A HIGHLY SENSITIVE AND QUANTITATIVE MULTIMODAL BLOOD TEST FOR THE DETECTION OF COLORECTAL ADENOMAS AND CANCER

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DDW Digestive Disease Week®

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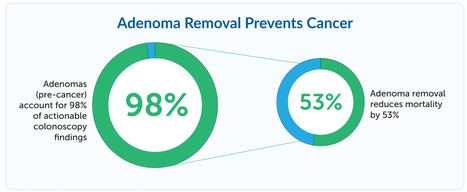
BACKGROUND

Colorectal cancer is among the most preventable cancers when detected early, yet, it is the second leading cancer killer in the U.S. There are 50,000 colorectal cancer (CRC) deaths per year in the U.S., many of which can be attributed to one-third of eligible Americans not following recommended screening guidelines.

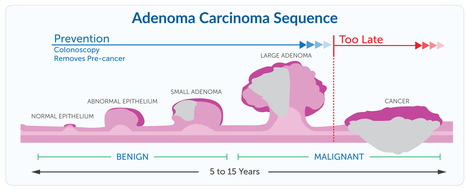
New guidelines from the American Cancer Society recommend screening for CRC **starting at age 45, down from age 50**. This means that 20 million Americans from the age of 45 to 50 are newly eligible for testing. Even so, an overwhelming **39 million Americans of the eligible 112 million** in the 50-plus age group have never been tested.

The two objectives of screening are early detection and prevention of CRC through removal of adenomas using colonoscopy. FDA-approved stool tests have poor compliance and low sensitivity for detection of advanced adenomas (24-42%) and non-advanced adenomas (8-17%). As colorectal adenomas account for 98% of actionable colonoscopies [Fig.1], there **is an unmet need for a highly sensitive non-invasive test for colorectal adenoma detection**.

The new understanding of the natural history of adenomas and CRC informs integration of clinically relevant biomarkers for detection of CRC and adenomas with a blood test [Fig.2]. We have conducted a prospective U.S. clinical study, **Zenith**, to assess a **highly sensitive multimodal blood test based on proprietary technologies detecting pre-cancer and cancer markers** in a sample of blood.



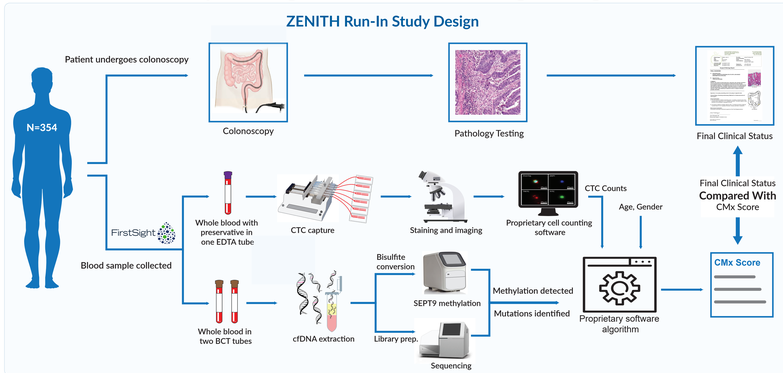
[Fig.1] Adenoma removal prevents cancer and is shown to reduce mortality from colorectal cancer. Actionable findings from a colonoscopy screening are mostly adenomas.



[Fig.2] Due to its slow progression, early detection can be effective in decreasing both the incidence and mortality rate of CRC. However, compliance with screening colonoscopy is low, around 38%.

METHODS AND STUDY DESIGN

A single-center, IRB-approved, prospective, blinded study was conducted at the Veterans Affairs Palo Alto Health Care System [Fig.3]. Interim results for 354 patients with no prior diagnosis of CRC who were scheduled for colonoscopy are presented. Indications for colonoscopy were 86% asymptomatic and 14% with symptoms or positive-FIT. Patients had blood drawn immediately prior to colonoscopy. The test analyzes three biomarkers: **circulating gastrointestinal epithelial cells, somatic mutations and methylation of cell-free DNA**. A quantitative age- and gender-adjusted composite CMx Score (Score) scaled from 0 to 100 was developed using ordinal and nominal logistic regression and bootstrapping methods.



Disease Category	Number of Patients
Colorectal Cancer & Advanced Adenomas	**64 (18.1%)**
Colorectal Cancer (TNM Stage I-IV)	11 (3.1%)
Advanced Adenomas (Adenomas ≥1cm, high-grade dysplasia, or ≥25% villous features)	53 (15.0%)
Non-Advanced Adenomas (Adenomas <1cm with <25% villous features and low-grade dysplasia)	178 (50.3%)
Non-Neoplastic Findings (Includes hyperplastic polyps <1cm)	33 (9.3%)
Negative Colonoscopy	79 (22.3%)

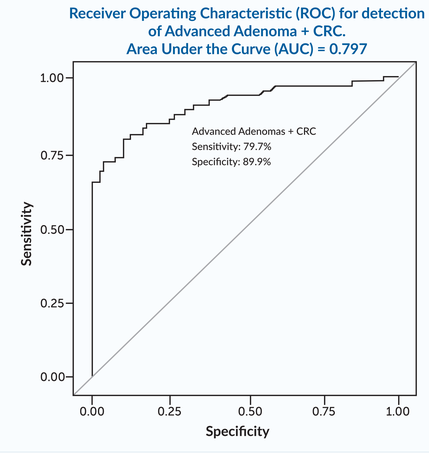
[Fig.3] Prospective study design to evaluate the performance of the CMx test for early and pre-cancer detection.

RESULTS

The test achieved **90% specificity, with sensitivity of 100% (95% CI: 71.5%-100%) and 76% (95% CI: 61.7%-86.2%) for detection of CRC and AA, respectively** [Fig. 4]. Univariate and multivariate logistic regressions demonstrated that **each biomarker contributes significant independent information to the Score**. Ordinal logistic regression demonstrated significant association between the quantitative Score and disease severity (Likelihood ratio p-value < 0.0001). Furthermore, the Score correlated with the size of the index adenomas. In patients with elevated Scores but with non-AA or negative colonoscopy clinical results, a chart review of patient histories revealed prior history of AA removal in several cases [Fig. 5], suggesting that a higher specificity can potentially be achieved by **excluding patients with a prior history of AA**, and that some **cellular and molecular changes detected by the assay persist even after removal** of those advanced adenomas.

ZENITH Run-In Study Interim Results

Disease Category	Number of Patients	Sensitivity (95% C.I.)	Mean Polyp Index Size (mm)	Mean CMx Score
Colorectal Cancer & Advanced Adenomas	**64** (18.1%)	**79.7%** (67.8, 88.7)		
Colorectal Cancer (TNM Stage I-IV)	11 (3.1%)	100% (71.5, 100)	38.8	71.3
Advanced Adenomas (Adenomas ≥1cm, high-grade dysplasia, or ≥25% villous features)	53 (15.0%)	75.5% (61.7, 86.2)	17.6	49.9
Non-Advanced Adenomas (Adenomas <1cm with <25% villous features and low-grade dysplasia)	178 (50.3%)	48.3% (40.8, 55.9)	5.1	35.6
Non-Neoplastic Findings (Includes hyperplastic polyps <1cm)	33 (9.3%)	9.1% (1.9, 24.3)	4.4	20.0
	Number of Patients	Specificity (95% C.I.)		
Negative Colonoscopy	79 (22.3%)	89.9% (81.0, 95.5)		18.1



[Fig.4] Results from this study show that CellMax Life's multimodal blood test can detect pre-cancers (advanced adenomas) with 75.5% (95% CI: 61.7%-86.2%) sensitivity, at a 90% specificity, while successfully detecting colorectal cancer with 100% (95% CI: 71.5%-100%) sensitivity.

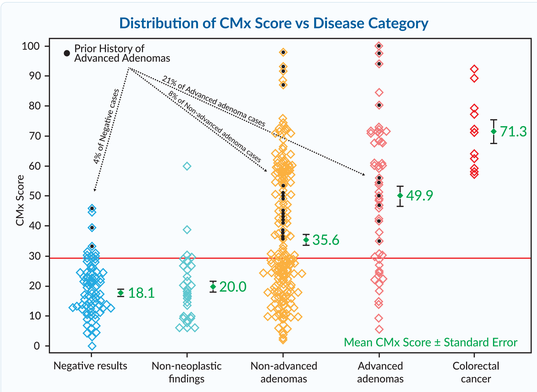
CONCLUSIONS

A novel noninvasive blood-based assay that analyzes cell-free DNA and circulating gastrointestinal epithelial cells, and integrates expected incidence rates can detect colorectal adenomas and cancer. Compared with FDA-approved tests, the **FirstSight blood test significantly improves the sensitivity for advanced and non-advanced adenomas with high specificity** [Fig.6]. A multicenter prospective clinical study is in design to further validate FirstSight as a sensitive and specific, non-invasive liquid biopsy for adenoma and CRC detection.

FirstSight Performance vs. FDA-Approved Colorectal Screening Tests

	Test	Sensitivity for AA	Sensitivity for CRC	Specificity
CellMax FirstSight	Blood	76%	100%	89.9%
FIT	Stool	24%	74%	94.9%
Stool DNA + FIT	Stool	42%	92%	86.8%
Methylated Septin9	Blood	22%	68%	78.8%

[Fig.6] Preliminary data for FirstSight test compared to current FDA-approved tests for colorectal cancer screening



[Fig.5] Correlation between CMx Score and disease status for all 354 patients. The black dot represents patients who had a prior history of advanced adenoma(s) removal. By excluding patients with any prior history of advanced adenomas, a higher specificity could potentially be achieved.

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