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INTRODUCTION AND OBJECTIVES

Colorectal cancer (CRC) is the second leading cause of cancer death in the Western world. It is often curable and preventable using current screening modalities. Unfortunately, screening compliance remains low, partly due to patient dissatisfaction with fecal and endoscopic testing procedures. Only 15-20% of the age-eligible population in Canada/Europe and about 50% in the US are regularly screened. As a result, most CRC continues to be initially diagnosed relatively late in the disease process, resulting in high mortality rates. In addition to this tragic and avoidable loss of life, the costs associated with treating advanced CRC have dramatically escalated over the past decade with the introduction of expensive biologic therapies.

Objectives

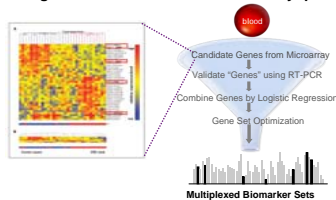
1. Develop a blood-based test for CRC screening in the average-risk population in order to improve patient compliance with screening and facilitate earlier detection of cancer.
2. Conform to the American Cancer Society's recent recommendation that CRC screening should begin with risk stratification by providing clinically-actionable information about a patient's relative risk of currently having CRC.
3. Develop a health economic model to assess the relative economic efficacy of ColonSentry.

RESULTS

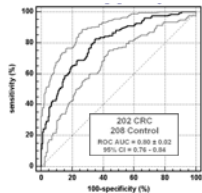
We have developed a seven-gene, blood-based biomarker panel that can stratify Current Risk of CRC in an average risk population^{5,7}. Across the Current Risk Scale, it is possible to identify clinically meaningful reference points that can assist patients and physicians in CRC screening decision-making.

The ColonSentry test works by measuring RNA biomarkers in whole blood by qRT-PCR

Gene profiling was used to identify blood-based disease biomarkers from microarray-derived candidates. We identified and validated a seven-gene biomarker panel for CRC detection on 642 well-categorized, sex-, BMI- and ethnically-matched CRC patients and controls.



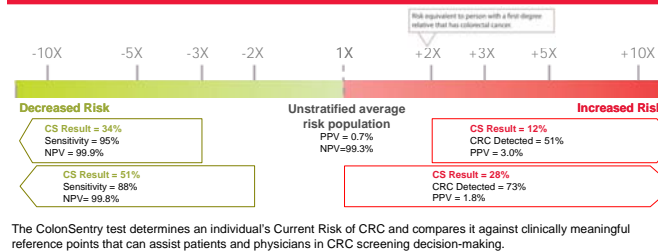
Blood samples were taken from screening colonoscopy subjects at twenty-five US and Canadian centres. qRT-PCR was performed to develop our CRC biomarker panel using a 232-sample training set (112 CRC/120 controls). Six genes (ANXA3, CLEC4D, LMNB1, PRRG4, TNFAIP6, VNN1) were overexpressed and one (IL2RB) was underexpressed in CRC as compared with controls.



Panel performance was tested against a 410-sample blind test set of average-risk patients (202 CRC/208 controls).

Panel performance characteristics and disease prevalence (0.7%) were then used to develop a scale assessing an individual's current risk of having CRC based on his/her gene signature.

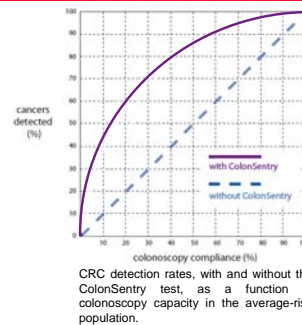
COLONSENTRY CURRENT RISK SCALE



The ColonSentry test determines an individual's Current Risk of CRC and compares it against clinically meaningful reference points that can assist patients and physicians in CRC screening decision-making.

DISCUSSION AND CONCLUSION

This seven-gene biomarker combination enabled development of a Current Risk scale that provides enriched information about an individual's likelihood of actually having CRC at the time of the test. As a blood test, it addresses one of the greatest challenges currently limiting CRC screening effectiveness: lack of compliance.



Additionally, by identifying patients with enhanced Current Risk (increased PPVs) and with diminished Current Risk (increased NPVs), this approach can help healthcare providers assess the need for increased monitoring or further workup, and help tailor the use of invasive and expensive procedures to those most likely to benefit.

The ColonSentry test can be incorporated into CRC decision-making in several ways:

Encourage patient compliance. A blood test would benefit patients who desire information about CRC status but refuse screening due to dislike of screening options. In particular, identifying individuals with increased Current Risk may facilitate colonoscopy decision-making for these patients.

Facilitate efficient colonoscopy capacity usage. In healthcare systems with limited colonoscopy capacity, this approach could help prioritize patients at greatest risk for CRC. Applying the ColonSentry test with follow-up by colonoscopy can detect 2.1 to 4.7 times more cancers, when colonoscopy capacity is between 10% and 40%, which is the case in most countries (see figure). In this way, the ColonSentry test can help ensure that finite colonoscopy resources are directed to those with greatest risk.

Individualize CRC screening decision-making. Identifying patients with diminished Current Risk for CRC can help enhance physician and patient decision-making. 34% of the average-risk population have a Current Risk score $\leq 3x$. Only 0.1% of patients in this range are expected to have CRC (NPV=99.9%). Provision of this novel information can help facilitate subsequent screening decision-making that is tailored to a patient's individual circumstances.

HEALTH ECONOMICS

Model⁶: A decision-analytic model in an average-risk population aged 50 years and older was employed. The model was constructed according to the principles outlined in the Canadian guidelines for conducting economic evaluations of health technologies.

Outputs: The results are presented as an incremental cost-utility analysis (cost per quality-adjusted life-year gained, \$/QALY). Incremental Cost-Effectiveness Ratio (ICER):

$$ICER = \frac{\text{Cost (new therapy)} - \text{Cost (established therapy)}}{\text{Effectiveness (new therapy)} - \text{Effectiveness (established therapy)}}$$

This analysis used conservative assumptions based on published data from scientific sources and Statistics Canada - the true economic benefits are likely to be higher. This model only reflects a one year cycle of screening. Regular screening with the ColonSentry test over time will yield a higher rate of early-stage CRC detection (i.e.: a higher program sensitivity), saving more lives and money.

All perspectives^{1,2,3} By encouraging compliance, screening with the ColonSentry test detected more CRC, extended survival, saved lives and reduced the amount spent on late-stage CRC cancer treatment. All perspectives are based on a model with 5000 average risk people. Costs are reported in 2008 Canadian dollars. Costs considered in this analysis included treatment costs, screening costs, long term disability (LTD), short term disability (STD) and life insurance.

The private payer perspective The ColonSentry test was dominant (produced better patient outcomes at lower costs) over no screening and FOBT.

Screening Approach	Incremental QALYs	Incremental Cost of Managing CRC Patients	Incremental Cost	ICER
ColonSentry vs. no screening	39.8	-\$2,161,792	-\$434,792	-\$10,916
ColonSentry vs. FOBT	33.6	-\$1,822,582	-\$95,582	-\$2,846
ColonSentry and FOBT vs. no screening	46.1	-\$2,501,002	-\$774,002	-\$16,797

Costs included: medical costs not covered by the public healthcare system, LTD, STD and life insurance claims.

The public healthcare perspective The ColonSentry test is cost-effective compared with the generally accepted oncology ICER benchmark. Screening is even more cost-effective for all perspectives when patients have the option of either FOBT or the ColonSentry test.

Screening Approach	Incremental QALYs	Incremental Cost of Managing CRC Patients	Incremental Cost	ICER
ColonSentry vs. no screening	39.8	-\$224,036	\$2,494,577	\$62,630
ColonSentry vs. FOBT	33.6	-\$54,198	\$2,420,472	\$72,080
ColonSentry and FOBT vs. no screening	46.1	-\$393,873	\$2,408,931	\$52,277

Compliance rates:

FOBT ⁴	18%
ColonSentry test ⁵	55%

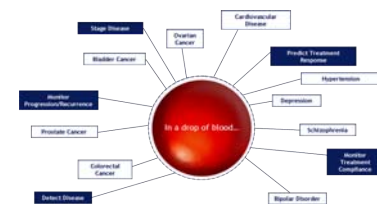
*Assumption: compliance rate for PSA in men



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FUTURE DIRECTION



The ColonSentry test is based on the Sentinel Principle®, a groundbreaking platform technology that identifies disease specific molecular signatures from blood. This technology has broad applications for early disease detection and personalized health management.