Doubeni CA et al. *Effectiveness of Screening Colonoscopy in Reducing the Risk of Death from Right and Left Colon Cancer: A Large Community-based Study*

Technical Appendix – METHODS OF THE SCOLAR STUDY

Study goals, design, and setting

The case-control study, *Effectiveness of Screening for Colorectal Cancer in Average-Risk Adults* (SCOLAR), was initiated in September 2009. The primary goal was to determine whether, and to what magnitude, the use of colonoscopy to screen asymptomatic average-risk persons for colorectal cancer (CRC) was effective in reducing the risk of CRC deaths. The primary interest was in the effectiveness of colonoscopy for reducing deaths from cancers in the right colon. The study was nested in two historical cohorts at Kaiser Permanente Northern California (KPNC) and Kaiser Permanente Southern California (KPSC). These two large integrated health care systems have a combined membership of nearly 8 million people, which is about 1 in 40 Americans. Study activities were discontinued at two prior sites, Fallon Clinic (or Reliant Medical Group) and Kaiser Permanente Georgia, due to low accrual and transferred to KPSC, which only accrued subjects during the later study years of 2011 and 2012.

Integrated Data Sources

KPNC and KPSC both participate in the Health Care Systems Research Network (*formerly* HMO Cancer Research Network),[1] have used electronic medical records systems since at least 2004, and have electronic health care utilization, and administrative data dating back to 1995 or earlier. They share similarly structured databases within a Virtual Data Warehouse,[1] which has identical variable names, formats, and specifications, allowing the use of centrally generated or distributed informatics tools to extract data at each site and ascertain covariate information. They each have tumor registries that report to the United States Surveillance Epidemiology and End Results (SEER) program. The registries provide cancer ascertainment and data quality that is >99% concordant with the SEER standard. They have vital records that are collected both locally and from the California vital status files; the lag for mortality ascertainment is 6–12 months. They also routinely link to US Census Bureau data and other publicly available data systems. These integrated data systems make it possible to identify the eligible population and determine outcomes such as cancer diagnosis and death. They also allow for construction of historical cohorts, and tracking of the enrollment and health care utilization histories of members over extended periods of time.

Study population and sample selection

We used a dynamic or open population approach to select study patients.[2] Our design required patients who were at average risk for CRC and had long-standing enrollment in the health plans. Thus, we required patients to have on the reference date (defined below): 1) a minimum of 5 years of prior enrollment in the participating health plan; 2) no previous history of gastrointestinal cancers, or partial or total colectomy for any reason; 3) no documented diagnosis of inflammatory bowel disease; and 4) no documented strong family history of CRC. We defined a strong family history as having 1) a CRC-associated syndrome such as familial adenomatous polyposis, 2) at least one first-degree relative diagnosed with CRC before the age of 50, or 3) two or more biological relatives diagnosed with CRC at any age.[3,4] As these risk factors are more likely to be documented in patients with CRC around the time of diagnosis than in disease-free (particularly unscreened) individuals, the exclusion criteria were not considered if they were only documented in the 30-day period prior to the reference date.

Cases definition

Cases are health plan members, men or women, who died from invasive colorectal adenocarcinoma between 2006 and 2012 and were 55-90 years old on the date of death. We only considered adenocarcinomas, which represent approximately 89% of all CRCs, because these tumors are believed to follow the adenoma-carcinoma sequence[5] and are potentially preventable through screening.

The diagnosis date of case patients is set as the reference date for determining study eligibility, matching cases to controls, and for ascertaining exposure information.

Matching of cases and controls

We selected eight eligible controls for each case individually matched on study site, sex, birth year (±1 calendar year), years of enrollment (±1 year) in the health plan, and geographic region within plans. For instance, a 57-year-old case man with 7 years of health plan enrollment and receiving care from a particular medical center in Northern California is matched to male control patients who are between 56 to 58 years of age, have had between 6 and 8 years of enrollment and are also receiving care from that medical center. We use incidence density-based matching with replacement, which means that a control patient may be selected for more than one case and can also become a case patient if the individual dies from CRC later in the study.[2]

Table 1: Study variables and data sources

Data elements	Data sources
Demographic characteristics	Tumor registry,
Age, sex, and race/ethnicity	administrative (e.g.,
Region	enrollment) data, and
Enrollment duration	both paper and electronic
	medical records
Risk factors	
Personal/family history of CRC,	Medical records
IBD, Lynch, FAP, colectomy	
General health (at reference date	
and within 2 years)	Electronic data on care
Height/weight	utilization (diagnoses,
Medications	procedures, laboratory
Family history	results), pharmacy files,
Comorbidities	medical records
Cancer diagnosis	
Stage	SEER registry
Location	
Histology	
Vital status	
Date and cause of death	Mortality files, vital records, NDI, SSDMF, death certificates
Fecal occult blood testing	
Number of fecal blood tests documented in the records	Electronic data on care utilization (diagnoses,
Date ordered, collected, or performed	procedures, laboratory results), and medical
Reason for test	records
Result of test	
Procedures	
Number of tests	Electronic data on care
Types and dates of tests	utilization and medical
Reasons for tests (e.g., screening, positive FOBT, symptoms)	records
Complications of tests (e.g., perforations or major bleeding)	
Provider characteristics	
Specialty, training	Electronic data on care
Rate of complete colonoscopies	utilization and medical
Rate of polyp and adenoma detection	records
Quality of colonoscopy	
Completeness to the cecum	Electronic data on care
Total duration of test, and withdrawal time	utilization and medical records
Polyps or lesions found	
Count and location	Electronic data on care
Size and shape	utilization and medical
Pathologic features	records

The matching process identified eight randomly selected candidate controls for each case on the assumption that at least one-quarter of those would be eligible for the study after examination of medical records. The two closest eligible matched controls for each case were then selected for detailed medical chart audit. The existence of a very large population in the two integrated systems made it possible to match patients on several variables within a relatively narrow range.

Data collection and integration

We integrated information from multiple complementary sources including electronic medical records, administrative data, and tumor and vital status registries. The information types and sources are summarized in **Table 1**.[6] These data were used for selection of study patients and for accurate measurement of exposure and outcomes. The main data collection tools, custom-built electronic chart audit forms and computer algorithms, were tested previously in a similarly designed smaller study at four other HMO Cancer Research Network sites.[7] The data collection protocol for the current study underwent a number of modifications based on the experience in that earlier study.

A SAS computer program automatically excluded those with documented prior history of a gastrointestinal

cancer, colectomy or inflammatory bowel disease using, in part, codes from the International Classification of Diseases, 9th Edition, Clinical Modification, Current Procedural Terminology and Healthcare Common Procedure Coding System. As part of the modified approach in this study, patients with a family history were not excluded by the program but flagged for comparison with chart audit data.[6] The computer program extracted patient demographics, health care utilization such as dates and types of clinical visits, evidence of high-risk conditions, dates and results of CRC-related laboratory tests including iron studies and FOBT, and the dates of colonoscopy, sigmoidoscopy, barium enema, and computed tomographic colonography (**Table 1**).

This information was used to prepopulate (or preload) the electronic chart audit form to facilitate chart review.[8] This then served to guide searching the medical records, and helped to standardize chart abstraction across sites, and enhanced the accuracy of data collection. Auditors were required to confirm the presence and, if confirmed, the date of tests identified by the computer program. They were also asked to carefully search the electronic and paper records of patients for whom there was no electronic record of colonoscopy or sigmoidoscopy.

Table 2: Pre-coded indication categories used for medical records audits and their primary classifications

1. **Definite diagnostic**
   a. Diagnostic for positive FIT/FOBT
   b. Diagnostic for sigmoidoscopy that found polyp/mass, or other abnormalities
   c. Diagnostic for abnormal barium enema or imaging exam (X-Ray, CT, MRI, UTS)
   d. Metastatic cancer work-up, suspected or confirmed
   e. Therapeutic or treatment of a condition
2. **Probable diagnostic**
   a. Anemia, iron deficiency type
   b. Other gastroinstinal bleeding, melena, black tarry stools, upper GI bleeding, or maroon stool
   c. Abnormal weight loss
   d. Rectal, bright red blood per rectum, melena, blood on stool or toilet paper
   e. Suspected colon cancer
   f. Abdominal mass
   g. Colitis other than IBD
   h. Other GI bleeding
3. **Possible diagnostic**
   a. Constipation
   b. Change in bowel habits
   c. Other types of anemia
   d. Abdominal pain [anywhere in the abdomen]
   e. Diarrhea, loose or watery stools
   f. Irritable bowel syndrome
   g. Unintentional weight loss
   h. Rectal pain
4. **High-risk**
   a. Crohn's or ulcerative colitis, IBD
   b. Family history of colon cancer
   c. Familial adenomatous polyposis or LYNCH
   d. Other familial syndromes
5. **Surveillance**
   a. History of CRC
   b. Colon/rectal polyps or adenomas
6. **Definite screening**
   a. Screening (routine)
   b. FOBT/FIT that was collected at home, was mailed or given to patient to take home

Collection of Data on Reasons or Indications for CRC tests

We determined exposures to and reasons for colonoscopies that were performed during the 10-year period prior to the reference date. We expanded the look-back interval to 15 years when necessary to obtain information about the initiating test for subsequent surveillance examinations to re-construct a full history of testing.

For each test found in the medical records, the auditors collected the reasons, separately, from each of three data sources (progress notes, referral note, and procedure report) according to pre-coded categories (see **Table 2**). Auditors also collected reason-related information in free-text format. We defined the progress notes as all parts of the medical records other than the referral note and procedure-related documentation.

We collected data electronic databases and by chart audit on the receipt and results of colonoscopy, sigmoidoscopy, double contrast barium enema, CT colonography and FOBT during the 10-year period prior to the reference date, which made it possible for us to assign the indications for the tests. Detailed data on fecal occult blood test (FOBT) including fecal immunochemical tests were collected including whether a test was positive or negative, and, for positive results, the type of diagnostic test received. After a series of pilots, we found that the details of reasons for FOBT were not consistently recorded in the medical records. The process of ordering FOBTs was different than other tests – there is no referral and no procedure reports. FOBT results were in laboratory data bases and when sent centrally through outreach, there was no corresponding information in the medical records analogous to other tests. However, diagnostic tests were fairly apparent either

because the reason for the diagnostic FOBT was given such as for monitoring bleeding in a patient with gastrointestinal bleeding, when found, were coded using the same coding approach.

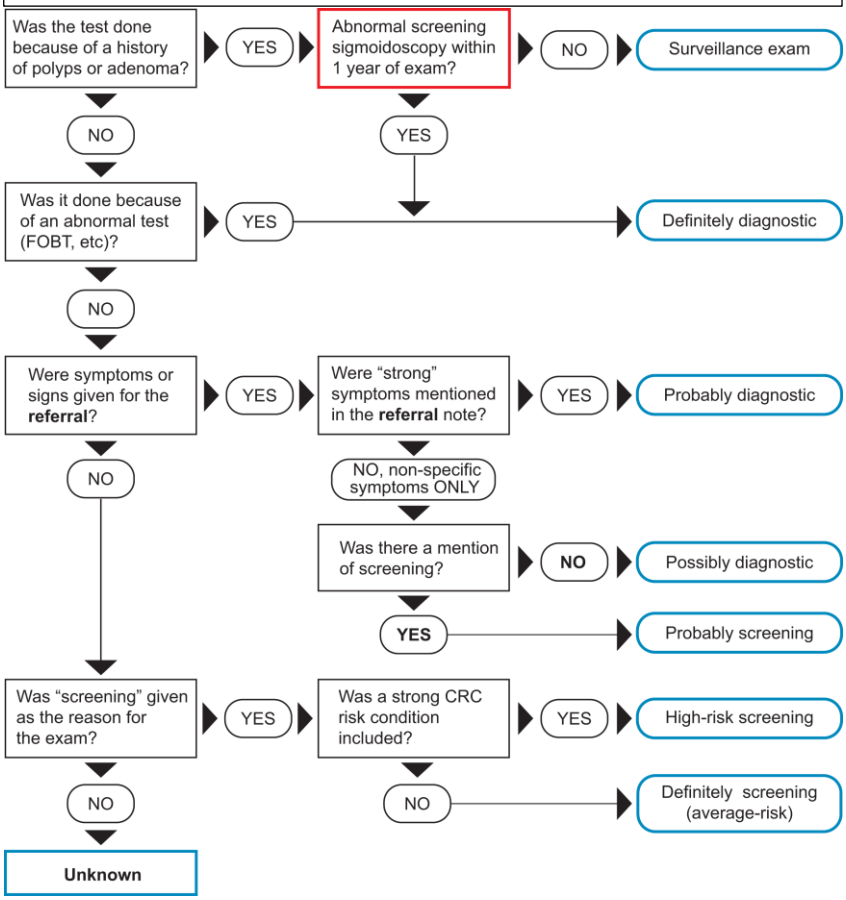
Using these data, we applied a computer-based decision algorithm to classify the indication for each colonoscopy test into one of eight mutually exclusive categories: 1) surveillance, 2) 'definite' diagnostic, 3) 'probable' diagnostic, 4) 'possible' diagnostic, 5) 'probable' screening, 6) 'definite' average-risk screening, 8) 'probable high-risk' screening, 9) 'high-risk' screening, or 10) unknown (**Figure 1**).

A colonoscopy was classified as surveillance if performed for follow-up of previously detected polyps; 'definite' diagnostic if used to work-up a positive FOBT, abnormal sigmoidoscopy, a mass or other abnormal finding such as on imaging; 'probable' diagnostic if the medical records noted clinical conditions that were deemed to represent a high pretest probability for CRC such as rectal bleeding; 'possible' diagnostic if the only documented reasons were non-specific medical conditions such as diarrhea or abdominal pain; or 'probable' screening if both non-specific symptoms and screening were recorded. The indication was considered 'high-risk' screening if the test was performed for screening and the patient had inflammatory bowel disease or a strong family history. The indication was considered 'definite' average-risk screening if screening was recorded and none of the CRC conditions or risk factors noted above were recorded. The indication was considered unknown if the reason was not specifically documented. FOBT/FIT recorded as being performed at home, done in the context of preventive care visit, because of patient preference, or if no specific reason was recorded were classified as screening.

The computer algorithm assigned each test a single indication irrespective of the number of reasons (or missing data) recorded by chart auditors (see **Figure 2**). Sometimes these sources agreed with each other and indication could be classified with a simple algorithm. However, stated reasons for colonoscopy sometimes differed among the three sources.

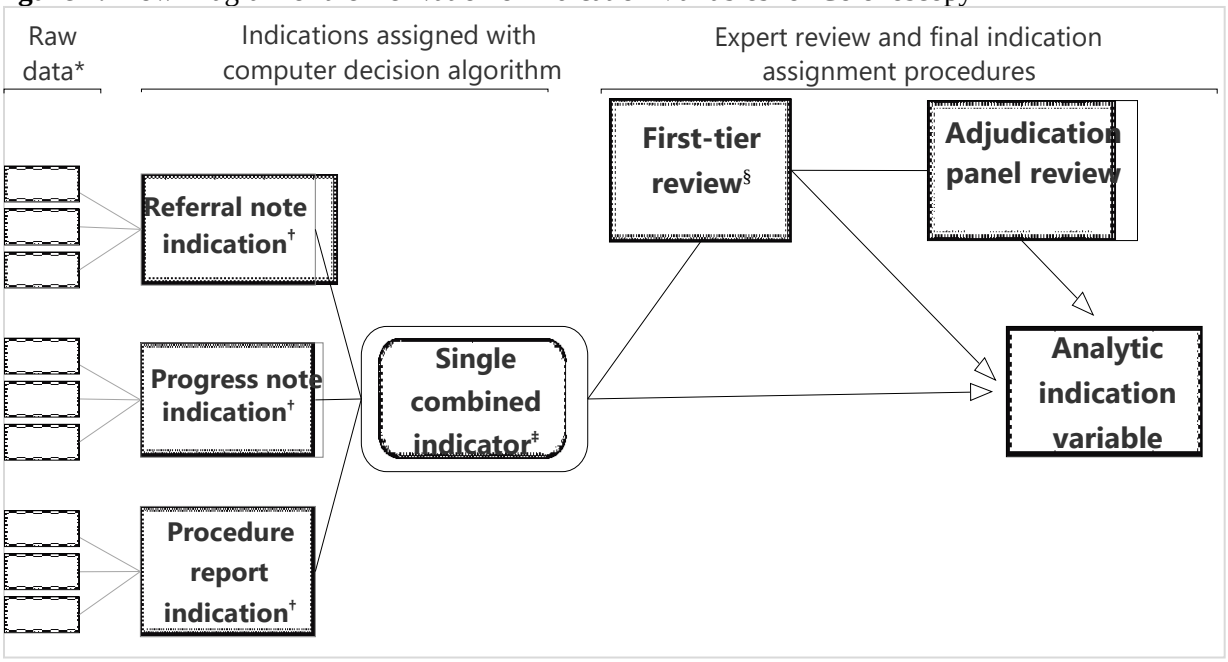
When a clear determination of the reason for colonoscopy could not be made directly from the medical records or coded data, the data on the test was subjected to review. Tests reviewed included those that could be assigned more than one indication, or indication was unknown in all data sources. Discordance due to classification as 'definite' diagnostic versus 'probable' diagnostic was considered non-substantive. Because non-coded information was not included in the algorithm, we also reviewed all tests that had data in relevant free-text variables. All tests classified as 'high-risk' screening, surveillance, or had

Figure 1: Decision Rule for Assigning Indication from Coded Data



rectal bleeding documented were adjudicated. This review was conducted in two steps, the first to determine whether or not a particular test required a second-tier a panel review. Once a test was selected for review, all the CRC tests of the particular patient (except FOBTs) were evaluated.

Figure 2: Flow Diagram of the Derivation of Indication Variables for Colonoscopy



*Up to three coded reasons were recorded from each data source during the chart audit
†One indication variable was derived for each data source.
‡This is a single indication assigned to each test combining all coded data collected on each test during chart audit using the computer algorithm shown in Figure 1. It combined data from referral note, progress note and procedure report.
§A test was selected for review if more than one indication could be assigned or was unknown in all data sources, or relevant free-text data.

The goal of adjudication was to derive a single indication for each selected test after careful review of all available data. Adjudications by three investigators were conducted blinded to study site, and whether a particular test was the reason a patient was selected for adjudication. In assigning indication, the adjudicators considered clinical conditions that were documented as reasons for CRC testing, in part, by grouping them as strong versus non-specific based on the pretest probability of CRC associated with each condition (**Table 3**).[9,10] Because gastrointestinal conditions are highly prevalent but are individually not highly predictive for CRC diagnosis[11-13], the grouping of clinical conditions was largely based on panel consensus. Disagreements among committee members on indication assignment were resolved using a majority rule. However, tests classified by different committee members as both screening and diagnostic were discussed until a consensus was reached.

Patients with multiple colonoscopies during the observation period were assigned a single patient-level indication in a temporally hierarchical manner by considering both the indication and the sequence of colonoscopies in relation to the reference date. We selected the 'definite' screening test that was farthest from the reference date first; if none, then we used the farthest 'probable' screening colonoscopy; and if none, then 'possible' diagnostic, 'probable' diagnostic and finally 'definite' diagnostic, in that

order. The indication was classified as surveillance if the first colonoscopy was for surveillance and there was no subsequent screening test.

Table 3: Classification of clinical conditions for colonoscopy indication adjudication according to pretest probability of colorectal cancer diagnosis

Strong symptoms (strongly associated)	**Non-specific symptoms**
Acute bowel obstruction	Weight loss
Perforation	Abdominal pain or fullness
Abdominal mass	Constipation
Massive lower GI bleeding	Change in bowel habits, diarrhea, or altered stools
Bright red blood per rectum	Rectal pain
Iron deficiency anemia	Fatigue
Elevated CEA	Other anemias
Suspected IBD	Other non-specific abdominal symptoms
	Nausea and vomiting, anorexia

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