

Physician Letter

PATIENT INFORMATION

NAME: _____

DOB: / / TEST DATE: / /

Dear Dr. _____,

PATIENT TEST RESULTS

This letter is in reference to the above patient, who was screened for colorectal cancer (CRC) with PreGen-Plus™, a non-invasive screening method that tests a single stool sample for 23 DNA markers proven to be associated with CRC and precancerous growths (see details below).

Your patient ordered testing from DNA Direct, a Web-based genetic testing service that provides pre-test education and post-test interpretation and counseling. For more information on our services or questions about your patient's test results, please phone us at 1-877-646-0222 or email expert@dnadirect.com, or visit www.dnadirect.com.

Your patient's test results are negative.

We have advised your patient to discuss an appropriate CRC screening schedule with you, if one has not yet been established. Please include this report in your patient's medical records.

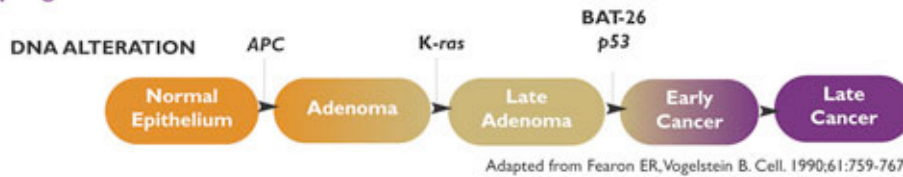
Negative Results. As with any screening test, a negative result should not be considered definitive evidence that a colorectal neoplasia is absent. At present, due to lack of definitive data, the optimal intervals for repeating PreGen-Plus remains uncertain. Based on studies thus far, there may be an advantage to initial repeat testing with PreGen-Plus at a one-year interval, in order to increase its sensitivity for early stage cancer. Subsequently, a three- to five-year interval can be considered in order to detect advanced adenomas, which are known to evolve from small adenomas over a long period of time. Colorectal symptoms should be evaluated regardless of stool test results.

OVERVIEW OF PreGen-Plus™

PreGen-Plus is a non-invasive screening test for colorectal cancer (CRC). PreGen-Plus is not intended to replace colonoscopy. However, it is currently the most accurate non-invasive screening tool for CRC, with a detection rate 4-fold greater than FOBT.

Using a single stool sample, it is designed to detect genetic changes that may have occurred in cells in the colon and rectum that are associated with clinically significant colorectal growths – both invasive cancer and certain precancerous growths (advanced adenomas with high-grade dysplasia) throughout the entire colon (see diagram on page 2). Not all abnormalities are present in any one tumor, nor do all tumors necessarily contain one or more of the abnormalities detected by PreGen-Plus.

Colorectal cancer develops in well-defined stages and arises from molecular alterations in multiple genes within an individual cell.



PreGen-Plus is a single test comprised of 23 molecular markers of colorectal cancer. These include:

- 21 point mutations in *APC*, *K-ras*, and *p53*
- One microsatellite instability marker, BAT-26
- One Long DNA marker, DNA Integrity Assay (DIA[®])

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PreGen-Plus does not diagnose CRC and does not look for inherited mutations associated with hereditary cancer syndromes.

Indications For Use. While PreGen-Plus is not intended to replace colonoscopy, it is currently the most accurate non-invasive screening tool for CRC.

PreGen-Plus is intended for people at average risk for developing CRC who:

- Are 50 years of age and older.
- Are unwilling or unable to undergo invasive CRC screening.
- Want interim screening between colonoscopies.
- Do not have signs and symptoms of CRC.

PreGen-Plus is NOT intended as a *primary* screening tool for people with:

- A positive fecal occult blood test (FOBT), a history of rectal bleeding, or signs and symptoms that suggest colorectal disease.
- Inflammatory bowel disease (ulcerative colitis and Crohn's disease).
- Cancers elsewhere in the proximal gastrointestinal tract, lungs, or head and neck area.
- A personal or family history of colorectal neoplasia.*
- Known or suspected hereditary colorectal cancer syndromes, including Familial Adenomatous Polyposis (FAP), Hereditary Non-Polyposis Colorectal Cancer (HNPCC) and other rare hamartomatous syndromes.*

* PreGen-Plus may also be valuable as an adjunctive screening test by supplementing other screening modalities or enhancing adherence to an overall screening regimen, depending on the specific needs of the patient.

Accuracy. PreGen-Plus performance characteristics – as demonstrated by five separate studies conducted in a variety of clinical settings and situations – suggest an approximate sensitivity of 65% for CRC (in 227 CRCs) with a specificity of 95% (in 1,564 asymptomatic, average risk individuals age 50 years or older). PreGen-Plus also has demonstrated an ability to detect advanced adenomas (pre-cancerous lesions most likely to progress to CRC).

Sample Collection. A single, whole stool specimen (<30g) is required with no bowel preparation, medication or dietary restrictions, or sample manipulation. A repeat specimen may be needed if a sample is not large enough, or has not been collected according to instructions.

SCREENING GUIDELINES

People At Average Risk. Currently, the American Cancer Society and many medical associations recommend that people age 50 and over who are at average risk for colon cancer follow one of these screening regimens:

- Colonoscopy every 10 years
- Double contrast barium enema every 5 years
- FOBT or FIT every year plus flexible sigmoidoscopy every 5 years
- Flexible sigmoidoscopy every 5 years
- FOBT or FIT every year. *Note: a take-home, multi-sample kit should be used. A single FOBT test done in the physician's office after a digital rectal exam is not recommended.*

The dwell stage of colorectal cancer in the average-risk person is thought to be approximately 8-10 years. This provides a large window of opportunity for screening, which can lead to early detection and even prevention of the disease.

PreGen-Plus and virtual colonoscopy are newer procedures, and the American Cancer Society and others are still evaluating the research to determine guidelines for these screening methods.

People At Increased Risk. People who are at increased risk of colorectal cancer because of family history or personal medical conditions should begin screening before age 50 and should be screened more often. Since recommendations vary depending on a person's personal and family history, it is important for physicians to determine the at-risk individual's screening plan.

If you have questions about your patient's results, or PreGen-Plus, please feel free to contact me at the number or email below.

Sincerely,

Elissa Levin, M.S., CGC
Clinical Director, DNA Direct
1-877-646-0222
expert@dnadirect.com

References

American Cancer Society. *Colorectal Cancer Facts & Figures Special Edition 2005*. Atlanta: American Cancer Society, 2005: www.cancer.org.

Centers for Disease Control and Prevention. Colorectal cancer: The importance of prevention and early detection (Fact Sheet). Atlanta, GA: 2003: www.cdc.gov/colorectalcancer.

Levin B et al. 2003. Emerging Technologies In Screening for Colorectal cancer: CT Colonographies, Immunochemical Fecal Occult Blood Tests, and Stool Screening Using Molecular Markers. *CA Cancer J Clin*. 53:44-55.

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