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Early Adoption of a Multitarget Stool DNA Test for Colorectal Cancer Screening

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Abstract

Objectives: To characterize early adoption of a novel multitarget stool DNA (MT-sDNA) screening test for colorectal cancer (CRC) screening and to test the hypothesis that adoption differs by demographic characteristics and prior CRC screening behavior and proceeds predictably over time.

Patients and Methods: We used the Rochester Epidemiology Project research infrastructure to assess the use of the MT-sDNA screening test in adults aged 50 to 75 years living in Olmsted County, Minnesota, in 2014 and identified 27,147 individuals eligible or due for screening colonoscopy from November 1, 2014, through November 30, 2015. We used electronic Current Procedure Terminology and Health Care Common Procedure codes to evaluate early adoption of the MT-sDNA screening test in this population and to test whether early adoption varies by age, sex, race, and prior CRC screening behavior.

Results: Overall, 2193 (8.1%) and 974 (3.6%) individuals were screened by colonoscopy and MT-sDNA, respectively. Age, sex, race, and prior CRC screening behavior were significantly and independently associated with MT-sDNA screening use compared with colonoscopy use after adjustment for all other variables ($P<.05$ for all). The rates of adoption of MT-sDNA screening increased over time and were highest in those aged 50 to 54 years, women, whites, and those who had a history of screening. The use of the MT-sDNA screening test varied predictably by insurance coverage. The rates of colonoscopy decreased over time, whereas overall CRC screening rates remained steady.

Conclusion: The results of the present study are generally consistent with predictions derived from prior research and the diffusion of innovation framework, pointing to increasing use of the new screening test over time and early adoption by younger patients, women, whites, and those with prior CRC screening.

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Colorectal cancer (CRC) is the second most frequent cause of cancer death in the United States.[1-3] Colorectal cancer screening can reduce the incidence of CRC and substantially improve CRC survival rates.[4-6] Several screening tests are available for the early detection of CRC, but nearly one-third of eligible US adults have never been screened.[2] Commonly identified barriers to CRC screening include lack of physician recommendation, lack of awareness and knowledge, cost of the test and its sequelae, invasiveness of the test, and fear of the results.[7-9] In addition, screening services are inconsistently delivered across practice settings[10,11] and continue to be underused overall and in certain ethnic minorities, age groups, and in persons with low socioeconomic status.[12] The Healthy People 2020[13] goal is that 70.5% of adults aged 50 to 75 years would have CRC screening.

A recently developed multitarget stool DNA (MT-sDNA) screening test for CRC screening (commercialized as Cologuard), codeveloped by Mayo Clinic and Exact Sciences (Madison, WI), holds promise for increasing population adoption of CRC screening. In particular, the MT-sDNA screening test addresses several barriers to CRC screening. Patient concerns with colonoscopy include the requirement to schedule a separate and lengthy clinic encounter, the need to undergo an arduous bowel preparation regimen, the exposure to sedation or anesthesia, and the discomfort associated with an invasive imaging process. By contrast, the MT-sDNA screening test is a

noninvasive, multimarker, stool-based CRC screening test that detects altered DNA, specifically mutant *KRAS* and methylated *BMP3* and *NDRG4*, as well as a fecal immunochemical test (FIT) for blood released from cancer and precancerous lesions of the colon; the presence of fecal hemoglobin, even in the absence of elevated DNA markers, can lead to a positive result given the weighted nature of the MT-sDNA algorithm.[14] Patients may collect and mail stool specimens from their homes, with no cathartic bowel preparations and no dietary or medication restrictions.

The results of a multicenter blinded case-control study[15] reported that the MT-sDNA screening test detects early-stage CRC and large adenomas with high levels of accuracy (92% sensitivity) throughout the colorectum. The MT-sDNA screening test outperformed FITs in detecting cancers (93% vs 74%), advanced precancerous lesions (42% vs 24%), polyps with high-grade dysplasia (69% vs 46%), and serrated sessile polyps 1 cm or greater (42% vs 5%). The MT-sDNA screening test was approved by the US Food and Drug Administration in 2014 for CRC screening, and the US Preventive Services Task Force (USPSTF)[16] recently issued its final CRC screening recommendations for 2016, assigning an overall grade A to CRC screening for people aged 50 to 75 years through the use of several screening examinations that include the MT-sDNA screening test. Therefore, the MT-sDNA screening test provides clinicians with a highly sensitive and specific screening test option.

The MT-sDNA screening test was introduced into the Mayo Clinic practice in Rochester, Minnesota, on October 27, 2014, and the purpose of this study was to characterize early patient adoption of this novel CRC screening test in our local population. Drawing on hypotheses derived from the diffusion of innovation (DOI) framework and prior research in cancer screening, we assessed whether early adoption of the MT-sDNA screening test differs by demographic characteristics and by prior CRC screening behavior. The DOI framework[17] is widely used to describe the adoption of health innovations in populations[18-23] and has been applied to adoption of cancer screening tests.[12,24] We examined adoption of the MT-sDNA screening test over time and assessed its effect on the use of colonoscopy, including second-tier testing. Based on prior research[25] examining the adoption of CRC screening tests, greater use of the MT-sDNA screening test was expected in older age groups and non-Hispanic whites. Although women generally exhibit higher rates of adoption of preventive services, this trend has not consistently been observed for CRC screening[26]; therefore, we did not explicate any specific hypothesis for the use of the MT-sDNA screening test by sex. On the basis of prior research[27-29] reporting a general clustering of cancer screening behaviors, we hypothesized greater use of the MT-sDNA screening test in individuals who have routinely engaged in other CRC screening. We also explored trends in CRC screening by MT-sDNA screening, colonoscopy, and overall CRC screening in individuals eligible and due for CRC screening from November 1, 2014, to November 30, 2015. On the basis of the tenets of the DOI, we expected to see an increase in the rate of MT-sDNA screening over time.

PATIENTS AND METHODS

We used the Rochester Epidemiology Project (REP) research infrastructure to assess the use of the MT-sDNA screening test in adults aged 50 to 75 years living in Olmsted County, Minnesota, in 2014. The REP data linkage infrastructure captures virtually all health care in Olmsted County.[30-33] Health care visit dates are linked to address information, and this information is used to define residency at any given point in time (REP census). Population coverage for Olmsted County is nearly complete.[32] We identified 42,577 individuals aged 50 to 75 years old residing in Olmsted County from November 1, 2014, to November 30, 2015, with authorization to use their medical records for research (96% of the eligible population) using the REP census.[34] The MT-sDNA screening test, although well publicized throughout the community, was available only at Mayo Clinic during the course of our study, whereas colonoscopy and other CRC screening tests were available and tracked at all the participating sites. The study procedures were approved by the institutional review boards of Mayo Clinic and Olmsted Medical Center.

The diagnostic indices of the REP were searched electronically to extract *International Classification of Diseases, Ninth Revision* Current Procedure Terminology and Health Care Common Procedure codes. Using these codes, we excluded individuals who were at high risk of CRC and who were not eligible for MT-sDNA screening. Exclusion criteria were as follows: previous CRC diagnosis or large polyps, screening before age 45 years or multiple screens before age 50 years, inflammatory bowel disease, familial adenomatous polyposis, or Lynch syndrome. In addition, we excluded individuals who were already up-to-date with colon screening (colonoscopy screening within 10 years, computed tomography [CT] colonography within 5 years, and sigmoidoscopy within 5 years with an annual fecal occult blood test [FOBT]). Overall, 27,147 individuals were eligible and due for CRC screening during the study period.

Identification of CRC Screening

Diagnostic indices of the REP were searched electronically to identify receipt of MT-sDNA screening, colonoscopy, CT colonography, and sigmoidoscopy with an annual FOBT. The MT-sDNA screening test and its results were identified using laboratory codes (58030-ROCLIS-Cologuard). Screening colonoscopy, CT colonography, and sigmoidoscopy were identified using Current Procedure Terminology codes for screening or diagnostic tests with a modifier indicating an initial screen (Supplemental Table, available online at http://www.mayoclinicproceedings.org). Only 27 patients screened with CT colonography or flexible sigmoidoscopy with an annual FOBT or FIT during this time frame, so use of these tests was not examined. Colonoscopy was the most frequently used screening test for colon cancer in our population, and MT-sDNA screening was introduced into our clinical practice as an alternative to colonoscopy screening for average-risk patients; therefore, we compared the use of MT-sDNA with that of colonoscopy.

Statistical Analyses

The proportion of eligible individuals who were initially screened by MT-sDNA and colonoscopy during the study period were described and compared separately by age, sex, race, and prior CRC screening behavior using chi-square tests. Prior cancer screening was defined as colonoscopy testing more than 10 years ago, CT colonography more than 5 years ago, or sigmoidoscopy with an annual FOBT more than 5 years ago. Multivariate logistic regression models were used to assess factors that might be associated with choosing the MT-sDNA screening test vs colonoscopy, including age, sex, race, and history of prior CRC screening. The results are presented as odds ratios and 95% CIs. In patients who had MT-sDNA screening, we calculated the percentage with Mayo Clinic employee and dependent insurance, other private insurance, government insurance, and no insurance.

The rate of MT-sDNA screening and colonoscopy screening per month, defined as the number screened each month divided by the eligible and due population, was plotted from November 1, 2014, through November 30, 2015. Generalized estimating equations with a Poisson distribution were used to test for temporal trends in MT-sDNA and colonoscopy screening.

RESULTS

The Table summarizes the results of CRC screening by colonoscopy and MT-sDNA screening by the sociodemographic characteristics of the eligible population who were due for CRC screening (n=27,147). The counts and percentages shown in the Table include only the first screening test within this time frame. The overall percentage of the eligible and due population who were screened by colonoscopy was higher than the percentage screened by MT-sDNA (8.1% vs 3.6%; $P \leq .001$).

The rates of adoption of MT-sDNA screening varied significantly by age, sex, race/ethnicity, and prior screening behavior ($P<.05$ for all; Table). The highest rate of adoption of MT-sDNA screening was observed in those aged 50 to 54 years (4.7%), with somewhat lower rates of adoption observed in those aged 60 to 75 years (Table) and a significantly lower rate in those aged 55 to 59 years (1.6%) ($P<.001$ for all). In men, 2.8% had an MT-sDNA screening test. The rate in women was significantly higher at 4.3% ($P<.001$). The highest rate of adoption of the MT-sDNA screening test by race/ethnicity was observed

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TABLE. Population Characteristics and Rates and Odds of MT-sDNA Screening (Compared With Colonoscopy) by Age, Sex, Race/Ethnicity, and Prior CRC Screening[a]

Variable	n (%)	Colonoscopy: n (%)	MT-sDNA screening: n (%)	Odds of MT-sDNA screening: OR (95% CI)[b]
Total	27,147 (100)	2193 (8.1)	974 (3.6)	
Age (y)		*P*<.001[c]	*P*<.001[c]	*P*=.002[b]
50-54	7294 (26.9)	739 (10.1)	346 (4.7)	Reference
55-59	7238 (26.7)	387 (5.4)	118 (1.6)	0.6 (0.5-0.8)
60-64	5514 (20.3)	489 (8.9)	225 (4.1)	1.0 (0.8-1.2)
65-69	4002 (14.7)	331 (8.3)	164 (4.1)	1.0 (0.8-1.2)
70-75	3099 (11.4)	247 (8.0)	121 (3.9)	0.9 (0.7-1.2)
Sex		*P*=.42[c]	*P*<.001[c]	*P*<.001[b]
Male	12,662 (46.6)	1041 (8.2)	357 (2.8)	Reference
Female	14,485 (53.4)	1152 (8.0)	617 (4.3)	1.6 (1.3-1.8)
Race/ethnicity		*P*<.001[c]	*P*<.001[c]	*P*=.03[b]
White	23,028 (84.8)	1929 (8.4)	892 (3.9)	Reference
Black	957 (3.5)	60 (6.3)	13 (1.5)	0.4 (0.2-0.8)
Asian	1063 (3.9)	70 (6.6)	27 (2.5)	0.9 (0.5-1.4)
Hispanic	1212 (4.5)	82 (6.8)	30 (2.5)	0.8 (0.5-1.2)
Other/unknown	887 (1.0)	52 (5.9)	12 (1.3)	0.6 (0.3-1.1)
Prior CRC screening		*P*=.6[c]	*P*<.001[c]	*P*<.001[b]
Yes	321 (1.2)	23 (7.2)	53 (16.5)	Reference
No	26,826 (98.8)	2170 (8.1)	921 (3.4)	0.2 (0.1-0.3)

[a]CRC = colorectal cancer; MT-sDNA = multitarget stool DNA; OR = odds ratio.

[b]Odds ratio and 95% CI are determined from the multivariate logistic regression analysis. The dependent variable for this analysis was screening method, and all characteristics listed in the table were included as explanatory variables. Odds ratios >1 indicate an increased likelihood of screening by MT-sDNA. The *P* value represents type 3 analysis of the effect across categories of the given characteristic.

[c]*P* value for the χ^2 test, comparing screening rates across categories of the given characteristic separately for colonoscopy and MT-sDNA screening.

in whites (3.9%), and the lowest rate was observed in blacks (1.5%).

Prior screening status was not significantly associated with colonoscopy (*P*=.55). However, compared with those without prior CRC screening (3.4%), a significantly higher percentage of those who had prior CRC screening adopted the MT-sDNA screening test (16.5%) (*P*<.001). In patients who had MT-sDNA screening, 54.2% had Mayo Clinic insurance, 15.4% had other private insurance, 29.3% had government insurance, and 1.1% did not have insurance.

The Table also summarizes the results of a multivariate logistic regression analysis exploring whether any of the demographic characteristics or prior screening were independently associated with the use of MT-sDNA screening in patients who were screened within our designated time frame. Younger age, female sex, white race, and prior CRC screening remained significantly associated with the use of MT-sDNA screening as compared with the use of colonoscopy after adjustment for all other variables. Specifically, those aged 55 to 59 years were significantly less likely (adjusted odds ratio [OR], 0.6; 95% CI, 0.5-0.8) to use MT-sDNA screening than were those aged 50 to 54 years. Compared with men, women were more likely (adjusted OR, 1.6; 95% CI, 1.3-1.8) to use MT-sDNA screening than colonoscopy. Compared with whites, blacks were less likely (adjusted OR, 0.4; 95% CI, 0.2-0.8) to use MT-sDNA screening than colonoscopy. Finally, compared with those who had a prior CRC screening test, those without a prior CRC screening test were less likely (adjusted OR, 0.2; 95% CI, 0.1-0.3) to use MT-sDNA screening than colonoscopy.

The Figure summarizes rates of MT-sDNA screening and colonoscopy screening per month during the study period, revealing a significant increase in the rate of MT-sDNA screening (*P*=.01) and a significant decrease in colonoscopy (*P*<.001). Overall, CRC screening rates observed over this 12-month

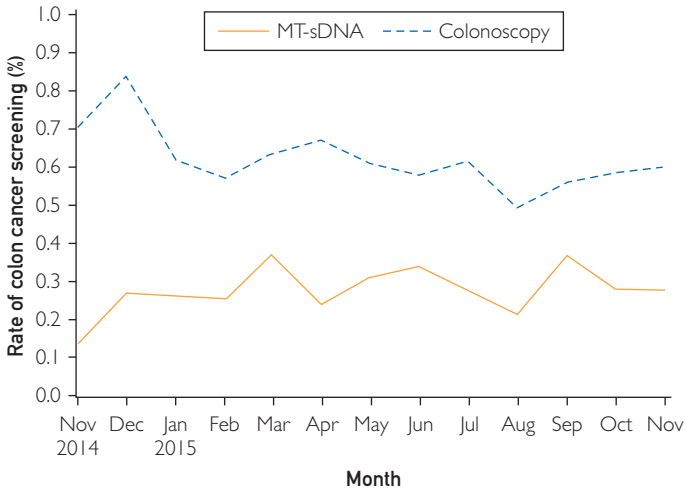

FIGURE. Rates of MT-sDNA screening and colonoscopy screening per month. There is a significant increase in the rate of MT-sDNA screening (P=.01) and a significant decrease in the rate of colonoscopy (P<.001). MT-sDNA = multitarget stool DNA.

period were consistent over time, with no significant increase or decrease observed. We also evaluated the rates of second-tier screening by colonoscopy after a positive MT-sDNA screening test result and found that 80.8% of those who had a positive MT-sDNA screening test result followed up within 3 months and 89.7% followed up with a colonoscopy by the end of February 2016.

DISCUSSION

We assessed whether early adoption of MT-sDNA screening differs by demographic characteristics and prior screening and examined the adoption of MT-sDNA screening over time and assessed its effect on the use of colonoscopy, including second-tier testing. Our hypothesis that greater use of MT-sDNA screening would be observed in older age groups was not supported; the rates of MT-sDNA screening adoption were highest in those aged 50 to 54 years. Given mixed results in prior research around sex differences in CRC screening, we did not make any specific hypothesis about differences in rates of MT-sDNA screening adoption by sex. However, we did observe higher rates of adoption in women than in men and this is consistent with prior research on use of other preventive services. Consistent with our prediction, non-Hispanic whites exhibited the highest rate of adoption of the MT-sDNA screening test than did other racial and ethnic groups.

We hypothesized greater use of MT-sDNA screening in individuals who have routinely engaged in other CRC screening and found that rates of MT-sDNA screening use were higher in those who had prior CRC screening, which is consistent with previous research.[27-29] The rates of CRC screening in Olmsted County are relatively high, with 81% of the population reporting a prior colonoscopy or sigmoidoscopy.[35] The comparable rate for Minnesota is 68.5%, and for the United States it is 61.3%.[35] This may, in part, explain why the adoption of MT-sDNA screening most frequently occurred in those with prior screening. The population of Olmsted County has socioeconomic characteristics similar to those of the upper Midwest.[36] However, the population of Olmsted County is more highly educated than the general US population (39% vs 28% with a bachelor's degree or higher) and has a higher median household income ($64,000 vs $52,000 per year).[37] The proportion of the population of Olmsted County with health insurance is high and is similar to that of the upper Midwest and the East Coast of the United States.[38] These factors may explain the higher rates of screening this population. In addition, uptake rates of this new test may be higher and more rapid than in other parts of the country, given the local media attention to the development of the test. However, studies such as these are necessary to understand how populations vary throughout the country and can serve as useful referent populations for understanding variability in health and health care and can highlight important differences that can be targeted for interventions.[39,40]

Diffusion of Innovation Framework

The DOI process proceeds along an S curve in a population with an initial small group adopting an innovation (*innovators/early adopters*), followed by greater adoption in a population, and then later in the process a small percentage of the population may adopt an innovation (*late adopters/laggards*).[20,22] As

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cancer screening tests have been introduced into clinical practice, they have generally followed the signature DOI process.[12]

According to the DOI framework, adoption is driven by the *relative advantage* of the innovation; *compatibility* with the values, experiences, and needs of potential adopters; perceived *complexity* of adopting the innovation; *trialability* or ability to try or test an innovation; and the visibility or *observability* of the innovation within the population of potential adopters.[20,22] The MT-sDNA screening test enjoys several advantages over colonoscopy across these domains from a patient-experience perspective. Colonoscopy requires unpleasant bowel preparation, is time-consuming, often requires patients to take time off work, and is more costly than MT-sDNA screening. Thus, MT-sDNA screening is likely to be perceived as more compatible with patient preferences and less complex than colonoscopy. However, at this early stage of diffusion, potential adopters and referring clinicians are likely to be more aware of colonoscopy as an option for CRC screening than for MT-sDNA screening. In applications relevant to cancer screening, lack of awareness of recommendations for screening practice among patients and clinicians (resulting in lack of referral or recommendation) have been cited consistently as barriers to screening adoption, particularly during the early stages of diffusion.[12]

We observed an overall increase in the adoption of MT-sDNA screening over time, which is consistent with the hypotheses derived from the DOI framework.[17] As the DOI framework would predict, the initial rates of adoption of MT-sDNA screening are low and lag behind those of adoption of previously diffused CRC screening technologies, in particular colonoscopy. Our results also suggest that certain groups (including men and blacks) may benefit from targeted campaigns to improve awareness of the screening test. The recent USPSTF grade A recommendation for CRC screening by DNA-based stool sample tests coupled with increasing insurance coverage will likely boost overall awareness of the test availability.

Over this same time period, we observed a decrease in use of colonoscopy and no change in overall CRC screening. This is consistent with our finding that the rate of adoption of the MT-sDNA screening test was much higher in those who previously had a CRC screening test. This suggests that the introduction of MT-sDNA screening into this patient population led to the use of MT-sDNA screening in persons who may have had a colonoscopy if MT-sDNA screening had not been made available rather than the use of MT-sDNA screening in persons who would have otherwise chosen not to have CRC screening. Prior research has provided evidence that nearly all patients (97%) who refused colonoscopy accepted alternative noninvasive stool-based or blood-based CRC screening options. Thus, the introduction of MT-sDNA screening as an alternative screening tool for CRC has potential to improve the overall CRC screening rates in the population if adopted by those previously resistant to the use of other screening modalities, such as colonoscopy. During the time frame of our investigation, the MT-sDNA screening test was not covered by all insurance payers; however, it was covered for Medicare and Medicaid patients and for patients who were employees or dependents of employees at Mayo Clinic. Indeed, patterns of use reflected insurance coverage, in which patients with insurance coverage engaged in MT-sDNA screening significantly more often than those who did not have coverage. With the recent USPSTF grade A recommendation, coverage rates will likely increase, thereby increasing access to and adoption of the test.

Study Limitations

The use of existing clinical and laboratory data in our analysis limits the data available for evaluation of our hypotheses. In particular, we did not have access to patients' income level, education level, and employment status—all known to predict early adoption of screening tests. Patient insurance data are available only for the Mayo Clinic practice sites, so we were not able to include the insurance status in all our analyses; however, we were able to examine the insurance status in those who had a prior MT-sDNA screening test. Another limitation of our study, and an area of inquiry that merits further investigation, is that with the available data we were unable to evaluate associations between health care provider

credentials and practice site with ordering of MT-sDNA screening.

CONCLUSION

The results of the present study are generally consistent with predictions derived from prior research and the DOI framework. Looking forward, this framework predicts that we will see a significant increase in population adoption of this screening test followed by an eventual leveling out. The recent USPSTF endorsement, and increasing coverage by health insurance companies, will likely accelerate this process. For average-risk patients, the MT-sDNA screening test offers an alternative screening test for CRC screening with potentially fewer barriers to use. Future research is encouraged to track continued dissemination of this test in the population, to assess its effect on the use of traditional CRC screening, and to ascertain patients' experiences relevant to this test.

SUPPLEMENTAL ONLINE MATERIAL

Supplemental material can be found online at: http://www.mayoclinicproceedings.org. Supplemental material attached to journal articles has not been edited, and the authors take responsibility for the accuracy of all data.

Abbreviations and Acronyms: **CRC** = colorectal cancer; **CT** = computed tomography; **DOI** = diffusion of innovation; **FIT** = fecal immunochemical test; **FOBT** = fecal occult blood test; **MT-sDNA** = multitarget stool DNA; **OR** = odds ratio; **REP** = Rochester Epidemiology Project; **USPSTF** = US Preventive Services Task Force

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Potential Competing Interests: Dr Kisiel reports other support (that could result in the sharing of potential future royalties) from Exact Sciences, outside the submitted work. In addition, Dr Kisiel has a patent (61/784,429) pending. Dr St. Sauver reports grants from the National Institute of Aging during the conduct of the study. Dr Tulledge-Scheitel reports other support in the form of shares of stock from Exact Science, outside the submitted work.

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