**APPENDIX**

**Age-specific rates and time-courses of gastrointestinal and non-gastrointestinal complications associated with screening/surveillance colonoscopy**

Uri Ladabaum, MD, MS1; Ajitha Mannalithara, PhD1; Manisha Desai, PhD2; Maanek Sehgal3;

Gurkirpal Singh, MD1,4

1. Division of Gastroenterology and Hepatology, Stanford University School of Medicine, Stanford, CA, United States; 2. Quantitative Sciences Unit, Department of Medicine, Stanford University School of Medicine, Stanford, CA, United States; 3. University of California, Los Angeles, CA, Unites States; 4. Institute of Clinical Outcomes Research and Education, Woodside, CA, United States

**Guarantor**/contact: Uri Ladabaum, MD, MS

Division of Gastroenterology and Hepatology  
Stanford University School of Medicine

430 Broadway Street; Pavilion C, 3rd Floor C-326     
Redwood City, CA 94063-6341

650-725-2850; Assistant 650-725-5135

E-mail: [uri.ladabaum@stanford.edu](mailto:uri.ladabaum@stanford.edu)

**METHODS**

**Data Sources, Study Population and the Colonoscopy Cohort**

California’s SASD has 21 available CPT fields, Florida’s SASD has 10 CPT fields in 2009 and 35 CPT fields in 2010-2015, and New York’s SASD has 20 CPT fields in 2009-2011 and 50 CPT fields in 2012-2015. We used all available CPT fields to identify colonoscopies (Appendix Table 1).

For each colonoscopy, we determined the CCS category using the DXCCS1 field, which is based on the primary ICD-9-CM code. We mapped CCS categories into groups of CCS categories consistent with screening or surveillance, as we have previously published (1, 2): CCS 258 (“other screening for suspected conditions”), CCS 256 (“medical examination/ evaluation”), CCS 47 (“other and unspecified benign neoplasm,” which includes colorectal polyps), and CCS categories reflecting primary care but not gastrointestinal diagnoses, reasoning that these reflect preventive care (Appendix Table 2).

Patient demographics consisting of age, gender, race, median household income by state quartile for patient ZIP Code, patient location and number of chronic conditions were identified from the SASD of each state. The Charlson-Deyo comorbidity index was calculated based on the encounters in the 365 days preceding the colonoscopy including the day of the procedure, with ICD-9-CM diagnosis and CPT procedure codes (Appendix Table 3) from the SASD, SEDD and SID of each state.

**Adverse Events**

We defined adverse events as emergency department visits or hospital admissions within 180 days preceding or following the colonoscopy. We identified adverse events based on ICD-9-CM codes (Appendix Table 4) using all the diagnosis fields available. California’s SEDD and SID have 25 diagnosis fields, Florida’s SEDD and SID have 31 diagnosis fields, and New York’s SEDD and SID have 15 diagnosis fields in 2009-2010 and 25 diagnosis fields in 2011-2015.

**Statistical Analysis**

For each of the 10 adverse event types, an analysis dataset was first created separately for each state, with indicator variables to identify the days of encounters with an adverse event in relation to the day of colonoscopy. Next, the 3 datasets for a given adverse event type were merged. Event rates per day per million colonoscopies in the 180 days before through 180 days after colonoscopy were calculated in each merged dataset. Analyses were performed for the entire population, and also stratified by age groups of age ≥65 years and <65 years.

*Adverse Events Time-Course: Changepoint Analyses*

A wide variety of changepoint algorithms have been developed and applied in publications across scientific fields (3). We applied the pruned exact linear time (PELT) search algorithm (4) and the cpt.meanvar function available in the changepoint package to identify periods with different means and variances of adverse event rates per million. The PELT method determines the optimal positioning and number of change points based on a penalized likelihood ratio test to avoid overfitting. The choice of appropriate penalty depends on factors such as the number of changes and length of segments, which are unknown prior to analysis. The “Changepoints for a Range of Penalties (CROPS)” option was used to generate a plot for each adverse event type with the number of change points on the x-axis and the associated penalty value on the y-axis. Based on this plot, a user can consider a smaller range of penalties to determine the optimal number of change points, using the premise that once all the true changes have been identified, the addition of false changes will not improve the model fit. The authors of the changepoint package recommend using clinical/expert judgement to decide on the location and number of change points (5). We inspected the change point graphs generated with a range of penalties, and chose the optimal number of change points for each adverse event type based on the independent judgement of the best fit by two of the authors (UL and AM), with disagreement resolved by discussion. It was decided *a priori* that when short segments with slight differences in event rates were identified next to longer segments, these shorter segments would be combined with the longer segments based on judgement, requiring fewer change points, and a lower penalty, to characterize the event rates over time.

*Background Adverse Event Rates and Excess Adverse Events Attributable to Colonoscopy*

Once the time points at which event rates changed were determined, the number of events in each segment post-colonoscopy were calculated, and mean event rates per day per segment, and the 95% confidence intervals (CI), were estimated using a Poisson regression model in the SAS procedure GENMOD, with an offset equal to the natural logarithm of the number of patient days in each of the risk periods, and no covariates.

The event rate per day of the last segment identified in the post-colonoscopy period was considered to be the steady state rate reflective of the background event rate. For each adverse event, change point analysis could identify periods of initial excess risk, and one or more periods of delayed excess risk, before reaching the background, steady state rate. For each individual period of elevated risk vs. background, and for the aggregated periods of elevated risk, the excess event rates were calculated by subtracting the background event rate from each time segment’s event rate. Excess events per million persons were calculated by multiplying the excess event rate by the number of days in a given segment, and the 95% CI of excess events were estimated using a Poisson regression model with an offset of natural logarithm of number of patients.

The ratio of observed events relative to the expected based on the background rate was calculated for days 0-7, 0-30 and 0-60, which are common periods for quality audit. The observed events were calculated as the sum of the event rate per day times the days in a given risk period. Expected events were calculated by multiplying the background event rate by the total number of days in the 0-7, 0-30 and 0-60 day periods. The 95% CI for each ratio was estimated using the confidence interval formula for rate ratios (6).

**References**

1. Ladabaum U, Levin Z, Mannalithara A, et al. Colorectal testing utilization and payments in a large cohort of commercially insured US adults. Am J Gastroenterol 2014;109:1513-25.

2. Wang L, Mannalithara A, Singh G, et al. Low Rates of Gastrointestinal and Non-Gastrointestinal Complications for Screening or Surveillance Colonoscopies in a Population-Based Study. Gastroenterology 2018;154:540-555.e8.

3. Killick R, Nam CFH, Aston JAD, et al. Changepoint.info: The changepoint repository. 2012. Accessed at <http://www.changepoint.info/publications.html> on January 29, 2021.

4. Killick R, Fearnhead P, Eckley IA. Optimal Detection of Changepoints With a Linear Computational Cost Journal of the American Statistical Association 2012;107:1590-1598.

5. Hocking TD, Killick R. Introduction to optimal change point detection algorithms. useR! International R User 2017 Conference 2017.

6. Rothman KJ, Greenland S, Lash TL. Modern epidemiology. Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins; 2008.

Appendix Table 1. CPT Codes for Colonoscopy

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | | |  |  |  |  |  |
| Diagnostic | 44388 | 45378 | G0105\* | G0121\* |  |  |  |
| Biopsy | 44389 | 45380 |  |  |  |  |  |
| Intervention | 44390 | 44391 | 44392 | 44393 | 44394 | 44397 | 45379 |
| 45381 | 45382 | 45383 | 45384 | 45385 | 45386 | 45387 |
| \*G codes are not included in California’s State Ambulatory Surgery and Services Databases (SASD) | | | | | | | |

|  |
| --- |
| Appendix Table 2. CCS Categories for Screening and Surveillance Colonoscopy |

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  |  |  |  |  |
| Medical examination/evaluation -- presumed screening | 256 |  |  |  |
| Other primary care/non-GI specialty problems -- possible screening | 1-5 | 7-11 | 19-46 | 48-58 |
| 60-119 | 121-134 | 136-137 | 143 |
| 156-249 | 252-255 | 257 | 650-670 |
| Screening specifically | 258 |  |  |  |
| Includes colorectal polyps -- presumed screening or surveillance | 47 |  |  |  |

Appendix Table 3. Comorbidities based on Charlson-Deyo Scoring

|  |  |  |
| --- | --- | --- |
| Complications | Complications (Specified) | ICD-9 |
| Myocardial infarction | Acute myocardial infarction | 410-410.9 |
| Old myocardial infarction | 412 |
| Congestive heart failure | Heart failure | 428- 428.9 |
| Peripheral vascular disease | Peripheral Vascular Disease Unspecified | 443.9 |
| Aortic aneurysm and dissection | 441.0- 441.9 |
| Gangrene | 785.4 |
| Blood vessel replaced by prosthesis | V43.4 |
| Angiectomy\* | 38.48\* |
| 35141Ɨ |
| 35142Ɨ |
| 35151Ɨ |
| 35152Ɨ |
| Cerebrovascular | Cerebrovascular Disease | 430-438.9 |
| Dementia | Dementia | 290-290.9 |
| Chronic pulmonary disease | Chronic obstructive pulmonary disease | 490-496 |
| Pneumoconioses | 500-505 |
| Chronic respiratory conditions due to fumes and vapors | 506.4 |
| Rheumatologic disease | Systemic lupus erythematosus | 710.0 |
| Systemic sclerosis | 710.1 |
| polymyositis | 710.4 |
| adult rheumatoid arthritis | 714.0-714.2 |
| Rheumatoid lung | 714.81 |
| polymyalgia rheumatica | 725 |
| Peptic ulcer disease | gastric, duodenal, and gastrojejunal ulcers | 531- 534.9 |
| Mild liver disease | alcoholic cirrhosis | 571.2 |
| cirrhosis without mention of alcohol | 571.5 |
| biliary cirrhosis | 571.6 |
| chronic hepatitis | 571.4-571.49 |
| Diabetes | Diabetes with or without acute metabolic disturbances | 250-250.3 |
| Diabetes with peripheral circulatory disorders | 250.7 |
| Diabetes with renal, opthalmic, or neurologic manifestations | 250.4-250.6 |
| Hemiplegia or paraplegia | paraplegia | 344.1 |
| hemiplegia | 342 -342.9 |
| Renal disease | Chronic glomerulonephritis | 582-582.9 |
| nephritis and nephropathy | 583-583.7 |
| chronic renal failure | 585 |
| renal failure, unspecified | 586 |
| disorders resulting from impaired renal function | 588-588.9 |
| Any malignancy | malignant neoplasms | 140-172.9 |
| malignant neoplasms | 174-195.8 |
| leukemia and lymphoma | 200-208.9 |
| Liver disease | hepatic coma, portal HTN, other sequelae of chronic liver disease | 572.2-572.8, 573.5 |
| esophageal varices | 456.0-456.21 |
| secondary malignant neoplasm of lymph nodes and other organs | 196-199.1, 209.71 |
| AIDS | AIDS | 042-044.98 |
| \*Because procedure codes were available in CPT codes only, we mapped the ICD-9 procedure codes into CPT instead | | |
| Ɨ ICD-9 to CPT mapping for ICD-9 Procedure | | |

Appendix Table 4. ICD-9 Codes for Complications

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Gastrointestinal | Lower gastrointestinal hemorrhage | 569.3 | 578.1 | 578.9 | 998.1x |  |  |  |  |  |
| Gastrointestinal Perforation | 569.83 | 998.2 | E870.8 | E870.9 |  |  |  |  |  |
| Cardiac | Acute MI | 410.x |  |  |  |  |  |  |  |  |
| Congestive Heart Failure | 398.91 | 428 | 428.0 | 428.1 | 428.2x | 428.3x | 428.4x | 428.9 | 402.01 |
| 402.11 | 402.91 | 404.01 | 404.11 | 404.91 | 404.03 | 404.1 | 404.9 | 415.0 |
| Cardiac Dysrhythmias | 427.x | 785.0 | 785.1 | 997.1 | V12.53 |  |  |  |  |
| Cerebrovascular | Ischemic Stroke | 346.00 | 346.01 | 346.6x | 433.x | 434.x | 436 | 437.x | 438.x |  |
| Hemorrhagic Stroke | 430 | 431 | 432.0 | 432.1 | 432.9 |  |  |  |  |
| TIA | 435.x | V12.54 | V12.59 |  |  |  |  |  |  |
| Pulmonary | Pneumonia | 507 | 507.0 | 997.3 | 997.32 | 997.39 | 486 |  |  |  |

Appendix Figure 1. Change-point analyses of the time-courses of adverse events peri-colonoscopy

Appendix Figure 2. Time-courses of adverse events for the population overall and at ages <65 vs ≥65 years

Appendix Figure 3. Change-point analyses of the time-courses of adverse events peri-colonoscopy, ages 45 to <55 years

Appendix Figure 4. Change-point analyses of the time-courses of adverse events peri-colonoscopy, ages 55 to <65 years

Appendix Figure 5. Change-point analyses of the time-courses of adverse events peri-colonoscopy, ages 65 to <75 years

Appendix Figure 6. Change-point analyses of the time-courses of adverse events peri-colonoscopy, ages ≥75 years