AMP case report: FDA-approved DNA blood test for colorectal cancer prompts patient to undergo colonoscopy

CAP TODAY and the Association for Molecular Pathology have teamed up to bring molecular case reports to CAP TODAY readers. AMP members write the reports using clinical cases from their own practices that show molecular testing's important role in diagnosis, prognosis, and treatment. The following report comes from Epigenomics. If you would like to submit a case report, please send an email to the AMP at amp@amp.org. For more information about the AMP and all previously published case reports, visit www.amp.org.

Nicholas Potter, PhD
Faisal Bhinder, MD
Jeffrey Cossman, MD

March 2019—Colorectal cancer is the third most diagnosed cancer and the second highest cause of cancer mortality in men and women, and in 2016 it accounted for about nine percent of all diagnosed cancers in the United States.[1] When CRC is detected at an early localized stage, the five-year survival rate is 90 percent. With progression to regional disease, five-year survival remains high, at 71 percent. However, when detected late and cancer has spread to distant organs, five-year survival drops to 14 percent. There is substantial evidence supporting a role for screening in the reduction of CRC-related mortality and incidence. Full implementation of CRC screening could dramatically reduce the impact and costs associated with this cancer.[1,2]

Recommendations and guidelines published by organizations and specialty societies, including the U.S. Preventive Services Task Force and the American Cancer Society, strongly advocate for CRC screening. In an attempt to increase screening rates, a broad coalition of more than 900 organizations developed the "80% by 2018" screening campaign. Despite these efforts, CRC screening rates remain suboptimal. One-third of Americans, or 23 million, who should be screened for colorectal cancer refuse screening. The American Cancer Society estimates that more than 10,000 American lives would be saved each year if screening rates improved by 15 percent.[1]

Here we describe a routine clinical encounter in which a molecular blood screening test for circulating cell-free tumor DNA,[3,4] approved by the Food and Drug Administration in 2016 (**Fig. 1**), prompted a patient who had missed his screening to undergo colonoscopy.

Case. An asymptomatic 70-year-old white male, who was noncompliant and overdue for his regular colonoscopy, received a screening test for circulating methylated *SEPT9* DNA (Epi proColon, Epigenomics) and the result was positive. He had no personal or family history of colorectal cancer. Fifteen years prior, at colonoscopy, the patient had a small adenomatous polyp and a single hyperplastic colonic polyp removed. Two subsequent colonoscopies, at five-year intervals each, were negative for polyps and cancer. Upon learning of his positive methylated *SEPT9* blood test result, he contacted his gastroenterologist to schedule a colonoscopy, which was performed within four weeks. The colonoscopy revealed 10 polyps, all benign; nine were hyperplastic and one was a diminutive sessile serrated adenoma. Colorectal cancer was not found.

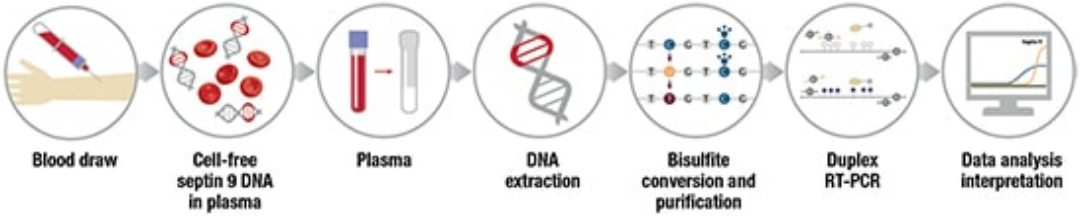

Fig. 1. Workflow for the analysis of methylated *SEPT9* from cell-free plasma DNA using the Epi proColon test kit. DNA was isolated from plasma by magnetic particles, then subjected to bisulfite conversion of unmethylated cytosines. In the unmethylated case, a blocker oligonucleotide prevents amplification of the target and the methylation-specific probe binds only to amplified methylated product. The qPCR amplification signal is read (Applied Biosystems 7500) and reported as positive or negative.

Discussion. These results are not unexpected since adenomatous polyps are frequently found in patients with a positive methylated *SEPT9* test who do not have cancer.[3,4] The results are also consistent with the large body of data supporting the significant difference in prevalence between adenomas and cancer across all screening-age-eligible groups.[5,6] As the detection and removal of precancerous lesions prevents CRC,[7,8] the referral of this patient for a diagnostic colonoscopy achieved the desired medical outcome.

The intended use of methylated *SEPT9*, under the FDA approval, is for those patients who have been offered other screening options (as per U.S. Preventive Services Task Force, 2008 guidelines) and have refused these forms of colorectal cancer screening. This patient decided to have the blood test based on the unremarkable results of two previous colonoscopies as well as interest in a novel molecular diagnostic technology. As it turned out, the positive methylated *SEPT9* result prompted the patient to quickly undergo a colonoscopy.

This colon cancer screening test involves a simple blood draw and serves the purpose of bringing unscreened patients to the gold standard of screening, which remains colonoscopy and histopathology. The intended use of the product is for those one of three adults in the United States who refuse all forms of colon cancer screening. It is known from clinical trials that even those who repeatedly refused colon cancer screening will go on to colonoscopy with a positive blood test result, and 99.5 percent of otherwise noncompliant patients will have their blood drawn for this test.[9] Since the patient experience is a simple blood draw, this molecular diagnostic test holds great promise as a key to bringing the unscreened in for screening and medical care to prevent deaths from advanced colon cancer.

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Dr. Potter is director of reimbursement and medical affairs, Epigenomics, Germantown, Md. Dr. Bhinder, a gastroenterologist, is with Capital Digestive Care, Rockville, Md. Dr. Cossman, a pathologist, is a consultant in Potomac, Md.

Test yourself: Here are three questions taken from the case report.

Answers are online now at www.amp.org/casereports *and will be published next month in* CAP TODAY.

1. The five-year survival for patients diagnosed with stage I CRC is closest to:

a. 10 percent
b. 35 percent
c. 50 percent
d. 90 percent

2. In the United States, the number of age-eligible individuals who are not compliant with guideline-recommended CRC screening is closest to:

a. 1 million
b. 10 million
c. 20 million
d. 100 million

3. The FDA-approved *SEPT9* test is indicated for:

a. Symptomatic patients who refuse other CRC screening methods.
b. Postoperative surveillance in patients with stage II CRC.
c. Asymptomatic, average-risk, age-eligible patients who have refused other screening methods.
d. Predictive testing in asymptomatic patients with a family history of CRC.

Test yourself answers for February 2019 case report

In the February 2019 issue was a case report, "Diagnostic pitfalls of testing rare molecular aberrations in lung

adenocarcinomas," written by members of the Association for Molecular Pathology. Here are answers to the three "test yourself" questions that followed that case report.

1. What is the most common molecular aberration of the *ALK* gene in lung adenocarcinomas?

a. Single nucleotide variant
b. Inversion
c. Amplification
d. Balanced translocation

2. A test with a sensitivity and specificity of 99 percent is used to detect a disease with a prevalence of 40 percent in one population and two percent in another population. What percentage of positive cases will represent true positives in each population, respectively?

a. 40 percent and two percent
b. 99 percent and 99 percent
c. 99 percent and 67 percent
d. 100 percent and 100 percent

3. Which statement is true about *EGFR* and *ALK* genetic aberrations in lung adenocarcinomas?

a. They are more common in never smokers.
b. They are more common in patients of Asian ethnicity.
c. The most common change observed is a single nucleotide variant.
d. They often occur together in the same tumor.