

**Supplementary Table 1.** Restricted to Subjects for Whom Qualifying was the First Lifetime Exam

| Category                 | Factor   | 3-year (N = 215) (%) | 5-year (N = 391) (%) | P value |
|--------------------------|--|----------------------|----------------------|---------|
| Subject                  | Age mean $\pm$ SD                                  | 58.0 $\pm$ 5.6       | 54.9 $\pm$ 5.7       | .82     |
|                          | Sex  |                      |                      | .40     |
|                          | Male   | 122 (56.7)           | 208 (53.2)           |         |
|                          | Female   | 93 (43.3)            | 183 (46.8)           |         |
|                          | Race   |                      |                      | .21     |
|                          | White  | 176 (81.9)           | 330 (84.4)           |         |
|                          | Black  | 18 (8.4)             | 25 (6.4)             |         |
|                          | Asian/Pacific Islander                             | 9 (4.2)              | 7 (1.8)              |         |
|                          | Other/multiple/unknown                             | 12 (5.6)             | 29 (7.4)             |         |
|                          | Hispanic ethnicity <sup>a</sup>                    |                      |                      | .84     |
|                          | No   | 196 (91.6)           | 360 (92.1)           |         |
|                          | Yes  | 18 (8.4)             | 31 (7.9)             |         |
|                          | Smoking status                                     |                      |                      | .15     |
|                          | Never  | 118 (54.9)           | 234 (59.9)           |         |
|                          | Former   | 72 (33.5)            | 129 (33.0)           |         |
|                          | Current  | 25 (11.6)            | 28 (7.2)             |         |
|                          | BMI <sup>a</sup>                                   |                      |                      | .05     |
| <25                      | 55 (25.6)  | 99 (25.5)            |                      |         |
| 25-29.9                  | 72 (33.5)  | 165 (42.4)           |                      |         |
| $\geq$ 30                | 88 (40.9)  | 125 (32.1)           |                      |         |
| Family history of CRC    |  |                      | .16                  |         |
| No                       | 170 (84.2)   | 326 (88.4)           |                      |         |
| Yes                      | 32 (15.8)  | 43 (11.7)            |                      |         |
| Exam                     | Indication <sup>a</sup>                            |                      |                      | .99     |
|                          | Screening  | 173 (80.5)           | 314 (80.5)           |         |
|                          | Follow up exam                                     | 0                    | 0                    |         |
|                          | Diagnostic   | 42 (19.5)            | 76 (19.5)            |         |
|                          | Quality of Pre-preparation <sup>a</sup>            |                      |                      | <.0001  |
|                          | Excellent  | 51 (23.7)            | 170 (43.5)           |         |
|                          | Good   | 86 (40.0)            | 130 (33.3)           |         |
|                          | Adequate   | 17 (7.9)             | 31 (7.9)             |         |
| Fair                     | 18 (8.4)   | 18 (4.6)             |                      |         |
| Poor                     | 1 (0.5)  | 0 (0.0)              |                      |         |
| Not stated in report     | 42 (19.5)  | 42 (10.7)            |                      |         |
| Endoscopist <sup>a</sup> | Age (mean $\pm$ SD)                                | 47.1 $\pm$ 7.9       | 48.2 $\pm$ 9.7       | .001    |
|                          | Gender   |                      |                      | .79     |
|                          | Male   | 184 (86.0)           | 333 (85.2)           |         |
|                          | Female   | 30 (14.0)            | 58 (14.8)            |         |
|                          | Specialty  |                      |                      | .03     |
|                          | Gastroenterology                                   | 187 (87.4)           | 365 (93.4)           |         |
| Internal medicine        | 14 (6.5)   | 19 (4.9)             |                      |         |
| General surgery          | 10 (4.7)   | 5 (1.3)              |                      |         |
| Other                    | 3 (1.4)  | 2 (0.5)              |                      |         |
| Index findings           | No. of adenomas                                    |                      |                      | <.0001  |
|                          | 1  | 156 (72.6)           | 345 (88.2)           |         |
|                          | 2  | 59 (27.4)            | 46 (11.8)            |         |
|                          | No. of serrated polyps                             |                      |                      | .01     |
|                          | 0  | 155 (72.1)           | 312 (79.8)           |         |
|                          | 1-2  | 51 (23.7)            | 75 (19.2)            |         |
|                          | 3+   | 9 (4.2)              | 4 (1.0)              |         |
|                          | Clinically significant serrated polyp <sup>b</sup> |                      |                      | .33     |
| No                       | 196 (92.0)   | 366 (94.1)           |                      |         |
| Yes                      | 17 (8.0)   | 23 (5.9)             |                      |         |

<sup>a</sup>Missing data not included above: Hispanic (n=1), BMI (n=3), Family history of CRC (n=106), exam indication (n=5), endoscopist information (n=1), clinically significant serrated polyp (n=21).

<sup>b</sup>A clinically significant serrated polyp is defined as a sessile serrated adenoma, a traditional serrated adenoma, a proximal serrated polyp, or a serrated polyp  $\geq$  1 cm.

**Supplementary Table 2.** Risk of Advanced Adenoma for Risk Factors in Table 1 of Paper

|                        |                      | N events/N (%) | Adjusted <sup>a</sup> RR (95% CI) |
|------------------------|----------------------|----------------|-----------------------------------|
| Race                   | White                | 97/1210 (8.0)  | reference                         |
|                        | Other                | 15/159 (9.4)   | 0.98 (0.55–1.74)                  |
| Smoking status         | Never                | 57/783 (7.3)   | reference                         |
|                        | Former/current       | 58/648 (9.0)   | 1.19 (0.83–1.71)                  |
| BMI                    | <30                  | 71/921 (7.7)   | reference                         |
|                        | ≥30                  | 44/509 (8.6)   | 1.09 (0.76–1.57)                  |
| Family history of CRC  | No                   | 94/1100 (8.6)  | reference                         |
|                        | Yes                  | 18/241 (7.5)   | 0.88 (0.54–1.43)                  |
| Indication             | Screening/diagnostic | 55/658 (8.4)   | Reference                         |
|                        | Follow-up exam       | 60/768 (7.8)   | 1.00 (0.68–1.45)                  |
| Quality of preparation | Excellent/good       | 89/1039 (8.6)  | Reference                         |
|                        | Adequate/fair/poor   | 14/187 (7.5)   | 0.66 (0.37–1.19)                  |
|                        | Not stated in report | 12/205 (5.9)   | 0.66 (0.34–1.28)                  |
| Endoscopist age        | ≤45                  | 47/561 (8.4)   | Reference                         |
|                        | >45                  | 68/869 (7.8)   | 0.93 (0.64–1.34)                  |
| Endoscopist gender     | Male                 | 100/1228 (8.1) | Reference                         |
|                        | Female               | 15/202 (7.4)   | 0.86 (0.50–1.47)                  |
| Specialty              | Gastroenterology     | 104/1325 (7.9) | Reference                         |
|                        | Other                | 11/105 (10.5)  | 1.41 (0.69–2.89)                  |
| No. of adenomas        | 1                    | 90/1141 (7.9)  | Reference                         |
|                        | 2                    | 25/290 (8.6)   | 1.08 (0.70–1.67)                  |
| No. of serrated polyps | 0                    | 82/1102 (7.4)  | reference                         |
|                        | 1+                   | 33/329 (10.0)  | 1.43 (0.96–2.12)                  |

<sup>a</sup>Adjusted for age, sex, study center, randomization group (2-group or group), Vitamin D treatment and Calcium treatment (women in the 2-group randomization who were taking non-randomized calcium are grouped with the calcium treated subjects).

**Supplementary Table 3.** Details of Follow-up Colonoscopies According to Recommended 3- or 5-year Follow-up

|   | 3-year recommendation<br>N (%) | 5-year recommendation<br>N (%) | P value |
|---|--------------------------------|--------------------------------|---------|
| Timing of study follow-up exam                  |                                |                                | <.0001  |
| More than 6 mos before due date                 | 6/559 (1.1)                    | 87/880 (9.9)                   |         |
| Within 6 mos before or after due date           | 455/559 (81.4)                 | 660/880 (75.0)                 |         |
| More than 6 mos after due date                  | 98/559 (19.9)                  | 133/880 (15.1)                 |         |
| Time from index to follow-up exam (mos)         |                                |                                |         |
| Mean (SD)                                       | 39.6 ± 7.2                     | 61.0 ± 8.5                     |         |
| Range   | 15.7–77.6                      | 19.1–101.9                     |         |
| Contributed follow-up outcome data <sup>a</sup> |                                |                                | .03     |
| No  | 35/594 (5.9)                   | 86/966 (8.9)                   |         |
| Yes   | 559/594 (94.1)                 | 880/966 (91.1)                 |         |

<sup>a</sup>This includes subjects who had any exam after randomization during the treatment phase of the parent study and there was sufficient pathology to ascertain at least 1 of our outcomes of interest.

**Supplementary Table 4.** Selected Study Participant, Colonoscopy Exam, and Endoscopist Characteristics for the 4 CRCs at Follow-up

| Category                              | Factor                     | n |
|---------------------------------------|----------------------------|---|
| Subject                               | Age = 51, 53, 58, 70       |   |
|                                       | Sex                        |   |
|                                       | Male                       | 1 |
|                                       | Female                     | 3 |
|                                       | Race                       |   |
|                                       | White                      | 4 |
|                                       | Hispanic ethnicity         |   |
|                                       | No                         | 4 |
|                                       | Smoking status             |   |
|                                       | Never                      | 2 |
|                                       | Current                    | 2 |
|                                       | BMI                        |   |
|                                       | <25                        | 1 |
|                                       | 25–29.9                    | 2 |
| ≥ 30                                  | 1                          |   |
| Family history of CRC                 |                            |   |
| No                                    | 4                          |   |
| Exam                                  | Indication                 |   |
|                                       | Screening                  | 1 |
|                                       | Follow-up exam             | 3 |
|                                       | Quality of pre-preparation |   |
|                                       | Excellent                  | 2 |
| Good                                  | 1                          |   |
| Fair                                  | 1                          |   |
| Endoscopist                           | Age = 33, 39, 45, 58       |   |
|                                       | Gender                     |   |
|                                       | Male                       | 3 |
| Female                                | 1                          |   |
| Specialty                             |                            |   |
| Gastroenterology                      | 4                          |   |
| Index findings                        | No. of adenomas            |   |
|                                       | 1                          | 3 |
|                                       | 2                          | 1 |
|                                       | No. of serrated polyps     |   |
|                                       | 0                          | 1 |
|                                       | 1–2                        | 3 |
| Clinically significant serrated polyp |                            |   |
| No                                    | 4                          |   |

**Supplementary Table 5.** Outcomes at Follow-up With Additional Covariates

| Outcome                               | Adjusted RR (95% CI) <sup>a</sup> | P value |
|---------------------------------------|-----------------------------------|---------|
| 1 or more adenomas                    |                                   |         |
| 3-year recommended follow-up          | 0.95 (0.82–1.10)                  | .49     |
| 5-year recommended follow-up          | reference                         |         |
| Advanced adenoma                      |                                   |         |
| 3-year recommended follow-up          | 0.89 (0.59–1.35)                  | .58     |
| 5-year recommended follow-up          | reference                         |         |
| Clinically significant serrated polyp |                                   |         |
| 3-year recommended follow-up          | 0.93 (0.64–1.33)                  | .68     |
| 5-year recommended follow-up          | reference                         |         |

<sup>a</sup>Adjusted for age, sex, study center, randomization group (2-group or 4-group), Vitamin D treatment and Calcium treatment (women in the 2-group randomization who were taking non-randomized calcium are grouped with the calcium treated subjects), race (white, black, other), smoking status (ever, never), BMI (continuous), family history of CRC (including those with missing history as a separate category (yes, no, missing), indication (screening, surveillance, symptoms), number of adenomas at baseline (1, 2), clinically significant serrated polyp at baseline (no, yes), bowel prep (excellent, good, satisfactory/fair/poor, missing), endoscopist age (continuous), endoscopist gender, endoscopist specialty (gastro/other).

**Supplementary Table 6.** Outcomes at Follow-up Colonoscopy for Participants With Surveillance Exams at 3 vs 5 Years (Actual Time of Exam, not Recommended Interval)

| Outcome  | N events/N (%) | $\chi^2$ P value | Adjusted RR (95% CI) <sup>a</sup> | P value |
|--|----------------|------------------|-----------------------------------|---------|
| 1 or more adenomas                                 |                | .21              |                                   |         |
| Follow-up at 30–42 mos                             | 183/495 (37.0) |                  | 0.90 (0.77–1.06)                  | .21     |
| Follow-up at 54–66 mos                             | 261/642 (40.7) |                  | reference                         |         |
| Advanced adenoma                                   |                | .42              |                                   |         |
| Follow-up at 30–42 mos                             | 40/500 (8.0)   |                  | 1.07 (0.69–1.65)                  | .78     |
| Follow-up at 54–66 mos                             | 44/652 (6.8)   |                  | reference                         |         |
| Clinically significant serrated polyp <sup>b</sup> |                | .83              |                                   |         |
| Follow-up at 30–42 mos                             | 54/488 (11.1)  |                  | 0.95 (0.66–1.36)                  | .79     |
| Follow-up at 54–66 mos                             | 72/627 (11.5)  |                  | reference                         |         |

Note there are 282 people not in this table who were in [Figure 3](#) in the paper because some subjects had exams outside the  $36 \pm 6$  and  $60 \pm 6$  month windows.

<sup>a</sup>Adjusted for age, sex, study center, randomization group (2-group or 4-group), Vitamin D treatment and calcium treatment (women in the 2-group randomization who were taking non-randomized calcium are grouped with the calcium treated subjects).

<sup>b</sup>A clinically significant serrated polyp is defined as a sessile serrated adenoma, a traditional serrated adenoma, a proximal serrated polyp, or a serrated polyp  $\geq 1$  cm.

**Supplementary Table 7.** Literature Survey of Management of Small Adenomas by Physicians

| Study   | Design  | Setting  | N  | Finding  |
|---|---|--|--|--|
| Mysliwiec et al, 2004, US <sup>28</sup>               | Survey from National Cancer Institute               | National representative study of endoscopists  | 349 gastroenterologists/<br>316 general surgeons                 | More than 50% recommended 3 or fewer years surveillance for a small adenoma  |
| Boolchand et al, 2006, US <sup>30</sup>               | Survey of primary care physicians                   | Random sample of 500 College of Physicians & 500 American Academy of Family Physicians | 568/1000 physicians responded                                    | 71% would survey a small tubular adenoma in $\leq 3$ years & 80% would survey 2 small tubular adenomas $\leq 3$ years                                |
| Krist et al, 2007, US <sup>11</sup>                   | Chart review  | Primary care practices in Maryland/Virginia  | 3000 charts from 10 practices                                    | 68.1% recommended surveillance interval of $< 5$ years for LRAs  |
| Saini et al, 2009, US <sup>15</sup>                   | Survey at board review course                       | Gastroenterologists at board review course for 2004 recertification                    | 116/203 completed the survey                                     | 48.2% correctly knew 5-year interval for LRAs<br>28.8% disagreed with this recommendation  |
| Laiyemo et al, 2009, US <sup>7</sup>                  | Prospective cohort analysis of PLCO participants    | PLCO subjects  | 1297 participants  | 30.3% of 431 subjects with LRAs had repeat colonoscopy within 4 years and probability of advanced adenoma was 5%                                     |
| Schoen et al, 2010, US <sup>14</sup>                  | Retrospective survey of PLCO participants           | PLCO trial in 9 US communities   | 3627/3876 (93.6%) responded                                      | 46.7% of subjects with low-risk findings had colonoscopy within 5 years of index<br>33.6% had surveillance colonoscopy within 4 years                |
| Ransohoff et al, 2011, US <sup>13</sup>               | Chart review  | Endoscopy practices in North Carolina  | 322 physicians' charts from 126 practices                        | 35% of subjects with LRAs were asked to return in 1–3 years  |
| Radaelli et al, 2012, Italy <sup>8</sup>              | Chart review  | Endoscopy units in Italy   | Charts from 902/7081 outpatients from 29 Italian endoscopy units | 67.4% subjects with LRAs had surveillance interval earlier than recommended  |
| Kruse et al, 2015, US <sup>12</sup>                   | Chart review of patient 50–65 years                 | Primary care patients at Harvard Vanguard Medical Associates (multispecialty group)    | 1740 patients' charts  | Endoscopists recommended earlier surveillance in 39% of 257 exams with LRAs  |
| Sohn et al, 2014, Korea <sup>27</sup>                 | Survey  | Members at a 64 <sup>th</sup> Annual Congress of Korean Surgical Society               | 38/41 responders   | More than 50% recommended a 3-year or less interval for LRAs   |
| Meneeset al, 2014, US <sup>29</sup>                   | Chart review  | Tertiary-care and VAMC in Michigan   | 922 colonoscopies  | 13.8% of endoscopies have $< 5$ year recommended surveillance interval   |
| van Heijningen et al, 2015, Netherlands <sup>26</sup> | Chart review of colonoscopies performed 1998–2002   | Endoscopy units in the Netherlands   | 2997 patients' exams   | $< 25\%$ of patients received proper surveillance<br>Higher rate advanced adenoma in delayed follow-up   |
| Johnson et al, 2015, US <sup>31</sup>                 | Retrospective review of EMR and administrative data | Multicenter Veterans Affairs   | 25 VA centers; charts from 1455 patients (50–60 y old)           | They did not report proportions of non adherence but observed that the risk for non adherence was higher for hyperplastic and high-risk but not LRAs |
| Murphy et al, 2016, US <sup>36</sup>                  | Retrospective review of EMR and administrative data | Multicenter Veterans Affairs   | 25 VA centers; charts from 1455 patients (age 50–60)             | 26% overuse for LRAs<br>Predictors of overuse; female sex of patient, general surgeon endoscopist and non-academic facility                          |

EMR, electronic medical record; LRAs, low-risk adenomas; PLCO. Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial