

# The Role of Fecal Occult Blood Test in the Screening of Colorectal Cancer and Inflammatory Bowel Disease

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## ABSTRACT

*Colorectal cancer (CRC) and inflammatory bowel disease (IBD) are a quite common colon disease in the world. The World Gastroenterology Organization (WGO) recommends screening test to detect colorectal cancer, i.e. fecal occult blood test (FOBT) and colonoscopy.*

*Diagnosis of CRC is established based on a good history taking, clinical manifestation, physical examination and laboratory examination. Other supporting laboratory tests include routine laboratory test of hemoglobin for detecting anemia, examination of bleeding stool either macroscopically or microscopically. Radiographic examination, either colon in loop or colonoscopy (if such modalities are available), shall be performed to confirm the occurrence of cancer mass in the colon. Moreover, biopsy examination is carried out to obtain the histopathological feature of tumor mass or the type of cancers. WGO has made a guideline for CRC screening, which consists of 6 cascades, which depend on the risk of colorectal cancer and local facilities available.*

*There are several kinds of FOBT, but the most frequently used include three methods, i.e.: the FOBT guaiac base/traditional, the fecal immunochemical test (FIT) and the FOB + transferrin rapid test (OT 102c & OT 103c). FIT and FOB + transferrin rapid test have a quite high sensitivity and specificity in detecting the lower gastrointestinal tract bleeding caused by colorectal cancer and IBD.*

**Keywords:** FOBT, colorectal cancer, IBD

## INTRODUCTION

Colorectal cancer (CRC) and inflammatory bowel disease (IBD) are a quite common colon disease in the world.<sup>1,2</sup> There is a trend in increased incidence rate of such disease in developing countries, including Indonesia. A study by Murdani demonstrates that 38.77% CRC in Indonesia is found in patients under 40 years of age.<sup>3</sup> The World Gastroenterology Organization (WGO) suggest screening tests for detecting CRC, i.e. the fecal occult blood test (FOBT) and colonoscopy.<sup>1-3</sup> CRC is one of important and significant factors in high morbidity and mortality rate in the United States of America and the world. CRC is a worldwide problem; with an annual incidence of approximately one million cases and an annual mortality rate more than 500,000 cases. Most CRC

arise from sporadic adenomas, and a few from genetic polyposis syndrome or IBD.<sup>1,2</sup>

## COLORECTAL CANCER

### Diagnosis

Diagnosis of CRC is established based on a good history taking, clinical manifestation, physical examination and laboratory examination. Questions about clinical manifestations that should be asked on history taking include change in defecation pattern – sometimes watery or hard stool, bleeding stool (hematochezia), weight loss, and pallor on the skin and body due to blood loss. The physical examination demonstrates pallor on skin and conjunctiva, weight loss and thin body indicating malnutrition. At the advanced stage, abdominal tumor mass may be found. Some laboratory tests are necessary, i.e. routine laboratory test of hemoglobin for detecting anemia, examination of bleeding stool either macroscopically or microscopically. Abdominal ultrasonography may reveal tumor mass/colon cancer,

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the occurrence of metastases to the liver and adjacent abdominal organ. Radiographic examination, either colon in loop or colonoscopy (if such modalities are available), shall be performed to confirm the occurrence of cancer mass in the colon. Moreover, biopsy examination is carried out to obtain the histopathological feature of tumor mass or the type of cancers. The CT-scan or abdominal magnetic resonance imaging (MRI) is intended to confirm the diagnosis of CRC and metastases; while the chest X-ray confirmed the lung metastases.<sup>1,3</sup>

### Screening

WGO has made a guideline for CRC screening, which consists of 6 cascades, which depend on the risk of CRC and local facilities available.<sup>1</sup>

- Cascade level 1

The cascade recommendation is appropriate for countries with a relatively high level of resources (financial, professional, facilities) and where the CRC mortality is high (The International Agency for Research on Cancer Data) and it becomes an important concern to public health priorities. Colonoscopy recommendation for average-risk male and female starts at the age of 50 and every 10 years in the absence of factors that would place them at increased risk.

Recommendation for screening people at increased risk is applied for: people with a family history of CRC or adenomatous polyps; people with a first-degree relative (parent, sibling, or child) with colon cancer or adenomatous polyps diagnosed under the age of 60; or people with two first-degree relatives diagnosed with CRC at any age should be advised to have screening colonoscopy starting at the age of 40 or 10 years younger than the earliest diagnosis in their family, whichever comes first and repeated every 5 years; people with a first-degree relative with a colon cancer or adenomatous polyp diagnosed when he/she was over the age of 60; or with the second-degree relative with CRC should be advised for screening as the average-risk people, but starting at the age of 40; people with second-degree relative (grandparents, aunt or uncle) or third-degree relative (greatgrandparent or cousin) with CRC should be advised for screening as the average-risk people.

Familial adenomatous polyposis (FAP). People who have a genetic diagnosis of FAP, or people who are at risk of having FAP but in whom genetic testing has not been performed or is not feasible, should have an annual sigmoidoscopy beginning at age of 10-12, to determine whether they are expressing the genetic abnormality. Genetic testing should be considered in patients

with FAP who have relatives at risk. Genetic counseling should precede the genetic testing and consideration of colostomy.

Hereditary nonpolyposis colorectal cancer (HNPCC). People with a genetic or clinical diagnosis of HNPCC or people who are at increased risk for HNPCC, should have colonoscopy every 1-2 years, starting at the age of 20-25 or 10 years earlier than the youngest age of colon cancer diagnosis in the family, whichever comes first. The genetic testing for HNPCC should be offered to first-degree relatives with a known inherited mismatch repair (MMR). It should also be offered when the family mutation is not already known, but one of the three modified Bethesda criteria is met.

People with a history of IBD or adenomatous polyp or CRC are candidates for follow-up surveillance, rather than screening. Guidelines have been published for the surveillance of these individuals.

- Cascade level 2

The recommendations are the same as for level 1, but they apply when colonoscopy resources are more limited; Recommendation of colonoscopy for average-risk male and female at age 50 to be performed once in a lifetime, in the absence of factors that would made increased risk. Recommendations for screening people who are at high risk are the same as for cascade 1.

- Cascade level 3

The recommendations are the same as for level 1, but they are applied when the colonoscopy resources are more limited and flexible sigmoidoscopy are available; recommendation for screening people at average risk: flexible sigmoidoscopy for average-risk male and female, starting at the age of 50 years, every 5 years, in the absence of factors that would made increased risk. Diagnostic work-up with colonoscopy when there is positive sigmoidoscopy; recommendations for people at high risk are the same as for cascade 1.

- Cascade level 4

The recommendations are the same as for level 3, but they are applied when the flexible sigmoidoscopy and colonoscopy resources are more limited; Recommendation on flexible sigmoidoscopy for average-risk male and female is once in a lifetime at the age of 50, in the absence of factors that would made increased risk. Diagnostic colonoscopy work-up for positive sigmoidoscopy or advanced neoplasia shall be performed depending on the available colonoscopy resources. Recommendations for

people at high risk are the same as for cascade 1.

- Cascade level 5

The recommendations are the same as for level 4 resources, but they are applied when the diagnostic colonoscopy is very limited; flexible sigmoidoscopy is recommended for average-risk male and female once in a life time at the age of 50. Diagnostic colonoscopy is performed only if advanced neoplasia is detected; recommendation for screening people at high risk depends on the colonoscopy resources available.

- Cascade level 6

Recommendations are the same as for level 1, but they can be applied when colonoscopy and flexible sigmoidoscopy resources are severely limited; fecal blood testing are recommended every year for average-risk male and female starting at the age of 50, in the absence of factors that would made increased risk. The type of test used depends on colonoscopy resources and the dietary habits of the population. Diagnostic work-up can be performed either with colonoscopy, if possible, or barium enema (colon in loop) if the colonoscopy is not available; Recommendation for screening people at high risk: the decision to identify separately people for special screening (level 1) depends on the available colonoscopy resources. If not available, those people can have screening as the people at average risk.

New tests: computed tomographic colonoscopy (CTC) and fecal DNA testing are available in a few countries with high/complete resources and generally not applicable globally; However, if available, those tests can be offered for male and female at average risk, starting at the age of 50, who do not wish to be screened by other more standard method, in order to increase the people being screening in those countries. Other colorectal screening that generally recommended are: fecal testing - fecal occult blood test, pyruvate kinase type M2 (M2-PK), K-ras, etc; colon in loop, CT-colonography, colonoscopy/rectosigmoidoscopy.

### Complication

The following complication of CRC may be found, i.e. lower gastrointestinal tract bleeding through anal bleeding (hematochezia) with bright red color or watery stool mixed with blood, anemia, ileus obstructive, malnutrition and metastases.<sup>1,3</sup>

## INFLAMMATORY BOWEL DISEASE

### Type

Inflammatory bowel disease (IBD) is categorized into ulcerative colitis (UC), Chron's disease (CD) and intermediate colitis (the intermediate form of UC and CD).<sup>2,4-7</sup>

### Etiology/Pathogenesis

The etiology of IBD is still vague until now; however, there are many predisposition factors that take role including genetic, antigenic trigger (pathogenic/non-pathogenic microbacteria, antigenic food) immune response (autoimmune), antibody secretion, cytokines, psychological stress.<sup>2,4-7</sup>

### Diagnosis

Diagnosis of IBD is made based on clinical manifestation collected by history taking, physical examination, supporting laboratory tests such as routine laboratory test, colon in loop or colonoscopy and histopathological examination. On history taking, we usually find chronic bleeding diarrhea, weight loss, fever, abdominal pain, extra-intestinal manifestation (tender joints, apthae). On physical examination, we may get abdominal pain on palpation, arthralgia, stomatitis, skin disorder (gangrenous pioderma, perianal fistulas, etc). There are no characteristic findings on laboratory tests but reduced hemoglobin (anemia) may be found, as well as increased C-reactive protein (CRP) level and positive anti *Saccharomyces cerevisiae* antibodies (ASCA), anti neutrophil cytoplasmic antibodies (ANCA) and nucleotide oligomerisation domain (NOD) serum level in some patients. Fecal testing may reveal blood or positive FOBT. In patients with Crohn disease, the colon in loop or barium enema examination would indicate the stricture, fistula, and cobble stone appearance in ascending colon; while in ulcerative colitis, the colon in loop or barium enema would reveal the color button appearances and rectosigmoid ulceration. On colonoscopy, the following abnor-malities will be found, i.e. ulceration with/without skip lesion, pseudopolyp (located on rectosigmoid indicating ulcerative colitis; when it is found on ascending colon/ileocaecal, it suggests Crohn's disease), granuloma, etc. Histopathological examination will reveal abnormalities such as crypti abscess, increased number of basal inflammatory cells, granuloma, Langhan's giant cell without caseous process, etc.<sup>2,4-7</sup>

### Complication

Complication of IBD that can be found include lower gastrointestinal tract bleeding through anal bleeding (hematochezia), chronic watery stool mixed with blood (chronic bleeding diarrhea), anemia,

stricture, perforation, fistulas and malnutrition.<sup>2,4-7</sup>

## FECAL OCCULT BLOOD TEST

Fecal occult blood (FOB) is a term for blood present in stool (feces) that is not visibly apparent by the naked eyes, but it shall be found by certain tests. Fecal occult blood test (FOBT) is a test for hidden (occult) blood in the stool. Conventional FOB looks for heme; while newer FOBT such as the FIT, look for globin in the stool. FOB and transferrin rapid test is a test that looks for hidden (occult) blood in the stool by checking the presence of globin and transferrin. The tests can detect 200 ng globin/mL feces and 40 ng transferrin/mL feces. It is considered normal when only 0.5-1.5 mL of blood a day that escapes from the blood vessel into the stool each day.

There are several types of FOBT, but the most common include the three methods,<sup>8-18</sup> which are: (1) The guaiac-based fecal occult blood test to detect minimal blood loss of at least 10 mL/day (+ 2 teaspoons); (2) Fecal immunochemical test (FIT) to detect blood loss at least 0.3 mL/day, it could detect blood of 50-200 ng/mL. The test does not detect blood from the stomach and proximal small intestine, so it is more specific for bleeding from the colon or lower gastrointestinal tract; (3) FOB and transferrin rapid test OT 102c & OT 103c, which is more sensitive and specific in looking for gastrointestinal bleeding rapidly. The test can detect at least 200 ng globin/mL feces and 40 ng transferrin/mL feces.

The blood detection in FOBT involves smearing some feces onto some absorbent paper or cloth which has been treated with a chemical substance. Afterward, a special chemical substance is dropped onto the stool specimens. If the paper has changed into blue color, it means that blood is present in the stool specimens. FOBT may show positive results in some diseases, such as CRC, hemorrhoid, anal fissures, colon polyp, inflammatory bowel disease (ulcerative colitis; Crohn's disease), gastric cancer, peptic ulcer, gastroesophageal reflux disease (GERD), aspirin or nonsteroidal antiinflammatory drugs (NSAIDs) treatment.

The traditional guaiac-based FOBT test has some disadvantage that it can be affected by some substances of food content. Therefore, some foods should be avoided in several days prior to the traditional FOBT test. Consuming red meat (the blood it contains can turn the test positive), radishes, turnips, cabbage, cauliflower, uncooked broccoli, horseradish and cantaloupe will cause false-positive results; while consumption of citrus fruits and vitamin C supplements can turn the test into false-negative result.

There are several methods of FOBT:<sup>8-18</sup> (1) Traditional method: stool guaiac hemocult or instacult seracult, coloscreen-detects heme; (2) New test: flushable reagent pads: EZ DetectT, ColoCARE; (3) Fecal porphyrin quantification: hemoquant – have a high false-positive result; (4) Immunochemical FOBT: HemeSelect, QuickVue iFOB, FOBGold or Automated SENTiFOB or OC Auto 80-Automated iFOBT – more specific in detecting globin in stool rather than heme. More sensitive and specific for lower gastrointestinal tract bleeding; (5) Fecal DNA tests: Pre-Gen-Plus is a more sensitive test than FOBT and FIT. One study found that the test is more sensitive than FOBT (51.6% vs. 12.9%); (6) FOB and transferrin rapid test: OT-103c/Oncoprobe® – detects globin and transferrin in stool, more sensitive and specific than guaiac based FOBT and immune chemical FOBT.

## Sensitivity and specificity of FOBT, FIT and FOB + transferrin rapid

The sensitivity of single FOBT has been found at 30-60%, but if three tests are performed directly (as in standard) and being used every 1-2 years, the sensitivity rises to 90-92%.<sup>11-13</sup> Sensitivity and specificity of FIT in detecting CRC are 81.8% and 96.9%, respectively. Moreover, the sensitivity and specificity of FIT in detecting advanced colorectal adenoma (non-malignant tumor) are 29.5% and 97.3%, respectively.<sup>15</sup>

Transferrin (Tf) has higher significant positiveness in CRC and pre-malignant lesion (76% Tf vs 61% immunochemical FOBT (IFOBT),  $p < 0.05$ ). Combination of Tf and IFOBT had 90% positive rate in cancer patients, 78% in premalignant patients, and 29% in low-risk subject. The overall accuracy of IFOBT and Tf tests for detecting CRC and pre-malignant lesion are 69.0% and 76.4%.<sup>14</sup>

Lower gastrointestinal bleeding (hematochezia) can occur<sup>1,2,10,11</sup> as gross bleeding (obvious and massive bleeding); occult (invisible, small amount); and obscure bleeding (unidentified bleeding source by regular endoscopy). Gross and obscure bleeding is apparently visible by the eyes, and therefore, FOBT is not necessary. In contrast, FOBT is extremely needed in occult bleeding to detect any bleeding occur. Obscure bleeding, which sometimes in the form of occult bleeding may not be readily visible by the eyes; thus, FOBT also necessary in this case.

## CONCLUSION

FOBT, FIT, FOB and transferrin rapid test are tests to look for any blood in the stool which are used for screening of CRC and IBD. FIT and FOB + transferrin rapid test are tests with the highest sensitivity and specificity.



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