ASSESSMENT OF FECAL IMMUNOHISTOCHEMICAL TEST (FIT) SCREENING FOR COLORECTAL CANCER AMONG APPARENTLY HEALTHY ADULTS AGED 50 YEARS AND ABOVE

Health Technology Assessment Philippines

BACKGROUND OF THE ASSESSMENT

Context of the nomination (1 of 2)

Nominator: DOH Disease Prevention and Control Bureau *(Nomination forms: gFOBT, FIT, COL)*

1. **Guaiac FOBT (gFOBT): Rationale for Nomination**

- Gold standard for diagnosis: Colonoscopy with biopsy or histopathology
- Screening procedure: Fecal occult blood test (FOBT)
- US Preventive Service Task Force (USPSTF): recommended the use of annual high-sensitivity gFOBT → less frequency of colonoscopy; gains in life years comparable to colonoscopy screening every 10 years.
- Nominated for potential inclusion of this service in government financing, however, it is already ***included in the Konsulta Package as screening for ages 50 years old and above*** → *removed as intervention of interest*

1. **FIT: Rationale for Nomination**

- More accurate than gFOBT for screening; Does not require patient preparation prior to testing (e.g., avoiding specific foods and medicines that may affect the result).
- Some can be used at home and are user-friendly (Note: context of nomination was for screening at primary care facilities)
- ***Not yet included in any policy or guidelines by the DOH nor covered by the PHIC through its Konsulta package.***

Context of the nomination (2 of 2)

3. **Confirmatory Colonoscopy: Rationale for Nomination**

- Studies supported using **FIT plus Colonoscopy** since it **is more cost-effective** than colonoscopy alone or FIT alone.
- Currently, there is **no national screening program** on colorectal cancer in the Philippines. Mostly European and American regions have existing national screening programs.
- The inclusion of Colonoscopy upon screening with FOBT and FIT in the development of more comprehensive outpatient benefit packages for the population may be critical to decrease morbidity and mortality from colorectal cancer by being able to detect and confirm diagnosis of cancer at its earlier stages.
    - Colonoscopy requires special instruments and expertise that may not be available at primary care level.

Context of the changes in the PICO

Removal of colonoscopy screening as a comparator

- Types of colorectal screening test recommended for average risk individuals *(NCCN, 2024)*:
    - Stool-based tests (i.e., high sensitivity gFOBT and FIT, multitargeted DNA test)
    - Visual screening (i.e., colonoscopy, flexible sigmoidoscopy, CT colonography)
- *2017 Joint Philippine Society of Gastroenterology (PSG) and Philippine Society of Digestive Endoscopy (PSDE)* recommended screening examinations:
    - Colonoscopy (Gold standard) – every 10 years
    - FOBT, in particular FIT (alternative screening test) – annually
    - Flexible sigmoidoscopy (FS) – every five years
- Government financing of CRC screening and diagnosis:
    - *Philhealth Konsulta Benefit Package(2024)*: FOBT
    - *PhilHealth case rates (2015)*: Colonoscopy and Flexible Sigmoidoscopy (FS)
    - *Z-Benefit package(2023)*: colonoscopy and biopsy with histopathology among the mandatory or minimum outpatient diagnostics for CRC diagnosis as basis for the reimbursement
- Despite government financing for colonoscopy (with biopsy or histopathology) as the gold standard for colorectal screening, **the lack of facilities and specialists, patient's hesitancy to undergo invasive tests, difficulty of doctors to convince patients, and potential out-of-pocket costs** are still barriers to the low utilization of colonoscopy in the local setting → ***Hence, the removal of colonoscopy screening as a comparator for the assessment of FIT screening***

Context of the changes in the PICO

Removal of colonoscopy as an intervention of interest

PICO Extracted from DPCB Nomination Forms			
Population	**Intervention**	**Comparator**	**Outcome**
Guaiac-based fecal occult blood test (gFOBT)			
Asymptomatic healthy adults aged at least 45 years old	Screening for CRC with a guaiac-based fecal occult blood test (gFOBT)	Screening for CRC with a fecal immunohistochemical test (FIT)	Early detection of colorectal cancer
Fecal immunohistochemical test (FIT)			
Asymptomatic healthy adults aged at least 45 years old	Screening for CRC with a fecal immunohistochemical test (FIT) *Note: Qualitative FIT (ex. OC-Light S FIT)*	Screening for CRC with a guaiac-based fecal occult blood test (gFOBT)	Early detection of colorectal cancer

Frequency of screening: Annual FIT for gFOBT (PHEX and OHG recommendation)

HTAC-Approved Policy Question

- Should **fecal immunochemical test (FIT) with confirmatory colonoscopy** after a positive result for screening of colorectal cancer (CRC) among apparently healthy adults 50 years old and above be funded by PhilHealth or the DOH?

HTAC-Approved Research Questions

C1. *Responsiveness to Disease Magnitude and Severity*

1. What is the magnitude and severity of colorectal cancer (CRC) among adults 50 years old and above in the country?

C2. Clinical Accuracy and Effectiveness

1. What are the performance characteristics of FIT (vs colonoscopy as the reference standard) for screening for colorectal cancer among apparently healthy adults 50 years old and above, compared to guaiac fecal occult blood test (gFOBT)?
2. What is the effectiveness of FIT for screening for colorectal cancer among apparently healthy adults 50 years old and above compared to gFOBT in the reduction of the risk of developing CRC and CRC-specific mortality?
3. What are the recommendations and guidelines of HTA agencies and ministries of health on the use of FIT for screening for colorectal cancer?

HTAC-Approved Research Questions

C3. Cost-Effectiveness

5. What is the cost-effectiveness of FIT with confirmatory colonoscopy after a positive result for screening for colorectal cancer compared to no screening and to gFOBT screening with confirmatory colonoscopy after a positive result among apparently healthy adults 50 years old and above?

C4. Affordability and Viability

5. What is the budget impact of FIT with confirmatory colonoscopy after a positive result for screening for colorectal cancer compared to no screening and to gFOBT screening with confirmatory colonoscopy after a positive result among apparently healthy adults 50 years old and above?

C5. Household Financial Impact

5. What is the household financial impact of colorectal cancer among adults 50 years and above?

C6. Ethical, Legal, Social and Health System Impact

5. What are the ethical, legal, social, and health systems implications of the use of FIT with confirmatory colonoscopy after a positive result for screening for colorectal cancer among apparently healthy adults 50 years old and above?

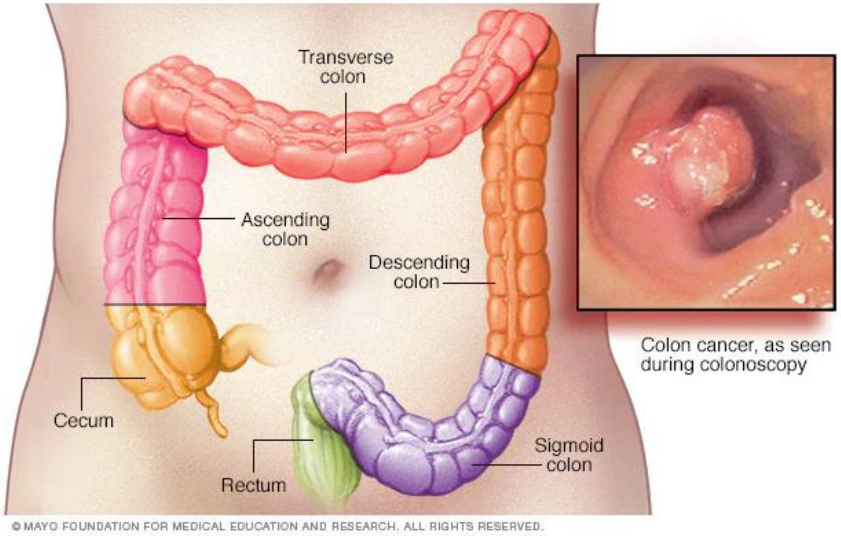
HTA PICO

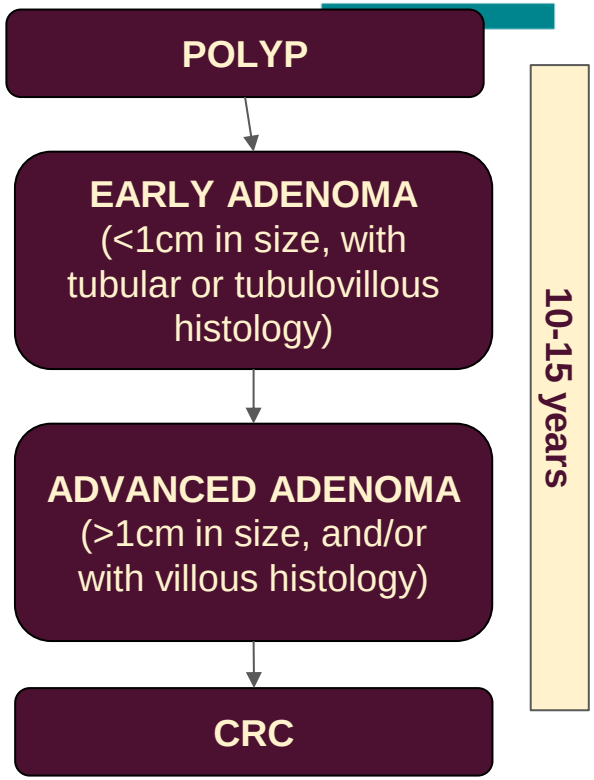
Population	Apparently healthy adults aged 50 years and above
Intervention	Annual screening using qualitative FIT with confirmatory colonoscopy after a positive result
Comparator	Annual screening using gFOBT with confirmatory colonoscopy after a positive result
Outcome	• Clinical: Performance characteristics, effectiveness • Economic: incremental cost-effectiveness ratio, budget impact, household financial impact • Ethical, legal, social, and health systems implications

OVERVIEW OF THE DISEASE

Colorectal Cancer (CRC)

Disease in which there is abnormal proliferation of cells in the colon, and/or the rectum–which consists of several inches of the intestine before the anus





Classic CRC Formation Model (Kuipers et al, 2019)

Colorectal Cancer (CRC)

RISK FACTORS

- Family history
- Age
- Inflammatory bowel disease
- Environmental lifestyle factors
  - Smoking
  - Obesity
  - Excessive alcohol intake
  - Sedentary behaviour
  - Consumption of red and processed meat intake

SYMPTOMS

- Changes in bowel habits that lasts more than a few days (diarrhea, constipation, narrowing of stool)
- Rectal bleeding with bright red blood
- Blood in stool
- Cramping or abdominal pain
- Weakness and fatigue
- Unintended weight loss

CRC: Staging and Prognosis *(AJCC 8th Edition)*

T (Refers to the primary **tumor**)	Tx	Primary tumor cannot be evaluated
	T0	No evidence as primary tumor
	Tis	Carcinoma in situ (Early cancer that has not spread to neighboring tissue)
	T1-4	Size and/or extent of the primary tumor
N (Describes whether or not cancer has spread to nearby **nodes**)	Nx	Regional lymph nodes cannot be evaluated
	N0	No regional lymph node involvement (no cancer found in the lymph nodes
	N1-3	Involvement of regional lymph nodes (number and/or extent of spread)
M (Refers to presence of distant **metastases**)	M0	No distant metastasis (cancer has not spread to other parts of the body)
	M1	Distant metastasis (cancer has spread to distant parts of the body)

CURRENT MANAGEMENT OPTIONS

- Screening and diagnosis
- Therapeutic management

Screening and diagnosis

- Prolonged natural history of CRC → more time to detect and eliminate early neoplastic lesions before they reach an advanced, incurable stage

Types of tests:

1. Detects cancer:
    - Fecalysis
        - Fecal occult blood (FOBT)
            - guaiac-based or immunochemical
        - Stool DNA test
1. Detect early cancer and adenomatous polyps
    - Flexible sigmoidoscopy
    - Colonoscopy
    - Double contrast barium enema (DCBE)
    - CT colonography (CTC)

Recommended by the *Philippine Society of Gastroenterology* and *Philippine Society of Digestive Endoscopy*

Discouraged due to: cost, lower sensitivity, and practical applicability

Screening and diagnosis

The Joint Philippine Society of Gastroenterology (PSG) and Philippine Society of Digestive Endoscopy (PSDE) Consensus Guidelines (2017)

- FOBT - **screening test of choice/first line screening** for colorectal cancer detection
  - Widely accepted
  - Most affordable
  - May be used to direct higher-risk individuals for colonoscopy

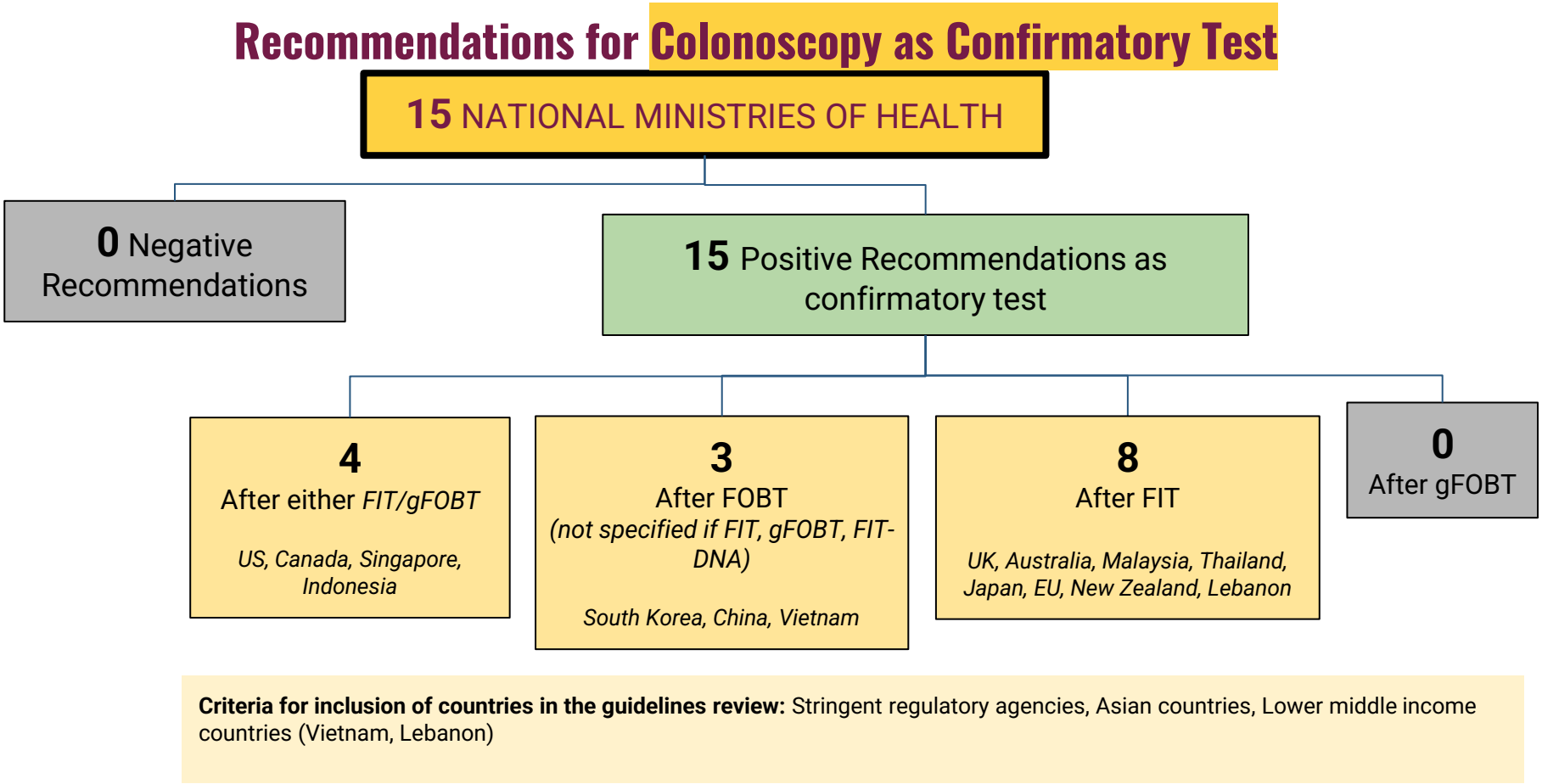
- **Preference for FIT/iFOBT** *("Annual fecal based occult blood testing (FOBT), preferably fecal immunochemical testing (FIT), is the recommended first line screening test for CRC in average risk individuals 50 years old and above.")*
  - Does not need the dietary restrictions imposed by gFOBT
  - Patient compliance
  - Better than gFOBT in detection of adenomas

- Positive findings in FOBT → colonoscopy

Management after FIT/gFOBT screening

- ***US Preventive Services Task Force (2021)***
  - recommends that a positive result on stool-based screening tests require follow-up with colonoscopy for the screening benefits to be achieved.
- ***Joint Philippine Society of Gastroenterology (PSG) and Philippine Society of Digestive Endoscopy (PSDE) 2017***
  - recommends colonoscopy for patients with an increased risk for CRC or have positive findings on sigmoidoscopy, FOBT, CT Colonography, or double contrast barium enema.
  - Individuals who are screened negative are usually continued with the recommended interval depending on the guideline being followed.

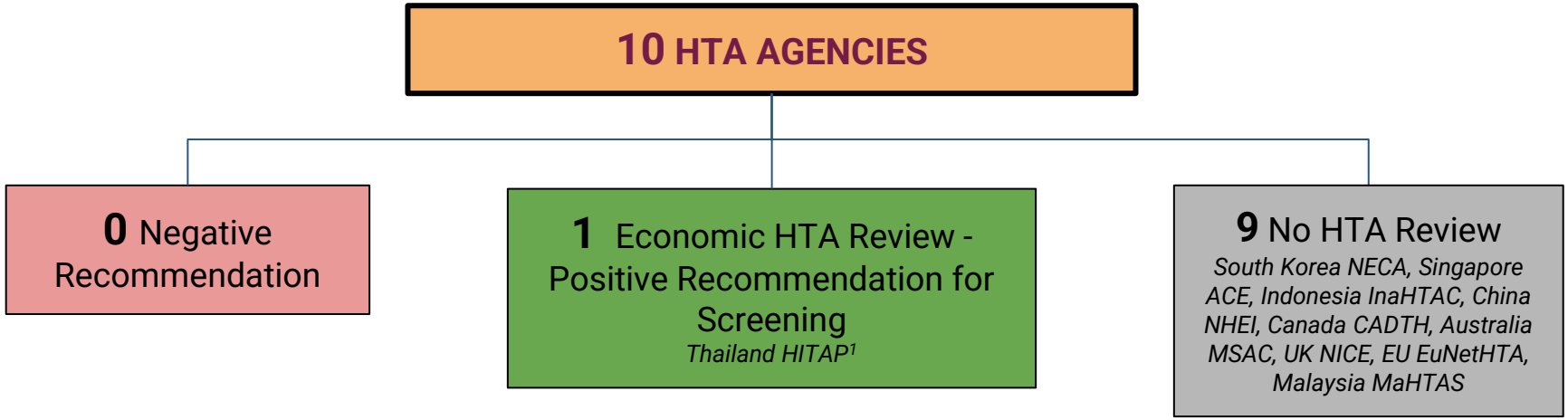
MOH Screening Guidelines with Confirmatory Colonoscopy



Criteria for inclusion of countries in the guidelines review: Stringent regulatory agencies, Asian countries, Lower middle income countries (Vietnam, Lebanon)

HTA Agencies Review of Colorectal Cancer Screening with Confirmatory Colonoscopy

Recommendations for Colonoscopy as Screening and/or Confirmatory Test



[1]*to screen persons at increased risk with a family history of colorectal cancer in first-degree relatives using COL as primary screening method once in a lifetime at age of 60 years*

Recap (from previous presentation): *MaHTAS recommended iFOBT as screening test but did not explicitly recommend colonoscopy as confirmatory test. However, colonoscopy was used as a reference standard in their review of diagnostic performance of iFOBT.*

MOH Screening Guidelines: Colonoscopy as Confirmatory Test

Risk Group Recommendations

	After either FIT/gFOBT (n=4)	After FOBT *not specified if FIT,gFOBT, FIT-DNA* (n=3)	After FIT (n=8)
Average/ Moderate Risk	US, Singapore, Indonesia, Canada	Vietnam	Australia, Malaysia, Lebanon
High Risk		China	
No Risk Group mentioned		South Korea	UK, Thailand, EU, New Zealand, Japan

All fifteen ministries of health guidelines scoped recommended the use of colonoscopy as a confirmatory test after a positive result from screening with fecal occult blood tests (gFOBT or FIT). Majority of these countries (8 out of 15) recommended the use of colonoscopy as a confirmatory test after FIT among average risk individuals. Overall, eight countries recommended the use of colonoscopy as a confirmatory test after FIT (UK, Australia, Malaysia, Thailand, Japan, EU, New Zealand, Lebanon), four MOH (US, Singapore, Indonesia, and Canada) recommend the use of colonoscopy as confirmatory test after either FIT/gFOBT tests, and 3 MOH recommend colonoscopy after FOBT (*type not specified*).

Meanwhile, out of ten HTA agencies scoped, only one (Thailand HITAP) was found to have an HTA review on the use of colonoscopy as a screening and confirmatory test for CRC. Specifically, it had an economic evaluation with a positive recommendation to screen persons with a family history of colorectal cancer in the first degree relatives.

These guidelines from other countries affirm the use of colonoscopy as a confirmatory test after FIT and gFOBT.

Treatment and Management

- Stage-specific approach of managing colorectal cancer based on the TNM staging system.
- Factors to be considered prior to selection of treatment modalities: comorbidity, overall health status (including nutritional status and social support), potential side effects of the chosen approach, and ongoing medication therapy

Stage of Cancer	**Treatment Modality** (*American Society of Cancer Oncology, 2022*)
0, I, II, III	Curable with surgery
II, III	Chemotherapy post-surgery, OR Combined with radiation pre or post-surgery.
IV	Cancer growth and symptoms can be managed but not often curable.

DESCRIPTION, CHARACTERISTICS, AND USES OF THE HEALTH TECHNOLOGIES

Description, Characteristics and Use of the Health Technology

Fecal Occult Blood Test (FOBT)

- Test used to find blood in the feces or stool, which may be a sign of colorectal cancer
- Types of FOBT:
  - **Guaiac-based FOBT (gFOBT)**
  - **Fecal immunochemical test (FIT) or immunochemical FOBT**

Description, Characteristics and Use of the Health Technology: FIT *(ACS, 2023,USPSTF, 2021)*

Fecal Immunochemical Test (FIT)

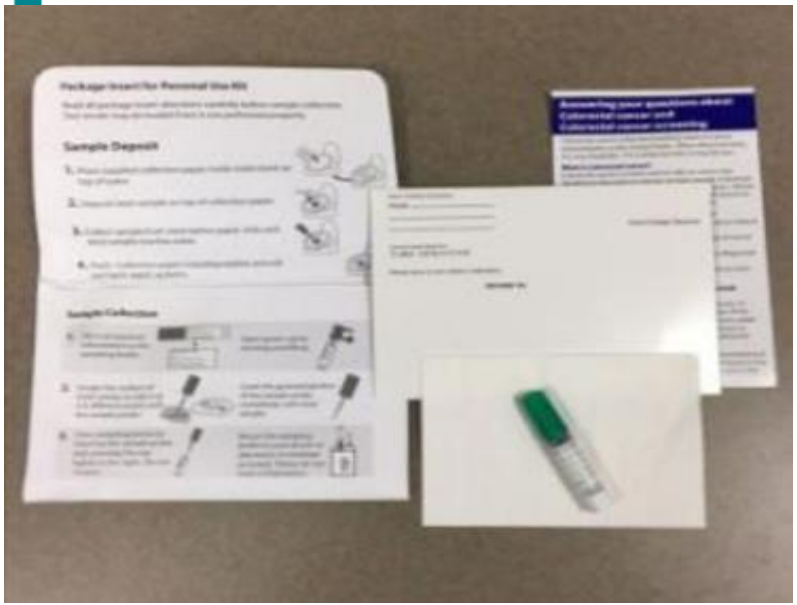
- Looks for occult (hidden) blood from the lower intestines.
- Based on the fragility of blood vessels in large colorectal polyps or cancers which can be easily damaged by passage of stool causing bleeding.
- Unlike gFOBT, **FIT is more specific and uses antibodies against a component of blood, usually hemoglobin, to form an antibody-hemoglobin complex to produce a detectable colored product.**
- **Easier than gFOBT** (no special considerations in terms of drug and dietary restrictions compared).
- **A single stool sample is collected** contrary to gFOBT that requires three (3) separate collection to achieve high-sensitivity gFOBT screening.

Description, Characteristics and Use of the Health Technology: FIT

- FIT can either be qualitative and quantitative but both have akin performance
- **Qualitative FIT*** provides dichotomous results (positive or negative) with predetermined cut-off (C50) in asymptomatic, population-based screening *(Fraser, 2017)*.
- **Quantitative FIT** allows users to make adjustments in the cut-off limit to best target sensitivity for advanced neoplasia *(Cusumano and May, 2020)*.

This particular assessment will focus only on the **qualitative FIT which is the intervention of interest in the DPCB nomination.*

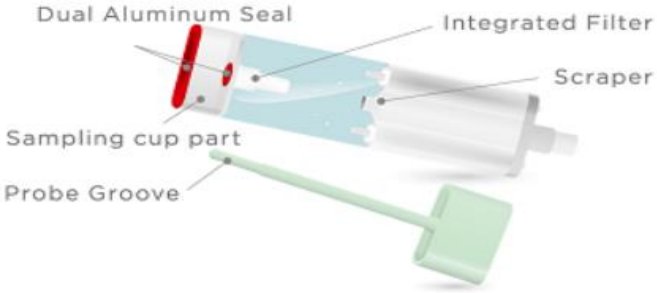
Description, Characteristics and Use of the Health Technology: FIT



OC-Light® S **FIT** Test Kits Polymedco**

Hemoccult ICT kit (FIT)

Description, Characteristics and Use of the Health Technology: FIT



Sample preparation is completed in a single stool collection.

OC Sensor Ceres is a fully automated test analyzer that can perform **FIT**s and fecal calprotectin tests

Description, Characteristics and Use of the Health Technology: gFOBT *(Kaur, 2023,)*

Guaiac-based Fecal Occult Blood Test (gFOBT)

- A test to **assess for hidden blood in the stool** and is commonly used as a screening test for CRC
- The test can detect fecal occult blood through the **oxidation of a chromogen called guaiac by oxygen liberated by the heme in blood**
- Can be performed either in the inpatient or outpatient setting

Description, Characteristics and Use of the Health Technology: gFOBT *(MedlinePlus, 2022)*

SPECIAL CONSIDERATIONS

Diet Restriction:

- Avoid red meat

Medication Restriction:

- Avoid Vitamin C supplements and NSAIDs such as ibuprofen, naproxen and aspirin

Sample Collection

- Samples are collected **on three different days and from different areas of the feces** due to varying presence of blood in the feces.
- Sample must be collected and dried onto the filter paper quickly since delay between sample collection and analysis may yield false negative result. (Rationale: *degradation of the pseudoperoxidase activity of heme in moist feces)*

Description, Characteristics and Use of the Health Technology: gFOBT

Hema Sense **FOBT** Kit - Hemasense 100T**

Hemocue Hemoccult Rapid Test (FOBT)

Description, Characteristics and Use of the Health Technology: gFOBT

Performing the FOBT

1

Prepare the Card

1. Remove the card from the paper envelope and write your name, age and address on the front of the card with a pen. You may store the card in this paper envelope.

2

Collect Stool

1. Write in the date you are collecting your stool sample on section 1 of the card just before your bowel movement.
2. Flush toilet bowl and allow to refill.
3. Unfold the flushable tissue paper that is included in the kit and float it on the surface of the toilet bowl water. Allow the edges of the paper to stick to sides of bowl. Your stool will fall on the tissue. (Note: Do not be concerned if some water collects on the tissue.)

3

Place Stool on the Card

1. Open front of section 1. Use one of the sticks in the kit to take a small sample of stool from the tissue paper. Put a thin smear of this on the area of the card marked A.
2. Collect a second sample from a different part of the stool with the same stick., Place a thin amount of this on the area of the card marked B. Flush the tissue paper down the toilet and discard the stick in a waste container.

4

Close the Cover

1. Close the cover of section 1 by inserting the front flap under the tab. Store the card in the paper envelope until your next bowel movement. Do not store the card in the refrigerator at any time.

5

Repeat and Then Mail

1. Repeat all the steps above for your next 2 bowel movements using sections 2 and 3. After completing the last section, return the card immediately to your doctor or clinic, or wait overnight for the card to dry in the paper envelope.
2. The next day, remove the card from the paper envelope and place in the mailing pouch. Seal the pouch carefully and mail it immediately to your doctor or clink.

UW · International Community Health Services · Harborview Medical Center · Fred Hutchinson Cancer Research Center

University of Washington

FDA Registration Status of FIT kits

- The most current issuance on the registration of in vitro diagnostic tests *(FDA Memorandum Circular 2014-005)* **do not include FIT and gFOBT as a registrable device**. FDA Circular 2018-002 which contains guidelines in the implementation of the 2015 ASEAN Medical Device Directive, did not mention FIT or gFOBT registration.
- Hence, being considered a non-registrable product, **an LTO of the establishment** shall be provided at the point of entry and as a requirement in bidding documents, in lieu of the Certificate of Exemption (FDA Circular 2020-001).

CI: BURDEN OF THE DISEASE
(MAGNITUDE AND SEVERITY)

RQ1. What is the magnitude and severity of colorectal cancer (CRC) among adults 50 years old and above in the country?

CRC: Global Burden of the Disease

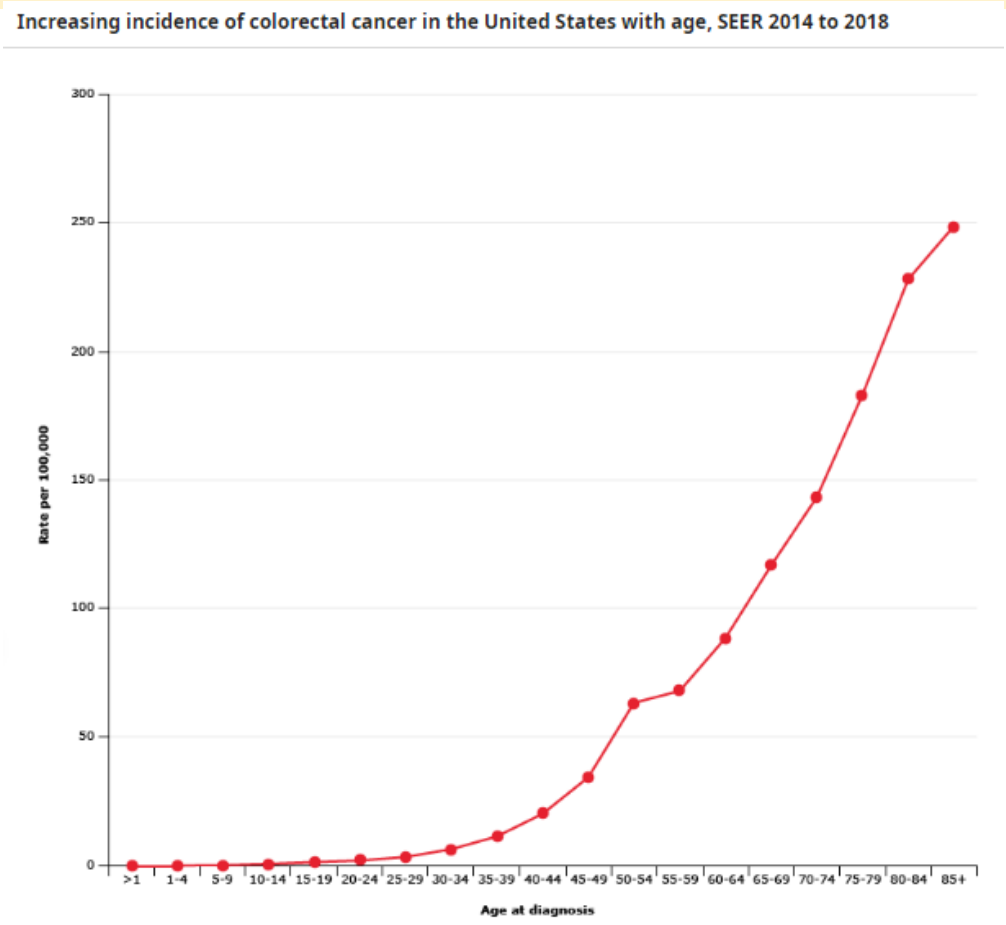
- [WHO] Majority of colorectal cancer cases occur in people aged 50 and above.
- The burden is shifting to the younger population as the median age of diagnosis of colorectal cancer in the US has dropped from 72 years to 66 years (from 2001-2002 to 2015-2016), as warned by the American Cancer Society.
- The US 2020 Colorectal Cancer Statistics also showed that while most cases are still among the older age group, 12% are estimated to belong to individuals below 50 years of age.

TABLE 1. Estimated Numbers of New Colorectal Cancer Cases and Deaths by Age, United States, 2020

	CASES						DEATHS	
AGE, YEARS	COLORECTUM	PERCENT	COLON	PERCENT	RECTUM	PERCENT	COLORECTUM[a]	PERCENT
Birth to 49	17,930	12%	11,540	11%	6,390	15%	3,640	7%
50 to 64	50,010	34%	32,290	31%	17,720	41%	13,380	25%
≥65	80,010	54%	60,780	58%	19,230	44%	36,180	68%
All ages	147,950	100%	104,610	100%	43,340	100%	53,200	100%

Note: Estimates are rounded to the nearest 10 and exclude in situ carcinoma.
[a]Deaths for colon and rectal cancers are combined because a large number of rectal cancer deaths are misclassified as colon.

CRC: Global Burden of the Disease



- Large bowel cancer is uncommon before the age of 40.
- **The incidence begins to increase significantly between the ages of 40 and 50, and age-specific incidence rates increase in each succeeding decade thereafter.**

(Surveillance, Epidemiology, and End Results (SEER) Program, 2014-2018)

Figure: *Incidence of CRC in the US (all genders and ages) in 2014 to 2018, increasing by age*

CRC: Burden of the Disease in the Philippines

(WHO, 2020; Ting et al, 2020)

South Bay Colon and Rectal Specialists | Association of South Bay Surgeons

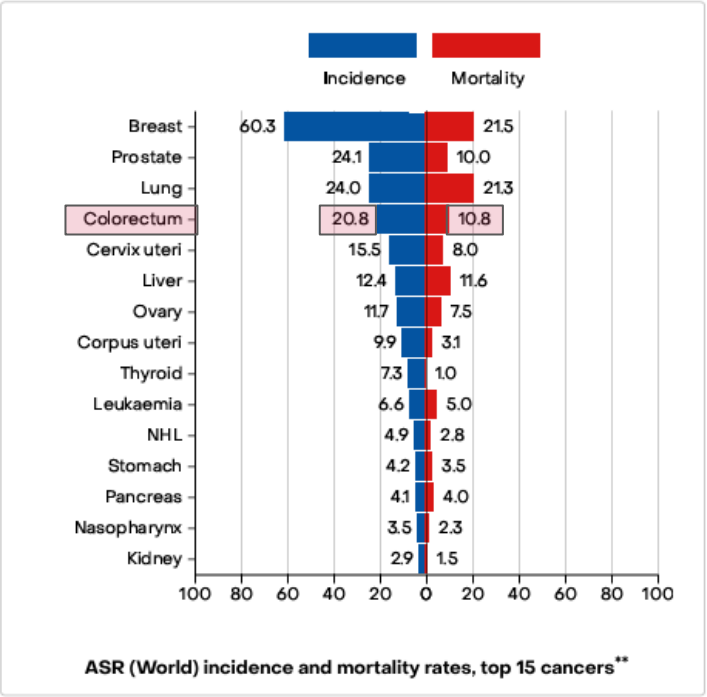
3rd leading site of malignancy

4th leading cause of mortality due to cancer

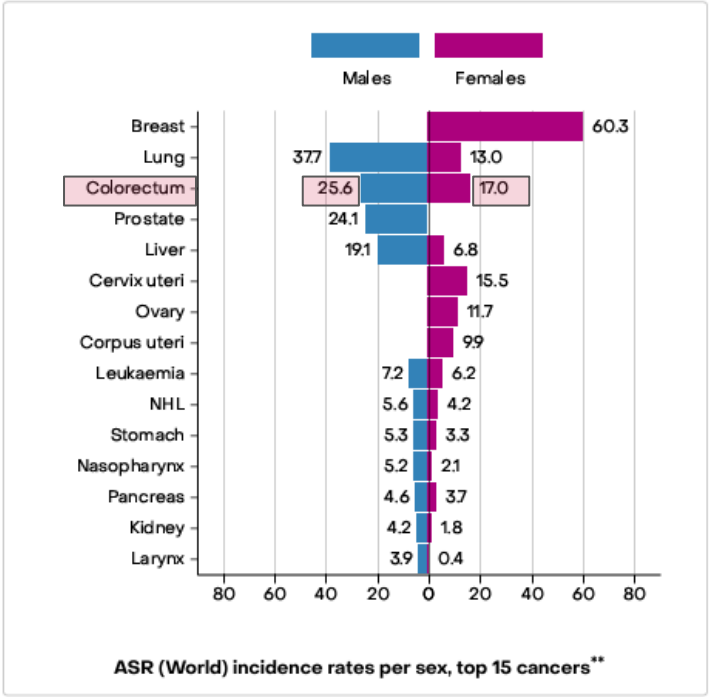
33.9% five-year survival rate for colon cancer

20.0% five-year survival rate for rectal cancer

CRC: Burden of the Disease in the Philippines (*Globocan, 2022)*



ASR (World) incidence and mortality rates, top 15 cancers**



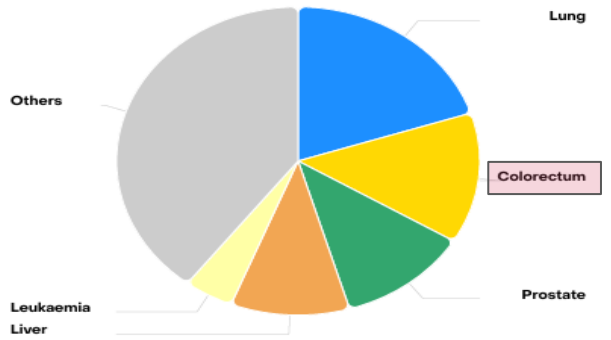
ASR (World) incidence rates per sex, top 15 cancers**

Globally, the **mortality rate of colorectal cancer is 10.8 per 100,000** while the **incidence rate is 20.8 per 100,000**. The age-standardized incidence rates of colorectal cancer is **25.6 and 17.0 per 100,000 for males and females,** respectively.

CRC: Burden of the Disease in the Philippines

(Globocan, 2022)

Males

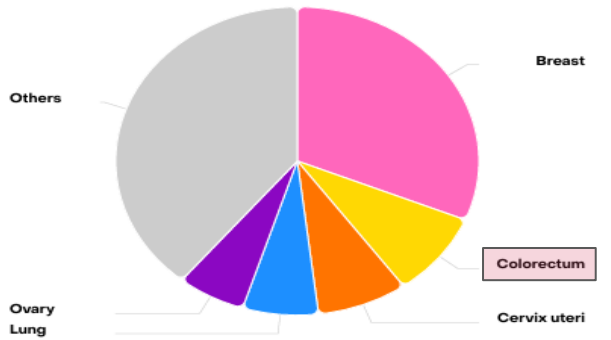


Total: 83 064

Rank	Cancer site	Number of cases	Percent
1st	Lung	16 588	20.0%
2nd	Colorectum	11 386	13.7%
3rd	Prostate	9 764	11.8%
4th	Liver	8 796	10.6%
5th	Leukaemia	3 667	4.4%
-	Others	32 863	39.6%

Number of new cases in 2022, males, all ages

Females



Total: 105 912

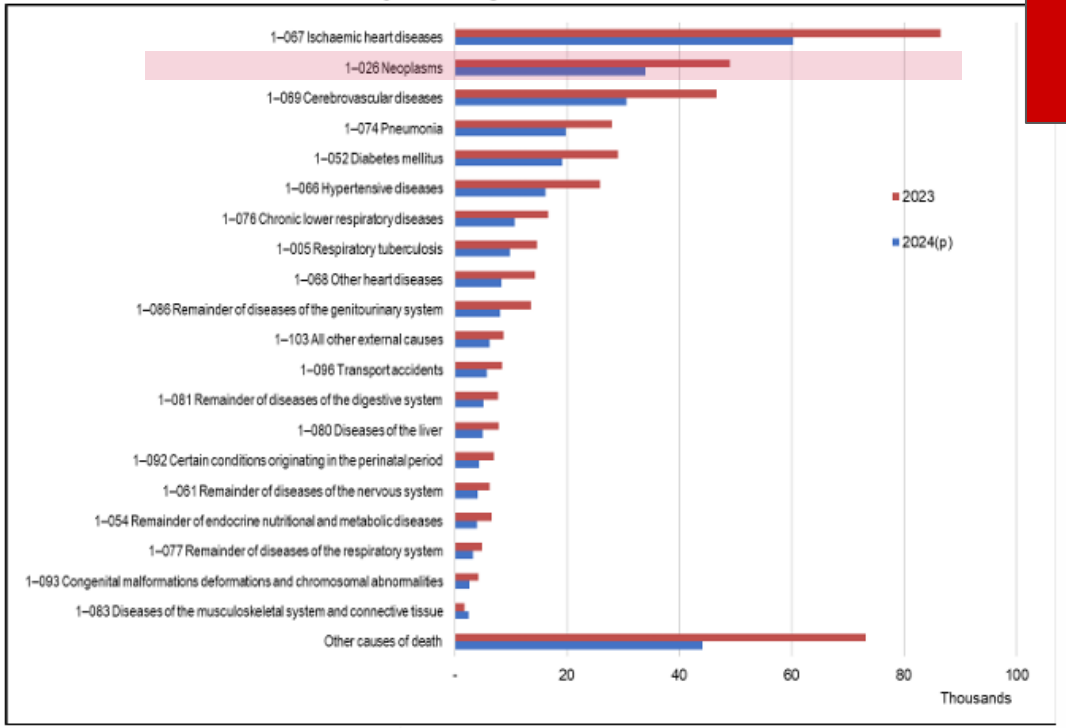
Rank	Cancer site	Number of cases	Percent
1st	Breast	33 079	31.2%
2nd	Colorectum	9 350	8.8%
3rd	Cervix uteri	8 549	8.1%
4th	Lung	7 140	6.7%
5th	Ovary	6 453	6.1%
-	Others	41 341	39.0%

Number of new cases in 2022, females, all ages

In the Philippines, colorectal cancer had the **2nd highest number of new cases in 2022 in males and females.**

4 minutes OVERTIME

Figure 1. Top 20 Causes of Mortality, Philippines: January to August, 2023 and 2024



Source: Philippine Statistics Authority *(Data on deaths are based on registration at the Office of the City/Municipal Civil Registrars nationwide, and submitted to the Office of the Civil Registrar General; derived from Certificate of Death-Municipal* Form No. 103)

Notes: Symptoms, signs, and abnormal clinical and laboratory findings, not elsewhere classified (R00-R99) are not included in the analysis due to the unspecified nature of these causes

Causes of death are coded based on the ICD-10 Rules and Guidelines and mortality grouping is based on the Mortality Tabulation List of ICD-10

Source: PSA as of Feb 2025

Common stage of presentation of patients who have not been screened at the time of diagnosis

Table 1.2. Stage distribution of colorectal cancer at the time of diagnosis, by country or region and time period

(data were collected predominantly before the full implementation of organized population screening programmes)

Region	Cancer site	Period of diagnosis	Stage at diagnosis (%)				Reference
			I	II	III	IV	
Northern Europe	Colorectum	1996–1998	12	33	20	11	Allemani et al. (2013)
Western Europe	Colorectum	1996–1997	16	32	22	18	Allemani et al. (2013)
Southern Europe	Colorectum	1996–1998	14	30	24	20	Allemani et al. (2013)
Eastern Europe	Colorectum	1996–1998	26	24	14	30	Allemani et al. (2013)
Denmark	Colon	2004–2007	11	30	27	31	Maringe et al. (2013)
Sweden	Colon	2000–2007	11	37	29	23	Maringe et al. (2013)
United Kingdom	Colon	2000–2007	9	39	35	17	Maringe et al. (2013)
Canada	Colon	2004–2007	18	31	26	26	Maringe et al. (2013)
USA registries	Colorectum	1997	17	28	38	10	Allemani et al. (2013)
Sub-Saharan Africa	Colorectum	Not reported	6	57	31	6	Graham et al. (2012)
Islamic Republic of Iran	Colorectum	2002–2007	7	32	32	16	Moghimi-Dehkordi et al. (2008)
China	Colorectum	1980s	13	30	36	21	Li & Gu (2005)
China	Colorectum	1990s	11	37	37	15	Li & Gu (2005)
Japan	Colon	1974–1993	12	37	28	19	Muto et al. (2001)
South Australia	Colorectuma	2003–2008	20	30	28	14	
TOTAL			**203**	**507**	**427**	**277**	

a Only populations between age 50 years and age 79 years are included.

Most cases were diagnosed at **Stages II and III.**

Challenges in obtaining the data:

Multiple and varying factors influence the stage of CRC diagnosis

- Reporting in cancer registries may not be strictly followed
- Population-based screening programs, opportunistic screening, increases awareness, and surveillance programs for high risk population leads to early detection → lower stages of diagnosis
- Available evidence have shown the increase in the number of early-stage cancers was accompanied with decrease in the number of CRC stage IV (Lindebjerg et al., 2014; Yang et al., 2014; Binefa et al., 2016; Kubisch et al., 2016).

Reference: *IARC, 2019*

Local data on patients enrolled in the Z-Package colorectal cancer benefit program from 2016 to 2018 revealed that majority of patients had rectal cancer (78%) and were **diagnosed with stage III disease (82%)** ***(Ting et al., 2020)***.

Stage-related survival of CRC

Table 1.3 Stage-related survival of colorectal cancer using four-tiered staging

Country (data source)	Cancer site	Period of diagnosis	Survival by stage of disease (%)				Follow-up	Reference
			I	II	III	IV		
Australia	Colorectum[a]	2003–2008	95	84	62	9	5-year survival	Beckmann et al. (2016)
Canada	Colon	2004–2007	94	87	71	13	3-year survival	Maringe et al. (2013)
Denmark	Colon	2004–2007	89	87	67	13	3-year survival	Maringe et al. (2013)
Europe (EUROCARE)	Colorectum	1990–1991	93	85	53	16	3-year survival	Ciccolallo et al. (2005)
Japan	Colon	1990–1992	94	90	82	16	5-year survival	Muto et al. (2001)
Sweden	Colon	2000–2007	98	91	69	16	3-year survival	Maringe et al. (2013)
United Kingdom	Colon	2000–2007	95	85	58	12	3-year survival	Maringe et al. (2013)
USA (SEER)	Colorectum	1990–1991	94	89	63	16	3-year survival	Ciccolallo et al. (2005)

EUROCARE, European Cancer Registry-based Study on Survival and Care of Cancer Patients; SEER, Surveillance, E

[a] Only populations between age 50 years and age 79 years are included.

Table 1.4 Stage-related survival of colorectal cancer using three-tiered staging

Country (region or data source)	Cancer site	Period of diagnosis	Survival by stage of disease (%)			Follow-up	Reference
			Local	Regional	Distant		
Australia	Colon	2000–2007	93	75	20	3-year survival	Maringe et al. (2013)
Canada	Colon	2004–2007	92	70	13	3-year survival	Maringe et al. (2013)
Cuba	Colon	1994–1995	65	45	21	5-year survi	Sankaranarayanan
Denmark	Colon	2004–2007	90	68	13	3-yea survi	
India (Mumbai)	Colon	1987–1991	61	32	9	5-yea survi	
Islamic Republic of Iran (Golestan)	Colorectum	2004–2007	81	52	0	5-yea survi	
Norway	Colon	2000–2007	91	77	14	3-yea survi	
Philippines (Manila)	Colon	1994–1995	69	34	0	5-yea survi	
Republic of Korea	Colorectum	2006–2010	93	78	18	5-yea survi	
Sweden	Colon	2000–2007	93	69	16	3-yea survi	
Singapore	Colon	1993–1997	67	43	7	5-yea survival	et al. (2011)
Thailand (Lampang)	Colon	1990–2000	60	57	2	5-year survival	Sankaranarayanan et al. (2011)
Turkey (Izmir)	Colon	1995–1997	60	54	21	5-year survival	Sankaranarayanan et al. (2011)
United Kingdom	Colon	2000–2007	87	59	12	3-year survival	Maringe et al. (2013)
USA (SEER)	Colorectum	1975–1977	82	52	6	5-year survival	Jemal et al. (2017)
USA (SEER)	Colorectum	2006–2012	91	73	14	5-year survival	Jemal et al. (2017)

SEER, Surveillance, Epidemiology, and End Results.

Key findings:

Evidence show that the **higher the disease stage, the lower the survival rate.**

Reference: IARC, 2019

Prognosis of screened and unscreened patients

Novotny et al, 2024

- **Setting: Spain (N=315)**
- Population: 1) CRC patients diagnosed through screening, and 2) CRC patients diagnosed due to symptoms

Patients diagnosed **by symptoms** (n=186)	Patients diagnosed **by screening** (n=129)

• Higher prevalence of
  • stage II CRC (OR 4.327, *p* = 0.0063),
  • stage III CRC (OR 3.661, *p* = 0.0113)
  • stage IV CRC (OR 5.732, *p* = 0.0023),
  • diabetes (OR 2.308, *p* = 0.0354),
  • proximal involvement (OR 2.444, *p* = 0.0096)
  • other chronic diseases (OR = 1.999, *p* = 0.0208)
• All-cause mortality (28.5%)
• CRC-mortality (73.6%)
• **Higher prevalence of Stage IV cancer at time of diagnosis** and **higher CRC mortality and all-cause mortality at the end of follow-up**
	• Higher prevalence of
	  • family history of CRC
	  • distal tumour location
	  • **stages 0 and I CRC**
	• All-cause mortality (17.8%,)
	• CRC-mortality (65.2%)
	• Lived longer than the symptomatic group (p = 0.039)

Key findings:

- Results show that compared to patients diagnosed by screening, patients diagnosed by symptoms have-higher prevalence of stage IV cancer at time of diagnosis.
- CRC screening enables an earlier diagnosis and improves survival.

CRC: Burden of the Disease

(PESO Study, 2018) *(CDC, 2022)*

https://images.app.goo.gl/cowQZ3VVntxRUGEz8

40.6% of Filipino households faced financial catastrophe after cancer diagnosis

$110,000 is the average per-patient cost for medical services in the US during the last year of life of CRC patients

$66,500 is the average per-patient cost for medical services in the US during the initial care phase for CRC

C1: Responsiveness to Disease Magnitude and Severity

RQ1: What is the magnitude and severity of colorectal cancer (CRC) among adults 50 years old and above in the country?

HTAC Judgment: Globally and in the country, colorectal cancer (CRC) continues to add significant burden due to its increasing incidence, prevalence, and mortality (Globocan, 2022/GBD, 2019 Colorectal Cancer Collaborators, 2022). In the Philippines, CRC ranks third in the list of cancer in terms of incidence (12.6% of new cancer cases), and second among Filipino men (13.7%; age-standardized incidence rate: 25.6 per 100,000) and women (8.8%; age-standardized incidence rate: 17.0 per 100,000) (Globocan, 2022). In terms of mortality, neoplasms ranked as the 2nd leading cause of death in the Philippines in 2023 and 2024 (*Philippine Statistics Authority, 2025*), while colorectal cancer ranks 4th among all cancer-related deaths. The reported age-standardized mortality rate is 10.8 per 100,000 people, regardless of sex (Globocan, 2022).

In terms of age, about 63.5% of individuals newly affected with cancer are aged 50 and above while only 2.2% were children aged 14 years old and below (Philippine Cancer Society, 2014). Similarly, colorectal cancer, in particular, predominantly affects older individuals aged 50 and above (WHO, 2023).

There is a higher prevalence of early stages of colorectal cancer (stages 0 and 1) among patients diagnosed through screening and a higher prevalence of late stages of colorectal cancer (stages II, III, IV) among patients diagnosed through their symptoms (Novotny et al, 2024). Similarly, during the period before the full implementation of organized population screening programs throughout the world, most cases of colorectal cancer were diagnosed at stages II and III (IARC, 2019).

In terms of mortality, patients diagnosed through screening had lower rates of all-cause mortality (17.8%) and CRC mortality (65.22%) patients diagnosed through their symptoms (all-cause mortality at 28.5% and CRC mortality at 73.6%) (Novotny et al, 2024). Additionally, there are lower rates of survival among patients at later stages of CRC (IARC, 2019).

Further, the associated poor prognosis and low survival rates of CRC at 38.1% and 33.9% for colon cancer; 31.3% and 20.0% for rectal cancer, in 3 and 5 years, respectively, aggravate the burden of the disease (*Ting et al., 2020*). In terms of severity, the late detection which requires expensive and complicated treatment poses a great disadvantage to both individuals at risk and suffering from the disease. Hence, the health technology assessment of colorectal screening strategies such as fecal immunochemical testing for its potential in the early detection of colorectal cancer and reduction of mortality is concurrently being conducted.

C2: CLINICAL ACCURACY AND EFFECTIVENESS

FIT VS GFOBT

DIAGNOSTIC ACCURACY (WITH COLONOSCOPY AS THE REFERENCE STANDARD)

RQ2. What are the performance characteristics of FIT (vs colonoscopy as the reference standard) for screening for colorectal cancer among apparently healthy adults 50 years old and above, compared to guaiac fecal occult blood test (gFOBT)?

Diagnostic Accuracy Studies

- PHEX Review (Phase 1 and 2)
- Systematic Reviews (k=1)

DOST

FIT and gFOBT

	PHEX Review	Grobbee et al., 2022
No. and Types of Studies Included	**k=50** [gFOBT: k=1, FIT: k=45, Both: k=4] Prospective, cross-sectional, screening programs, and nested case control studies	**k=63** [gFOBT: k=13, FIT: k=44, gFOBT and FIT: k=6] Prospective and retrospective studies
Date of Search	July 2021	June 2019 to September 2021
Quality of Individual Studies Included	Fair*(k=34) to Good quality (k=10) [k=1 excluded which did not report Sn and Sp for CRC; k=5 with no quality appraisal from PHEX/USPSTF]	High Quality (overall)
AMSTAR-2 Judgement	Critically low	Low
Comparison of Studies	23 Studies common for both 4 Updated studies in PHEX compared to those in Grobbee 4 Older studies in PHEX compared to those in Grobbee 19 Studies present in PHEX but missing in Grobbee 31 Studies present in Grobbee but missing in PHEX	
Outcomes Reported	FIT Sensitivity and Specificity for detection of CRC	FIT Sensitivity and Specificity for detection of CRC

AMSTAR appraisal of SRs (Grobbee et al. 2022 and PHEX)

	Grobbee et al. 2022	PHEX 1 and 2
Critical weaknesses	**No assessment of publication bias**	• No protocol, missing info (RoB and inclusion/exclusion criteria) in methods • Did not use a comprehensive search strategy • Did not provide a list of excluded studies and justify the exclusions • No RoB results included in the appendix nor was confounding and selection bias included in the measurement of RoB. • Did not explain the process of combining data from RCTS in the meta-analysis and estimates from NRSIs that were adjusted for confounding. • Did not account for RoB in individual studies when interpreting/discussing the results of the review • Did not assess publication bias
Non-critical flaws	**No reported sources of funding for individual studies included in the review**	• No explanation for study design • Did not report source of funding for studies included • Did not assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis
Overall rating	**Low**	**Critically low**

Summary of Findings from the *PHEX Review* and *Grobbee et al., 2022 (SR)*

	Brand	Type of Stool Test (No. of studies, cutoff level)	CRC	
			Sensitivity	Specificity
PHEX Review *Note: For gFOBT, only range was provided*	Hemoccult SENSA	gFOBT (k=2)	**50% to 79%** (95% CI 1% to 99%)* **62% to 79%** (95% CI 36% to 94%)**	**87% to 98%** (95% CI 86% to 99%)* **87% to 96%** (95% CI 86% to 97%)**
	OC-Sensor Family	**FIT** (k=9) (20 ug Hb/g) cutoff)	**74%** (95% CI, 64% to 83%, I2=31.6%)* **81%** (95% CI 74% to 88%, I2=98.6%)**	**94%** (95% CI, 93% to 96%, ; I2=96.6%)* **95%** (95% CI, 94% to 96%, I2=98.5%)**
	Other FIT brands	**FIT (OC Light, k=3)** (10 ug Hb/g) cutoff) (2 to 100 ug Hb/g) cutoff)	**81%** (95% CI, 70% to 91%, I2=0)	**93%** (95% CI, 91% to 96%, I2=99%)
		FIT (Other brands, k=8) (10 ug Hb/g cutoff) (2 to 100 ug Hb/g cutoff)	**50% to 97%** (95% CI 90% to 100%)	**83% to 97%** (95% CI 82% to 97%)
Grobbee et al. 2022 *(Note: heterogeneity analyses were not conducted due to insufficient heterogeneity between studies and convergence difficulties)*	Different Brands	gFOBT (k=9***, k=12****)	**39%** (95% CI: 25%, 55%)*** **59%** (95% CI: 55%, 64%)****	**94%** (95% CI: 91%, 96%)*** **98%** (95% CI: 98%, 99%)****
	Different Brands	**FIT** (k=13***, k=23**** (10 ug Hb/g) cutoff	**76%** (95% CI: 57%, 88%)*** **89%** (95% CI: 80%, 95%)****	**94%** (95% CI: 87%, 97%)*** **94%** (95% CI: 92%, 95%)****
		FIT (k=11***, k=23**** (20 ug Hb/g) cutoff	**65%** (95% CI: 46%, 80%)*** **89%** (95% CI: 85%, 92%)****	**96%** (95% CI: 91%, 98%)*** **95%** (95% CI: 94%, 96%)****

Ref Std.: Colonoscopy; ** Ref Std.: Cancer Registry; ***Ref Std-All; ****Ref Std-Positive. Abbreviations: CRC-colorectal cancer

Values used for the Sn and Sp of FIT and gFOBT in the EE

Diagnostic Accuracy Studies

- PHEX Review (Phase 1 and 2)
- Systematic Reviews (k=1)

DOST

FIT and gFOBT

Colorectal Cancer Screening: PHEX Phase 1 and Phase 2

- Reviews were conducted as evidence for development of guidelines
- **Only a rapid review, not a full systematic review**
- ***General methodology:***
  - Searched for existing international CPGs; if good quality and within 5 years → adopt evidence summary
  - Conducted separate systematic search, de novo SR-MA, if needed (based on the results of the appraisal of existing CPGs and ES)
  - Also searched relevant local databases and medical society websites
  - Last search: July 2021
  - Authors of relevant articles were also contacted
  - Studies were appraised for directness, methodological validity, results, and applicability
  - RevMan, STATA, and GRADEPro were used for quantitative synthesis

Colorectal Cancer Screening: PHEX Phase 1 Summary

Recommendation:

*Among **asymptomatic apparently healthy adults aged at least 50**, we recommend to **screen for colorectal cancer using annual FOBT or FIT, followed by colonoscopy, when indicated.** (strong recommendation, high certainty evidence).*

Considerations of the consensus panel:

- Screening has net benefits and uses accurate tests
- Age group was based on prevalence of CRC
- Only gFOBT has more direct evidence on benefits than FIT
- gFOBT requires 3 tests vs FIT that requires only 1
- FOBT, FIT, and colonoscopy are acceptable and feasible
- High cost of colonoscopy and limited number of trained practitioners
- FIT is more accurate than gFOBT

Colorectal Cancer Screening: PHEX Phase 2 Summary

Recommendation:

*Among **average risk and apparently healthy adults**, there is **insufficient evidence** to suggest screening for colorectal cancer using fecal immunochemical test over fecal occult blood test (no recommendation, insufficient evidence)*

Considerations of the consensus panel:

- CRC is a priority health problem
- Majority of panelists favored screening using FIT due to the large benefit, small harm, and diagnostic accuracy of the test.
- Screening using FIT: acceptable and feasible, would probably increase equity, and is with possible important uncertainty or variability in terms of patient values and preferences.
- Other Asian populations use FIT for screening CRC.
- Indirect evidence as studies compared FIT vs no screening

Summary of Findings for PHEX Review

		CRC	
		Pooled Sensitivity	**Pooled Specificity**
Hemoccult SENSA	**gFOBT** (k=2)	**0.50 to 0.79** (95% CI 0.01 to 0.99)* **0.62 to 0.79** (95% CI 0.36 to 0.94)**	**0.87 to 0.98** (95% CI 0.86 to 0.99)* **0.87 to 0.96** (95% CI 0.86 to 0.97)**
OC-Sensor Family	**FIT** (k=9) (20 ug Hb/g) cutoff)	**0.74** (95% CI, 0.64 to 0.83, I2=31.6%)* **0.81** (95% CI 0.74 to 0.88, I2=98.6%)**	**0.94** (95% CI, 0.93 to 0.96, ; I2=96.6%)* **0.95** (95% CI, 0.94 to 0.96, I2=98.5%)**
	FIT (OC Light, k=3) (10 ug Hb/g) cutoff) (2 to 100 ug Hb/g) cutoff)	**0.81** (95% CI, 0.70 to 0.91, I2=0)	**0.93** (95% CI, 0.91 to 0.96, I2=99%)
Other FIT brands	**FIT** (Other brands, k=8) (10 ug Hb/g) cutoff) (2 to 100 ug Hb/g) cutoff)	**0.50 to 0.97** (95% CI 0.90 to 1.00)	**0.83 to 0.97** (95% CI 0.82 to 0.97)

Ref Std.: Colonoscopy, ** Ref Std.: Cancer Registry
Abbreviations: CRC-colorectal cancer

- **Only the range of sensitivities and specificities are reported for gFOBT**
- **The pooled sensitivity and specificity of FIT for different brands are generally within the range of sensitivities from the different studies.**

Colorectal Cancer Screening: PHEX Phase 1 Summary

Recommendation:

*Among **asymptomatic apparently healthy adults aged at least 50**, we recommend to **screen for colorectal cancer using annual FOBT or FIT, followed by colonoscopy, when indicated.** (strong recommendation, high certainty evidence).*

Considerations of the consensus panel:

- Screening has net benefits and uses accurate tests
- Age group was based on prevalence of CRC
- Only gFOBT has more direct evidence on benefits than FIT
- gFOBT requires 3 tests vs FIT that requires only 1
- FOBT, FIT, and colonoscopy are acceptable and feasible
- High cost of colonoscopy and limited number of trained practitioners
- FIT is more accurate than gFOBT

CRC Screening: PHEX Phase 1 Clinical Evidence [Diagnostic Performance]

Performance of gFOBT (PHEX report, based on USPSTF review)

Number of studies	5 prospective, fair quality studies (N=19,742)
Population	Average-risk individuals with ages ranging from 50 to 80 years
Index test	Guaiac-based FOBT
Reference standard	Colonoscopy (2 studies, n=3,503) Cancer registry (3 studies, n=15,969)
Outcomes	Sensitivity and specificity for detecting colorectal carcinoma
Results	(Ref Std: colonoscopy and cancer registry) Range of sensitivities: 0.50 to 0.79 (95% CI 0.01 to 0.99) Range of specificities: 0.87 to 0.98 (95% CI 0.86 to 0.99) Note: No subgroups by age, sex, race, or ethnicity

CRC Screening: PHEX Phase 1 Clinical Evidence [Diagnostic Performance]

Performance of gFOBT - US Preventive Services Task Force Review

Number of studies	5 cross-sectional test-accuracy studies (fair quality), (US, Israel, UK)
Population	Adults 50 years or older (N=range 1,006 to 7,904)
Index test	One-time high sensitivity gFOBT (Brand: Hemoccult Sensa)
Reference standard	Colonoscopy (2 studies, n=3,503) Cancer registry (3 studies, n=15,969)
Outcomes	Sensitivity and specificity for detecting colorectal cancer, advanced adenomas, adenomatous polyps
Results (colonoscopy as ref std)	***CRC (k=2, colonoscopy as ref)*** Range of sensitivities for CRC: 0.50 to 0.75 (95% CI range, 0.09 to 1.0) Range of specificities for CRC: 0.96 to 0.98 (95% CI range, 0.95 to 0.99)
Results (registry follow-up data as ref std)	***CRC (k=2, ff-up as ref)*** Range of sensitivities for CRC: 0.62 to 0.79 (95% CI range, 0.36 to 0.94) Range of specificities for CRC: 0.87 to 0.96 (95% CI range, 0.86 to 0.97) ***Distal CRC (k=2, ff-up and FS as ref)*** Sensitivity for distal CRC: 0.64 (95% CI, 0.36 to 0.86) Specificity for distal CRC: 0.90 (95% CI, 0.89 to 0.91) *Note: No subgroups by age, sex, race, or ethnicity*

CRC Screening: PHEX Phase 1 Clinical Evidence [Diagnostic Performance]

Performance of FIT - US Preventive Services Task Force Review

Number of studies	45 studies (US, Taiwan, Germany, Japan, the Netherlands, South Korea, Spain, Hong Kong, Italy, Denmark, France, Slovenia, Sweden, Israel, UK, Australia, Asia - 28 cross-sectional (n=307 to 9,989; 21,805) - 17 screening programs (n=2,235 to 956,005) - 1 nested case-control (n=516)
Population	Adults age 40 to 50 years
Index test	FIT (Qualitative and quantitative): OC- Sensor Family, other FITs
Reference standard	Colonoscopy for all (k=26) Cancer registries and direct visualization for abnormal FIT (k=19)
Outcomes	Accuracy of detecting of CRC

CRC Screening: PHEX Phase 1 Clinical Evidence [Diagnostic Performance]

Performance of FIT - US Preventive Services Task Force Review

Results	OC-Sensor Family **CRC (ref std: colonoscopy)** ● **For cutoff of 20 µg Hb/g feces, k=9** Sensitivity: 0.74 (95% CI, 0.64 to 0.83; I2=31.6%) Specificity: 0.94 (95% CI, 0.93 to 0.96; I2=96.6%) ● **For cutoff of 15 µg Hb/g feces, k=3** Sensitivity: 0.92 (no 95% CI reported) Specificity: 0.92 (no 95% CI reported) ● **For cutoff of 10 µg Hb/g feces, k=3** Sensitivity: 0.99 (no 95% CI reported) Specificity: 0.90 (no 95% CI reported) **CRC (ref std: cancer registry follow-up), cutoff of 20 µg Hb/g feces, k=8** Sensitivity: 0.81 (95% CI 0.74 to 0.88) Specificity: 0.95 (95% CI, 0.94 to 0.96)

Among the three cutoffs, **10 µg Hb/g feces** has the highest sensitivity and lowest specificity

CRC Screening: PHEX Phase 1 Clinical Evidence [Diagnostic Performance]

Performance of FIT - US Preventive Services Task Force Review

Results

OC-Sensor Family

CRC by location (k=1, ref std: colonoscopy)

- **For cutoff of 20 µg Hb/g feces**
  - Sensitivity (distal CRC): 0.91 [95% CI, 0.88 to 0.93]
  - Sensitivity (proximal CRC): 0.74 [95% CI, 0.66 to 0.80]

CRC by stage (k=2, ref std: cancer registries)

- Sensitivity: decreasing trend as stage increased, but confidence intervals overlapped and one of the studies 2 had a very low number of CRCs (9 Stage I, 3 Stage II, 6 Stage III, 2 Stage IV), no definitive conclusions

CRC by age (k=6, ref std: either colonoscopy or registry)

- No patterns or differences in the sensitivity and specificity among different age groups, although one study demonstrated that programmatic sensitivity and specificity both decreased with age.

CRC by sex (k=2, ref std:either colonoscopy or registry)

- Different test accuracy studies of OC-Sensor to detect CRC had different findings (k=2)
  - Study 1: No differences between male and female subgroups (cutoff: 20 µg Hb/g feces, k=1)
  - Study 2: Increased Sn and decreased Sp in men compared with women (cutoff: 20 µg Hb/g feces, k=1)

CRC by race/ethnicity (k=3, ref std: colonoscopy)

- Comparison of black and white race (k=1), no differences.
- Comparison limited to Alaska Natives (k=1) and ethnic Chinese (k=1), no differences.

CRC Screening: PHEX Phase 1 Clinical Evidence [Diagnostic Performance]

Performance of FIT - US Preventive Services Task Force Review

Results	**<u>Other FITs (k=11)</u>** **CRC (ref std: colonoscopy)** ● **OC-Light, qualitative (cutoff: 10 µg Hb/g feces), (k=3)** Sensitivity: 0.81 (95% CI, 0.70 to 0.91; I2=0%) Specificity: 0.93 (95% CI, 0.91 to 0.96; I2=99.0%) ● **Other FITs (varied cutoffs from 2 to 100 ug Hb/g), (k=8)** Sensitivity range: 0.50 to 0.97 (95% CI range, 0.09 to 1.00) Specificity range: 0.83 to 0.97 (95% CI range, 0.82 to 0.97) **CRC (ref std: cancer registry follow-up)** ● **OC-Hemodia (cutoff range: 2.2 to 20 µg Hb/g feces), (k=2)** Sensitivity: 0.81 to 0.87 (95% CI range, 0.75 to 0.92) ● **Remaining FITs (k=8)** Sensitivity range: 0.69 to 0.90 (95% CI range, 0.45 to 0.94) Specificity range: 0.84 to 0.96 (95% CI range, 0.84 to 0.96).

CRC Screening: PHEX Phase 1 Clinical Evidence [Diagnostic Performance]

Performance of FIT - US Preventive Services Task Force Review

Results	Other FITs **CRC by location (k=5, ref std: either colonoscopy or registry)** ● No clear patterns were identified for distal versus proximal CRC detection **CRC by stage (k=1, ref std: cancer registries)** ● Higher sensitivity for Stage I versus Stage IV detection, however, there were few Stage IV CRC cases (n=13) and the confidence intervals overlapped using OC-Sensor or FOB Gold **CRC by age (k=2, ref std: either colonoscopy or registry)** ● No clear difference in test accuracy by age was found. **CRC by sex (k=2, ref std: registry)** ● No differences using OC-Sensor or FOB Gold ● Sensitivity to detect CRC for females was lower than males at higher cutoffs, but did not differ at lower cutoffs. Using FOB Gold ** No subgroup for race/ethnicity or family history*

Colorectal Cancer Screening: PHEX Phase 2 Summary

Recommendation:

*Among **average risk and apparently healthy adults**, there is **insufficient evidence** to suggest screening for colorectal cancer using fecal immunochemical test over fecal occult blood test (no recommendation, insufficient evidence)*

Considerations of the consensus panel:

- CRC is a priority health problem
- Majority of panelists favored screening using FIT due to the large benefit, small harm, and diagnostic accuracy of the test.
- Screening using FIT: acceptable and feasible, would probably increase equity, and is with possible important uncertainty or variability in terms of patient values and preferences.
- Other Asian populations use FIT for screening CRC.
- Indirect evidence as studies compared FIT vs no screening

CRC Screening: PHEX Phase 2 Clinical Evidence [Diagnostic Performance]

Diagnostic Performance of FIT vs gFOBT

- **Same as previously presented evidence from PHEX Phase 1**

Number of studies	5 prospective, fair-quality studies (N=19,742)
Population	Average-risk individuals with ages ranging from 50 to 80 years
Index test	Guaiac-based FOBT
Reference standard	Colonoscopy (2 studies, n=3,503) Cancer registry (3 studies, n=15,969)
Results	Range of sensitivities for detecting CRC: 0.50 to 0.79 (95% CI 0.01 to 0.99) Range of specificities for detecting CRC: 0.87 to 0.98 (95% CI 0.86 to 0.99) Note: No subgroups by age, sex, race, or ethnicity

CRC Screening: PHEX Phase 2 Clinical Evidence [Diagnostic Performance]

Diagnostic Performance of FIT vs FOBT

- **Same as previously presented evidence from PHEX Phase 1**

Number of studies	9 good quality studies (n=34,352)
Population	Participants 40 or older and were average-risk, excluding those with the first-degree relative with CRC
Index test	**OC-Sensor FIT family** (Polymedco in the US or Eiken Chemical outside the US) Quantitative FIT (cutoff: 20ug Hb/g)
Reference standard	Colonoscopy
Results	Sensitivity for detecting CRC: 74% (95% CI 64% to 83%; I2=31.6%) Specificity for detecting CRC: 94% (95% CI 93% to 96%; I2=96.6%)

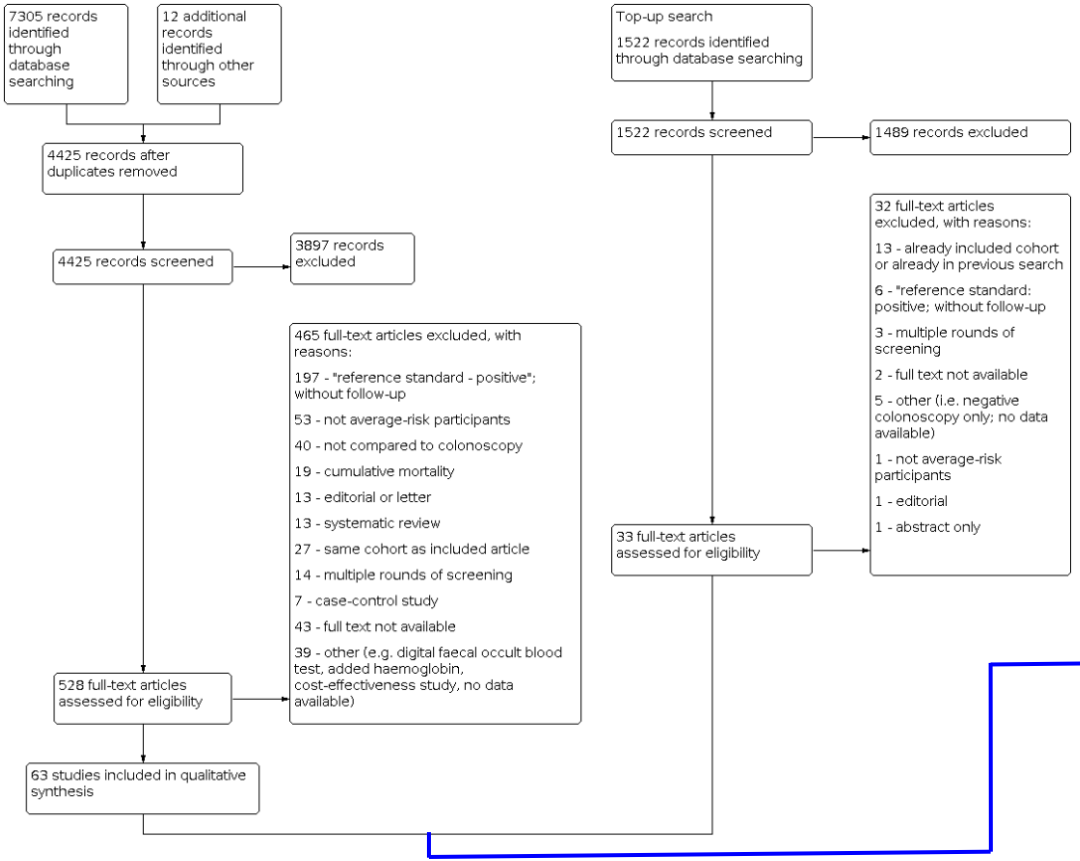
Diagnostic Accuracy Studies

- PHEX Review (Phase 1 and 2)
- Systematic Reviews (k=1)

DOST

FIT and gFOBT

Diagnostic Accuracy Studies (SRs): *Inclusion and Exclusion of Studies, Grobbee et al., 2022*



Inclusion criteria:

- *Prospective and retrospective studies including average-risk individuals invited for colorectal cancer screening*
- *"Reference standard: all": all screenees underwent both the index test and colonoscopy (n = 33)*
- *"Reference standard: positive": only screenees with a positive index test underwent colonoscopy and all screen negative participants were followed for at least one year (n = 30)*

Total included studies for meta-analysis= 63

Reference standard-all= 33

Reference standard-positive=30

Study Characteristics of Diagnostic Accuracy Studies on CRC Screening

Guaiac-based faecal occult blood tests versus faecal immunochemical tests for CRC in average-risk individuals ***Grobbee et al., 2022*** **[Part 1 of 2]**	
Study Settings	US, Europe, Asia
Study Design included	Diagnostic accuracy studies (excluded: diagnostic case control studies); k=63 **a) Reference std all:** all participants underwent both the index test and the reference standard; k=33 **b) Reference std positive:** participants with a positive index test = reference standard; negative index test = one year ff-up to identify development of interval carcinomas; k=30
Inclusive Search dates	Last search date: 25 June 2019; top-up search: 14 Sep 2021
Population	Asymptomatic average-risk individuals aged 40 years and above a) Reference std all: 104,640 participants b) Reference std positive: 3,664,934 participants

Study Characteristics of Diagnostic Accuracy Studies on CRC Screening

Guaiac-based faecal occult blood tests versus faecal immunochemical tests for CRC in average-risk individuals ***Grobbee et al., 2022*** **[Part 1 of 2]**

Intervention	FIT (both qualitative and quantitative) - 1 sample gFOBT - 3 samples per test **FIT** SD Bioline OC-Sensor Immocare FOBGold OC-Light RIDASCREEN Hb ELISA Immunodiagnostik Clearview Quidel Quickvue Iatro Hemocheck **gFOBT** Hemosure ACON Laboratories Abon Biopharm OC-Micro OC Hemodia Hemoccult Hemoccult II Hemocare
Comparator	• Colonoscopy as the primary reference standard (in case of incomplete colonoscopy, CT-colonography or double-contrast barium enema as ref std were accepted) • 1 year follow-up to assess for the development of interval carcinomas
Outcomes	Target condition: Colorectal cancer and advanced neoplasia* (ref std all); colorectal cancer** (ref std positive) Main outcome measure: Sensitivity and specificity for early detection of bleeding colorectal neoplasia

****Advance neoplasia (AN)** is defined as colorectal cancer (CRC) or advanced adenomas (size of 10 mm or larger, and/or at least 25% villous histology, and/or high grade dysplasia).*
*****Colorectal cancer (CRC)** is the invasion of malignant cells beyond the lamina muscularis mucosa*

AMSTAR of Grobbee et al. 2022

Critical flaw: 1

- **No assessment of publication bias**
  - Explanation from the review: *"Investigation of publication bias in diagnostic test accuracy studies has proven to be problematic because many studies are done without ethical approval or study registration (Deeks, 2005; Leeflang 2008; Song 2002). Therefore, identification of studies from registration until final publication of the results is not possible (Leeflang, 2008). Thus, we have not assessed reporting bias in this review."*

Non-critical Weakness: 1

- **No reported sources of funding for individual studies included in the review**

Overall Confidence Rating	Low

Results of *Grobbee et al. 2022*

Outcome: Colorectal cancer (CRC)* (Reference std all)

	Range in studies	Pooled estimate
Sensitivity		
gFOBT	13% to 100%	39% (95%CI: 25%, 55%)
FIT (10 ug Hb/g) cutoff	0% to 100%	76% (95%CI: 57%, 88%)
FIT (20 ug Hb/g) cutoff	9% to 100%	65% (95%CI: 46%, 80%)
Specificity		
gFOBT	80% to 98%	94% (95%CI: 91%, 96%)
FIT (10 ug Hb/g) cutoff	87% to 99%	94% (95%CI: 87%, 97%)
FIT (20 ug Hb/g) cutoff	88% to 96%	96% (95%CI: 91%, 98%)

Sensitivity of gFOBT was significantly lower than FIT for both cutoffs (P=0.001, P=0.035)

No significant differences in specificities between FIT and gFOBT

Results of *Grobbee et al. 2022*

Heterogeneity analysis

- No significant difference between studies using a quantitative or a qualitative FIT for AN or CRC.
- Did not perform heterogeneity analyses for the number of stools per screening round or gender as there was insufficient heterogeneity between the studies.

Sensitivity analysis

- Excluded high ROB studies → FITs remained significantly superior in the detection of AN and CRC compared to gFOBTs.

Results of *Grobbee et al. 2022*

Outcome: Colorectal cancer (CRC)* (Reference std positive)

	Range in studies	Pooled estimate
Sensitivity		
gFOBT	10% to 67%	59% (95%CI: 55% to 64%),
FIT (10 ug Hb/g) cutoff	75% to 100%	89% (95%CI: 80% to 95%)
FIT (20 ug Hb/g) cutoff	63% to 94%	89% (95%CI: 85% to 92%)
Specificity		
gFOBT	96% to 99%	98% (95% CI: 98% to 99%)
FIT (10 ug Hb/g) cutoff	88% to 98%	94% (95%CI: 92% to 95%
FIT (20 ug Hb/g) cutoff		95% (95%CI: 94% to 96%)

Sensitivity of gFOBT was significantly lower than FIT for both cutoffs (P=0.001, P=0.035)

Specificity of gFOBT significantly higher than FIT (P<0.001)

Results of *Grobbee et al. 2022*

Heterogeneity analysis

- No significant difference between studies using a quantitative or a qualitative FIT for AN or CRC.
- Did not perform heterogeneity analyses for the number of stools per screening since all studies for gFOBT used 3 stools.
- Heterogeneity analyses not possible due to convergence difficulties: gender for FITs, and number of stools for FITs.

Sensitivity analysis

- Excluded high ROB studies → FITs remained significantly superior in the detection of AN and CRC compared to gFOBTs.
- Excluded studies that did not describe the proportion of index test positives that underwent the reference standard (i.e. colonoscopy) → FITs remained significantly superior to gFOBTs

Summary of Findings for Diagnostic Accuracy Study by *Grobbee et al. 2022*

	CRC	
	Sensitivity	**Specificity**
gFOBT	**39%** (95% CI: 25%, 55%)* **59%** (95% CI: 55%, 64%)**	**94%** (95% CI: 91%, 96%)* **98%** (95% CI: 98%, 99%)**
FIT (10 ug Hb/g) cutoff	**76%** (95% CI: 57%, 88%)* **89%** (95% CI: 80%, 95%)**	**94%** (95% CI: 87%, 97%)* **94%** (95% CI: 92%, 95%)**
FIT (20 ug Hb/g) cutoff	**65%** (95% CI: 46%, 80%)* **89%** (95% CI: 85%, 92%)**	**96%** (95% CI: 91%, 98%)* **95%** (95% CI: 94%, 96%)**

Ref Std-All , **Ref Std-Positive

FIT is more sensitive than gFOBT in detecting CRC but with almost similar specificity values.

AMSTAR-2 Quality Appraisal of PHEX 1 & 2

Critical flaw: 7

- No protocol, missing info (RoB and inclusion/exclusion criteria) in methods
- Did not use a comprehensive search strategy
- Did not provide a list of excluded studies and justify the exclusions
- No RoB results included in the appendix nor was confounding and selection bias included in the measurement of RoB.
- Did not explain the process of combining data from RCTS in the meta-analysis and estimates from NRSIs that were adjusted for confounding.
- Did not account for RoB in individual studies when interpreting/discussing the results of the review
- Did not assess publication bias

Non-critical Weakness: 3

- No explanation for study design
- Did not report source of funding for studies included
- Did not assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis

Overall Confidence Rating	CRITICALLY LOW

Summary of Findings from the *PHEX Review* and *Grobbee et al., 2022 (SR)*

	Brand	Type of Stool Test (No. of studies, cutoff level)	CRC	
			Sensitivity	Specificity
PHEX Review *Note: For gFOBT, only range was provided*	Hemoccult SENSA	**gFOBT** (k=2)	**50% to 79%** (95% CI 1% to 99%)* **62% to 79%** (95% CI 36% to 94%)**	**87% to 98%** (95% CI 86% to 99%)* **87% to 96%** (95% CI 86% to 97%)**
	OC-Sensor Family	**FIT** (k=9) (20 ug Hb/g) cutoff)	**74%** (95% CI, 64% to 83%, I2=31.6%)* **81%** (95% CI 74% to 88%, I2=98.6%)**	**94%** (95% CI, 93% to 96%, ; I2=96.6%)* **95%** (95% CI, 94% to 96%, I2=98.5%)**
	Other FIT brands	**FIT (OC Light, k=3)** (10 ug Hb/g) cutoff) (2 to 100 ug Hb/g) cutoff)	**81%** (95% CI, 70% to 91%, I2=0)	**93%** (95% CI, 91% to 96%, I2=99%)
		FIT (Other brands, k=8) (10 ug Hb/g) cutoff) (2 to 100 ug Hb/g) cutoff)	**50% to 97%** (95% CI 90% to 100%)	**83% to 97%** (95% CI 82% to 97%)
Grobbee et al. 2022 *(Note: heterogeneity analyses were not conducted due to insufficient heterogeneity between studies and convergence difficulties)*	Different Brands	**gFOBT** (k=9***, k=12****)	**39%** (95% CI: 25%, 55%)*** **59%** (95% CI: 55%, 64%)****	**94%** (95% CI: 91%, 96%)*** **98%** (95% CI: 98%, 99%)****
	Different Brands	**FIT** (k=13***, k=23**** (10 ug Hb/g) cutoff	**76%** (95% CI: 57%, 88%)*** **89%** (95% CI: 80%, 95%)****	**94%** (95% CI: 87%, 97%)*** **94%** (95% CI: 92%, 95%)****
		FIT (k=11***, k=23**** (20 ug Hb/g) cutoff	**65%** (95% CI: 46%, 80%)*** **89%** (95% CI: 85%, 92%)****	**96%** (95% CI: 91%, 98%)*** **95%** (95% CI: 94%, 96%)****

Ref Std.: Colonoscopy; ** Ref Std.: Cancer Registry; ***Ref Std-All; ****Ref Std-Positive. Abbreviations: CRC-colorectal cancer

C2: Diagnostic Accuracy

RQ2: What are the performance characteristics of FIT (vs colonoscopy as the reference standard) for screening for colorectal cancer among apparently healthy adults 50 years old and above, compared to guaiac fecal occult blood test (gFOBT)?

HTAC Judgment: According to the *PHEX review* (critically low quality) the resulting pooled sensitivity (**81%**, 95% CI, 70% to 91%, I^2=0) and specificity (**93%** ,95% CI, 91% to 96%, I^2=99%) of qualitative FIT (estimated from one brand) is higher than the range of sensitivities of gFOBT and within the range of specificities of gFOBT. Meanwhile, the resulting ranges of specificities and sensitivities of the different brands of FIT (both quantitative and qualitative) for the detection of colorectal cancer are generally within the range of sensitivities of gFOBT from the different studies.

Based on one systematic review with low quality (*Grobbee et al. 2022*), FIT (both quantitative and qualitative) has higher sensitivity of **76% (95% CI: 57%, 88%)** at 10 ug Hb/g cutoff and **65% (95% CI: 46%, 80%)** at 20 ug Hb/g cutoff than gFOBT which has sensitivity of **39% (95% CI: 25%, 55%)** in detecting colorectal cancer among average-risk individuals. In terms of specificity, similar values were provided at **94% (95% CI: 91%, 96%), 94% (95% CI: 87%, 97%)**, and **96% (95% CI: 91%, 98%)** for gFOBT and FIT (10 and 20 ug Hb/g cutoffs), respectively.

Overall, based on the PHEX review (local CPG) and one systematic review (low quality) reviewed, FIT offers higher sensitivity but similar specificity than gFOBT in detecting colorectal cancer among average-risk individuals.

FIT VS GFOBT

EFFECTIVENESS

RQ3. What is the effectiveness of FIT for screening for colorectal cancer among apparently healthy adults 50 years old and above compared to gFOBT in the reduction of the risk of developing CRC and CRC-specific mortality?

Effectiveness Studies

- PHEX Review (Phase 1)
- Systematic Review (k=1)

DOST

FIT and gFOBT

Colorectal Cancer Screening: PHEX Phase 1 Summary

Recommendation:

*Among **asymptomatic apparently healthy adults aged at least 50**, we recommend to **screen for colorectal cancer using annual FOBT or FIT, followed by colonoscopy, when indicated.** (strong recommendation, high certainty evidence).*

Considerations of the consensus panel:

- Screening has net benefits and uses accurate tests
- Age group was based on prevalence of CRC
- Only gFOBT has more direct evidence on benefits than FIT
- gFOBT requires 3 tests vs FIT that requires only 1
- FOBT, FIT, and colonoscopy are acceptable and feasible
- High cost of colonoscopy and limited number of trained practitioners
- FIT is more accurate than gFOBT

CRC Screening: PHEX Phase 1 Clinical Evidence [Benefits and Harms]

Benefits of gFOBT

Number of studies	5 RCTs (n=404,396)
Interventions	Screening with gFOBT (Hemoccult II) vs no screening
Outcomes	CRC-specific mortality
Rounds of screening	2 to 9 rounds
Years of follow-up	11 to 30 years
Results	Annual and biennial screening: RR 0.82 (95% CI 0.76 to 0.89) Biennial screening only: RR 0.87 (95% CI 0.82 to 0.91) Annual screening only: RR 0.67 (95% CI 0.56 to 0.80)

CRC Screening: PHEX Phase 1 Clinical Evidence [Benefits and Harms]

Benefits of FIT

EXCLUDED

Number of studies	1 fair quality prospective cohort study (N=5,417,699)
Population	Participants aged 50 to 79 years
Interventions	Biennial screening with FIT vs no screening
Outcomes	CRC-specific mortality
Results	Biennial screening: RR 0.9 (95% CI 0.84 to 0.95)

Note: Only study for FIT but was excluded by the jSC since I and C are not relevant to our research question

CRC Screening: PHEX Phase 2 Clinical Evidence [Benefits and Harms]

Benefits of FIT

- **All-cause mortality and CRC-specific mortality**
  - No RCTs for FIT
  - Biennial screening with FIT using either OC-Sensor or HM Jack done 1–3 times was associated with lower CRC-specific mortality after a 6-year follow-up (adjusted RR 0.90, 95% CI 0.84 to 0.95)
- **Adverse events - Serious Bleeding and Perforations**
  - No studies, non-invasive test
  - Possible harm: diagnostic inaccuracy or eventual harm from follow-up tests like scoping procedures
  - Risk of serious bleeding and perforations are same as PHEX Phase 1

CRC Screening: PHEX Phase 1 Clinical Evidence [Benefits and Harms]

Harms of FOBT screening

- **No harms directly related to testing for fecal occult blood**
- **Complications arising from diagnostic colonoscopies following an abnormal stool test**

Number of studies	11 studies from the US Preventive Task Force Review (N=78,793) (cannot identify these studies)
Population	Not specified
Intervention	Diagnostic colonoscopy conducted after abnormal FOBT/FIT (n=78,793)
Outcomes	Risk of serious bleeding and risk of perforations
Results	Risk of serious bleeding: 7.5 per 10,000 procedures (95% CI 7.6 to 27.5; I2=89.3%) Risk of perforations: 5.7 per 10,000 procedures (95% CI 2.8 to 9.7; I2=47.8%)

Effectiveness Studies

- PHEX Review (Phase 1 and 2)
- Systematic Reviews (k=1)

FIT and gFOBT

DOST

CRC Screening: *Methodology and Results of Search*

Date of Search: August 30; October 24 2023
Search filter: Systematic reviews, meta-analysis
Date filter: 2021-present; No date restriction

Number of detected studies considered (after title and abstract screening), k=8	
Excluded Studies (k=7)	Reason for exclusion: ● No effectiveness of FOBT/FIT in terms of incidence and mortality, biennial and quantitative FIT. gFOBT vs FIT outcomes were diagnostic accuracy (k=1) ● No outcomes for effectiveness (k=2) ● Biennial FIT and C is no screening (k=2) ● C is no screening (k=1) ● C is no screening; FIT only used simulation studies, low quality of evidence (k=1)
Included Studies (k=1)	Reason for inclusion: ● Low quality NMA comparing the effectiveness of different screening strategies [2/4 annual and 2/4 biennial; 2/4 qualitative, 1/4 quantitative, 1/4 cannot be determined/did not indicate]

CRC Screening: *Methodology and Results of Search*

Date of Search: October 12 ; October 25, 2023
Search filter: Randomized controlled trial, observational study, clinical study, clinical trial
Date filter: 2021-present; 2016-2021

Number of detected studies considered (after title and abstract screening) k=4	
Excluded primary studies (k= 4)	Reason for exclusion: ● Intervention is biennial screening instead of annual (k=4) ● Intervention is quantitative FIT instead of qualitative (k=4) ● Comparator is no screening instead of gFOBT (k=4)
Included primary studies	None

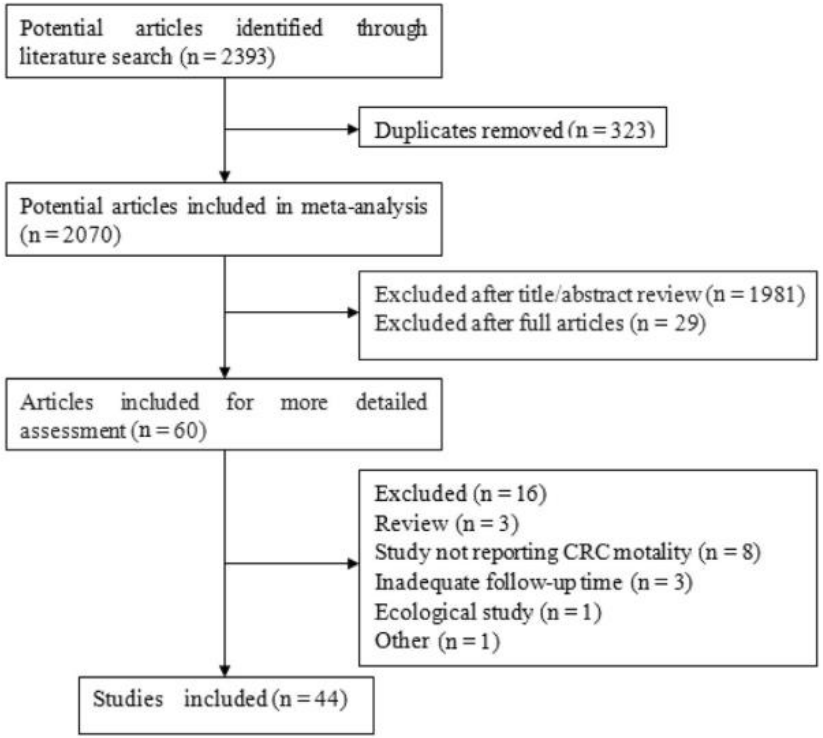
Study Characteristics: Effectiveness of FIT Screening vs gFOBT screening [1 of 2]

Effectiveness of Screening Modalities in Colorectal Cancer: A Network Meta-Analysis (*Zhang et al. 2017*)	
Study Settings	Switzerland, Italy, Denmark, Norway, France, US, Canada, UK, Japan, Taiwan
Study Designs included	Published RCTs, Cohort, Quasi-experimental, Case-control studies, and Meta-analyses
Inclusive Search dates	January 1992 - March 2016
Population	General population at average risk for CRC: gFOBT vs no screening = 2,264,603 participants FIT vs no screening = 5,493,865 participants FS vs no screening = 950,452 participants Colonoscopy vs no screening = 2,858,087 participants FS with FOBT vs no screening = 98,792 participants

Study Characteristics: Effectiveness of FIT Screening vs gFOBT screening [2 of 2]

Effectiveness of Screening Modalities in Colorectal Cancer: A Network Meta-Analysis (*Zhang et al. 2017*)	
Intervention	gFOBT, FIT, FS, Colonoscopy, FS with FOBT
Comparator	No screening
Outcomes	CRC* incidence or mortality
Follow-up Period	Range: gFOBT: 4.5 - 30 years FIT: 6 - 13.1 years FS: 6 - 13.1 years Colonoscopy: 5.7 - 15.8 years FS with FOBT: 10.9 years
***Colorectal cancer (CRC)** is one of the most frequently diagnosed malignancies in the world.*	

Effectiveness Studies: Inclusion and Exclusion of Studies, Zhang et al. 2017



Inclusion criteria:

- Study design: published RCTs, observational studies, and cohort studies
- Studies with 4 years of follow-up (for RCT and cohort studies)
- Outcome: mortality due to CRC
- Relative risk (RR), odds ratio (OR), or hazard ratio estimated with 95% CI or sufficient data to calculate these were reported
- Studies with reported number of events and total number of participants
- Assessed the effects of colonoscopy, gFOBT, FIT, FS, CT colonography, or some combination versus no screening on CRC incidence or mortality, or both in the general population at average risk for CRC.

Total included studies= 44

Critical appraisal (Jansen et al., 2014 NMA Tool): Zhang et al., 2017

Domain	Judgment	Remarks
Relevance	Relevant	The assessors deem that the SR is applicable to our setting because it matches our PICO, the included interventions of interest (FIT and gFOBT) studied are recommended by local medical societies for screening of CRC, and Asian studies were included
Evidence base used	Weakness	Systematic differences between studies were not considered; and they did not look at the risk of bias of included studies
Analysis	Fatal flaw	Did not preserve within study randomization and did not minimize bias in differences in effect modifiers
Reporting quality and transparency	Weakness	The assessors deem that discussing the results along with the impact of patient characteristics is important in the analysis, which the review did not do.

Critical appraisal (Jansen et al., 2014 NMA Tool): Zhang et al., 2017

Domain	Judgment	Remarks
Conclusion / Interpretation	Weakness	Concerns on the methodology of the NMA that affects the credibility of the conclusion of the study: - No ROB of individual studies - Did not describe the timing of the intervention (ex. If annual or biennial screening with the FOBT) - Did not have subgroup analysis for timing of the screening if there are differences, no subgroup analysis for ff-up period - Combined RCT and non-RCTs in the MA and NMA - Only gFOBT and FS have RCTs (and additional observational studies) while the rest of the screening modalities only rely on observational studies.
Conflict of interest	Strength	The authors declared no COI
OVERALL CREDIBILITY	**"Insufficient credibility" due to weaknesses in the analysis, evidence base used, reporting quality and transparency, interpretation of the results and conclusion. Additionally, there is a fatal flaw on the statistical method used in combining and comparing the results of the individual studies.**	

Results of *Zhang et al. 2017*

Pairwise meta-analysis

	CRC Mortality RR (95% CI)	CRC Incidence RR (95% CI)
gFOBT vs no screening	0.86 (95%CI, 0.82 to 0.90)	0.99 (95% CI, 0.73 to 0.90)
FIT vs no screening	0.41 (95% CI, 0.29 to 0.59)	0.79 (95% CI, 0.69 to 0.92)
FS vs no screening	0.67 (95% CI, 0.58 to 0.78)	0.78 (95% CI, 0.72 to 0.84)
Colonoscopy vs no screening	0.39 (95% CI, 0.31 to 0.50)	0.43 (95% CI, 0.30 to 0.60)
FS+FOBT vs no screening	0.62 (95% CI, 0.42 to 0.91	0.88 (95% CI, 0.74 to 1.05)

Results of *Zhang et al. 2017*

Network meta-analysis

	CRC Mortality RR (95% CI)	Interpretation
FIT vs annual or biennial gFOBT	0.21 (0.09 to 0.6)	Significant difference
Colonoscopy vs gFOBT	0.25 (0.13 to 0.54)	Significant difference
Colonoscopy vs FIT	0.97 (0.43 to 3.07)	No significant difference
Colonoscopy vs FS	0.46 (0.22 to 1.14)	No significant difference
Colonoscopy vs FS+gFOBT	0.67 (0.08 to 2.54)	No significant difference
FS vs gFOBT	0.48 (0.25 to 1.05)	No significant difference
FIT vs FS+gFOBT	0.63 (0.07 to 2.57)	No significant difference

Results of *Zhang et al. 2017*

Rank probability analysis

Table 2 Rank Probability Analysis of Screening Tests on Colorectal Cancer Mortality

Treatment	SUCRA	SD	2.50%	Median	97.50%
gFOBT	10.1	0.1331	0	0	0.4
FIT	62.8	0.1502	0	0.6	1
FS	75.7	0.1802	0	0.8	1
Colonoscopy	94.6	0.09786	1	1	1
FS With FOBT	33.6	0.2495	0	0.4	0.8
No Intervention	23.2	0.1284	0	0.2	0.4

Abbreviations: FIT = fecal immunohistochemical testing; FOBT = fecal occult blood testing; FS = flexible sigmoidoscopy; gFOBT = guaiac fecal occult blood testing; SUCRA = surface under the cumulative ranking.

Interpretation: Colonoscopy had a 94.6% probability of being the most effective test to reduce CRC mortality. **FIT came in third with a rank probability of 62.8% for being the most effective test to reduce CRC mortality**, FS and FOBT was fourth with a rank probability of 33.5% while **gFOBT alone came in last (sixth) with 10.1%**.

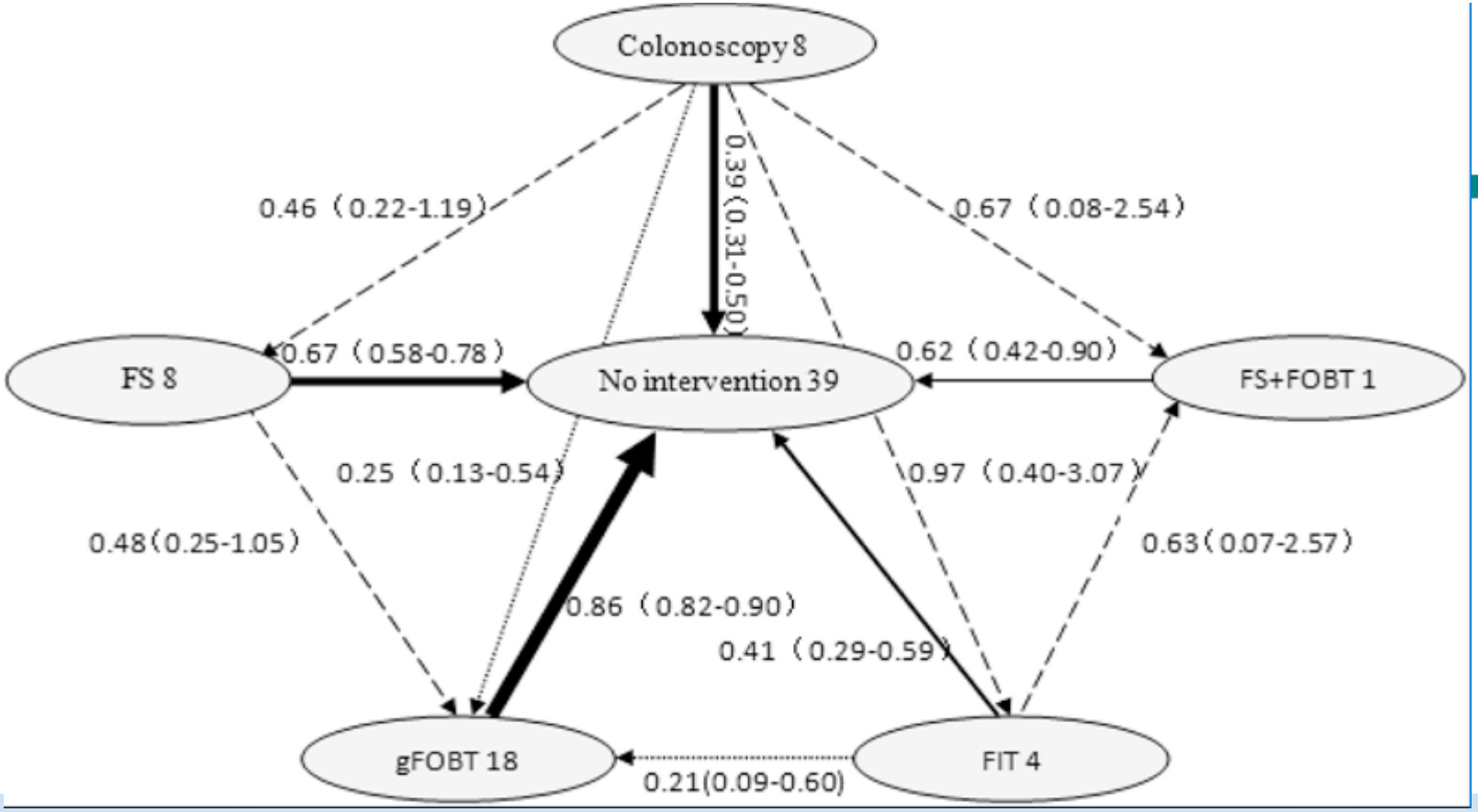


Fig. 5 Evidence Network of the Effect of Screening Methods on Colorectal Cancer Mortality. General Meta-analysis–Generated Direct Comparisons are Denoted by Solid Lines, and NMA-Generated Indirect Comparisons are Denoted by Dashed Lines and Those with Statistical Significance are Denoted by Short Dashed Lines, Direction of the Arrow Denotes Superiority. Values in Parenthesis Indicate 95% Confidence Interval

C2: Clinical Effectiveness

RQ3: What is the effectiveness of FIT for screening for colorectal cancer among apparently healthy adults 50 years old and above compared to gFOBT in the reduction of the risk of developing CRC and CRC-specific mortality?

HTAC Judgment: Compared to no screening, FIT screening reduced the risk of CRC-specific mortality significantly by **59% (RR 0.41, 95%CI 0.29 to 0.59)** based on one network meta-analysis (rated as "of insufficient credibility") of RCTs, cohort studies, quasi-experimental studies, case-control studies, and meta-analysis (Zhang et al, 2017). On the other hand, gFOBT screening reduced the risk of CRC-specific mortality by **14% (RR 0.86, 95% CI 0.82 to 0.90)** based on the same NMA. FIT was found to significantly reduce the risk of CRC-specific mortality by **79% (RR 0.21, 95% CI 0.09 to 0.6)** compared to annual/biennial gFOBT (Zhang et al, 2017).

As for the effectiveness of screening on CRC incidence compared to no screening, FIT reduced the risk of developing CRC by **21% (RR 0.79, 95% CI 0.69 to 0.92)**, while gFOBT screening reduced the risk of developing CRC **by 1% (RR 0.99, 95% CI 0.73 to 0.90)** based on one NMA (Zhang et al, 2017).

Overall, based on the results of one NMA, FIT and gFOBT have been found to be more effective than no screening. Moreover, it was found that FIT significantly decreased CRC-mortality compared to gFOBT.

GUIDELINE RECOMMENDATIONS ON FIT AND gFOBT

RQ4. What are the recommendations and guidelines of HTA agencies and ministries of health on the use of FIT for screening for colorectal cancer?

Summary of Health Technology Agencies (HTA) Recommendations (*n=10*)

1 Recommended iFOBT/FIT	**8 No Recommendations**	**1 Excluded**
MAHTAS (2021)	**EUnetHTA** **Australia MSAC** **CADTH** **China NHEI** **InaHTAC** **Singapore ACE** **South Korea NECA** **HITAP**	**UK NICE** ***Excluded due to differences in population (symptomatic individuals)**

MAHTAS Assessment (2021)

Policy Question

1. Should iFOBT be used in Malaysia as a screening test for CRC?
2. Which test method (qualitative or quantitative) for iFOBT is the most suitable to be used for CRC screening?

Considerations:

- Sensitivity and specificity of iFOBT varies with the cut-off points or positivity threshold of haemoglobin (fair level evidence) → cutoff points in the studies were between 100 to 150 ng/mL
- Screening programme using iFOBT can be effective for the ff:
  - Prevention of advanced CRC from 28.0% to 46.0%
  - Reduced mortality from 23.0% to 60.0%
- iFOBT or FIT was cost-effective in comparison with no screening (looked at CE studies in Canada and Taiwan)

MaHTAS Recommendations (2021)

- iFOBT can be used in Malaysia as a screening test for CRC
- Fully automated (quantitative) iFOBT assay
  - Highly desirable for a screening programme:
    - Large number of tests to be done
    - Involving large number of laboratories
- Recommended cut-off points between from 100 ng/ml to 150 ng/ml.
- Two-day faecal collection method more cost-effective vs three-day faecal collection method

Summary of Ministries of Health and Government Agencies Recommendations (*n=15*)

4 Recommended both FIT and gFOBT	**9** Recommended FIT only	**1** Did not specify whether gFOBT or FIT is recommended	**1** No Recommendation
• ***US CDC****** • ***Philippines****** • ***Canada Task Force and Public Health Canada****** • ***Singapore***** ***Note:*** *The recommendations did not specify a screening test for a particular subgroup*	• ***South Korea******** • ***UK**** • ***Australia**** • ***Malaysia**** • ***China/China CDC**** • ***European Countries and European CDC**** • ***New Zealand**** • ***Thailand MOH**** • ***Japan Ministry of Health Labor and Welfare*****	• ***Vietnam***	• ***Indonesia MOH***

***Qualitative FIT, **Quantitative FIT, *** Did not specify if Qualitative or Quantitative FIT, ****Either Qualitative or Quantitative FIT**

Summary of recommendation (BOTH FIT and gFOBT) from ministries / government agencies - *POPULATION*

Country and Agency	Population
United States (CDC) (2021)	• Adults **45 years and older** who *do not have signs or symptoms* of colorectal cancer and who are at *average risk* for colorectal cancer (selectively screen for 76-85 y.o.)
Philippines (DOH) (2022)	• Adults **50 years of age** and above with *average risk factor (Not recommended after 85 years old).*
Canada Task Force on Preventive Health (2016)	• Adults aged **≥50 years** who are *not at high risk* for colorectal cancer (CRC) [strong recom for 60-74 years; weak recom 50-59] (Stop screening at 75 y.o.)
Singapore Ministry of Health (2010)	• *Average risk* starting at ***50 years***

Summary of recommendation (FIT only) from ministries / government agencies - *POPULATION*

Country and Agency	Population
South Korea Ministry of Health and Welfare (2023)	• All individuals (men and women) **aged 50 years and above**
Australia Department of Health and Aged Care (2023)	• Adults **50-74 years old** *without signs or symptoms* of bowel cancer
Malaysia Ministry of Health (2021)	• *Asymptomatic* individuals aged **50-75 years**
China (National Cancer Center of China) (2022)	• Adults aged **50** (for *low and medium risk patients*) **until 75 years** of age
European Health Union (2022)	• Individuals **50-74 years old**
United Kingdom National Health Service (2021)	• Everyone aged **60-74 years** who is registered, with a general practitioner and lives in England
New Zealand Ministry of Health (2023)	• Eligible New Zealanders, aged **60-74 years**

Summary of recommendation (BOTH gFOBTand FIT) from ministries / government agencies - *SCREENING STRATEGY, TIMING, and RATIONALE* [1 of 2]

Country	Screening strategy	Timing	Rationale
United States (2021)	**High-sensitivity gFOBT** **FIT**	**gFOBT/ FIT:** annually	*"RCTs demonstrate direct evidence of decreased deaths from colorectal cancer when screening with non–high sensitivity gFOBT is performed."* *"gFOBT more difficult to administer"*
Philippines (2022)	**gFOBT** **FIT**	**gFOBT/FIT:** annually	No rationale for recommending both but choice should be discussed with patient regarding preference and availability

Summary of recommendation (BOTH gFOBT and FIT) from ministries / government agencies - *SCREENING STRATEGY, TIMING, and RATIONALE* [2 of 2]

Country	Screening strategy	Timing	Rationale
Canada (2016)	FOBT (either gFOBT or FIT)	Every two years	*"There was insufficient data in our included studies to be able to determine the difference in the clinical benefits for the various screening tests, or by subgroups that may influence the underlying risk of colorectal cancer."*
Singapore (2010)	FOBT (preference for FIT) *gFOBT: 3 specimens on consecutive days *FIT: 2 specimens on 2 separate days	Annually	*"FIT is more sensitive than guaiac tests in the detection of colorectal cancer, and is the recommended type of stool testing."*

Summary of recommendation (FIT only) from ministries / government agencies - *SCREENING STRATEGY, TIMING, and RATIONALE* [1 of 2]

Country	Screening strategy	Timing	Rationale
South Korea (2023)	Immunochemical FOBT (iFOBT)	Annual	No reason given for choice of screening strategy
United Kingdom (2021)	FIT	Biennial	*"FIT kit is quicker to use and was shown to have an increased uptake than the previous bowel cancer screening home testing kit (gFOBT: Hema-screen). Generates fewer false positives and finds more polyps"*
Australia (2023)	iFOBT	Biennial	*"FIT has been clinically proven to be a sensitive and reliable test for CRC screening"*

Summary of recommendation (FIT only) from ministries / government agencies - *SCREENING STRATEGY, TIMING, and RATIONALE* [2 of 2]

Country	Screening strategy	Timing	Rationale
Malaysia (2021)	iFOBT	Biennial	No reason given
China (2022)	FIT	None mentioned	None mentioned
EU countries (2022)	Quantitative FIT	None mentioned	None mentioned
New Zealand (2023)	FIT	Biennial	None mentioned

Summary of recommendation from ministries / government agencies - *CRITERIA FOR POSITIVE RESULT and RECOMMENDATION* (n=10)

Country	Criteria for positive result	Recommendation
United States (2021), Canada (2016), Singapore (2010), Europe (2022), Malaysia (2021)*	None mentioned	Colonoscopy
South Korea (2023)	None mentioned	Colonoscopy or double contrast barium enema if with positive FIT
United Kingdom (2021) Australia (2023)	20 micrograms or more of Hgb/g of stool found in 1 or 2 of the samples sent	Visit physician; undergo colonoscopy
New Zealand (2023)	None mentioned	●Complete colonoscopy or CTC within 45 working days of (+) FIT ●Complete colonoscopy or CTC within 60 working days of positive FIT result
Philippines (2022), China (2023)	None mentioned	None mentioned

Summary of recommendation from ministries / government agencies - *CRITERIA FOR NEGATIVE SCREEN and RECOMMENDATION* (n=10)

Country	Criteria for negative screen	Recommendation
United States (2021) ***Philippines (2022)*** ***Singapore (2010)*** ***South Korea (2023)***	None mentioned	Repeat test annually
Canada (2016) ***United Kingdom (2021)*** ***Australia (2023)*** ***Malaysia (2021)*** ***New Zealand (2023)***		Repeat test biennially
Europe (2022) ***China (2022)***		None mentioned

Summary of Health Organizations and Medical Societies Recommendations Reviewed (*n=20*)

6 Recommended both FIT and gFOBT	6 Recommended only FIT	8 No Recommendations
• *American Cancer Society* • *National Comprehensive Cancer Network* • *Canadian Association of Gastroenterology* • *Philippine Society of Medical Oncology* • *Philippine Society of Gastroenterology and Philippine Society of Digestive Endoscopy* • *Health Canada*	• *U.S. Multi-Society Task Force on Colorectal Cancer (FIT)* • *Royal Australian College of General Practitioners (FIT)* • *New Zealand Cancer Control Agency (FIT)* • *Japanese Association of Gastrointestinal Cancer Screening (FIT)* • *Korea Medical Association (FIT)* • *Malaysian Medical Societies (FIT)*	• *UK* • *Singapore* • *Indonesia* • *Thailand* • *Global Society* • *Europe* • *Vietnam* • *IARC (WHO)*

Recommendation from Health Organizations and Medical Societies

- Scoping was performed among health organizations and medical societies which recommend colorectal cancer screening. However, only the following organizations gave reasons for choosing FIT over gFOBT:
  - Royal Australian College of General Practitioners stated that FIT is more sensitive and specific than gFOBT
  - Canadian Association of Gastroenterology stated that while they endorse both, they prefer FIT because it is "*superior in terms of patient uptake and sensitivity for CRC and advanced adenomas while having similar specificity and positive predictive value as gFOBT*"
  - Philippine Society of Gastroenterology and Philippine Society of Digestive Endoscopy endorsed both but prefer FIT because it is better in detecting adenomas and has no dietary restrictions which improves patient compliance

Summary of Guidelines and Recommendations

Recommended both FIT and gFOBT	***Recommended FIT only***	***Recommended FOBT but did not specify (if gFOBT or FIT)***	***No Recommendation***
4 MOHs and Government Agencies **6** Health Organizations and Medical Societies	**1** HTA Agency **9** MOHs and Government Agencies **6** Health Organizations and Medical Societies	**1** MOH	**8** HTA Agencies **1** MOHs and Government Agencies **8** Health Organizations and Medical Societies

HTA agencies scoped: k=10 (Excluded recommendation: k=1)
MOH and government agencies scoped: k=15
Health Organizations and Medical Societies scoped: k=20

C2: Guidelines and Recommendations for FIT and gFOBT

RQ4: What are the recommendations and guidelines of HTA agencies and ministries of health on the use of FIT and gFOBT for screening for colorectal cancer?

HTAC Judgment: Among the ten (10) HTA agencies reviewed: one agency (MaHTAS) recommended quantitative (fully automated) iFOBT as a highly desirable screening strategy due to the large number of tests that can be done; UK NICE focused their recommendation for symptomatic patients; and eight HTA agencies did not have a recommendation for screening strategies for CRC.

With regard to fifteen (15) MoHs and government agencies reviewed, **four (4) recommended both FIT and gFOBT** (US, Philippines, Canada, Singapore), **nine (9) recommended FIT only** (South Korea, UK, Australia, Malaysia, China/China CDC, European Countries/European CDC, New Zealand, Thailand, and Japan), **one (1) recommended FOBT but did not specify whether gFOBT or FIT** (Vietnam), while **only one (1) MOH had no recommendation** for CRC screening modalities (Indonesia).

Among the countries that recommended **FIT, one (1) recommended either qualitative or quantitative test** (South Korea), **two (2) recommended the qualitative test** (Australia and China), **five (5) recommended the quantitative test (**EU countries, UK, Malaysia, New Zealand, and Thailand), **and five (5) did not specify the type of FIT recommended** (Canada, Philippines, Singapore, Vietnam, Japan, and US) screening using FIT.

The positive recommendations of various MoHs and HTA agencies abroad strengthen the need for the health technology assessment of CRC screening through gFOBT and FIT in the early detection of CRC among Filipino adults.

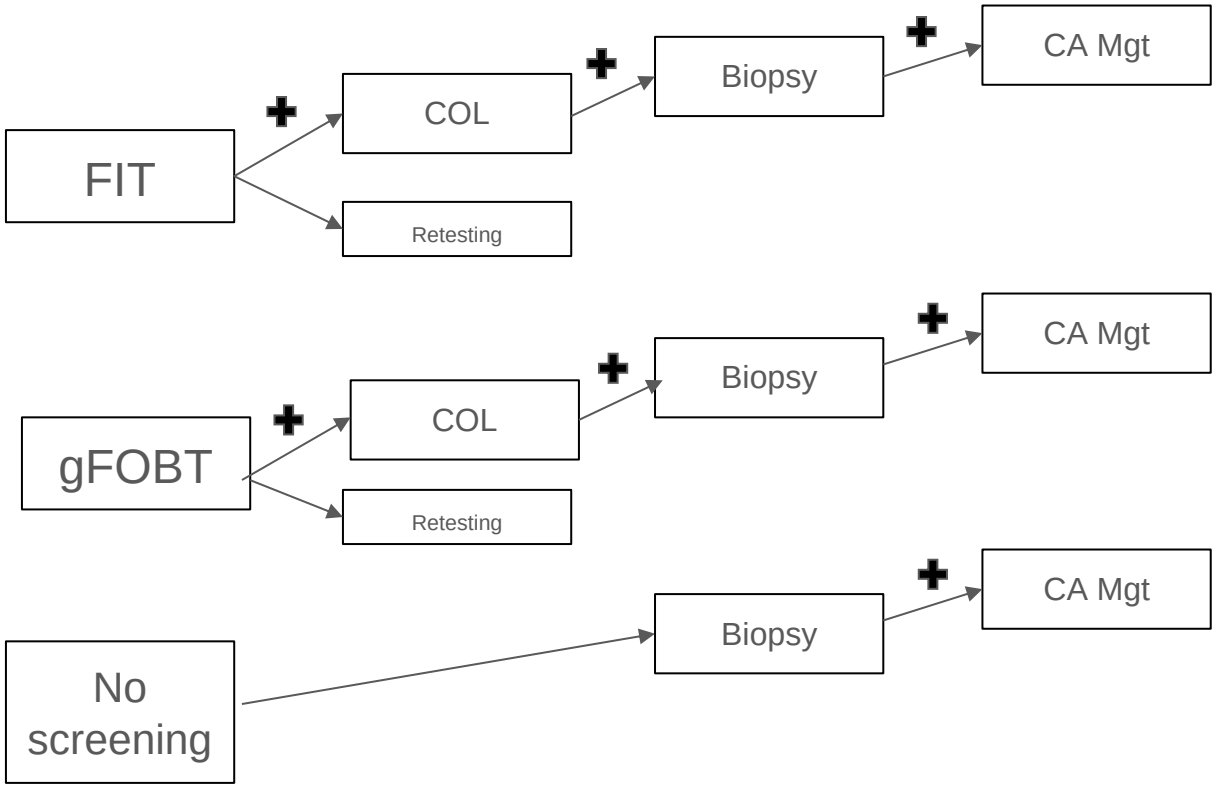
C3: COST-EFFECTIVENESS

RQ5: What is the cost-effectiveness of FIT with confirmatory colonoscopy after a positive result for screening for colorectal cancer compared to no screening and to gFOBT screening with confirmatory colonoscopy after a positive result among apparently healthy adults 50 years old and above?

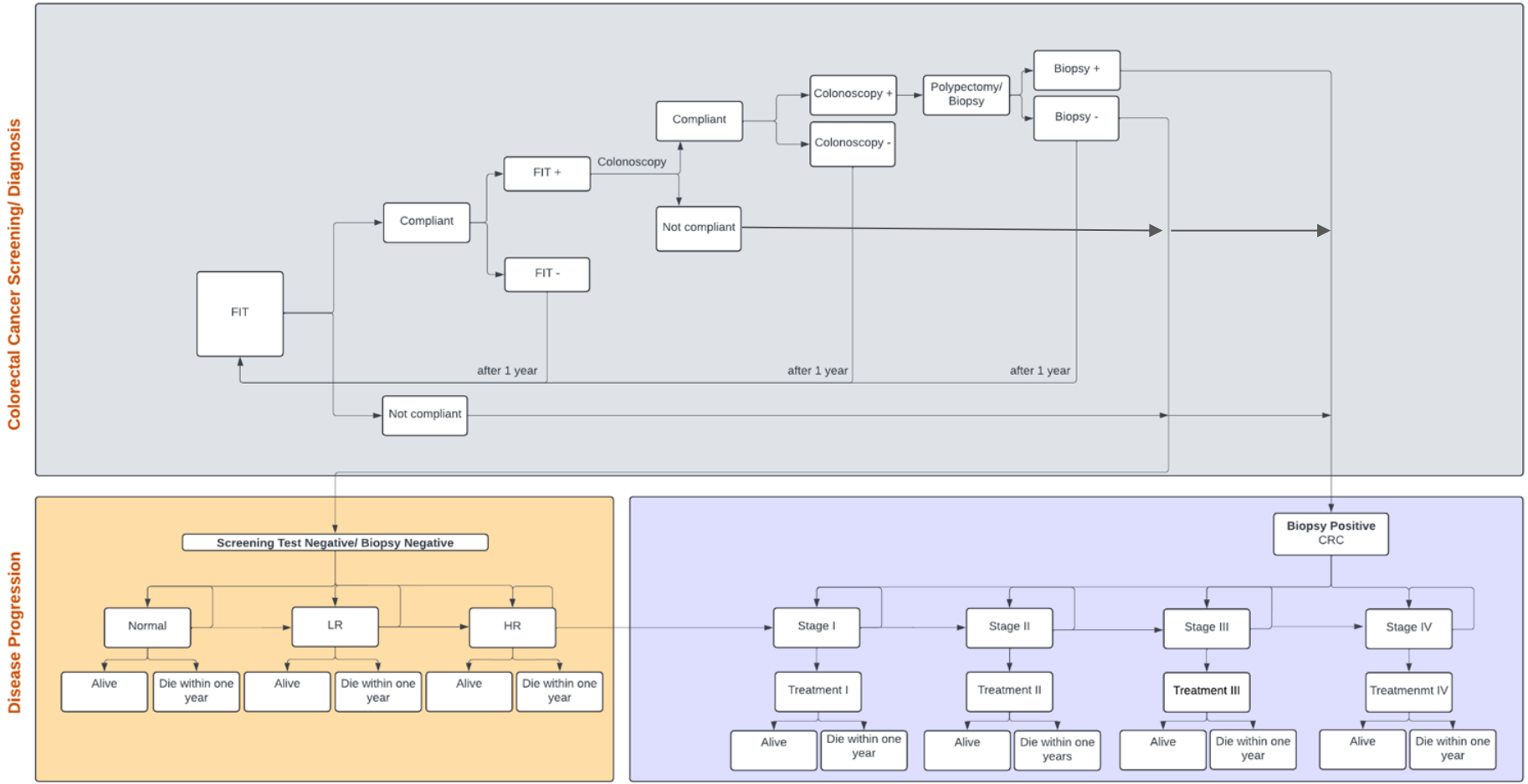
Cost-Utility Analysis

- Markov model that simulates the patient pathways from screening to diagnosis to management of cancer
- Hypothetical cohort of 100,000 average-risk Filipinos aged 50 years and above
- Cycle length of 1 year, with repeat screening until 75 years (average life span of Filipinos)
- Discount of 7% per year
- CE Thresholds: 0.5x, 0.75x, and 1x GDP of PHP 218,391.74 (2023 GDP x Nov 2024 exchange rate)
- Assumption: All patients with findings on colonoscopy will undergo a biopsy, even if the polyp is thought to be benign in nature

Cost-Utility Analysis: Model Summary

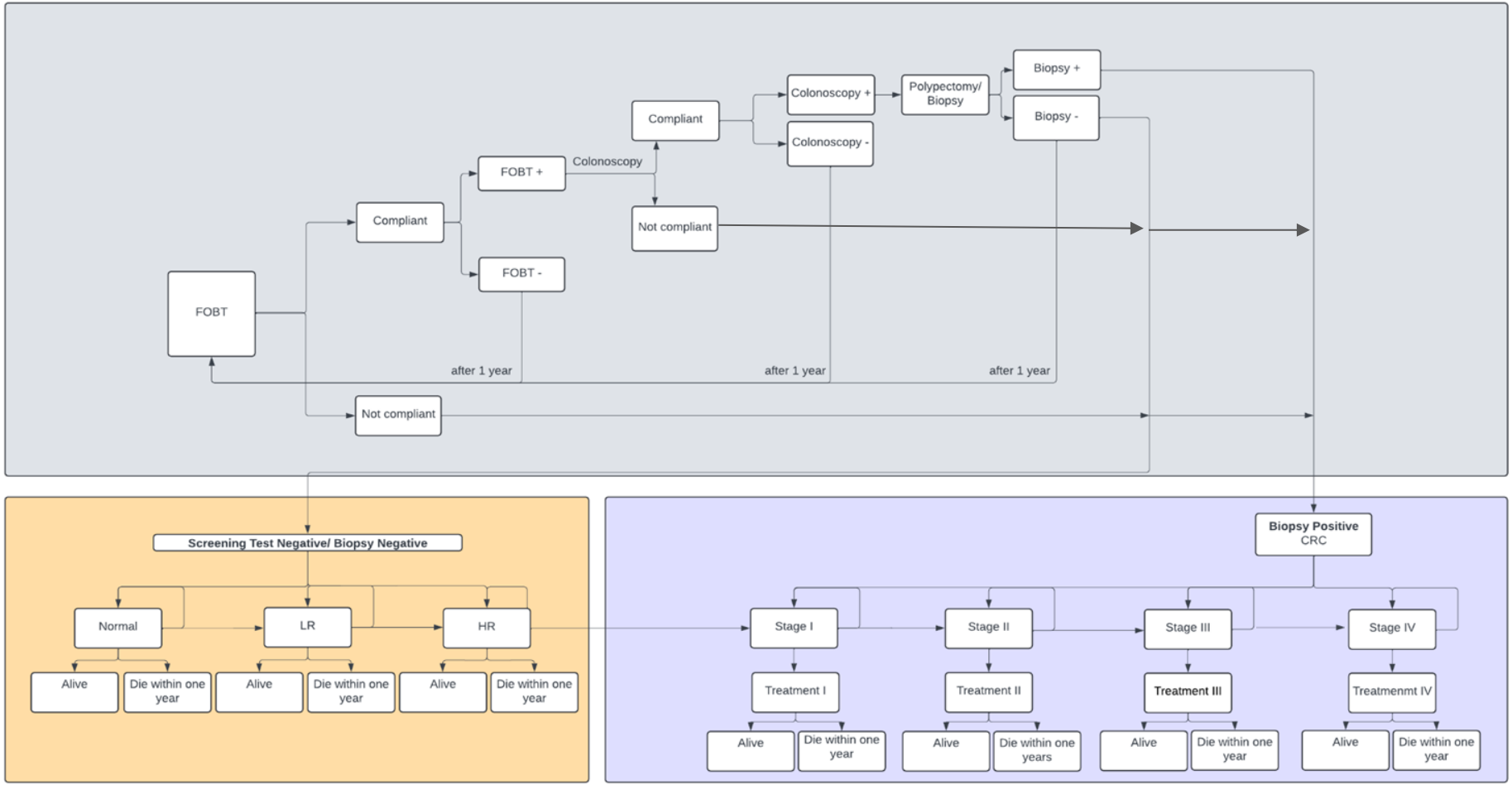


Clinical Pathway: FIT

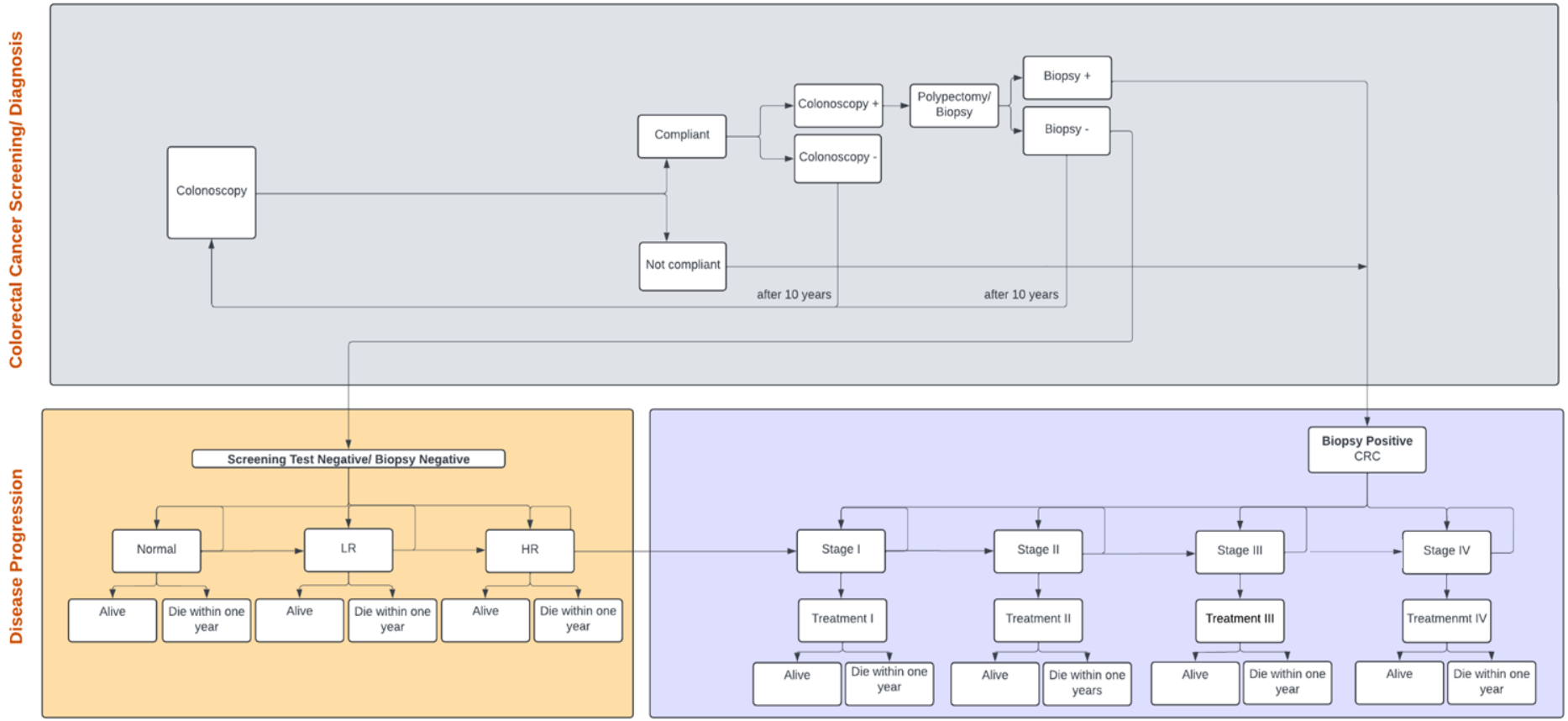


Clinical Pathway: qFOBT

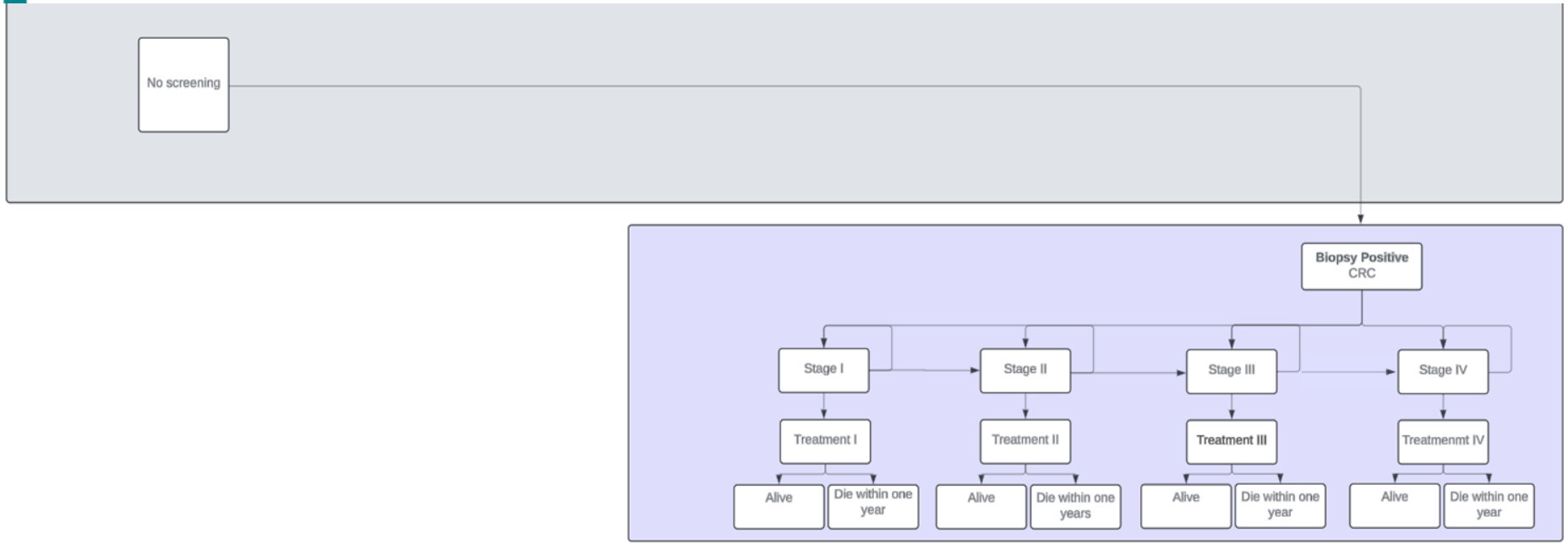
Note: Same as FIT



Clinical Pathway Colonoscopy



Clinical Pathway No screening



Data Collection for Input Parameters in the Model

- Literature search on PubMed, Herdin, Google scholar, and unpublished Philippine data
- Search terms: guaiac test" OR "fecal occult blood test", "fecal immunochemistry test", "colonoscopy" OR "large intestine endoscopy", "colorectal cancer screening" OR "large intestine cancer screening", "cost-effectiveness" OR "cost-benefit" OR "cost-utility" OR "economic evaluation" OR "budget-impact"
- Inclusion criteria: average risk adults at least 50 years old, English language studies with full text available from 2018 to 2023, except if Philippine / Filipino data
- Exclusion criteria: analysis did not separate average from high-risk population

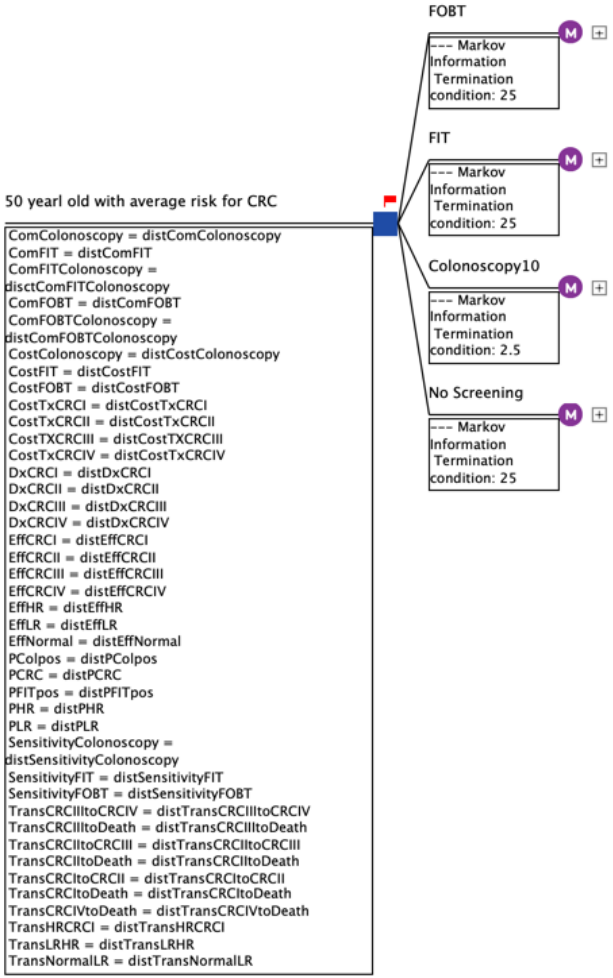
Input parameters	Distribution	Mean (Range)	Reference
Baseline parameters			
Annual discount rate for costs and outcomes(%)		7	19
Prevalence			
Low-risk polyp	Beta	0.113 (0.105-0.121)	20 21
High-risk polyp	Beta	0.070 (0.063-0.077)	20 21
Colorectal Cancer Stage I	Beta	0.259 (0.020-0.300)	20-23
Colorectal Cancer Stage II	Beta	0.249 (0.160-0.370)	20-23
Colorectal Cancer Stage III	Beta	0.299 (0.280-0.370)	20-23
Colorectal Cancer Stage IV	Beta	0.194 (0.150-0.367)	20-23
Effectiveness of fecal occult blood test			
Overall sensitivity	Beta	0.625 (0.500-0.750)	PHEX
Overall specificity	Beta	0.970 (0.960-0.980)	PHEX
Fecal occult blood screening compliance rate	Beta	0.636 (0.462-0.900)	20 21
Compliance for colonoscopy after FOBT	Beta	0.800 (0.712-0.875)	20 21
Effectiveness of fecal immunochemical test			
Overall sensitivity	Beta	0.810 (0.700-0.910)	PHEX
Overall specificity	Beta	0.930 (0.910-0.960)	
Fecal immunochemical test screening compliance rate	Beta	0.600 (0.372-1.000)	20 21
Compliance for colonoscopy after FIT	Beta	0.800 (0.712-0.875)	20 21
Effectiveness of colonoscopy			
Overall sensitivity	Beta	0.900 (0.880-1.000)	20
Overall specificity	Beta	1.000 (0.900-1.000)	20
Colonoscopy screening compliance rate	Beta	0.750 (0.250-0.990)	20 21

Annual transition probabilities			
Normal to low-risk polyp	Beta	0.008 (0.007-0.008)	20 21
Low-risk polyp to high-risk polyp	Beta	0.020 (0.012-0.028)	20 21
High-risk polyp to colorectal cancer stage I	Beta	0.050 (0.024-0.028)	20 21
Colorectal cancer stage I to II	Beta	0.280 (0.244-0.316)	20 21
Colorectal cancer stage II to III	Beta	0.280 (0.244-0.316)	20 21
Colorectal cancer stage III to IV	Beta	0.630 (0.594-0.666)	20 21
Colorectal cancer stage I to death	Beta	0.230 (0.138-0.322)	20 21
Colorectal cancer stage II to death	Beta	0.039 (0.027-0.051)	20 21
Colorectal cancer stage III to death	Beta	0.088 (0.069-0.108)	20 21
Colorectal cancer stage IV to death	Beta	0.248 (0.133-0.364)	20 21
Annual direct costs			
Fecal occult blood test	Gamma	570.00 (360.00-843.00)	18 20
Fecal immunochemical test	Gamma	405.00 (275.00-650.00)	18 20
Colonoscopy	Gamma	11,113.24 (8,817.00-34,701.65)	18 20
Treatment of colorectal cancer stage I	Gamma	150,000.00 (120,000.00-180,000.00)	17
Treatment of colorectal cancer stage II	Gamma	320,000.00 (150,000.00-450,000.00)	17
Treatment of colorectal cancer stage III	Gamma	320,000.00 (300,000.00-450,000.00)	17
Treatment of colorectal cancer stage IV	Gamma	320,000.00 (300,000.00-800,000.00)	17
Utilities			
Normal to low-risk polyp	Beta	0.830 (0.740-0.920)	20 21
Low-risk polyp	Beta	0.830 (0.740-0.920)	20 21
High-risk polyp	Beta	0.830 (0.740-0.920)	20 21
Colorectal cancer stage I	Beta	0.750 (0.720-0.760)	20 21
Colorectal cancer stage II	Beta	0.667 (0.610-0.730)	20 21
Colorectal cancer stage III	Beta	0.600 (0.500-0.670)	20 21
Colorectal cancer stage IV	Beta	0.250 (0.220-0.280)	20 21

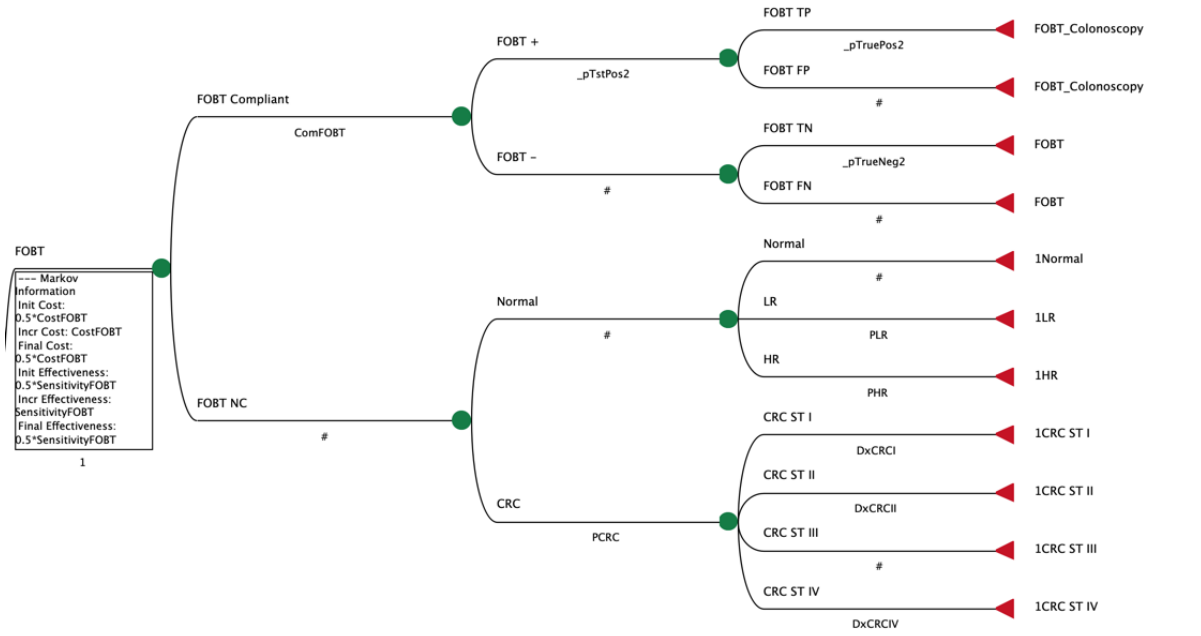
Philhealth case rates for colorectal cancer (Z package)

Rate for the Treatment and Management of Colorectal Cancer (*PhilHealth Z package, 2015*)		
• Low risk colon cancer (Stage I and II)		Php 150,000.00
• High risk colon cancer (stage II to III)		Php 300,000.00
• Rectal cancer (stage I only), clinical and pathologic		Php 150, 000.00
• Colorectal cancer, preoperative stage I with post-operative pathologic stages II-III • Rectum cancer with clinical stages I to III	Radiotherapy using linear accelerator	Php 320,000.00
	Radiotherapy using cobalt mode	Php 400,000.00
Reimbursement of medical procedures relevant to colorectal cancer with case rates such as colonoscopy, sigmoidoscopy, biopsy and cryosurgery *(PhilHealth Procedure Case Rates)*		

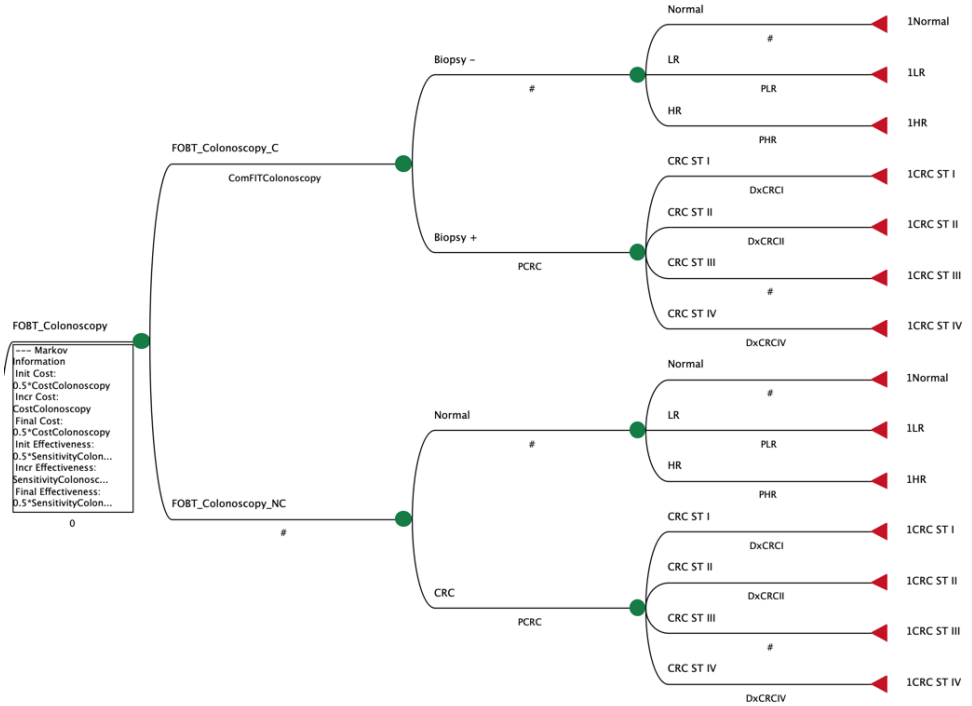
Main Screening Tree

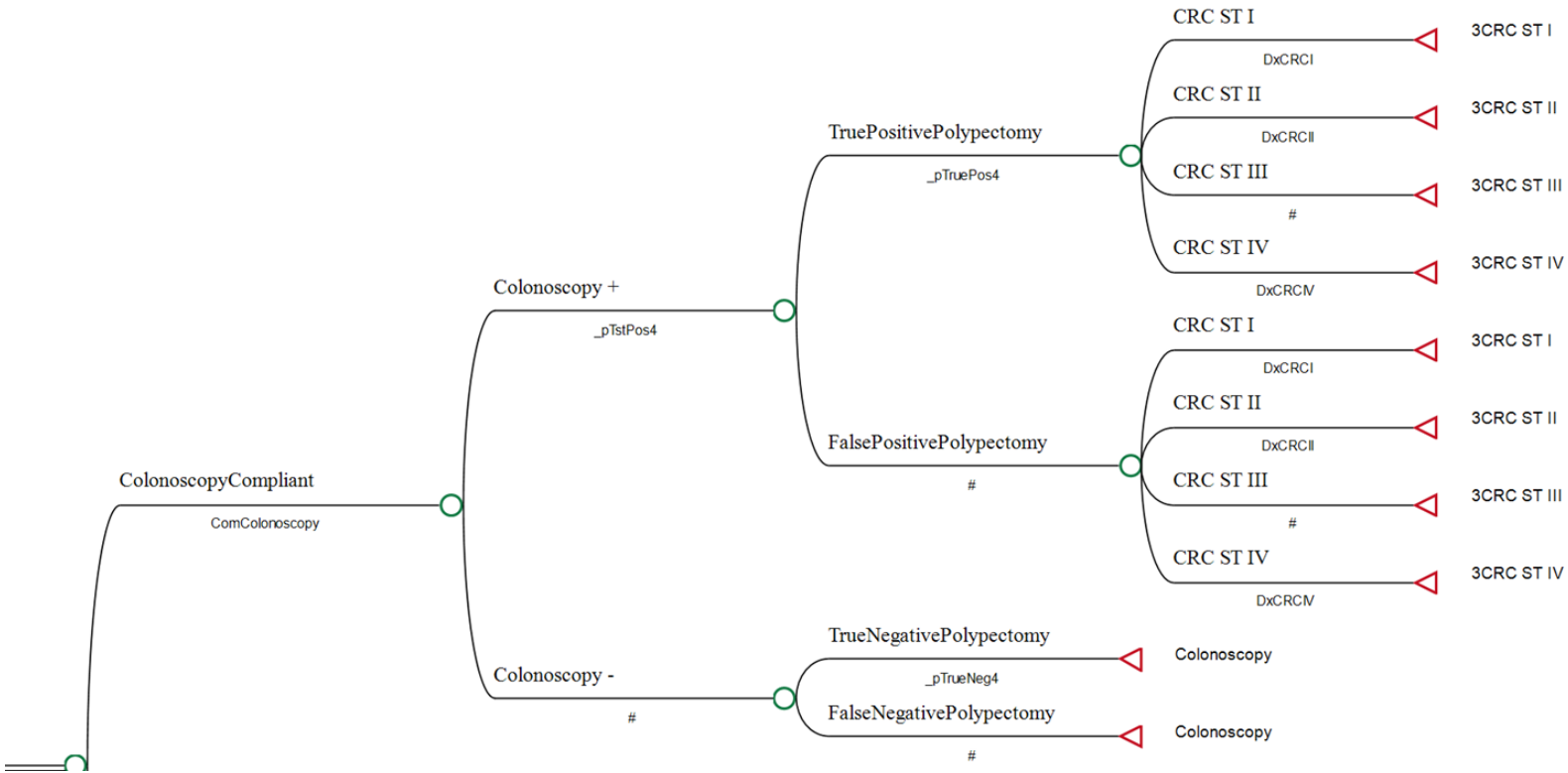


FOBT / FIT Screening Subtree

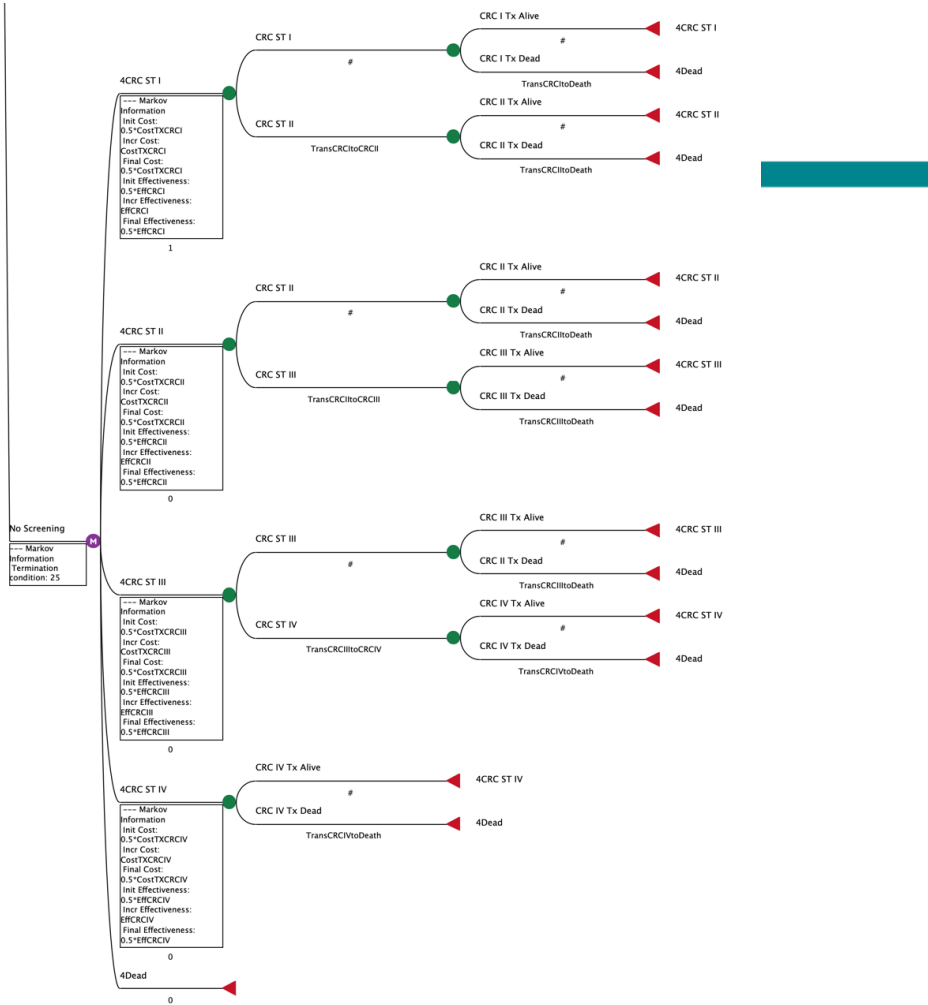


FOBT/ FIT - Colonoscopy Subtree

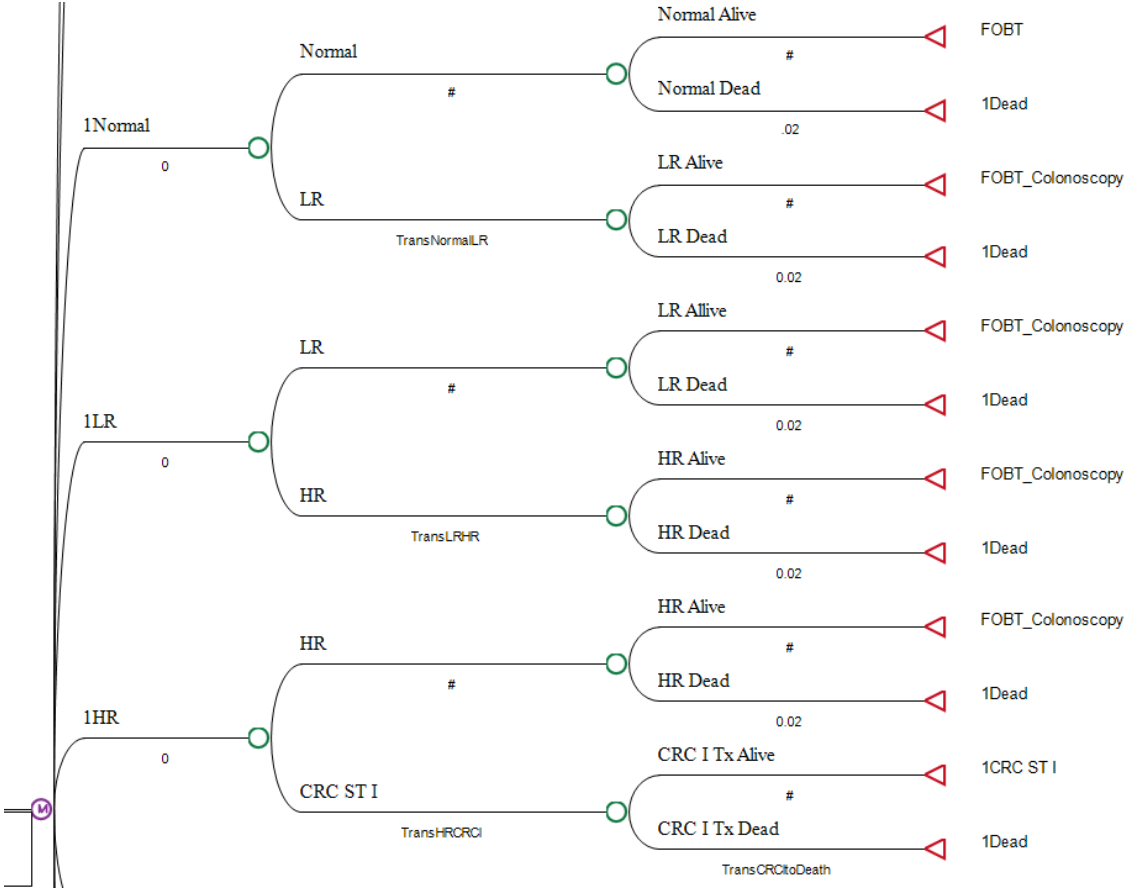



ColonoscopyCompliant
ComColonoscopy
Colonoscopy +
_pTstPos4
Colonoscopy -
#
TruePositivePolypectomy
_pTruePos4
FalsePositivePolypectomy
#
TrueNegativePolypectomy
_pTrueNeg4
FalseNegativePolypectomy
#
CRC ST I
DxCRCI
CRC ST II
DxCRCII
CRC ST III
#
CRC ST IV
DxCRCIV
CRC ST I
DxCRCI
CRC ST II
DxCRCII
CRC ST III
#
CRC ST IV
DxCRCIV
3CRC ST I
3CRC ST II
3CRC ST III
3CRC ST IV
3CRC ST I
3CRC ST II
3CRC ST III
3CRC ST IV
Colonoscopy
Colonoscopy

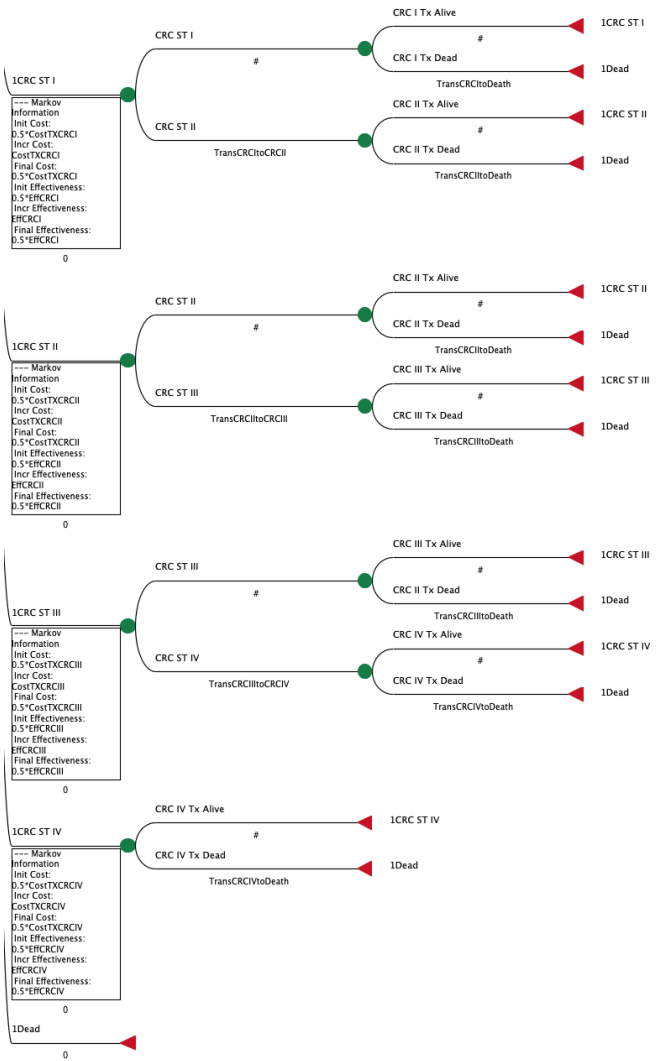
No screening Subtree



Normal, LR, HR Subtree



CRC Subtree


1CRC ST I
--- Markov
Information
Init Cost:
0.5*CostTXCRCI
Incr Cost:
CostTXCRCI
Final Cost:
0.5*CostTXCRCI
Init Effectiveness:
0.5*EffCRCI
Incr Effectiveness:
EffCRCI
Final Effectiveness:
0.5*EffCRCI
0
CRC ST I
#
CRC ST II
TransCRCItoCRCII
CRC I Tx Alive
#
CRC I Tx Dead
TransCRCItoDeath
1CRC ST I
1Dead
CRC II Tx Alive
#
CRC II Tx Dead
TransCRCIItoDeath
1CRC ST II
1Dead
1CRC ST II
--- Markov
Information
Init Cost:
0.5*CostTXCRCII
Incr Cost:
CostTXCRCII
Final Cost:
0.5*CostTXCRCII
Init Effectiveness:
0.5*EffCRCII
Incr Effectiveness:
EffCRCII
Final Effectiveness:
0.5*EffCRCII
0
CRC ST II
#
CRC ST III
TransCRCIItoCRCIII
CRC II Tx Alive
#
CRC II Tx Dead
TransCRCIItoDeath
1CRC ST II
1Dead
CRC III Tx Alive
#
CRC III Tx Dead
TransCRCIIItoDeath
1CRC ST III
1Dead
1CRC ST III
--- Markov
Information
Init Cost:
0.5*CostTXCRCIII
Incr Cost:
CostTXCRCIII
Final Cost:
0.5*CostTXCRCIII
Init Effectiveness:
0.5*EffCRCIII
Incr Effectiveness:
EffCRCIII
Final Effectiveness:
0.5*EffCRCIII
0
CRC ST III
#
CRC ST IV
TransCRCIIItoCRCIV
CRC III Tx Alive
#
CRC II Tx Dead
TransCRCIIItoDeath
1CRC ST III
1Dead
CRC IV Tx Alive
#
CRC IV Tx Dead
TransCRCIVtoDeath
1CRC ST IV
1Dead
1CRC ST IV
--- Markov
Information
Init Cost:
0.5*CostTXCRCIV
Incr Cost:
CostTXCRCIV
Final Cost:
0.5*CostTXCRCIV
Init Effectiveness:
0.5*EffCRCIV
Incr Effectiveness:
EffCRCIV
Final Effectiveness:
0.5*EffCRCIV
0
CRC IV Tx Alive
#
CRC IV Tx Dead
TransCRCIVtoDeath
1CRC ST IV
1Dead
1Dead
0

Results of the CUA (Deterministic analysis)

Resulting total costs and QALYs

Strategy	Cost (Rank)	Effectiveness in QALYs (Rank)
No Screening	2,434,610.66 (4)	5.32 (4)
Annual gFOBT + confirmatory colonoscopy	196,385.81 (1)	11.21 (3)
Annual FIT + confirmatory colonoscopy	210,250.86 (2)	13.19 (2)
10-yearly colonoscopy	2,006,671.71 (3)	48.59 (1)

Rank (1 to 4): lowest cost to highest cost; most effective to least effective

Results of the CUA (Deterministic analysis)

Comparison of the screening tests: 1) vs no screening; 2) FIT vs gFOBT

	Incr Cost	Incr Eff	Deterministic ICER	0.50 x GDP	0.75 x GDP	1x GDP
FIT/gFOBT/Colonoscopy vs No Screening						
Annual FIT + confirmatory colonoscopy vs No screening	-2,224,359.80	7.87	-282,637.84	Cost-saving	Cost-saving	Cost-saving
Annual gFOBT + confirmatory colonoscopy vs No screening	-2,238,224.85	5.89	-380,004.22	Cost-saving	Cost-saving	Cost-saving
10-yearly colonoscopy vs No screening	-427,938.95	43.27	-9,889.97	Cost-saving	Cost-saving	Cost-saving
FIT vs gFOBT						
Annual FIT + confirmatory colonoscopy vs Annual gFOBT + confirmatory colonoscopy	13,865.05	1.98	7,002.55	Cost-effective	Cost-effective	Cost-effective

0.5xGDP: Php109,196.00
0.75xGDP: Php163,794.00
1xGDP: Php218,392.00

PROBABILISTIC SENSITIVITY ANALYSIS

Results of the CUA (Probabilistic analysis - **100,000 simulations**)

Mean ICERs from PSA – Comparison of the screening tests: 1) vs no screening; 2) FIT vs gFOBT

	Incr Cost	Incr Eff	Mean ICER	0.50 x GDP	0.75 x GDP	1x GDP
FIT/gFOBT/Colonoscopy vs No Screening						
Annual FIT + confirmatory colonoscopy vs No screening	-2,483,627.16	7.73	-321,297.17	Cost-saving	Cost-saving	Cost-saving
Annual gFOBT + confirmatory colonoscopy vs No screening	-2,499,610.09	5.73	-436,232.13	Cost-saving	Cost-saving	Cost-saving
10-yearly colonoscopy vs No screening	-432,182.16	42.13	-10,258.30	Cost-saving	Cost-saving	Cost-saving
FIT vs gFOBT						
Annual FIT + confirmatory colonoscopy vs Annual gFOBT + confirmatory colonoscopy	15,982.93	2	7,991.47	Cost-effective	Cost-effective	Cost-effective

0.5xGDP: Php109,196.00
0.75xGDP: Php163,794.00
1xGDP: Php218,392.00

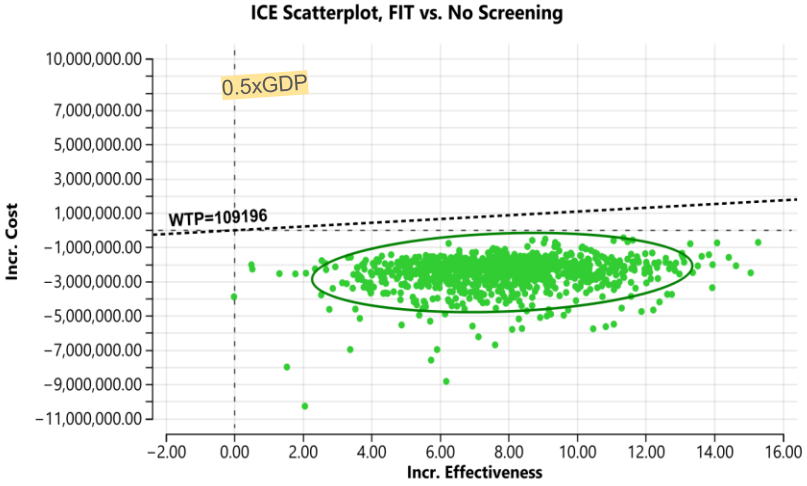
Results of the CUA (Probabilistic analysis)

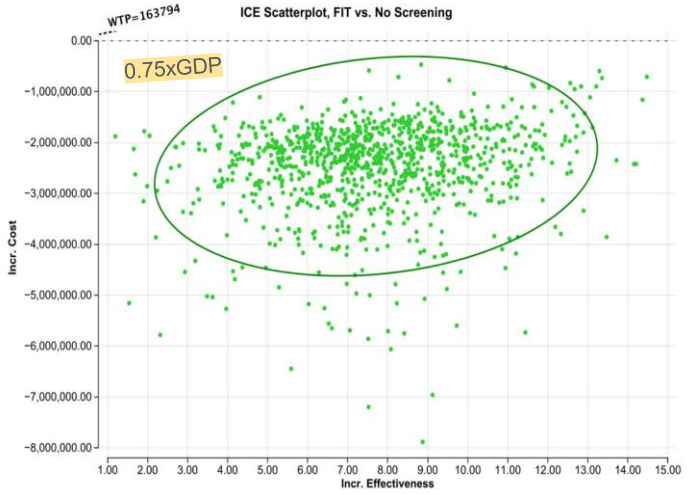
% of simulations in the PSA where the ICER is below the CE threshold

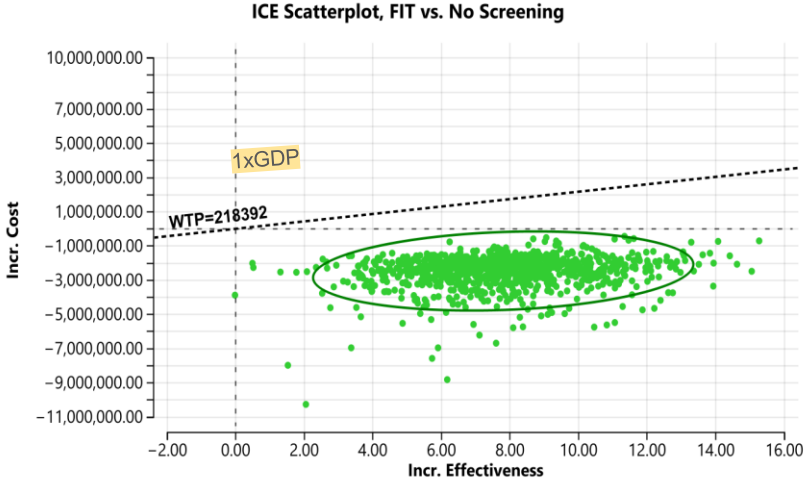
CE Threshold	% probability of cost-effectiveness	
	FIT vs gFOBT	FIT vs No screening
0.5 GDP	74.50%	99.97%
0.75 GDP	76.49%	99.95%
1.00 GDP	77.56%	100.00%

0.5xGDP: Php109,196.00
0.75xGDP: Php163,794.00
1xGDP: Php218,392.00

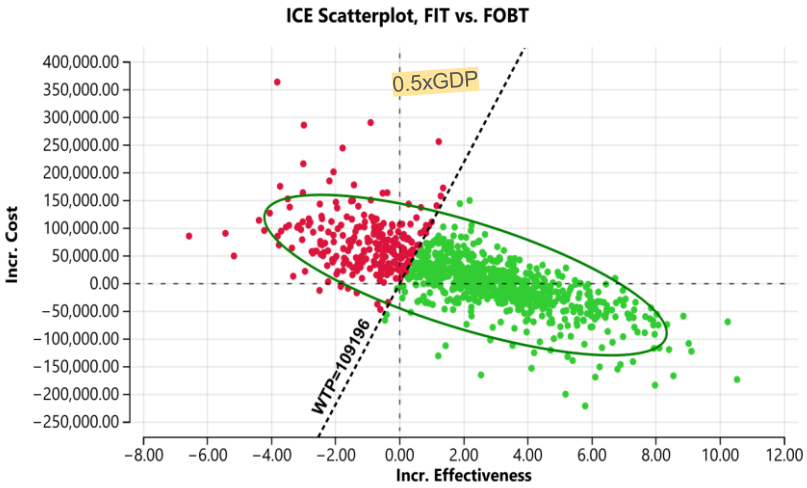
FIT vs No Screening

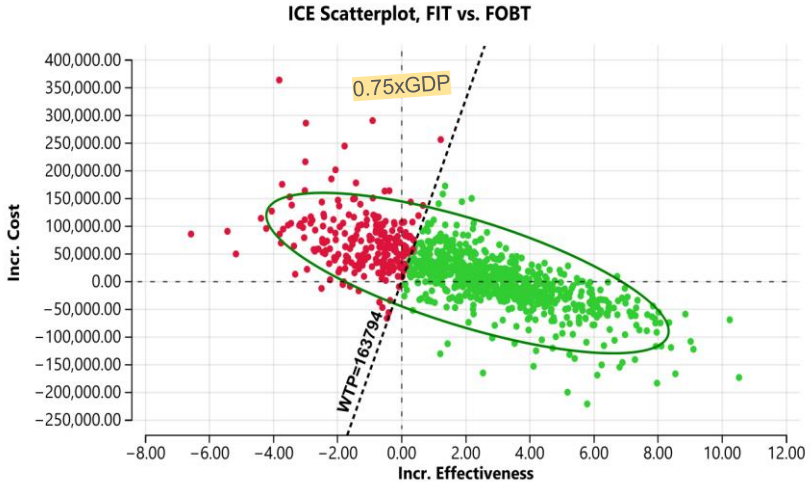






FIT vs gFOBT


ICE Scatterplot, FIT vs. FOBT
0.5xGDP
WTP=109196
Incr. Cost
Incr. Effectiveness
400,000.00
350,000.00
300,000.00
250,000.00
200,000.00
150,000.00
100,000.00
50,000.00
0.00
−50,000.00
−100,000.00
−150,000.00
−200,000.00
−250,000.00
−8.00
−6.00
−4.00
−2.00
0.00
2.00
4.00
6.00
8.00
10.00
12.00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Incr. Effectiveness
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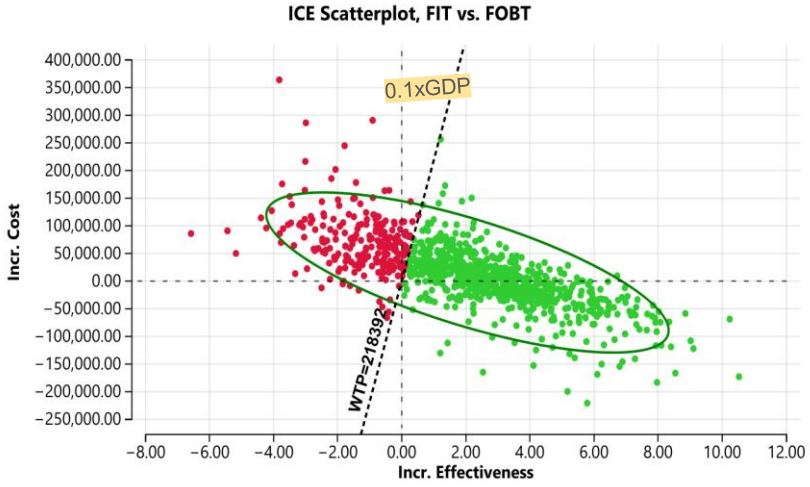
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Incr. Effectiveness
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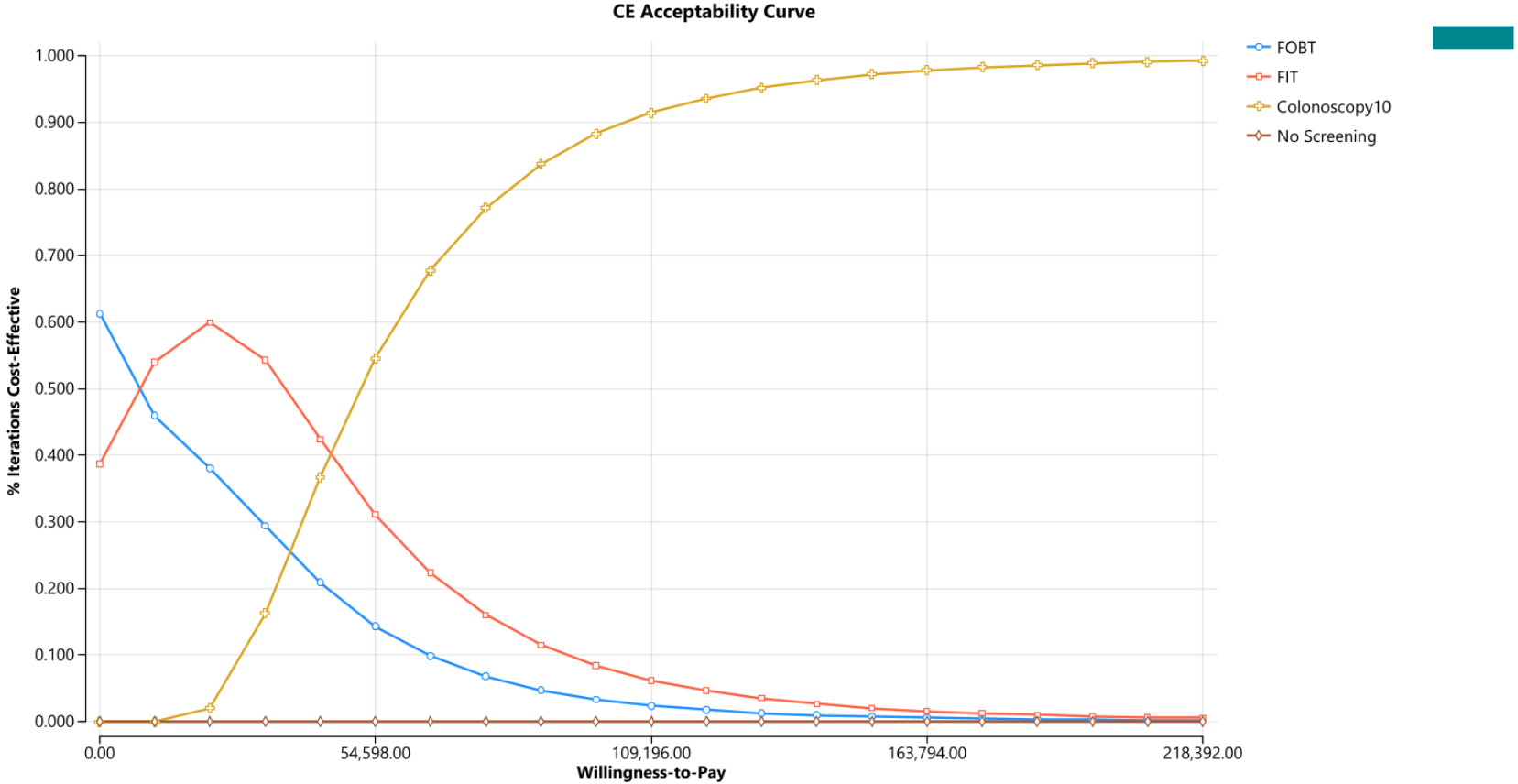
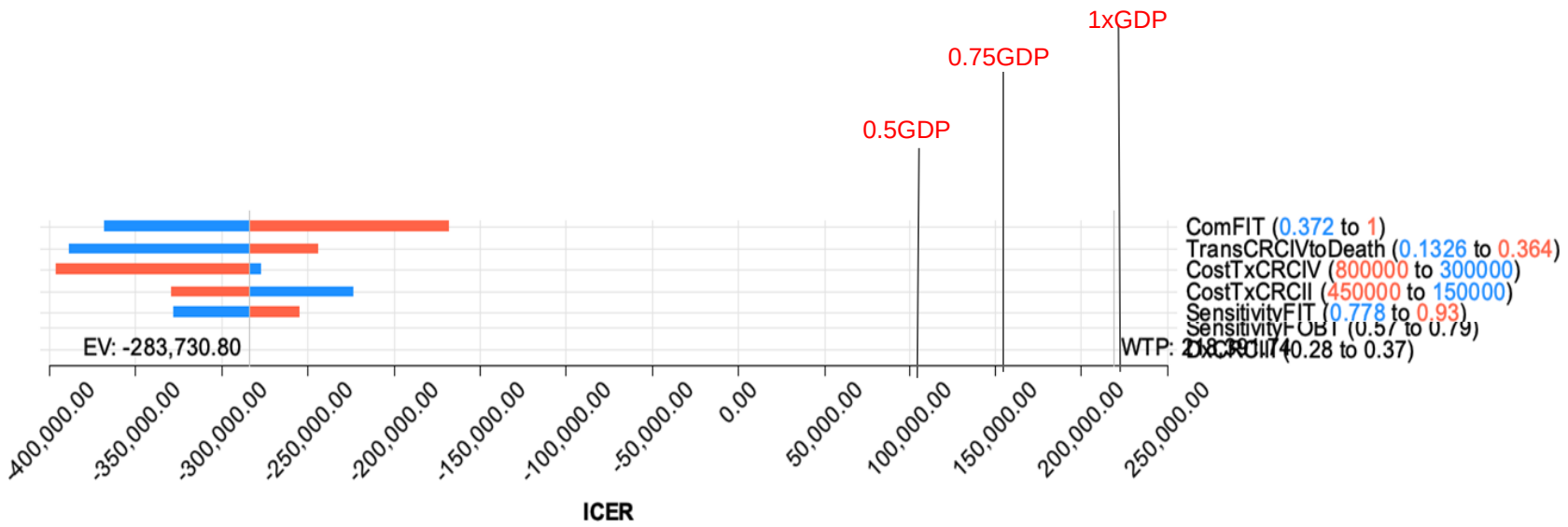
Cost-Effectiveness Acceptability Curve



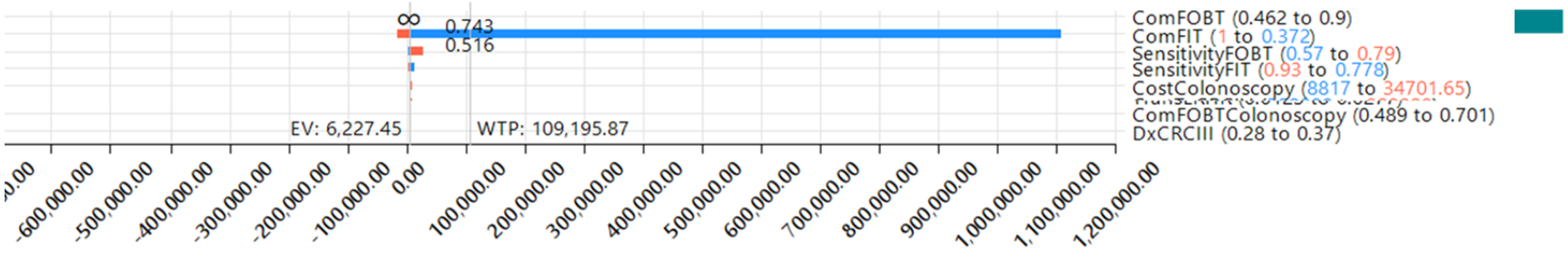
ONE-WAY SENSITIVITY ANALYSIS

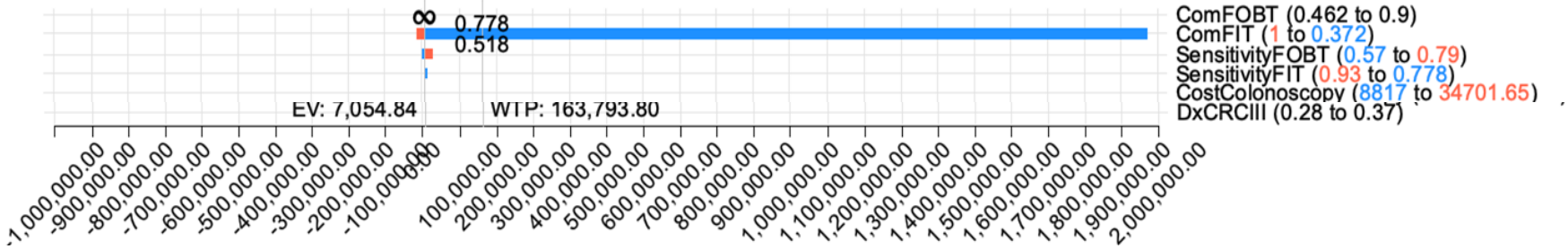
One-way sensitivity analysis: FIT vs No Screening

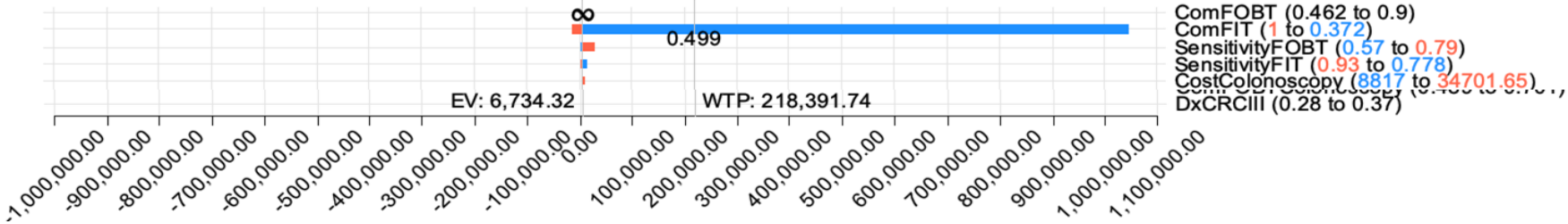


FIT is cost-effective and the ICER is most sensitive to **compliance to FIT screening, transition probability from CRC stage IV to death, cost of treatment of CRC stages IV and II, and sensitivity of FIT.**

One-way sensitivity analysis: FIT VS gFOBT







C3: Cost-effectiveness

RQ5: What is the cost-effectiveness of FIT with confirmatory colonoscopy after a positive result for screening for colorectal cancer compared to no screening and to gFOBT screening with confirmatory colonoscopy after a positive result among apparently healthy adults 50 years old and above?

HTAC judgment:

Compared to no screening, annual FIT screening with confirmatory colonoscopy after a positive result is cost-saving. FIT screening has a lower cost compared to no screening by Php 2,483,627.16, but has higher effectiveness by 7.73 QALYs gained (ICER: Php -321,297.17/QALY gained).

Annual FIT screening has higher costs but higher QALYs compared to annual gFOBT screening (incremental cost: Php 15,982.93; incremental effectiveness: 2.00 QALYs). Therefore, shifting to annual FIT screening is estimated to be cost-effective at all thresholds (ICER: Php 7,991.47/QALY gained).

The one-way sensitivity analyses show that the ICERs of FIT vs no screening is most sensitive to the following parameters: 1) compliance to FIT screening, 2) transition probability from CRC stage IV to death, 3) treatment cost for CRC stage II, 4) treatment cost for CRC stage IV, and 5) sensitivity of FIT. Meanwhile the ICER of FIT vs gFOBT is most sensitive to the following parameters: 1) compliance to annual gFOBT screening, and 2) compliance to FIT screening.

C4: AFFORDABILITY AND VIABILITY

RQ6: What is the budget impact of FIT with confirmatory colonoscopy after a positive result for screening for colorectal cancer compared to no screening and to gFOBT screening with confirmatory colonoscopy after a positive result among apparently healthy adults 50 years old and above?

BUDGET IMPACT ANALYSIS

	Year 1	Year 2	Year 3	Year 4	Year 5	Total 5 years	Average Per year
Annual FIT as first choice							
FIT ideal scenario (increasing population by 1.5%)	17,608,238	17,872,362	18,140,447	18,412,554	18,688,742	90,722,343	18,144,469
Compliance in FIT screening at 60%	10,564,943	10,723,418	10,884,269	11,047,533	11,213,246	54,433,409	10,886,682
Positive FIT test at 4.67% (Ding 2022)	493,383	500,784	508,296	515,920	523,659	2,542,042	508,409
Compliance to colonoscopy after (+)FIT 80%	394,707	400,628	406,637	412,736	418,928	2,033,636	406,728
FIT screening (PHP 405)	₱4,278,801,915.00	₱4,342,984,290.00	₱4,408,128,945.00	₱4,474,250,865.00	₱4,541,364,630.00	₱22,045,530,645.00	₱4,409,106,129.00
Colonoscopy (PHP11,113.24)	₱4,386,473620.68	₱4,452,275,114.72	₱4,519,054,573.88	₱4,586,834,224.64	₱4,655,647,406.72	₱22,600,284,941.00	₱4,520,056,988.13
	₱8,665,275,535.68	*₱8,795,259,404.72*	*₱8,927,183,518.88*	*₱9,061,085,089.64*	*₱9,197,012,036.72*	*₱44,645,815,586.00*	*₱8,929,163,117.13*
Budget impact of FIT	**₱8.67 B**	**₱8.80 B**	**₱8.93 B**	**₱9.06 B**	**₱9.20 B**	**₱44.65 B**	**₱8.93 B**
Annual gFOBT as first choice							
gFOBT ideal scenario	17,608,238	17,872,362	18,140,447	18,412,554	18,688,742	90,722,343	18,144,469
Compliance in gFOBT screening is 63%	11,093,190	11,259,589	11,428,482	11,599,910	11,773,908	57,155,079	11,431,016
Positive gFOBT test at 10.71% (Gingold 2019)	1,188,081	1,205,902	1,223,991	1,242,351	1,260,986	6,121,311	1,224,262
Compliance to colonoscopy after (+)gFOBT at 80%	950,465	964,722	979,193	993,881	1,008,789	4,897,050	979,410
gFOBT screening (PHP570)	₱6,323,118,300.00	₱6,417,965,730.00	₱6,514,234,740.00	₱6,611,948,700.00	₱6,711,127,560.00	₱32,578,395,030.00	₱6,515,679,006.00
Colonoscopy (PHP11,113.24)	₱10,562,745,656.60	₱10,721,187,119.28	₱10,882,006,815.32	₱11,045,238,084.44	₱11,210,914,266.36	₱54,422,091,942.00	₱10,884,418,388.40
	₱16,885,863,956.60	*₱17,139,152,849.28*	*₱17,396,241,555.32*	*₱17,657,186,784.44*	*₱17,922,041,826.36*	*₱87,000,486,972.00*	*₱17,400,097,394.40*
Budget impact of gFOBT	**₱16.89 B**	**₱17.14 B**	**₱17.40 B**	**₱17.66 B**	**₱17.92 B**	**₱87 B**	**₱17.40 B**

BUDGET IMPACT ANALYSIS

	Annual FIT with confirmatory colonoscopy as first choice	Annual gFOBT with confirmatory colonoscopy as first choice
TOTAL FOR 5 YEARS	**₱44.65 billion** *₱44,645,815,585.64*	**₱87 billion** *₱87,000,486,972.00*
Average per Year	**₱8.93 billion** *₱8,929,163,117.13*	**₱17.40 billion** *₱17,400,097,394.40*

C4: Affordability and viability

RQ6: What is the budget impact of FIT with confirmatory colonoscopy after a positive result for screening for colorectal cancer compared to no screening and to gFOBT screening with confirmatory colonoscopy after a positive result among apparently healthy adults 50 years old and above?

HTAC judgment: Over a 5-year horizon, with an initial target population of 17.6 million apparently healthy adults age 50 to 75 years and an annual population growth rate of 1.5%, annual FIT with confirmatory colonoscopy after positive result has a lower cost at ₱44.65 billion, averaging ₱8.93 billion per year compared to annual gFOBT with confirmatory colonoscopy after positive result which has an estimated 5-year cost of ₱87 billion and an annual average cost of ₱17.40 billion.

C5: HOUSEHOLD FINANCIAL IMPACT

RQ7. What is the household financial impact of colorectal cancer among adults 50 years and above?

Household Financial Impact of Colorectal Cancer

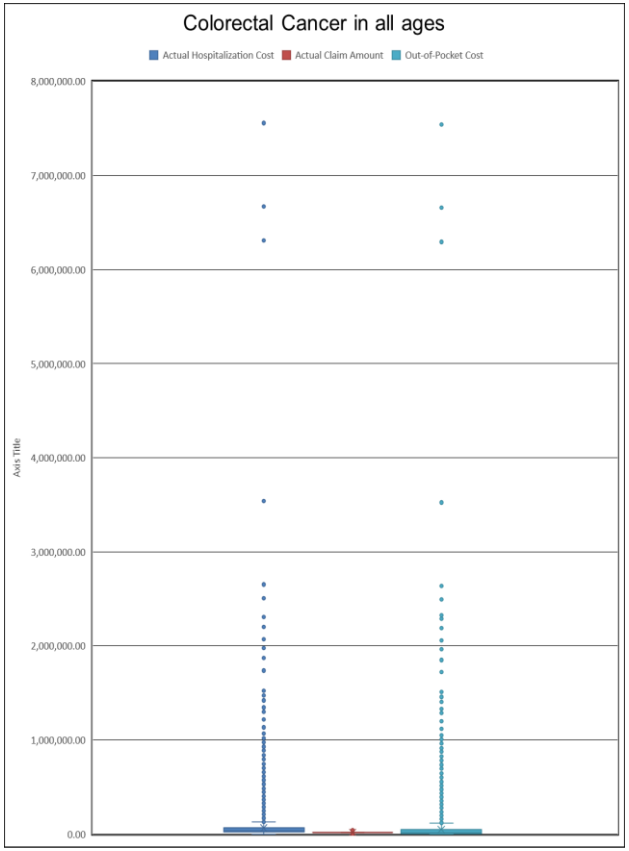
Methodology

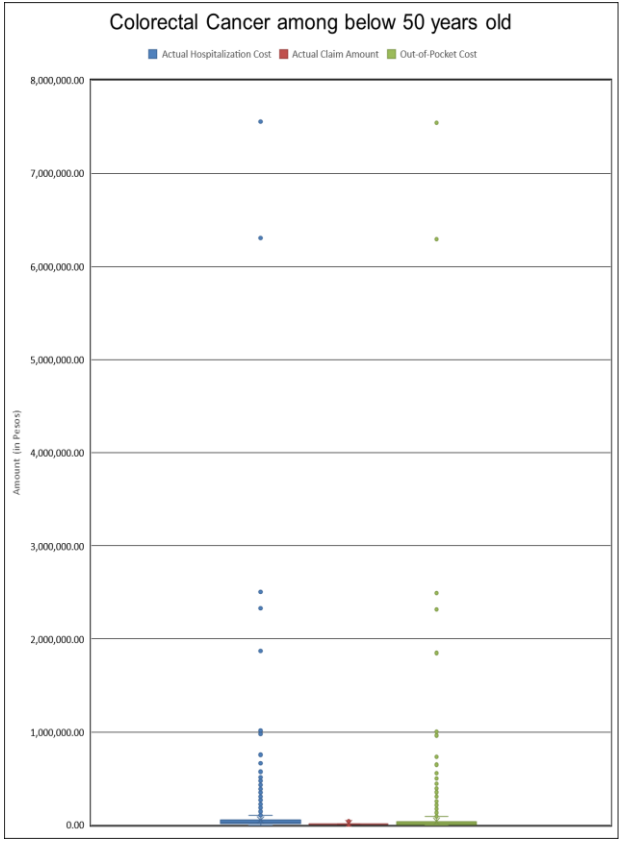
- Source of data is from PhilHealth claims from 2018 to 2023 for the following medical case rate groups:
  - **Malignant neoplasm of colon** *(ICD C18.2 to C18.9)*
  - **Malignant neoplasm of rectosigmoid junction** *(ICD C19)*
  - **Malignant neoplasm of rectum** *(ICD C20)*
  - **Malignant neoplasm of anus and anal canal** *(ICD C21.0, C21.1, C21.2, C21.8)*
  - **Secondary malignant neoplasm of large intestine and rectum** *(ICD C78.5)*
- Used **PAID** claims only

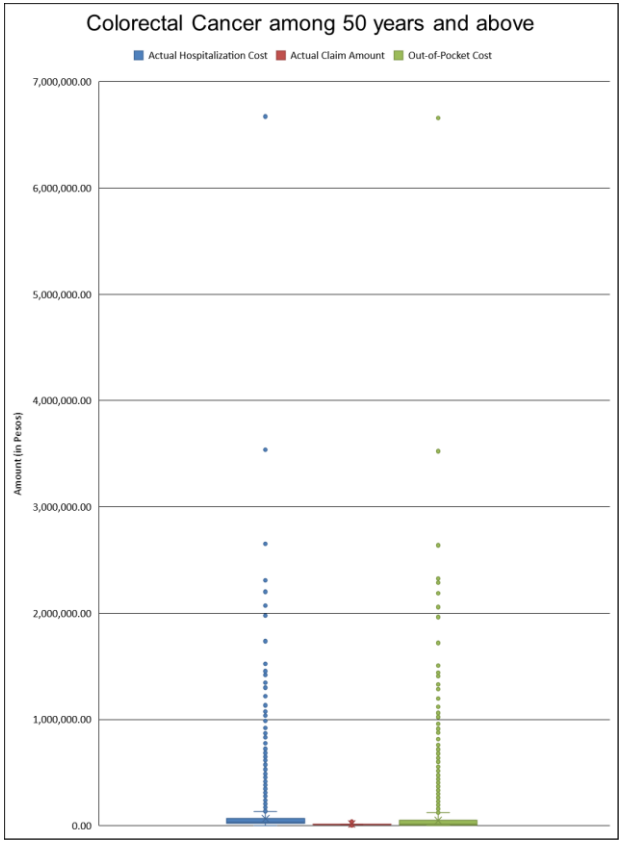
Household Financial Impact of Colorectal Cancer

	All ages	Less than 50 years.	50 years and above
Total Number of Paid Claims	19,896	4,141	15,755
Average Hospitalization Cost	₱ 62,465.69	₱ 55,458.12	₱ 64,307.54
Median Hospitalization Cost	₱ 34,479.35	₱30,631.85	₱ 35,710.73
Hospitalization Cost Range	₱ 0 to ₱ 7,557,139.25	₱ 0 to ₱ 7,557,139.25	₱ 0 to ₱ 6,672,308.00
Median Claims Cost	₱ 14,200.00	₱14,200.00	₱ 14,200.00
Claims Cost Range	₱ 1,612.99 to ₱ 70,200.00	₱ 2,600.00 to ₱ 47,200.00	₱ 1,612.99 to ₱ 70,200.00
Median Out-of-Pocket Cost	₱ 18,673.37	₱19,905.05	₱ 19,905.05
Out-of-Pocket Cost Range	₱ 0 to ₱ 7,542,939.25	₱ 0 to ₱ 7,542,939.25	₱ 0 to ₱ 6,658,108.00
Average % Coverage	50.41%	55.59%	49.05%

Household Financial Impact of Colorectal Cancer







C5: Household financial impact

RQ7: What is the household financial impact of colorectal cancer among adults 50 years and above?

HTAC judgment:

Among adults 50 years and above, the median hospitalization cost for colorectal cancer is Php 35,710.73. Meanwhile, the median cost of PhilHealth claims is Php 14,200.00, making the median out-of-pocket cost of colorectal cancer for in-patient hospitalization Php 19,905.05. On average, PhilHealth covers 49.05% of the hospitalization costs for colorectal cancer among adults 50 years and above. However, there are outlier claims with hospitalization costs and out-of-pocket costs reaching up to millions of pesos.

The household financial impact of colorectal cancer justifies the adoption of a screening program for the detection of colorectal cancer for reducing the risks of unfavourable outcomes of colorectal cancer.

C6: ETHICAL, LEGAL, SOCIAL, HEALTH SYSTEMS IMPACT

RQ8. What are the ethical, legal, social, and health systems implications of the use of FIT with confirmatory colonoscopy after a positive result after a positive result for screening for colorectal cancer among apparently healthy adults 50 years old and above?

Included studies

	Population	Methodology	Findings
Khalil 2022	16 Filipinos in the US, median age 41 years	Online FGD, semi-structured interview	Doctor's recommendation was very important for screening decisions
Fernandez 2024	288 urban and rural respondents, median age 49.9 years	Rawl Questionnaire translated to Filipino; KAP on FOBT and colonoscopy	86% willing to undergo screening Median annual expense P3000 >75% identified being asymptomatic as barrier to screening
Crochietere 2025	105 Filipinos in the US, 85% aged 40-49 years old	cross-sectional, self-administered, online survey to estimate the preference to do annual fecal immunochemical test or colonoscopy every 10 years	2 in 3 Filipinos prefer fecal immunochemical test to colonoscopy for their colorectal cancer screening.
PHEX 2021	Filipino population	Literature review	Need to overcome low awareness and knowledge on CRC Screening through health education, promotion of physician's role and adequate funding

Summary of ELSHI findings: Literature review

Ethical	• FOBT for screening and colonoscopy for diagnosis are covered by PhilHealth while FIT requires out-of-pocket • Accessibility and availability of healthcare services has a substantial impact on screening behavior *(PHEX, Tran et al 2021, Fernandez et al 2024)*
Legal	• Data privacy should be considered when contacting patients for screening results • Consent for procedure should be ensured for colonoscopy in consideration of potential complications and for screening tests in consideration of FP or FN results
Social	• Patient preference showed that FIT is preferred than colonoscopy *(Crochetiere 2025)* • Awareness of the benefits of screening and reducing perceived barriers will help increase screening uptake (Gimeno 2012; Khalil 2022)
Health Systems Impact	• Need for health promotion to increase awareness • Need for human resources for health • Ease of use of home screening kits = need for patient education on interpretation

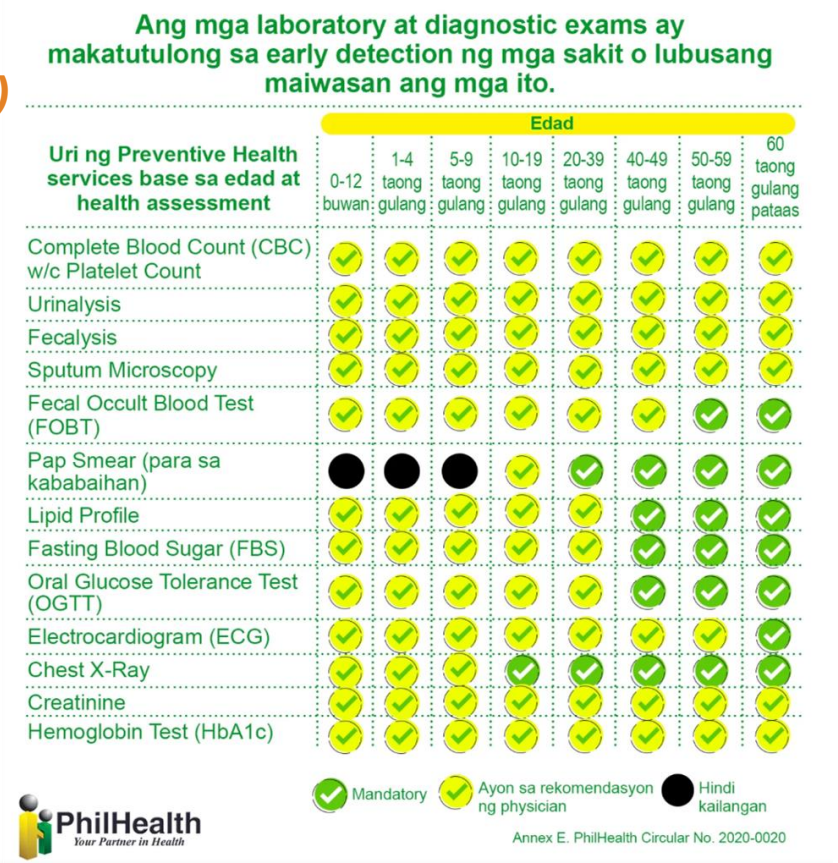
ETHICAL *(1 of 5)*

EQUITY/ AVAILABILITY OF THE TEST (1 of 3)

FOBT

- Full coverage of the test thru Konsulta Package Providers
- Most of the time recommended by primary care physicians > GI specialists

**No national screening program available in the philippines*



PhilHealth Konsulta
Konsultasyong Sulit at Tama

ETHICAL *(2 of 5)*

EQUITY / AVAILABILITY OF THE TEST (2 of 3)

FIT

- Out of pocket
- Least requested test among the 3 screening tests according to a local survey of 61 hospitals

Appendix 3. Frequency of hospitals providing the recommended screening tests and facility prices

Service	Frequency (n=61)	%
Guaiac Fecal Occult Blood Test (g-FOBT)	40	65.6
Immunological Fecal Occult Blood Test (i-FOBT/FIT)	23	37.7
Colonoscopy	50	82.0
Flexible Sigmoidoscopy	42	68.9

(Wong et al 2018)

ETHICAL *(3 of 5)*

EQUITY / AVAILABILITY OF THE TEST (3 of 3)

COLONOSCOPY

- As of 2024, there are almost 600 gastroenterologists in the Philippines, and 40 hospital-based colonoscopy centers. The country only has 22 training programs for adult gastroenterology.
- 1 gastroenterologist : 28, 334 average risk patients → 17,001 patients annually, 47 patients / day
- PHIC coverage:
  - PHP 12,120-18,000/ case rate
  - Full coverage of procedure in government hospitals
  - Most of the time recommended by GI specialists > primary care physicians

ETHICAL *(4 of 5)*

ACCESSIBILITY OF CRC SERVICES

- Access to healthcare is one of the factors associated with being up to date with CRC screening **(Tran et al 2018)**

ETHICAL *(5 of 5)*

FINANCIAL ACCESS TO SCREENING

- PHIC coverage
  - Konsulta: < 50 yo, opportunistic screening, > 50 yo mandatory screening
  - Hospital-based government hospital: full-coverage after recommendation of specialist

- Out of pocket
  - Majority (86.1%) were willing to participate in CRC screening programs initiated by the government and 46.9% agreed to undergo screening tests even as out-of-pocket expense.
  - Of the 115 respondents, the median yearly amount they are willing to spend was PhP 3,000 (PHP 100 -PHP 50,000) (Fernandez et al 2024)
    - Average monthly income: amount willing to spend
      - PHP 25,000: PHP 2,000 per year
      - PHP 25,000 to PhP 140,000: PHP 3,000 per year
      - > PHP 140,000: PhP 5,000 per year

LEGAL

DATA PRIVACY

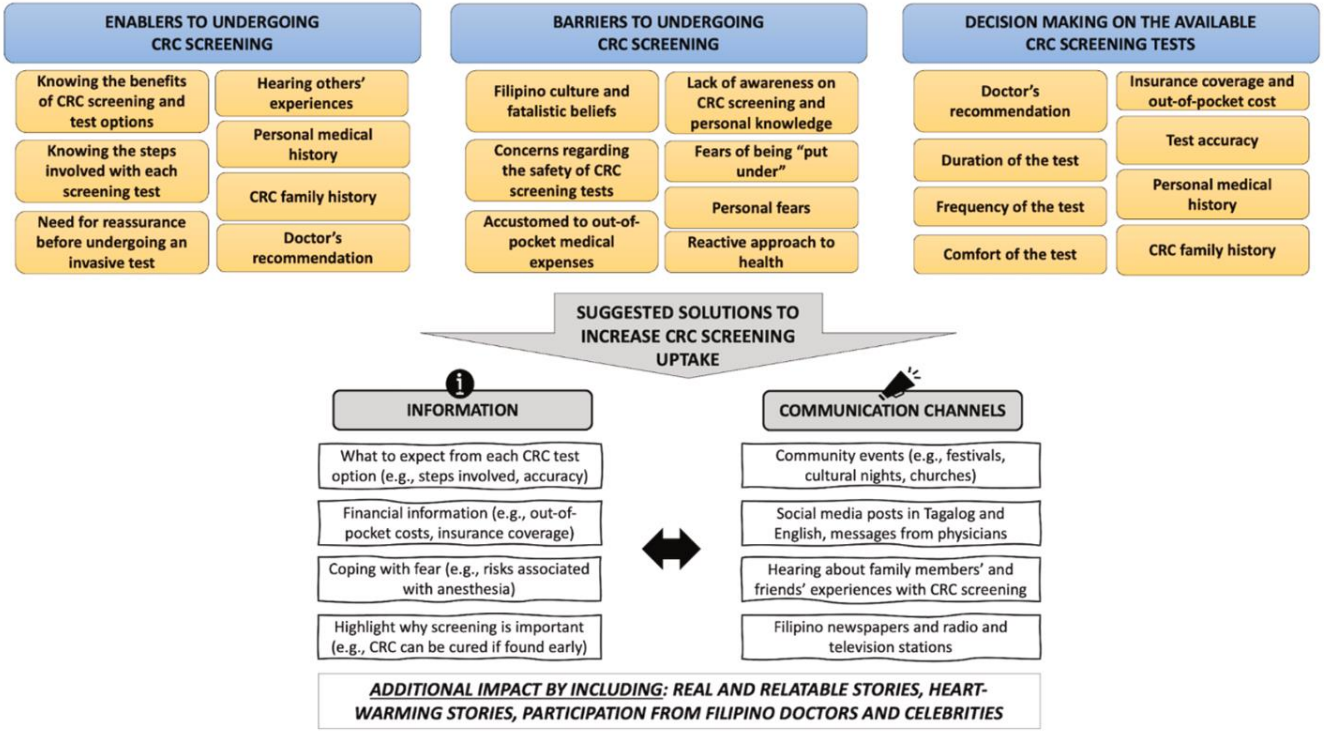
Screening scenario: Health Worker contacting patient after a positive test

- Contacting for confirmatory colonoscopy
- Training of BHW's or other healthcare team about non-disclosure

CONSENT FOR PROCEDURE

- False positive/ false negative screening results
- Complications from colonoscopy procedure

SOCIAL *(1 of 3)*



(Khalil 2022)

SOCIAL *(2 of 3)*

PATIENT PREFERENCE

Annual FIT> Colonoscopy

- Male > Female
- Not married
- < $100,000 income
- Unemployed
- With first-degree relative with CRC

(Crochietere 2025)

Factors affecting patient preference:

- Personal health beliefs
- Family contributions to decision-making
- Educational attainment
- Household income
- Cultural/social stigma

(Gimeno 2012; Francisco et al 2014; Sacdalan et al 2020; Zauber 2010; Maxwell et al 2013)

SOCIAL *(3 of 3)*

ACCEPTABILITY OF EARLY SCREENING FOR CRC

- 82% of Filipinos enrolled in the CRC Philhealth Z benefit program had stage III disease, while only 2% had stage I disease (Ting et al. 2020)
- Filipinos have lower CRC screening rate and worse outcomes compared to non-Hispanic whites in the USA (Khalil 2022)

INCREASING AWARENESS

- Awareness of the benefits of screening and reducing perceived barriers will help increase screening uptake (Gimeno 2012; Khalil 2022)

HEALTH SYSTEM IMPACT (1 of 3)

NEED FOR HEALTH PROMOTION

- Additional budget for advertising using social media and well-known personalities may be needed (Khalil 2022)
- Working with community health advisors to promote colorectal cancer screening (Maxwell et al 2013)

NEED FOR HUMAN RESOURCES FOR HEALTH

COLONOSCOPY:

- As of 2024, there are almost 600 gastroenterologists in the Philippines, and 40 hospital-based colonoscopy centers. The country only has 22 training programs for adult gastroenterology.
- 1 gastroenterologist : 28, 334 average risk patients → 17,001 patients annually, 47 patients / day

FIT

- BHW's may be tasked with distributing the kits and collecting the results

HEALTH SYSTEM IMPACT (2 of 4)

ACCREDITED TRAINING INSITUTIONS FOR GASTROENTEROLOGY 2024

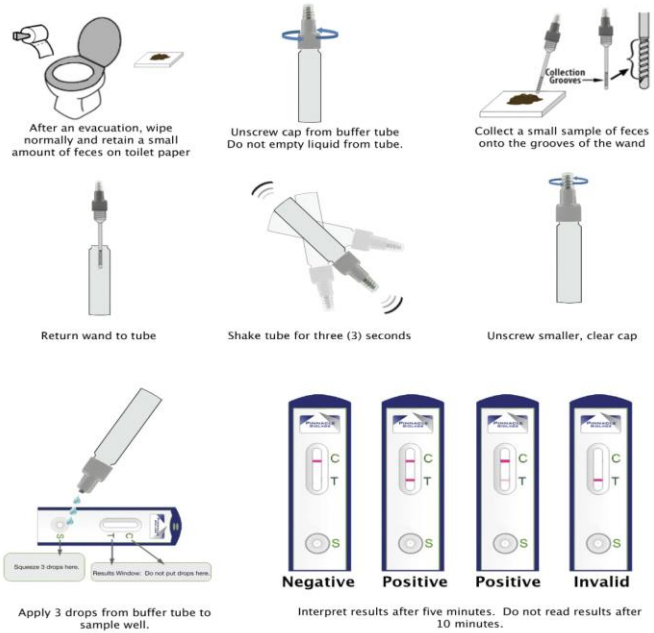
1. Cebu Doctors University Hospital
2. Chinese General Hospital and Medical Center
3. Cardinal Santos Medical Center
4. Chong Hua Hospital
5. East Avenue Medical Center
6. De La Salle University Medical Center
7. Metropolitan Medical Center
8. Makati Medical Center
9. Manila Doctors Hospital
10. University of the Philippines – Philippine General Hospital
11. St. Luke's Medical Center Quezon City
12. St. Luke's Medical Center Global City
13. The Medical City
14. University of the East Ramon Magsaysay Memorial Medical Center
15. University of Sto. Tomas Hospital
16. Veterans Memorial Medical Center
17. Vicente Sotto Memorial Medical Center
18. Baguio General Hospital and Medical Center
19. Southern Philippines Medical Center
20. Dr. Pablo O. Torre Memorial Hospital
21. Capitol Medical Center
22. Mary Mediatrix Medical Center

HEALTH SYSTEM IMPACT (2 of 3)

HOME KITS: EASE OF USE AND ACCEPTABILITY

- 76.3% (95% CI = 73.7% to 78.6%) disagreed FIT was unhygienic
- 78.1% (95% CI = 75.6% to 80.4%) preferred FIT to colonoscopy
  (Delisle et al 2022)

- Wordless instructions might aid efforts to raise the rates of colorectal cancer screening among low-literacy and non-English-speaking populations
  (Coronado et al 2014)



HEALTH SYSTEM IMPACT (3 of 3)

HOME KITS: CONCERNS ON INTERPRETATION

Concern on who should interpret results of screening tests for home kits: the layperson or a healthcare professional

- Might induce anxiety to layperson, thinking they are positive for CRC if the home kit screens positive

However, the DPCB nomination intend the use of FIT in the primary care facility level, not as home kit.

CRC Screening: PHEX Phase 1 Other Evidence Considered

Cost implications	gFOBT yearly: Php 600.00 FIT yearly: Php 415.00 Colonoscopy every 10 years: Php 15,537
Ethical	• Income, education level, age, location of residence, and immigration status affect screening intervention • Differential availability of screening resources (initial screening tests, subsequent tests and treatment) limits the uptake of screening programs
Social	• Non-invasive procedure: patients may be more amenable to comply • Geographic factors and maldistribution of specialist care for secondary visualization tests → hinders adoption of FIT/FOBT
Health Systems Impact	Need to improve access to healthcare through systematic interventions • Increase health insurance coverage • Consistent follow-up • Increase awareness and reduce perceived barriers • Proper facilities and evidence-based interventions

C6: Ethical, legal, social, health systems impact

RQ8: What are the ethical, legal, social, and health systems implications of the use of FIT with confirmatory colonoscopy after a positive result after a positive result for screening for colorectal cancer among apparently healthy adults 50 years old and above?

HTAC judgment: For equity, there is a need for a national screening program for colorectal cancer in the Philippines to improve access to early detection and prevention of CRC. The accessibility and availability of healthcare services have a substantial impact on screening behavior. The available literature compared annual FIT with colonoscopy every 10 years. Patient preference showed that screening with annual FIT is preferred over screening with colonoscopy. Leveraging patient preference for FIT and promoting awareness are key to maximizing uptake of the screening programs at the early stage of disease.

Based on the literature review, the use of annual FIT for colorectal cancer screening in the country, has no foreseen negative ethical, legal, social, and health systems impact. However, for the successful implementation of a CRC screening program, the following essential elements are recommended: data privacy protocols, protocols for consent for the procedure regardless of screening test, increase in human resources for health, and enhanced health promotion on available screening programs and patient education.