August 29, 2007

Stephen Phurrough, M.D., M.P.A.
Division Director
Division of Medical and Surgical Services
Coverage and Analysis Group
Office of Clinical Standards and Quality
Room C1-11-08
Mail Stop C1-09-06
7500 Security Boulevard
Baltimore, MD 21244-1850

Re: National Coverage Analysis for Screening DNA Stool Test for Colorectal Cancer (CAG – 00144N)

Dear Dr. Phurrough:

Enterix, Inc. is submitting this comment in response to the CMS request for public comment on the National Coverage Analysis for Screening DNA Stool Test for Colorectal Cancer (CAG-00144N). Thank you for the opportunity to provide our perspective on this important issue.

As we have noted previously in communications with CMS (particularly during the National Coverage Analysis process that we initiated for Medicare coverage for colorectal cancer screening with immunoassay fecal-occult blood tests, which resulted in a positive coverage decision), Enterix supports expanded options for colorectal cancer screening for Medicare beneficiaries and Medicaid recipients. The position taken by the CMS previously was that such coverage should be based on the principles of evidence-based medicine. We agree and recommend that the CMS apply that same standard in this case.

We believe this request for expansion of the Medicare colorectal cancer screening benefit to include the periodic use of a DNA stool test (and particularly the PreGen-Plus test) fails to meet established requirements for such coverage and basic principles of evidence-based medicine. We believe the following issues should prevent CMS from issuing a positive coverage decision:

1. We understand from the Tracking Sheet that the requestor asks CMS to cover the PreGen-Plus test every 5 years, as an alternative to a screening colonoscopy every ten years or to a screening flexible sigmoidoscopy every five years. We have not seen

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and are not aware of any published scientific data that would support such a novel screening protocol. The concept of interval screening is based on important observations of disease pathology and screening test performance. If the requestor believes that an appropriate screening interval with the PreGen-Plus technology is once every five years, it should undertake sufficient clinical studies to justify the proposed screening rationale (perhaps to include screening of an appropriate population over the course of five year cycles).

The requestor speculates that it is possible to indirectly infer some degree of potential net health benefit from periodic use of PreGen-Plus as a screening tool. We do not think that this speculation is an appropriate basis for coverage, without published large scale morbidity and mortality reduction trials conducted to support this claim. The very different nature of the underlying detection method embodied in the PreGen-Plus test from any currently covered colorectal cancer screening method precludes any reliance upon an indirect inference of potential net health benefits.

2. Another issue of concern is what specific test CMS is being asked to consider for coverage. The title of the NCA refers to a "Screening DNA Stool Test for Colorectal Cancer." On the tracking sheet of the NCA, additional detail is provided in the "Issue" section, which appears to specify the PreGen-Plus test, version 1.1 as the "Screening DNA Stool Test" in question. Scientific literature and third-party evaluations of the Exact Sciences test over the past five to six years have recorded substantial changes in: a) the number and type of markers that are sought for detection; and b) the method of sample collection and test processing.[1,2] Furthermore, Exact Sciences Corp. recently stated the following in their August 8, 2007 Securities and Exchange Commission Form 10-Q Quarterly Report for the period ended June 30, 2007; "LabCorp informed the FDA during 2006 that they were working on changes to PreGen-Plus that could eliminate the use of Effipure in PreGen-Plus." In addition, Exact Sciences Corp. stated "Our success will also depend upon a number of factors that are largely out of control, including the following: the positioning of stool-based DNA screening within guidelines such that it is not limited among the screening options offered and that any inclusion in screening guidelines includes our Version 2 technologies"[3] Therefore, since it appears that the actual test for which a coverage determination is requested may be Version 2 of this Screening DNA Stool Test, we suggest the CMS may want to wait to reach a coverage decision once appropriately documented scientific evidence exists for this new Version 2.

3. We believe that the data set relating to the test performance of PreGen-Plus is insufficient to allow for reasonable, evidence-based conclusions about the utility of this test as a population screening tool. We are aware of only two studies of PreGen-Plus that <u>may</u> in any way relate to the subject of this coverage. These two studies (Imperiale et. al. N Engl J Med 2004, and Ahlquist et. al. Gastroenterology 2005) were single iteration prospective comparative tests on substantial screening age populations.[4] The aim of each was to compare the test performance of PreGen-Plus

to the least sensitive (but highly specific) version of the standard guaiac FOBT, Hemoccult II (Beckman Coulter). Imperiale concluded that PreGen-Plus had a relatively low sensitivity for cancer and for advanced adenoma with high-grade dysplasia (52% and 41%, respectively). We also note the PreGen-Plus testing on which the study was based was performed at Exact Sciences (the test developer), and therefore these data were not obtained under conditions that are the current practice for PreGen-Plus (all tests are performed at Laboratory Corporation of America facilities). Others have raised numerous additional limitations to these studies.[5] The Ahlquist study reported substantially lower sensitivity of the PreGen-Plus test for screen-relevant neoplasia (defined to include cancer, high-grade dysplasia and adenomas greater than or equal to 1 cm in diameter), specifically, only 20%. These figures compare poorly to the generally accepted sensitivity figures for other, currently-covered colorectal cancer screening methods (e.g. 10 year interval colonoscopy – >90%; 5 year interval sigmoidoscopy – 68-78%; annual or biennial Immunochemical FOBT – 35 - 62%; annual or biennial guaiac FOBT – 30 - 50%).[6] Also, in a recently published a study in the Journal of Cancer (Smith A., Young GP, Cole SR. Cancer 2006; 107:2152-2159) that described sensitivity with Immunochemical FOBT of 35-87%.[7] Without a substantial body of clear and scientifically convincing clinical evidence that the performance of the PreGen-Plus (Version 1.1) test offers consistent benefit to the Medicare and Medicaid population, we recommend that the CMS not make a positive coverage decision.

4. At this time, it is our understanding that fecal DNA screening, including PreGen-Plus, is not included as a recommended option in the major colorectal cancer screening guidelines. Specifically, the U.S. Preventative Services Task Force, American Cancer Society, and National Comprehensive Cancer Network each have developed and periodically updated guidelines for population screening for colorectal cancer, yet none of these three organizations has determined that DNA-based screening is recommended.[8] We take this lack of inclusion of PreGen-Plus in these guidelines to indicate that these respected bodies have perceived fundamental issues with the use of PreGen-Plus as a regular screening tool, similar to the points we have raised in this letter. While future guidelines may evolve to include such tests, the PreGen-Plus test has been available for approximately six years and has not been included in the guidelines to date.

Colorectal cancer screening is a critically important health and safety issue that involves many millions of Medicare and Medicaid beneficiaries. Enterix supports expanded options for beneficiaries in the critical area of colorectal cancer screening. However, novel-screening options proposed for coverage should be clearly supported by the principles of evidence-based medicine. The request by Exact Sciences et. al. to include a Screening DNA Stool Test for Colorectal Cancer (specifically, PreGen-Plus) as a covered option under the colorectal cancer screening benefit fails to satisfy basic evidentiary requirements for inclusion in the Medicare benefit and therefore should result in a non-coverage decision.

Thank you for the opportunity to comment on this important question of public interest.

Sincerely,

Edwin Diaz /DB

Edwin Diaz
Managing Director

CC: Joseph Chin MD
William Larson

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[1] An illustrative history of the evolution of the Exact Sciences Fecal DNA test is incorporated into the comprehensive Blue Cross and Blue Shield Technology Evaluation Center document "Special Report: Fecal DNA Analysis for Colon Cancer Screening," published in Volume 21, No. 6, August, 2006 and accessed at www.bcbs.com/betterknowledge/tec/ .

[2] See Ahlquist DA, Sargent DJ, Levin TR, et. al., "Stool DNA Screening for Colorectal Cancer: Prospective Multicenter Comparison With Hemoccult," *Gastroenterology*, 128(suppl 2):A63 (2005) for informative comment regarding the evolution of the PreGen-Plus test during the recruitment period for an NCI-funded multicenter study.

[3] Exact Sciences Corporation, Form 10-Q filed with the United States Securities and Exchange Commission for the fiscal quarter ended June 30, 2007. See the "Overview" section of Management's Discussion and Analysis of Financial Condition and Results of Operation.

[4] Imperiale TF, Ransohoff DF, Itzkowitz SH et. al. for the Colorectal Cancer Study Group (2004). Fecal DNA versus fecal occult blood for colorectal-cancer screening in an average-risk population. N Engl J Med, 351(26):2704-14. Ahlquist DA, Sargent DJ, Levin TR, et. al. Stool DNA Screening for Colorectal Cancer: Prospective Multcenter Comparison With Hemoccult. Gastroenterology, 128(suppl 2):A63.

[5] Blue Cross Blue Shield TEC Special Report, ibid, note 1. See page 13 of the TEC Special Report for detailed discussion of concerns regarding the Imperiale 2004 study.

[6] Blue Cross Blue Shield TEC Special Report, ibid, note 1. See Table 4: Average-Risk Screening: Comparison of Methods, page 15.

[7] See Smith A, Young GP, Cole SR, Bampton P. Comparison of a Brush-Sampling Fecal Immunochemical Test for Hemoglobin With a Sensitive Guiac Based Fecal Occult Blood Test in Detection of Colorectal Neoplasia. Cancer 2006 ;107:2152-2159

[8] See www.nccn.org/professionals/physician_gls/PDF/colorectal_screening.pdf; Smith RA, Cokkinides V, Eyre HJ. American Cancer Society guidelines for the early detection of cancer, 2006. CA Cancer J Clin. 2006;56:11-25; and www.ahrq.gov/clinic/3rduspstf/colorectal/colorr.htm.

JAMES P. McGOVERN
3RD DISTRICT, MASSACHUSETTS

VICE CHAIRMAN
COMMITTEE ON RULES

COMMITTEE ON BUDGET

Congress of the United States
House of Representatives
Washington, DC 20515–2103

http://www.mcgovern.house.gov

438 CANNON HOUSE OFFICE BUILDING
WASHINGTON, DC 20515–2103
(202) 225–6101

DISTRICT OFFICES:
34 MECHANIC STREET
WORCESTER, MA 01608
(508) 831–7356

ATTLEBORO OFFICE:
8 NORTH MAIN STREET, ROOM 200
ATTLEBORO, MA 02703
(508) 431–8025

FALL RIVER OFFICE:
218 SOUTH MAIN STREET, ROOM 204
FALL RIVER, MA 02721
(508) 677–0140

MARLBOROUGH OFFICE:
255 MAIN STREET, ROOM 104
MARLBOROUGH, MA 01752
(508) 460–9292

August 15, 2007

Mr. William Larson
Coverage and Analysis Group
NCA for Screening DNA Stool Test
For Colorectal Cancer (CAG-00144N)
7500 Security Blvd.
Mail Stop-C-1-09-06
Baltimore, MD 21244

Dear Mr. Larson,

I am writing to you today in support of EXACT Sciences Corporation application for DNA-based screening for colon cancer for national coverage determination. It is my belief that the 43 million Medicare beneficiaries would greatly benefit from this added medical coverage. Existing screening methods are only reaching 30% of our beneficiaries while more than 50,000 people die each year from colon cancer. These new screening methods will make early detection easier and more affordable for many.

Fighting colorectal cancer was cited as a priority in the Balanced Budget Act of 1997 which enables CMS to provide colorectal cancer screening to beneficiaries and to add new tests to the ones specified as technology advances. According to the American Cancer Society, fecal DNA screening is one of these tools and will be necessary in order to win the battle against cancer.

My wife, Lisa McGovern is currently serving as the Executive Director of the Congressional Families Action for Cancer Awareness Program which is dedicated to not only the prevention of cancer but increasing early detection rates and therefore protecting more from this deadly disease.

Cancer affects almost everyone living in our country today, either personally or a family member. Any additional effective tools that we can make available to our citizens so that they can go on to live happy and healthy lives should be seriously considered.

Your consideration of EXACT's application is appreciated.

Sincerely,

James P. McGovern
Member of Congress

1520 Kensington Rd, Suite 202
Oak Brook, IL 60523
(P) 630/573-0600 / (F) 630/573-0691
Email: info@asge.org
Web site: www.asge.org

August 31, 2007

Mr. William Larson
Centers for Medicare and Medicaid Services
7500 Security Boulevard
Baltimore, MD 21244-1850

Re: NCA/CAL: Screening DNA Stool Test for Colorectal Cancer (CAG-00144N)

Dear Mr. Larson:

The American Society for Gastrointestinal Endoscopy (ASGE) appreciates the opportunity to offer comments on the proposed NCA/CAL: Screening DNA Stool Test for Colorectal Cancer (CAG-00144N) released by the Centers for Medicare and Medicaid Services (CMS) on August 1, 2007. ASGE is a professional organization representing over 10,000 gastroenterologists across the United States practicing in a wide variety of healthcare settings.

We have reviewed the coverage analysis of EXACT Sciences' DNA Stool Test. Based on our assessment of the request and supporting literature we do not support the coverage of this test every 5 years as an alternative to a screening colonoscopy that may be covered every 10 years or as an alternative to a screening flexible sigmoidoscopy that may be covered every 4 years for such individuals as provided in 42 CFR 410.37 (e) and (g).

ASGE is very supportive of efforts to expand the coverage of colorectal cancer (CRC) screening. It has been shown to lower mortality and the incidence of the disease. As practicing physicians we are acutely aware of the challenges of current screening options. The invasiveness and pre-procedure fasting make patients very reluctant to undergo colonoscopies. Screening compliance rates for CRC are very low and any less invasive method that would encourage Medicare beneficiaries to undergo screenings at the regularly recommended intervals would be very welcomed by the Society.

Unfortunately we feel that the lack of scientific evidence on the efficacy of this test makes it premature to support a national coverage decision. The accuracy of this test in an asymptomatic population is unclear. Additional research needs to be conducted in order to determine the specificity of the test to detect

colorectal neoplasia in the general Medicare population. In our review of the research we found that this position is supported by a wide variety of researchers in the field.

American Cancer Society – In 2007 the American Cancer Society (ACS) concluded, "Recent studies that have combined DNA tests to look for gene mutations and for intact-appearing DNA have shown promising results. Nonetheless, more research is needed to confirm the accuracy of these tests before widespread use can be recommended."

National Cancer Institute – In 2007 the NCI concluded that f-DNA testing every year five years appears both effective and cost-effective compared with no screening but inferior to other strategies (e.g. FOBT and colonoscopy).

Centers for Disease Control – In 2006 concluded that the testing of genetic material such as DNA in stool is promising and potentially a screening option for the future.

The *ASGE Guide: Colorectal Screening and Surveillance* addresses this issue as well. Published by the Standards of Practice Committee, this document does not recommend fecal DNA testing as a screening strategy for average-risk individuals. A copy of this document is attached. This position is also supported by recent reviews of this test that were conducted by CIGNA and the Blue Cross Blue Shield Association. Copies of these assessments are attached for your reference.

With the reality of limited available resources for Medicare, we must consider also consider the cost-effectiveness when evaluating coverage. The test is currently priced at approximately $700. We concluded that with the high cost of this test compared with other stool tests, it would be unreasonable to support such an expensive test until studies show greater value.

ASGE is very supportive of the expansion of CRC screening. As the third most frequently diagnosed cancer in the United States for both men and women we support any effort that encourages Medicare beneficiaries to undergo a CRC screening. We understand the preference of patients for less invasive screening methods. Nevertheless, we have concluded that current evidence does not support the coverage of EXACT Sciences' DNA Stool Test to other currently approved CRC screening methods for the Medicare program.

We appreciate the opportunity to provide continued input on this important issue. Thank you once again for your attention to our comments. If you have any questions or need additional information, please contact Mr. Randy Fenninger, of MARC Associates. He can be reached at 202-833-0007 or randy@marcassoc.com. Thank you in advance for your consideration.

Sincerely yours,

Klaus Mergener, MD, PhD, FASGE, CPE
Committee Chair, Practice Management Committee
American Society for Gastrointestinal Endoscopy (ASGE)