

Brief Summary of the Molecular and Clinical Genetics Panel Meeting – March 26, 2014

Introduction:

The Molecular and Clinical Genetics Panel of the Medical Devices Advisory Committee to the Food and Drug Administration met on March 26, 2014 to make recommendations and vote on the premarket approval application sponsored by Epigenomics AG for Epi proColon. The Epi proColon test is a qualitative *in vitro* diagnostic test for the detection of methylated Septin 9 DNA in plasma derived from patient whole blood specimens. Methylation of the target Septin 9 DNA sequence has been associated with the occurrence of colorectal cancer (CRC). The test is indicated to screen patients for CRC who are defined as average risk for CRC by current CRC screening guidelines. The Epi proColon test is not intended to replace colorectal screening by colonoscopy. Patients with a positive Epi proColon test result should be referred for diagnostic colonoscopy. The Epi proColon test results are intended to be used in conjunction with the physician's assessment of history, other risk factors, and professional guidelines.

Panel Deliberations/FDA Questions:

Panel Question 1: Safety, Effectiveness, and Risk vs. Benefit

- a. Do these outcomes adequately demonstrate effectiveness of Epi proColon within the context of the proposed intended use and current recommendations for colorectal cancer screening?

The Panel had mixed views. Few members believed effectiveness is demonstrated and that the test is a new way of testing for CRC, which may be easier and more accessible for patients. However, other members noted that there is no data to support these potentially compelling arguments. Some Panel members stated that sensitivity of the test is not adequate for a first-line screening test; others noted that the specificity is not adequate for a screening test. The majority thought that the intended use is too broad.

- b. If yes, do the data support screening with Epi proColon as (i) a second-line option only in patients declining FIT, (ii) an alternative for FIT, (iii) other option?

Most of the Panel agreed that if the intended use is not altered, then Epi proColon should be a second-line option only in patients declining FIT. However, if the intended use is changed to indicate a narrower population, then Epi proColon should be an alternative for FIT. In either case, the Panel agreed that patients should be sufficiently informed and educated

- about the performance of both tests. Also, patients should be explained and educated on the meaning of sensitivity and specificity.
- c. Based on the results of the pivotal and supplemental clinical studies, do the data allow for adequate assessment of the benefits versus risks of Epi proColon?

The Panel agreed that the data is inconclusive. Although the blood test may increase the CRC screening participation rate, there is no data to support this. Also, the pre-specified specificity goal was not met, indicating that there is a relatively high rate of false positives with the test.

Panel Question 2: Additional Labeling and Precautions

- a. Additional labeling considerations (e.g., warning, limitation) for patients who are above 75 years of age and/or African Americans?
- b. Precaution about potential for increased false positive rate in patients who are above 75 years of age and/or African Americans?

The Panel generally believed that the labeling should not include a warning against the use of this test in African Americans since more data is needed. These differences, however, could be included in the labeling to better inform healthcare providers. For age, the Panel agreed that a warning should be included in the labeling to inform users that the test has a higher false positive rate in the older population.

Panel Question 3: One-time screening and additional screening concerns

- a. Based on the available data, should the Epi proColon assay claims be limited to one-time screening?
 - i. If no, please discuss whether a longitudinal study should be required to address long-term safety and effectiveness.
 - ii. If yes, please advise if a longitudinal study should be optional.

The Panel believed that Epi proColon should be limited to a one-time screening claim and that a longitudinal study should be mandatory.

- b. The Sponsor has proposed a warning (i.e., A negative Epi proColon test result does not guarantee absence of cancer. Patients with a negative Epi proColon test result should be advised to continue participating in a colorectal cancer screening program that also includes colonoscopy, fecal tests and/or other recommended screening methods.). Does this adequately address considerations (e.g., time interval and testing method) in product labeling to assure safety and effectiveness for follow-up evaluation of patients testing negative with Epi proColon?

The Panel agreed that, in addition to the need for a longitudinal study, a carefully worded warning is needed in the intended use to advise patients that

additional testing should be “based on advice/recommendation from your healthcare provider.”

Panel Question 4: Post-Approval Study

Assuming that a longitudinal study is needed to evaluate performance with Epi proColon, please comment on the following:

- a. Is comparison to a recommended CRC screening option (e.g., annual FIT) needed to evaluate study results and to mitigate study limitations as currently proposed by the sponsor (such as controlling for incident CRC cases, lack of objective criteria for evaluating study results)?

The Panel agreed that comparison to another non-invasive test, such as FIT, is needed.

- b. Is the sponsor’s proposed post-approval study adequate to address the following issues?
 - i. Performance (e.g., number of test negative to positive conversions, diagnostic yield of significant findings, predictive values, adherence to screening and diagnostic follow-up);
 - ii. Performance across different clinicopathologic characteristics;
 - iii. Safety concerns (e.g., in the sponsor’s proposal, subjects would forgo annual FIT screening during the study duration and repeat Epi proColon testing will occur annually);
 - iv. Appropriate study population (e.g., general average risk population vs. average risk population who are unwilling, unable or do not undergo screening by other recommended screening methods).
- c. Are there any additional considerations that should be taken into account for the post-approval study?

The Panel had the following recommendations for the PAS design:

- A longitudinal study is needed in order to address lack of necessary data;
- The study should have at least two arms (Epi proColon vs. FIT), although a 3-arm design (Epi proColon vs. FIT vs. combination of Epi proColon and FIT) is preferred;
- The effect of demographic factors, such as age and ethnicity, may be addressed in the longitudinal study with sufficient statistical power;
- Other outcomes (i.e., cancer types other than CRC that are detected by the test) may be incorporated to assess their contribution to the false positive results;
- Test preference/adherence (in the general average risk population vs. average risk population who are unwilling, unable or do not undergo screening by other recommended screening methods) should be evaluated in either a separate side study or a run-in to the longitudinal study;

- Consequences (e.g., adverse events) of false positive results should be assessed. The false positive rate should be collected and the changes from year to year should be evaluated.

Vote:

The panel voted on the safety, effectiveness, and risk-benefit ratio of Epi proColon from Epigenomics AG.

On Question 1, the panel voted 9 yes, 1 abstain that the data shows that there is reasonable assurance that Epi proColon is safe for use in patients who meet the criteria specified in the proposed indication.

On Question 2, the panel voted 5 yes, 5 no (chair voted no in tie breaker) that there is reasonable assurance that Epi proColon is effective for patients who meet the criteria specified in the proposed indication.

On Question 3, the panel voted 5 yes, 4 no, 1 abstain that the benefits of Epi proColon do outweigh the risks for use in patients who meet the criteria specified in the proposed indication.

Contact: Jamie Waterhouse, Designated Federal Officer,
(301) 796- 3063 Jamie.Waterhouse@fda.hhs.gov

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Food and Drug Administration

Freedom of Information Staff (FOI)

5600 Fishers Lane, HFI-35

Rockville, MD 20851

(301) 827-6500 (voice), (301) 443-1726