Pivotal Clinical Study

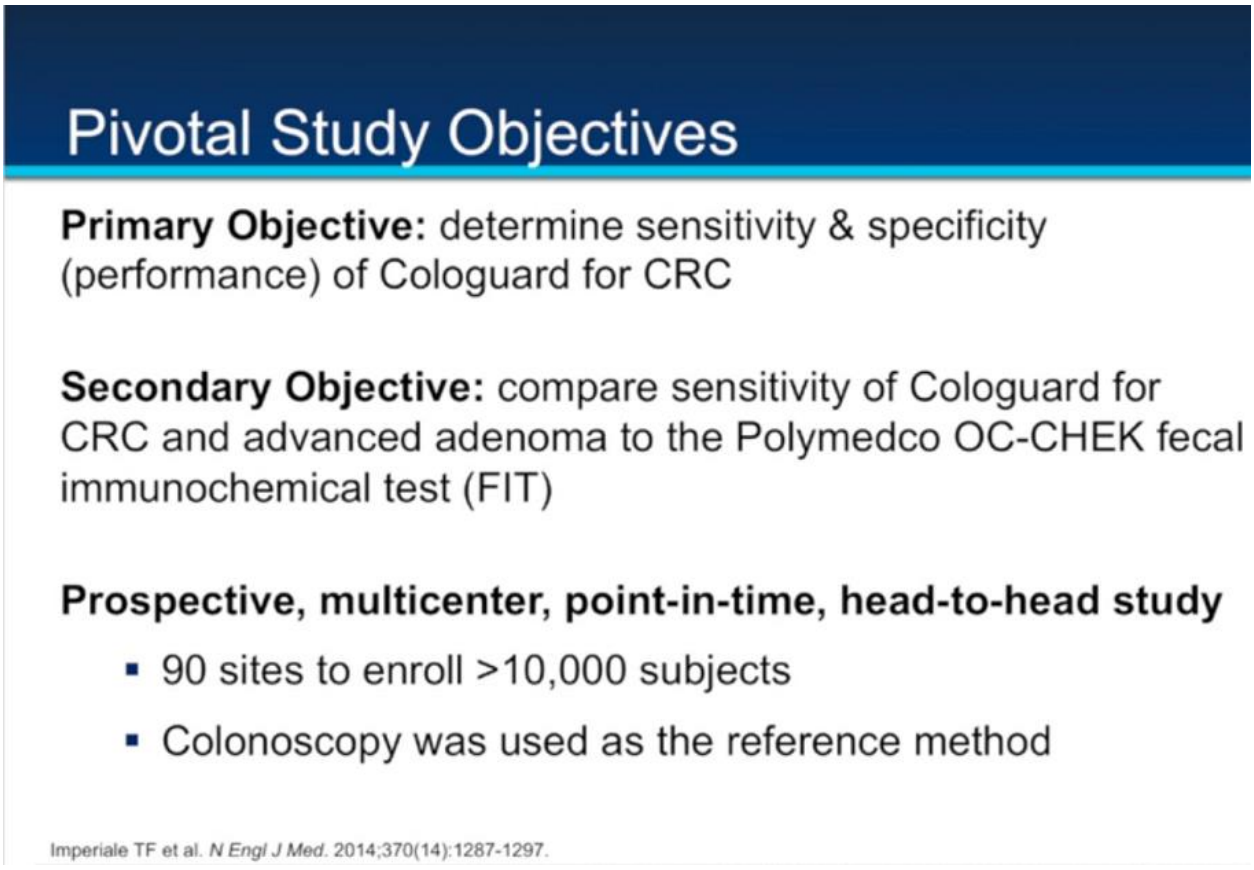
In a clinical study published in 2014 that included more than 90 sites throughout the US and Canada, Cologuard's stool DNA technology was evaluated in 10,000 participants:

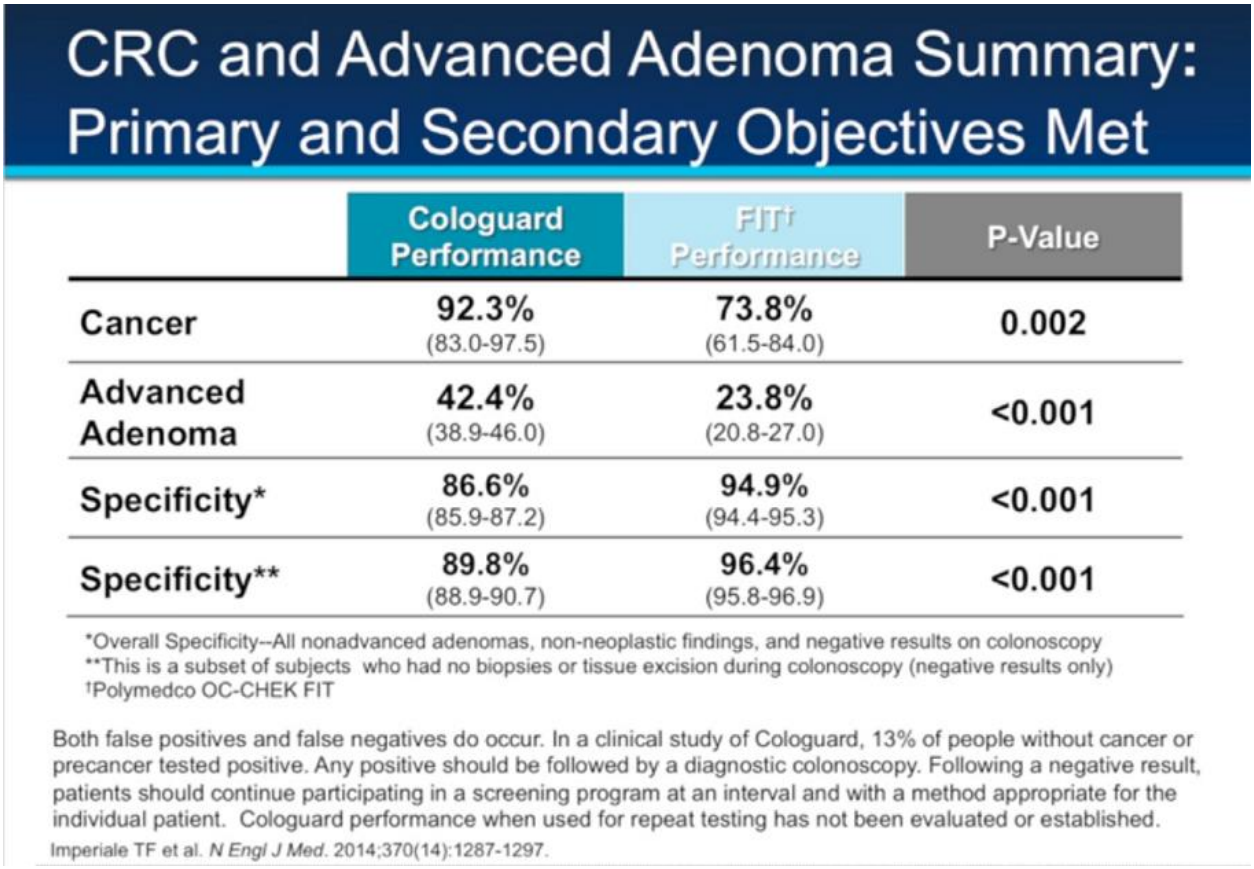
- Evaluated Cologuard for detecting colorectal cancer and precancer
- One of the largest colorectal cancer studies ever conducted
- Compared Cologuard to a leading fecal immunochemical test (FIT)*
- Prospective cross-sectional study

*OC FIT-CHEK, Polymedco, Inc.

Visit the New England Journal of Medicine website and search "stool DNA" to view the clinical study.

Exact Sciences and Cologuard are not affiliated with the New England Journal of Medicine.





Clinically Proven Sensitivity in a Noninvasive Colorectal Cancer Screening Test[1]

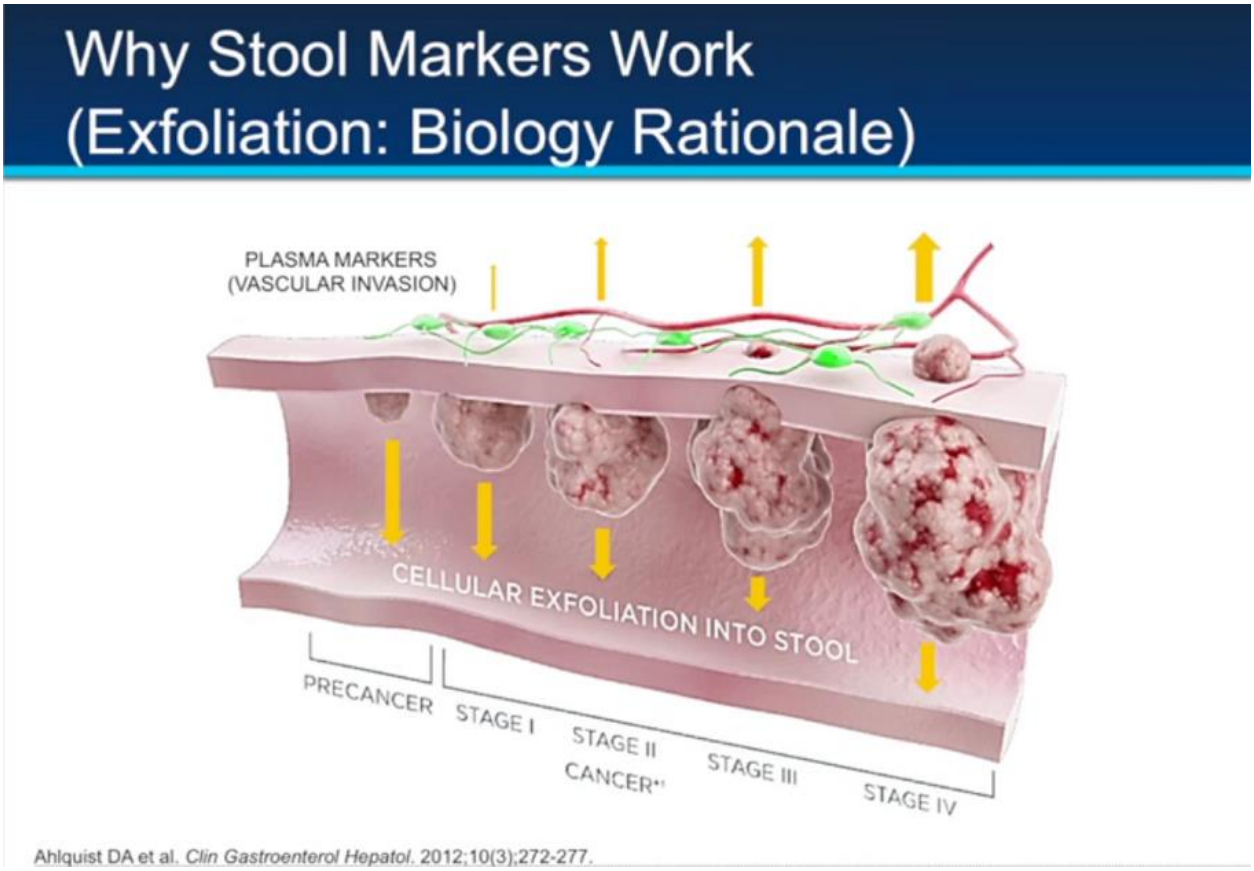
- **92% sensitivity** in detecting cancer stages I-IV (compared to ~74% for FIT)
- **94% sensitive in detecting early-stage colorectal cancer** (stage I-II)
- 87% specificity compared to 95% for a leading fecal immunochemical test (FIT)*

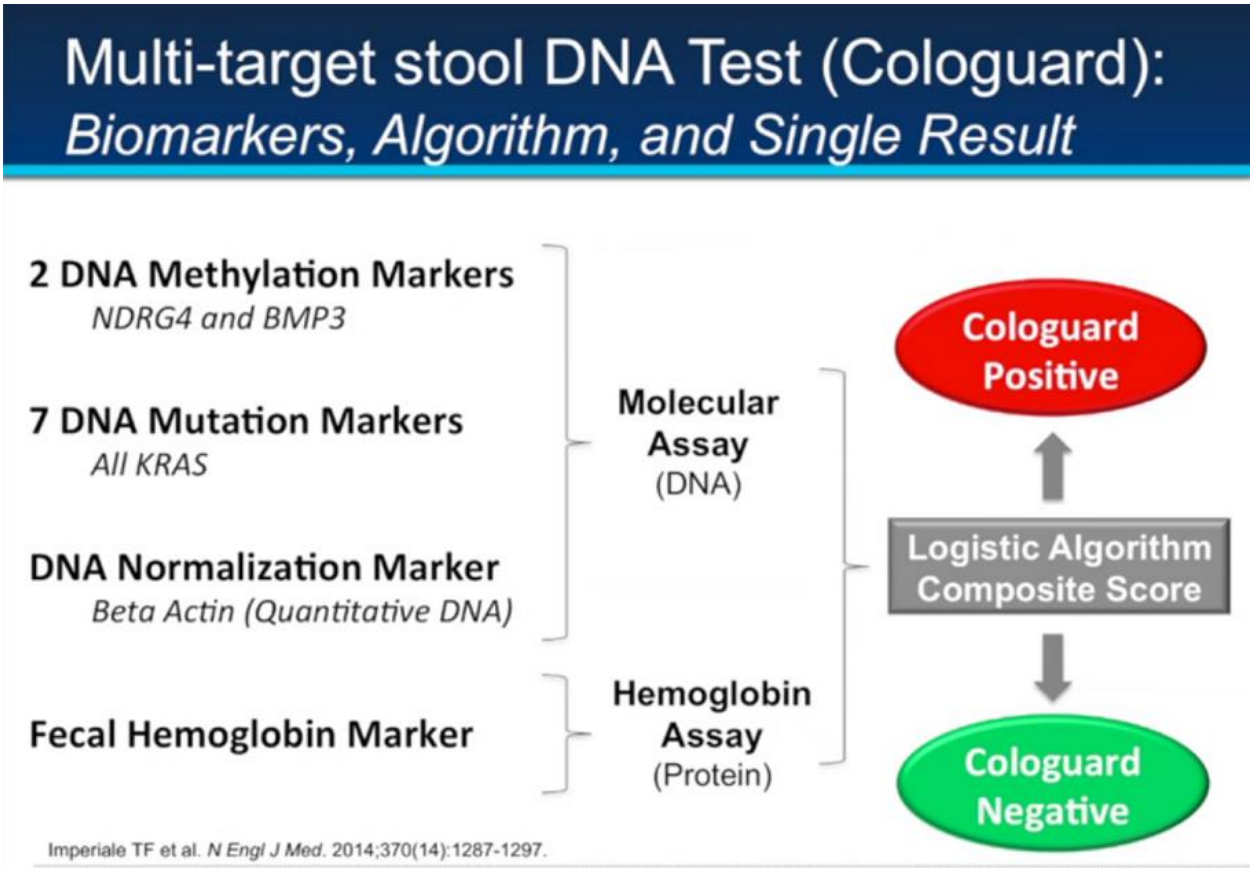
*OC FIT-CHEK, Polymedco, Inc.

Innovative multiple-marker stool DNA technology and how it works

Cologuard is the only screening test that uses multiple-marker, stool DNA (sDNA) technology to detect colorectal cancer and precancer.

- Eleven distinct biomarkers
- DNA methylation and mutation biomarkers are incorporated that are associated with cancer and precancer
- Cellular exfoliation of DNA into stool occurs continuously





Intended Use

Cologuard is intended for the qualitative detection of colorectal neoplasia associated DNA markers and for the presence of occult hemoglobin in human stool. Cologuard is for use with the Cologuard collection kit and the following instruments: BioTek ELx808 Absorbance Microplate Reader; Applied Biosystems® 7500 Fast Dx Real-Time PCR; Hamilton Microlab® STARlet; and the Exact Sciences System Software with Cologuard Test Definition.

Indications for Use

Cologuard is intended for the qualitative detection of colorectal neoplasia associated DNA markers and for the presence of occult hemoglobin in human stool. A positive result may indicate the presence of colorectal cancer (CRC) or advanced adenoma (AA) and should be followed by diagnostic colonoscopy. Cologuard is indicated to screen adults of either sex, 50 years or older, who are at typical average-risk for CRC.

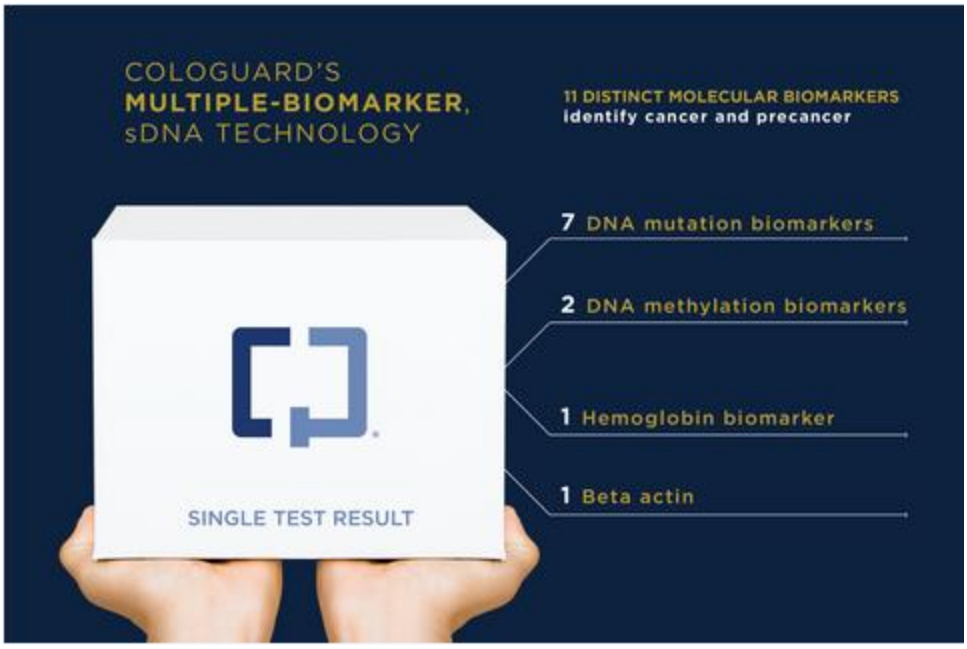
Cologuard is not a replacement for diagnostic colonoscopy or surveillance colonoscopy in high risk individuals.

The science behind the test: stool DNA technology

Cutting-edge stool DNA (sDNA) technology for cancer and precancer detection means more curable-stage cancers can be found than with fecal blood alone.

Cologuard utilizes a multi-target approach to detect DNA and hemoglobin biomarkers associated with colorectal cancer and precancer.

Eleven biomarkers are targeted and provide a stronger connection between colorectal cancer and precancer.



Methylation, mutation, and hemoglobin results are combined in the laboratory analysis to provide a single **positive** or **negative** reportable result.

Cologuard technology

The patient stool samples are processed at the laboratory to isolate the DNA for testing and for detection of fecal occult hemoglobin.

DNA Biomarker Detection

Amplification and detection of methylated target DNA (*NDRG4, BMP3*), *KRAS* point mutations, and *ACTB* (a reference gene for quantitative estimation of the total amount of human DNA in each sample) is performed using the Quantitative Allele-specific Real-time Target and Signal Amplification (*QuARTS*™) technology.

Multiplexed *QuARTS* reactions are processed using a real-time cycler with each biomarker (*NDRG4, BMP3, KRAS,* and *ACTB*) monitored separately through independent fluorescent detection channels.

Hemoglobin Biomarker Detection

The stool sample is prepared and analyzed for fecal occult blood in a quantitative Enzyme-Linked Immunosorbent Assay (ELISA) that determines the concentration of hemoglobin in the sample.

Quality Controls

Control samples for both the *QuARTS* assays and hemoglobin assay are tested along with patient samples to show that the process has been performed appropriately.

Results

Outputs from the DNA and hemoglobin are integrated during analysis with an algorithm to determine a Cologuard positive or negative result.