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Sequential Combination of Serum Pyruvate Kinase Isoenzyme M2 and Colonoscopy-A Promising Screening Protocol for Colorectal Cancer Early Diagnosis

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Abstract

Background: Early diagnosis and treatment through mass screening is practical against colorectal cancer (CRC). Low compliance for current screening tests affects the effectiveness of CRC mass screening. An efficient screening protocol with high compliance is needed for CRC mass screening.

Methods: Systematic searches were done through Medline and Cochrane Library databases - initial Medline searches were in February 2010 and additional searches in March/April 2010. Search terms included [("Colorectal cancer" AND "screening program" AND "incidence") OR ("Colorectal cancer" AND "screening program" AND "mortality")] AND ["fecal occult blood test" OR "sigmoidoscopy" OR "colonoscopy" OR "Double-contrast barium enema"].

Results: This review explored the current CRC mass screening protocols to find a more efficient and practical mass screening protocol and problems suitable for further research. Considering the current economic crisis and limited available resources, combination of high risk factor questionnaire and immunochemical fecal occult blood test approach as primary CRC mass screening can currently be used as a risk stratification tool to identify high-risk populations from the community, especially for medically and economically underserved areas/countries before a new better test comes. Using serum Pyruvate Kinase Isoenzyme M2 (M2-PK) as primary and colonoscopy as secondary screening test sounds more efficient with higher compliance than current CRC mass screening protocols.

Conclusion: Recommendations for CRC mass screening are suggested for each risk population based on risk stratification. Serum M2-PK- may be developed as a promising CRC primary mass screening test. Sequential combination of serum biomarker such as Pyruvate Kinase Isoenzyme M2 (M2-PK) and colonoscopy can be a promising CRC mass screening protocol.

Keywords: Colorectal cancer mass screening; Serum pyruvate kinase isoenzyme M2; Serum M2-PK; Fecal occult blood testing; High risk factor questionnaire; Colonoscopy; Stool DNA testing; Risk stratification tool

Abbreviations: CRC: Colorectal Cancer; FOBT: Fecal Occult Blood Testing; M2-PK: Pyruvate Kinase Isoenzyme M2; HRFQ: High Risk Factor Questionnaire

Introduction

Colorectal cancer (CRC) has been a major public health problem worldwide in past decades; CRC is the second leading cause of cancer death in North America and Western Europe [1-17]. The incidence and mortality of CRC are increasing in both China and Japan recently [2,4,5,14]. However, causes for sporadic CRC have not been determined [2,4]. Thus mass screening becomes more important and is practical against CRC. Low compliance for current screening test affects the effectiveness of CRC mass screening programs [5].

Most sporadic adenocarcinomas arise from adenomatous polyps. Progression from normal mucosa through polyp formation and subsequent transformation into cancer (adenoma-carcinoma sequence) is a process occurring over a five to fifteen year period [18]. This relatively long duration of the carcinogenesis for CRC and the removal of adenomatous polyps (second prevention) warrant a screening effort. Overall, CRC has characteristics that make it well-suited for screening and prevention based on WHO (World Health Organization) criteria [1,17].

Screening for CRC has the potential not only to allow early diagnosis, thereby reducing CRC mortality rates, but also to prevent development of CRC due to the removal of adenomas [4,13,14,17]. Because of this point, it sounds CRC screening programs should be more successful than most other types of cancer screening programs (e.g., breast, cervix, and prostate). However, CRC screening is not as successful as other cancer screening programs due to many problems such as low compliance due to natural flaws of current screening tests, fear of pain and bowel preparation, lack of time, financial and other issues [5,19].

Consistent evidence shows that screening asymptomatic

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individuals can reduce mortality and incidence of CRC, though the magnitude of effectiveness for each test is relatively small in terms of mortality reduction due to many barriers [1,4,14]. In order to successfully prevent and control CRC incidence and mortality in the population, mass screening is the best choice. However, due to the huge aging population worldwide, especially in China, there is an increasing concern whether current limited resources can meet the requirement for CRC mass screening.

Considering the current worldwide economic crisis, a newer more cost-efficient mass screening strategy for CRC, with higher validity, is desirable. A tool should be used to identify high risk populations from the general population and focus CRC screening on these high risk individuals. Thus, limited resources can be efficiently utilized. This review summarizes the current status of CRC screening tests or protocols to find a more efficient mass screening protocol as well as problems in CRC screening for further research.

Literature Search

Systematic searches were done through Medline and Cochrane Library databases - initial Medline searches were in February 2010 and additional searches in March/April 2010. Search terms used included [("Colorectal cancer" AND "screening program" AND "incidence") OR ("Colorectal cancer" AND "screening program" AND "mortality")] AND ["fecal occult blood test" OR "sigmoidoscopy" OR "colonoscopy" OR "Double-contrast barium enema"]. A total of 298 abstracts, 44 reviews and 66 full-text reports between 1975 and February 2010 (searching time) were initially reviewed. Additional relevant full-text reports were also solicited by email from the corresponding authors. Finally, full-text reports published in either English or Chinese were included.

Current CRC Screening Tests/Protocols

Currently used CRC mass screening tests/protocols reported in the literature include fecal occult blood testing (FOBT) [5,6,20-40], a mass screening protocol of combining immunochemical FOBT (iFOBT) and a high risk factor questionnaire (HRFQ)- simultaneous testing design [6,41], flexible sigmoidoscopy [42-48], and colonoscopy [37,39,49-60]. Available evidence does not support choosing one CRC screening test over another; none is ideal, but all save lives [4,13-14,18]. Different CRC screening protocols are associated with varying efficacy in terms of the risk of dying from cancer, test performance (sensitivity and specificity), cost, preparation, safety (side effects), and inconvenience. How the screening is offered, process, sensitivity, rate of unnecessary colonoscopy, expected mortality reduction, method of screening test result transmission, safety, and cost are the main factors influencing the implementation of mass CRC screening [62]. Population participation/compliance is fundamental for the success of CRC mass screening as for any disease screening program. There are a few recently developed and still evolving CRC screening tests. They are computed tomographic colonography [39,60,63-70], DNA-based stool tests [71-83], and serum biomarker tests [82-85]. Table 1 summarizes the pros and cons for each test as a primary CRC mass screening test.

Fecal occult blood testing (FOBT) [1,14,18,61,88-90]

FOBT is used to detect bleeding from a benign or premalignant polyp or cancer. An FOBT positive for blood is used to select who should have a follow-up colonoscopy. The FOBT is the simplest, inexpensive, and non-invasive CRC screening method and has been the most widely used in CRC screening for decades [1,4,5,89]. The samples are collected at home for three consecutive days. No bowel preparation is required. Based on current evidence, iFOBT is the best among all the methods of FOBT. Sensitivities for CRC were 67 to 90 percent for 1-day, 2-day and 3-day iFOBT in an asymptomatic population screening test with specificities from 95 to 98 percent. But the iFOBT has a lower sensitivity for detection of adenomas than cancer. Another challenge is to implement reminder methods to ensure compliance with repeated annual/biennial testing.

A successful FOBT screening program should include proper performance of the test: 3-day home sample, adherence to initial test, annual/biennial repeat testing after negative test, follow-up of positive test - colonoscopy preferred, colonoscopic surveillance after detection and removal of adenomas, and cancer care for detected cancers. However, not all health care providers follow the recommendations. For example, data from the National Health Interview Survey showed

Measures	iFOBT	HRFQ+iFOBT	Colonoscopy	Serum M2-PK	Fecal DNA
Sensitivity	67-90%	Better than iFOBT	High	100% at 2.0U/ml cutoff	71-91%
Specificity	95-98%	Lower than iFOBT	High	67-81% at 4.0 U/ml cut off	93-100%
Cost/person/procedure	$22.22	$25.00	$662.00 for without polypectomy; 846.00 with polypectomy or biopsy; Treatment with complications: $12,446 for perforation; $5208 for serosal burn; $5208 for bleeding with transfusion; $320 for bleeding without transfusion	$5.22	No data, expected to be expensive
Safety	Non-invasive Home-based	Non-invasive Home-based	Invasive with risk of complications Hospital/office-based	Non-invasive Hospital/office-based	Non-invasive Hospital/office-based
Compliance	High	High	Low	Highest	High
Bowel preparation	No	No	required	No	No
Diet restriction	No	No	Yes	No	No
Sedation	No	No	Yes	No	No
Frequency	Every 1-2 years	Every 1-2 years	Every 10 years	Annual	No data
Cancer prevention	Low potential	Potential increase compared to iFOBT alone	High potential	High potential	Low potential
Mortality reduction	Up to 60%	No data	Should be high, but no data	No data	No data

Abbreviations: iFOBT, Immunochemical Fecal Occult Blood Test; HRFQ, High-Risk-Factor Questionnaire; M2-PK, Pyruvate Kinase Isoenzyme M2.

Table 1: Comparison of pros and cons of feasible primary colorectal cancer mass screening tests/strategies based on current evidence [41,93].

that 30% recommended repeating the FOBT test after a positive FOBT and 23% recommended sigmoidoscopy alone [14].

In resource-limited Asian countries, the FOBT is the first choice for CRC screening because of its higher effectiveness in the population [6]. However, bleeding from cancers and precancerous polyps may be intermittent and most small colorectal neoplasms do not tend to bleed. Therefore, the FOBT alone inevitably misses some important lesions that do not bleed, or bleed intermittently which may give the FOBT a high false negative predictive value [6,39].

Simultaneous testing design: iFOBT and a high risk factor questionnaire (HRFQ) [6,39]

Based on the theory of simultaneous testing design, the net sensitivity of combining iFOBT and HRFQ as primary screening tests should be higher than iFOBT alone. Investigation of HRFQ has been used in the diagnosis of CRC in clinical processes [41,91,92]. Based on HRFQ, the general practitioners select high risk population for colonoscopy and average risk population for FOBT in some countries where mass screening is implemented but this relatively passive screening strategy may delay diagnosis or miss cases among people who not frequently or rarely see the general practitioners. To include HRFQ in an active mass screening program is a very useful method to identify high and average risk population from the general population. From our mass screening programs in both Jiashan county and Hangzhou city [6,41], about 40% of adenomas, 50% of nonadenomatous polyps, and 30% of advanced neoplasms are identified by HRFQ and missed by the iFOBT. Although the CRC detection rate is not improved by HRFQ, it can be used as a complementary primary screening method for colorectal adenoma and non-adenomatous polyps to make up for a deficiency of iFOBT.

HRFQ has a relatively high false-positive rate that increases the number of colonoscopies, but it is cheap, accessible, of no obvious risk, and has a considerable capacity for finding colorectal adenoma and non-adenomatous polyps, especially advanced adenoma, which is very important to medically and economically underserved populations. In our study, HRFQ found about 30% of advanced adenomas, which is of vital importance to prevent and control CRC for its apt malignancy transforming.

Flexible sigmoidoscopy (FS) [14,18,39,93-107]

Observational studies have demonstrated that screening with FS can reduce CRC mortality. No randomized trials demonstrated the efficacy of FS in preventing CRC outcomes. Due to examining at most the distal colon of the large bowel, the role of FS in a population-based CRC screening program is limited. FS is likely to be less effective with advancing age and among women, because of the tendency for older individuals to develop neoplasia in the proximal colon and because women are more likely to have advanced neoplasia in the proximal colon without a distal index lesion [14].

Colonoscopy [14,18,61,108-123]

Colonoscopy is the most sensitive and specific test for evaluation of the colon, offering both diagnostic and therapeutic capabilities [14]. It completely examines the entire colon and rectum and provides the opportunity for the endoscopic removal of adenomas and biopsy of suspicious mass lesions. A small proportion of patients (0.3% - 0.9%) may develop CRC within 2 to 3 years of a baseline colonoscopy due to the possibility of new fast-growing lesions or missed lesions at the baseline examination or incompletely removed lesions [14]. Colonoscopy may cause complications such as bleeding, perforation, and cardiopulmonary events. Capacity and expertise to perform a colonoscopy of high quality may be limited in some countries, and in regions within countries. There is compelling evidence that a screening colonoscopy with removal of detected polyps leads to a substantial reduction in the incidence of CRC, with its efficacy rivaling or superior to annual FOBT, FS, and DCBE [113]. The prevalence of adenomas in the 50-59 years age group in the United States is 11% with a prevalence of advanced adenomas of 3.5%. The prevalence is increasing with aging [41] and higher for the population that had one or more first-degree relatives with a history of CRC [113,124]. This makes colonoscopy well-suited for CRC screening in the population. However, due to the risk of complications, cost, required bowel preparation, low compliance rate of colonoscopy and limited resources such as the number of gastroenterologists, health care authorities in many countries do not consider colonoscopy as a primary screening test option in the general population, but rather as a follow-up screening and or diagnostic test after primary screening [6,41,125].

Stool DNA testing [71-83,93,126]

Stool DNA test sounds like a promising new test for CRC screening. Patients who have CRC have specific mutations in the neoplastic tissue. During apoptosis, cells of cancers and pregnant adenomas with DNA are shed into stool. DNA from neoplasms remains relatively stable in the stool. Specific mutations can be identified in stool samples using methodologies to amplify DNA. Multi-target DNA testing has a 71 to 91% sensitivity for detection of cancer. This technology is still evolving. It is likely to improve and become less costly. But there are unsolved issues: What is the optimal genetic profile for screening? If the test is negative, how often should it be repeated? The genetic test may still be a true positive despite the absence of visible pathology at colonoscopy. What is the significance of a positive test if no colon pathology is found? Also, a positive test could be an indicator of pathology beyond the colon and the test is still a fecal test which compliance may be not as high as a serum test.

Serum biomarker [84-87]

Any serum biomarker with high sensitivity should be ideal as a primary screening test for CRC mass screening. So far there is no good serum biomarker available for CRC mass screening although a few serum biomarkers have been tested for CRC screening [84-87]. Recently we have completed a pilot study of the performance of serum Pyruvate Kinase Isoenzyme M2 (M2-PK) in CRC mass screening (Manuscript has been revised and submitted). Results show that the sensitivity is 100.00% for CRC when the cut-off value of serum M2-PK is 2.00 U/mL. The price is about $5 per person per procedure. Serum M2-PK may be a promising non-invasive biomarker for CRC mass screening. It is cheap, convenient, safe, and efficient test with a high sensitivity for CRC primary mass screening. This test needs to be tested in other population settings with a big sample size such as medically and economically underserved populations.

CRC two-stage (sequential) mass screening protocol in China [5,6,41]

The implementation of CRC mass screening in China is obviously more challenging than in any other countries in the world. Due to a huge aging population, the target population for CRC screening is 0.43 billion (one-third of 1.3 billion) people age 50 and older in China. Are current resources such as number of physicians, colonoscopy centers and other related resources available to accomplish CRC screening in such a large population? Based on limited resources and current screening technology, a two-phase screening strategy is

used. Combination of iFOBT twice by one-week interval for the first screening and follow up once annually and investigation of HRFQ is used as primary screening methods in the first phase. HRFQ positive means 1) individuals having one of the following events: a) a history of cancer, b) a history of polyps, and/or c) a family history of CRC in first-degree relatives and/or 2) at least two of the following events: a) chronic coprostasis, b) chronic diarrhea, c) phlegmatically blood feces, d) serious unhappy life events such as death among first degree relatives, e) chronic appendicitis or appendectomy, and/or f) chronic cholecystitis or cholecystectomy [6,41,127]. If either the iFOBT or HRFQ is positive, a colonoscopy is recommended in the second phase.

Based on our preliminary data and published papers [6,41], this two-stage (sequential) mass screening protocol - combining iFOBT and HRFQ as primary and colonoscopy as secondary screening tests is more efficient and practical than the other protocols. It has a higher net sensitivity and a high specificity which makes sure more people with high risk of CRC will not be missed in the first stage and more people without CRC risk will not be misdiagnosed in the late stage. It is cheap, safe, more efficient and practical. The positive predictive value of our mass screening protocol of combining iFOBT and HRFQ as primary screening for advanced neoplasm is 5.7%, which was higher than that of iFOBT (2.2%) or guaiac FOBT (gFOBT) (1.2%) 12 alone [41,128]. Combination of HRFQ and iFOBT improves the detection capacity of colorectal neoplasm compared with iFOBTs alone. Overall, combination of iFOBT and HRFQ is more effective than iFOBT alone in CRC prevention and control in the population, especially for developing countries and underserved populations in developed countries.

Problems for Future Research

Low compliance

The effectiveness of a screening program depends on participant compliance with testing and follow-up. Screening (compliance) rates for CRC in the general population vary widely and are generally low and well below those for mammography [5]. This issue has consistently existed in past decades. Barriers to CRC screening have extensively been investigated recently [5,19]. Patient-related barriers such as poor awareness of CRC and its screening programs, characteristics of screening tests, and lack of time and system-related barriers such as difficulty with bowel preparation and financial costs affect screening rate. Financial support is one of the main barriers to a colonoscopy as a screening test. In the United States, the policy of Medicare reimbursement for screening FOBT, flexible sigmoidoscopy and colonoscopy may increase screening rate within an insured population. Raising public awareness of CRC and its screening program, integrating CRC screening into the health care system, and using a painless colonoscopy should motivate an increased CRC screening rate.

Limited resources for implementation

Nationwide implementation of CRC screening in the population is a major challenge due to an aging population worldwide. In the United States, the target population is 70 million adults age 50 and older, and, as mentioned before, China has 0.43 billion people eligible for CRC screening. Are current physicians, colonoscopy centers, and other related resources available to accomplish CRC screening in such a large population? Eliminating barriers to implementation of CRC mass screening should be considered in the future.

Better screening test

In time, newer, better screening tests or strategies are anticipated to be developed to replace current options. For example, compliance would be increased if the primary screening test or the follow-up test is a blood test instead of colonoscopy, etc. Noninvasive methods should be developed to further risk-stratify those currently considered at average risk for CRC. Nevertheless, currently available screening tests should be continuously used and not wait until something better comes along.

Risk Stratification	Definition and Characteristic	Recommendation
High-risk population	High high-risk individuals: hereditary syndromes such as familial polyposis and Lynch syndrome associated with specific inherited gene mutations; lifetime risk for CRC is 100% familial polyposis and 40% women and 80% men in Lynch Syndromes; account for 4% of all CRC Medium high-risk individuals: one or more family members having CRC without one of the hereditary syndromes; lifetime risk for CRC is 10-12% if one first-degree relative having CRC; account for 15-20% of all CRC Low high-risk individuals: personal history of chronic ulcerative colitis or Crohn colitis or Crohn colitis; account for 1% of all CRC in USA.	Identified through HRFQ; taking a careful family history followed by genetic testing; colonoscopy begins as early as possible, at least before age 40 years Identified through HRFQ; taking a careful family history; colonoscopy begins at an age at least 10 years younger than the age at which the index family member had CRC or age 40 whichever comes first Identified through HRFQ and iFOBT annual approach as primary screening; followed by full colonoscopy if either HRFQ or iFOBT positive; routine screening initiated before the onset of symptoms at age 50 years
Asymptomatic, average-risk (not low risk) population	Low high-risk individuals: aged 40 - 80 years having one or more of the following: 1. Positive iFOBT; 2. A personal history of cancers or intestinal polyps; 3. Two or more of the following: (a) chronic diarrhea; (b) chronic constipation; (c) phlegmatically blood feces; (d) history of appendicitis or appendectomy; (e) history of chronic cholecystitis or cholecystectomy; (f) history of psychiatric trauma (e.g. divorce, death of relatives); 4. high-risk lifestyles: smoking, heavy alcohol consumption, obesity, physical inactivity, and diet high in animal fat and low in vegetables, fruit and fibers; lifetime risk for CRC is 5-6% in the West and Japan and China; sporadic CRC in such patients accounts for 75% of all CRC in the west.	Identified through HRFQ and the iFOBT every 1-2 years approach as primary screening; followed by full colonoscopy if either HRFQ or iFOBT positive; routine screening (iFOBT every 1-2 years, FS every 5 years or combination of iFOBT every 1-2 years and FS every 5 years, Colonoscopy every 10 years) initiated before the onset of symptoms at age 50 years

Note: CRC, colorectal cancer; iFOBT, immunochemical fecal occult blood test; FS, flexible sigmoidoscopy; HRFQ, high risk factor questionnaire.

Table 2: Updated recommendation for colorectal cancer (CRC) mass screening strategy based on currently available tests.

Recommendations for CRC mass screening

Based on limited resources and current screening technology, the best strategy is to conduct CRC mass screening based on risk stratification. Ideal screening would target high-risk populations. For example, familial, unhealthy lifestyle and other risk assessments may be used as a risk-stratification tool to identify high-risk populations for intense follow-up surveillance and low or no-risk populations for less intensive or no follow-up surveillance. Different populations may have different risk factors. Therefore, questionnaires with different risk factors may be applied to different populations from different countries.

Detailed recommendations for CRC mass screening based on current evidence are suggested in Table 2. The recommended flow chart of currently feasible CRC mass screening protocol, especially for medically and economically underserved populations is shown in Figure 1. For medically and economically underserved populations, the iFOBT combing with a HRFQ can be recommended for 2-day sample tests for the first screening and follow up once (1-day sample test) every 1-2 years. For some populations in the developed areas or countries with sufficient medical resources and good economic support, screening frequency and test could be flexible. The iFOBT can be recommended for 3-day sample tests for every 1-2 years. Or colonoscopy might be recommended as primary screening test for them.

Combination of HRFQ and iFOBT can be currently used as risk stratification tools to identify high-risk populations from the general population, especially medically and economically underserved populations, before a new more efficient screening test comes. High high-risk individuals defined as having hereditary syndromes such as familial polyposis and Lynch syndrome should take a careful family history followed by genetic testing [14]. Colonoscopy screening should begin as early as possible, at least 10 years before age 40 years and a colonoscopy every 2-3 years is preferred. Medium high-risk individuals defined as one or more first-degree family members having CRC without one of the hereditary syndromes should take a careful family history. Colonoscopy screening should begin at an age that is at least 10 years younger than the age at which the index family member had CRC or age 40, whichever comes first; colonoscopy every 5 years is preferred. Low high-risk individuals include personal history of chronic ulcerative colitis or Crohn colitis, identified through a HRFQ and the annual three-day iFOBT approach as primary screening followed by full colonoscopy if either HRFQ or iFOBT is positive. If negative, routine screening (iFOBT annual, FS every 5 years, both iFOBT annual and FS every 5 years, and colonoscopy every 10 years) should be initiated before the onset of symptoms at age 50 years. Other high-risk asymptomatic (average-risk but not low risk) individuals of CRC can be defined as low high-risk identifying from aged 40 - 80 years who have one or more of the following: 1. Positive results from the annual iFOBT; 2. A personal history of cancers or intestinal polyps; 3. Two or more of the following: (a) chronic diarrhea; (b) chronic constipation; (c) phlegmatically blood feces; (d) history of appendicitis or appendectomy; (e) history of chronic cholecystitis or cholecystectomy; (f) history of psychiatric trauma (e.g. divorce, death among the first degree relatives); 4. High-risk lifestyles such as smoking, heavy alcohol consumption, obesity, physical inactivity, and diets high in animal fat and low in vegetables, fruit, and fiber. Screening for these individuals can be the same as low high-risk individuals described above and the screening frequency can be flexible. Those individuals not identified by any above stratification should be encouraged to continue routine HRFQ and iFOBT every 1-2 years screening from age 50 to 80 years.

Addressing and considering patient and system-related barriers with each individual should help improve CRC screening compliance. Uniform, up-to-date guidelines on CRC mass screening practices should be used by physicians and other related stakeholders. Attention to family history and personal risk assessment is needed. Regular workshops to educate physicians and other related stakeholders to utilize and be aware of the CRC screening tests should be established.

Colon surveillance after polypectomy or cancer resection should be considered part of a comprehensive screening program [14]. It may be useful for physicians to recommend risk-reduction strategies. Considerable epidemiologic evidence shows that environmental factors such as smoking, heavy alcohol, obesity, physical inactivity, and diets high in animal fat and low in vegetables, fruit, and fiber may increase the risk of CRC. Any intervention to stop these environmental risk factors would be helpful in reducing some incidence of CRC. Nevertheless, patients should understand risk-reduction strategies and do not take the place of effective screening.

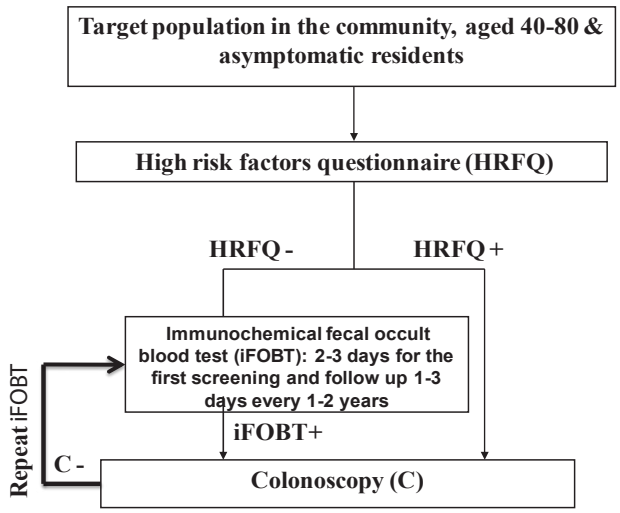

Figure 1: Flow chart of currently feasible colorectal cancer mass screening protocol, especially for medically and economically underserved populations.

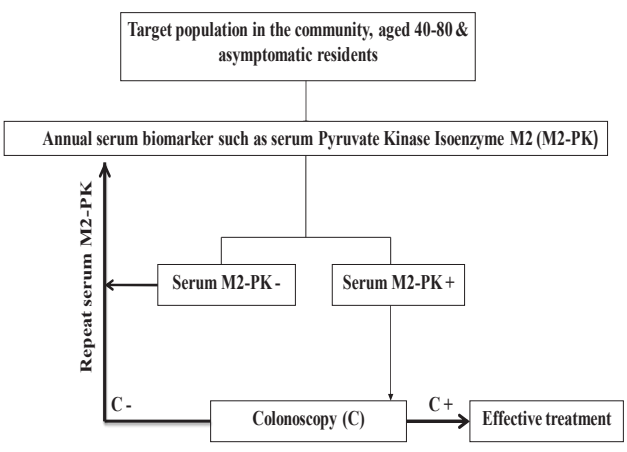

Figure 2: Flow chat of promising new colorectal cancer mass screening protocol-serum biomarker-M2-PK as primary screening test and colonoscopy as screening diagnosis test.

Based on the theory of mass screening and characteristic of CRC, a promising mass screening protocol should include two-stage (consequential testing design) screening- using serum biomarker such as serum M2-PK as primary screening test and colonoscopy as a follow-up or secondary screening test in the population. First, to use serum M2-PK as a primary screening test avoids inconvenience, expensive costs, and colonoscopy-related complications during CRC screening which would increase the compliance for a CRC mass screening to a high level which is a key to success in a CRC mass screening program. Second, serum M2-PK has high sensitivity -100% at the cut-off value of 2.00 U/mL which guarantees almost no CRC cases would be missed at the first stage of screening. Third, almost cases would be diagnosed by colonoscopy due to its high sensitivity and high specificity in the follow-up or secondary stage of screening. Thus the effectiveness of CRC mass screening program should be improved tremendously. In the long run, the health care burden from CRC would be minimized due to low CRC incidence and mortality in the population which is the beneficial outcome of a successful CRC mass screening program. A flow chart of promising colorectal cancer mass screening protocol - serum biomarker such as M2-PK as primary screening test and colonoscopy as secondary screening diagnosis test is presented in Figure 2.

Summary

Current CRC mass screening can be more effective if compliance rate is higher and quality of the screening program is high. Due to limited resources, combining HRFQ and iFOBT can be currently used as risk stratification tools to identify high-risk populations from the general population. Detailed recommendations for CRC screening based on current evidence are suggested for each risk group. Serum biomarker such as serum M2-PK can be developed as a new CRC primary mass screening test with non-invasion, no bowel preparation, high sensitivity, and more efficiency. Using serum biomarker such as serum M2-PK as primary screening test and colonoscopy as a follow-up or secondary screening test in the population would be a promising mass screening protocol for CRC.

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