April 12, 2019

Tamara Syrek Jensen, JD
Director, Coverage and Analysis Group
Center for Clinical Standards and Quality
Centers for Medicare & Medicaid Services
7500 Security Boulevard
Baltimore, MD 21244

By email, tamara.syrekjensen@cms.hhs.gov

RE: Formal Request for a National Coverage Determination (NCD) for Epi proColon, a blood-based screening test for Colorectal Cancer as a covered Colorectal Cancer Screening test (210.3) under the Soc Sec Act § 1861 (pp)1

Dear Ms. Syrek Jensen:

Epigenomics formally requests a National Coverage Determination for Epi proColon, a blood-based screening test for Colorectal Cancer.

Benefit category of the Medicare program to which the service applies: colorectal cancer screening test (Soc Sec Act § 1861 (pp)(1). This assay would be subject to Medicare Part B.

Epi proColon is an FDA-approved molecular diagnostic test (P130001, 4/12/2016) that is indicated for use in average risk individuals who are unwilling or unable to be screened by 2008 USPSTF-endorsed screening methods (including colonoscopy and fecal immunochemical testing). With this indication, Epi proColon fills a major unmet medical need, since participation in colorectal screening remains sub optimal among both the general population over age 50 and Medicare beneficiaries.

The Epi proColon test is a qualitative in vitro diagnostic test for the detection of methylated Septin 9 DNA in EDTA plasma derived from patient whole blood specimens. Methylation of the target DNA sequence in the promoter region of the *SEPT*9_v2 transcript has been associated with the occurrence of colorectal cancer (CRC). The test uses a real-time polymerase chain reaction (PCR) with a fluorescent hydrolysis probe for the methylation specific detection of the Septin 9 DNA target.

As the Epi proColon test is not a fecal occult blood assay (gFOBT or FIT), a screening flexible sigmoidoscopy or a screening colonoscopy, it is not currently a covered colorectal cancer screening test. The Administrator of the Center for Medicare and Medicaid Services (CMS) has the authority to provide coverage for other test procedures. Therefore, we are submitting this request for an NCD as allowed in 42CFR§ 410.37 (a)(1)(v).

As part of the National Coverage Analysis process, Epigenomics has previously submitted a letter to CMS that contained a complete description of the test, a description of the proposed use of the test,

supporting medical and scientific information, an explanation of the design/purpose/method of the item, and the FDA status of the test.

As part of the NCD request, Epigenomics is submitting the list of references previously submitted to CMS as part of the NCA process.

Dr. Jorge Garces, President and Chief Scientific Officer of Epigenomics AG and Noel Doheny, CEO of Epigenomics, Inc. are the primary requestors for the NCD. Dr. Jorge Garces will serve as the principal point of contact and may be reached as shown below for additional information or clarification.

Sincerely,

Dr. Jorge Garces

President and Chief Scientific Officer

608-358-8017

Jorge.garces@epigenomics.com

cc: Greg Hamilton
Noel Doheny

Appendix A: List of Reference Materials

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[1] Brenner, H. et al. 2015. Prevention, early detection, and overdiagnosis of colorectal cancer within 10 years of screening colonoscopy in Germany. Clin Gastroenterol Hepatol; 13(4): 717-723.
[2] MMWR Weekly / March 3, 2017 / 66(8);201–206 Cancer Screening Test Use — United States, 2015
[3] Joseph, D.A. et.al. Preventing Chronic Disease: 15 (2018) 170535. DOI: http://dx.doi.org/10.5888/pcd15.170535. Use of Colorectal Cancer Screening Tests by State
[4] https://www.healthypeople.gov/2020/topics-objectives/topic/cancer/objectives
[5] Gimeno-Garcia, A.Z. 2012. Factors influencing colorectal screening participation.Gastroenterol. Res. Pract. Volume 2012, Article ID 483417. doi:10.1155/2012/483417
[6] Winawer S.J. eta l. 2016. Evidence-based, reality-driven colorectal cancer screening guidelines. JAMA 315:2065-66. doi:10.1001/jama.2016.3377
[7] Kaur A, Salhab J, Sobrado J (2016) Recognizing Diagnostic Gap in Colorectal Cancer. Intern Med 6: 219. doi: 10.4172/2165-8048.1000219.
[8] Doubeni, Chyke A. et al. Modifiable Failures in the Colorectal Cancer Screening Process and Their Association With Risk of Death. Gastroenterology , Volume 156 , Issue 1 , 63 - 74.e6.
[9] deVos T, Molnar B. Screening for Colorectal Cancer Based on the Promoter Methylation Status of the Septin 9 Gene in Plasma Cell Free DNA. J Clin Epigenet. 2017, 3:1. doi: 10.21767/2472-1158.100040
[10] Potter et.al. 2014 – Clin Chem 60(9):1183-91. Validation of a Real-Time PCR-Based Qualitative Assay for the Detection of Methylated SEPT9 DNA in Human Plasma.
[11] Knudsen, A.B. et al. 2016. Estimation of benefits, burden, and harms of colorectal cancer screening strategies: modeling study for the US Preventative Services Task Force. JAMA 315(23); 2595-609.
[12] Johnson, D.A. et.al. 2014. Plasma Septin9 versus fecal immunochemical testing for colorectal cancer screening: a prospective multicenter study. PLoS ONE 9(6): e98238. doi:10.1371/journal.pone.0098238
[13] Liles et.al. Uptake of a colorectal cancer screening blood test is higher than of a fecal test offered in clinic: A Randomized Trial. Cancer Treatment and Research Commun 10:27-31 2017
[14] United States Preventive Services Task Force - Screening for Colorectal Cancer: US Preventive Services Task Force Recommendation Statement. JAMA 2016;315:2564-75.
[15] Church TR, Wandell M, Lofton-Day C, et al. Prospective evaluation of methylated SEPT9 in plasma for detection of asymptomatic colorectal cancer. Gut 2014;63:317-25.
[16] Mergener K, Potter NT. Colorectal Cancer Screening Recommendations. JAMA. 2016 Oct 25;316(16):1716. doi: 10.1001/jama.2016.14915
[17] Rex DK, Boland CR, Dominitz JA, et al. Colorectal Cancer Screening: Recommendations for Physicians and Patients from the U.S. Multi-Society Task Force on Colorectal Cancer. Am J Gastroenterol 2017.

February 10, 2020

Tamara Syrek Jensen, JD
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By email, tamara.syrekjensen@cms.hhs.gov

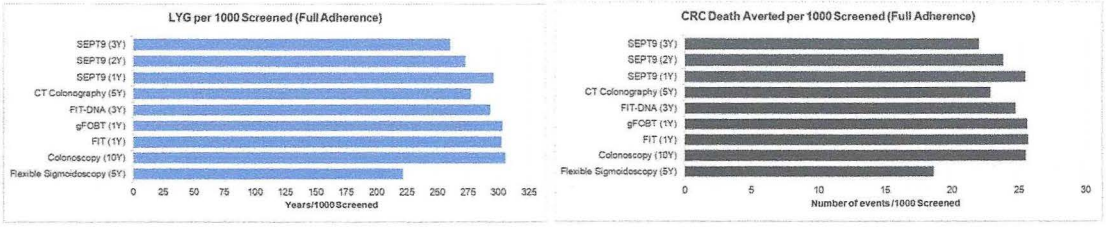
RE: Addendum to Epi proColon National Coverage Determination (NCD) request

On April 12, 2019, Epigenomics submitted a formal request to the Centers for Medicare & Medicaid Services (CMS) for an NCD for Epi proColon®, a Food and Drug Administration (FDA) approved blood-based screening test for colorectal cancer. On April 18, 2019, CMS notified us that our request was accepted. Consistent with CMS's process for soliciting additional evidence after it has accepted a request for an NCD, as requested by CMS, additional supportive data for the clinical utility and benefit of this test have been subsequently published in the peer reviewed literature that were not included in the original NCD request letter.

Microsimulation is a standard method for evaluation of colorectal cancer screening (CRC) methods employed by the US Preventive Services Task Force (USPSTF) and the American Cancer Society (ACS). D'Andrea et al.[1] published a microsimulation analysis of colorectal cancer screening methods that included the Epi proColon test. The article reports on several key findings relevant to the utility of Epi proColon as outlined below. Together with previous data on test performance and FDA approval of the test for CRC screening, we believe these additional data on clinical utility strongly support a favorable coverage decision for Epi proColon.

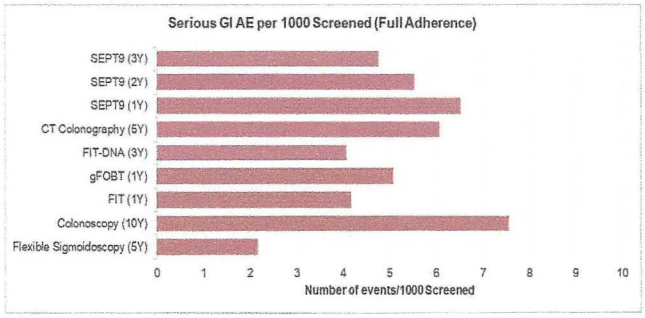
I. Benefits of Screening: As measured by Life Years Gained (LYG) and CRC Deaths averted (reduction in mortality), annual screening with Epi proColon yields similar benefits as compared to all other CRC screening methods currently covered by CMS. (Fig 1). Comparable outcomes were also reported for CRC cases averted (reduction in CRC incidence) using Epi proColon annually versus other methods currently covered by Medicare.

Figure 1. Comparison of screening benefits (Life Years Gained, CRC Deaths Averted) for 9 Screening Strategies: SEPT9 (3Y), (2Y), (1Y) indicate Epi proColon testing every 3 years, every 2 years, or annually; CT Colonography (5Y) every 5 years; FIT-DNA (3Y) – Cologuard every 3 years; gFOBT (1Y) High sensitivity guaiac fecal occult blood test every year; FIT (1Y) – immunochemical fecal occult blood every year; Colonoscopy (10Y) – every 10 years; Flexible Sigmoidoscopy (5Y) – every 5 years.



II. Harms of Screening – There is essentially no harm associated with the blood draw procedure for Epi proColon. However, as reported for all other CRC screening methods, harms are assessed based on the overall colonoscopy burden (lifetime number of colonoscopies required) associated with each strategy. That is, harms are measured as the overall number of colonoscopies resulting from the positivity rate (referral to colonoscopy rate) reported for any particular screening strategy. This is also in line with the FDA assessment of harms for the product. The adverse event rate associated with colonoscopy (serious GI bleeding and colon perforation) is directly proportional to colonoscopy burden. As illustrated in Fig. 2, the number of harms associated with the use of Epi proColon are less than those that result from using colonoscopy, as the primary screening method, every ten years.

Figure 2. Comparison of Harms for 9 Screening Strategies: Strategy Key as in Fig. 1



III. Screening Interval – It is clear from Figure 1 that annual screening with Epi proColon provides greater benefit than screening every 2 or 3 years, though with some consequent increase in harms. Harm to benefit ratios or efficiency ratios (calculated as the incremental number of colonoscopies divided by the incremental life-years gained) are used to determine the optimal efficiency of various CRC screening strategies. On this basis, annual screening was reported as the optimal interval for CRC screening with Epi proColon.

IV. Reference:

1. D'Andrea E, Ahnen DJ, Sussman DA, Najafzadeh M. 2020. Quantifying the impact of adherence to screening strategies on colorectal cancer incidence and mortality. Cancer Med. 2020 Jan;9(2):824-836. doi: 10.1002/cam4.2735. Epub 28 Nov 2019

Please let us know if you have any questions or if you need any additional information. We look forward to working with you to secure national coverage for CRC screening with Epi proColon and to help ensure that more Medicare beneficiaries are screened for this largely preventable but deadly disease.

Sincerely,

Dr. Jorge Garces

President and Chief Scientific Officer

608-358-8017

Jorge.garces@epigenomics.com

Cc: Greg Hamilton

Beth Roberts (Hogan Lovells US LLP)