

Optimization of Ensemble Supervised Learning Algorithms for Increased Sensitivity, Specificity, and AUC of Population-Based Colorectal Cancer Screenings

Anirudh Kamath¹, Raj Ramnani², Jay Shenoy³, Aditya Singh⁴, and Ayush Vyas⁵

¹*Northeastern University*

²*Yale University*

³*University of California–Berkeley*

⁴*The Wharton School, University of Pennsylvania*

⁵*The Harker School*

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Abstract

Over 150,000 new people in the United States are diagnosed with colorectal cancer each year. Nearly a third die from it (American Cancer Society). The only approved noninvasive diagnosis tools currently involve fecal blood count tests (FOBTs) or stool DNA tests. Fecal blood count tests take only five minutes and are available over the counter for as low as \$15. They are highly specific, yet not nearly as sensitive, yielding a high percentage (25%) of false negatives (Colon Cancer Alliance). Moreover, FOBT results are far too generalized, meaning that a positive result could mean much more than just colorectal cancer, and could just as easily mean hemorrhoids, anal fissure, proctitis, Crohn’s disease, diverticulosis, ulcerative colitis, rectal ulcer, rectal prolapse, ischemic colitis, angiodysplasia, rectal trauma, proctitis from radiation therapy, and others. Stool DNA tests, the modern benchmark for CRC screening, have a much higher sensitivity and specificity, but also cost \$600, take two weeks to process, and are not for high-risk individuals or people with a history of polyps. To yield a cheap and effective CRC screening alternative, a unique ensemble-based classification algorithm is put in place that considers the FIT result, BMI, smoking history, and diabetic status of patients. This method is tested under ten-fold cross validation to have a .95 AUC, 92% specificity, 89% sensitivity, .88 F1, and 90% precision. Once clinically validated, this test promises to be cheaper, faster, and potentially more accurate when compared to a stool DNA test.

Keywords: *Machine Learning, Ensemble Learning, Biotechnology, Cancer Research, Colorectal Cancer, Cancer Screening*

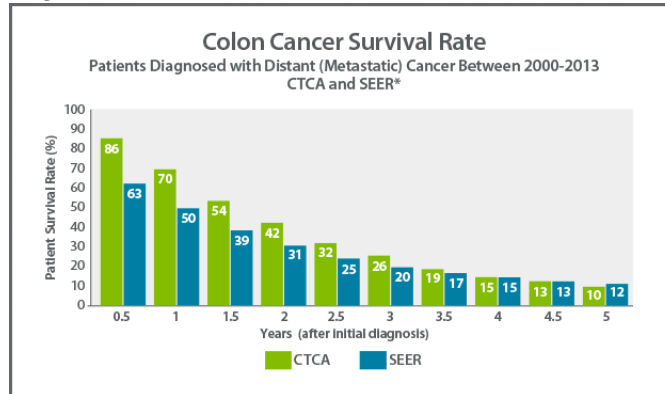
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1 Overview

Colorectal cancer (CRC) is the third most common cancer and the second leading cause of cancer-related deaths in the United States. The American Cancer Society predicts approximately 135,000 new cases of CRC in 2017 and 50,000 deaths just in the United States. There is a strong inverse association with CRC screening and CRC incidence and mortality, yet more than one in three eligible Americans are not up-to-date with the recommended screening (Burke and Mankaney, 2017).

Figure 1: Source: Cancer Treatment Centers of America



2 Problem

Once detected, a colonoscopy can typically remove most polyps or small cancers, but as stated earlier, screening itself is a major problem. Current noninvasive tests are most commonly fecal occult blood count tests or stool DNA tests.

Fecal Occult Blood Count Tests

These tests, most commonly seen as guaiac fecal occult blood tests (gFOBT) or fecal immunochemical tests (FIT) inject biochemicals into the stool to account for occult, or hidden, blood. Occult blood in the stool is typically a biomarker for bleeding polyps, which very often grow into carcinomas. They are currently what most doctors use for CRC screening due to their extremely high patient compliance from their accessibility and ease of use. The test is available over-the-counter, takes five minutes, and is completely done at home. There is no further work needed once the patient receives his/her results. Moreover, these tests are highly specific, meaning the people it falsely marks positive is less than 5%. The problem arises with its use cases. A positive FIT result is simply indicative of abnormal gastrointestinal activity and not necessarily the presence of CRC. For example, causes of blood in the stool just as easily indicate the presence of hemorrhoids, anal fissure, proctitis, Crohn's disease, diverticulosis, ulcerative colitis, rectal prolapse, ischemic colitis, angiodysplasia, rectal trauma, proctitis from radiation therapy, and others. Therefore, the FIT is not the most reliable test to screen for just CRC.

Stool DNA Testing

At this time of writing, the only such test is Cologuard, developed by Exact Sciences. This test is brand new in the market, but it has shown very promising results. This method analyzes the genes expressed in fecal matter and finds the ones associated with CRC. As a result, its complicated analysis requires a lab test as opposed to a home test like occult blood testing, which can take up to two weeks to get a result instead of the five-minute occult blood test. Moreover, the test is not designed for high-risk individuals, namely people who have had a history of polyps/cancer or for people for whom CRC runs in the family. On top of that, it comes at a cost upwards of \$600, with availability requiring a prescription. This is quite easily understood because these conditions alter stool DNA that may lead to inaccurate results. Regardless, its specificity is 89%, while sensitivity is 92% (Colon Cancer Alliance). These results

are stunning, given the comparison to the occult blood testing. However, the price, accessibility, and restrictions on who can use it have yielded hesitation in both doctors and patients.

3 Solution

CounteractIO calculates predisposition to CRC through inputs such as age, BMI, diabetes, and smoking habits. When combined with results of fecal occult blood testing, ensemble learning methods are put into place in order to boost specificity/sensitivity such that a patient can have the accessibility, ease, and quickness of an occult blood test with the accuracy of a stool DNA test.

Process

The process is rather straightforward. The patient takes an occult blood test, then opens the CounteractIO app. The app will ask for the patient's age, BMI, presence of diabetes, and smoking habits and use these inputs to come up with a probability result of positive or negative for CRC. Since the app does not collect personal identifying information such as name or even date of birth, it should not be in violation of any HIPAA regulations. The entirety of the system was developed using data from Dr. Schloss' lab at the University of Michigan (Baxter et al., 2016).

Ensemble Learning

The following definitions are used to present the underlying concepts of ensemble methods according to classic literature (Kuncheva, 2004).

1. Let $\Omega = \{\omega_1, \omega_2, \dots, \omega_M\}$ be a set of class labels. Then, a function $D : \mathbb{R}^n \rightarrow \Omega$ is called a classifier, while a vector $\vec{\chi} = (\chi^1 + \chi^2 + \dots + \chi^n) \in \mathbb{R}^n$ is called a feature vector.
2. Let $h_1, h_2, \dots, h_M, h_i : \mathbb{R}^n \rightarrow \mathbb{R}, i = 1 \dots M$ be so-called discriminator functions corresponding to the class labels $\omega_1, \omega_2, \dots, \omega_M$, respectively. Then, the classifier D belonging to these discriminator functions is defined by $D(\vec{\chi}) = \omega_{j^*} \Leftrightarrow h_{j^*}(\vec{\chi}) = \max_{1 \leq j < M} (h_j(\vec{\chi}))$ for all $\chi \in \mathbb{R}^n$
3. Let D_1, D_2, \dots, D_L be classifiers. Then, the majority voting ensemble classifier $D_{maj} : \mathbb{R}^n \rightarrow \Omega$ formed from these classifiers is defined as $D_{maj}(\vec{\chi}) = \omega_{i^*} \Leftrightarrow |\{j : D_j(\vec{\chi}) = \omega_i, j = 1 \dots M\}|$.

Inputs

The inputs, represented as feature vectors, are as such:

1. χ_1 -FIT result: this is the result of the occult blood test. Blood in the stool is presents a high risk of CRC.
2. χ_2 -BMI: a unique weight/height ratio. Higher BMIs put a patient at higher risk of CRC.
3. χ_3 -Age: older people are more likely to get CRC.
4. χ_4 -Diabetes: Presence of diabetes imposes a risk of CRC
5. χ_5 -Smoking: Patients who smoke are much more likely to get CRC than those who do not.

Classifiers

To select the best classifiers for classification, quite a few well-known classifiers were trained on the dataset. Classifiers were selected using backward search methods investigated in (Ruta and Gabrys, 2005) for a fixed set of classifiers. A backward search starts out with all classifiers as part of the ensemble, but as the performance of the ensemble increases, classifiers are then removed, thereby resulting in

the optimal ensemble. The end result ensemble is composed of extreme gradient boosted trees, logistic regression, random forests, decision trees, an artificial neural network, and a support vector machine.

Hyperparameters were adjusted to adjust for a small dataset with multiple inputs. Most notably, the artificial neural network has an L-BFGS solver to account for a small dataset and inter-related inputs in combination with a hyperbolic tangent activation function. The logistic regression classifier has a liblinear solver for optimization of small datasets. The support vector machine has a linear kernel.

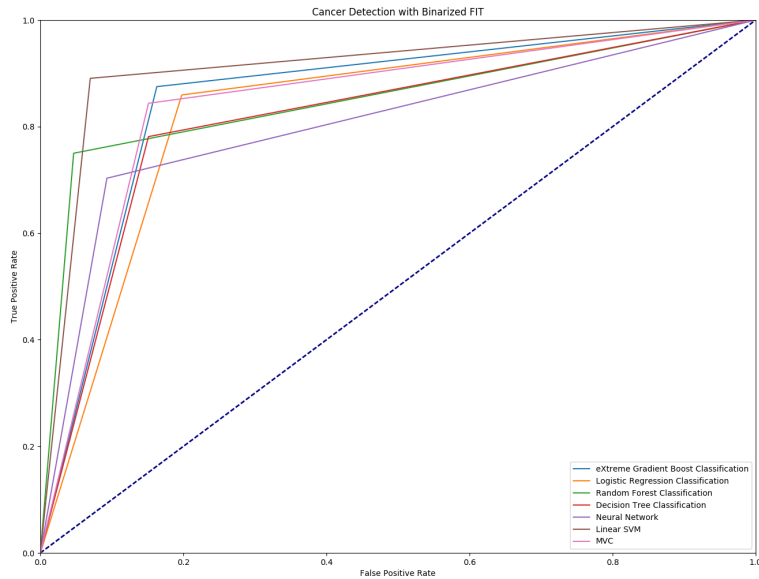
Metrics

Metrics were calculated as follows after ten-fold cross validation:

1. Precision: $\frac{TP}{TP+FP}$
2. Sensitivity/Recall: $\frac{TP}{TP+FN}$
3. Specificity: $\frac{TN}{TN+FP}$
4. F-Score: $\frac{2TP}{2TP+FN+FP}$
5. AUC: $\int_{-\infty}^{\infty} TPR(T)(-FPR'(T))dT$

| <i>Classifier</i> | <i>Scores</i> |
|--------------------------------|---|
| eXtreme Gradient Boosted Trees | Precision: .89 Sensitivity: .86 AUC: .95 Specificity: .91 |
| Logistic Regression | Precision: .89 Sensitivity: .86 AUC: .94 Specificity: .92 |
| Random Forest | Precision: .92 Sensitivity: .89 AUC: .93 Specificity: .91 |
| Support Vector Machine | Precision: .89 Sensitivity: .86 AUC: .95 Specificity: .92 |
| Artificial Neural Network | Precision: .90 Sensitivity: .89 AUC: .95 Specificity: .89 |
| Majority Vote | Precision: .90 Sensitivity: .89 AUC: .95 Specificity: .92 F1: .88 |

These results were then extrapolated onto a test set and plotted on a receiver operating characteristic (ROC) curve. The results are below:



| <i>Method</i> | <i>Statistics</i> |
|--------------------------|---|
| Fecal Occult Blood Tests | Specificity: .96 Sensitivity: .74 Cost: \$15 Time: 5 minutes |
| CT Colonography | Specificity: .88 Sensitivity: .84 Cost: \$439 Time: 30 minutes |
| Stool DNA Test | Specificity: .89 Sensitivity: .92 Cost: \$600 Time: 2 weeks |
| CounteractIO | Specificity: .92 Sensitivity: .89 Cost: \$10 Time: 5 minutes |

Comparison with existing methods

4 Shortcomings

This has been tested for patients in the United States and Canada. Clinical research locations include the MD Anderson Cancer Center, the University of Michigan in Ann Arbor, the Mayo Clinic, and the Dana Farber Cancer Institute, thereby representing people from all over the country. However, the methodology described in this paper has not been tested outside of the United States/Canada. This is significant because people outside of the States may show different biomarkers of CRC as a result of a different cultural upbringing. We are working on getting a larger and more diverse sample set to further validate our results.

5 Conclusion

CounteractIO fills a void that has a great need in the current world of CRC detection. Current tests are not accessible, accurate, quick, as well as noninvasive. The fact that CounteractIO is able to fit all four of those criteria makes it highly desirable to patients in the gastroenterology and oncology fields.

6 References

- [1] Baxter, NT., Ruffin MT., Rogers M.A., Schloss, P.D. Microbiota-based model improves the sensitivity of fecal immunochemical test for detecting colonic lesions. *Genome Med.* 2016.
- [2] Burke, C., Mankaney, G., 2017. Colorectal Neoplasia. Cleveland Clinic.
- [3] Colon Cancer Survival Statistics — CTCA. (0001, January 01).
- [4] Key Statistics for Colorectal Cancer. (n.d.). American Cancer Society
- [5] Kuncheva, L. I., 2004. Combining Pattern Classifiers. *Methods and Algorithms.* Wiley.
- [6] Ruta, D., Gabrys, B., 2005. Classifier selection for majority voting. *Information Fusion* 6 (1), 63 – 81
- [7] Screening Methods - Colon Cancer Alliance - Prevention, Research, Patient Support. (n.d.).