probabilistic sensitivity analyses.

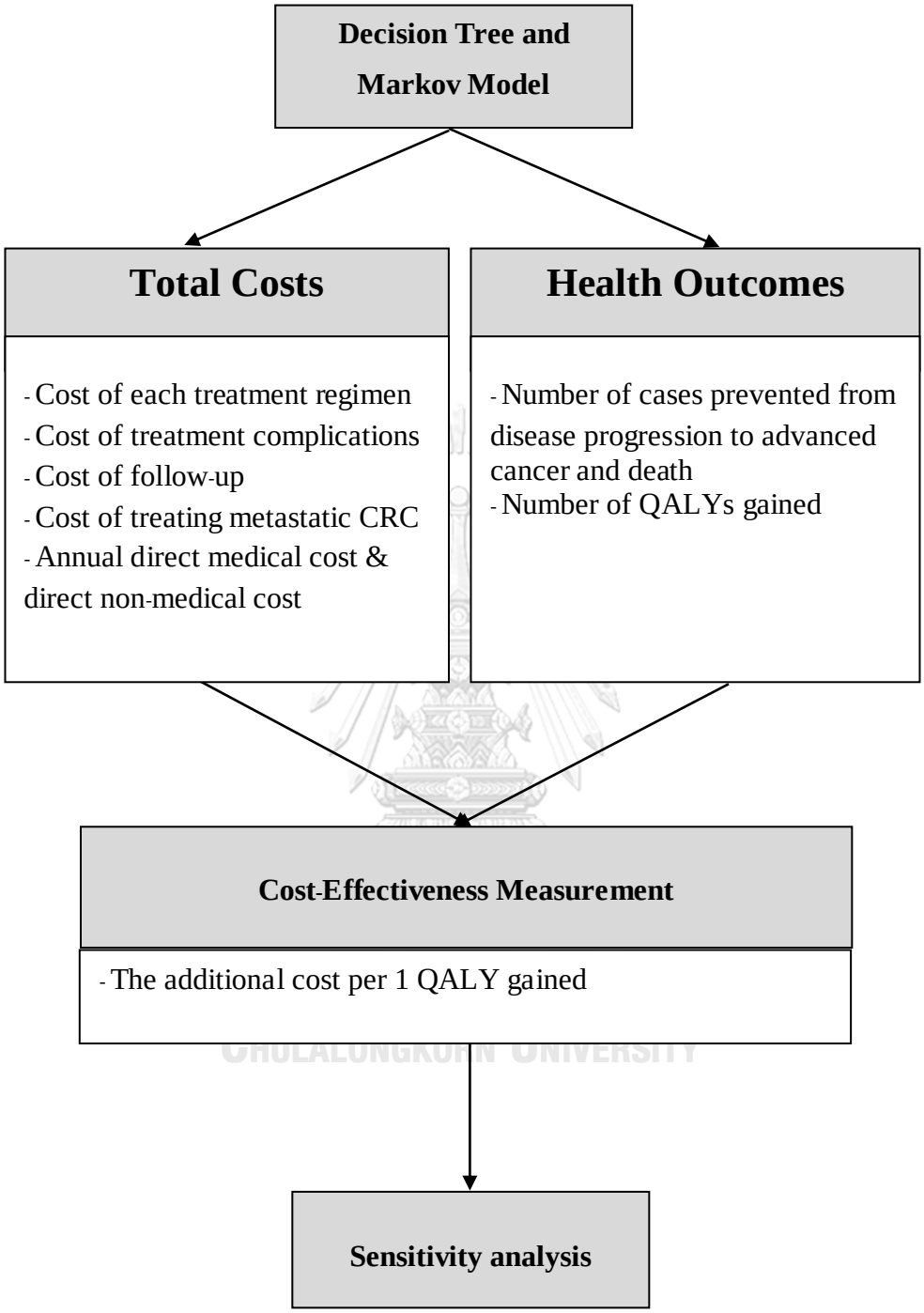

Figure 6. Conceptual framework of stage III colorectal cancer treatment

4.2.4 The economic model

The hybrid model consisting of decision tree and Markov models was shown in Figure 7. A decision tree model is constructed to divide CRC patients into 2 groups; treatment with one regimen and treatment with another regimen. However, the whole effect of treatment with different drug regimens such as death and long-term effects of treatment in the disease progression cannot be captured with only a decision tree model. Thus, the estimation of long-term clinical and economic outcomes is vital since they are associated with those who have survived using another model. Therefore, Markov models are developed using a lifetime horizon with a one-year cycle length to capture long-term costs and health outcomes of each CRC treatment modality for CRC patients compared to another treatment regimen based on a societal perspective in costing calculation. The Markov models consisted of 3 health stages i.e. stable disease (stage III CRC), progressive disease (stage IV CRC), and death (Figure 7). All hypothetical patients were newly diagnosed with stage III CRC in the first cycle. We assumed that the disease could progress orderly to the adjacent stage or death in the next cycle. The patients could also stay in the same stage but they could not reversely move to any previous health stages. All of the hypothetical patients were followed until death. We assumed the patient's age was 63 years as it was the average age at diagnosis of Thai stage III CRC patients (data from Siriraj Hospital electronic database, n=951) ("Siriraj Colorectal Cancer Registry Project (2009-2019)," 2019). Total costs and the effectiveness between the groups of patients who received one treatment regimen versus another were compared.

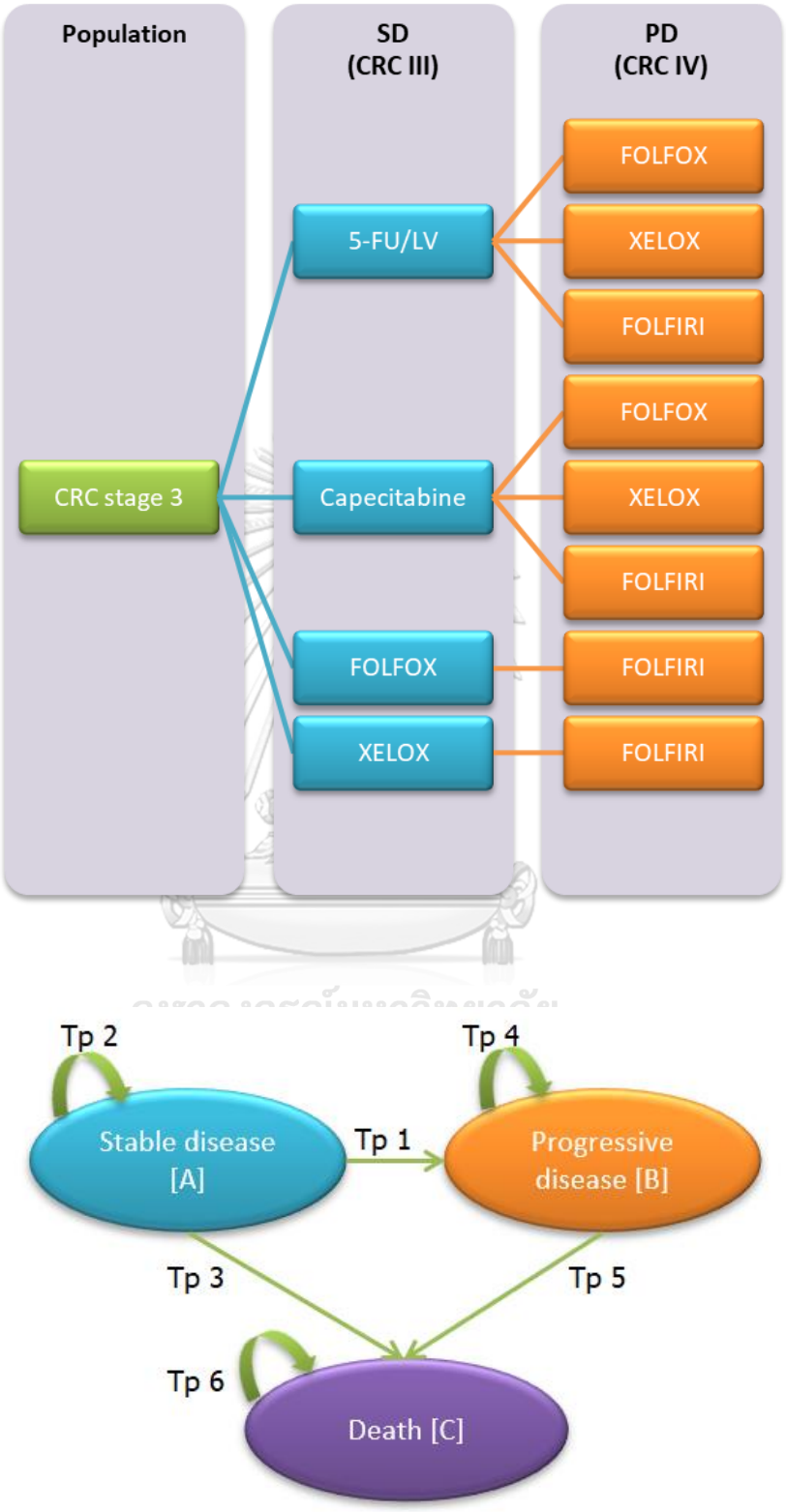

Figure 7. Decision tree and Markov models of stage III colorectal cancer treatment

Model input parameters (Table 18)

Treatment regimens, response rate of treatment, adverse events, survival rate, annual transitional probabilities, annual CRC-specific mortality rate, costs, and utilities which fill in the Markov models as the input parameters are demonstrated in Table 18. They were mainly based on the primary data collected from Siriraj CRC registry in the electronic database of Siriraj Hospital and systematic reviews and meta-analyses from other studies (local and international publications).

Treatment options and effectiveness

According to the current CRC treatment practice of Thailand, stage III CRC patient was mostly treated by 4 common chemotherapy regimens i.e. 5-FU/LV, capecitabine, FOLFOX, and XELOX. The effectiveness of each regimen was reflected in transitional probabilities from stable disease to progressive disease stage and death. After the progression of disease, clinically patient would be treated as stage IV CRC patient. The choices of stage IV CRC treatment composed of 3 regimens i.e. FOLFOX, XELOX, and FOLFIRI. Newer treatments such as immunotherapy and targeted therapy were not included in this study. The doses of chemotherapy were calculated based on the recommended dose according to the Thai CRC treatment guideline by using an average Thai population body surface area of 1.7 m^2.

Probability data

The probability data were derived from the Siriraj CRC registry ("Siriraj Colorectal Cancer Registry Project (2009-2019)," 2019) and a previous study in Thailand (Lerdkiattikorn et al., 2015). The transitional probabilities to the death stage were considered all-cause mortality which depends on the disease status, patient's age, and the time duration of being in the same state. The probabilities of death calculated by combining ASMR, adopted from WHO life table 2015 (Bhala et al., 2011), and disease-specific mortality rate of stage III and IV CRC patients from Siriraj CRC registry ("Siriraj Colorectal Cancer Registry Project (2009-2019)," 2019).

Cost data

This study is undertaken using the societal perspective in costing calculation because it is already included all stakeholders. Direct medical costs and direct non-medical costs are included. Indirect costs were not included in the model because the loss or impaired ability to work or engage in leisure activities due to morbidity was already captured by the decreased value of QALY to evade double counting (Thai Working Group on Health Technology Assessment Guidelines in Thailand, 2013). All costs were converted and reported in 2017 USD (1 USD=34 THB) and using the consumer price index (CPI) (Bank of Thailand, 2017; "Consumer Price index (CPI) of Thailand, Economic and Trade Indices Database (ETID)," 2017). Drug costs were obtained from the national drug reference price database, Drug and Medical Supply Information Center, Ministry of Public Health (DMSIC) (Ascha et al., 2010). We used the median of median reference prices of generic drugs in our analysis, as recommended in Thai HTA guideline (Thai Working Group on Health Technology Assessment Guidelines in Thailand, 2013). Where no data were available, the prices from NLEM were applied. We assumed no product wastages in our analysis, total chemotherapy cost per dose was calculated from net cost per milligram of drug multiplied by milligrams required per dose (Table 19). Other healthcare costs such as surgical treatment, intravenous drug administration, OPD follow-up, IPD visit due to the worsening disease status, and adverse event treatment costs were obtained from Siriraj electronic database. IPD visit for drug administration and direct non-medical costs (food and transportation) were obtained from the reference prices published by Thai standard cost lists for Health Technology Assessment (Riewpaiboon, 2011a). Costs from all visits related to CRC treatment were included and classified into 5 groups according to the American Joint Committee on Cancer (AJCC) CRC staging at diagnosis (i.e. CRC stage I, II, III, IV, and unidentified). A total of 1,747 cases were included in the cost analysis (951 cases of stage III CRC and 796 cases of stage IV CRC).

Utility data

We adopted utility data from the study by Lerdkiattikorn et. al who did the survey by using the EQ-5D questionnaire to estimate the utility of Thai CRC patients in different states of disease. The results were also shown the difference in utility from receiving chemotherapies which required different routes of administration (Lerdkiattikorn et al., 2015).

Table 18. Model input parameters of stage III colorectal cancer treatment

Input parameters	Distribution	Mean (SE)	Reference
Time horizon		lifetime	(Thai Working Group on Health Technology Assessment Guidelines in Thailand, 2013)
Cycle length (years)		1	
Annual discount rate		3% (0%-6%)	(Thai Working Group on Health Technology Assessment Guidelines in Thailand, 2013)
Age-specific incidence rate of CRC stage III		0.003972%	(National Cancer Insitiute Thailand, 2015)
%Eligible case		80%	("Siriraj Colorectal Cancer Registry Project (2009-2019)," 2019)
Population growth rate		0.3%	("Official Statstics Registration Systems," 2018)
Body weight (kg)		60	
Body surface area (m^2)		1.7	Mosteller's formula
Annual transitional probabilities			
5-FU/LV			
SD to PD	Beta	0.175 (0.012)	(Lerdkiattikorn et al., 2015)
SD to death year 1	Beta	0.053 (0.014)	("Siriraj Colorectal Cancer Registry Project (2009-2019)," 2019)
SD to death year 2	Beta	0.152 (0.024)	("Siriraj Colorectal Cancer Registry Project (2009-2019)," 2019)
SD to death year 3	Beta	0.199 (0.029)	("Siriraj Colorectal Cancer Registry Project (2009-2019)," 2019)
SD to death year 4	Beta	0.108 (0.025)	("Siriraj Colorectal Cancer Registry Project (2009-2019)," 2019)
SD to death subsequent years	Beta	0.121 (0.028)	("Siriraj Colorectal Cancer Registry Project (2009-2019)," 2019)
Capecitabine			
SD to PD	Beta	0.149 (0.101)	(Lerdkiattikorn et al., 2015)
SD to death year 1	Beta	0.057 (0.018)	("Siriraj Colorectal Cancer Registry Project (2009-2019)," 2019)
SD to death year 2	Beta	0.073 (0.021)	("Siriraj Colorectal Cancer Registry Project (2009-2019)," 2019)
SD to death year 3	Beta	0.108 (0.026)	("Siriraj Colorectal Cancer Registry Project (2009-2019)," 2019)
SD to death year 4	Beta	0.105 (0.028)	("Siriraj Colorectal Cancer Registry Project (2009-2019)," 2019)
SD to death subsequent years	Beta	0.072 (0.025)	("Siriraj Colorectal Cancer Registry Project (2009-2019)," 2019)
FOLFOX			
SD to PD	Beta	0.133 (0.009)	(Lerdkiattikorn et al., 2015)
SD to death year 1	Beta	0.000 (0.000)	("Siriraj Colorectal Cancer Registry Project (2009-2019)," 2019)
SD to death year 2	Beta	0.082 (0.032)	("Siriraj Colorectal Cancer Registry Project (2009-2019)," 2019)
SD to death year 3	Beta	0.060 (0.029)	("Siriraj Colorectal Cancer Registry Project (2009-2019)," 2019)
SD to death year 4	Beta	0.063 (0.031)	("Siriraj Colorectal Cancer Registry Project (2009-2019)," 2019)
SD to death subsequent years	Beta	0.068 (0.033)	("Siriraj Colorectal Cancer Registry Project (2009-2019)," 2019)
PD to death year 1	Beta	0.208 (0.048)	("Siriraj Colorectal Cancer Registry Project (2009-2019)," 2019)
PD to death year 2	Beta	0.351 (0.063)	("Siriraj Colorectal Cancer Registry Project (2009-2019)," 2019)
PD to death year 3	Beta	0.514 (0.082)	("Siriraj Colorectal Cancer Registry Project (2009-2019)," 2019)
PD to death subsequent years	Beta	0.222 (0.098)	("Siriraj Colorectal Cancer Registry Project (2009-2019)," 2019)
XELOX			
SD to PD	Beta	0.140 (0.010)	(Lerdkiattikorn et al., 2015)
SD to death year 1	Beta	0.012 (0.009)	("Siriraj Colorectal Cancer Registry Project (2009-2019)," 2019)
SD to death year 2	Beta	0.037 (0.015)	("Siriraj Colorectal Cancer Registry Project (2009-2019)," 2019)
SD to death year 3	Beta	0.071 (0.021)	("Siriraj Colorectal Cancer Registry Project (2009-2019)," 2019)
SD to death year 4	Beta	0.069 (0.021)	("Siriraj Colorectal Cancer Registry Project (2009-2019)," 2019)
SD to death subsequent years	Beta	0.030 (0.015)	("Siriraj Colorectal Cancer Registry Project (2009-2019)," 2019)

Input parameters	Distribution	Mean (SE)	Reference
PD to death year 1	Beta	0.176 (0.030)	("Siriraj Colorectal Cancer Registry Project (2009-2019)," 2019)
PD to death year 2	Beta	0.435 (0.043)	("Siriraj Colorectal Cancer Registry Project (2009-2019)," 2019)
PD to death year 3	Beta	0.318 (0.070)	("Siriraj Colorectal Cancer Registry Project (2009-2019)," 2019)
PD to death subsequent years	Beta	0.267 (0.081)	("Siriraj Colorectal Cancer Registry Project (2009-2019)," 2019)
FOLFIRI			
PD to death year 1	Beta	0.474 (0.046)	("Siriraj Colorectal Cancer Registry Project (2009-2019)," 2019)
PD to death year 2	Beta	0.574 (0.063)	("Siriraj Colorectal Cancer Registry Project (2009-2019)," 2019)
PD to death year 3	Beta	0.462 (0.097)	("Siriraj Colorectal Cancer Registry Project (2009-2019)," 2019)
PD to death subsequent years	Beta	0.500 (0.121)	("Siriraj Colorectal Cancer Registry Project (2009-2019)," 2019)
Costs (2017 USD)			
Direct medical costs			
Cost of chemotherapy and administration (2017 USD per course)			
5-FU/LV	Gamma	524 (67)	(von Karsa et al., 2013)
Capecitabine*	Gamma	1,895 (242)	(von Karsa et al., 2013)
FOLFOX	Gamma	2,775 (354)	(Summart et al., 2017; von Karsa et al., 2013)
XELOX	Gamma	2,961 ()378	(Marmot et al., 2007; von Karsa et al., 2013)
FOLFIRI	Gamma	4,472 (570)	(Marmot et al., 2007; von Karsa et al., 2013)
Other healthcare cost (2017 USD per year)			
SD year 1	Gamma	6,706 (855)	("Siriraj Colorectal Cancer Registry Project (2009-2019)," 2019)
SD year 2	Gamma	1,870 (238)	("Siriraj Colorectal Cancer Registry Project (2009-2019)," 2019)
SD year 3 and subsequent years	Gamma	1,718 (219)	("Siriraj Colorectal Cancer Registry Project (2009-2019)," 2019)
PD year 1	Gamma	7,736 (987)	("Siriraj Colorectal Cancer Registry Project (2009-2019)," 2019)
PD year 2	Gamma	3,471 (443)	("Siriraj Colorectal Cancer Registry Project (2009-2019)," 2019)
PD year 3 and subsequent years	Gamma	2,873 (366)	("Siriraj Colorectal Cancer Registry Project (2009-2019)," 2019)
Direct non-medical costs (2017 USD per visit)			
Food	Gamma	2 (0.2)	(Riewpaiboon, 2011b)
Transportation	Gamma	5 (0.4)	(Riewpaiboon, 2011b)
Visits rate			
5-FU/LV (per course)		30	(National Cancer Institute Thailand, 2015)
Capecitabine (per course)		6	("Siriraj Colorectal Cancer Registry Project (2009-2019)," 2019)
FOLFOX (per course)		12	(National Cancer Institute Thailand, 2015)
XELOX (per course)		8	(National Cancer Institute Thailand, 2015)
FOLFIRI (per course)		12	(National Cancer Institute Thailand, 2015)
SD, latter half of year 1 (off treatment)		6	("Siriraj Colorectal Cancer Registry Project (2009-2019)," 2019)
SD, year 2		13	("Siriraj Colorectal Cancer Registry Project (2009-2019)," 2019)
SD, year 3 and subsequent years		11	("Siriraj Colorectal Cancer Registry Project (2009-2019)," 2019)
PD, latter half of year 1 (off treatment)		9	("Siriraj Colorectal Cancer Registry Project (2009-2019)," 2019)
PD, year 2		20	("Siriraj Colorectal Cancer Registry Project (2009-2019)," 2019)
PD, year 3 and subsequent years		18	("Siriraj Colorectal Cancer Registry Project (2009-2019)," 2019)

Input parameters	Distribution	Mean (SE)	Reference
Utilities			
SD, on IV CMT	Beta	0.600 (0.063)	(Lerdkiattikorn et al., 2015)
SD, on oral CMT	Beta	0.650 (0.047)	(Lerdkiattikorn et al., 2015)
SD, off treatment	Beta	0.850 (0.100)	(Lerdkiattikorn et al., 2015)
PD, on IV CMT	Beta	0.560 (0.101)	(Lerdkiattikorn et al., 2015)
PD, off treatment	Beta	0.624 (0.043)	(Lerdkiattikorn et al., 2015)
Death	Beta	0.000 (0.000)	(Lerdkiattikorn et al., 2015)

CMT, chemotherapy; IV, intravenous administration; PD, progressive disease; SD, stable disease

*Assumed that patients would have a monthly hospital visit for drug dispensary.

Table 19. Chemotherapy dosage regimens of stage III colorectal cancer treatment

Chemotherapy	Regimen	Reference
5-FU/LV	- Leucovorin 20 mg/m^2/day IV bolus, days 1-5 - 5-FU 400 mg/m^2/day IV bolus after leucovorin, days 1-5 - Repeat every 4 weeks for 6 cycles	(National Cancer Institute Thailand, 2015)
Capecitabine	- Capecitabine 2,000 mg/m^2/day divided into 2 doses, days 1-14, followed by 7 days rest - Repeat every 3 weeks for 8 cycles	(National Cancer Institute Thailand, 2015)
FOLFOX	- Oxaliplatin 85 mg/m^2/ day IV infusion over 2 hours, day 1 simultaneously with - Leucovorin 400 mg/m^2/ day IV infusion over 2 hours, day 1 - 5-FU 400 mg/m^2/day IV bolus day 1, then 2,400 mg/ m^2 IV continuous infusion over 46 hours - Repeat every 2 weeks for 12 cycles	(National Cancer Institute Thailand, 2015)
XELOX	- Capecitabine 2,000 mg/m^2/ day PO divided into 2 doses, days 1-14, followed by 7 days rest - Oxaliplatin 130 mg/m^2 IV infusion over 2 hours, day 1 - Repeat every 3 weeks for 8 cycles	(National Cancer Institute Thailand, 2015)
FOLFIRI	- Irinotecan 180 mg/ m^2 IV infusion over 90 minutes, day 1 - Leucovorin 400 mg/ m^2 IV infusion over 2-hour infusion during irinotecan, day 1 - 5-FU 400 mg/ m^2 IV bolus, then 2,400 mg/m2 IV continuous infusion over 46 hours - Repeat every 2 weeks for 12 cycles	(National Cancer Institute Thailand, 2015)

4.2.5 Data analysis

All data are analyzed by using the CUA. The total costs and the effectiveness of each CRC treatment regimen are compared in terms of ICER.

Cost-effectiveness analysis

Base-case analysis

We compared total lifetime costs and health outcomes of each drug regimen in patient age 63 years. The cost-effectiveness of each CRC treatment regimen is assessed by calculating its ICER according to the following formula:

$$\frac{\text{Total costs}_{\text{one regimen}} - \text{Total costs}_{\text{another regimen}}}{\text{Outcomes}_{\text{one regimen}} - \text{Outcomes}_{\text{another regimen}}}$$

The results are presented as ICER of a CRC treatment regimen compared to another treatment regimen in USD/QALY gain. For base-case analysis, we calculate the expected lifetime costs and outcomes for each group. If ICER is negative, it indicated cost-saving. In the case of ICER being positive, a threshold value interpretation of the cost-effectiveness of the findings is founded on an official WTP of the Thai Health Economic Working Group (HEWG). They recommend a ceiling threshold of cost-effective intervention at 160,000 THB/QALY gained (4,706 USD/QALY).

4.2.6 Sensitivity analysis

One-way sensitivity analyses were adopted to evaluate the effect of uncertainties of parameters in the model. The analyzed parameters included all clinical effects, costs, and utilities within the ranges of 95%CI in the models. The results were demonstrated by Tornado diagrams to orderly show the parameters by their levels of impact on the ICERs. For each uncertainty variable considered, the estimates for what the low, base, and high outcomes would be. The sensitive variable is modeled as an uncertain value while all other variables are constant at baseline values. In tornado diagrams, the first ten bars represent the items that contribute the most to the variability of the outcome. The decision maker should focus on these parameters.

Probabilistic sensitivity analyses were performed by Monte Carlo simulation 1,000 times to evaluate to effect of parameter uncertainties. The distributions of each probability are assigned following: (a) probability and utility parameters, whose values range between zero and one, are specified to beta distributions, (b) costs, whose characters values above zero, are assigned to gamma distributions. The results of PSA were presented as cost-effectiveness acceptability curves. The expected NMB was calculated for range of the WTP threshold to show the probability of being the best buy option of each choice of treatment.

Moreover, threshold sensitivity analyses were performed to determine the optimal chemotherapy drug price that would make the non-cost-effective choice of treatment cost-effective at Thai social WTP. We analyzed by varied only capecitabine and irinotecan price because they are the standard choices in developed countries whereas they are the only drugs that are accessible by the Civil Servant Medical Benefit Scheme (CSMBS) covering. The patients in other schemes would pay out of their own pockets.

4.2.7 Budget impact analysis

Budget impact analysis of base case regimen and the possible potential treatment regimen were performed to estimate the amount of budget consumption in the next 5 years and to show the difference in budget consumption among each set of treatment. The total population, incidence rate of stage III CRC, and relapse rate of each regimen were used to calculate the number of patients required treatment. We performed the BIA by using both current drug price and reduced price from threshold sensitivity analysis. The BIA was performed in the perspective of payer, we included only drug price and their administration cost in the analyses.

4.2.8 Ethical issues

The study was ethically approved by Siriraj Institutional Review Board (SIRB) No. 301/2560 (EC1).

4.3 Results

Base-case analysis

This study showed that if compared to current practice in Thailand (5-FU/LV+FOLFOX), only 5-FU/LV+FOLFIRI regimen was considered cost-effective at the Thai ceiling threshold of social WTP of 4,706 USD/QALY. However, 5-FU/LV+FOLFIRI provided the least QALYs of all treatment. Capecitabine+FOLFIRI was dominated by 5-FU/LV+XELOX. In addition, FOLFOX+FOLFIRI was dominated by capecitabine+FOLFOX which provided more QALYs by consuming less lifetime cost. 5-FU/LV+XELOX, capecitabine+FOLFOX, and capecitabine+XELOX were not cost-effective. The regimen of XELOX+FOLFIRI provided the highest QALYs and also the highest costs per lifetime. Its ICER was 10,471 USD/QALY gain (Table 20).

Table 20. Lifetime costs and health outcomes of each treatment option for stage III colorectal cancer

Treatment options	Total cost (USD)	LYs	QALYs	ICERs (USD/QALY)	Interpretation
5-FU/LV+FOLFIRI	19,645	4.50	2.13	2,677	Cost-effective[a]
5-FU/LV+FOLFOX	20,687	5.27	2.52	-	Base case
Capecitabine+FOLFIRI	22,754	5.19	2.53	-	Dominated[b]
5-FU/LV+XELOX	20,904	5.31	2.54	9,463	Not cost-effective[a]
FOLFOX+FOLFIRI	24,907	5.63	2.80	-	Dominated[c]
Capecitabine+FOLFOX	23,928	6.08	2.97	7,067	Not cost-effective[a]
Capecitabine+XELOX	24,174	6.12	3.00	7,195	Not cost-effective[a]
XELOX+FOLFIRI	26,209	6.07	3.04	10,471	Not cost-effective[a]

a, compared to base case; b, dominated by 5-FU/LV+XELOX; c, dominated by Capecitabine+FOLFOX

Sensitivity analyses

One-way sensitivity analyses

According to the analyses, the ICER of 5-FU/LV+FOLFOX vs. XELOX+FOLFIRI was most sensitive to the probability of death of progressive disease patient treated by FOLFOX in year 4 and subsequent years, utility of patient in stable disease during off treatment period, and cost of FOLFIRI, respectively as shown in Figure 8. Additionally, the tornado diagram of 5-FU/LV+FOLFOX vs. Capecitabine+XELOX showed that the ICER was most sensitive to the probability of death of progressive disease patient treated by FOLFOX in year 4 and subsequent years. The parameter that had the second and third most impact it ICER were utility of patient in stable disease during off-treatment period and cost of capecitabine, respectively (Figure 9).

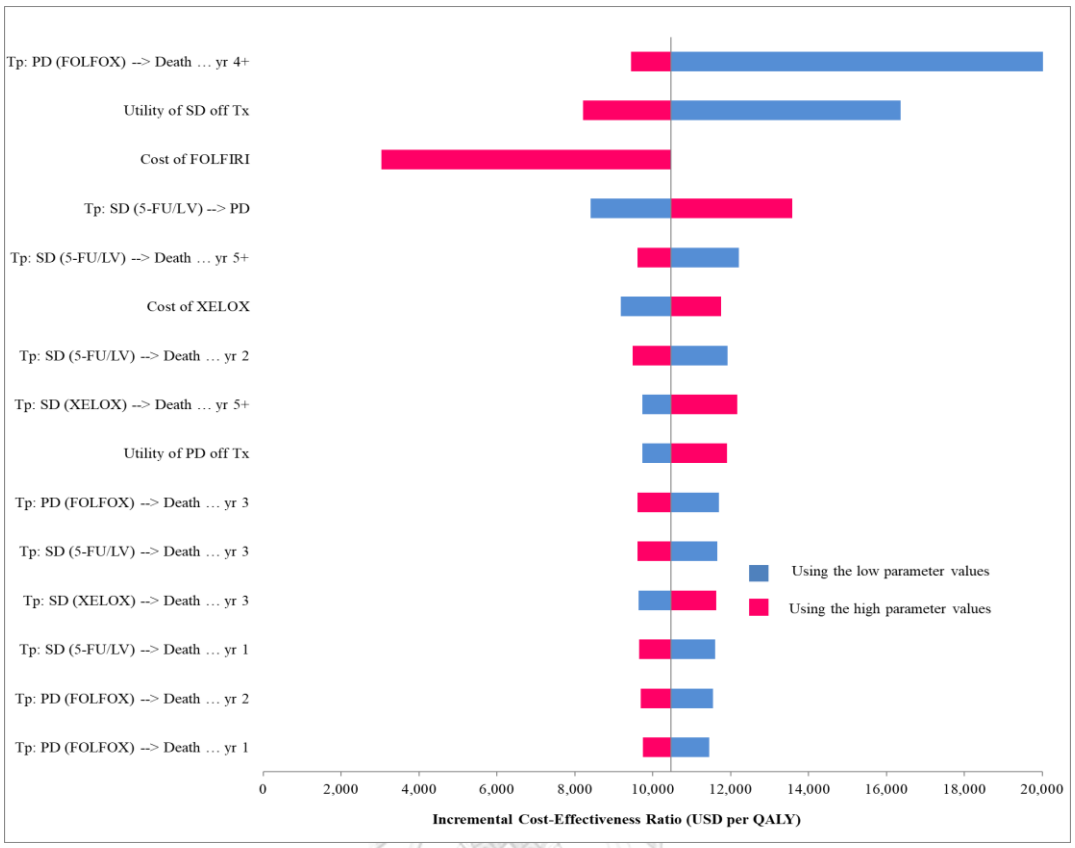

Figure 8. Tornado diagram of XELOX+FOLFIRI vs. 5-FU/LV+FOLFOX

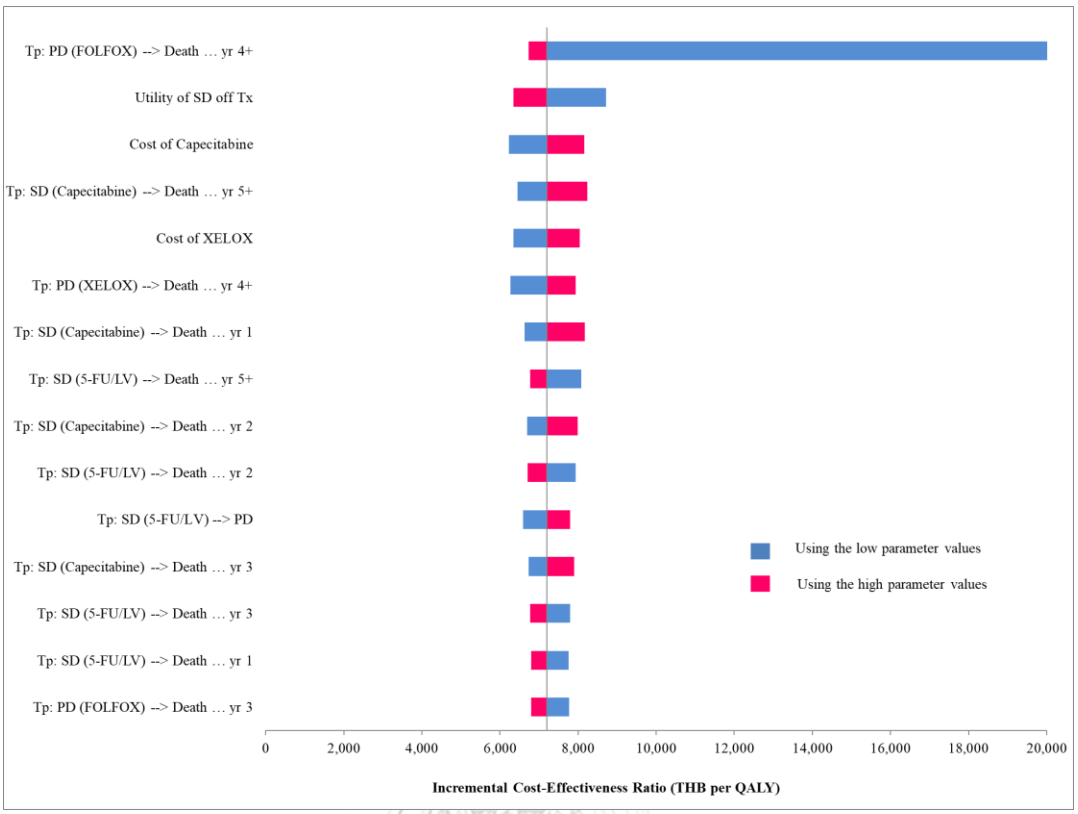

Figure 9. Tornado diagram of Capecitabine+XELOX vs. 5-FU/LV+FOLFOX

Multivariate probabilistic sensitivity analyses (PSA)

At the current WTP, among 7 choices compared to the standard regimen of 5-FU/LV+FOLFOX, 5-FU/LV+FOLFIRI had a high probability of being cost-effective. Moreover, XELOX+FOLFIRI, which provides the most QALYs gained, had the probability of being cost-effective only 8% compared to standard treatment (Figure 10&11).

According to acceptability curve (Figure 11), when compared to standard treatment, the probabilities of being cost-effective of Capecitabine+FOLFOX, Capecitabine+XELOX, Capecitabine+FOLFIRI, FOLFOX+FOLFIRI, XELOX+ FOLFIRI were increasing as the WTP rising whereas the probability of being cost-effectiveness of 5-FU/LV+XELOX compare to standard treatment was about 50% and did not depend on WTP.

When compared all 8 choices of treatment together, 5-FU/LV+XELOX, 5-FU/LV+FOLFIRI, Capecitabine+FOLFIRI, FOLFOX+FOLFIRI, and XELOX+ FOLFIRI would never be the best choice of treatment on the value of WTP that we

varied (0-20,000 USD). At the WTP from 0 to less than about 7,000 USD, 5-FU/LV+FOLFOX was the best buy option. At above 7,000 to less than 13,000 USD, Capecitabine+FOLFOX was the best buy option. Finally, if the WTP was 13,000 USD and more (about 3-time of the current WTP), Capecitabine+XELOX would be the best buy option (Figure 12).

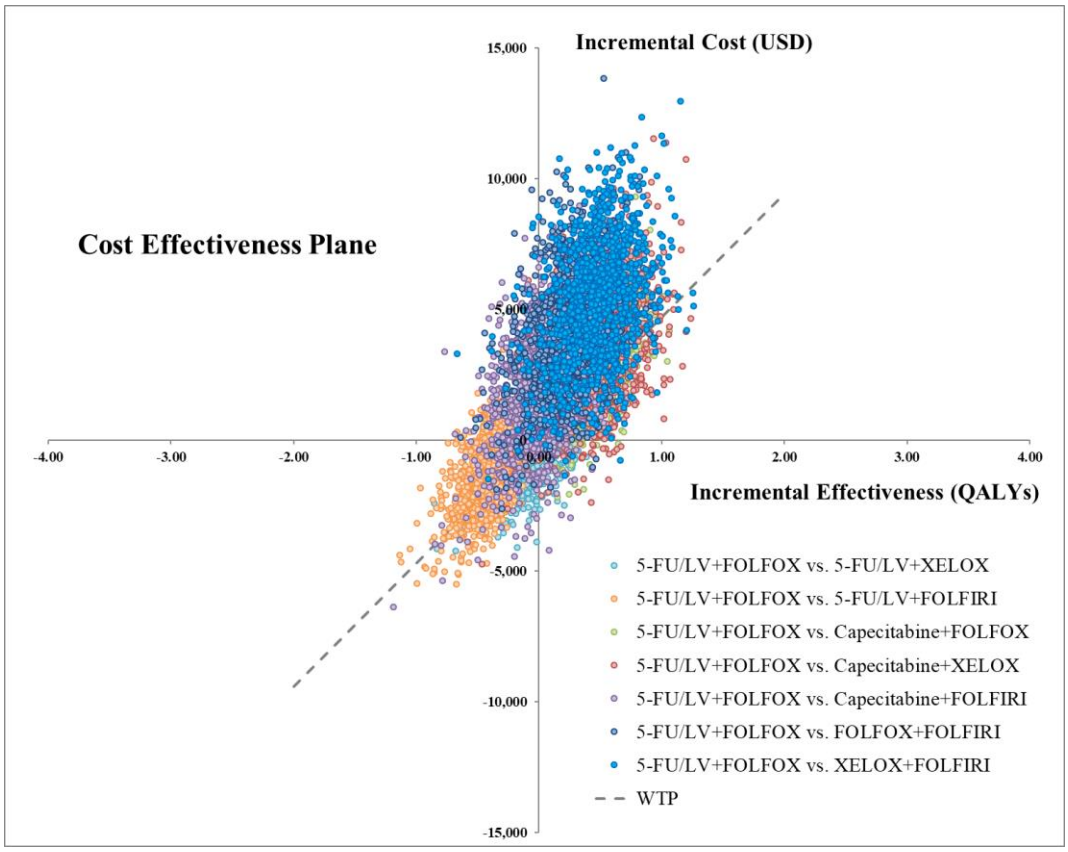

Figure 10. Cost-effectiveness plane of stage III colorectal cancer treatment

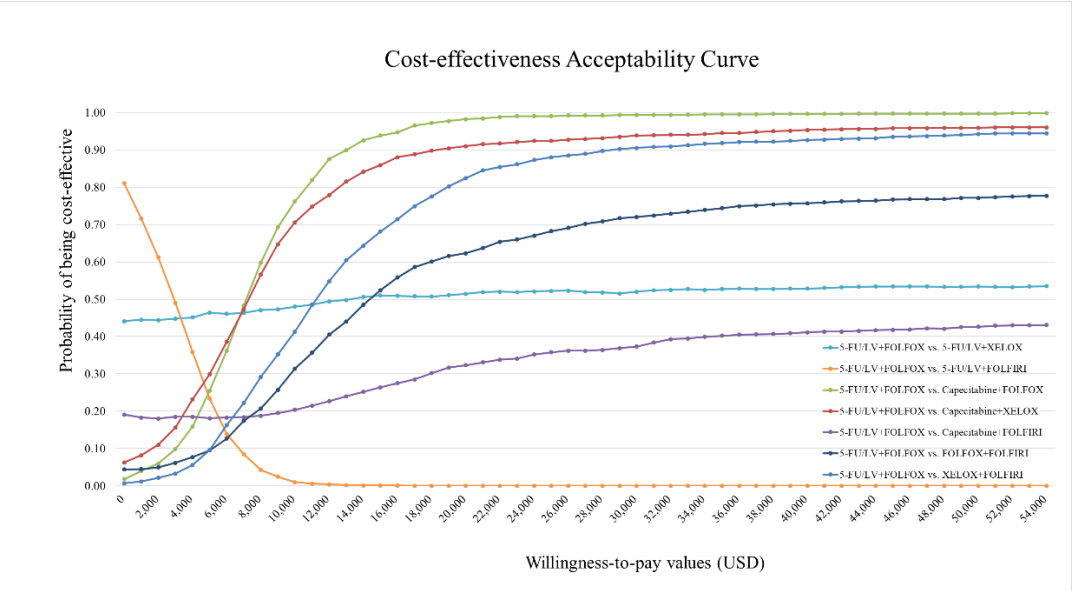

Figure 11. Cost-effectiveness acceptability curve of seven choices of stage III colorectal cancer treatment compared to 5-FU/LV+FOLFOX

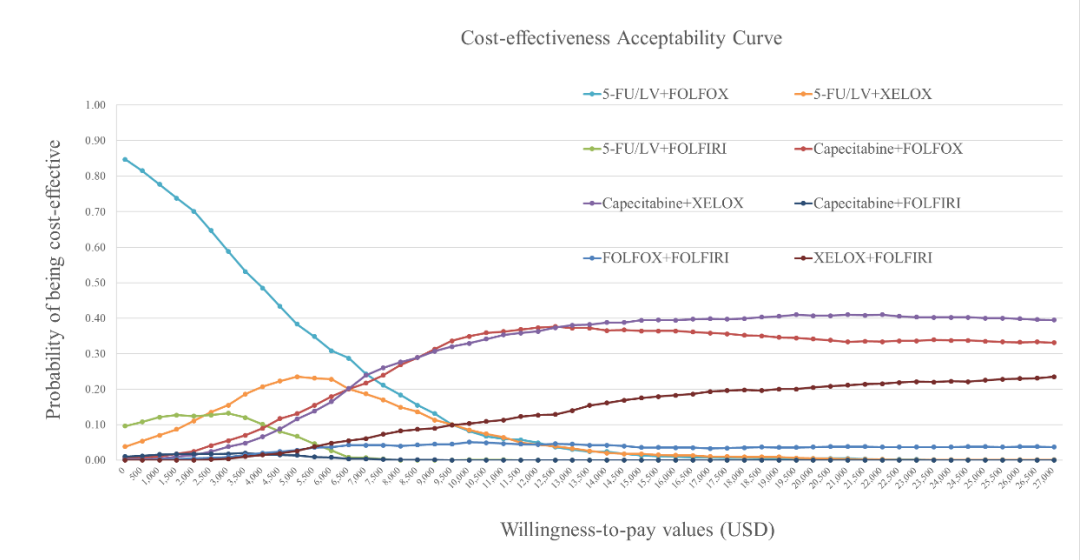

Figure 12. Cost-effectiveness acceptability curve of all choices of stage III colorectal cancer treatment

Threshold sensitivity analysis

In threshold sensitivity analyses, we analyzed the optimal prices of all treatments that contain capecitabine or irinotecan that were not dominated by any other treatments because the only group of patients that are currently able to access these 2 drugs were those who covered by CSMBS and those who are able to pay by themselves, as mentioned above. In order to make the treatment cost-effective at Thai WTP, the price of capecitabine needed to be reduced by at least 11% of the current price, this would make 5-FU/LV+XELOX cost-effective. Capecitabine+XELOX and Capecitabine+FOLFOX would be cost-effective, if the price of capecitabine was reduced by 40% and 58%, respectively. Moreover, XELOX+FOLFIRI would be cost-effective if the price of capecitabine and irinotecan each reduced by at least 83%, by reducing the price of only one drug was unable to make this set of treatment cost-effective (Table 21).

Table 21. Threshold sensitivity analyses of stage III colorectal cancer treatment

Choice of treatment	Regimen	Regimen cost before price reduction (USD per course)	%Price reduction	Regimen cost after price reduction (USD per course)
5-FU/LV+XELOX	XELOX	2,727	11% of capecitabine original price	2,523
Capecitabine+FOLFOX	Capecitabine	1,881	58% of capecitabine original price	799
Capecitabine+XELOX	Capecitabine	1,881	40% of capecitabine original price	1,131
	XELOX	2,727	40% of capecitabine original price	1,977
XELOX+FOLFIRI	XELOX	2,727	83% of capecitabine original price	1,159
	FOLFIRI	3,034	83% of irinotecan original price	928

Budget impact analysis

Five-year BIA showed that at the current drug price in Thailand, the treatment regimen that impacts the least amount of budget, about 9.2 million USD, was 5-FU/LV+FOLFOX which is the current practice. This amount of money could treat about 80% of newly diagnosed stage III CRC patients and 80% of those who relapsed. According to the database of Siriraj Hospital, the other 20% was handle by palliative care ("Siriraj Colorectal Cancer Registry Project (2009-2019)," 2019). The treatment that consumed the highest budget at the current drug price was XELOX+FOLFIRI, around 38.1 million USD. By using the optimal drug price from threshold sensitivity analyses, the BIA decreased ranged from 11.7 to 16.8 million USD (Table 22).

Table 22. Budget impact analysis of stage III colorectal cancer treatment

Regimen	%Price reduction		Year					Total (USD)
	SD	PD	1	2	3	4	5	
5-FU/LV+FOLFOX	Full price		1,104,843	1,542,170	1,897,282	2,185,994	2,421,080	9,151,370
5-FU/LV+XELOX	Full price		1,104,843	1,993,843	2,715,076	3,300,815	3,777,125	2,891,703
	-	11%	1,104,843	1,927,528	2,595,006	3,137,134	3,578,027	2,342,539
Capecitabine+FOLFOX	Full price		3,998,706	4,374,588	4,692,812	4,962,679	5,191,992	3,220,777
	58%	-	1,714,588	2,083,709	2,395,171	2,658,278	2,880,830	1,732,577
Capecitabine+XELOX	Full price		3,998,706	4,753,408	5,390,454	5,928,824	6,384,440	6,455,832
	40%	40%	2,414,657	2,960,211	3,420,489	3,809,252	4,138,037	6,742,646
XELOX+FOLFIRI	Full price		6,248,872	7,039,940	7,716,773	8,296,600	8,794,052	8,096,236
	83%	83%	2,939,707	3,180,379	3,386,751	3,563,997	3,716,508	16,787,343

4.4 Discussion

According to the results, oral chemotherapy such as capecitabine seemed to be more favorable than intravenous chemotherapy in terms of both costs and outcomes. The data from the Siriraj CRC registry showed that the annual mortality rate of oral chemotherapy was lower than intravenous chemotherapy in both stable and progressive diseases. The treatment that provided most QALYs gained per lifetime is XELOX+FOLFIIRI. It is currently considered the most effective CRC treatment among chemotherapy. For those who previously treated by an oxaliplatin-based regimen, irinotecan is the only available choice left when the disease relapses. Capecitabine-based regimens not only provide a benefit in terms of better efficacy, but it also involved with lower administration and direct non-medical costs because it required lower human resources to administer the drug and patients also visit the hospital less frequently.

Our study is the second economic evaluation of CRC treatment in Thailand. The findings were similar to the first study (Lerdkiattikorn et al., 2015) that oral chemotherapy provided high lifetime QALYs than intravenous chemotherapy. However, the total cost of treatment was much different mainly because of the drug price which was significantly dropped because the generic version was available in the market. Nevertheless, our other healthcare costs were similar to this study (Lerdkiattikorn et al., 2015) and other previously published studies (Chindaprasirt et al., 2012; Kankamon Kittrongsiri, Praditsitthikorn, Chaikledkaew, & Teerawattananon). The finding of the previous cost-utility study showed that FOLFOX+FOLFIRI provided the most QALYs gained and the lowest ICER compared to the base case of 5-FU/LV+Capecitabine. Nevertheless, our study proclaimed that Capecitabine+FOLFOX provided higher QALYs with a slightly lower cost of treatment than FOLFOX+FOLFIRI. This happened because we used different sources of input parameters, our input parameters were more update-to-date and more specific to Thai patients as they were mainly extracted from the Siriraj CRC registry database which covered 1,747 stage III-IV CRC patient ("Siriraj Colorectal Cancer Registry Project (2009-2019)," 2019). We also changed the base case or standard treatment of our model to 5-FU/LV+FOLFOX to align with current medical practice, because FOLFOX

provides better efficacy in relapsed patients than capecitabine (Lerdkiattikorn et al., 2015). Moreover, it is currently included in Thai NLEM and is accessible by every patient with stage III CRC in every scheme unless they could not tolerate the drug due to their poor health condition or their own decision to not treat by this regimen.

Moreover, the results from threshold sensitivity analyses showed that capecitabine+XELOX and capecitabine+FOLFOX would be cost-effective if the price of capecitabine was reduced by 40-58%. In addition, XELOX+FOLFIRI would be cost-effective if the price of capecitabine and irinotecan each reduced by at least 83%. This is similar to the experience from using CUA results for drug price negotiation of oxaliplatin (Lerdkiattikorn et al., 2015). After the cost-effective results of that study were published, oxaliplatin became in the NLEM list for stage III CRC treatment with the 69% reduced price. Thus, the policy maker can use our data to negotiate the new drug prices such as capecitabine and irinotecan. Thai patients would be more access to these chemotherapies as well as the other regimens in the NLEM list.

4.5 Strengths and limitations

We believe that our findings will be highly valid and contextually relevant due to 3 main reasons. First, the gastroenterologist subspecialties are involved throughout the process of conducting this CUA. Second, this study uses as much local data as possible in the model. We directly collected the stages of disease, treatment regimens, response rate of treatment, adverse events, and survival rate in CRC patients from the Siriraj CRC registry project. This has made the results more reliable in Thai context. In addition, this model is adjusted by using the mortality rates of the patients by incorporating Thai ASMR to reflect Thai population. Our paper has provided the most up-to-date information on parameters used in the model. Moreover, this is the first study evaluating the cost-effectiveness of CRC treatment for Thai CRC patients. We use Thailand as an example to demonstrate the value of CRC treatment in LMICs. Our findings will draw attention to clinicians and policy makers to this important issue of which global burden has been rapidly rising.

There are several limitations in our study. First, our analysis was not included immunotherapy and targeted therapy in the choices of treatment due to its high cost and the recent data showed indifferent benefit in stage III CRC treatment (Alberts et al.,

2012; de Gramont et al., 2012). Second, due to the big data set, we could not separate the cost from comorbidity care from the total cost of CRC related treatment, so we had to include it in the analysis. This could result in slightly overestimate the cost of CRC treatment.

4.6 Conclusion

Our study showed that only 5-FU/LV+FOLFIRI regimen was considered cost-effective at the Thai ceiling threshold when compared to current practice. The regimen of XELOX+FOLFIRI provided the highest QALYs and also the highest costs. The probability of death of progressive disease, the utility of stable disease, and the cost of FOLFIRI are the most sensitive parameters. When all choices of treatment were compared at the Thai WTP threshold, 5-FU/LV+FOLFOX was the best buy option. Capecitabine+XELOX and Capecitabine+FOLFOX would be cost-effective if the prices of capecitabine were reduced near half. In addition, XELOX+FOLFIRI would be cost-effective only when the price of capecitabine and irinotecan were reduced by more than 80%. This study provides an opportunity for stage III CRC treatment with the new regimens by using the results from CUA for drug price negotiation. Health policy makers and clinicians may consider our results for including capecitabine and irinotecan in NLEM with significantly lower prices. Stage III CRC patients will receive the appropriate treatment which may prolong their survival with the less burden national budget.

CHAPTER V Conclusions and policy implications

Although CRC has a large impact on public health, but it still has the room for improvement. Since the introduction of the first USPSTF guidelines on population-based CRC screening more than 2 decades ago, the incidence and mortality rates have decreased in the US and have stabilized in some parts of the world. Furthermore, rates and effectiveness of screening are increasing.

Nevertheless, significant public health challenges remain. The most pressing inequality is the inadequate access to prevention and treatment services in disadvantaged populations. Eliminating socioeconomic barriers to CRC screening and treatment could lead to the most substantial gains in quality and quantity of life.

Another challenge is the suboptimal rate of CRC screening. Attendance is an important determinant of the effectiveness of CRC screening programs. Uptake of CRC screening in a pilot screening program in many countries has remained suboptimal.

The first part of this study used DCE to determine the factors associated with individuals' preferences for CRC screening. The respondents preferred screening with high risk reduction of CRC-related mortality, no complication, 5-year interval, less bowel preparation, and lower cost. FIT is the preferred choice of screening with the highest willingness-to-pay and uptake rate. The symptomatic subgroup preferred screening test with more frequency than 10 years.

This information can be used to improve the information provided to CRC screening invitees and identify targets for increasing participation rates. These results are useful for health policy makers to incorporate in improving the success rate of CRC screening campaign.

However, further compounding this problem is that the numbers of gastroenterologists vary within and between countries. It is clear that countries, and even regions within countries, require tailored approaches to CRC screening and treatment that balance the financial, cultural, and political realities that shape the practice of gastroenterology.

The second part of this study showed that both early and late stages of CRC can be prevented by CRC screening including FIT and colonoscopy, especially when applied the policy since starting age of screening before 50 years as they provide an

opportunity for early diagnosis and treatments in order to prevent the development of advanced CRC stages resulted in the avoidable higher costs of treatments.

Both annual FIT and colonoscopy every 10 years in average-risk Thai persons are cost-effective when compared to no screening. Although colonoscopy every 10 years is more cost-effective compared to annual FIT, from BIA results, about 8-times higher in the budget was required to conduct colonoscopy screening policy among Thai population, as compared to FIT. Thus, annual FIT is more feasible in terms of human resources and budgetary burdens. In addition, the transferability and practicability are important to consider for real-world applications of both national and international policies.

This study contributes a new evidence-based knowledge for Thailand as an example of LMICs which health care financing sustainability is challenged in the long-run. Health policy makers and practitioners may consider our study results as part of the evidence-based decision for including either the annual FIT or 10-yearly colonoscopy screening in the CRC screening program of Thailand.

For the patients who do not receive CRC screening, they may be diagnosed as the late stages of CRC. These patients have many choices of treatment especially in stage III. Adjuvant chemotherapy is required to prolong their survival.

The last part of this study showed that only 5-FU/LV+FOLFIRI regimen was considered cost-effective at the Thai ceiling threshold when compared to current practice. The regimen of XELOX+FOLFIRI provided the highest QALYs and also the highest costs. The probability of death of progressive disease, utility of stable disease, and cost of capecitabine and FOLFIRI are the most sensitive parameters.

When all choices of treatment were compared at the Thai WTP threshold, 5-FU/LV+FOLFOX or current practice was the best buy option. Capecitabine would be cost-effective if the prices of capecitabine were reduced near half. In addition, XELOX+FOLFIRI would be cost-effective only when the price of capecitabine and irinotecan were reduced by more than 80%.

This study provides a new opportunity for the treatment of CRC stage III by using CUA for price negotiation. Health policy makers and clinicians may consider our results for including capecitabine and irinotecan in NLEM with lower prices for increasing drug accessibility in Thailand. CRC stage III patients will receive the

appropriate treatment which may prolong their survival with the less burden national budget.

However, the budget impact of late treatment was significantly higher when compare to early screening and early treatment. The improvement of CRC screening success rate by a combination of patients' preference and cost-effectiveness evidence is necessary.

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