

# CRC Protect™

A Blood Test for  
Colorectal Cancer Screening  
**Guide**

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## I. Background

### Colorectal Cancer and Screening in Taiwan

In Taiwan, less than 30% of the eligible population undergoes regular colorectal cancer (CRC) screening, even though Taiwan has one of the highest incidence of colorectal cancer in the world. Inaccurate stool tests, invasive and inconvenient colonoscopy procedures, no family history, and no symptoms present are many of the reasons why so many Taiwanese ignore routine screening.

In fact, colorectal cancer is one of the most preventable diseases because of its slow progression. The 5-year survival rate for stage 1 colorectal cancer is 92%, but falls to 12% for stage 4 patients. This is why it is so important to undergo regular yearly screening to ensure that there are no abnormalities developing inside the colon.

The primary purpose of screening is to detect potential early disease indicators or risk factors for disease in apparently healthy, asymptomatic individuals. A screening test should have a high sensitivity, so that the chance of missing potential disease is low. A positive result should ideally give a strong indication of the presence of a disease, but will always warrant a follow-up confirmation and diagnosis. A positive result in a screening test is not an indicator of degree or progression of disease. If screening is started early enough, the chances are the cancer can be found early. All screening tests will have false-positives as they are optimized for sensitivity i.e. to minimize false-negatives. In general, there is no perfect test of any kind—every test will have false-positives and false-negatives.

The primary purpose of a diagnostic test is to confirm the presence or absence of a disease in symptomatic or positively-screened individuals. It can be invasive and time-consuming, may be preceded by extensive imaging, but is needed to provide a definitive diagnosis. For cancer, the only definitive diagnosis is a tissue biopsy. A colonoscopy will help physicians find any abnormal growths in the colon, but a tissue biopsy is needed to diagnose whether or not the growth is actually cancer.

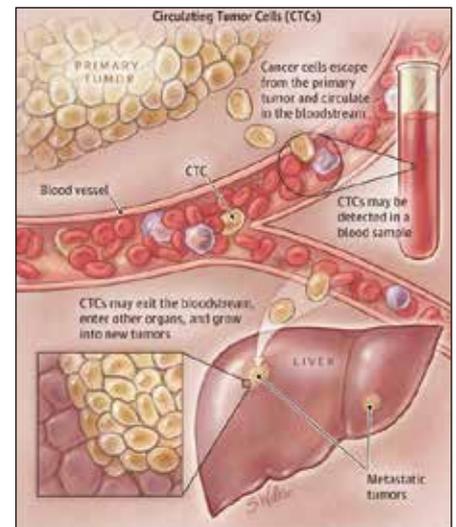
One important point to note is that for screening to be effective, two characteristics are vital: One, it should be able to detect disease early, and two, it must be convenient to administer so that compliance is high. For screening to be effective, a person must take the test regularly: either annually or more frequently in the case of high risk. Regular screening has the potential to dramatically reduce cancer deaths

## II. CellMax CRC Protect

CRC Protect is a convenient, non-invasive screening blood test to help prevent colorectal cancer. It has been clinically tested and optimized for Taiwanese people in multiple clinical trials at leading hospitals.

### What is CRC Protect?

- CRC Protect is a clinically proven blood test specifically designed to be an early-warning screening method for colorectal cancer (CRC).
- CRC Protect can detect extremely rare cells called CTCs. CTCs are cells that have detached from a tumorous growth in the colon and are circulating through the bloodstream.
- CRC Protect can find a single CTC in billions of blood cells, with just a routine blood draw, detecting the presence of colorectal cancer and even precancerous lesions very early.
- Annual testing with this new, simple blood test is an effective and easy way for early detection of colorectal cancer.



### Indications for Use :

- CRC Protect is an annual ancillary test for colorectal cancer screening.
- CRC Protect is indicated for adults at average risk of colorectal cancer.
- Individuals with a positive CRC Protect test result must undergo diagnostic colonoscopy.

### Eligibility Criteria :

- Adults 18 years and older of any sex.
- Average risk of colorectal cancer (based on general risk assessment criteria below).
- At least 2–3 months have lapsed since last infectious gastrointestinal disease.

### Contraindications

- Medical history of treated or untreated colorectal cancer polyps, colorectal cancer or other gastrointestinal cancers.
- Medical history of inflammatory bowel disease (IBD) such as ulcerative colitis and Crohn's disease.
- Recent (past 6 months) positive colorectal cancer test results with other screening modalities.
- Patients who have had a colonoscopy or any surgical procedure in the last 6 weeks.

## Warnings and Considerations

- CRC Protect is not a diagnostic test, and is not intended to replace diagnostic colonoscopy.
- A “High Score” on the CRC Protect test report means that an elevated number of CTCs were detected in the patient’s peripheral blood. The latter could be due to the presence of colorectal cancer, precancerous lesions, various types of colorectal polyps, or acute or chronic inflammatory conditions of the gastrointestinal tract.
- Clinical studies show NO correlation between “High” CRC Protect scores and stages of colorectal cancer. Thus, a “High” score should not be interpreted as an indication of the presence of a more advanced stage colorectal cancer.
- Individuals with inflammatory bowel disease (ulcerative colitis and Crohn’s disease) may report “High” CRC Protect results due to increased inflammation in the GI tract. Hence, CRC Protect is contraindicated for individuals with inflammatory bowel disease.
- All individuals with a positive CRC Protect test result should undergo diagnostic testing, such as colonoscopy.
- A CRC Protect “Low” or “Borderline” test score does not rule out colorectal cancer. However, it indicates a lower chance of having colorectal cancer or other colorectal diseases that may increase susceptibility to colorectal cancer.
- Patients with acute infectious gastrointestinal diseases should wait 2–3 months before taking CRC Protect, until the inflammation clears out.
- False positive or false negative test results are possible with all medical tests.

## Is CRC Protect Right for Your Patient ?

CRC Protect is not for suited everyone and is intended to be used in conjunction with other colorectal cancer screening modalities.

## CRC Protect is appropriate for individuals who are :

- At average risk of developing colorectal cancer.
- No recent history of inflammatory bowel disease.
- Not compliant with routine annual colorectal cancer screening.

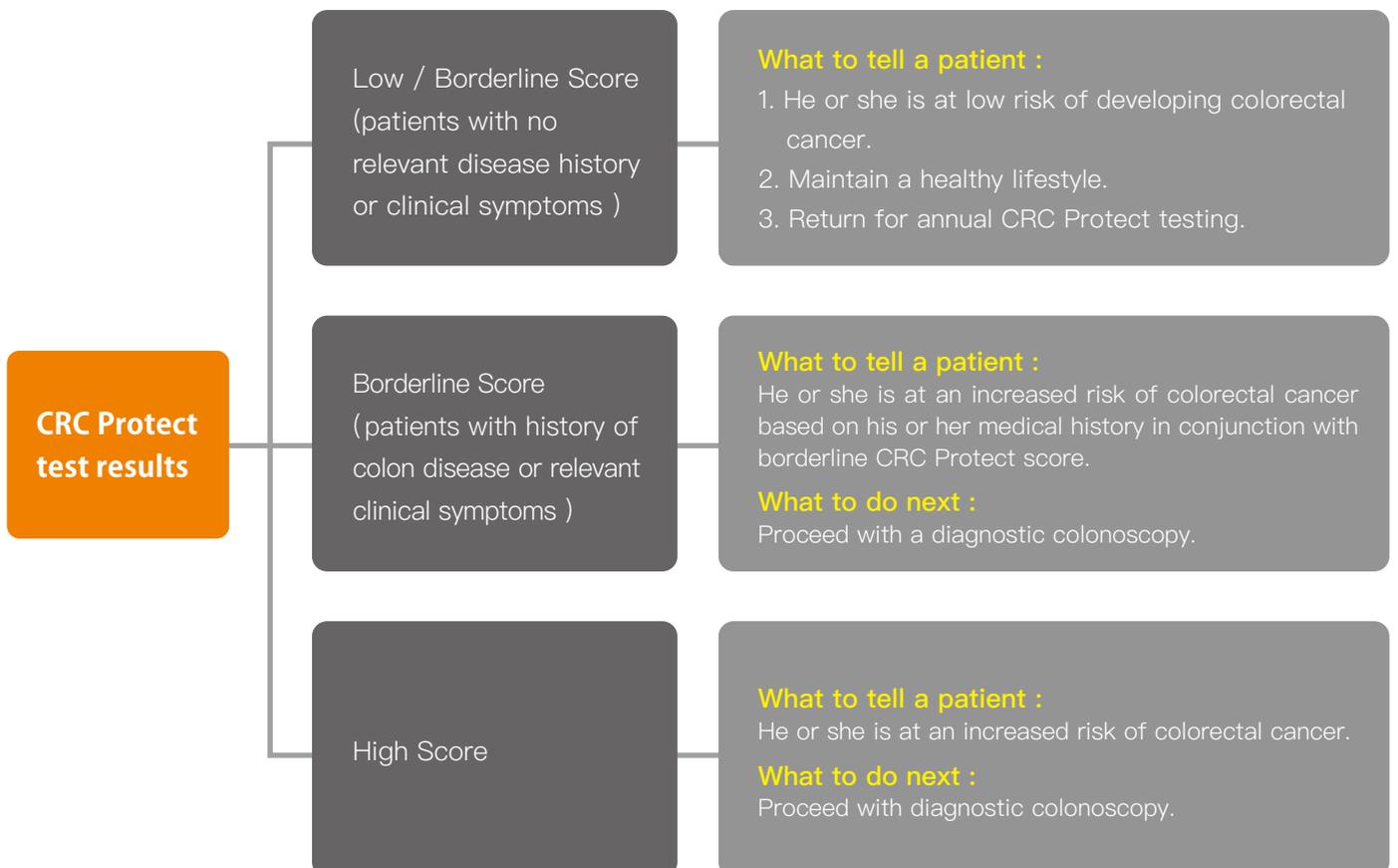
## Stepwise Guide for Physicians

- Step I: Correctly identify patients who may benefit from CRC Protect (see pages 2–4).
- Step II: Obtain patient’s peripheral blood sample in your facility per CellMax recommendations and send it to CellMax’s laboratory in the CellMax Protect test kit.

- Step III: Obtain CRC Protect test results and use as ancillary information for colorectal cancer screening per recommended algorithms depicted in Diagram 1 and Table 1 below.
- Step IV: Review test results with your patient and come up with a management plan based on patient history and all test results

Patient Test Result / 評估結果			
Score Range 風險值	0-50 LOW / 低	51-75 BORDERLINE / 臨界值	76-100 HIGH / 高
Your Score 您的分數	_____		
Recommendation 建議	Continue testing annually for your health and protection 每年檢測一次		

**Diagram 1: Sample Patient Test Result**



**Table 1: Follow Up Guide After Diagnostic Colonoscopy**

CRC Protect Test Result	Subsequent Colonoscopy Result	What to Do	What to Tell a Patient
<b>High Score (76-100)</b>	Positive colonoscopy result (diagnosed with colorectal cancer)	Follow up with CRC Monitor test every 3 months after surgery / treatment	<ul style="list-style-type: none"> <li>Your risk for CRC or precancerous lesions was found to be high and the presence of CRC was confirmed by colonoscopy</li> <li>To closely monitor cancer recurrence, you may consider regular testing with CRC Monitor test every three months after initial surgical treatment</li> </ul>
<b>High Score (76-100)</b>	Positive colonoscopy result (diagnosed with colon polyps)	Follow up with CRC Monitor every 6 months after polypectomy	<ul style="list-style-type: none"> <li>Your risk for CRC or precancerous lesions was found to be high and the presence of polyps was confirmed by colonoscopy</li> <li>To closely monitor polyp recurrence, you may consider taking CRC Monitor every six months after polypectomy</li> </ul>
<b>High Score (76-100)</b>	Negative colonoscopy result	<ul style="list-style-type: none"> <li>Double check to ensure CRC-Protect was not contra-indicated due to IBD or similar indications (see list on page 1).</li> <li>Based on individual's personal risk-profile and history, their physician should determine the best screening plan for them.</li> </ul>	<ul style="list-style-type: none"> <li>CRC Protect may produce false-positive results, similar to other screening tests.</li> <li>Some reasons for this may include               <ul style="list-style-type: none"> <li>- You are unsuited to take CRC Protect based on your personal history of colon polyps or other conditions</li> <li>- You have inflammatory bowel disease</li> <li>- You have suffered from infectious gastrointestinal disease within the last 2 months</li> <li>- You have undergone recent surgery</li> <li>- You may have abnormalities in your upper GI tract</li> </ul> </li> </ul>
<b>Borderline Score (51-75)</b>	Positive colonoscopy result (diagnosed with colorectal cancer)	Follow up with CRC Monitor every 3 months after an initial surgical treatment	<ul style="list-style-type: none"> <li>Your risk for CRC or precancerous lesions was found to be borderline and the presence of CRC was confirmed by colonoscopy</li> <li>To closely monitor cancer recurrence, you may consider regular testing with CRC Monitor test every three months after initial surgical treatment</li> </ul>
<b>Borderline Score (51-75)</b>	Positive colonoscopy result (diagnosed with colon polyps)	Follow up with CRC Monitor every 6 months after polypectomy	<ul style="list-style-type: none"> <li>Your risk for CRC or precancerous lesions was found to be borderline and the presence of polyps was confirmed by colonoscopy</li> <li>To closely monitor polyp recurrence, you may consider taking CRC Monitor every six months after polypectomy</li> </ul>

**Table 1: Follow Up Guide After Diagnostic Colonoscopy**

CRC Protect Test Result	Subsequent Colonoscopy Result	What to Do	What to Tell a Patient
<b>Borderline Score (51-75)</b>	Negative colonoscopy result	Continue annual screening with CRC Protect	<ul style="list-style-type: none"> <li>• Colonoscopy found no polyps in your colon</li> <li>• Maintain a healthy lifestyle and continue annual testing with CRC Protect</li> </ul>
<b>Low Score (1-50)</b>	No subsequent colonoscopy	Continue annual screening with CRC Protect	Maintain a healthy lifestyle and return for annual testing with CRC Protect
<b>Low Score (1-50)</b>	Negative colonoscopy result	Continue annual screening with CRC Protect	<ul style="list-style-type: none"> <li>• Your risk of colon disease was found to be low and colonoscopy has confirmed absence of colorectal cancer / polyps</li> <li>• Maintain a healthy lifestyle and continue annual testing with CRC Protect</li> </ul>
<b>Low Score (1-50)</b>	Positive colonoscopy result (diagnosed with colorectal cancer)	Follow up with CRC Monitor every 3 months after surgery / treatment	<ul style="list-style-type: none"> <li>• CRC Protect may produce false–negative results, similar to any other screening test</li> <li>• To closely monitor cancer recurrence, you may consider regular testing with CRC Monitor test every three months after initial surgical treatment</li> </ul>
<b>Low Score (1-50)</b>	Positive colonoscopy result (diagnosed with colon polyps)	Follow up with CRC Monitor every 6 months after polypectomy	<ul style="list-style-type: none"> <li>• CRC Protect may produce false–negative results, similar to any other screening test</li> <li>• To closely monitor polyp recurrence, you may consider taking CRC Monitor test every six months after polypectomy</li> </ul>

### What Does the Risk Score Mean ?

The CRC Protect test report uses a 0–100 ranking, where a percentile of 0 has the lowest chance of having abnormalities (polyps or cancer) in the colon, and a percentile of 100 has the highest chance of having abnormalities in the colon. Thus for example, a patient with a score of 82 means he or she will have a higher relative risk of having abnormalities when compared to a patient with a score of 50. A score of 45 does not mean the patient has a 45% chance of having colorectal cancer now, or developing the disease over a future time period.

### What the risk score will tell you :

The likelihood of having abnormalities in the colon, which may be due to diseases like polyps or cancer.

### What the risk score will not tell you :

- If the patient actually has polyps or colorectal cancer.
- The absolute risk that the patient will develop polyps or cancer.
- The severity or stage of colorectal cancer.
- The number or size of polyps.

Points for the risk assessment score are assigned based on risk factors for colon disease, like colon polyps or colorectal cancer. These factors include CTC count, age, gender, personal history of colorectal cancer, smoking history, alcohol consumption, and clinical symptoms.

### Reducing the Risk of Colorectal Cancer

Many lifestyle changes can help reduce the risk of colorectal cancer.

- Reducing alcohol intake – Alcohol use is a known risk factor for colorectal cancer, and risk increases as alcohol intake increases. If the patient chooses to drink, intake should be limited to no more than one drink daily.
- Quit smoking – Smoking is not just a risk factor for lung cancer, but for all digestive system cancers, including colorectal, stomach and esophageal cancers.
- Increasing exercise – Sedentary lifestyles are associated with an increased risk of digestive system cancers. Available research suggests that the most active adults have a 40 to 50 percent reduced risk of developing colon cancer, compared to the least active adults. Importantly, the protective effect of exercise appears to be independent of weight status, meaning that regular physical activity appears to reduce risk of colon cancer even in people who are overweight or obese.
- Lose weight – Obesity is a strong risk factor for colorectal cancer, and researchers estimate that risk increases about 15 percent with each five additional points of body mass index beyond the upper end of normal range. So, for example, weight loss that results in a reduction of BMI from 35 to 30 would be expected to result in about a 15 percent risk reduction.

- Eat less red meat – There is strong evidence supporting high intake of red meat as a risk factor for colorectal cancer. One large study that examined the diets of adults aged 50 to 71 showed that people with the highest intakes of red meat – an average of 5 ounces per day – had a 24 percent greater risk of developing colorectal cancer compared to those with the lowest intake – an average of about half an ounce per day.
- Avoid processed / preserved meats – Processed meats like bacon, salami and hot dogs are commonly preserved with sodium nitrite. When sodium nitrite encounters stomach acid during digestion, it may convert to a compound called a nitrosamine, which is a known carcinogen. Indeed, both high intake of nitrites and processed meats have been associated with increased risk of colorectal cancer compared to lower intakes.
- Eat more vegetables – Fruits and vegetables have a protective effect against colorectal cancer, likely as the result of a combination of factors that includes their antioxidant content, fiber and species-specific phytochemicals. Research has shown that people with diets highest in fruit and vegetables have lower risk of developing digestive system cancers (including colorectal) compared to people whose diets contain the least amount of these foods.
- Get plenty of fiber in the diet – Fiber is non-digestible plant material that travels through the length of the intestines and arrives to the colon intact. Once there, it may trap dietary carcinogens in the stool, escorting them out of the body expeditiously before they have the chance to cause trouble

### III. Frequently Asked Questions

#### Section 1 : About CRC Protect

##### 1-1. What is CRC Protect ?

CRC Protect is a clinically proven blood test specifically designed to be an early-warning method for colorectal cancer (CRC). It provides an advanced warning of colorectal cancer by identifying the smallest traces of circulating tumor cells (CTCs) in a person's blood. Taking this simple blood test once a year, is an effective and easy way to detect colorectal cancer early.

##### 1-2. How will it help beyond what already exists ?

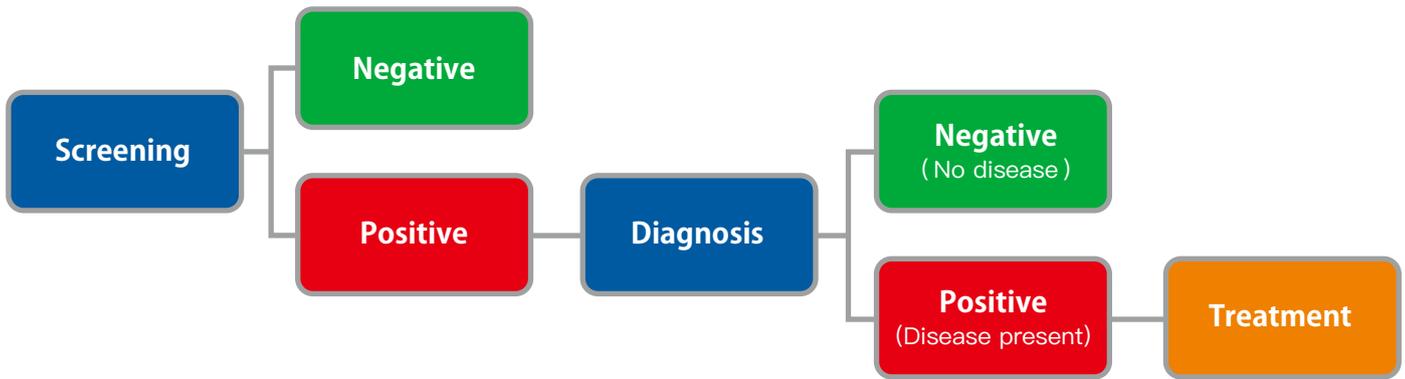
In Taiwan, less than 30% of the population choose to have regular CRC screening, even though Taiwan has one of the highest incidence of colorectal cancer in the world. Messy inaccurate stool tests, invasive and inconvenient colonoscopy procedures, no family history, and no symptoms present are many of the reasons why so many Taiwanese ignore routine screening.

In fact, colorectal cancer is one of the most preventable disease because of its slow progression. The 5 year survival rate for stage 1 colorectal cancer is 92%, but it falls to 12% for stage 4 patients. This is why it is so important to undergo regular yearly screening to ensure that there are no abnormalities developing inside the colon. CRC Protect is a convenient, non-invasive screening blood test to help prevent colorectal cancer. It has been clinically tested and optimized for Taiwanese people in multiple clinical trials at leading hospitals.

##### 1-3. How is screening different than diagnosis ?

**The primary purpose of screening is to detect potential early disease indicators or risk factors in apparently healthy, asymptomatic individuals.** A screening test should have a high sensitivity, so that the chance of missing potential disease is low. A positive result should ideally give a strong indication of the presence of a disease, but will always warrant a follow-up confirmation and diagnosis. A positive result in a screening test is not an indicator of degree or progression of disease. If screening is started early enough the chances are the cancer can be found early. All screening tests will have false-positives as they are optimized for sensitivity i.e. to minimize false-negatives. In general, there is no perfect test of any kind — every test will have false-positives and false-negatives.

**The primary purpose of a diagnostic test is to confirm the presence or absence of a disease in symptomatic or positively-screened individuals.** It can be invasive and time-consuming, and may be preceded by extensive imaging, but is needed to provide a definitive diagnosis. For cancer, the only definitive diagnosis is a tissue biopsy. A colonoscopy will help physicians find any abnormal growths in the colon, but a tissue biopsy is needed to diagnose whether or not the growth is actually cancer.



One important point to note is that for screening to be effective, two characteristics are vital: One, it should be able to detect disease early, and two, it must be convenient to administer so compliance is high. For screening to be effective, a person must take the test regularly: either annually or more frequently in the case of high risk.

#### 1-4. Is colonoscopy a screening test ?

Colonoscopy is a diagnostic procedure intended to confirm the presence or absence of colorectal cancer or colon polyps. There may be some limitations to using colonoscopy as a screening test. The bowel preparation by the patient is important for cleansing the colon to allow the physician to adequately perform the colonoscopy. If the patient did not prepare properly beforehand, there is a greater chance of missing polyps during colonoscopy.



Additionally, the effectiveness of the colonoscopy may depend on the experience level of the performing physician. There is always a chance that some polyps are missed because of their size or location, and the limited time to perform the procedure. Due to improper bowel preparation or other reasons, colonoscopies can miss small polyps 20–30% of the time. Side effects after the procedure have also been reported, such as abdominal pain or bleeding. There is also a low but potential chance for perforation during the procedure, causing injury to the patient.

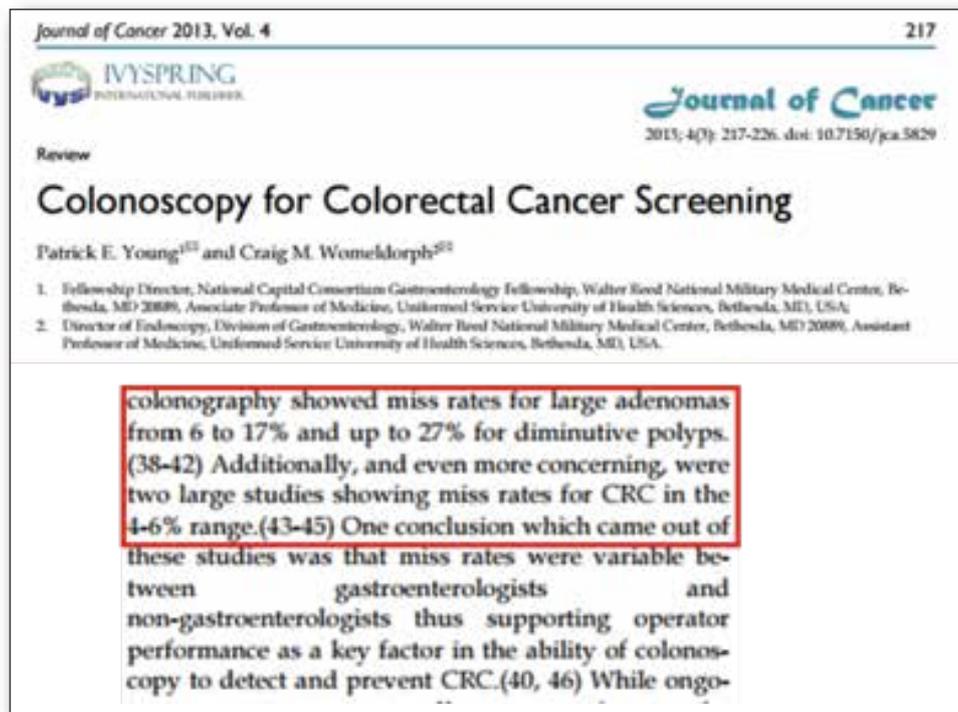
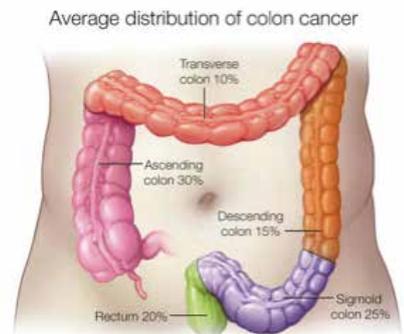
Thus, utilizing potentially invasive colonoscopy for screening purposes may not be ideal for a healthy individual with an average risk for colorectal cancer, while it is an invaluable modality for diagnosis of colorectal cancer.

### 1-5. What are some other types of screening tests for colorectal cancer ?

One of the major screening tests for colorectal cancer in Taiwan is the stool test (FOBT). This test requires the patient to handle their stool which is a very messy and unpleasant process, and has dietary restrictions before the test is taken. It works by checking for hidden blood in the stool. However, FOBT suffers from poor sensitivity (~70% for colorectal cancer, ~25% for “advanced adenoma”) so it is not an ideal test to get the earliest warning possible. A negative FOBT test also does not indicate for certain that colorectal cancer does not exist, since not all polyps bleed all the time.

A popular, inexpensive blood based test in Taiwan for colorectal cancer screening is the CEA test. However, the sensitivity (~30%) and specificity (~50%) is even worse than FOBT. CEA may be elevated in a wide variety of other conditions aside from colorectal cancer such as IBS, liver diseases, respiratory diseases, and other cancers. CEA is more useful as a biomarker once cancer has been diagnosed.

Screening colonoscopy is another major screening test in Taiwan. A day prior to the procedure, the patient has to undergo bowel preparation so that the physician can perform the colonoscopy adequately. Improper bowel preparation, which is not infrequent, impairs proper visibility of bowel mucosa (inner layer) leading to misses of

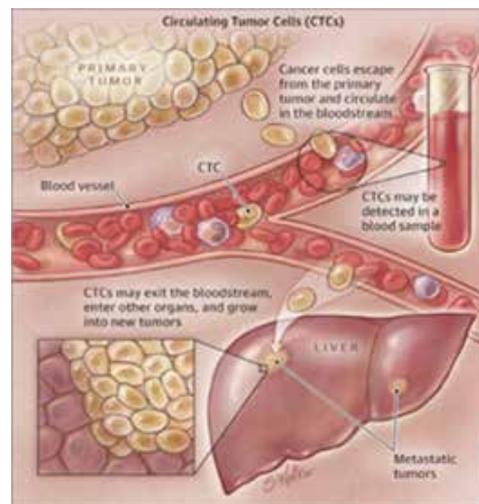


small polyps which may be adenomatous hence increasing risk of colon cancer. The procedure itself is considered to be invasive, inconvenient and time-consuming. **Hence, it is best to be used as a diagnostic tool in conjunction with a non-invasive screening test.** For example, Taiwan guidelines recommend annual FOBT test followed by diagnostic colonoscopy in positive cases.

### 1-6. How does CRC Protect screen for colorectal cancer ?

CRC Protect is unique as it has been validated in double-blind clinical studies in hundreds of Taiwanese people to establish the ability to detect colon disease early. This is important because tests, in general, screening tests can perform dramatically differently in people with different ethnicities.

CRC Protect can find a single CTC in billions of blood cells, with just a routine blood draw., detecting the presence of colorectal cancer and even precancerous lesions very early. Annual testing with this new, simple blood test is an effective and easy way for early detection of colorectal cancer.



### 1-7. What is the accuracy (sensitivity and specificity) of CRC Protect ?

In Taiwanese double-blind, multi-site clinical studies, CellMax found the overall sensitivity and specificity to be around 90%.

### 1-8. What is the gold standard which you measure the performance of CRC Protect ?

All clinical studies for CRC Protect use colonoscopy with biopsy as the gold standard. The test was clinically validated through double blind studies with leading hospitals in Taiwan like CGMH and NTUH. In several hundred Taiwanese patients with different stages of colorectal cancer and precancerous lesions, the performance of CRC Protect was compared against colonoscopy with biopsy. The results of these clinical trials, published in peer-reviewed journals, show the early detection capability of the CRC Protect test.

### 1-9. Will CRC Protect have any false-positives ? Under what conditions will there be false-positive results ?

Screening tests are designed to identify individuals who may be at higher risk of developing cancer compared to the rest of the population. **Thus, high sensitivity is a critical performance characteristic for every screening test. Very high sensitivity may result in occasional false-positive results for any screening test. CRC Protect is no different. Every positive CRC Protect test result should be followed by additional diagnostic testing. The best screening tests are those that are convenient to administer (so there is high adherence) and have high sensitivity in order not to miss potential precancerous lesions.**

Based on clinical studies in Taiwan, CRC Protect demonstrated a false-positive rate of ~10%, which largely was caused by the inflammation of gastrointestinal mucosa. **Inflammatory state of gastrointestinal mucosa leads to higher turnover of the epithelial cells, thus increasing chances for epithelial cells to end up in the peripheral circulation.** Follow up colonoscopy of such patients may be negative. Thus, in such individuals, CRC Protect test

is recommended a few months later after the inflammation clears out. In general, CRC protect should not be recommended to patients until after the gastrointestinal tract inflammation has cleared out. False positives are also possible in patients with Inflammatory Bowel Disease (IBD), like Crohn's disease or ulcerative colitis.

There is no such thing as a perfect screening test, without the possibility of false-positives. **However, all positive results with any screening test, including CRC Protect, should be considered as true positives and immediately proceeded with a follow-up diagnosis.**

**IMPORTANT:** A “High” CRC Protect score means that there is a higher-probability of disease. For healthy individuals, it could be precancerous lesions or early stage cancer. Most patients with a “High” result are diagnosed with pre-cancerous lesions or polyps. A high score must NOT be interpreted to mean that the severity of the disease is higher. Further, do NOT assume that a “positive” or “high-score” is necessarily a bad result, until having gone through further diagnostic testing.

### 1-10. Does CRC Protect replace colonoscopy ?

CRC Protect is intended to be used in conjunction with colonoscopy, not as a replacement. CRC Protect helps individuals take an easy, convenient, annual blood test to warn them about any abnormal conditions in their colon. Individuals with a positive CRC Protect result may more inclined to get a colonoscopy procedure. **This could increase the number of necessary colonoscopies.**

### 1-11. Will CRC Protect detect benign polyps ?

In the double blind clinical studies, CRC Protect was capable of detecting polyps in patients, as confirmed by colonoscopy. **All polyps, whether benign or malignant, are abnormally growing cells on the tissue lining and will release CTCs into the blood.** This is why CRC Protect will detect these polyps in the majority of cases.

Some physicians will argue that polyps are no cause for concern, since less than 5–10% are adenomas. Although it is true all polyps do not impose an increased risk of colorectal cancer, **there is no way of knowing whether or not the polyp is benign or malignant with a visual inspection**, thus a tissue biopsy is needed. This is why so many medical associations and institutes around the world (ASGE, BSG, ASCRS, Dana-Farber) **recommend the removal of all polyps during colonoscopy to reduce the risk of developing colorectal cancer in the future.**

Leading medical institutions recommend that all polyps should be removed



*“... it is recommended that all adenomatous polyps be removed. Removal of colorectal polyps is key in preventing colorectal cancer.”*

[http://www.asge.org/cplodedfiles/Publications\\_and\\_Products/Practice\\_Guidelines/2006\\_colorectal.pdf](http://www.asge.org/cplodedfiles/Publications_and_Products/Practice_Guidelines/2006_colorectal.pdf)



*“Since there is no fool-proof way of predicting whether a colorectal polyp will become a cancer, removal of polyps is advised. Removal of polyps during colonoscopy reduces the risk of developing colorectal cancer in the future.”*

[https://www.facs.org/sites/default/files/download/publication/practice\\_parameters\\_for\\_the\\_management\\_of\\_colon\\_21.pdf](https://www.facs.org/sites/default/files/download/publication/practice_parameters_for_the_management_of_colon_21.pdf)



*“We believe that all malignancies of the bowel probably start off as benign polyps. We know that removing benign polyps can prevent cancer developing later.”*

<http://www.bsg.org.uk/patient/general/bowel-cancer.html>



*“Most adenomas will not turn into cancer. However, regular screening to remove them reduces the risk of developing colon cancer.”*

<http://www.dana-farber.org/Adult-Care/Treatment-and-Support/Colon-Cancer/About-Colon-Cancer.aspx>

**1-12. My patient has stomach / digestive issues right now. Do you recommend taking CRC Protect under these circumstances ?**

If the patient has symptoms such as diarrhea, irritable bowel syndrome, hemorrhoids, or a gastrointestinal tract infection, CellMax recommends waiting at least 3 months before taking CRC Protect. This will allow the patient's GI tract to return to a healthier condition, and reduce the chances of getting a false-positive result.

**1-13. My patient had colorectal cancer / polypectomy several years ago. Is this test right for him / her ?**

CRC Protect is contraindicated for people previously diagnosed with any CRC (please see page 1-4 for more details on contra-indications). However, patients who have already had colorectal cancer/polyps will always be at an elevated risk for recurrence. There is a special test called CRC Monitor designed specifically for those individuals who have previously been diagnosed with colorectal cancer or polyps. CRC Monitor is designed to detect the recurrence of colorectal cancer (or polyps) after any procedure or treatment has taken place. CellMax strongly recommends taking a baseline CTC count 6 months with CRC Monitor after the polypectomy/biopsy, and follow-on testing every 6 months after the baseline reading. If the procedure was over 6 months ago, a baseline reading should still be done. Repeat testing with CRC Monitor is recommended every 3 months for former colorectal cancer patients, or every 6 months for patients with polyps. This should only be done under the care of an oncologist (for colorectal cancer survivors) or gastroenterologists (for patients with a history of polyps).

**1-14. What marker do you use to detect colorectal cancer ? Is this colorectal cancer specific ? Is there the possibility of detecting other cancers with CRC Protect ?**

The set of biomarkers that CRC Protect utilizes includes biomarkers such as EPCAM and CK20. Although, both of the biomarkers detect epithelial cells, CK20 is specific for gastrointestinal tract epithelium and routinely utilized for colorectal cancer diagnosis on surgical and biopsy specimens. Based on extensive investigation, CellMax has developed an algorithm that utilizes set of biomarkers in conjunction with other parameters (such as cell size, nuclear to cytoplasmic ratio, CK20 staining patterns, nuclear shape etc.) to define circulating tumor cells in the peripheral blood. These studies were extensively validated by CellMax in double blind clinical studies.

**III. Frequently Asked Questions**

**Section 2 : About CellMax CRC Protect Test Report**

**2-1. What are the possible results of CRC Protect and what do they mean?**

**Low** – This result indicates that the patient most likely does not have colorectal cancer as detectable by the test. However, cancer is an evolving disease where early detection is the key for prevention and survival. In order to maintain a healthy status, annual testing with CRC Protect is advised. If you feel the patient’s risk is higher, he/she has relevant clinical symptoms, or other similar concerns, the test can be taken every 6 months. This is the advantage of a simple, convenient blood test.

**Borderline** – This result means that it is unclear from testing whether the patient has a high risk for colorectal cancer. It is up to the patient’s physician to make a judgment call on what follow-up should be required based on the patient disease history, clinical symptoms and overall risk profile. If the patient has been leading a healthy lifestyle and does not have a family history of colorectal cancer, then there shouldn’t be any immediate concern with the “Borderline” result and a follow-up test can be recommended 6–12 months later. However, if the patient has been leading an unhealthy lifestyle (diet, smoking, drinking, stress, etc.), has a family history of colorectal cancer, or clinical symptoms like blood in stool, then follow-on diagnostic testing could be recommended.

**High** – This result indicates that there is a strong possibility of colon disease, or pre-cancer benign polyps and warrants a more definitive diagnosis with colonoscopy as soon as possible. However, there is usually no need to panic. A high score does not mean that cancer is present! There are three likely scenarios following a high risk score result, which are outlined in the next point. Do NOT assume that a “positive” or “high-score” is necessarily a bad result, until having gone through further diagnostic testing.

Patient Test Result / 評估結果				
<p>Score Range 風險值</p>	<table style="width: 100%; text-align: center;"> <tr> <td style="width: 33%; background-color: #00a651; color: white; padding: 10px;"> <b>0-50</b> LOW / 低                 </td> <td style="width: 33%; background-color: #f1c232; color: white; padding: 10px;"> <b>51-75</b> BORDERLINE / 臨界值                 </td> <td style="width: 33%; background-color: #e34a33; color: white; padding: 10px;"> <b>76-100</b> HIGH / 高                 </td> </tr> </table>	<b>0-50</b> LOW / 低	<b>51-75</b> BORDERLINE / 臨界值	<b>76-100</b> HIGH / 高
<b>0-50</b> LOW / 低	<b>51-75</b> BORDERLINE / 臨界值	<b>76-100</b> HIGH / 高		
<p>Your Score 您的分數</p> <hr style="border: 0.5px solid #ccc;"/>	<p>Recommendation 建議</p> <p style="color: #00a651; text-align: center;">Continue testing annually for your health and protection 每年檢測一次</p>			

## 2-2. If the patient has a high risk score with CRC Protect, and follows up with colonoscopy, what is the percentage that the patient will have cancer ?

CRC Protect is NOT a diagnostic test, but an early warning system to establish the presence or absence of a disease as early as possible. The most important purpose of CRC Protect is as an “early–warning test”, to inform the patient of any abnormalities in the colon, which warrant a follow–up diagnostic test. If the patient has a high risk score, **there is a strong possibility that abnormalities are present and further follow–up is necessary**. To actually know if the patient does have cancer, a colonoscopy will have to be performed and the biopsied tissue will need to be tested for a final confirmation.

There are four likely scenarios with a high risk score result :

- a. The patient is a high risk individual and unsuited to take CRC Protect based on their personal history of colorectal cancer.
- b. The patient has a disease such as IBD, GI tract infection, etc. triggering the high risk score. This may cause a false–positive test result after colonoscopy.
- c. The patient has small polyps developing in the colon. However, due to improper bowel preparation, small size/location of the polyps, or other factors, nothing was detected by the colonoscopy, leading to a “false–positive” conclusion by the physician. Unfortunately, there is no way to verify this. To avoid this scenario, the patient should be advised to always follow the necessary preparatory steps before a colonoscopy and the physician should spend extra time and care to observe for any abnormal growth during the procedure.
- d. The patient does have colon disease and should undergo surgery / treatment immediately. **This can only be confirmed after a colonoscopy / tissue biopsy has been performed.**

## 2-3. Your test report includes a number score of 0-100. What does this mean? What does a score of 25 mean ? How is this score calculated ?

The score correlates to the risk being low, borderline, or high for the patient. Points for the risk assessment score are assigned based on risk factors for colon disease, like colon polyps or colorectal cancer. These factors include CTC count, age, gender, personal history of colorectal cancer, smoking history, alcohol consumption, and clinical symptoms.

So a score of 82 means a higher risk of presence of disease compared to a score of 10. Please also read Section 2.1 again.

## 2-4. The patient received a CD in his / her test report but when they opened up the image on the computer, all they saw was a black hole. What does this mean ?

The image is actually a high–resolution camera capture of all the cells in the patient’s blood sample. This was taken

with our analyzer after the blood was processed. If the patient zooms in enough, he / she will actually see the individual cells. However, this information is hard for the patient to interpret themselves, but CellMax has included it just for their reference.

### **2-5. The patient is concerned with a borderline result. Does this mean the patient has cancer or not?**

A borderline reading means that it is unclear from testing whether the patient has a high risk for presence of disease. But the patient is probably at a higher risk than normal, healthy people. It is up to you, as the patient's physician, to make a judgment call on what follow-up should be required based on the patient's history. If the patient has been leading a healthy lifestyle and does not have any relevant clinical symptoms, then there shouldn't be any immediate concern to the borderline result and a follow-up test can be recommended 6–12 months later. However, if the patient has been leading an unhealthy lifestyle (diet, smoking, drinking, stress, etc.), has a family history of colorectal cancer, or clinical symptoms like blood in stool, then follow-on diagnostic testing could be recommended.

### III. Frequently Asked Questions

#### Section 3 : After CRC Protect - Physician-Patient Interaction

##### **3-1. My patient's test report shows high risk. How do I guide him / her through this frightening period ?**

Tell the patient there is no immediate cause for alarm and not to worry. A “High” score does not necessarily mean cancer is present! The goal of CRC Protect is to detect disease early, including pre-cancer. A “high” score does not have any correlation at all with any stage of cancer. It means there is a higher risk of having an abnormality in the colon— in most cases this would be very early, even pre-cancer. In order to know exactly what is causing this abnormality, the patient needs to consult their physician or GI doctor and have further testing, including a colonoscopy for a diagnosis as soon as possible.

Please also read Section 2.1 again.

##### **3-2. My patient took CRC Protect and he / she had a high risk score. However, after colonoscopy, we only found 1-2 small (<1cm) polyps which were removed. That patient went through a traumatic period and was expecting to be diagnosed with cancer after colonoscopy.**

CRC Protect is meant to be a highly sensitive early-warning test, and to detect colorectal cancer before it becomes a serious problem. Polyps are still abnormal growths, some of which have the potential to become cancer. It is just a matter of time before this happens. The patient's “High” score does not have any correlation with the seriousness or stage of colorectal cancer, it just means that the patient has a higher risk of an abnormality in their colon. In this patient's case, this abnormality was confirmed as being from polyp growth. Many of the world's top gastrointestinal associations all recommend the removal of all polyps found. If this patient had not taken CRC Protect, this polyp may not have been found. Now that this patient has removed the polyps, he/she can rest easier knowing they are free from abnormal growths in their colon. It is this patient's responsibility now to continue living a healthy lifestyle and continue annual testing.

##### **3-3. My patient took CRC Protect and he / she had a high risk score. However, after colonoscopy, nothing was found.**

CRC Protect is meant to be a highly sensitive screening test, and to detect colorectal cancer as early as possible before it becomes a serious problem. Although rare, CellMax has found a few cases where a positive test result was due to other health conditions such as IBD or a GI infection. These conditions will give off positive readings with other screening tests like FOBT as well. Another possibility is that the patient has a personal history of colorectal cancer or polyps. These types of individuals are considered to be in a high risk category and are unsuited for screening with CRC Protect. All of these scenarios may be applicable to this patient's situation. Fortunately,

the colonoscopy confirmed that there is no cause for concern and this patient's colon is healthy. It is the patient's responsibility now to use this experience to continue living a healthy lifestyle and get tested every year.

### **3-4. My patient went for a colonoscopy and had polyps / tumor removed. Can he / she use CRC Protect in the future ?**

After a polypectomy/biopsy has been performed, CellMax believes this patient will be at an elevated risk for colorectal cancer. CRC Monitor is designed to detect the recurrence of colorectal cancer (or polyps) after any procedure or treatment has taken place. CellMax strongly recommends taking a baseline CTC count 6 months with CRC Monitor after the polypectomy/biopsy, and follow-up testing every 3 months for colorectal cancer patients, or every 6 months for individuals who had polyps.

### **3-5. Do you have a list of doctors where we can send patients for follow-up testing if necessary ?**

Yes, we do. Please visit CellMax's website for the list of doctors specializing in gastrointestinal disease who can help patients with follow-up testing.