Effectiveness of Screening Colonoscopy to Prevent Colorectal Cancer Among Medicare Beneficiaries Aged 70 to 79 Years
A Prospective Observational Study
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Background: No randomized, controlled trials of screening colonoscopy have been completed, and ongoing trials exclude persons aged 75 years or older. The Medicare program, however, reimburses screening colonoscopy without an upper age limit.

Objective: To evaluate the effectiveness and safety of screening colonoscopy to prevent colorectal cancer (CRC) in persons aged 70 to 74 and those aged 75 to 79 years.

Design: Large-scale, population-based, prospective study. The observational data were used to emulate a target trial with 2 groups: colonoscopy screening and no screening.

Setting: United States.

Participants: 1 355 692 Medicare beneficiaries (2004 to 2012) aged 70 to 79 years at average risk for CRC who used Medicare preventive services and had no previous diagnostic or surveillance colonoscopies in the past 5 years.

Measurements: 8-year risk for CRC and 30-day risk for adverse events.

Results: In beneficiaries aged 70 to 74 years, the 8-year risk for CRC was 2.19% (95% CI, 2.00% to 2.37%) in the screening colonoscopy group and 2.62% (CI, 2.56% to 2.67%) in the no-screening group (absolute risk difference, −0.42% [CI, −0.24% to −0.63%]). Among those aged 75 to 79 years, the 8-year risk for CRC was 2.84% (CI, 2.54% to 3.13%) in the screening colonoscopy group and 2.97% (CI, 2.92% to 3.03%) in the no-screening group (risk difference, −0.14% [CI, −0.41 to 0.16]). The excess 30-day risk for any adverse event in the colonoscopy group was 5.6 events per 1000 individuals (CI, 4.4 to 6.8) in the 70- to 74-year age group and 10.3 per 1000 (CI, 8.6 to 11.1) in the 75- to 79-year age group.

Limitation: CRC-specific mortality was not available, but CRC incidence and stage were studied at diagnosis.

Conclusion: Screening colonoscopy may have had a modest benefit in preventing CRC in beneficiaries aged 70 to 74 years and a smaller benefit in older beneficiaries. The risk for adverse events was low but greater among older persons.

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E ach year in the United States, 132 000 new cases of colorectal cancer (CRC) are diagnosed and 50 000 CRC-related deaths occur (1). Colonoscopy is expected to reduce CRC mortality by identifying asymptomatic, curable cancer, and decrease CRC incidence by detecting and removing precancerous polyps. However, despite its widespread use in the United States (2), no randomized, controlled trials of screening colonoscopy have been completed. The findings of 3 ongoing randomized trials (3–5) will be not be available before the mid-2020s. Previously conducted randomized trials showed the effectiveness of other screening methods: Periodic fecal occult blood testing (FOBT) reduces CRC mortality (6–10), and sigmoidoscopy (performed once [11–14] or twice within 3 to 5 years [15]) reduces both CRC incidence and CRC mortality (16).

Colonoscopy is an invasive, resource-intensive procedure that requires a thorough large-bowel cleansing, and often patient sedation, and carries a risk for complications, such as bowel perforation. Establishing the effectiveness and safety of colonoscopy is important because less burdensome screening methods (FOBT and sigmoidoscopy) are available. Currently, the U.S. Preventive Services Task Force (USPSTF) advises routine CRC screening with any method for persons aged 50 through 75 years at average CRC risk and recommends that screening decisions be individualized for those aged 76 to 85 (17). Other guidelines recommend colonoscopy screening with no upper age limit (18, 19). None of the ongoing colonoscopy trials include persons older than 75 years (only 1 trial has participants aged 70 or older [Supplement Table 1, available at www.annals.org]); however, healthy persons older than 75 years may live long enough to benefit from CRC screening.

For more than a decade, the Centers for Medicare & Medicaid Services has reimbursed screening colonoscopies with no upper age limit. We used the extensive experience of Medicare beneficiaries to estimate the effectiveness of screening colonoscopy in preventing CRC among elderly persons with no recent history of colonoscopy, CRC, or adenomas. We studied beneficiaries aged 70 to 74 and those aged 75 to 79 years separately.

Methods
Study Data
For a random 20% sample of Medicare beneficiaries from 1999 to 2012, we extracted information on
demographic characteristics (age, sex, race, original reason for Medicare entitlement, and U.S. Census Bureau division), enrollment characteristics (reason for entitlement and enrollment type and period), and Medicare Chronic Conditions Data Warehouse condition categories (including CRC diagnosis) from the denominator files. We obtained data regarding colonoscopies and FOBT from outpatient standard analytic files, inpatient hospital claims, and carrier files (to identify physician services). We used the outpatient and carrier files to extract information on the use of preventive services and wellness visits. We computed a combined comorbidity score (20) and used the procedure codes on the colonoscopy claim form, along with the presence of a bill for the pathologic examination of a colorectal polyp or biopsy within 7 days of the procedure, to determine whether the colonoscopy included polypectomy (21). We used the Surveillance, Epidemiology, and End Results (SEER)-Medicare linked data set (22) (from 1999 to 2009) to evaluate CRC stage (for details, see the Supplement, available at www.annals.org).

Eligibility Criteria
Our analyses included beneficiaries aged 70 to 79 years with no history of CRC who in the 5 years before baseline (to be discussed later), had no history of adenoma, inflammatory bowel disease, or colectomy and had not had a colonoscopy, sigmoidoscopy, or FOBT. These eligibility criteria were as similar as possible to those of the ongoing colonoscopy trials (3–5) (Supplement Table 1), which generally target an average-risk population.

To ensure complete capture of health information, we included only beneficiaries enrolled in Medicare parts A and B, but not in Medicare Advantage, during the preceding 5 years. To reduce the probability of including beneficiaries who had a colonoscopy for reasons other than screening, we excluded those who had abdominal computed tomography; a barium enema; or a diagnosis (23) of anemia, gastrointestinal bleeding, constipation, diarrhea, abdominal pain, irritable bowel syndrome, bowel habit change, weight loss, ischemic bowel disease, or diverticular disease in the previous 6 months and included only health-conscious beneficiaries who had received at least 2 of the 3 preventive services offered yearly by Medicare for the average population (annual wellness visit, influenza vaccine, and breast or prostate cancer screening) in the previous 2 years (24). Although the effectiveness of some of these services (such as prostate-specific antigen–based cancer screening) is questionable, we used them only as surrogates for health consciousness. We relaxed these constraints in sensitivity analyses (Supplement).

Treatment Groups and Follow-up
To emulate a trial of screening colonoscopy and CRC incidence in the elderly population, we exploited the experiences of Medicare beneficiaries after their 70th birthday. Specifically, we identified all 70-year-old beneficiaries who met the eligibility criteria on the day they turned 70 (baseline) and followed them until CRC diagnosis, death, violation of Medicare enrollment criteria, or December 2012, whichever occurred first. At baseline, we classified beneficiaries into the screening colonoscopy group if they received a colonoscopy in the next 7 days and into the no-screening group otherwise. To reduce computational time, we used a 5% random subsample of those in the no-screening group.

Next, using an approach previously described (25–29), we emulated a second trial with baseline a week after that of the first trial, and so on for every week while an individual was aged 70 years. At the baseline week of each of the 52 sequential trials, eligibility criteria were reassessed. Beneficiaries who stopped meeting the eligibility criteria (for example, because of a recent colonoscopy) were excluded from that trial; all others were reclassified into the 2 groups according to whether they had a colonoscopy during that week. We repeated the entire process for beneficiaries aged 71 to 79, resulting in a total of 520 emulated trials. Each beneficiary could contribute as an eligible individual to as many trials as he or she was eligible for between the week the beneficiary turned age 70 until the week he or she turned 80. Emulation of sequential trials is a valid and efficient procedure if participants meet eligibility criteria at several time points (25, 30).

To check the validity of our method, we conducted analyses with an FOBT group to assess the performance of our observational estimates against the published estimates from the FOBT randomized trials. We did not evaluate sigmoidoscopy because it is used infrequently in the Medicare population (Supplement Figure 1, available at www.annals.org).

Outcomes
The primary outcome was CRC incidence. We also identified all adverse events occurring within 30 days after baseline that were severe enough to require an emergency department visit or hospitalization. We classified adverse events as serious gastrointestinal (perforation, gastrointestinal bleeding requiring transfusion), other gastrointestinal (gastrointestinal bleeding not requiring transfusion, paralytic ileus, nausea, vomiting and dehydration, abdominal pain), or cardiovascular (myocardial infarction or angina, arrhythmias, congestive heart failure, cardiac or respiratory arrest, syncope, hypotension or shock) events (21). We evaluated tumor stage among diagnosed CRC cases.

Statistical Analysis
We pooled the individuals across all emulated trials and analyzed the data by age group (70 to 74 and 75 to 79 years). We estimated curves for CRC cumulative incidence, both unadjusted and standardized to the baseline characteristics shown in Table 1: sex, race, age (linear and quadratic terms), original reason for entitlement, comprehensive preventive evaluation in the previous 2 years, use of 3 preventive services in the previous 2 years, U.S. Census Bureau division, combined comorbidity score, presence of each Chronic Condition Warehouse condition, and calendar month. As in randomized trials, these curves estimate risks under hypo-
thetical scenarios in which individuals do not die from causes other than CRC (16).

To estimate the standardized curves, we fit a pooled logistic regression model for monthly CRC risk (31, 32) that included an indicator for the screening group, a flexible function of months of follow-up (linear, quadratic, and exponentially decreasing term), product terms for group and month, and the trial-specific baseline covariates (33) (for a detailed explanation, see the Appendix, available at www.annals.org).

We also estimated the 30-day risk for adverse events standardized by age, sex, and comorbidity.
score. We used a nonparametric bootstrap based on 500 individual-level resamplings to compute 95% CIs. All analyses were done using SAS 9.4 (SAS Institute). The Partners Human Research Committee and the Institutional Review Board at Harvard T.H. Chan School of Public Health approved our research.

Role of the Funding Source
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RESULTS

Of 3,586,046 Medicare beneficiaries reaching age 70 between 2004 and 2012, 674,306 had no previous CRC; were asymptomatic; and had no history of adenoma, inflammatory bowel disease, colectomy, or screening within the previous 5 years. Of this group, 136,310 were users of Medicare annual preventive services and thus eligible for our analyses. On average, each of these beneficiaries was eligible for 49.7 of the 52 emulated trials starting each week during the following year. Random selection of 5% of individuals in the no-screening group and pooling over all sequential trials resulted in 348,025 (nonunique) individuals: 10,034 assigned to the screening colonoscopy and 337,991 to the no-screening group (Figure 1). Supplement Figure 2 (available at www.annals.org) shows the selection and assignment of beneficiaries aged 71 to 79 years. After pooling was performed over all age groups, 78,065 individuals were assigned to the screening colonoscopy group and 3,390,836 to the no-screening group. Median follow-up was 40 months (interquartile range, 18 to 67 months).

Although individual baseline characteristics were similar in both groups, the colonoscopy group had a lower proportion of some chronic diseases (Alzheimer disease and related disorders, chronic heart failure, chronic obstructive pulmonary disease, diabetes, ischemic heart disease, and stroke), a higher proportion of preventive services use in the 2 years before inclusion, and a higher proportion of some diagnoses (cataracts, benign prostatic hyperplasia, and hyperlipidemia) that might reflect more use of health care services (Table 1).

Effectiveness of Screening

During follow-up, 1,282 individuals in the colonoscopy group (685 aged 70 to 74 and 597 aged 75 to 79 years) and 45,530 in the no-screening group (21,954 aged 70 to 74 and 23,576 aged 75 to 79 years) received a diagnosis of CRC.

Because of prevalent cancer detected at screening, the risk for CRC at baseline was higher in the colonoscopy group (0.89% among individuals aged 70 to 74 and 1.14% in those aged 75 to 79 years) than the no-screening group (0.03% in both age groups), as expected. The curves crossed about after 4.5 years for those aged 70 to 74 and 5.5 years for those aged 75 to 79 years, when the CRC risk became greater in the no-screening group (Figure 2). Adjustment for baseline covariates did not materially change the curves (Supplement Figure 3, available at www.annals.org).

Among individuals aged 70 to 74 years, the standardized 8-year risk for CRC was 2.19% (95% CI, 2.00% to 2.37%) for those in the screening colonoscopy screening and 2.62% (CI, 2.56% to 2.67%) for those in the no-screening group (risk difference, −0.42% [CI, −0.24% to −0.63%]). Among individuals aged 75 to 79 years, it was 2.84% (CI, 2.54% to 3.13%) for those in the screening colonoscopy screening and 2.97% (CI, 2.92% to 3.03%) for those in the no-screening group (risk difference, −0.14% [CI, −0.41% to 0.16%]). Sensitivity

Table 1. Effect of colonoscopy screening on selected outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Colonoscopy group</th>
<th>No-screening group</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRC cases: 122 (unique)</td>
<td>86</td>
<td>3906 (1505 unique)</td>
</tr>
<tr>
<td>Person-years of follow-up: 37 705</td>
<td>1 460 496</td>
<td></td>
</tr>
<tr>
<td>Colorectal cancer (n = 10 034 individuals)</td>
<td>29 973</td>
<td>19 299</td>
</tr>
<tr>
<td>Adenoma or benign lesion (n = 312 933)</td>
<td>19 299</td>
<td>11 988</td>
</tr>
<tr>
<td>Inflammatory bowel disease (n = 19 294)</td>
<td>11 988</td>
<td></td>
</tr>
<tr>
<td>Colonoscopy (n = 562 493)</td>
<td>562 493</td>
<td>348 025</td>
</tr>
<tr>
<td>Sigmoidoscopy (n = 21 921)</td>
<td>21 921</td>
<td>337 991</td>
</tr>
<tr>
<td>FOBT (n = 420 637)</td>
<td>420 637</td>
<td>3 390 836</td>
</tr>
<tr>
<td>Barium enema (n = 3461)</td>
<td>3461</td>
<td></td>
</tr>
</tbody>
</table>

FOBT = fecal occult blood testing; GI = gastrointestinal.

* 5% random sampling applied to no-screening candidates.

Figure 1. Flow into colonoscopy screening groups of Medicare beneficiaries aged 70 years, 2004–2012.
analyses with different cutoff points for age (70 to 73 vs. 74 to 79 years and 70 to 75 vs. 76 to 79 years) did not materially change the results. A sensitivity analysis excluding enrollment from 2010 to 2012 (median follow-up, 58 months) yielded similar results: The risk difference was −0.43% (CI, −0.65% to −0.21%) in the individuals aged 70 to 74 and −0.14% (CI, −0.45% to 0.18%) in those aged 75 to 79 years. Results did not vary by calendar time (Supplement Figure 4, available at www.annals.org).

In the subgroup of CRC cases linked to the SEER registry, 1102 cases were diagnosed at screening colonoscopy and 24,969 without screening. The proportion of stage 0 CRC cases was 14.3% for screening colonoscopy versus 8.1% for no screening; stage I, 37.8% versus 24.6%; stage II, 19.1% versus 26.7%; stage III, 22.1% versus 24.0%; and stage IV, 6.7% versus 16.7%, respectively. Results were similar in both age groups (Supplement Table 2, available at www.annals.org).

We also evaluated colonoscopy-based surveillance after the initial screening. The use of colonoscopy peaked at years 3 and 5 among individuals who had a polyp removed during screening colonoscopy and was very low until year 5 among those in whom the screening did not reveal a polyp. These patterns were present in both age groups (Supplement Figure 5, available at www.annals.org).

In analyses comparing FOBT with no screening, the CRC risk was always greater in the FOBT than the no-screening group because of the detection of some (but not all) prevalent cancers at baseline (Supplement Table 3, available at www.annals.org, and Supplement Figure 3), as expected. Individuals in the FOBT group frequently received a colonoscopy shortly after inclusion in the study, presumably because of a positive FOBT result (Supplement Figure 5).

**Safety of Screening**

Compared with the no-screening group, the excess 30-day risk for any adverse event requiring hospitalization or an emergency department visit in the colonoscopy group was 5.6 adverse events per 1000 individuals (CI, 4.4 to 6.8) in the 70- to 74-year and 10.3 per 1000 (CI, 8.6 to 11.1) in the 75- to 79-year age group.

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**Figure 2.** Cumulative incidence and incidence rates of CRC, by screening and age group, in Medicare beneficiaries, 2004–2012.
The increased risk for each adverse event was low (fewer than 2 cases per 1000), except for arrhythmia, which had an excess risk of 2.4 cases per 1000 (CI, 1.6 to 3.2) in the 70- to 74-year and 5.5 per 1000 (CI, 4.4 to 6.9) in the 75- to 79-year age group (Table 2).

**DISCUSSION**

We estimated that screening colonoscopy reduced the 8-year risk for CRC from approximately 2.6% to 2.2% in beneficiaries aged 70 to 74 years and from 3.0% to 2.8% in those aged 75 to 79 years. The excess risk for serious adverse events after colonoscopy was small, especially among younger beneficiaries.

Our findings are consistent with the USPSTF recommendations for routine screening through age 75, followed by individualized decisions afterward (17). Because the ongoing trials (3–5) do not include the older age groups (Supplement Table 1), our study provides helpful information for benefit-risk analyses. Our estimates of the effect of screening colonoscopy on CRC incidence and complication rates in older persons are particularly important in view of current policies to increase screening uptake: The Healthy People 2020 goal is a 70% CRC screening rate (34).

Based on Medicare surveillance patterns (Supplement Figure 5), our screening colonoscopy group approximately corresponds to the following strategy: Receive a screening colonoscopy. If a polyp is detected, repeat at 3 or 5 years; if no polyp is detected, repeat at 5 years or later. Our estimates are not directly comparable with previous observational analyses of colonoscopy and CRC incidence, which were based on comparisons that are less relevant for decision making (for example, “receiving a negative colonoscopy” or “polypectomy” vs. “no lower endoscopy” [35]), were restricted mostly to younger age groups, and did not estimate absolute risks (36–40).

The follow-up of our study—25% of individuals were followed for longer than 5.5 years—may be insufficient to detect the full benefits of screening colonoscopy, although our estimates suggest a CRC absolute risk reduction at 8 years greater than that found in the screening sigmoidoscopy trials (11, 12, 14, 15), especially in the younger age group. Although the absence of cause-of-death information in Medicare data precludes the evaluation of CRC-specific mortality, we would expect both CRC mortality and morbidity to be lower in the screening group. In addition to the lower CRC incidence, more than half of the CRC cases detected through screening colonoscopy were stage 0 or I, compared with one third of those detected by means other than screening. Because cases of stage 0 and I cancers have an excellent prognosis and do not require adjuvant chemotherapy, earlier detection by screening contributes to increased cancer-specific survival and better quality of life. A concern of population-based cancer screening programs is overdiagnosis (41, 42) and treatment of indolent cancer that might never become symptomatic. Screening colonoscopy, however, identi-
ies and removes precancerous lesions, which do not require further treatment, and is a low-risk procedure (as opposed to, for example, removal of a pulmonary node detected on low-dose computed tomography screening). Therefore, screening colonoscopy might face fewer challenges than other screening programs.

As in any observational study, our estimates may be confounded by unmeasured CRC risk factors. However, in this case, substantial confounding is doubtful for several reasons. First, our estimates are consistent with those of observational analyses of 3 randomized sigmoidoscopy trials (11, 12, 14) that ignored randomization by comparing the CRC incidence in the control group with that of the nonadherent participants in the intervention group. These trials consistently found no differences in CRC incidence, which suggests little, if any, confounding; that is, CRC risk factors seem to have little association with the reasons individuals decide to be screened. Second, previous observational studies found very little difference in the effect estimates after adjustment for potential confounders (39, 43, 44). Third, our FOBT estimates in the younger age group were compatible with the benchmark provided by FOBT trials (7, 45), further supporting the validity of our approach to emulate a randomized CRC screening trial. Sensitivity analyses (46) confirm that the conclusions of our study would not change under realistic scenarios of unmeasured confounding (Supplement Figure 6, available at www.annals.org). In contrast, as in the observational analyses of the sigmoidoscopy trials, we suspect that substantial confounding exists for the effect of CRC screening on all-cause mortality (16) (Supplement Figure 7, available at www.annals.org), for which unmeasured lifestyle prognostic factors, such as cigarette smoking, are more relevant.

Further, to reduce confounding and increase the specificity of our classification of colonoscopies as screening tests, we included only users of Medicare preventive services. Although this selection may have reduced external validity, as it would in any clinical trial applying a set of eligibility criteria, it increased internal validity by reducing the differences between study groups with respect to measured variables (data not shown) and therefore probably also to unmeasured ones. A sensitivity analysis without this selection would yield the same effect estimate but an implausibly high cancer prevalence (Supplement Figure 8, available at www.annals.org), possibly because of the inclusion of colonoscopies conducted for diagnostic purposes, which supports our selection as a strategy to reduce misclassification of screening colonoscopies. Thus, the slightly higher prevalence of CRC at the baseline colonoscopy in our study compared with that reported in 2 ongoing randomized trials (3, 47) and several observational studies (48–50) likely is the result of a higher prevalence of asymptomatic CRC in our older population rather than a misclassification of diagnostic colonoscopies. We also found a higher baseline prevalence of CRC in our FOBT group (Supplement Figure 3) than in published FOBT studies (7, 45), and FOBT rarely is used for reasons other than screening.

In summary, we provide precise estimates of the effectiveness and safety of screening colonoscopy in persons aged 70 or older, an underrepresented population in randomized trials. Our findings suggest a modest benefit of screening colonoscopy for preventing CRC in persons aged 70 to 74 years and a smaller (if any) benefit in those who are older. The risk for adverse events was low in both age groups. Our findings may help patients, physicians, and policymakers make informed decisions about CRC screening.

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Appendix: Technical Details
As described in the main text, we emulated a hypothetical trial of colonoscopy screening—the target trial (25)—in the Medicare population. The eligibility criteria, treatment outcomes, start and end of follow-up, outcome, and statistical analysis of our target trial are described in the Methods section. In this Appendix, we provide a step-by-step description of our approach and describe its advantages. We start by specifying the target trial.

The Target Trial
Our goal was to emulate a pragmatic randomized trial of colonoscopy screening. An outline of the protocol of this target trial is as follows:

- Eligibility criteria: asymptomatic persons with no history of CRC, aged 70 to 79 years, enrolled in Medicare parts A and B; and with no adenoma, inflammatory bowel disease, colectomy, or CRC screening in the 5 years before enrollment.
- Treatment strategies or groups: screening colonoscopy or no screening at study entry. Individuals in both groups can receive subsequent colonoscopies following standard practice (for example, for diagnostic purposes or according to his or her preferred screening strategy).
- Assignment procedures: Participants are randomly assigned to 1 of the 2 groups at baseline.
- Follow-up period: For each individual, follow-up starts at randomization and ends at CRC diagnosis, at death, at loss to follow-up, 8 years after baseline, or on 31 December 2012 (administrative end of follow-up), whichever occurs first.
- Outcome: CRC diagnosis within 8 years of baseline.
- Causal contrast of interest: intention-to-treat effect.

Analysis plan: comparison of 8-year CRC risks among individuals assigned to each treatment strategy. If some baseline variables are found to be unbalanced between groups, then the risks need to be estimated within levels of the baseline variables and subsequently standardized. To do so, we fit a pooled logistic model (31, 32) for the monthly probability of outcome-free survival conditional on the group indicator, baseline covariates, month of follow-up (linear, quadratic, and an exponentially decreasing term), and a product term between group and month. For each participant, we multiply the model’s predicted values, under each value of the group indicator, through time t to estimate their probability conditional on the baseline variables and standardize the conditional probabilities to the distribution of the baseline variables in the study population. Specifically, we average the estimated conditional probabilities over all individuals under each value of the group indicator (33). The monthly cumulative incidence is then obtained as 1 minus the corresponding standardized probability. A percentile-based nonparametric bootstrap can be used to calculate 95% CIs.

Appendix Figure, top represents the first 4 time intervals (for example, weeks) of follow-up for 7 hypothetical beneficiaries in our database of 20% of Medicare beneficiaries between 1 January 2004 and 31 December 2012. Interval 0 corresponds to the week starting 1 January 2004. Each circle represents the outcome of the beneficiary in a given interval. Solid black circles represent times when the beneficiary received a CRC diagnosis, white circles times with no diagnosis, and faded circles times when the individual did not meet Medicare enrollment criteria. A “C” within the circle represents a screening colonoscopy, and an “X” indicates that the beneficiary does not meet all the eligibility criteria for reasons other than Medicare enrollment requirements (for example, the presence of symptoms in the previous 6 months, screening in the previous 5 years, or history of CRC). For example, beneficiary 2 has anemia (an exclusion criterion) during interval 2, and beneficiary 3 receives a screening colonoscopy during interval 0 followed by a CRC diagnosis (becoming ineligible after both intervals). Beneficiary 7 is younger than 70 during intervals 0 to 3. Individuals 1, 4, and 5 meet the Medicare enrollment criteria at different times after interval 0.

To conduct the target trial in this population, we would use the database to identify eligible individuals during a particular time and randomly assign them to the colonoscopy or no-colonoscopy group. Suppose we implemented the target trial during interval 3. Then only beneficiaries 1, 5, and 6 meet the eligibility criteria.

Suppose that beneficiary 1 is randomly assigned to screening colonoscopy and beneficiaries 5 and 6 to the no-colonoscopy group. Appendix Figure, middle rep-
represents the randomized clinical trial population and follow-up. The follow-up of beneficiary 1 ends at interval 4 because of death and that of beneficiary 6 ends at interval 6 because of disenrollment from Medicare. Beneficiary 5 deviates from protocol and receives a screening colonoscopy during interval 4.

The analytic data set of this randomized clinical trial is shown in Appendix Table 1.

**Emulation of the Target Trial With an Arbitrarily Chosen Time Zero**

To emulate the aforementioned target trial using the Medicare data, we first identify the beneficiaries eligible during interval 3 (the same ones shown in Appendix Figure, middle). Then, rather than assigning a random sample of these individuals to screening colonoscopy, we classify them into the “screening colonoscopy” group if they happen to receive a screening colonoscopy during interval 3 and into the “no-screening colonoscopy” group otherwise. Therefore, the analytic database for this observational study would look identical to that of the true randomized trial.

However, because beneficiaries who have a colonoscopy may have a distribution of CRC risk factors different from those who do not, we need to adjust the analysis of the observational study for those differences. To do so, we can standardize the survival curves by the baseline risk factors as described earlier for the scenario in which randomization does not yield balanced groups in the randomized target trial.

In our actual Medicare population, only 56 eligible individuals had a screening colonoscopy during interval 3, only 2 of whom received a diagnosis of CRC during follow-up. Therefore, the estimates will be very imprecise or even impossible to obtain, because the low number of events may prevent estimation of the parameters of the logistic model if we want to standardize the incidence curves. In general, the strategy of emulating target trials using a fixed baseline will result in inefficient estimates if the outcome is rare.

**Emulation of a Sequence of Target Trials**

One way to increase the efficiency of our estimates is to emulate a sequence of target trials starting at every interval during our study period (27–29). Appendix Figure, middle, shows the beneficiaries eligible for an emulated target trial starting at interval 3; Appendix Figure, bottom, shows those eligible for a target trial starting at interval 4.

Note that beneficiary 1 was eligible for the target trial starting at interval 3 but not for the trial starting at interval 4, because of her previous colonoscopy. In contrast, beneficiary 4 becomes eligible because she begins to meet Medicare enrollment criteria, and beneficiary 7 becomes eligible because she turns 70. Beneficiary 5 was eligible for the no-colonoscopy group of the target trial starting at interval 3 but is classified in the colonoscopy group starting at interval 4.

Analogously, we could show 8 additional figures revealing the beneficiaries eligible for target trials starting at all other intervals. The analytic database combining the 10 emulated trials is shown in Appendix Table 2.

In each emulated trial, baseline is a different time. However, the end of follow-up is always CRC diagnosis, death, withdraw from Medicare, or administrative end of follow-up, whichever occurs first.

In this analytic database, each beneficiary may contribute up to 10 replicates, 1 per emulated target trial for which he or she meets the eligibility criteria. Each replicate is treated as a separate individual in the analysis; therefore, the variance of the estimate needs to be adjusted (for example, by bootstrapping) for the dependence between replicates corresponding to the same person.

In our Medicare population, each beneficiary contributed an average of 50 eligible replicates per year of eligibility. Of the 78,065 eligible replicates who received a screening colonoscopy at the baseline interval of their corresponding trial, 1282 had a diagnosis of CRC during follow-up. Of the 1,924,836 who did not have a colonoscopy at the baseline interval, 45,530 received a CRC diagnosis. The standardized cumulative incidence curves were estimated via a logistic model that pooled all 2,002,901 eligible replicates.

**Discussion**

Our approach has 2 components: a follow-up design that explicitly emulates a target trial, and the generalization of this design to emulate a sequence of target trials.

The first component has several advantages. It ensures that, unlike previous case–control studies (39, 43, 44), the absolute risk for the outcome can be estimated. It also ensures that time zero of the follow-up is assigned appropriately as the time when the eligibility criteria are met, the treatments of interest are assigned, and the events start to be counted (30). The synchronization of these 3 aspects of the design at time zero directs investigators to the precise time when baseline confounders must be measured, prevents immortal time bias (30) and some forms of selection bias, and facilitates the translation of the study results to clinical decision making. Specifically, studies that do not explicitly emulate a target trial (such as the follow-cohort study by Stock and colleagues [40], which defined the exposure as having received a colonoscopy for any indication in the 10 years before baseline) have none of these advantages.

The second component has only 1 advantage: It increases statistical efficiency. The emulation of a target trial with a fixed time zero often leads to unstable esti-
mates because of the small number of persons who meet the eligibility criteria or receive some of the treatment strategies of interest. The emulation of several trials partly overcomes this problem.

Appendix Figure. Schematic representation of the Medicare population (top), the randomized clinical trial within the Medicare population (middle), and the target trial starting at interval 4 (bottom).

Appendix Table 1. Analytic Data Set of the Target (Hypothetical) Randomized Trial

<table>
<thead>
<tr>
<th>Beneficiary ID</th>
<th>Group</th>
<th>Follow-up, Time Interval</th>
<th>Colorectal Cancer*</th>
<th>Baseline Covariate†</th>
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<td>0 1</td>
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<tr>
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<td>No colonoscopy</td>
<td>3 5</td>
<td>1 0</td>
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<tr>
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<td>No colonoscopy</td>
<td>3 6</td>
<td>0 1</td>
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ID = identification number.
* 0 = no; 1 = yes.
† For example, comorbidity score (ranges from 0 to 2).
## Appendix Table 2. Analytic Database Combining 10 Emulated Trials

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<th>Colorectal Cancer*</th>
<th>Baseline Covariate†</th>
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