Cenogenics

TRI-SLIDE™, SINGLE SLIDE and TAPE STOOL BLOOD TESTS

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INTENDED USES

The CENOGENICS' TRI-SLIDE™, SINGLE SLIDE, and STOOL BLOOD TAPE tests are ready-to-use diagnostic aids designed for rapid, clean handling of fecal specimens to be tested for occult blood. CENOGENICS' stool blood tests are recommended for routine primary physical examinations of individuals aged 50 years or older, office practices and hospital testing, screening programs for colo-rectal cancer, and testing of newborns and postoperative patients. All CENOGENICS' Stool Blood slides include a quality control dot panel to assure the test system is functioning properly. Since the test requires only a thin application of specimen, the transport and storage of fecal specimens are eliminated and unpleasant odors are minimized. All CENOGENICS' Stool Blood tests fit easily into a pocket, providing convenient, reliable testing for occult blood on hospital rounds, examination rooms, or wherever on-the-spot testing is required. Additionally, a patient can test three consecutive bowel movements in the privacy of their own home using the CENOGENICS' Tri-Slide ™ Upon completion of the three test series, the patient uses the envelope provided to return the test to the physician's office or designated address for analysis.

Clinical experience demonstrates that CENOGENICS' slide tests for stool blood provide an established method of detecting asymptomatic gastrointestinal conditions including early detection of polyps and colorectal cancer,[3,4,7] the second leading cause of cancer deaths in the United States.[1,2] Additionally, CENOGENICS' slides are used to detect bleeding problems other than cancer that may come from digestive tract pathologies such as peptic ulcer, colitis, diverticulitis, and gastritis.[8]

The American Cancer Society updated its guidelines and recommendations for colorectal cancer detection to include annual fecal occult blood tests, beginning at the age of 50, in conjunction with flexible sigmoidoscopic and digital rectal exam every five years, thus increasing the likelihood of early detection of gastrointestinal carcinoma at a stage amenable to cure.[5,6,7]

SUMMARY AND EXPLANATION

Although the concept of occult blood detection using gum guaiac as an indicator was first introduced by Van Deen in 1864, chemical tests for the recognition of small amounts of blood were first applied to fecal specimens in 1901 by Boas using the guaiac test method.[9,13] However, the application as a test for home use was not proposed until 1967 by Greegor[10] with the advent of a test that involved guaiac-impregnated paper slides. It was a CENOGENICS' company subsidiary, Laboratory Diagnostics Company, who invented the original guaiac stool occult blood test slide method. Greegor used the Laboratory Diagnostics' guaiac stool blood slide in the classic clinical studies which established the diagnostic reliability of the guaiac stool occult blood test.[19]

CENOGENICS' Stool Blood slides and tape test feature ready-to-use, stabilized guaiac-impregnated, electrophoretic paper based on Greegor's classical approach and method of choice for the detection of blood in feces.[11]

When a fecal specimen containing occult blood is applied directly to the CENOGENICS' guaiac test paper, the hemoglobin portion of the occult blood will exert a pseudoperoxidase reaction upon the addition of CENOGENICS' Developing Solution. The oxidation reaction of alpha guaiaconic acid in the guaiac paper by hydrogen peroxide in the developing solution forms a quinone structure, guaiacum blue, which becomes visible as blue or blue-green color change within 30 seconds in the presence of occult blood.[12] Since the structure, of hematin is similar in structure to that of peroxidase, it is probably the hermatin fraction of hemoglobin in the occult blood specimen which catalyzes the oxidation of the guaiac in the test paper.[9]

REAGENTS

CENOGENICS' SLIDES AND TAPE: Special, high quality electrophoresis paper impregnated with natural guaiac resin.

CENOGENICS' DEVELOPING SOLUTION: An aqueous solution containing a stabilized mixture of hydrogen peroxide and specially denatured ethyl alcohol.

MATERIALS SUPPLIED

CENOGENICS' TRI-SLIDE™: A ready-to-use three test configuration for multiple or consecutive fecal specimen testing with an easy to read QUALITY CONTROL DOT PANEL to assure integrity of the test.

TRI-SLIDES™ are available in three kit versions: SB-20 containing 100 TRI-SLIDE™, SB-19 containing 50 TRI-SLIDE™ Patient Envelopes, and SB-19F containing 50 TRI-SLIDE™ Patient Foil Pouches. Current U.S. Postal Regulations require test slides to be mailed in the approved foil pouches provided in the SB-19F kits. The foil pouches may also be ordered separately.

CENOGENICS' SINGLE SLIDE: A convenient single specimen test configuration with an easy to read QUALITY CONTROL DOT PANEL to assure integrity of the test.

SINGLE SLIDES are available in an SB-21 kit containing 100 SINGLE SLIDES.

CENOGENICS' STOOL BLOOD TEST TAPE: A 100-inch roll of 1-inch wide guaiac impregnated test tape for economical testing of specimens for stool blood.

CENOGENICS' DEVELOPING SOLUTION: 10 ml of solution per bottle. Bottle is provided with a special dropper tip. Solution is interchangeable between CENOGENICS' kits. Do not use other manufacturers' developing solution.

Applicator sticks for specimen collection.

Product Insert including toll free telephone number for assistance.

MATERIALS REQUIRED BUT NOT SUPPLIED

Timer or watch.

STORAGE CONDITIONS AND STABILITY

CENOGENICS' SLIDES AND TEST TAPE: Stored as recommended, the product will maintain its sensitivity for five years from date of manufacture.

Do not refrigerate.

Store at room temperature 59°- 86°F (15°-30°C).

Protect from heat and light.

CENOGENICS' DEVELOPING SOLUTION: Stored as recommended, the solution will remain stable for five years from date of manufacture.

Do not refrigerate.

Store at room temperature 59°- 86°F (15°-30°C).

Protect from heat and light.

Keep tightly closed when not in use to prevent evaporation.

CAUTIONS

CENOGENICS' SLIDE AND TEST TAPE:

For *in vitro* diagnostic use only.

Keep testing area, hands, and specimen containers clean and free of blood.

The guaiac paper is light and heat sensitive and many discolor and/or lose sensitivity if not properly stored.

Do not use product if blue discoloration of the normally cream colored test paper is observed **PRIOR** to sample application. Discoloration may result from direct exposure of the guaiac paper to sunlight, fluorescent or ultraviolet light. Therefore, keep flaps of slide closed before and after testing.

Do not store in the vicinity of volatile oxidizing reagents such as iodine, chlorine, bromine or ammonia.

If patient or person conducting the test is visually impaired or color blind, have another person observe test for color changes.

Do not use after the expiration date printed on the test slide.

CENOGENICS' DEVELOPING SOLUTION:

For *in vitro* diagnostic use only.

Do not allow solution to contact skin or eyes. Wash immediately with water on contact and seek medical attention.

Do not use after the expiration date printed on the bottle.

Solution is flammable. Do not use near open flame(s).

Do not use other manufacturers' developing solution.

CLIA COMPLEXITY: Waived test.

SPECIMEN COLLECTION

A stool specimen may be collected from the toilet bowl, from toilet paper or caught in a clean cup. When stool is be to collected from the toilet, avoid use of bowl cleansers and continuous cleaning products. If tank cleanser is present, remove and flush toilet several time before bowel movement. Only a THIN LAYER OR SMEAR of specimen is needed to conduct the CENOGENICS' Stool Blood Test. The test may be prepared and developed immediately or stored at room temperature away from heat and light for up to twelve days before development. Each sample should be taken from a different part of each day's stool to increase the probability of detecting occult blood in each specimen. Samples from the outside of the stool specimen will reflect conditions in the lower colon. Samples from the inside of the stool sample will be more representative of the upper gastrointestinal tract. Greegor [5,15] historically recommended taking two test areas per stool. Since bleeding from intestinal lesions may be intermittent, it is recommended that specimens be collected for at least three consecutive days. CENOGENICS' TRI-SLIDE™ offers three individual test sites to allow testing of consecutive bowel movements. It is suggested specimen collection be suspended if hemorrhoids, menstrual bleeding, nosebleeds, colitis, diverticulitis, diarrhea, or constipation occur[6] during the test period or, if the patient has had recent dental work.

PATIENT PREPARATION AND SUGGESTED DIET

Patients should be placed on a **high roughage diet free of rare red meat** two days before and continuing through the testing period. Uncooked foods which contain high peroxidase activity (turnips, horseradish, radish, cantaloupe, cauliflower) should be avoided during the test period.[16] In addition, there are certain medications and substances that may interfere with the results of the test and should be avoided or discontinued two days before and during the test period but only on the approval and instruction of the patient's physician or healthcare professional.

INTERFERING SUBSTANCES

Oral medications such as **aspirin** or other salicylates, **nonsteroidal anti-inflammatory drugs (NSAID)** such as **indomethacin** and **phenylbutazone**, **anticoagulants (heparin, Coumadin),** and **corticosteroids,** can cause gastrointestinal irritation and bleeding and, therefore, inaccurate results. Additionally, **colchicine, oxidizing drugs (iodine, bromides,** and **boric acid)** and **reserpine** have been reported to cause false positive results.[8] On the advice of the physician, these medications might be temporarily discontinued for 7 days prior to and during the test period. Recent studies suggest that large amounts of **Vitamin C** in excess of 250 mg daily intake will diminish a positive reaction and possibly cause a false negative result.[31] Therefore, it is recommended that Vitamin C doses in excess of 250 mg daily be discontinued 2 days prior and during the test period. **Provodineiodine** that inadvertently comes in contact with a stool specimen or the guaiac impregnated paper will give a false positive reaction.[26] Recent studies suggest that medicinal iron preparations, though causing *in vitro* positive reactions, may not cause false positive guaiac stool occult blood results.[24,25] However, the black color of the stools caused by **medicinal iron** products may mask weak reactions.[24] Until the effect of oral iron on guaiac occult blood test results is further explored, test results from patients receiving iron should be interpreted with care. It is recommended that iron medications be stopped two days before and during the test period if permitted by the patient's physician.

SUGGESTED DIET

Foods which **should be consumed** two days before and during the testing period are as follows:
VEGETABLES: Lettuce, spinach and corn
FRUITS: Prunes, grapes, plums apples, apricots, bananas, dates, oranges and raisins
BRAN: Bread, cereal and muffins
PEANUTS AND POPCORN: moderate amounts
ALLOWED: chicken, turkey, fish and ham

Foods which **should be avoided** two days prior and continuing through the test period are:
MEAT: Rare red meats such as beef
RAW VEGETABLES: Turnips, horseradish, radishes, broccoli, carrots, cauliflower, mushrooms and cucumbers, cooking the raw vegetables listed for 20 minutes will destroy their peroxidase activity.
FRUITS: Cantaloupes and grapefruit

The suggested diet helps reduce the occurrence of false positives and most importantly, provides roughage to help uncover silent lesions which may bleed only intermittently. The diet suggested is minimally restrictive in order to encourage test compliance. In the event that any of the foods in the suggested diet cause the patient discomfort, the patient should be instructed not to eat the food in

question and to make an appropriate substitution. A patient who disregards the suggested diet may develop one or more positive tests. Noncompliant patients who test positive should be placed on the suggested diet and retested.

TEST INSTRUCTIONS

A. TEST IDENTIFICATION

In the spaces provided, fill in the patient's name, age, address, phone number, and date, or, if applicable, the hospital and room number.

B. TEST PREPARATION FOR TRI-SLIDE™

1. Using the wooden applicator stick, collect a small sample from bowel movement on the end of the applicator.
2. Apply a thin layer of specimen inside the first test window labeled **SECTION 1 A.**
3. Using the same wooden applicator stick, collect another small sample from a different area of the **same fecal** specimen and apply a thin layer inside the test window labeled **SECTION 1 B.**
4. Repeat this procedure for three consecutive days using test window areas **SECTION 2A and 2B** for the second days' bowel movement sample and test window areas **SECTION 3A and 3B** for the third day's bowel movement sample.
5. Close and reseal the test slide after each specimen application and protect from heat and light.

C. TEST PREPARATION FOR SINGLE SLIDE

1. Using the wooden applicator stick, collect a small sample from bowel movement on the end of the applicator.
2. Apply a thin layer of specimen inside test window **A.**
3. Using same wooden applicator stick, collect another small sample from a different area of the same fecal specimen and apply a thin layer inside of test window **B.**
4. Close and reseal the test slide upon completion of specimen application and protect from heat and light.

SAMPLES SHOULD BE TESTED WITHIN 7 DAYS OF COMPLETING TEST. *DO NOT MAIL TO CENOGENICS.* IF ADDITIONAL ASSISTANCE IS REQUIRED, CALL OUR TOLL FREE HELP LINE AT 800-747-9457, MONDAY THROUGH FRIDAY, 8 A.M. - 4 P.M. EASTERN STANDARD TIME.

D. TEST DEVELOPMENT

1. Open perforated panel(s) on the backside of the slide.
2. Apply one to two drops of CENOGENICS' Developing solution **directly over** each specimen area.
3. Wait 30 seconds to read and interpret the test results as follows:
   a. Any trace of blue or blue-green color indicates the presence of occult blood and is considered a **POSITIVE** result. **It is important to know that a strong blue color and a weak, very light blue color have equal diagnostic significance.** A trace reaction is just as diagnostically significant as a strong reaction.
   b. No trace of blue color is considered a **NEGATIVE** result for occult blood.
4. After developing the patient areas, check the validity of the test system by applying one drop of CENOGENICS' Developing solution to each of the Quality Control dots. The pink POSITIVE control dot must turn blue and the yellow NEGATIVE control dot should not show any trace of blue color. Though unlikely, if the Quality Control Panels do not show the results described above, patient results are suspect. Contact Cenogenics Corporation toll free at 800-747-9457.

TEST INSTRUCTIONS FOR TAPE TEST

1. Tear approximately a 1" (ONE INCH) piece of the TAPE test using the dispenser provided.
2. Wearing gloves, apply a very thin smear of stool in the center of the tape.
3. Turn the tape over to the opposite side and apply one to two drops of CENOGENICS' Developing solution **directly over** the specimen area.
4. Wait 30 seconds and read results as follows:
   a. Any trace of blue color is a **POSITIVE** result for occult blood.
   b. No trace of blue color in indicative of a **NEGATIVE** result for occult blood.

IT IS IMPORTANT THAT THE CENOGENICS' SLIDES AND TAPE TEST BE READ AND INTERPRETED THIRTY (30) SECONDS FROM APPLICATION OF THE DEVELOPING SOLUTION. THOUGH THE CENOGENICS' STOOL BLOOD POSITIVE BLUE REACTIONS ARE VERY STABLE AND MAY PERSIST FOR TWO HOURS OR MORE, WEAK TRACE REACTIONS MAY FADE WITHIN ONE OR TWO MINUTES.[28]

GASTRIC SPECIMEN CONSIDERATIONS AND LIMITATIONS

Guaiac occult blood tests are insensitive in detecting blood in unbuffered gastric juice. Layne determined that full neutralization of gastric juice obtained by nasogastric aspiration with 0.1 N NaOH could "considerably restore the ability of the guaiac stool blood method to detect blood."[27] Layne observed that a minimum of 100μL of blood/dL could be detected by the method devised. Neutralization was done by the following method:

> To an aliquot of gastric juice, add small amounts of 0.1 N NaOH dropwise with frequent pH paper testing to approximate neutrality. The neutralized gastric juice can then be tested directly on the guaiac slide.

Since various ingestible substances can lead to misleading findings and the neutralization procedure still permits false negative results, results obtained on gastric samples should be interpreted with extreme care.[32]

LIMITATIONS OF PROCEDURE

Extensive clinical studies have substantiated the diagnostic efficiency of the guaiac stool blood procedure to screen for bleeding symptoms common to many gastrointestinal pathologies. However, cancerous lesion, adenomatous polyps and other gastrointestinal lesions typically bleed intermittently, possibly allowing positive cases to go undetected. Further, blood in stool is not always homogeneously distributed,[14] a phenomenon which can allow a false negative sample to be taken. Therefore, all stool blood tests regardless of type are intended only to be used as adjuncts in combination with diagnostic procedures such as barium enema, sigmoidoscopy, colonoscopy, x-ray or other imaging studies. Some authorities have recommended applying a few drops of water to thick, dry specimens to rehydrate the specimen or to increase the sensitivity of the test. This procedure can lead to false positive results. To avoid the need to rehydrate the test, it is recommended the patient be instructed to apply a thin smear and to return the specimen within seven days of completing the test.

PERFORMANCE CHARACTERISTICS

A well controlled colorectal screening program conducted in the Austrian district of Oberpullendorf studied 18,241 individuals utilizing the CENOGENICS' test system. Of the 6,512 (36% compliance) who completed the test, 472 (7.2%) were positive. The patients with positive results were examined by colonoscopy, gastroscopy and abdominal sonography in combination with routine procedures.

The screening method revealed 19 colorectal cancers with the favorable pathological staging: Dukes A: 12 (63%), Dukes B: 5 (26%), Dukes C: 2 (11%), Dukes D: 0. Eleven polyps with carcinoma in situ and 122 polyps from 86 patients, of which 70% were adenomas, were removed.[30]

The value of screening programs was dramatically revealed by data accumulated from patients who were encouraged to participate in the screening project but did not. Of the non-responders, subsequent pathological staging of carcinomata revealed the following: Dukes A: 7 (23%), Dukes B: 10 (33%), Dukes C: 8 (27%) and Dukes D: 5 (17%). The authors concluded that there was no doubt that the screening technique was capable of detecting asymptomatic colorectal neoplastic polyps and carcinomata. Moreover, the carcinomata detected showed an altogether more favorable pathological staging compared with that for carcinomata found in an unscreened patient group.[30]

In a 1992 study performed in Czechoslovakia, 300 patients were tested with CENOGENICS' Stool Blood test system and Hemoccult. Of the 276 pairs of tests returned, CENOGENICS' test system identified 25 positive and 251 negative cases. Hemoccult detected only 19 positive and 257 negatives. Of the 5 positive samples not detected by Hemoccult, 4 were shown to be positive by subsequent endoscopic, colonscopic or x-ray examination showing Hemoccult had been falsely negative in these four cases.[29]

A Canadian study [28] demonstrated that the CENOGENICS' Stool Blood products gave increased color stability and stronger blue signal when compared to Hemoccult and Hemoccult Sensa. It was further noted that the CENOGENICS' product sensitivity has remained unchanged since 1980. In the study cited, the hemoglobin concentration and samples tested are shown in the following table:

Hb Conc.*	CENOGENICS' Slides Tested	Hemoccult Slides Tested	Sensa Slides Tested
7.5mg/ml	100	100	80
2.0mg/ml	100	68	100
0.9mg/ml	76	60	71

The Hemoglobin (Hb) concentrations chosen represented values that tested the upper strongly positive and lower trace limits of the CENOGENICS' Stool Blood guaiac/developer test system. The results which were read immediately and also at 2 minutes are shown in the following table. An average score and standard deviation were calculated for each dilution. The reactions were graded 0 for no blue color, 1+ for very faint trace of blue, 2+ for faint blue color, 3+ for definitely blue color and 4+ for intense blue color (area of blue wider than 3+).

AVERAGE SCORE AND STANDARD DEVIATION WHEN READ IMMEDIATELY

Hb Concentration	CENOGENICS	Hemoccult	Sensa
7.5 mg/ml	3.5 ± 0.0	3.2 ± 0.31	3.44 ± 0.33
2.0 mg/ml	1.89 ± 0.29	1.08 ± 0.35	1.8 ± 0.29
0.9 mg/ml	0.53 ± 0.19	0.21 ± 0.25	0.75 ± 0.3

AVERAGE SCORE AND STANDARD DEVIATION WHEN READ AT TWO MINUTES

Hb Concentration	CENOGENICS	Hemoccult	Sensa
7.5 mg/ml	3.5 ± 0.25	2.7 ± 0.35	3.1 ± 0.22
2.0 mg/ml	1.4 ± 0.37	0.05 ± 0.42	1.28 ±0.3
0.9 mg/ml	0.22 ± 0.21	0.4 ± 0.12	0.3 ± 0.23

The results of the comparison indicate that the CENOGENICS' guaiac slides provide the user with a stronger blue signal than the Hemoccult tests. The Hemoccult slide demonstrated wide variability as the hemoglobin concentration drops to 0.9mg/ml while the CENOGENICS' slides maintained standard deviations of one half of the mean value. The ability of the CENOGENICS' slides to provide a strong blue color and maintain it for significantly longer period of time is emphasized at two minutes. At weak and trace reaction concentrations of Hb, 2.0mg/ml and 0.9mg/ml respectively, the Hemoccult products provided virtually no signal (0.04 and 0.05). The improved color stability of the CENOGENICS' slide promotes easier readability and reliable interpretation.[28]

EXPECTED RESULTS

In vitro studies have shown that guaiac impregnated slides and tapes are capable of detecting 2 to 4 ml of blood in 150 grams of feces (equivalent to 2 mg hemoglobin per gram of stool[18]), about two the normal daily fecal blood loss in an adult.[16,17,18] Greegor[5,15,19,20] pioneered the use of guaiac paper slides as supplied by CENOGENICS' subsidiary, Laboratory Diagnostics Co., as an aid in the detection of colorectal cancer in patients. A study of 900 patients showed a positive result of 5%. Utilizing barium enema examination, 1 % of those patients were shown to have asymptomatic colon cancer. An additional 3% had some other type of bowel pathology. A false positive rate of only 1 % was reported in this study. In a second study, Greegor[20] detailed 2000 physicians who had used the guaiac slides over a 6 month period; colon cancer was detected in 47 patients. These patients were asymptomatic other than the positive guaiac slide test.

Another study conducted on 20 health volunteers by Ostrow et al[21], involved instilling varying quantities of radioactive chromium (Cr^{51})- tagged red blood cells via nasogastric tube. The reactions obtained with guaiac paper slides were compared to two other chemical test methods for detecting fecal blood, benzidine and orthotolidine tablets. The guaiac slide was found to be about one-quarter as sensitive as the benzidine and orthotolidine test procedures but virtually free of false positive reactions. The benzidine and orthotolidine tests were demonstrated to give 31% and 37% false positive reactions. Consequently, the guaiac stool blood method became the method of choice to detect stool occult blood.

A collaborative test was conducted to compare CENOGENICS' Stool Blood test and 2 different Hemoccult slides. Hemoglobin was diluted in deionized water to the following concentrations: 1 mg/ml, 2mg/ml, 4mg/ml, 6mg/ml and 12mg/ml (equivalent to 0.1, 0.2, 0.4, 0.6 and 1.2 grams hemoglobin per 100 grams of stool, respectively). These dilutions were used to test the sensitivity of the CENOGENICS' test and compare the reactions to the reactions of the Hemoccult tests. The CENOGENICS' Stool Blood test gave a trace reaction at a hemoglobin concentration of 1 mg/ml in less than one minute while the Hemoccult II and Hemoccult Sensa produced a negative result. At 2mg/ml, a 1+ positive reaction was observed in less than two minutes with the CENOGENICS' test, while both Hemoccult II and Hemoccult Sensa produced a trace reaction. At 4mg/ml, a 2+ positive reaction was observed in less than two minutes with the CENOGENICS' test system while both Hemoccult II and Hemoccult Sensa products produced only a trace to a 1+ reaction. At 6mg/ml CENOGENICS' test produced a 3+ positive reaction and at 12mg/ml a 4+ positive reaction was observed in less than two minutes, whereas the Hemoccult II and Hemoccult Sensa produced only a 1+ to 2+ reaction at the 6mg/ml dilution and only a 2+ to 3+ reaction at the 12mg/ml dilution.[28]

In summary, data from numerous studies have shown the positive rate to be approximately 3% - 7.2% in screening programs. The false positive rate has been between 1 % and 2% in patients who receive proper preparation. The guaiac stool blood test will detect 90% of all colorectal lesions that bleed provided that three consecutive bowel movements are tested.[33,34]

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