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# Cologuard: Medical and Economic Effects of its Use

Markella Bibidakis[1] and Patricia Talarczyk[1]

[1]Mentor High School, Mentor, OH, USA

## ABSTRACT

In 2014, the FDA approved the non-invasive and economical Cologuard test for colorectal cancer diagnosis for people reaching the age of 50, a milestone previously met with the "gold standard" of colorectal cancer diagnosis: the colonoscopy. Though prevention and treatment for the third most common cancer in the world have been heavily researched, the diagnosis has been thought to be set with the colonoscopy, without much room for modifications. To assess the possibility of replacing the invasive and costly colonoscopy with Cologuard screening as the first step in colorectal cancer diagnosis, a retrospective cohort study was done with data collected from a medical health record database of a northeast Ohio hospital. Medical record numbers were matched with age, sex, any personal or family history, and the results of the colonoscopies of 111 patients with positive Cologuard tests. Of the 111 patients, 92 proceeded with the colonoscopy. The sensitivities, or true-positive rates of results, were calculated for groups organized with respect to age, sex, and previous family and personal oncologic history. Since the data is categorical, a goodness of fit chi-square was done for the statistical analysis, resulting in a failure to reject the null hypothesis with $\chi^2$=0.09318 and p=6.571. In conclusion, the replacement of the invasive colonoscopy with Cologuard non-invasive screening as the first step in colorectal cancer diagnosis could not be proven statistically significant and, therefore, medically favorable.

## Introduction

With the increasing incidence and mortality rates associated with cancer, oncologists around the world spend lifetimes in efforts to perfect the global approach on the first and third steps of living a cancer-free life: prevention and treatment. When considering colorectal cancer, the third most common cancer in the world, following lung and breast cancer, these two stages are already heavily researched.[1] They are seen as the steps that are subject to change, while the diagnosis is thought to be set with the colonoscopy, without much room for modifications. The timely detection of cancer, however, is just as crucial as prevention and treatment, if not more. The stage at which cancer is first detected can be the deciding factor for a patient's life. A study with access to the nationwide database of 39,900 patients with colorectal cancer found that individuals who waited 31-150 days from the date of a confirmed diagnosis to the beginning of the treatment had 1.51 times greater risk of death than those who received treatment within the first 30 days, corroborating the importance of timeliness throughout the process of battling cancer.[2] Considering the role that detection of colorectal cancer plays in the likelihood of survival, it is crucial to know which approach of detection is best and how the allocation of vital resources, such as time and money, should be distributed in the global objective for lowering colorectal cancer mortality.

In the medical community, the "dreaded turning-50" test is the term colloquially used to describe the screening for colorectal cancer, which many people opt for once they turn 50 years old. The most trusted procedure for this screening is the colonoscopy, dubbed the "gold standard" of colorectal cancer detection.[3] The procedure is an invasive examination that requires placing a long, flexible colonoscope about half an inch in diameter in the rectum and further advancing it into the large intestine. The small intestine, ranging from 10 to 16 feet, consists of the duodenum, jejunum, and ileum. The large intestine, which is about five feet long, consists of the cecum, colon, rectum, and anus, in that order of digestion.[4] Depending on the reason for the colonoscopy, a doctor may advance different lengths into the lower gastrointestinal tract. For example, diagnosing Crohn's disease or looking for a cause of bleeding in the intestines requires examining all of the large intestine and the ileum of the small intestine. When screening for colorectal cancer, the colonoscope is advanced to the rectum and the full length of the large intestine, but no farther into the small intestine.[5] During the colonoscopy, the physician, most commonly a gastroenterologist, will examine the rectum and large intestine for adenomatous polyps, or abnormal tissue growths in the shape of small clumps on the inner mucous membrane of the colon or rectum. If not caught early, these adenomatous polyps can develop into metastatic cancer, requiring invasive, expensive, and time-consuming treatment, with increasingly diminishing chances of survival as time passes. The physician can examine the entire length of the large intestine by observing the video feed displayed by the microscopic camera of the colonoscope on a nearby monitor, while the patient is under light anesthesia.

Depending on the individual patient, the colonoscopy may not always be the optimal choice, despite its current status as the "gold standard" of colorectal cancer detection. Considering the procedure is only a preliminary examination and includes no form of treatment for any abnormal findings, this form of screening is too costly and far too invasive for patients who do not show risk factors such as increased alcohol consumption or a family history of colorectal cancer.[6] The colonoscopy is completed regardless of the presence of symptoms and is recommended to all people over the age of 50, often proving to be unnecessarily draining of energy, time, and money. Additionally, the dangers associated with any medical procedure, especially those linked with the side effects of anesthesia should not be overlooked. All types of sedatives that can be used during the colonoscopy are associated with the adverse effect of respiratory depression, the failure of the lungs to exchange oxygen and carbon dioxide. Some sedatives also have additional health consequences. For example, Propofol is known for commonly inducing apnea, the repeated starting and stopping of the lungs' functionality. Similarly, Midazolam is associated with retrograde amnesia, which damages the memory-storing areas of the brain.[7] Besides these health concerns, the complicated procedure of the colonoscopy also has additional disadvantages. With these examinations, some patients wake up with uncomfortable fatigue and weakened cognitive function for up to 24 hours. Patients' work and home schedules have to be delayed and an accompanying person has to drive them home after the colonoscopy.[7] Despite these disadvantages of the colonoscopy, a replacement for the invasive and costly procedure has not yet been found by medical researchers.

An FDA-approved alternative to the invasive colonoscopy is the inexpensive and non-invasive Cologuard DNA screening of a stool sample.[8] The take-home kit allows individuals to non-invasively test for colorectal cancer with 92.3% sensitivity, or true-positive rate of results, and 90% specificity, or true-negative rate of results.[9] With the kit, a stool sample is individually collected by the patient at home and sent to a family doctor for laboratory testing. The results come from a series of DNA analyses that test for many mutated genes that are associated with colorectal cancer polyps. The fact that the Cologuard screening tests for genetic indicators of the disease and not the cancer itself often misleads non-medically educated individuals about its reliability. This reason also plays into the fact that the

test has not been researched as a replacement of the colonoscopy, but only as an additional option for those who request it. This misinformation and gap in the research base occur despite Cologuard's FDA approval, statistical evidence of efficacy, the American Cancer Society's inclusion of the test in its national guidelines for colorectal cancer screening, and a ubiquitous medical consensus of its effectiveness.[10] Due to Cologuard's affordability and non-invasive nature, it is mostly used by those who wish to avoid all invasive procedures for as long as possible. Those who are only appeased with unquestionable results tend to opt for the invasive and costly colonoscopy, regardless of whether the test is truly required for the individual patient by the medical probability of colorectal cancer occurrence. The probability can be calculated by known risk factors, such as a family history of the disease, chemical carcinogen subjection, prolonged exposure to radiation, viral infections, increased alcohol consumption, and so on.[11,6] It is possible that the avoidance of the Cologuard screening by these individuals may be due to improper advertising of the options for the detection of colorectal cancer and the predictive odds of each choice.

The tenacity to the colonoscopy procedure by the medical community may have been determined prematurely, especially since a comfortable consistency has been created due to the colonoscopy's undeviating use since 1969.[12] The Cologuard test, with only five complete years of FDA approval, is yet to be extensively researched as an alternative to the invasive colonoscopy as the first step in colorectal cancer diagnosis. It may now be time to reevaluate where the colonoscopy fits in the timeline of colorectal cancer detection, since its $3000-4000 price tag may be too expensive to be covered by health insurance for all. Cases have been reported of patients that had the first "dreaded turning-50" colonoscopy covered by their insurance but had to pay for the costly procedure out-of-pocket when it became necessary for a second time.[13] Similar surveillance testing may be denied coverage for other reasons, such as age, if insurance companies do not consider the screening a priority. These patients had the same need for the procedure both times, yet insurance companies would not financially support them. The proper management of colorectal cancer screening capital may allow insurance companies to pay for all medically-necessary colonoscopies if the colonoscopies that are statistically determined to be unnecessary are instead replaced with economical Cologuard tests.

The Cologuard test was approved by the FDA in 2014 and is now medically accepted by the medical community as a form of screening, for those who request it. Nevertheless, a gap exists in the current body of knowledge since this reliable, non-invasive, and economical form of screening is not currently being researched further in order to promote its use for adenomatous polyp detection, raising the question: How medically favorable is the replacement of the invasive colonoscopy with Cologuard non-invasive screening as the first step in colorectal cancer diagnosis?

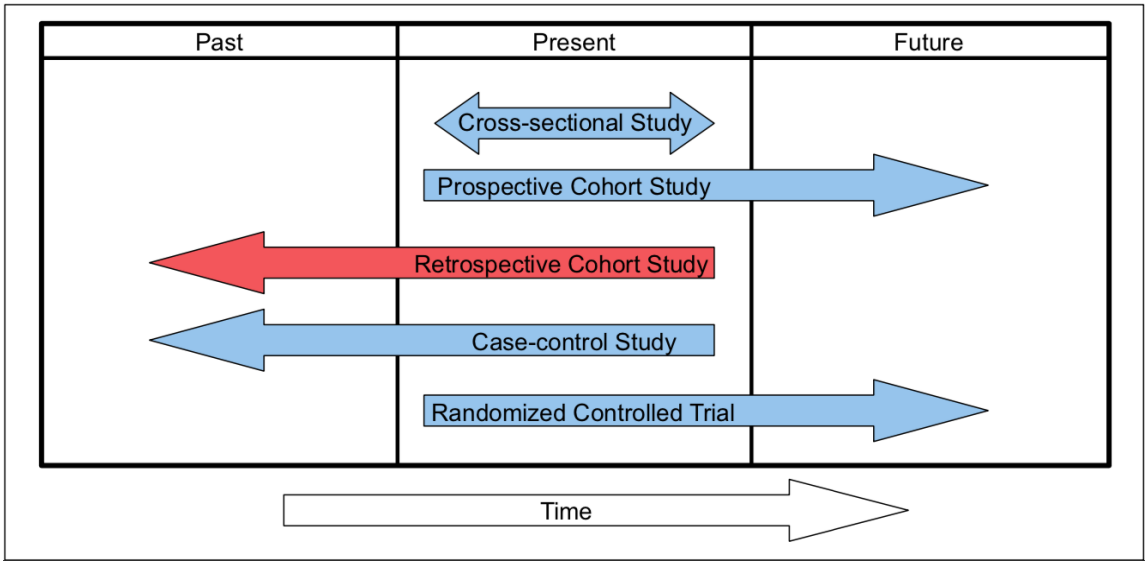
## Method

The best approach to assess the possibility of the colonoscopy's replacement with the Cologuard test as the first step in colorectal cancer diagnosis is with a retrospective cohort study. Figure 1 on the following page shows the chronological details of different types of studies. For an observational study that assesses the favorability of a certain approach to the prevention, diagnosis, or treatment of a disease, researchers must look back in time to understand which observational group had the best results. For this reason, the only two possible study types for the assessment of colorectal cancer diagnoses are a retrospective cohort study and a case-control study, which is always retrospective. A retrospective cohort study organizes the participants of the sample by the exposure, or past care provided, and analyzes how it affected their present outcome. A case-control study, on the other hand, organizes the sample by the

present outcome, in order to understand what past exposure led to that result.[14] Either way, both studies look back in time to find the cause of a certain dependent variable.

Figure 1.

*Chronological Differentiation of Possible Study Types*




Ideally, a randomized controlled trial, or experiment, could be run, where treatment groups of participants with and without colorectal cancer could be separated. Results of colonoscopies and Cologuard tests could be gathered for both groups to analyze how the detection rate would be affected if each patient began with a Cologuard test, compared to a colonoscopy, and how the cost would have been impacted. Since this study would require human experimental participants, this is not feasible within the restrictions of the AP Research course. Normally, this type of study would require a longer time span and more control over the human participants, which were not feasible due to time restrictions and ethical constraints. The observational study that comes closest to this approach, however, is a retrospective cohort study. Though it does not manipulate the treatment of each group, it still organizes participants by exposure to assess how the results were affected.

When randomized controlled trials are not feasible in the medical field, researchers often borrow data for retrospective cohort studies from medical record databases. This data collection is approved for studies involving anything from cesarean section complications to head and neck cancer diagnoses.[15, 16]

Due to the fact that the restrictions of the AP course did not make a randomized controlled trial feasible as a study type, not all statistics regarding the Cologuard test could be analyzed. Though it would have been preferable to conduct a statistical analysis with both sensitivity and specificity, determining specificity from secondary data collected in the past is not possible. This is because specificity is the measure for the true negative rate of results from the test. To find this value, a researcher would need a statistically significant sample size of Cologuard tests that were negative and the patients proceeded to have the colonoscopies anyway. Since a negative Cologuard is an indication

that a colonoscopy is not required, this data is not available for studies other than randomized controlled trials where the researcher has results for all participants for both the Cologuard test and the colonoscopy. On the other hand, finding the sensitivity, or true positive rate of results is, in fact, feasible, since patients who receive positive Cologuard results usually verify those results with a colonoscopy, excluding a small percentage who avoid the procedure due to its cost or invasive approach. This gives researchers the number of positive Cologuard results, as well as how many were verified with the "golden standard" colonoscopy of colorectal cancer detection. For this reason, the sensitivity of the Cologuard test was used as a rough estimation to check if the test was more accurate in predicting colorectal cancer than previously believed. Though it does not present the entire picture about the accuracy of the test, sensitivity is often used in studies with limited access to necessary data. This is done in order to approximate any change in the accuracy that would adjust the current knowledge about the favorability of a test. A prime example of this is found in a peer-reviewed study that analyzed the sensitivity rates of autoantibody testing for celiac disease for the two sexes.[17] For the data collection of the results of the colonoscopies corresponding with the positive Cologuard tests, a medical record database was used to find a sample. Permission was granted by a northeast Ohio local hospital to find all of its positive Cologuard results within the last three years in order to target an initial sample of at least 100 participants. The primary data collection by the hospital is performed when family doctors remind people over the age of 50 to get tested for colorectal cancer. All medical records include these types of procedures and tests so locating the sample included a request from the hospital to isolate the positive Cologuard tests. Medical record numbers were used as patient tags instead of names due to HIPAA regulations to ensure anonymity. Each medical record number was matched with age, sex, any personal or family oncologic history, and the results of the colonoscopies, making up a set of both qualitative and quantitative data. All of this data was available in the hospital's system of electronic medical records (EMR) using the Epic EMR software. Other software for EMR databases could also be used that include the same information. Since some colonoscopies were scheduled for a date after the original data collection day, the hospital was contacted after the indicated procedure dates to fill in any blanks in the data. Any patients that had originally scheduled a date for a colonoscopy but either canceled the procedure or had it done elsewhere were excluded from the statistical analysis. The organization of the data is seen in the appendix.

Although the data used was originally collected from human participants, no contact was made with them. Consequently, no consent forms were required by the participants. Additionally, permission was granted from the hospital to use data from the medical records. This, coupled with the consent for anonymous data analysis given to each patient's primary care physician when each exam was administered, is sufficient consent to run the analysis of an observational study as long as anonymity is maintained.

## Results

The medical record database that was used had 111 patient records with positive Cologuard tests within the three years before the request for the data was made. One row of the table seen in the appendix was completed for each patient. Each medical record number was accompanied by patient age, sex, whether or not any personal or family history of cancer was known, and the findings of the colonoscopy, if performed. Of the 111 patients that had positive Cologuard results, 92 proceeded with the colonoscopy. Though this creates an underrepresented portion of the population, cancellations of the colonoscopies were based on individual preferences and had nothing to do with the results of the

Cologuard test or the colonoscopy. This is known because when the hospital was contacted to check on any blanks in the data, the individuals that did not proceed with the colonoscopy either had the procedure at a different hospital or avoided it because of its invasive nature. It can be assumed, therefore, that no specific group of the population had insufficient representation. By extension, even without those who did not continue with the colonoscopy, the sample remained representative of the population of positive Cologuard tests.

After the data were separated into groups of those under 60 years old, over 60 years old, under 65 years old, over 65 years old, under 70 years old, over 70 years old, under 75 years old, over 75 years old, male, female, with a personal oncologic history, without a personal oncologic history, with a family oncologic history, and without a family oncologic history, the sample sensitivity was found for each. This value was determined by dividing the number of positive colonoscopies by the total number of colonoscopies. This way, the portion of the positive colonoscopies that were verified to be true-positives could be found. These values, along with the number of positive colonoscopies, negative colonoscopies, canceled or unscheduled colonoscopies, total colonoscopies, and total patients for each group are shown in Table 1 in the previous page. To clarify, the values of the sample sensitivities were rounded to the nearest ten-thousandth, if necessary.

**Table 1**

*Colonoscopy Results of Positive Cologuard Tests Grouped with Respect Age, Sex, and Medical History*

| | Positive | Negative | No Colonoscopy | Number of Results | Total | Sample Sensitivity |
|---|---|---|---|---|---|---|
| Overall | 81 | 11 | 19 | 92 | 111 | 0.8804 |
| Under 60 | 17 | 3 | 2 | 20 | 22 | 0.85 |
| 60+ | 64 | 8 | 17 | 72 | 89 | 0.8889 |
| Under 65 | 24 | 3 | 3 | 27 | 30 | 0.8889 |
| 65+ | 57 | 8 | 16 | 65 | 81 | 0.8769 |
| Under 70 | 45 | 3 | 5 | 48 | 53 | 0.9375 |
| 70+ | 36 | 8 | 14 | 44 | 58 | 0.8182 |
| Under 75 | 62 | 5 | 6 | 67 | 73 | 0.9254 |
| 75+ | 19 | 6 | 13 | 25 | 38 | 0.76 |

| | | | | | | |
|---|---|---|---|---|---|---|
| Male | 31 | 6 | 8 | 37 | 45 | 0.8378 |
| Female | 50 | 5 | 11 | 55 | 66 | 0.9091 |
| Personal Hx | 11 | 0 | 6 | 11 | 17 | 1 |
| No Personal Hx | 70 | 11 | 13 | 81 | 94 | 0.8642 |
| Family Hx | 63 | 6 | 16 | 69 | 85 | 0.9130 |
| No Family Hx | 18 | 5 | 3 | 23 | 26 | 0.7826 |

## Analysis

Since the data consisted of one sample, had one score for each measurement, and had more than one category of measurement, the appropriate statistical analysis test is a chi-square goodness of fit.[18] This test shows if a group of observed values is statistically significant from the expected values. The sample sensitivities for each group were used as the observed values and the known 92.3% sensitivity reported by the Mayo Clinic for the Cologuard test was used as the expected value for all groups.[9] The chi-square value for this test was 0.09318. At the significance level of $\alpha$=0.05, with 14 degrees of freedom and a p-value of p=6.571, the null hypothesis cannot be rejected. The direct conclusion from these values is that the test failed to reject that there is no statistically significant difference between the reported 92.3% sensitivity of the Cologuard test and the sensitivities of the groups of the sample. Consequently, the conclusion that can be drawn is that Cologuard does not have a higher accuracy as a predictive genetic test than previously reported. Therefore, this test failed to show that the replacement of the invasive colonoscopy with Cologuard non-invasive screening as the first step in colorectal cancer diagnosis would be medically favorable.

It is important to note that 19 of the 111 patients with positive Cologuard tests had no known colonoscopy. In the best-case scenario, if all 19 colonoscopies had been positive for adenomatous polyps, the overall sample sensitivity would have been 0.9009, instead of 0.8804.

**Table 2**

*Group sensitivities from highest to lowest*

| Group | Sample Sensitivity |
|---|---|

| | |
|---|---|
| Personal Hx | 1 |
| Under 70 | .9375 |
| Under 75 | .9254 |
| Family Hx | .9130 |
| Female | .9091 |
| 60+ | .8889 |
| Under 65 | .8889 |
| 65+ | .8769 |
| No Personal Hx | .8642 |
| Under 60 | .85 |
| Male | .8378 |
| 70+ | .8182 |
| No Family Hx | .7826 |
| 75+ | .76 |

An additional chi-square goodness of fit test was run with the best-case scenario for each group. The data still proved statistically insignificant at the $\alpha$=0.05 significance level, with a chi-square value of 0.002883. This means that if the inconclusive results had all been positive, there would still be no statistically significant difference to show that Cologuard is more reliable than previously believed. Therefore, the claim that the Cologuard non-invasive screening should replace the colonoscopy as the first step in colorectal cancer diagnosis still could not be supported in the best-case scenario.

Though the two tests show that the data, as a whole, is not statistically significant to reject the null hypothesis, trends for the groups, individually, can still be noticed. The highest sample sensitivity is seen in the group of patients with a personal oncologic history. With a sensitivity of 1, all patients with a positive Cologuard test that had a previous history of cancer had true-positive results. The order of groups from highest to lowest sensitivity within the sample is shown in Table 2 in the previous page, not including the sample sensitivity of the overall group.

The fact that 17.1% of the sample of positive Cologuard tests did not have a colonoscopy performed does create some non-response bias. Additionally, five of the 14 groups that participants were divided into did not have the recommended 30 participants for a statistically significant sample. Though these limitations exist in this study, the results still place focus on which groups of people had the highest sensitivity within the sample and create room for future studies to validate the findings.

## Conclusion

The inconclusive statistical analysis shows that the sample of positive Cologuard tests could not show that there is a statistically significant difference between the sample sensitivities and the previously medically-determined sensitivity. The previously determined 92.3% sensitivity corresponds with the current understanding that Cologuard is an alternative to the standard colonoscopy. Since it could not be shown that the sensitivity was increased, there is no evidence to show that the current understanding is false.

Based on the negative results of the chi-square test, it is expected that future directions regarding this topic will include the validation of results. This can simply be a repeat of the same method for a different northeast Ohio hospital, an application of the same method for a different part of the world, or a broadened approach by collecting samples from hospitals over a larger area and accumulating data to analyze using the same method. Additionally, with the information known about the ranking of the groups of people regarding specificity within the sample collected from the local northeast Ohio hospital, additional follow-up studies are anticipated. It is expected, as well as recommended, that future researchers collect a statistically significant sample size of positive Cologuard tests to show that any of the groups used in this study have a statistically significant difference in sensitivity compared to the reported value by the Mayo Clinic, rather than the overall sensitivity of the group as a whole, as used in this study. This means separating a specific group and applying the method to those individuals. It is advised that this application of the method begins with the group that has the highest sample sensitivity: those with a personal oncologic history. Furthermore, future studies, especially double-blinded randomized controlled trials, could be executed in the order of highest to lowest sample sensitivity as seen in Table 2 of the analysis section.

Moreover, future studies can be conducted to show how additional risk factors for colorectal cancer affect the results of this study. Populations of people with oncologic risk factors are expected to show a higher sensitivity and a higher chance for conclusive results. Examples of such risk factors are chemical carcinogen subjection, prolonged exposure to radiation, viral infections, and increased alcohol consumption.[11,6] If it is known that Cologuard is a more medically favorable approach for populations with these risk factors, these individuals can use the non-invasive Cologuard test when more frequent follow-ups are needed to replace some required colonoscopies and space out the yearly expensive and invasive procedure.

The limits of the applications of this study have to be understood before analyzing the implications to the medical field. For example, the 17.1% nonresponse portion of the population has to be accounted for and compared to the response rate for research that is accepted by medical professionals in order to have the findings integrated into the medical field. The medically-accepted standard value for the response rate is one that is over 80%.[19] Though the 82.9% response rate of this study is above the accepted minimum, it still comes close to this value. For this reason, the implications of these simply require additional verification to ensure that the results were accurate.

Additionally, another limitation of this study is that, as previously mentioned, the analysis of the accuracy of the Cologuard test was solely based on the sensitivity and not the specificity. This means that only the test's ability to accurately predict a positive result was a factor in this study. There was no element of this method dedicated to analyzing the Cologuard test's ability to accurately predict a negative result. For that reason, this method cannot wholly and conclusively determine the accuracy of the test, knowing that the ability to correctly predict a negative diagnosis is excluded from the method altogether. For this aspect, a prospective double-blinded randomized controlled trial in which patients of both positive and negative Cologuard results undergo colonoscopies will provide results to satisfy

all predictive components of the Cologuard test. To have enough statistical power for the test, a multi-institutional prospective study is required.

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