CA 11-19: A Tumor Marker to Detect Colorectal Cancer

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Background

Colorectal cancer (CRC) remains the second most frequent cause of cancer deaths in the US and Europe. In Europe, it is expected that approximately 436,000 new cases will be reported with the majority of these reported as late stage cancer[1].

When detected early in stage I, there is an approximate 5 year survival rate of 90%. However, when detected late, the 5 year survival rate is near 10%. In developed countries, screening rates range from 40-80%, with developing countries significantly below those rates.

Evidence demonstrates that screening for CRC results in reduced mortality and morbidity from colon cancer[2]. However, the gold standard, colonoscopy is expensive and invasive. Other non-invasive, lower cost, accurate tests could improve screening rates.

Objective

The primary objective of this study was to determine the correlation between elevated levels of the CA 11-19 tumor marker in blood and the presence of colorectal cancer or pre-cancer.

Summary

Method	• Enrolled 522 Colonoscopy Confirmed Subjects • CA11-19 measured by ELISA
Results	• Using Cut-off of ≤6.4U/mL for normal • 128/131 CRC Elevated – Observed Sensitivity 98% • 275/326 Normal – Observed Specificity 84%
Conclusion	• CA11-19 is a Serologic Tumor Marker for CRC • Sensitivity of 98% and Specificity of 84% • For people over 50 years of age PPV of 3.6% and NPV of 99.98%

Materials and Methods

Study Population

- Human serum collected from 522 colonoscopy confirmed individuals enrolled in approved IRB studies.
- 200 of the 522 samples came from 36 clinics in Texas the remaining 322 came from one clinic in Tennessee operating with 9 different experienced endoscopists.
- All serum samples were blinded and stored at 2-8 C before use.
- 391 blood samples were obtained from sequentially enrolled patients undergoing screening, surveillance, or diagnostic colonoscopies with the serum specimens drawn immediately prior to the colonoscopy.
- 69 of these patients came from free colonoscopy screenings.
- From patients with known CRC, 72 samples came from the 36 clinics in Texas and 59 came from the one clinic in Tennessee.

Patients were assigned by diagnosis to one of 5 groups:
1. Normal 2. Hyperplasic polyps 3. Other benign GI disease 4. Adenomatous polyps 5. Colorectal cancer.

The other benign GI disease group included patients with hemorrhoids, diverticulosis, GI bleeds, positive fecal occult blood tests, and those who reported a change in bowel habits. Patients with HIV, Hep C or previously diagnosed with cancer were excluded from the study.

CA11-19 Characteristics

CA 11-19 is a tumor antigen and recent amino acid sequencing data suggests that the 100 KDa, CA11-19 antigen is a 701 amino acid glycoprotein. The non-glycosylated 70 KDa protein is believed to be CEACAM5x1 (CEA) with one important distinction, an alanine deletion occurring at amino acid position 320. CA 11-19 antigen does not cross-react with CEA antibodies.

CA11-19 Testing

The quantitative measurement of CA11-19 in serum was performed using a classic sandwich enzyme-linked immune-absorbent assay (ColoMarker® ELISA, EDP Biotech Knoxville, Tn). A cocktail of two monoclonal antibodies to CA11-19 is coated to the surface of 96-well microtiter plate as the capture antibody. Anti-CA11-19 polyclonal antibody conjugated with alkaline phosphatase (AP) enzyme is used for detecting the antibody antigen complex via pNPP substrate and calibrators are used to calculate the amount of antigen present in the blood reported as U/mL.
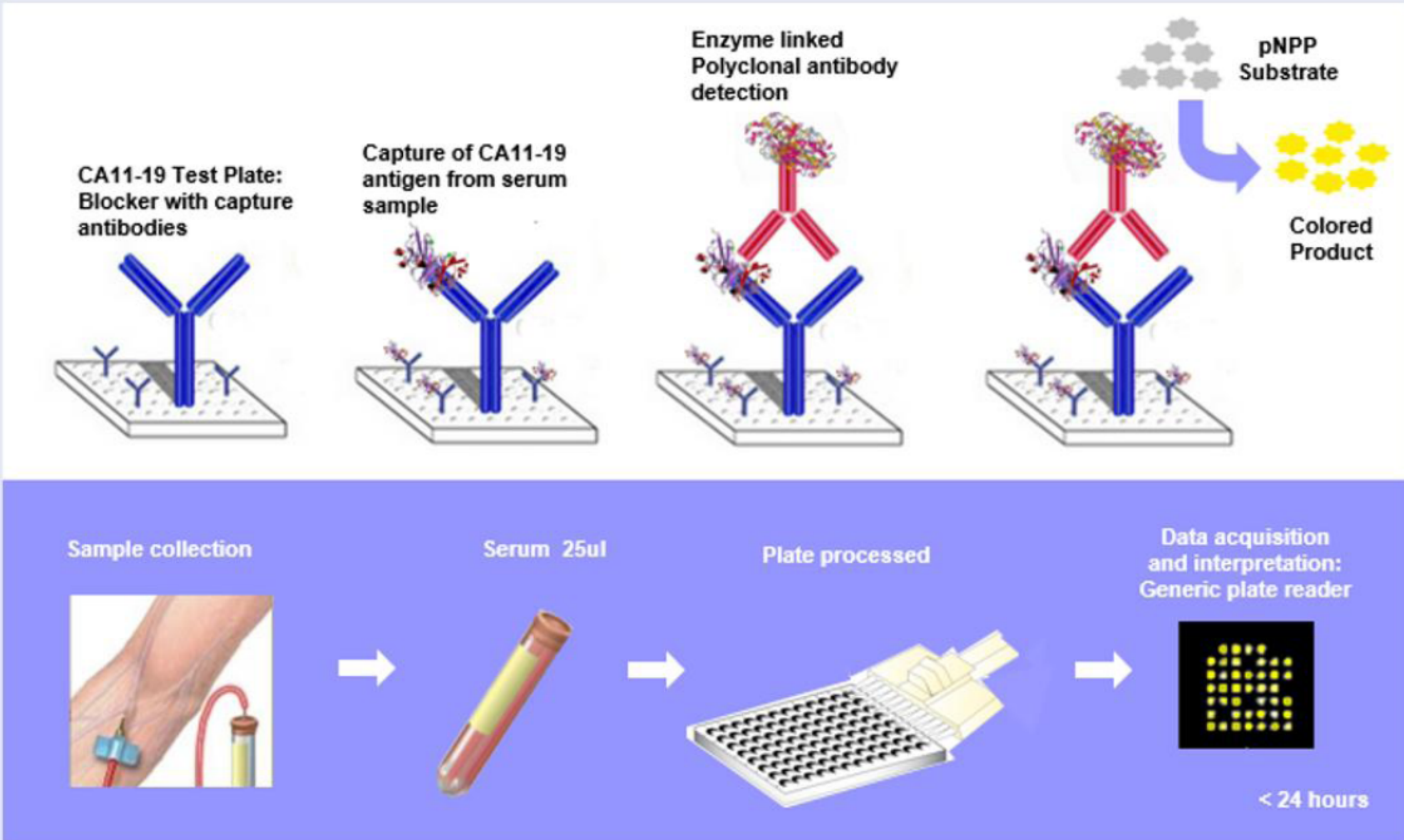

Various tumor markers (CEA, CEA-CAM6, CEA-CAM5, CA125, CA15-3, and PSA) were tested and did not interfere or cross-react with the assay. In addition, eleven of the more frequently used chemotherapy drugs including 5FU showed no interference in the CA11-19 ELISA Assay

ColoMarker® is a registered trademark of EDP Biotech Corporation

Results

- Using a cut off of ≤6.4 U/ml as normal, CA 11-19 was positive (≥6.5) in 128 of 131 colorectal cancer cases.
- 100% of 63 stage I and II were positive.
- True negative results were found in 86.1% of normal (124/144) and 83% of benign GI disease (151/182).

Confirmed Clinical Status	Negative Assays	Positive Assays	Total Number	% Negative	% Positive
Normal	90	13	103	87.40%	
Hyperplastic Polyp	34	7	41	82.90%	
Benign GI Diseases	151	31	182	83.00%	
Adenomatous Polyps	39	26	65		40.00%
Colorectal Carcinoma	3	128	131		97.70%

- Observed sensitivity of 98% (95% CI 93.1% to 99.5%) specificity of 84% (95% CI 80.0% to 87.9%).

CA11-19 Sensitivity in % by CRC Stage
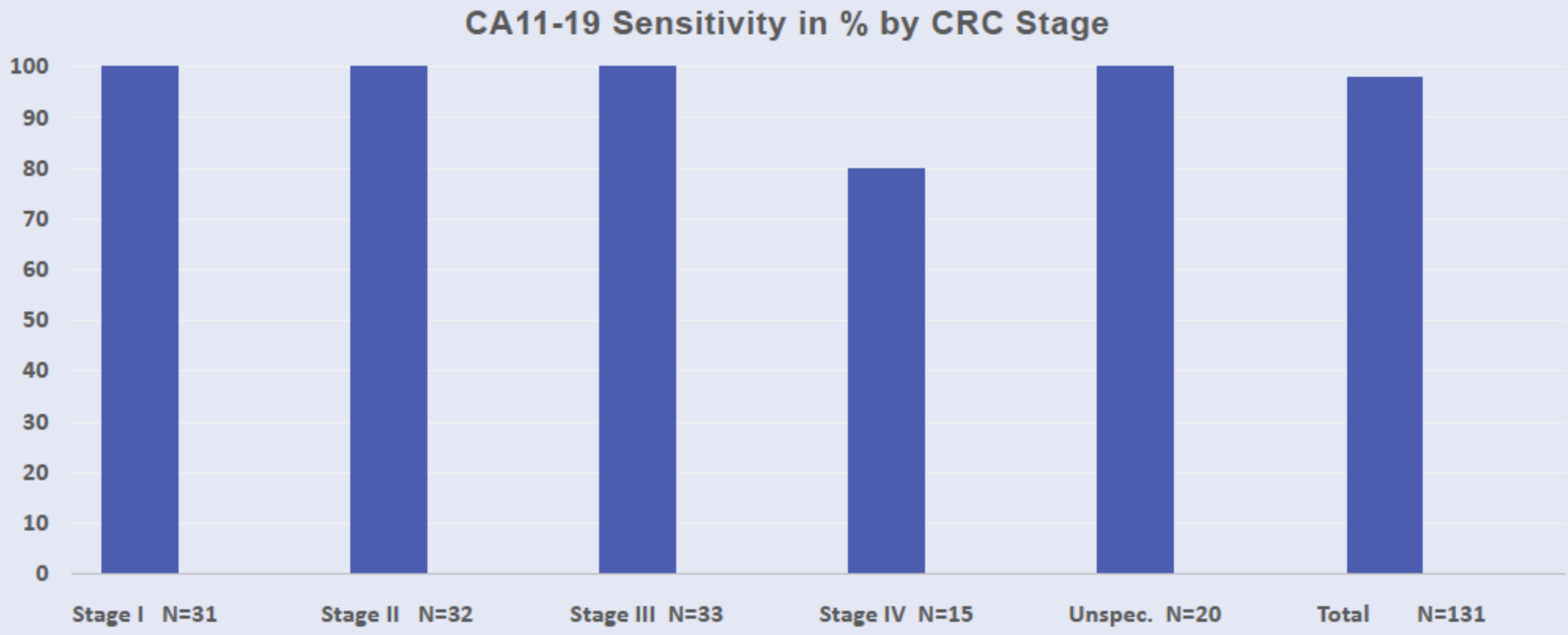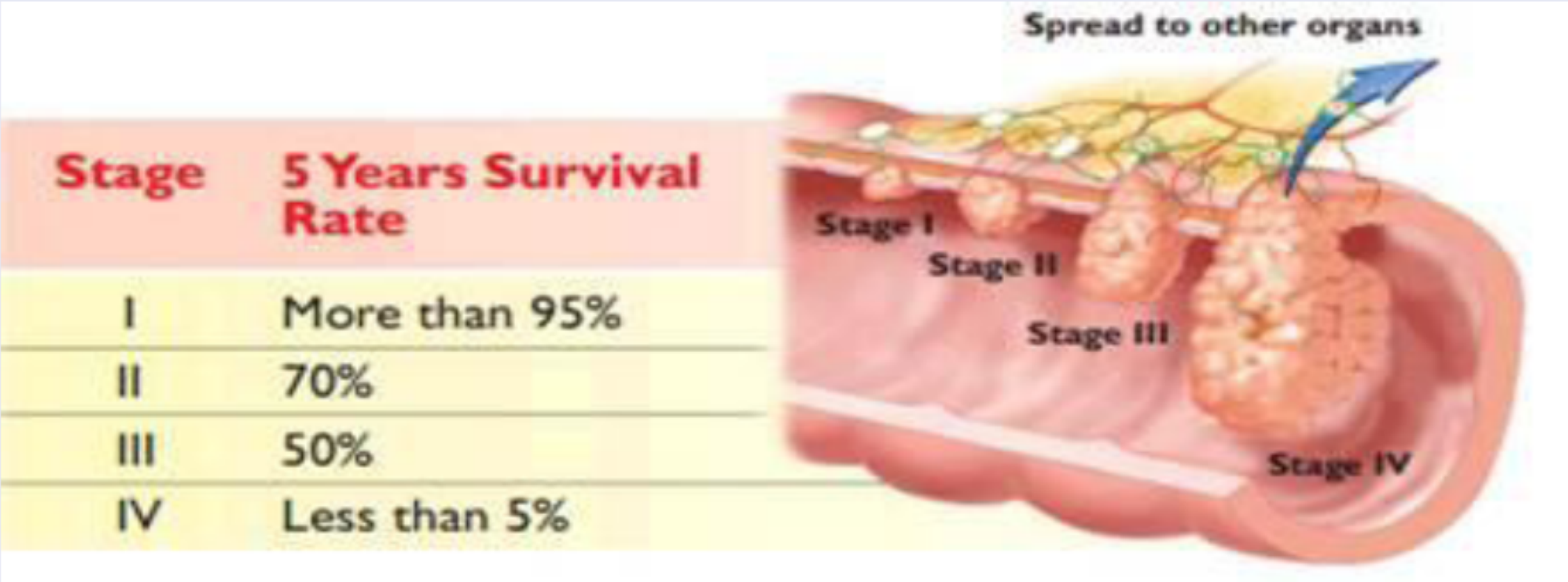
- The 95% Confidence Interval for Early Stage Sensitivity is 96% to 100%

Discussion

- Using the American Cancer Society incidence rates [4] and this study's sensitivity and specificity, the likelihood that a person over 50 years of age with elevated CA11-19 has colorectal cancer has been computed.
- In people with a positive assay results the Odds of having CRC increased five fold (PPV is 3.6%)
- From the table below, a negative assay result for men over 50, only about 1 in 4000 negative assay results will be a false negative.
- For women over 50 only about 1 in 5400 negative assay results will be a false negative. For those under 50 false negatives are even less likely.

Estimate of Diagnostic Uses of Negative Assay			
Group	Incidence of CRC per 100,000	Likelihood per 100,000 of CRC with Negative Assay	Decrease in Odds of CRC
Males over 20	57	1.63	57/1.63 = 35.0
Females over 20	43	1.23	43/1.23 = 34.9
Males over 50	855	24.7	855/24.7 = 34.6
Females over 50	645	18.6	645/18.6 = 34.7

- **A negative assay (NPV 99.98%) is strong evidence that an individual is unlikely to have colorectal carcinoma.**

Conclusions

- CA 11-19 is a serologic tumor marker for colorectal cancer with a sensitivity and specificity of 97.7% and 84.4% respectively.
- Diagnostically, a positive assay result increases the odds of finding colorectal cancer by a factor of five.
- The test appears to be highly sensitive for the detection of early stage colorectal cancer.
- Additional prospective studies are needed to validate the use of CA11-19 as a screen for or an aid in the diagnosis of colorectal cancer.

References

1. Siegel R, Ma J, Zou Z, Jemal A. Cancer statistics, 2014. CA: A Cancer Journal for Clinicians. 2014; 64: 9-29
2. Zauber AG, Winawer SJ, O'Brien JM, Lansdorp-Vogelaar I, van Ballegooijen M, Hankeyt BF, Shi W, Bond JH, Schapiro M, Panish JF, Stewart ET and Waye JD. Colonoscopic Polypectomy and Long-Term Prevention of Colorectal-Cancer Deaths. N Engl J Med. 2012; 366: 687–696.
3. Vital Signs: colorectal cancer screening test use - United States, 2012. Morbidity and Mortality Weekly Report (MMWR). Centers for Disease Control and Prevention. 2013 (Nov 5);62:1-8.
4. American Cancer Society. Colorectal Cancer Facts and Figures, 2011-2013. pg 1-27. Atlanta: American Cancer Society, 2011.

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