

## JAMA Clinical Evidence Synopsis

# Blood Measurement of Carcinoembryonic Antigen Level for Detecting Recurrence of Colorectal Cancer

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**CLINICAL QUESTION** What is the trade-off between sensitivity and specificity at specific carcinoembryonic antigen (CEA) thresholds for detecting recurrent colorectal cancer?

**BOTTOM LINE** To detect colorectal cancer recurrence, the sensitivity of CEA ranges from 68% for a threshold of 10 µg/L to 82% for a threshold of 2.5 µg/L and the specificity ranges from 97% for a threshold of 10 µg/L to 80% for a threshold of 2.5 µg/L.

## Introduction

Regular monitoring of blood carcinoembryonic antigen (CEA) level is recommended to identify recurrent colorectal cancer as part of a 5-year follow-up strategy after primary curative treatment.<sup>1</sup> Typically, CEA level is measured every 3 months for the first 2 years after curative treatment (when most recurrences occur), and then every 6 months.<sup>2</sup> Further evaluation (usually by diagnostic imaging) is recommended if the blood CEA level increases above a threshold level; however, there is substantial variation in the threshold applied. False-positive results can be caused by smoking and certain diseases. This JAMA Clinical Evidence Synopsis summarizes a recent Cochrane diagnostic test accuracy review<sup>3</sup> that was conducted to determine the diagnostic performance of CEA at different thresholds.

## Summary of Findings

A wide range of thresholds was studied (2 µg/L to 40 µg/L) but only 3 had sufficient data for a meta-analysis (2.5 µg/L, 5 µg/L,

and 10 µg/L). A bivariate meta-analytic method was used, which takes account of the correlation between sensitivity and specificity. At the most commonly reported CEA threshold of 5 µg/L (23 studies), the pooled sensitivity was 71% (95% CI, 64%-76%) and the specificity was 88% (95% CI, 84%-92%). At the CEA threshold of 10 µg/L (7 studies), the pooled sensitivity was 68% (95% CI, 53%-79%) and the specificity was 97% (95% CI, 90%-99%). At the CEA threshold of 2.5 µg/L (7 studies), the pooled sensitivity was 82% (95% CI, 78%-86%) and the specificity was 80% (95% CI, 59%-92%).

The **Table** shows the relationship between the CEA thresholds and identified recurrences, missed recurrences, and unnecessary referrals. For every 1000 patients tested during the first 2 years, there would be 29 unnecessary referrals for further investigation (false-positive results) at a CEA threshold of 10 µg/L, 116 at a CEA threshold of 5 µg/L, and 194 at a CEA threshold of 2.5 µg/L. The outcome was similar during years 3 through 5.

Exclusion of studies that did not confirm high CEA levels by repeat testing were at high risk of bias using the QUADAS-2 assessment tool, or were conducted before the introduction of the international reference standard for CEA measurement, made no significant difference to the pooled estimated sensitivity and specificity.

## Discussion

For every 1000 CEA measures collected after treatment of colorectal cancer, the use of a CEA threshold of 10 µg/L rather than 5 µg/L would result in 78 fewer false-positive results and lead to 1 missed recurrence. Adding an imaging study (such as a single abdominal or pelvic computed tomographic scan at 12-18 months) may overcome the lower sensitivity associated with using a higher CEA threshold.<sup>5</sup> An updated search in January 2016 did not identify any additional studies for these analyses. No clinical trial evidence demonstrated that monitoring CEA levels after definitive treatment for colon cancer improved survival.<sup>5,6</sup>

## Limitations

There are limitations to this review. First, most studies were analyzed retrospectively. Second, the timing between CEA measurement and the reference test was often not reported. Third, the specific test used to diagnose recurrence was seldom reported. Fourth,

### Evidence Profile

No. of studies: 52

No. of randomized clinical trials: 3

Study years: Conducted, 1971-2012 (14 trials did not report years); published, 1974-2014

No. of patients: 9717

Age range: 20-96 years (based on 22 studies that reported age)

Smoking status and comorbidity: Inconsistently reported

No. of colorectal cancer recurrences: 2951 (29%)

Setting: Secondary care (50 studies); primary and secondary care (1 study)

Countries: Australia, China, Finland, France, Germany, Greece, India, Italy, Japan, Korea, Norway, Poland, Scotland, Spain, Sweden, Switzerland, Taiwan, United Kingdom, United States, Uruguay

Comparison: Blood carcinoembryonic antigen level (index test) vs clinical diagnosis of recurrence (reference standard)

Primary outcome: Recurrence of colorectal cancer (locoregional, metastatic) following curative resection

Table. Carcinoembryonic Antigen (CEA) Thresholds and Number of Identified Recurrences, Missed Recurrences, and Unnecessary Referrals After Curative Resection of Colorectal Cancer<sup>a</sup>

						No. of Participants With Outcome by Time After Curative Resection of Colorectal Cancer	
	No. of Studies	No. of Participants	Sensitivity, % (95% CI)	Specificity, % (95% CI)	Follow-up Outcome for Every 1000 CEA Measures Collected	1-2 y	3-5 y
CEA threshold, µg/L							
≥2.5	7	1515	82 (78-86)	80 (59-92)	Recurrences detected	26	23
					Recurrences missed	6	5
					Unnecessary referrals	194	195
≥5	23	4585	71 (64-76)	88 (84-92)	Recurrences detected	22	20
					Recurrences missed	9	8
					Unnecessary referrals	116	117
≥10	7	2341	68 (53-79)	97 (90-99)	Recurrences detected	20	19
					Recurrences missed	10	9
					Unnecessary referrals	29	29

<sup>a</sup> These estimates are based on the timing and rate of recurrence detected in 20 898 patients enrolled in 18 trials of adjuvant therapy for colorectal cancer reported by Sargent et al.<sup>4</sup>

there was considerable variation in study quality, including reporting of smoking status, comorbidity, stage of primary disease, approach to ensuring no residual disease, treatment received, and recurrence site. Fifth, many clinicians initiate further diagnostic workup on the basis of a change in the CEA level (rather than a single CEA level measurement) but the initial search identified few studies and the review provides no evidence about this approach. Sixth, patient characteristics such as smoking status, baseline CEA level, and the patient's ability to withstand an invasive procedure influence interpretation and management of an elevated CEA level in clinical practice. These issues were not addressed in the review.

### Comparison of Findings With Current Practice Guidelines

This review suggests that a threshold of 10 µg/L will result in fewer unnecessary tests than the 5 µg/L recommended by the American Society of Clinical Oncology.<sup>1</sup>

### Areas in Need of Further Study

Further study is needed to determine whether monitoring CEA trends over time is better for identifying recurrences than a single CEA level measurement.<sup>7,8</sup> Further evidence is also needed to demonstrate that early detection and treatment of recurrent colorectal cancer improves overall survival.

### ARTICLE INFORMATION

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**Submissions:** We encourage authors to submit papers for consideration as a JAMA Clinical Evidence Synopsis. Please contact Dr McDermott at [mdm608@northwestern.edu](mailto:mdm608@northwestern.edu).

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