Fecal DNA Testing of TWIST1 Methylation Identifies Patients With Advanced Colorectal Adenoma Missed by Fecal Immunochemical Test for Hemoglobin

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INTRODUCTION: We have reported previously that fecal DNA testing of TWIST1 methylation in combination with the fecal immunochemical test for hemoglobin (FIT) (combination test) is useful for colorectal neoplasia screening. In this study, using larger sample sizes, we studied the clinical performance of the combination test for the detection of colorectal neoplasia and, especially, advanced colorectal adenoma.

METHODS: We performed a prospective study in which FIT, fecal DNA testing of TWIST1 methylation, and colonoscopy were performed on 372 patients with colorectal neoplasia and 71 subjects without colorectal neoplasia. We assessed the individual clinical performance of each of FIT and fecal DNA testing of TWIST1 methylation and of the combination test for the detection of colorectal neoplasia including advanced adenoma based on morphologic subtypes.

RESULTS: The FIT alone had a sensitivity of 7.5% (3/40) for nonadvanced adenoma, 32.3% (41/127) for advanced adenoma, and 93.7% (192/205) for colorectal cancer and a specificity of 87.3% (62/71). The combination test had a sensitivity of 35.0% (14/40) for nonadvanced adenoma, 68.5% (87/127) for advanced adenoma, and 95.6% (196/205) for colorectal cancer and a specificity of 80.3% (57/71). For morphological subtypes of advanced adenoma, the sensitivity of FIT was only 28.2% (20/71) for polypoid type and 16.1% (5/31) for nonpolypoid type, whereas the combination test increased the sensitivities to 64.8% (46/71) and 71.0% (22/31), respectively.

DISCUSSION: The combination of the fecal DNA test with FIT seemed to be useful to detect colorectal neoplasia and, especially, advanced adenoma of the nonpolypoid type.

INTRODUCTION
Colorectal cancer is the second most commonly diagnosed cancer in females and the third most in males in the world (1). It is estimated that 1.8 million new cases and 861,663 deaths occurred worldwide in 2018 (1). Because more than 95% of patients with colorectal cancer would benefit from curative surgery if diagnosed at an earlier or precancerous stage (2), it is important to develop highly sensitive and specific assays that are noninvasive, inexpensive, and easy to perform to detect precancerous lesions and colorectal cancer at the early stage.

The main approach to colorectal cancer screening throughout the world is the fecal immunochemical test for hemoglobin (FIT). Patients with positive FIT are referred for colonoscopy.
(3). Although the sensitivity of FIT for the diagnosis of colorectal neoplasia is 65.8%–73.8% for colorectal cancer, it decreases to 23.8%–27.1% for the detection of advanced adenoma (4,5). To improve the sensitivity of FIT for the detection of colorectal neoplasia, in 2014, the US Food and Drug Administration approved Cologuard, the first fecal-based colorectal screening test consisting of the combination of FIT and fecal DNA testing for the mutation of KRAS proto-oncogene, GTPase (KRAS) and methylation of BMP3 and NDRG4. Cologuard improved the sensitivity for colorectal cancer to 92.3%. However, its sensitivity for advanced adenoma remained at a low level of only 42.4% (4,6).

Previously, we reported that TWIST1 methylation is specific to colorectal neoplasia. Furthermore, we developed a new methylation assay without bisulfite treatment and methylated DNA immunoprecipitation—the combined restriction digital polymerase chain reaction assay (CORD assay). This assay has more than 100 times higher sensitivity for minute quantities of the target methylated gene than the conventional bisulfite-based methylation assay and, thus, overcomes the issue of limited input of DNA (7,8). In our previous study, fecal DNA testing of TWIST1 methylation by the CORD assay in combination with FIT exhibited a sensitivity of 82.4% for the detection of advanced adenoma (7). However, because the sample size in the previous study was small (10 healthy subjects and 99 patients with colorectal neoplasia), we additionally performed this study using larger sample sizes to better evaluate the clinical performance of the combination test to detect colorectal neoplasias and morphological subtypes of advanced adenoma.

METHODS
We followed the Standards for the Reporting of Diagnostic Accuracy Studies (9).

Clinical materials
This prospective study designed to investigate the impact of the combination test for the detection of colorectal neoplasias was conducted in Yamaguchi University Hospital, IMSUT Hospital, St. Hill Hospital, and Ajisu Kyoritsu Hospital. The study protocol was approved by the institutional review board of each hospital (protocol number: H29-228). Potentially eligible participants were 20 years of age or over and consisted of asymptomatic persons (n = 80) and symptomatic patients who were scheduled to undergo colonoscopy for medical check-up and patients referred for further examinations and treatments of colorectal neoplasias (n = 400) from October 2007 to December 2019 in each hospital. Consecutive participants who provided a written informed consent for this study were eligible for enrollment (Figure 1). We excluded participants with a history of inflammatory bowel disease, colorectal cancer, or colorectal surgery. All participants were required to provide a fecal specimen for FIT and fecal DNA testing and to undergo colonoscopy. We excluded 30 participants because of a shortage of fecal sample for the DNA testing and 7 patients with colorectal lymphoma, carcinoma, endometriosis, or submucosal tumor as determined by colonoscopy and pathologic examination. The median interval between fecal sampling and colonoscopy was 1 day (range, 0–58 days). Although colonoscopists reported the location and size of all lesions, only the most advanced colorectal epithelial lesion and its location were used to categorize the participants for the analysis. The proximal colon was considered to include the splenic flexure and all segments proximal to it; the distal colon was considered to include all other segments. We enrolled 480 participants of whom 443 showed results that could be fully evaluated, including 71 subjects without colorectal neoplasia as determined by colonoscopy (no neoplasm group), 40 patients with nonadvanced colorectal adenomas, 127 patients with advanced colorectal adenoma, and 205 patients with colorectal cancer of stages I–IV diagnosed by colonoscopy or surgical resection. Clinicopathologic features are summarized in Table 1. Criteria for advanced adenoma were defined as adenomas of 1 cm or greater in size, or with villous components (tubulovillous or villous), or with high-grade or severe dysplasia (4). Staging was classified according to the International Union Against Cancer (Union for International Cancer Control) (10). Of the 127 patients with advanced adenoma, morphologic classification was available for 102 patients who underwent endoscopic resection in Yamaguchi University Hospital. The adenomas were independently classified into 2 types: polyoid type (subtype 0-I) and nonpolyoid type (subtype 0-II) according to the Paris classification of superficial neoplastic lesions (11) by 2 endoscopists with more than 9 years of experience in colonoscopy and without any previous information of the results of the FIT and fecal DNA test. Subtype 0-I includes the pedunculated type (0-1p) and sessile type (0-1s) of which the elevation above the surface of mucosa is more than 2.5 mm (11). Subtype 0-II includes the slightly elevated type (0-Iia, the elevation above the surface of mucosa is less than 2.5 mm), flat type (0-Iib), and slightly depressed type (0-Iic) (11). When there was discordance between the classifications of the 2 endoscopists, the final classification of the morphology was determined after discussion by the 2 endoscopists.

Fecal specimens for DNA testing were collected before bowel preparation for colonoscopy or surgical treatment in Yamaguchi University Hospital, The Hospital of The Institute of Medical Science, IMSUT Hospital, Ajisu Kyoritsu Hospital, or St. Hill Hospital and were stored at −20°C until DNA extraction.

FIT
Fresh fecal specimens were collected into the sampling containers filled with 2 mL of a hemoglobin-stabilizing buffer solution (Eiken Chemical, Tokyo, Japan) before bowel preparation for the colonoscopy procedure. FIT was performed using OC-HEMODIA (Eiken Chemical). The OC-Sensor IO instrument HEMODIA (Eiken Chemical) processed and quantified the FIT results at the cutoff value of 20 μg hemoglobin (Hb)/g feces (100 ng Hb/mL buffer) for a positive test result (12,13).

CORD assay
Fecal samples were thawed from −20°C, and approximately 200 mg of each sample was used for DNA extraction using the QIAamp DNA Stool Mini kit (QIAGEN, Tokyo, Japan), as described previously (7). Eluted DNA (10 μL) was digested for 16 hours at 37°C by the addition of 10 units of HhaI, 10 units of HpaII, and 20 units of exonuclease I (Exo I) (all from Thermo Fisher Scientific, Tokyo, Japan). Additional digestion of DNA was performed for 16 hours at 60°C using 10 units of BsmUI (New England Biolabs, Hitchin, United Kingdom). After the restriction was complete, the mixture was heated for 10 minutes at 98°C. We performed multiplex droplet digital polymerase chain reaction to simultaneously count the absolute copy numbers of human telomerase reverse transcriptase (hTERT) and the
methylated target gene (TWIST1), as described previously (7). Laboratory testing was performed without the knowledge of the results of either the comparator FIT or clinical findings.

**Statistical analyses**

To compare variables, the Mann-Whitney U test, Fisher test, and receiver operating characteristic curve analysis were used. A P value of less than 0.05 was considered statistically significant. Statistical analyses were performed with GraphPad InStat Ver. 3 and GraphPad Prism Ver. 6 statistical software (GraphPad Software, La Jolla, CA).

### RESULTS

**FIT**

The criterion for a positive result of FIT was above a cutoff of 20 μg Hb/g feces. FIT resulted in a sensitivity of 7.5% (3/40; 95% confidence interval [CI], 1.6%–20.4%) for nonadvanced adenoma, 32.3% (41/127; 95% CI, 24.2%–41.2%) for advanced adenoma, and 93.7% (192/205; 95% CI, 89.4%–96.6%) for colorectal cancer screening and in a specificity of 87.3% (62/71; 95% CI, 77.3%–94.0%) (Table 2).

**Fecal DNA testing of TWIST1 methylation**

The distributions of copy numbers of TWIST1 methylation and the methylation ratio of TWIST1 are shown in Figure 2a, c, respectively. We set 20 copies of methylated TWIST1 and a TWIST1 methylation ratio of 19% as the cutoff points to discriminate between the no neoplasia group and colorectal cancer group. Each cutoff value was determined so that the specificity would be approximately 95% (Figure 2b, d), which is compatible with the specificity of FIT in screening setting populations (4,14). The TWIST1 methylation ratio was calculated according to the ratio of methylated TWIST1 copy numbers to hTERT copy numbers. The criterion for a positive result with the fecal DNA testing of TWIST1 is either the copy number of methylated TWIST1 is above the cutoff point (≥20 copies) or the TWIST1 methylation ratio is above the cutoff point (≥19%), or both are above the cutoff points.

Positive results of the fecal DNA testing of TWIST1 were found in 8.5% (6/71) of the individuals in the no neoplasia group (specificity of 91.5%; 95% CI, 82.5%–96.8%), in 27.5% (11/40; 95% CI, 14.6%–43.8%) of the nonadvanced adenoma group, in 47.2% (30/63; 95% CI, 38.4%–56.4%) of the advanced adenoma group, and in 44.4% (91/205; 95% CI, 37.4%–51.5%) of the colorectal cancer group (Table 2 and Figure 3a).

**Combination of FIT and fecal DNA testing of TWIST1 methylation**

The criterion for a positive result with the combination of FIT and the fecal DNA testing of TWIST1 methylation (combination test) is either FIT (a cutoff of 20 μg Hb/g feces) or fecal DNA testing of TWIST1 is positive or both are positive. The combination test resulted in a sensitivity of 35.0% (14/40; 95% CI,
Table 2. Sensitivity and specificity of fecal DNA test of methylated TWIST1 and FIT for the findings of colonoscopy

| Most advanced findings | Colonscopy (n = 443), No. | FIT | Fecal DNA test | Combination |
|------------------------|--------------------------|-----|----------------|------------|
|                        |                          | Positive result, No. | Sensitivity (95% CI), % | P Value | OR (95% CI) | Positive result, No. | Sensitivity (95% CI), % | P Value | OR (95% CI) | Positive result, No. | Sensitivity (95% CI), % | P Value | OR (95% CI) |
| Negative results on colonoscopy | 71 | 9 | 87.3% (77.3–94.4) | 1.0 | 6 | 91.5% (82.5–96.6) | 1.0 | 14 | 80.3% (69.1–88.8) | 1.0 |

CI, confidence interval; FIT, fecal immunochemical test for hemoglobin; OR, odds ratio.

For a positive result with the combination of FIT and fecal DNA test is either a positive FIT or fecal DNA test or both are positive.

**Sensitivity for polypoid and nonpolypoid advanced adenomas**

The morphologic classification available for 102 of the 127 patients with advanced adenoma was either polypoid type or nonpolypoid type. As shown in Figure 4, the sensitivity of FIT was only 28.2% (20/71; 95% CI, 18.1%–40.2%) for polypoid type and 16.1% (5/31; 95% CI, 5.4%–33.7%) for nonpolypoid type, whereas that of fecal DNA testing of TWIST1 methylation was 47.9% (34/71; 95% CI, 35.9%–60.1%) and 54.8% (17/31; 95% CI, 36.0%–72.7%), respectively. The combination test resulted in an increase in the sensitivities to 64.8% (46/71; 95% CI, 52.6%–75.7%) and 71.0% (22/31; 95% CI, 52.0%–85.8%), respectively. The results of FIT and fecal DNA testing were considerably mutually exclusive in polypoid type and completely mutually exclusive in nonpolypoid type (Figure 4).

**DISCUSSION**

Regarding the cutoff point of the CORD assay of TWIST1 methylation, we had set 5 copies of methylated TWIST1 in our previous study as a tentative cutoff point to discriminate between the no neoplasia group and the colorectal cancer group, resulting in a specificity of 100% in the small sample size (10 subjects without colorectal neoplasia and 99 patients with colorectal neoplasia) (7). In this study, using a larger sample size, we changed the cutoff point from 5 to 20 copies so that the specificity would be approximately 95%. Furthermore, we found that setting the cutoff point by the copy number alone is not enough because the copy number is influenced by a substantial amount of water in the fecal samples (fecal forms). Watery feces classified as types 6 and 7 on the Bristol Stool Form Scale (15) results in a low concentration of extracted DNA that leads to low copies of methylated TWIST1 and might be assessed as a false-negative result even if the tumor has hypermethylated TWIST1. To solve this problem, we added another cutoff point calculated according to the ratio of methylated TWIST1 copy numbers to hTERT copy numbers so that the methylation level of TWIST1 can be assessed even if the fecal DNA contains only a small amount of DNA. By contrast, there is a disadvantage in assessment by the TWIST1 methylation ratio. When normal DNA (normal cells) is increased in a fecal sample for reasons including inflammation of the gastrointestinal tract, an increase in hTERT copies reduces the ratio of TWIST1 methylation copies/hTERT copies, which might lead to a false-negative result even if the individual has colorectal neoplasm with TWIST1 hypermethylation. To solve this problem, the assessment by absolute copy number of methylated TWIST1 is also needed. Therefore, we determined the criterion for a positive result with the fecal DNA testing of TWIST1 to be either that the copy number of methylated TWIST1 is above the cutoff point (≥20 copies) or the TWIST1 methylation ratio is above the cutoff point (≥19%), or both are above their respective cutoff points.

**Colorectal cancer screening**

FIT is inevitably used for colorectal cancer detection because of its considerably high sensitivity (65.8%–78.6%) and very high specificity (92.8%–96.4%) (4,5,16). The use of FIT in symptomatic patients presenting in primary care can help rule out colorectal cancer rather than rule it in (17). In this study, the sensitivity of 93.7% was higher than those in reports by other investigators, as mentioned earlier (4,5,16). The difference in sensitivity between this study and those of reports by other groups seems to be because of the difference in the target population of each study. Our study comprised asymptomatic persons, symptomatic patients, and patients referred for further examinations and treatments, whereas the studies by other investigator were limited to asymptomatic persons who were at average risk for colorectal cancer (screening settings) (4,5,16). In this study, although most of the patients with colorectal cancer had positive results of FIT, 13 patients with

20.1%–51.7%) for nonadvanced adenoma, 68.5% (87/127; 95% CI, 59.7%–76.4%) for advanced adenoma, and 95.6% (196/205; 95% CI, 91.8%–98.0%) for colorectal cancer, and the specificity was 80.3% (57/71; 95% CI, 69.1%–88.8%) (Table 2 and Figure 3a, b).
Colorectal cancer had negative results of FIT, suggesting screening by FIT alone may occasionally miss the detection of colorectal cancer. The advantage of fecal DNA testing of TWIST1 methylation in addition to FIT is to provide a chance to identify some patients with colorectal neoplasia who are missed by FIT. Indeed, of the 13 patients with colorectal cancer who had a negative result of FIT, 4 patients with stage I colorectal cancer were positive for fecal DNA testing of TWIST1 methylation (Figure 3b). Thus, the combination of fecal DNA testing of TWIST1 methylation with FIT may be more useful for colorectal cancer detection than FIT alone. Further studies using a screening setting population are needed to support our findings.

**Advanced adenoma detection**

In this study, although screening tests for advanced adenoma by independent use of the FIT and fecal DNA testing of TWIST1 methylation had low or moderate performance (sensitivities of 31.5% and 47.2%, respectively), the combination test increased the sensitivity to 68.5%, showing about twice higher sensitivities than that of FIT alone and an absolute difference of approximately 20 percentage points compared with the sensitivity by the fecal DNA test alone. The synergistic effect of both tests may be because of the mutual exclusiveness of FIT and fecal DNA testing for advanced adenoma screening. Of the 87 patients with positive result(s) of FIT and/or fecal DNA testing of TWIST1 methylation, 27 (31.0%) had a positive result of FIT alone, 46 (52.9%) had...
a positive result of fecal DNA testing of TWIST1 methylation alone, and only 14 (16.1%) had positive results of both FIT and fecal DNA testing of TWIST1 methylation. Thus, fecal testing with the combination of different modalities would increase the sensitivity for the detection of advanced adenoma. The sensitivity of our combination test for advanced adenoma is superior to that of Cologuard, which also uses a combination of FIT and fecal DNA markers (68.5% vs 42.4%) (4,6). However, because Cologuard is currently not available in Japan, we cannot directly compare the clinical performance of both tests. Therefore, further examination outside Japan will be required to compare clinical performance between the 2 tests.

The sensitivities of FIT for the morphologies of polypoid type and nonpolypoid type were 28.2% and 16.1%, respectively, similar to those of another report in which the sensitivities were 30.1% and 18.5%, respectively (16). In this study, the combination test resulted in a higher sensitivity for each tumor type, especially for the nonpolypoid type. The sensitivity of the combination test for polypoid type was 2.3 times higher than that of FIT alone (64.8% vs 28.2%) and that for nonpolypoid type was 4.4 times higher than that of FIT alone (71.0% vs 16.1%). The synergistic effect of both tests also seems to be because of the mutual exclusiveness of FIT and fecal DNA testing as mentioned earlier. Interestingly, the results of FIT and fecal DNA testing in nonpolypoid type were completely mutually exclusive. Thus, fecal DNA testing of TWIST1 methylation would complement FIT for the detection of advanced adenoma. To our knowledge, this is the first report to show the usefulness of the combination of FIT and fecal DNA testing of TWIST1 methylation for the detection of advanced adenoma based on morphological findings.

Although we set a cutoff of 20 μg Hb/g feces for FIT and our combination test, a threshold of 10 μg Hb/g feces for FIT could decrease the number of false negatives of FIT. Indeed, other investigators reported changes of the cutoff point from 20 to 10 μg Hb/g feces decreased false negatives of FIT for advanced adenoma detection from 72.8% (67/92) to 67.4% (62/92) (18). However, changing the cutoff value resulted in a slight decline in specificity from 97.8% (515/527) to 94.7% (499/527) (18). Because fecal hemoglobin concentration is directly related to the severity of colorectal neoplastic disease (19), further studies are needed to confirm the best cutoff point of FIT for our combination test.

Regarding other methylated genes, 2 blood-based tests (detection of circulating tumor DNA in plasma or serum samples) are reported. One is COLVERA and the other is the Epi
proColon 2.0 test. COLVERA detects 2 methylated genes (BCAT1 and IKZF1), and Epi proColon detects 1 methylated gene (septin 9). COLVERA is not intended for screening but can be used with carcinoembryonic antigen for surveillance of recurrent colorectal cancer after primary treatment (20). The Epi proColon 2.0 test can be used for screening, and its sensitivity for colorectal cancer is 61%–83% with specificity of 82%–98% (21). However, the sensitivity falls to 27% for advanced adenoma (22). We previously reported that the combination of circulating methylated septin 9 level by the CORD assay with FIT moderately increases the sensitivity for advanced adenoma from 24% to 44% with a slight decline in the specificity from 92% to 80% compared with the serum methylated septin 9 test alone. Thus, the combination of the fecal DNA test of TWIST1 methylation with FIT seems to offer a better clinical performance to detect advanced adenoma compared with the blood-based test alone and the combination of the blood-based test with FIT. Further studies with larger sample sizes are warranted to confirm our findings.

Specificity
In cancer-screening tests, specificity is as important as sensitivity because specificity affects the number of persons who may have false-positive test results. In this study, the specificity of FIT alone was superior to that of the combination test by a difference of 7.0 percentage points (87.3% vs 80.3%, respectively), resembling another report in which the specificity of FIT alone was superior to that of the combination of FIT with fecal DNA testing of the K-ras mutation and methylation of NDRG4 and BMP3 by 6.6 percentage points (96.4% vs 89.8%, respectively) (4). The baselines of the specificity of the FIT between this study (87.3%) and the reports by other investigator (92.8%–96.4%) (4,5,16) are somewhat different because the target population in each study is different as mentioned earlier. Therefore, further studies using a screening setting population are needed to assess the clinical performance of the combination test.

Implications for future study
Removing adenomatous polyps of the colon and rectum by colonoscopic polypectomy reduces the incidence of colorectal cancer by up to 90% (23). Furthermore, colonoscopic removal of adenomatous polyps prevents death from colorectal cancer through a 53% reduction in mortality (24). Colonoscopy is the best available method to detect and remove colonic polyps and can, therefore, be considered the gold standard for this purpose (25,26). However, the miss rate of colonoscopy for adenomas of any size is 20.9%–24% and that by size is 26%–27% for adenomas of 1–5 mm, 13% for adenomas of 6–9 mm, and 2.1%–6% for adenomas ≥10 mm (27–29). Furthermore, the overall miss rate for adenomas of the flat type is higher than that for the protruding type (44.3% vs 15.1%) (27). The miss rate for flat adenoma by size is 57.8% for adenomas of 1–5 mm, 48.3% for adenomas of 6–9 mm, and 7.6% for adenomas ≥10 mm (27). Because the combination of FIT and fecal DNA testing of TWIST1 methylation by the CORD assay seems to be useful to predict individuals with advanced colorectal adenoma, especially advanced adenoma of the nonpolypoid type, a positive result of the combination test will motivate individuals to undergo colonoscopy. Furthermore, performing the combination test before colonoscopy may predict the presence of colorectal neoplasia, which may lead to more intensive examination during colonoscopy. Confirmatory studies are needed to support our hypothesis.

CONFLICTS OF INTEREST
Guarantor of the article: Yutaka Suehiro, MD, PhD.
Specific author contributors: Y.S.: study concept and design, data collection, statistical analysis, analysis and interpretation of data, drafting of the manuscript, critical revision of the manuscript, and approval of final submission. S. Hashimoto: patient visits, study concept and design, data collection, interpretation of data, critical revision of the manuscript, study supervision, and approval of final submission. A.G., Y.Y., N.Y., and N.S.: patient visits, data collection, interpretation of data, critical revision of the manuscript, and approval of final submission. C.S., T. Tsutsumi, L.A.L., Y.M., and H.Y.: patient visits, data collection, and approval of final submission. T.H.: data collection and approval of final submission. T.M. and T. Takami: interpretation of data, critical revision of the manuscript, and approval of final submission. S.Y. and S. Hazama: patient visits, data collection, interpretation of data, critical revision of the manuscript, and approval of final submission. H.N., I.S., and T.Y.: study concept and design, analysis and interpretation of data, drafting manuscript, critical revision of the manuscript, study supervision, and approval of final submission.

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Study Highlights

WHAT IS KNOWN

- The main approach to colorectal cancer screening is the FIT for which the sensitivity for the detection of advanced colorectal adenoma is low, ranging from 23.8% to 27.1%. For morphological subtypes of advanced adenoma, its sensitivity is 30.1% for polypoid type but only 18.5% for nonpolypoid type.
- Colonoscopy is the gold standard for the detection of colonic polyps. However, the miss rate of colonoscopy is 20.9%–24% for adenomas of any size, and the overall miss rate for adenomas of the flat type is higher than that for the protruding type (44.3% vs 15.1%).
- Fecal DNA testing in combination with FIT has recently been introduced for colorectal neoplasia detection. However, its sensitivity for advanced adenoma remains at a low level of only 42.4%.
- We reported that TWIST1 methylation is specific to colorectal neoplasia and developed a new methylation assay without bisulfite treatment and methylated DNA immunoprecipitation, the CORD assay.

WHAT IS NEW HERE

- Fecal DNA testing of TWIST1 methylation by the CORD assay in combination with the FIT increased sensitivity to 68.5% for the detection of advanced adenoma.
- For morphological subtypes of advanced adenoma, the sensitivity of the combination test for polypoid type was 2.3 times higher than that of FIT alone (54.8% vs 28.2%), and that for nonpolypoid type was 4.4 times higher than that of FIT alone (71.0% vs 16.1%).

TRANSLATIONAL IMPACT

- Performing fecal DNA testing of TWIST1 methylation by the CORD assay in combination with the FIT before colonoscopy might predict the presence of colorectal neoplasia, which might lead to more intensive examination during colonoscopy.

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