Korean J Gastroenterol Vol. 86 No. 1, 43-52
https://doi.org/10.4166/kjg.2025.129
pISSN 1598-9992 eISSN 2233-6869

ORIGINAL ARTICLE | Lower GI Tract

KJG

증상이 없는 평균 위험군 수검자에 대한 대장종양 선별 검사를 위한 분변기반 SDC2 메칠화 검사에 대한 연구

최형일[1], 차재명[1,2], 김영상[3], 조대현[4], 박한주[5], 나수영[6], 김지혜[7], 김현건[8], 박영진[9], 권혜정[10], 김경옥[11], 이건호[12], 이유진[13]

강동경희대학교병원 내과[1], 경희대학교 의과대학 내과[2], CHA 의과학대학교 분당차병원 가정의학과[3], 성균관대학교 의과대학 삼성창원병원 내과[4], 유성선병원 가정의학과[5], 가톨릭대학교 의과대학 인천성모병원 내과[6], 연세대학교 의료원 세브란스 체크업 건강증진센터[7], 순천향대학교 의과대학 내과[8], 동아대학교 의과대학 동아대학교병원 가정의학과[9], 일신기독병원 내과[10], 영남대학교 의과대학 내과[11], 대구가톨릭대학교병원 가정의학과[12], 계명대학교 의과대학 소화기내과[13]

Stool DNA-based SDC2 Methylation Test for the Screening of Colorectal Neoplasia in an Asymptomatic, Average-Risk Population

Hyoung Il Choi[1], Jae Myung Cha[1,2], Young Sang Kim[3], Dae Hyeon Cho[4], Han Ju Pack[5], Soo-Young Na[6], Ji Hye Kim[7], Hyun Gun Kim[8], Young-Jin Park[9], Hye Jung Kwon[10], Kyeong Ok Kim[11], Geon Ho Lee[12], and Yoo Jin Lee[13]

Department of Internal Medicine, Kyung Hee University Hospital at Gangdong[1], Seoul; Department of Internal Medicine, Kyung Hee University College of Medicine[2], Seoul; Department of Family Medicine, CHA Bundang Medical Center, CHA University[3], Seoul; Department of Internal Medicine, Samsung Changwon Hospital, Sungkyunkwan University of Medicine[4], Changwon; Department of Family Medicine, Yuseong Sun Hospital[5], Daejeon; Department of Internal Medicine, Incheon St. Mary's Hospital, College of Medicine, The Catholic University of Korea[6], Incheon; Department of Health Promotion, Severance Check-Up, Yonsei University Health System[7], Seoul; Department of Internal Medicine, Soonchunhyang University College of Medicine[8], Seoul; Department of Family Medicine, Dong-A University College of Medicine, Dong-A University Medical Center[9], Busan; Department of Internal Medicine, Ilsin Christian Hospital[10], Busan; Department of Internal Medicine, Yeungnam University College of Medicine[11], Daegu; Department of Family Medicine, Daegu Catholic University Medical Center[12], Daegu; Division of Gastroenterology and Hepatology, Department of Internal Medicine, Keimyung University School of Medicine[13], Daegu, Korea

Background/Aims: Programmatic screening for colorectal cancer (CRC) could maximize the impact of screening in the average-risk population, but the diagnostic performance of a stool DNA-based *Syndecan-2* methylation (*meSDC2*) test has only been reported in case-control studies or high-risk populations. This study examined the performance of a stool DNA-based *meSDC2* test for CRC in an average-risk population from a real-world setting.

Methods: This retrospective, multicenter study included consecutive asymptomatic, average-risk individuals for CRC who completed a *meSDC2* stool test at 18 hospitals. The clinical performance of the *meSDC2* stool test, including the positive rate, adherence to confirmatory colonoscopy, and the positive predictive value (PPV) for colorectal neoplasia (CRN), was assessed.

Results: Over 54 months, 4,910 individuals completed the *meSDC2* stool test, with 249 (5.1%) testing positive. The colonoscopy compliance rate after a positive test was 61.0% (n=152). Among 121 individuals with available colonoscopy data, the PPV for any CRN, advanced neoplasia, and CRC were 39.7%, 12.4%, and 2.5%, respectively. Colonoscopy after a positive meSDC2 test ensured a high-quality examination, as reflected by the 100% cecal intubation rate, 97.5% adequate preparation quality, and an average withdrawal time of 11.2 min. Among those with a positive *meSDC2* test, a family history of CRC was a significant predictor of any CRN (p=0.029) and advanced neoplasia (p=0.003).

Conclusions: A stool DNA-based meSDC2 test in average-risk individuals for CRC revealed a high PPV for any CRN in a real-world setting, highlighting its potential as a screening modality in programmatic CRC screening. **(Korean J Gastroenterol 2026;86:43-52)**

Key Words: Biomarkers; Colorectal neoplasms; DNA methylation; Feces; Mass screening

Received November 7, 2025. **Revised** November 11, 2025. **Accepted** November 12, 2025.

교신저자: 차재명, 05278, 서울시 강동구 동남로 892, 강동경희대병원 내과
Correspondence to: Jae Myung Cha, Department of Internal Medicine, Kyung Hee University Hospital at Gangdong, 892 Dongnam-ro, Gangdong-gu, Seoul 05278, Korea.
Tel: +82-2-440-6113, Fax: +82-2-440-6295, E-mail: drcha@khu.ac.kr, **ORCID:** https://orcid.org/0000-0001-9403-230X

Financial support: None. Conflict of interest: None.

INTRODUCTION

Colorectal cancer (CRC) is the fourth most common malignancy and the fifth leading cause of cancer-related deaths globally among the 36 major cancers.[1] The incidence of CRC is five times higher in North America, Europe, and Japan, and four times higher in South Korea and China compared to regions with the lowest incidence.[1] In South Korea, CRC ranked second in incidence and third in mortality among the top ten major cancers in 2022. The US Multi-Society Task Force on CRC recommends a colonoscopy every 10 years and an annual fecal immunochemical test (FIT) as Tier 1 options for CRC screening.[2] Although colonoscopy is the gold standard, it is limited by low compliance, high cost, challenges in bowel preparation, and its invasive nature with potential complications.[3] FIT is used widely in organized CRC screening programs, but it also has limitations, including low participation rates, difficulties in sample collection, and a low positive predictive value (PPV) for colorectal neoplasia (CRN). Therefore, expanding CRC screening modalities to less invasive yet more effective methods is necessary.

CRC development is associated with genetic and epigenetic changes. Hypermethylation of CpG islands in gene promoters is a common epigenetic alteration in human carcinogenesis.[3] DNA methylation biomarkers are stable in various sample types and offer high diagnostic sensitivity. Therefore, stool DNA methylation tests may improve CRC detection.[3,4] Methylation of Syndecan-2 (*meSDC2*) is a frequent epigenetic alteration in CRC carcinogenesis, detectable in tissue, stool, and blood samples.[5] Recently, a stool DNA-based *meSDC2* test was approved for commercial use in South Korea because of its high sensitivity and specificity for CRC.[3,5] A recent prospective study revealed its diagnostic performance and value in a high-risk CRC population.[6] The use of this test has increased post-approval owing to its non-invasive nature and greater convenience compared to colonoscopy, and promising diagnostic performance compared to FIT.[3,5,6] Nevertheless, real-world post-approval performance data are lacking.

The effectiveness of any CRC screening modality depends on the diagnostic performance and patient adherence, which can vary across populations. Currently, no data exist on adherence and diagnostic performance of stool DNA-based *meSDC2* testing in average-risk individuals because previous studies primarily involved a case-control design[5] or high-risk populations.[6] Programmatic CRC screening—system-wide, organized screening for all members of a healthcare plan—typically targets average-risk individuals. Thus, understanding the diagnostic performance of the stool DNA-based *meSDC2* test in this population is a key step toward developing a population-based CRC screening strategy using stool DNA testing.

This study evaluated the diagnostic performance of the stool DNA-based *meSDC2* test for CRN in an average-risk population within a multicenter, real-world setting.

SUBJECTS AND METHODS

1. Study design

This retrospective, multicenter, consecutive cohort study included all asymptomatic, average-risk individuals who underwent a stool DNA-based *meSDC2* test (EarlyTect®ColonCancer; Genomictree, Inc., Daejeon, Korea) between February 2019 and July 2023 at 18 medical institutions. The *meSDC2* stool test was approved for commercial use in August 2018 in South Korea. In January 2019, online and offline education sessions were conducted across various medical institutions, covering the assay procedure, instrument usage, variable definitions, and the importance of data quality. This study was approved by the Institutional Review Board of Kyung Hee University Hospital at Gangdong, Seoul, South Korea (IRB No. KHNMC 2023-10-016), as well as by all data-providing institutions. A public Institutional Review Board approved the primary care institutions without an Institutional Review Board. Informed consent from each individual was waived because the study was retrospective in nature, and anonymous clinical data without personal identifiers were used.

2. Participants

All participants were asymptomatic, average-risk adults aged 30–80 years who underwent a *meSDC2* stool test during the study period. In clinical practice, the *meSDC2* stool test was recommended for individuals seeking CRC screening during routine health check-ups who wanted to avoid the inconvenience of a colonoscopy or bowel preparation. This test was also recommended for CRC screening in individuals at high risk of complications during a colonoscopy because of poor general condition, comorbid diseases, or previous failure of cecal intubation.

The age criteria in this study were consistent with the labeling from the Ministry of Food and Drug Safety of South Korea for this test. Individuals were excluded if they had any of the following high-risk factors of CRC: a previous history of CRC, inflammatory bowel disease, hereditary CRC syndromes, or signs or symptoms suggestive of CRC, such as colorectal bleeding, iron-deficiency anemia, recent changes in bowel habits, or significant weight loss. Individuals were also excluded from data analysis if they submitted inadequate stool samples (<2 g of stool, samples submitted >4 weeks after collection, or samples collected during the bowel preparation for colonoscopy) or had incomplete clinical information. An average-risk population for CRC was defined as the screening-eligible population, excluding those at higher risk based on a prior CRC diagnosis, family history of CRC, or presence of inflammatory bowel disease or Lynch syndrome.[7] Therefore, all individuals included in this study were considered average-risk based on the exclusion criteria. The definition of family history has varied across studies and is often unavailable in retrospective data. Thus, individuals with a family history of CRC were not excluded.

3. Data collection

A uniform case report form, including the definitions of all variables, was used for data abstraction. The following medical information was collected: institution and physician data (hospital location, physician specialty, and hospital type), patient data (age, sex, body mass index [BMI], smoking status, alcohol use, family history of CRC, and prior colonoscopy), *meSDC2* test results, and colonoscopy data (size, location, number, and histology of CRNs, withdrawal time, cecal intubation rate, and bowel preparation quality).

In clinical practice, only individuals with a positive *meSDC2* stool test were recommended to undergo a confirmatory colonoscopy. All individuals were included in the primary analysis regardless of the colonoscopy preparation quality. Only the subsequent adequate colonoscopy was included in the analysis if the initial diagnostic colonoscopy was inadequate.

The *meSDC2* test results were independently compared with the colonoscopy and pathology findings as reference standards. Based on the complete colonoscopy and pathology results, individuals were categorized as having any CRN, advanced neoplasia (AN), or CRC. AN was defined as CRC, advanced adenoma, or both, with advanced adenomas being defined as adenomas ≥10 mm in size, with high-grade dysplasia, or with ≥25% villous components. The lesion sizes were obtained from pathology reports and endoscopic estimates. Right-sided lesions were defined as those located at or proximal to the splenic flexure. Left-sided lesions were defined as those distal to the splenic flexure. The most advanced or largest lesion was used for classification when a participant had multiple CRN types.

4. Stool DNA–based *meSDC2* test

The stool collection procedure has been described in previous studies.[8,9] All participants were required to provide at least 2 g of stool using a plastic collection tube provided in the kit, with no dietary or medication restrictions. The collected fecal samples were sent to a central laboratory from each hospital according to the standard operating procedure, within four weeks of collection, and at ambient temperature. The stool DNA was isolated using either the GT Nucleic Acid PREP Kit II (Genomictree, Inc.) or the Chemagic 360-D instrument with the Chemagic DNA Stool 3k Kit H24 (PerkinElmer, Waltham, MA, USA), as reported elsewhere.[6,9] The DNA concentration was measured using the Qubit dsDNA BR Assay Kit (Thermo Fisher Scientific, Waltham, MA, USA).

The methylation status of *SDC2* DNA in the stool samples was determined using a real-time polymerase chain reaction.[9] The *meSDC2* tests were conducted with two DNA concentrations (0.5 ng and 0.1 ng) diluted in 2 μg of *meSDC2*-negative stool DNA.[6,8,10] The reproducibility, repeatability, lot-to-lot variation, mean C_T, standard deviation, and coefficient of variation (%) have been reported in previous studies.[6,8,10] The test positivity was determined based on a predefined cutoff value.[6,8,10]

5. Statistical analysis

The primary study endpoints included the test positivity rate, adherence to diagnostic colonoscopy, and the PPV of any CRN for the *meSDC2* stool test. No statistical calculation was performed for the sample size because this was not a randomized controlled trial. Based on previous studies,[5,8,10] a *meSDC2* test positivity rate of approximately 4% was assumed, and it was anticipated that at least 60% of test-positive participants would undergo colonoscopy. Therefore, at least 120 colonoscopy results were expected from 5,000 *meSDC2* stool tests. With 5,000 tests, including 200 positive

and 4,800 negative cases with a 4% positive rate, it was calculated that the power to detect a difference between the two groups at the 5% significance level can be expected to exceed 90%.

Continuous variables were presented as the mean ± standard deviation (SD) or as medians with interquartile ranges (IQRs), and compared using the Student's *t*-test or Wilcoxon rank-sum test, as appropriate. The categorical variables were reported as numbers (percentages) and compared between subgroups using Fisher's exact test or X^2 tests. All statistical tests were two-sided, and a p-value <0.05 was considered significant. Statistical analyses were conducted using the Statistical Package for the Social Sciences Korea plus 28.0 network version (IBM Co., Armonk, NY, USA).

RESULTS

A total of 4,968 tests were completed during the study period; 58 participants were excluded from data analysis (Fig. 1) for the following reasons: inadequate stool sample (n=1), insufficient clinical data (n=8), age <30 years (n=4), and age >80 years (n=45).

1. Baseline characteristics

Table 1 lists the baseline clinical characteristics of the 4,910 participants included in this analysis. The mean age was 51 years, with 48.7% and 51.3% aged 30–49 years and 50–80 years, respectively. The cohort had a male predominance (63.1%). Among the participants, 36.2%, 42.7%, and 40.4% were obese (BMI ≥25 kg/m²), alcohol drinkers, and current or former smokers, respectively. In addition, 5.9% had a positive family history of CRC, and 34.8% had no history of colonoscopy within the past five years.

2. Characteristics according to *meSDC2* stool tests

Among the 4,910 participants included in the analysis, 249 tested positive, yielding an overall test-positive rate of 5.1%

Table 1. Baseline Characteristics of the Study Participants

Clinical characteristics	Results
Number of subjects	4,910
Age	51.0±11.2
Age groups	
30–49 years	2,393 (48.7)
50–80 years	2,517 (51.3)
Sex (men)	3,100 (63.1)
Body mass index (kg/m^2)	24.1±3.5
Obesity (≥ 25 kg/m^2)	1,776 (36.2)
Alcohol drinking (yes)	2,099 (42.7)
Smoking (current or Ex)	1,986 (40.4)
Family history of CRC (yes)	290 (5.9)
History of colonoscopy within 5 years	
Yes	2,060 (42.0)
No	1,711 (34.8)
Uncertain	1,139 (23.2)

Values are presented as number (%) or mean±standard deviation.
CRC, colorectal cancer.

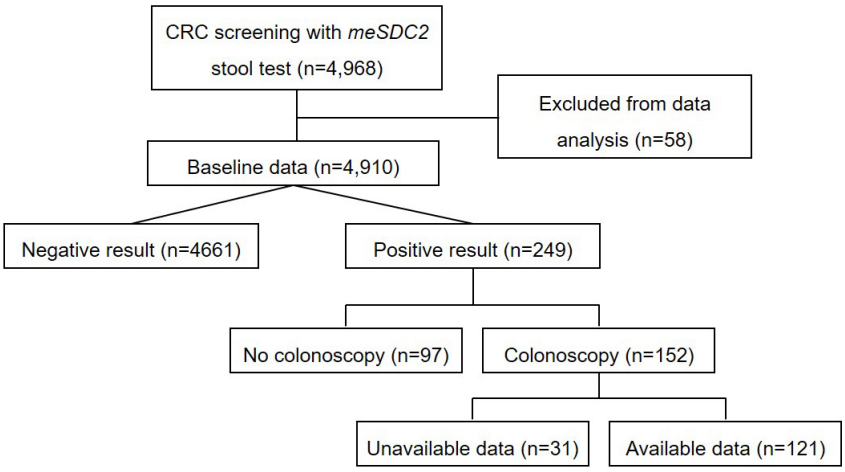

Fig. 1. Study flow diagram. A total of 4,968 subjects completed *meSDC2* stool tests over the study period, and 58 subjects were excluded from data analysis. Among 4,910 baseline subjects, 249 subjects had positive results, and only 152 of them underwent diagnostic colonoscopy. Finally, colonoscopy data were available for 121 of 152 participants.

Table 2. Characteristics According to the *meSDC2* Stool Tests

Clinical characteristics	*meSDC2* stool tests		p-value
	Negative (n=4,661)	Positive (n=249)	
Age	50.7±11.1	55.0±12.3	<0.001
Age groups			<0.001
30–49 years	2,301 (49.4)	92 (36.9)	
50–80 years	2,360 (50.6)	157 (63.1)	
Sex (men)	2,934 (62.9)	166 (66.6)	0.236
Body mass index (kg/m^2)	24.1±3.5	24.3±3.5	0.317
Obesity (≥ 25 kg/m^2)	1,683 (36.1)	93 (37.3)	0.610
Alcohol drinking (yes)	1,990 (42.7)	109 (43.8)	0.615
Smoking (current or Ex)	1,864 (40.0)	122 (49.0)	0.002
Family history of CRC (yes)	265 (5.7)	25 (10.0)	0.007
History of CS within 5 years (yes)	1,930 (41.4)	130 (52.2)	<0.001

Values are presented as mean±standard deviation or number (%).
CRC, colorectal cancer; CS, colonoscopy.

Table 3. Colonoscopy Data of Subjects who had Positive *meSDC2* Stool Tests

Colonoscopy data	Results
Colonoscopy compliance	152/249 (61.0)
Days from *mSDC2* to CS	61.5 (28.0–355.3)
Available colonoscopy data	121/152 (79.6)
Colonoscopy outcomes	
Quality data	
Cecal intubation rate	121 (100.0)
Adequate preparation (fair–excellent)	118 (97.5)
Withdrawal time (min)	11.2±6.7
Histopathology data	
Any colorectal neoplasia	48 (39.7)
Colorectal cancer	3 (2.5)
Advanced neoplasia	15 (12.4)
Number of neoplasia	1.2±1.4
Size of neoplasia	6.2±4.5
Proximal location of neoplasia	25 (52.1)

Values are presented as number (%), median (interquartile range), or mean±standard deviation.
CS, colonoscopy.

(Fig. 1). Table 2 lists the clinical characteristics according to *meSDC2* stool test results. Participants with a positive test were more likely to be older (p<0.001), smokers (p=0.002), and have a family history of CRC (p=0.007). In particular, 49.8% of the participants with a positive test had no history of colonoscopy within the past five years.

3. Colonoscopy data

One hundred and fifty-two participants (61.0%) underwent diagnostic colonoscopy, with a median delay of 61.5 days (IQR 28.0–355.3) after receiving a positive test result. The remaining 97 participants (39.0%) did not undergo a diagnostic colonoscopy (Table 3). Of those who did, the colonoscopy data were available for 121 participants (79.6%) because the remaining 20.4% had procedures performed at other hospitals where medical records could not be accessed (Fig. 1).

The colonoscopy quality was high, with a 100% cecal intubation rate, 97.5% adequate bowel preparation, and a mean withdrawal time of 11.2 min. Neoplastic lesions were observed in 48 participants (39.7% PPV for CRN). Of these, 15 had AN (12.4% PPV for AN), and three were diagnosed with CRC (2.5% PPV for CRC). Right-sided neoplasia was present in 25 of the 48 participants with CRN (52.1% PPV for proximal CRN).

4. Predictors of colorectal neoplasia

Table 4 lists the clinical predictors of any CRN and AN among participants with a positive *meSDC2* stool test. A family history of CRC was significantly associated with any CRN (p=0.029) and AN (p=0.003). Older age was associated only with any CRN (p=0.039).

DISCUSSION

Most programmatic CRC screening is based on stool tests

Table 4. Predictors of Colorectal Neoplasia and Advanced Neoplasia in Subjects Who had Positive *meSDC2* Stool Tests

Variables	Any neoplasia			Advanced neoplasia		
	Negative (n=73)	Positive (n=48)	p-value	Negative (n=106)	Positive (n=15)	p-value
Age	52.6±11.1	57.0±11.6	0.039	54.5±11.4	52.9±12.1	0.616
Age groups			0.214			0.461
30–49 years	31 (42.5)	15 (31.3)		39 (36.8)	7 (46.6)	
50–80 years	42 (57.5)	33 (68.8)		67 (63.2)	8 (53.4)	
Sex (men)	43 (58.9)	35 (72.9)	0.115	71 (38.7)	7 (46.7)	0.124
BMI (kg/m^2)	24.7±3.8	24.4±3.8	0.681	24.6±3.6	24.5±5.1	0.930
Obesity	28 (38.4)	18 (37.5)	0.878	41 (38.7)	5 (33.3)	0.670
Alcohol drinking	28 (38.4)	22 (45.8)	0.488	42 (39.6)	8 (53.4)	0.342
Smoking	43 (58.9)	21 (43.8)	0.071	47 (44.3)	8 (53.4)	0.554
Family history of CRC	5 (6.8)	11 (22.9)	0.029	10 (9.4)	6 (40.0)	0.003
No history of CS within 5 years	22 (30.1)	18 (37.5)	0.625	67 (63.2)	7 (46.7)	0.157

Values are presented as mean±standard deviation or number (%).
BMI, body mass index; CRC, colorectal cancer; CS, colonoscopy.

such as FIT, whereas colonoscopy remains the dominant screening modality for opportunistic CRC screening. Although FIT is a non-invasive and simple screening test that does not require dietary or medication restriction, it is limited by its relatively lower sensitivity for detecting CRC, false negatives, reduced sample stability under high temperatures, the inconvenience of stool sampling, and the need for annual testing. Therefore, emerging tests, such as stool DNA tests, could offer higher sensitivity for CRN and allow for less frequent testing. Compared to the multi-target stool DNA test, the *meSDC2* stool test provides several notable advantages (Supplementary Table 1), suggesting its potential as a promising tool for programmatic CRC screening. The major clinical implication of this study is that the diagnostic performance of a stool DNA-based *meSDC2* test was evaluated in the average-risk population for CRC, suggesting this test as a potential screening modality in programmatic CRC screening.

The stool DNA-based *meSDC2* test shows promise for CRN detection because methylation occurs in precancerous lesions or early-stage CRCs.[5,8,10] To the best of the authors' knowledge, this is the second largest real-world study evaluating the clinical performance of a stool DNA-based *meSDC2* test in an asymptomatic, average-risk population. Most previous studies on the *meSDC2* stool test were either case-control in design[5,8,10] or focused on high-risk populations.[6,9] Therefore, real-world, multicenter studies such as the present study are necessary to determine its utility in average-risk, asymptomatic individuals.[11] In this study, 5.1% of the participants tested positive on the *meSDC2* stool test, and the PPV was 39.7% and 12.4% for any CRN and AN, respectively. Among the participants with a positive meSDC2 test, those with a family history of CRC were significantly more likely to have CRN or AN. Therefore, individuals with a family history of CRC who are reluctant to undergo a colonoscopy could be recommended for the *meSDC2* stool test.

Importantly, the overall PPV of the *meSDC2* test for CRC in the present cohort was 2.5%, which is 2.5 times higher than the 1% PPV reported for multi-target stool DNA testing in real-world settings.[12] A next-generation multi-target stool DNA test, designed to improve the specificity and reduce false positives compared to the original test approved in 2014, reported PPVs for AN and CRC of 11.1% and 3.4%, respectively.[13] Thus, the diagnostic performance of the *meSDC2* stool test for CRN appears promising.

The 5.1% positivity rate of the *meSDC2* test was 2.8 times lower than the 14.1% reported in multi-target stool DNA testing,[12] suggesting that the *meSDC2* test may be a more efficient method for CRC screening with fewer false positives. In the Korean national CRC screening program, the pooled PPV of FIT for CRC over 14 years was only 2.1%,[14] which is much lower than the PPV observed for the *meSDC2* test in the present study. In a recent Chinese study, the *meSDC2* test had a higher area under the curve (AUC) value for CRC than FIT, but the difference was not statistically significant.[11] Hence, head-to-head comparisons between the *meSDC2* test, FIT, and multi-target stool DNA tests in the same population

are needed. In this study, 49.8% of the participants testing positive for *meSDC2* had not undergone a colonoscopy within the past five years. This figure is similar to previous reports using multi-target stool DNA tests.[12] Thus, stool DNA tests such as *meSDC2* or multi-target DNA tests may provide a valuable gateway to colonoscopy engagement for individuals reluctant to undergo a colonoscopy. Moreover, colonoscopy following a positive *meSDC2* test may result in high-quality procedures. The overall PPV for any CRN in the present cohort was 39.7%, which is approximately 15% higher than the benchmark adenoma detection rate (ADR) for average-risk screening colonoscopies.[15] A meta-analysis of real-world observational studies, involving 31 studies and 3,644,561 participants, reported ADRs of only 26.5% overall, 34.4% after fecal occult blood testing, and 26.6% for primary colonoscopy screening.[16] These findings reflect the suboptimal quality of a colonoscopy in average-risk populations in real-world settings.

The high PPV in the present study is likely due to CRN enrichment in the population tested (i.e., those with positive *meSDC2* results) and the high quality of the colonoscopy exams. The quality indicators in this study, such as a 100% cecal intubation rate, 97.5% adequate bowel preparation, and a mean withdrawal time of 11.2 min, may reflect more careful examinations performed by endoscopists aware of the positive *meSDC2* test results. Unfortunately, 39% of patients with a positive *meSDC2* test result did not undergo a diagnostic colonoscopy, despite the potential risk of CRC. This may be due to patient refusal of an invasive procedure or a lack of understanding about the implications of a positive test result. Such selection bias could have resulted in an overestimation of the PPV because 39% did not undergo a colonoscopy, and 20.4% were excluded because the medical records from outside hospitals were unavailable. In a recent, prospective, multicenter, community-based study, similarly, the colonoscopy completion rate was only 32.6% after a positive *meSDC2* test.[11] The low colonoscopy uptake after a positive *meSDC2* test is similar to the low acceptance rates of colonoscopy observed following positive FIT results. These findings highlight the need for widespread education for physicians and patients to promote optimal use of the *meSDC2* stool test in CRC screening. Several evidence-based interventions could be implemented to enhance the colonoscopy completion rates following a positive *meSDC2* stool test, including patient navigation programs, mitigation of the structural barriers to colonoscopy, such as cost and scheduling difficulties, and the strategic use of incentives and motivation.[17,18]

As a potential biomarker for CRN, the *meSDC2* serum test showed 87.0% sensitivity and 95.2% specificity for CRC detection.[5] Nevertheless, stool samples may be more appropriate for CRC screening because neoplastic cells exfoliate into the colon lumen before vascular invasion occurs during carcinogenesis.[3] Recently, the *meSDC2* stool test showed excellent performance for CRC detection, with a sensitivity, specificity, and AUC of 90.2%, 90.2%, and 0.90, respectively (95% confidence interval [CI] 0.88–0.93).[8] A multicenter, prospective study in Korea focused on a high-risk CRC population.[6,9] The *meSDC2* stool test detected 20 CRCs out of 1,124 participants, with a sensitivity, specificity, and AUC of 95%, 81.5%, 8.6%, respectively, and a negative predictive value (NPV) of 99.9%. A study in Taiwan that included 138 participants (62 CRC patients and 76 healthy participants) reported sensitivity, specificity, PPV, NPV, and AUC values for the *meSDC2* stool test of 77.4%, 88.2%, 84.2%, 82.7%, and 0.87 (95% CI 0.76–0.89), respectively.[19] In a Chinese study of 497 participants (196 CRC patients, 122 with adenomas, and 179 normal participants), the AUC of the *meSDC2* stool test for CRC was 0.92 (95% CI 0.89–0.95), and 81.1% of CRC cases were detected at a specificity of 93.3%.[20] Nevertheless, both studies were limited by their case-control design and small sample sizes.[19,20]

Recently, the *meSDC2* stool test was also introduced commercially in China as "Colosafe®," with its performance evaluated in three Chinese hospitals.[21] Among the 1,110 participants who underwent testing and reference colonoscopy, the sensitivity and specificity for CRC (n=359) were 83.8% and 98.0%, respectively. The test also showed 42.1% sensitivity for advanced adenomas (AA, n=38) and 87.0% sensitivity for early-stage CRC.[21] Nevertheless, the results are limited because the study population was a highly selected Chinese cohort, with a high CRC detection rate (32.3%). In another study of 1,035 high-risk Chinese individuals, the sensitivity of the *meSDC2* test for CRC and AA was 87.5% and 40.0%, respectively. The PPV for CRC, AA, and AN was 16.1%, 29.9%, and 46.0%, respectively.[22] This study was also limited by the use of an arbitrary definition of a high-risk group, which included factors such as a family history of CRC in first-degree relatives, history of polyps, or a history of two or more of the following: chronic diarrhea, chronic constipation, mucoid

bloody feces, chronic appendicitis or appendectomy, chronic cholecystitis or cholecystectomy, and psychiatric trauma.[21] Hence, the performance of the *meSDC2* stool test depends on the study population. Accordingly, further studies will be needed to determine the optimal target population for this promising application.

Two meta-analyses have reported the pooled diagnostic performance of *meSDC2* for CRC detection.[23,24] In a meta-analysis of 11 published articles, the pooled diagnostic odds ratio and AUC for *meSDC2* were 52.46 (95% CI 30.43–90.45) and 0.94 (95% CI 0.92–0.96), respectively.[23] This analysis, however, included *meSDC2* results from stool, plasma, serum, and bowel lavage fluid. Another meta-analysis of 12 studies reported a pooled sensitivity and specificity of 0.81 (95% CI 0.74–0.86) and 0.95 (95% CI 0.93–0.96), respectively.[24] This study also included stool and blood-based *meSDC2* tests, which limits its applicability to stool testing alone. Therefore, new meta-analyses focusing exclusively on *meSDC2* stool tests are warranted. Novel stool DNA biomarker panels that combine methylated SDC2 with other markers, such as SFRP2, KRAS mutations, and hemoglobin,[25] or methylated *SDC2* and SEPT9,[26] have shown excellent diagnostic performance for CRC detection. These findings suggest that combining *meSDC2* with other biomarkers may enhance the accuracy of CRC screening. The global incidence of early-onset CRC has been increasing in recent years, and its prognosis is generally less favorable than that of late-onset CRC.[27,28] Therefore, there is a growing need for tailored screening strategies targeting the younger population. The role of non-invasive *meSDC2* stool test may be gaining attention, particularly in younger populations who are less inclined to undergo invasive colonoscopy.

This study had some limitations. First, its retrospective design is a significant limitation because the test-negative participants did not undergo a colonoscopy in clinical practice. Nevertheless, this design allowed an examination of the largest number of cases in a real-world setting. Second, despite the inclusion of a multicenter, hospital-based cohort ranging from primary to tertiary care, it remains uncertain whether the data can represent the general population eligible for mass CRC screening from a different population. Furthermore, the study population was composed almost entirely of Korean individuals. Therefore, validation in other racial and ethnic groups from large-scale validation studies will be necessary to evaluate its effectiveness in that context. Third, the performance of the *meSDC2* test was not compared with FIT, a widely used tool for mass CRC screening. Currently, there is only one direct comparison between the *meSDC2* stool test and FIT.[29] In that Chinese study,[29] among 111 CRC cases, the sensitivities of the *meSDC2* stool test and FIT were 79.3% (95% CI 70.5–86.4%) and 93.7% (95% CI 87.4–97.4%), respectively. Given that the previous meta-analysis has reported a pooled sensitivity of 78% for FIT in detecting CRC,[30] the markedly higher sensitivity observed in the previous Chinese study indicates the need for further validation. Considering the low positivity rate (only 1.1–2.0%) of quantitative FIT in Korea's National Screening Program [31,32] and the pooled PPV of FIT for CRC,[18] the *meSDC2* stool test may offer advantages over FIT. Nevertheless, comparative studies between the two are needed. Fourth, the relatively small number of CRC and AN cases in the present study limits its statistical power for assessing the test performance, particularly in estimating the PPV of AN according to size, histologic features, and location. This limitation may be explained by the fact that this study focused on an average-risk, asymptomatic population, which naturally has a low prevalence of CRC and AN compared to high-risk groups. Fifth, although this study targeted an average-risk population, individuals with a family history of CRC were not excluded. A family history of CRC is typically defined as having ≥1 first-degree relative diagnosed before 60 years of age or ≥2 first-degree relatives diagnosed at any age. Individuals with a family history of CRC were not excluded from this study because such detailed information was not available in this retrospective dataset. Finally, the sensitivity and specificity of the *meSDC2* test could not be calculated because the test-negative participants did not undergo colonoscopy, and these performance metrics have been reported in previous case-control studies.[8]

In conclusion, this large real-world study of the *meSDC2* stool test in asymptomatic, average-risk individuals for CRC showed a high PPV for CRN, which may serve as a complementary modality in programmatic CRC screening. Nevertheless, these findings need to be confirmed in other racial and ethnic populations.

AUTHOR CONTRIBUTIONS

Conceptualization: Jae Myung Cha. Data curation: Young Sang Kim, Dae Hyeon Cho, Han Ju Pack, Soo-Young Na, Ji

Hye Kim, Hyun Gun Kim, Young-Jin Park, Hye Jung Kwon, Kyeong Ok Kim, Geon Ho Lee, Yoo Jin Lee. Formal analysis: Hyoung Il Choi, Jae Myung Cha. Investigation: Hyoung Il Choi, Jae Myung Cha. Methodology: Hyoung Il Choi, Jae Myung Cha. Resources: Young Sang Kim, Dae Hyeon Cho, Han Ju Pack, Soo-Young Na, Ji Hye Kim, Hyun Gun Kim, Young-Jin Park, Hye Jung Kwon, Kyeong Ok Kim, Geon Ho Lee, Yoo Jin Lee. Supervision: Jae Myung Cha. Writing – original draft: Hyoung Il Choi, Jae Myung Cha. Writing – review & editing: All authors. Approval of final manuscript: all authors.

ACKNOWLEDGEMENTS

We specially thank you for the data collection for Dong Hyun Choi (Han Sarang Hospital), Gyu Hyuk Shim (We Want Healthcare), Hyo Seon Kim (Seoul Hyundai Hospital), Hyeong Joong Jeong (Daehang Hospital), Yong Min Cho (Hu-Hospital), Hye Jin Go (Kyungpook National University Hospital) and A Sol Kim (Kyungpook National University Chilgok Hospital).

SUPPLEMENTARY MATERIAL

Supplementary material is available at the Korean Journal of Gastroenterology website (https://www.kjg.or.kr/).

REFERENCES

1. Bray F, Laversanne M, Sung H, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2024;74:229-263.
2. Rex DK, Boland CR, Dominitz JA, et al. Colorectal cancer screening: recommendations for physicians and patients from the u.s. multi-society task force on colorectal cancer. Gastroenterology 2017;153:307-323.
3. Kim JH, Park SC. Syndecan-2 methylation as a new biomarker for early detection of colorectal neoplasm. Gut Liver 2018;12:479-480.
4. Park YS, Kim DS, Cho SW, et al. Analysis of syndecan-2 methylation in bowel lavage fluid for the detection of colorectal neoplasm. Gut Liver 2018;12:508-515.
5. Oh T, Kim N, Moon Y, et al. Genome-wide identification and validation of a novel methylation biomarker, SDC2, for blood-based detection of colorectal cancer. J Mol Diagn 2013;15:498-507.
6. Kim CW, Kim H, Kim HR, et al. A Stool DNA-based SDC2 methylation test for the early detection of colorectal cancer in an asymptomatic, high-risk population: A multicenter prospective randomized trial. Am J Gastroenterol 2025;120:614-622.
7. Ebner DW, Kisiel JB, Fendrick AM, et al. Estimated average-risk colorectal cancer screening-eligible population in the US. JAMA Netw Open 2024;7:e245537.
8. Han YD, Oh TJ, Chung TH, et al. Early detection of colorectal cancer based on presence of methylated syndecan-2 (SDC2) in stool DNA. Clin Epigenetics 2019;11:51.
9. Kim CW, Kim H, Kim HR, et al. Colorectal cancer screening using a stool DNA-based SDC2 methylation test: a multicenter, prospective trial. BMC Gastroenterol 2021;21:173.
10. Oh TJ, Oh HI, Seo YY, et al. Feasibility of quantifying SDC2 methylation in stool DNA for early detection of colorectal cancer. Clin Epigenetics 2017;9:126.
11. Zhao S, He Z, Sui X, Zhang S, Li Z, Bai Y. Real-world stool-based syndecan-2 methylation test improved detection of advanced colorectal neoplasia for colorectal cancer screening: a prospective, multicenter, community-based study. Gastroenterology 2024;167:611-614.e7.
12. Eckmann JD, Ebner DW, Bering J, et al. Multitarget stool DNA screening in clinical practice: high positive predictive value for colorectal neoplasia regardless of exposure to previous colonoscopy. Am J Gastroenterol 2020;115:608-615.
13. Imperiale TF, Porter K, Zella J, et al. Next-Generation multitarget stool DNA Test for colorectal cancer screening. N Engl J Med 2024;390:984-993.
14. Park B, Her EY, Lee K, et al. Overview of the National cancer screening program for colorectal cancer in Korea over 14 years (2004-2017). Cancer Res Treat 2023;55:910-917.
15. Rex DK, Schoenfeld PS, Cohen J, et al. Quality indicators for colonoscopy. Gastrointest Endosc 2015;81:31-53.
16. Fernandes C, Estevinho M, Marques Cruz M, et al. Adenoma detection rate by colonoscopy in real-world population-based studies: a systematic review and meta-analysis. Endoscopy 2025;57:49-61.
17. Selby K, Baumgartner C, Levin TR, et al. Interventions to improve follow-up of positive results on fecal blood tests: a systematic review. Ann Intern Med 2017;167:565-575.
18. Jain S, Maque J, Galoosian A, Osuna-Garcia A, May FP. Optimal strategies for colorectal cancer screening. Curr Treat Options Oncol 2022;23:474-493.
19. Su WC, Kao WY, Chang TK, et al. Stool DNA test targeting methylated syndecan-2 (SDC2) as a noninvasive screening method for colorectal cancer. Biosci Rep 2021;41:BSR20201930.
20. Niu F, Wen J, Fu X, et al. Stool DNA test of methylated syndecan-2 for the early detection of colorectal neoplasia. Cancer Epidemiol Biomarkers Prev 2017;26:1411-1419.
21. Wang J, Liu S, Wang H, et al. Robust performance of a novel stool DNA test of methylated SDC2 for colorectal cancer detection: a multicenter clinical study. Clin Epigenetics 2020;12:162.
22. Luo WF, Jiao YT, Lin XL, et al. Effectiveness of fecal DNA syndecan-2 methylation testing for detection of colorectal cancer in a high-risk Chinese population. World J Gastrointest Oncol 2024;16:1361-1373.
23. Yue C, Zhang Y, Wang Y, et al. The application value of syndecan-2 gene methylation for colorectal cancer diagnosis: a clinical study and meta-analyses. Front Med (Lausanne) 2022;9:753545.
24. Wang L, Liu Y, Zhang D, et al. Diagnostic accuracy of DNA-based SDC2 methylation test in colorectal cancer screening: a

meta-analysis. BMC Gastroenterol 2022;22:314.
25. Sun M, Liu J, Hu H, et al. A novel panel of stool-based DNA biomarkers for early screening of colorectal neoplasms in a Chinese population. J Cancer Res Clin Oncol 2019;145:2423-2432.
26. Zhao G, Liu X, Liu Y, et al. Aberrant DNA methylation of SEPT9 and SDC2 in stool specimens as an integrated biomarker for colorectal cancer early detection. Front Genet 2020;11:643.
27. Ionescu VA, Gheorghe G, Baban IA, et al. Prognostic differences between early-onset and late-onset colorectal cancer. Medicina (Kaunas) 2025;61:390.
28. Park SB, Yoon JY, Kwak MS, Cha JM. Clinical and pathological characteristics of early-onset colorectal cancer in South Korea. Saudi J Gastroenterol 2023;29:358-364.
29. Zeng T, Huang Z, Yu X, et al. Combining methylated SDC2 test in stool DNA, fecal immunochemical test, and tumor markers improves early detection of colorectal neoplasms. Front Oncol 2023;13:1166796.
30. Lee JK, Liles EG, Bent S, Levin TR, Corley DA. Accuracy of fecal immunochemical tests for colorectal cancer: systematic review and meta-analysis. Ann Intern Med 2014;160:171.
31. Shin HY, Suh M, Baik HW, et al. Performance of the fecal immunochemical test for colorectal cancer screening using different stool-collection devices: preliminary results from a randomized controlled trial. Gut Liver 2016;10:925-931.
32. Kim DH, Cha JM, Kwak MS, et al. Quality metrics of a fecal immunochemical test-based colorectal cancer screening program in Korea. Gut Liver 2018;12:183-189.

Supplementary Table 1. Stool DNA-based *meSDC2* Tests Compared with Multi-target Stool DNA Test

Category	Stool DNA-based *meSDC2* tests (Earlytect®)	Multi-target stool DNA test (Cologuard®)
Marker simplicity	Single methylation marker	Multi-target DNA and fecal immunochemical test
Sensitivity	90–95%	94%
Specificity	88–91%	93%
Cost	Low cost (~90$)	High cost (650$)
Complexity of kit	Simple design	More complex
Sample volume	1–2 g stool	Whole stool
Handling	Easier	More stringent
Chemical stability	More stable	Less stable
Compliance of patient	Good	Moderate
Potential for organized screening	More suitable	More limited