DEVELOPMENT AND CLINICAL VALIDATION OF A BLOOD TEST FOR EARLY DETECTION OF COLORECTAL ADENOMAS AND CANCER

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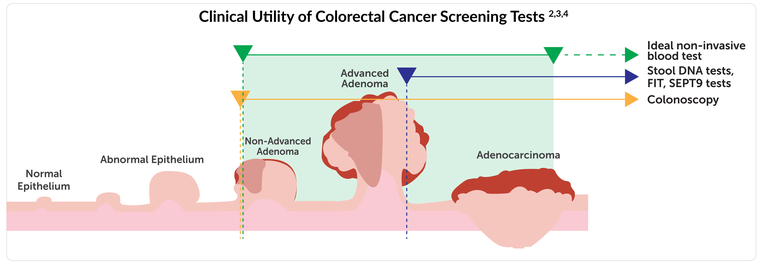
BACKGROUND

Colonoscopic polypectomy is the primary reason for declining colorectal cancer incidence and mortality. However, many of the ~50,000 annual colorectal cancer (CRC) deaths can be attributed to 1/3 of eligible Americans not following screening guidelines or approximately 1/2 of the population not adherent to the follow-up post-polypectomy guidelines. CRC is among the most preventable cancers when **adenomatous polyps are detected and removed at an early stage** because of its slow progression. The new understanding of the natural history and shared etiology of adenomas and CRC inform integration of clinically relevant and orthologous biomarkers.

The two objectives of CRC screening and surveillance are early cancer detection to improve survival and prevention of CRC through removal of adenomas using colonoscopy. Colonoscopies are the gold standard for CRC screening because this procedure allows the gastroenterologist to visually inspect the entire GI tract. Though effective, this procedure is invasive and requires quality bowel preparation, resulting in high non-compliance and repeat colonoscopies among the eligible screening population. Stool tests not only have poor compliance rates, but also low sensitivity for advanced adenomas (AA, 24-42%). As colorectal adenomas account for 98% of actionable colonoscopies[1], **there is an unmet need for a more sensitive non-invasive test for colorectal adenoma detection that would be in equipoise with colonoscopy**.

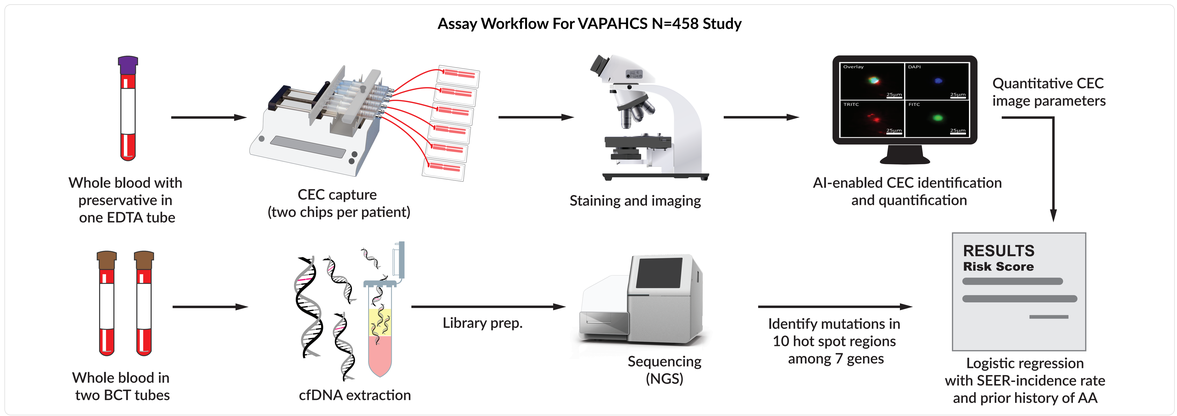


[Fig.1] Due to its slow progression, early detection can be effective in decreasing both the incidence and mortality rate of CRC. Ideally, the development of a non-invasive blood test for colorectal adenoma detection would help with compliance among the eligible screening population.

METHODS

A single-center, IRB-approved, prospective, blinded study was conducted at the Veterans Affairs Palo Alto Health Care System (VA PAHCS) to assess a **blood test (FirstSight) detecting adenoma-carcinoma pathway markers** in a sample of blood. The test analyzes two biomarkers: **circulating gastrointestinal epithelial cells (CECs) and somatic mutations of cell-free tumor DNA**. CECs are captured and quantified using the CellMax CMx platform, a highly sensitive proprietary platform that has been used in several clinical studies outside of the U.S., with results presented at the 2018 and 2019 ASCO GI conferences.

Patients who met the inclusionary and exclusionary criteria and consented to participate had their blood drawn prior to colonoscopy. The blood was procesed at CellMax Life without any prior knowledge of colonoscopy or pathology results. The probability of advanced neoplasia was obtained by ordinal/nominal logistic regression methods together with SEER-incidence rate (age, gender) and prior history of AA on a training set of 346 subjects. The cutpoint for the quantitative score was fixed and the remaining 112 subjects were tested.



[Fig.2] Workflow landscape of study to evaluate the performance of the FirstSight test for colorectal adenoma detection.

Research Highlights

- Analysis of the blood-based FirstSight test revealed 90% specificity, with sensitivity of 100% and 80% for detection of CRC and advanced neoplasia, respectively, on training set subjects
- The quantitative nature of the FirstSight score has the potential to enable prognostic stratification of patients for screening or post-polypectomy surveillance colonoscopy.

RESULTS

Interim results for 458 patients with no prior diagnosis of colorectal cancer (CRC) are presented. The cohort included both screening (239) and surveillance (219) subjects. Indications for colonoscopy were 86% asymptomatic and 14% with symptoms or positive-FIT.

Balanced distribution of roughly 3/4th subjects in each disease category were randomly selected for training and algorithm development and the remaining 1/4th subjects were used for validation. A cutpoint was selected to obtain a test specificity (non-neoplastic finding or negative colonoscopy) of 90% resulting in a **sensitivity of 100% and 80.0% for detection of CRC and advanced neoplasia (AN = CRC+AA)**, respectively, on the training subjects.

The area under the ROC curve is 0.91. Validation using the fixed cutpoint and 112 test subjects achieved 91.4% specificity and 100% and 75.0% sensitivity for CRC and AN, respectively.

Study Results: FirstSight Test Performance for Adenomas and Cancer

Study Results	# Training Subjects	# Validation Subjects	Training N=346	Validation N=112
Screening/Surveillance			176/170	63/49
			Sensitivity (95% CI)	
CRC	10	4	100% (72.3-100)	100% (51.0-100)
AA (Adenomas ≥ 1cm, high grade dysplasia, ≥ 25% villous)	50	16	76.0% (62.6-85.7)	68.8% (44.4-85.8)
Non-advanced Adenoma	168	57	48.8% (41.4-56.3)	54.4% (41.6-66.6)
Advanced Neoplasia (CRC + AA)	60	20	80.0% (68.2-88.2)	75.0% (53.1-88.8)
			Specificity (95% CI)	
All Negative (Non-neoplastic findings + negative colonoscopies)	118	35	90.7% (84.1-94.7)	91.4% (77.6-97.0)

[Fig.3] Results from this study show that CellMax Life's FirstSight blood test can detect advanced neoplasias (CRC+AA) with 80% (95% CI: 68.2%-88.2%) sensitivity at a 90% specificity for the training set, and advanced neoplasias with 75% (95% CI: 53.1%-88.8%) sensitivity at a 90% specificity for the validation set.

CONCLUSIONS

A noninvasive multimodal FirstSight blood test that analyzes cell-free tumor DNA and circulating epithelial cells, and integrates SEER incidence risk is developed for the early detection of colorectal neoplasia.

This blood test has high sensitivity for colorectal advanced neoplasia while retaining high specificity. The quantitative nature of the score has the potential to enable prognostic stratification of patients for screening or post-polypectomy surveillance colonoscopy.

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