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Ethics declarations

Ethics approval

The data herein were retrospectively reviewed as part of ongoing laboratory (Exact Sciences Laboratories, LLC) quality management processes in compliance with the Health Insurance Portability and Accountability Act (HIPAA). The study was deemed exempt from IRB review by the Mayo Clinic Institutional Review Board.

Consent to participate/consent for publication

Not applicable; retrospective review of deidentified data.

Disclosure

LAMW, JVT, and BO are employees and shareholders of Exact Sciences. LJFR offers scientific input to research studies through a contracted services agreement between Mayo Clinic and Exact Sciences. PJL serves as Chief Medical Officer for Screening at Exact Sciences through a contracted services agreement with Mayo Clinic. PJL and Mayo Clinic have contractual rights to receive royalties through this agreement.

Conflict of interest

The authors declare no competing interests.

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ORIGINAL ARTICLE

Cross-sectional adherence with the multi-target stool DNA test for colorectal cancer screening in a large, nationally insured cohort

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Abstract

Purpose Colorectal cancer (CRC) is the second most deadly cancer in the USA. Early detection can improve CRC outcomes, but recent national screening rates (62%) remain below the 80% goal set by the National Colorectal Cancer Roundtable. Multiple options are endorsed for average-risk CRC screening, including the multi-target stool DNA (mt-sDNA) test. We evaluated cross-sectional mt-sDNA test completion in a population of commercially and Medicare-insured patients.

Methods Participants included individuals ages 50 years and older with commercial insurance or Medicare, with a valid mt-sDNA test shipped by Exact Sciences Laboratories LLC between January 1, 2018, and December 31, 2018 ($n = 1{,}420{,}460$). In 2020, we analyzed cross-sectional adherence, as the percent of successfully completed tests within 365 days of shipment date.

Results Overall cross-sectional adherence was 66.8%. Adherence was 72.1% in participants with Traditional Medicare, 69.1% in participants with Medicare Advantage, and 61.9% in participants with commercial insurance. Adherence increased with age: 60.8% for ages 50–64, 71.3% for ages 65–75, and 74.7% for ages 76 + years. Participants with mt-sDNA tests ordered by gastroenterologists had a higher adherence rate (78.3%) than those with orders by primary care clinicians (67.2%). Geographically, adherence rates were highest among highly rural patients (70.8%) and ordering providers in the Pacific region (71.4%).

Conclusions Data from this large, national sample of insured patients demonstrate high cross-sectional adherence with the mt-sDNA test, supporting its role as an accepted, noninvasive option for average-risk CRC screening. Attributes of mt-sDNA screening, including home-based convenience and accompanying navigation support, likely contributed to high completion rates.

Keywords Colorectal cancer screening/prevention · Colorectal neoplasms · Early detection of cancer · Mt-sDNA · Insurance

Introduction

Colorectal cancer (CRC) is the second leading cause of cancer deaths and fourth most diagnosed cancer in the USA [1], representing an ongoing public health concern, with estimates of 149,500 incident and 52,980 fatal cases in 2021 [2]. Average-risk CRC screening can favorably impact the CRC public health burden by identifying patients with premalignant or localized malignant neoplasia for earlier, more effective intervention. National organizations such as the United States Preventive Services Task Force (USPSTF) in their 2021 Final Recommendation Statement and the American Cancer Society (ACS) recommend lowering the age for average-risk CRC screening (beginning at the age of 45 years) using one of several equally endorsed test options, including the multi-target stool DNA assay [3–5] (mt-sDNA; marketed as Cologuard®; Exact Sciences, Madison, WI). Since receiving approval from the US Food and Drug Administration in August 2014, the mt-sDNA assay has been prescribed by over 200,000 providers and completed by more than 4 million patients nationwide.

Between 2015 and 2018, estimated CRC screening rates increased overall by 4.2%, from 61.7 to 65.9% according to National Health Interview Survey data [6, 7]. The same National Health Interview Survey (NHIS) data showed that for those who completed screening, 4.1% used mt-sDNA, and use was consistent across demographic subgroups such as sex, age, and race/ethnicity, with no apparent

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disparities. The number of people screened with the mt-sDNA test further increased in 2019, with 1.7 million patients successfully screened using mt-sDNA testing [8]. Despite the COVID-19 disruption, the at-home mt-sDNA test with its built-in navigation component for patients and providers and door-to-door shipping is uniquely positioned to sustain colorectal cancer screening efforts, potentially tempering the backlog of CRC screening delays and corresponding late-stage disease.

One critical component of effective CRC screening programs is patient adherence with completing the selected test option. The practical effectiveness of available screening strategies may be reduced by suboptimal adherence to screening recommendations [9]. Discouragingly, prior research has demonstrated relatively low completion rates for other stool-based CRC screening tests [9–14], and several recently conducted trials have revealed differences in CRC screening completion rates by test modality [9–11, 14]. These differences in completion rates may be exacerbated by multiple factors, such as socioeconomic status [15, 16] and race [17, 18]. Given the differences between endoscopic, radiologic, and stool-based screening strategies, accurate understanding of test-specific patient adherence is critical for population-, provider-, and payor-level discussions.

To date, analyses of mt-sDNA adherence have demonstrated high cross-sectional adherence rates (71%) but have been limited to Medicare beneficiaries to minimize the influence of insurance variability on test completion rates [19]. Given the growing adoption of mt-sDNA screening by commercial insurance plans, nearly all insured (>94%) average-risk patients now have access to mt-sDNA screening with no out-of-pocket costs [20]. Thus, additional real-world assessment of mt-sDNA test adherence in non-Medicare patients is both feasible and timely. Here, we evaluated cross-sectional mt-sDNA test completion in a fully insured population and identified associated factors, to better inform shared decision-making, quality monitoring, and comparative effectiveness studies related to average-risk CRC screening.

Methods

Aggregate laboratory data from Exact Sciences Laboratories LLC (ESL; Madison, WI), the sole-source national laboratory for mt-sDNA testing, were retrospectively reviewed as part of ongoing laboratory quality management processes and in compliance with the Health Insurance Portability and Accountability Act. Per Mayo Clinic Institutional Review Board (IRB) criteria, this study was deemed as exempt from review.

Study population, design, and data acquisition

Eligible study participants included individuals who met the following criteria: ages 50 years and older, covered by commercial insurance or Medicare, with a valid mt-sDNA test shipped to the order-specified address from ESL between January 1, 2018 and December 31, 2018. At the time of the study, the USPSTF recommendation was to start screening at 50 years old. Valid mt-sDNA test shipments were defined as having all information required for ESL to analyze the sample and report a positive or negative test result. Deidentified data referent to available patient (sex, age), provider (specialty, practice location), and test order features (testing status, time to completion) were sourced from the ESL internal data systems. Of note, patient race/ethnicity is listed as an optional field on the mt-sDNA order form and was additionally collected when available.

Information from ESL internal data systems regarding order characteristics was initially collected for 1,508,087 patients. Inclusion and exclusion criteria (including provider/patient cancellations, duplicate orders, missing information, and reasons for ineligibility) were utilized to comprise the final analysis cohort consisting of 1,420,460 patients. The cohort attrition flow chart outlines that cross-sectional adherence was defined as the percentage of eligible participants who successfully completed the test within 365 days of the shipment date (Fig. 1).

Sociodemographic characteristics including income and education are not tracked in the ESL test order data system. Therefore, these data were ascertained at the residential zip code level from public data sources, including the United States Census and American Community Surveys database [21–23].

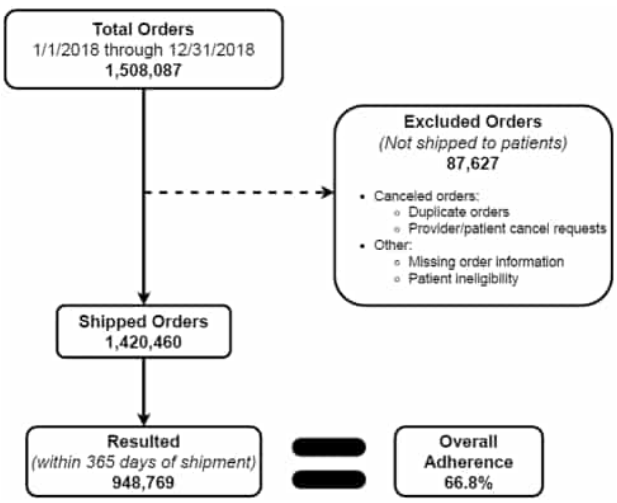


Fig. 1 Study cohort—attrition flowchart

Statistical analysis

Descriptive statistics were used to describe the baseline characteristics of the study population overall and by insurance type. Counts and percentages were used to describe population-level statistics while distribution statistics (mean and median) were provided, where appropriate, to further describe the study populations' time to adherence, overall adherence, and age. Descriptive statistics were principally stratified by patient insurance type. Distribution statistics relating to skewness and other appropriate tests (e.g., chi-square test) were used as needed to describe the study population.

Given that the study population comprises the entirety of mt-sDNA patients during this time ($N = 1{,}420{,}460$), point estimates and *p*-value testing do not provide necessary context or support better comparison. In essence, very small differences, even if significant, are likely to arise due to the population size though do not reflect meaningful differences among populations. In contrast to significance tests, effect size is independent of sample size, while statistical significance can be dependent upon both sample size and effect size [24, 25]. To avoid confounding the meaning of significance due to such a large sample size, we decided not to report two-sided 95% confidence intervals for point estimates or two-sided *p*-values for subgroup comparisons.

Results

Of 1,420,460 patients who met the study criteria (Fig. 1), 61.2% were female with a mean age of 64.9 years. Age distributions were 50–64 years (47.3%), 65–75 years (40.0%), and 76 + years (12.7%), with the majority of the cohort residing in urban areas (70.4%). Of those who specified a race/ethnic category, the majority of participants were white, although most participants (85.6%) did not provide this optional information (Table 1). Within the study population, 46.1% had commercial insurance coverage, 33.5% had Traditional Medicare coverage, and 20.4% were covered by Medicare Advantage (Table 2). Patients residing in zip codes with above average Bachelor's degree attainment rates (35.0% of all adults above 25 in the USA had a Bachelor's degree as of 2018) [22] accounted for 31.2% of all shipments. Patients in zip codes with a median income greater than the national median ($33,706 per the American Community Survey conducted in 2018) [23] accounted for 43.3% of mt-sDNA test orders. Geographically, the highest adherence in the study population was observed for those dwelling in highly rural locations: urban (66.0%), rural (68.5%), and highly rural (70.8%) (Table 3). Most mt-sDNA test orders were placed by primary care clinicians (72.2%), followed by nurse practitioners and physician assistants (19.3%), gastroenterologists (3.2%), and obstetrics and gynecologists

Table 1 Study population demographics by insurance coverage type

Category (% of cohort)	Insurance type			
	Commercial	Traditional Medicare	Medicare advantage	Total
Age				
50–64, *n* (%)	573,126 (87.5)	56,953 (12.0)	41,501 (14.3)	671,580 (47.3)
65–75, *n* (%)	71,187 (10.9)	307,007 (64.5)	190,617 (65.8)	568,811 (40.0)
76^{+}, *n* (%)	10,546 (1.6)	112,111 (23.5)	57,412 (19.8)	180,069 (12.7)
Totals	654,859	476,071	289,530	1,420,460
Sex				
Male, *n* (%)	260,436 (39.8)	178,860 (37.6)	110,708 (38.2)	550,004 (38.7)
Female, *n* (%)	394,174 (60.2)	296,962 (62.4)	178,732 (61.7)	869,868 (61.2)
Unspecified, *n* (%)	249 (0)	249 (0)	90 (0)	588 (0)
Race				
White (%)	87,625 (13.4)	60,967 (12.8)	35,393 (12.2)	183,985 (13.0)
Black or African American (%)	6999 (1.1)	4304 (0.9)	4298 (1.5)	15,601 (1.1)
American Indian/Alaska Native (%)	244 (0)	176 (0)	103 (0)	523 (0)
Asian (%)	2844 (0.4)	1034 (0.2)	820 (0.3)	4698 (0.3)
Native Hawaiian or other Pacific Islander (%)	190 (0)	119 (0)	79 (0)	388 (0)
Not specified (%)	556,957 (85.0)	409,471 (86.0)	248,837 (86.0)	1,215,265 (85.6)
Geography				
Urban (%)	471,962 (72.1)	317,426 (66.7)	210,140 (72.6)	999,528 (70.4)
Rural (%)	165,099 (25.2)	141,133 (29.6)	72,247 (25.0)	378,479 (26.7)
Highly rural (%)	17,798 (2.7)	17,512 (3.7)	7143 (2.5)	42,453 (3.0)

Table 2 Cross-sectional adherence by patient factors

Patient-level factors	Cross-sectional adherence											
	Total			Commercial (46.1%)			Traditional Medicare (33.5%)			Medicare advantage (20.4%)		
	Completed/shipped	%	TTA	Completed/shipped	%	TTA	Completed/shipped	%	TTA	Completed/shipped	%	TTA
All eligible study patients	948,769/1,420,460	66.8	22	405,652/654,859	61.9	24	343,135/476,071	72.1	21	199,982/289,530	69.1	21
Age, years												
50–64	408,516/671,580	60.8	24	351,850/573,126	61.4	24	32,106/56,953	56.4	24	24,560/41,501	59.2	24
65–75	405,662/568,811	71.3	21	46,642/71,187	65.5	22	225,931/307,007	73.6	21	133,089/190,617	69.8	21
76^{+}	134,591/180,069	74.7	20	7160/10,546	67.9	20	85,098/112,111	75.9	20	42,333/57,412	73.7	20
Sex												
Male	369,655/550,004	67.2	21	162,896/260,436	62.5	23	129,790/178,860	72.6	20	76,969/110,708	69.5	20
Female	578,748/869,868	66.5	22	242,611/394,174	61.5	25	213,183/296,962	71.8	21	122,954/178,732	68.8	22
Not specified	366/588	62.2	26	145/249	58.2	27	162/249	65.1	27	59/90	65.6	21
Race												
White	118,016/183,985	64.1	23	52,668/87,625	60.1	25	42,056/60,967	69.0	22	23,292/35,393	65.8	22
Black or African American	7,972/15,601	51.1	24	3373/6999	48.2	26	2228/4304	51.8	23	2371/4298	55.2	23
American Indian/Alaska Native	290/523	55.4	24	145/244	59.4	24	88/176	50.0	23	57/103	55.3	23
Asian	2593/4698	55.2	23	1451/2844	51.0	24	667/1034	64.5	23	475/820	57.9	23
Native Hawaiian or other Pacific Islander	233/388	60.1	23	101/190	53.2	23	83/119	69.7	25	49/79	62.0	21
Not specified	819,665/1,215,265	67.4	22	347,914/556,957	62.5	24	298,013/409,471	72.8	21	173,738/248,837	69.8	21

TTA time to adherence (median days)

Table 3 Cross-sectional adherence by zip code population factors

Zip code population statistics	Cross-sectional adherence											
	Total			Commercial			Traditional Medicare			Medicare advantage		
	Completed/ordered	%	TTA	Completed/ordered	%	TTA	Completed/ordered	%	TTA	Completed/ordered	%	TTA
Employment status—unemployment rate												
Above national rate (70.9%)	667,427/1,006,915	66.3	21	276,955/451,104	61.4	22	241,674/337,704	71.6	21	148,798/218,107	68.2	21
Below national rate (29.1%)	281,342/413,545	68.0	22	128,697/203,755	63.2	23	101,461/138,367	73.3	21	51,184/71,423	71.7	22
Education level—bachelor's degree rate												
Above national rate (31.2%)	292,479/443,321	66.0	23	119,511/195,280	61.2	24	103,612/146,796	70.6	22	69,356/101,245	68.5	22
Below national rate (68.8%)	656,290/977,139	67.2	21	286,141/459,579	62.3	22	239,523/329,275	72.7	21	130,626/188,285	69.4	21
Median income												
Above national rate (43.3%)	419,161/614,364	68.2	22	192,521/303,687	63.4	24	147,879/199,270	74.2	22	78,761/111,407	70.7	22
Below national rate (56.7%)	529,608/806,096	65.7	22	213,131/351,172	60.7	22	195,256/276,801	70.5	21	121,221/178,123	68.1	21
Geography												
Urban (70.4%)	659,291/999,528	66.0	23	289,431/471,962	61.3	24	226,679/317,426	71.4	22	143,181/210,140	68.1	22
Rural (26.7%)	259,403/378,479	68.5	22	104,651/165,099	63.4	23	103,155/141,133	73.1	22	51,597/72,247	71.4	21
Highly rural (3.0%)	30,075/42,453	70.8	22	11,570/17,798	65.0	23	13,301/17,512	76.0	21	5204/7143	72.9	22

TTA time to adherence (median days)

(1.8%), with the remaining mt-sDNA test orders placed by other specialties (3.5%) (Table 4).

The overall cross-sectional adherence rate for the entire study population was 66.8% (948,769/1,420,460 patients received and completed the mt-sDNA test and had a valid result) with a median time-to-adherence (TTA) of 22 days. The difference in adherence between males and females was small (67.2 vs. 66.5%, respectively). Cross-sectional adherence was highest in patients with Traditional Medicare coverage (72.1%) and lowest in patients with commercial insurance coverage (61.9%). Adherence increased with age: 50–64 years (60.8%), 65–75 years (71.3%), and 76 + years (74.7%) overall, and within each of the insurance types (Table 2). Relative to those with commercial insurance, increases in adherence by age were more pronounced among those with Traditional Medicare or Medicare Advantage plans, who demonstrated lower rates of adherence among those 50–64 compared to those with commercial insurance (Table 2). Moreover, adherence was 73.6% for Traditional Medicare patients ages 65–75.

Statistically, cross-sectional adherence with the mt-sDNA test was not shown to be associated with level of education or median income of the zip code wherein patients resided. Adherence was 66.0% in zip codes with an above average Bachelor's degree attainment rate compared with 67.2% in zip codes with a below average Bachelor's degree attainment rate. Similarly, adherence was 68.2% compared to 65.7% in zip codes with median incomes above and below the national median, respectively (Table 3).

Adherence also varied among ordering provider specialty and practice location. Patients with mt-sDNA tests ordered by gastroenterologists exhibited a higher adherence rate (78.3%) than those with orders placed by primary care clinicians (67.2%), nurse practitioners and physician assistants (63.5%), obstetricians and gynecologists (63.1%), and other specialties (67.3%). Adherence rates were highest among patients with ordering providers in the Pacific region (71.4%) and West North Central region (70.1%). Contrastingly, the lowest adherence was observed in the Mid-Atlantic region (65.7%), New England (65.2%), West South-Central region (64.6%), and Puerto Rico/US Territories (60.7%) (Table 4).

Discussion

Results from this retrospective study of a large, insured population demonstrate relatively high cross-sectional adherence with the mt-sDNA test for CRC screening. Adherence rates were similar between males and females and increased with age. Of note, area-level education and median income of patients' residential zip codes were not significantly associated with differences in adherence rates. Consistent with previous observations in Medicare patients [19], adherence rates were also higher for orders placed by gastroenterologists compared to other provider specialties. Geographically, the greatest adherence was observed among those living in highly rural areas; however, that population was only 3% of the overall cohort. Although GIs ordered the fewest mt-sDNA tests, the rate of adherence to recommendations by disease specialists may relate in part to more detailed discussion during encounters regarding the importance of completing CRC screening; albeit, this speculative interpretation requires further evaluation.

With nearly 1.5 million participants included in the study population, our data contributes to the emerging literature regarding mt-sDNA test adherence in the clinical setting, although in a younger and larger cohort than seen previously [19]. Overall adherence approached 67%, with meaningful differences observed between age groups. The highest rate was seen in the 76 + years subgroup having Traditional Medicare coverage. Adherence also increased with age, from 60.8% in those 50–64 to 74.7% in patients ≥ 76 + years, while Traditional Medicare patients ages 65–75 exhibited 73.6% adherence.

The mt-sDNA test is offered in conjunction with patient and provider navigation support (available 24 h per day, 365 days per year, with translation services in over 240 languages). Previous studies have shown that patient navigation has a beneficial effect on patient health behavior, demonstrating increased CRC screening rates [19, 26, 27]. The amalgamation of test and navigation services was shown to be successful in a separate study of Medicare beneficiaries where individuals who were previously non-adherent with CRC screening were offered the mt-sDNA test, resulting in 88% completion and 96% diagnostic colonoscopy exam follow-up for those with a positive mt-sDNA result [28]. This intricate feature adds inherent value to the mt-sDNA test at no additional cost to the payor, health system, patient, or provider, while also improving the probability of test completion compared with no intervention [19–29]. This information may be helpful to consider as a guiding input variation for CRC modeling studies to investigate comparative effectiveness between screening modalities.

There is general agreement concerning the effectiveness of colorectal cancer screening; however, in contrast to other organ sites, major guideline groups have endorsed more than one test option for average-risk CRC screening in order to maximize engagement. Informed health care provider discussions and screening decisions are better guided by implementation considerations that can help patients select the testing option they are most likely to complete, and this factor is essential for reducing the number of CRC-related deaths in the USA. Prior research has demonstrated low completion rates for other CRC screening tests [9, 10], and existing literature on repeat screening with other non-mt-sDNA

Table 4 Cross-sectional adherence by provider-level factors

Provider-level factors	Cross-sectional adherence											
	Total			Commercial			Traditional Medicare			Medicare advantage		
	Completed/ordered	%	TTA	Completed/ordered	%	TTA	Completed/ordered	%	TTA	Completed/ordered	%	TTA
Specialty												
GI (3.2%)	35,381/45,204	78.3	20	8,830/12,106	72.9	22	19,296/23,920	80.7	20	7255/9178	79	20
OB/GYN (1.8%)	16,149/25,597	63.1	24	10,817/17,220	62.8	26	3660/4855	75.4	22	1672/3522	47.5	23
Primary care (72.2%)	689,393/1,025,331	67.2	22	288,894/462,109	62.5	24	249,634/345,462	72.3	21	150,865/217,760	69.3	21
NP/PA (19.3%)	174,441/274,694	63.5	22	83,070/141,027	58.9	24	57,167/83,264	68.7	21	34,204/50,403	67.9	21
Other (3.5%)	33,405/49,634	67.3	22	14,041/22,397	62.7	24	13,378/18,570	72	21	5986/8667	69.1	21
Practice location (region)												
East North Central	200,228/301,581	66.4	21	93,746/151,818	61.7	23	63,003/89,215	70.6	20	43,479/60,548	71.8	20
East South Central	67,801/101,257	67	20	25,800/41,222	62.6	22	24,040/33,879	71	19	17,961/26,156	68.7	20
Mid-Atlantic	112,383/171,083	65.7	23	49,104/79,746	61.6	25	38,759/55,519	69.8	21	24,520/35,818	68.5	22
Mountain	63,508/95,063	66.8	23	23,060/36,321	63.5	26	23,203/30,882	75.1	22	17,245/27,860	61.9	23
New England	44,068/67,562	65.2	24	21,710/35,799	60.6	27	14,606/20,885	69.9	22	7752/10,878	71.3	23
Pacific	56,805/79,522	71.4	25	23,117/34/519	67	27	26,858/35,750	75.1	23	6830/9253	73.8	24
South Atlantic	229,657/342,664	67	21	93,501/152,993	61.1	23	89,721/123,081	72.9	20	46,435/66,590	69.7	21
West North Central	67,400/96,140	70.1	22	30,671/46,937	65.3	23	25,984/34,687	74.9	20	10,745/14,516	74	21
West South Central	106,707/165,239	64.6	22	44,860/75,362	59.5	24	36,878/52,044	70.9	21	24,969/37,833	66	22
Puerto Rico and US Territories	212/349	60.7	24	83/142	58.5	25	83/129	64.3	24	46/78	59	23

GI gastroenterology, *GYN* gynecology, *NP* nurse practitioner, *OB* obstetrics, *PA* physician assistant, *TTA* time to adherence (median days)

stool-based screening tests suggests a need for improvement [9–11, 30]. A more sensitive test, such as mt-sDNA, is less susceptible to drops in adherences rates. Mt-sDNA has a higher single application sensitivity for all stages of CRC, which distinguishes it from single marker fecal occult blood tests (FIT/gFOBT) [31]. The 10,000-person mt-sDNA pivotal study by Imperiale et al. [31] reported 92% sensitivity for CRC (vs 74% for FIT). This performance difference held true in receiver operating characteristic (ROC) analysis, regardless of the cutoff chosen for FIT. Higher one-time test sensitivity is relevant given that FIT adherence to recommended screening frequency can drop off substantially after the first cycle of annual testing [32].

As an integral part of the screening process, the follow-up colonoscopy to a positive non-colonoscopy CRC screening exam is becoming increasingly appreciated in the literature. Follow-up colonoscopy after a positive first-line test is necessary for complete and effective CRC screening [33, 34]. Failure to, and delay of follow-up after a positive stool-based test has been associated with increased risk of later stage CRC and CRC mortality [33, 35–37]. Doubeni et al. found that patients failing to follow-up on abnormal FIT results face a sevenfold higher risk of dying of CRC than those who complete the follow-up process [37].

Differences have also been revealed in CRC screening completion rates by modality [13, 14]. In a study by Rutten et al. [14] among residents of Olmsted County, MN, eligible and due for CRC screening, it was revealed that CRC screening incidence rates remained stable from 2016 to 2018, while test-specific rates for mt-sDNA significantly increased. Moreover, the study revealed that adherence with follow-up colonoscopy within 6 months after a positive stool-based test was significantly higher among patients who underwent mt-sDNA screening versus FIT/FOBT (84.9% vs 42.6%, respectively). At real-world (imperfect) adherence rates of 40% for annual FIT and 70% for triennial mt-sDNA derived from a critical assessment of meta-analyses and retrospective cross-sectional data [19, 38] (in systems using FIT without a navigation program) [39], modeling illustrates that the number of LYG and reductions in CRC incidence and mortality were higher for triennial mt-sDNA [40].

Several geographic variations in adherence aligned with the currently reported US percentage of adults being up-to-date with CRC screening tests by state [41], with the highest rates seen in the Pacific and West North Central regions in our study, although adherence was lower in the New England and Middle Atlantic regions where up-to-date screening hovers around $\geq 70\%$ and $\geq 65\%$, respectively.

Additionally, practice specialty was associated with higher cross-sectional adherence. Although gastroenterologists ordered fewer tests, adherence was lower among primary care providers. The observed difference in adherence by specialty could be related to various provider factors (strength of screening recommendation, patient perception of specialty-related knowledge), patient factors (attitude concerning referral/follow-up completion), or a combination. It is also likely that patients who present to a gastroenterologist bring with them specific concerns which may serve as motivation to screen. Although test adherence rates differed by practice, recent literature has shown widespread awareness of the 2018 ACS CRC guidelines among primary care providers [42]. A 2020 survey study by the Montana Cancer Control Program revealed that fecal DNA testing has become much more popular since 2016, with more than a third (35.2%) of primary care providers reporting discussing it with patients in 2020 compared to only 4% in 2016 [43]. The same report from the Montana Department of Public Health and Human Services highlighted that in 2020 the fecal DNA test was the 3rd highest ranked CRC screening test prescribed with 86% of ordering providers considering the test effective. Future CRC screening studies can be tailored to garner information on provider ordering characteristics to better inform screening strategy, assess prescription differences, and develop provider education initiatives.

We would like to acknowledge several limitations of our study. First, there was limited reporting of ethnicity in this study population, with less than 15% of patients specifying a racial category. The unavailability of such data prohibited us from examining an important demographic aspect associated with screening adherence; thus, the differences observed among race/ethnicity were not overly considered due to a large percentage of participants not providing the optional information. Patient and provider factors analyzed in our study were limited to those characteristics that could be captured from the existing laboratory database. A more detailed assessment of factors suspected to influence mt-sDNA screening adherence, such as socioeconomic status along with a closer look at social determinants of health, will benefit future investigations. Secondly, we relied on determination of the mt-sDNA ordering clinician to define CRC average-risk status. Although indicated for mt-sDNA, we assumed that each provider appropriately followed test eligibility indications before prescribing, and we did not have access to sufficient data to confirm risk status for all participants in this real-world study. Thus, a percentage of off-label use can be logically assumed. Lastly, given the relative recency of mt-sDNA availability and adoption in clinical practice, we did not assess longitudinal adherence for the current study. Mt-sDNA test adherence was only evaluated on a cross-sectional basis with a review of associated patient and provider factors over a 1-year study period. Further evaluation of longitudinal adherence with triennial mt-sDNA screening is anticipated in future studies.

Conclusions

Novel data from this large retrospective cohort of both Medicare and commercially insured patients revealed favorable adherence to CRC screening with the mt-sDNA assay test among eligible patients who met the study criteria, having a valid mt-sDNA test shipped to their order-specified address from ESL between January 1, 2018, and December 31, 2018. Innovative features of the mt-sDNA test such as the accompanying patient navigation system, together with its noninvasive approach and feasibility, likely impacted test completion rates. The highest adherence rates were observed among those covered by Medicare and for tests ordered by gastroenterologists. Our findings contribute valuable real-world data to the existing evidence base and provide clinical decision-makers with supportive information to recommend a guideline-endorsed CRC screening strategy, with the goal of increasing adherence through test completion. Future investigations examining longitudinal completion rates in accordance with national guidelines, as well as more detailed analyses of associations with socioeconomic, race/ethnicity, and other demographic factors on mt-sDNA test completion rates, are anticipated to complement this study.

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Author contribution Conceptualization—Lesley-Ann Miller-Wilson, Lila J Finney Rutten, Paul J Limburg, Ahmet Burak Ozbay. Data curation—Jack Van Thomme. Formal analysis—all authors. Investigation—Lesley-Ann Miller-Wilson, Jack Van Thomme. Methodology—all authors. Project administration—Lesley-Ann Miller-Wilson, Jack Van Thomme. Resources—Lesley-Ann Miller-Wilson, Jack Van Thomme, Paul J Limburg. Software—Jack Van Thomme. Supervision—Lesley-Ann Miller-Wilson, Paul J Limburg. Validation—Lesley-Ann Miller-Wilson, Jack Van Thomme. Visualization—Lesley-Ann Miller-Wilson, Jack Van Thomme. Writing (original draft)—all authors. Writing (review & editing)—all authors.

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Availability of data and materials Study data are available upon reasonable request.

Declarations

Ethics approval The data herein were retrospectively reviewed as part of ongoing laboratory (Exact Sciences Laboratories, LLC) quality management processes in compliance with the Health Insurance Portability and Accountability Act (HIPAA). The study was deemed exempt from IRB review by the Mayo Clinic Institutional Review Board.

Consent to participate/consent for publication Not applicable; retrospective review of deidentified data.

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Conflict of interest The authors declare no competing interests.

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References

1. American Cancer Society (2020) ACS Cancer Facts & Figures. https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/annual-cancer-facts-and-figures/2020/cancer-facts-and-figures-2020.pdf. Accessed 16 Nov 2020
2. Siegel RL, Miller KD, Fuchs HE, Jemal A (2021) Cancer Statistics, 2021. CA Cancer J Clin 71(1):7–33. https://doi.org/10.3322/caac.21654
3. Bibbins-Domingo K et al (2016) Screening for colorectal cancer: US preventive services task force recommendation statement. JAMA - J Am Med Assoc 315(23):2564–2575. https://doi.org/10.1001/jama.2016.5989
4. American Cancer Society (2020) Colorectal cancer guideline how often to have screening tests. https://www.cancer.org/cancer/colon-rectal-cancer/detection-diagnosis-staging/acs-recommendations.html. Accessed 03 April 2021
5. Davidson KW et al (2021) Screening for colorectal cancer. JAMA 325(19):1965. https://doi.org/10.1001/jama.2021.6238. Accessed May 2021
6. U.S. Department of Health & Human Services (2015) NHIS - 2015 data release. National Center for Health Statistics. https://www.cdc.gov/nchs/nhis/nhis_2015_data_release.htm. Accessed 05 Feb 2020
7. U.S. Department of Health & Human Services (2018) NHIS - 2018 data release. National Center for Health Statistics. https://www.cdc.gov/nchs/nhis/nhis_2018_data_release.htm. Accessed 05 Feb 2020
8. Exact Sciences Corporation LLC (2020) United States Securities And Exchange Commission (Form 10-K) Annual Report Pursuant To Section 13 Or 15(D) Of The Securities Exchange Act Of 1934; Transition Report Pursuant To Section 13 Or 15(D) Of The Securities Exchange Act Of 1934. Accessed 12 Nov 2020. [Online]. Available: http://d18rn0p25nwr6d.cloudfront.net/CIK-0001124140/32330bf1-f821-4b65-a147-638835b3a7e3.pdf
9. Singal AG et al (2017) Effect of colonoscopy outreach vs fecal immunochemical test outreach on colorectal cancer screening completion a randomized clinical trial. JAMA - J Am Med Assoc 318(9):806–815. https://doi.org/10.1001/jama.2017.11389

Exact Sciences Ex. 2008, Page 295 of 344

10. Cyhaniuk A, Coombes ME (2016) Longitudinal adherence to colorectal cancer screening guidelines – PubMed. Am J Manag Care. https://pubmed.ncbi.nlm.nih.gov/26885670/. Accessed 17 Nov 2020
11. Liang PS et al (2016) Adherence to competing strategies for colorectal cancer screening over 3 years. Am J Gastroenterol 111(1):105–114. https://doi.org/10.1038/ajg.2015.367
12. Inadomi JM et al (2012) Adherence to colorectal cancer screening: a randomized clinical trial of competing strategies. Arch Intern Med 172(7):575–582. https://doi.org/10.1001/archinternmed.2012.332
13. Segnan N et al (2005) Randomized trial of different screening strategies for colorectal cancer: patient response and detection rates. J Natl Cancer Inst 97(5):347–357. https://doi.org/10.1093/jnci/dji050
14. Rutten LJF et al (2020) Colorectal cancer screening completion: an examination of differences by screening modality. Prev Med Rep 20. https://doi.org/10.1016/j.pmedr.2020.101202
15. Vutien P, Shah R, Ma K, Saleem N, Melson J (2019) Utilization of census tract-based neighborhood poverty rates to predict non-adherence to screening colonoscopy. Dig Dis Sci 64(9):2505–2513. https://doi.org/10.1007/s10620-019-05585-8
16. Blair A, Gauvin L, Ouédraogo S, Datta GD (2019) Area-level income disparities in colorectal screening in Canada: evidence to inform future surveillance. Curr Oncol 26(2):e128–e137. https://doi.org/10.3747/co.26.4279
17. Daskalakis C, DiCarlo M, Hegarty S, Gudur A, Vernon SW, Myers RE (2020) Predictors of overall and test-specific colorectal cancer screening adherence. Prev Med (Baltim) 133. https://doi.org/10.1016/j.ypmed.2020.106022
18. Ni K et al (2020) Low colorectal cancer screening uptake and persistent disparities in an underserved urban population. Cancer Prev Res 13(4):395–402. https://doi.org/10.1158/1940-6207.CAPR-19-0440
19. Weiser E et al (2020) Cross-sectional adherence with the multitarget stool DNA test for colorectal cancer screening: real-world data from a large cohort of older adults. J Med Screen. https://doi.org/10.1177/0969141320903756
20. Exact Sciences Corporation LLC (2020) Support & Coverage | Cologuard® For HCPs. https://www.cologuardtest.com/hcp/coverage-and-support/coverage. Accessed 17 Nov 2020
21. United States Census Bureau (2018) 2018 data release new and notable. American Community Survey (ACS). https://www.census.gov/programs-surveys/acs/news/data-releases/2018/release.html#par_textimage_copy. Accessed 18 Nov 2020
22. United States Census Bureau (2019) Number of people with master's and doctoral degrees doubles since 2000. America Counts: Stories Behind The Numbers. https://www.census.gov/library/stories/2019/02/number-of-people-with-masters-and-phd-degrees-double-since-2000.html. Accessed 18 Nov 2020
23. Semega J, Kollar M, Creamer J, Mohanty A (2018) Income and poverty in the United States: 2018. United States Census Bureau. https://www.census.gov/data/tables/2019/demo/income-poverty/p60-266.html. Accessed 18 Nov 2020
24. Sullivan GM, Feinn R (2012) Using effect size—or why the P value is not enough. J Grad Med Educ 4(3):279–282. https://doi.org/10.4300/jgme-d-12-00156.1
25. Ellis PD (2009) Thresholds for interpreting effect sizes. https://www.polyu.edu.hk/mm/effectsizefaqs/thresholds_for_interpreting_effect_sizes2.html. Accessed 18 Nov 2020
26. Rice K et al (2017) Increasing colonoscopy screening in disparate populations: results from an evaluation of patient navigation in the New Hampshire Colorectal Cancer Screening Program. Cancer 123(17):3356–3366. https://doi.org/10.1002/cncr.30761
27. Dougherty MK et al (2018) Evaluation of interventions intended to increase colorectal cancer screening rates in the United States: a systematic review and meta-analysis. JAMA Intern Med 178(12):1645–1658. https://doi.org/10.1001/jamainternmed.2018.4637
28. Prince M, Lester L, Chiniwala R, Berger B (2017) Multitarget stool DNA tests increases colorectal cancer screening among previously noncompliant Medicare patients. World J Gastroenterol 23(3):464–471. https://doi.org/10.3748/wjg.v23.i3.464
29. Champion VL et al (2018) A randomized trial to compare a tailored web-based intervention and tailored phone counseling to usual care for increasing colorectal cancer screening. Cancer Epidemiol Biomarkers Prev 27(12):1433–1441. https://doi.org/10.1158/1055-9965.EPI-18-0180
30. Gellad ZF et al (2011) Longitudinal adherence to fecal occult blood testing impacts colorectal cancer screening quality. Am J Gastroenterol 106(6):1125–1134. https://doi.org/10.1038/ajg.2011.11
31. Imperiale TF et al (2014) Multitarget stool DNA testing for colorectal-cancer screening. N Engl J Med 370(14):1287–1297. https://doi.org/10.1056/nejmoa1311194
32. Murphy CC, Halm EA, Skinner CS, Balasubramanian BA, Singal AG (2020) Challenges and approaches to measuring repeat fecal immunochemical test for colorectal cancer screening. Cancer Epidemiol Biomarkers Prev 29(8):1557–1563. https://doi.org/10.1158/1055-9965.EPI-20-0230
33. Corley DA et al (2017) Association between time to colonoscopy after a positive fecal test result and risk of colorectal Cancer and Cancer stage at Diagnosis. JAMA - J Am Med Assoc 317(16):1631–1641. https://doi.org/10.1001/jama.2017.3634
34. Martin J et al (2017) Reasons for lack of diagnostic colonoscopy after positive result on fecal immunochemical test in a safety-net health system. Am J Med 130(1):93.e1-93.e7. https://doi.org/10.1016/j.amjmed.2016.07.028
35. Tørring ML, Frydenberg M, Hamilton W, Hansen RP, Lautrup MD, Vedsted P (2012) Diagnostic interval and mortality in colorectal cancer: U-shaped association demonstrated for three different datasets. J Clin Epidemiol 65(6):669–678. https://doi.org/10.1016/j.jclinepi.2011.12.006
36. Thomson CS, Forman D (2009) Cancer survival in England and the influence of early diagnosis: what can we learn from recent EUROCARE results? Br J Cancer 101(Suppl 2):S102–S109. https://doi.org/10.1038/sj.bjc.6605399
37. Doubeni CA et al (2019) Modifiable failures in the colorectal cancer screening process and their association with risk of death. Gastroenterology 156(1):63-74.e6. https://doi.org/10.1053/j.gastro.2018.09.040
38. Hassan C et al (2012) Meta-analysis: adherence to colorectal cancer screening and the detection rate for advanced neoplasia, according to the type of screening test. Aliment Pharmacol Ther 36(10):929–940. https://doi.org/10.1111/apt.12071
39. Piscitello A et al (2020) Estimating the impact of differential adherence on the comparative effectiveness of stool-based colorectal cancer screening using the CRC-AIM microsimulation model. bioRxiv. https://doi.org/10.1101/2020.08.30.271858
40. Fendrick M et al (2020) Sa1658 microsimulation study of life-years gained from screening versus follow-up colonoscopy using the CRC-AIM model. Gastroenterol AGA Abstr 158(6):S-372. https://doi.org/10.1016/S0016-5085(20)31623-1
41. Joseph DA, King JB, Richards TB, Thomas CC, Richardson LC (2018) Use of colorectal cancer screening tests by state. Prev Chronic Dis 15(6). https://doi.org/10.5888/pcd15.170535
42. Read AJ, Waljee AK, Saini SD (2020) A national survey of adoption of the 2018 American Cancer Society Colorectal Cancer Screening Guideline in Primary Care. Clin Gastroenterol Hepatol. https://doi.org/10.1016/j.cgh.2020.08.060
43. Montana Department of Public Health and Human Services (2020) Primary care provider survey: colorectal cancer screening knowledge and attitudes. Accessed 18 Nov 2020. [Online]. Available: http://www.dphhs.mt.gov/publichealth/cancer

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Abstract

Purpose of Review

Multi-target stool DNA (MT-sDNA) was approved in 2014 for use in screening average-risk patients for colorectal cancer (CRC). Here, we highlight recent literature from post-market

studies to provide an update on clinical use and utility not possible from pre-approval studies.

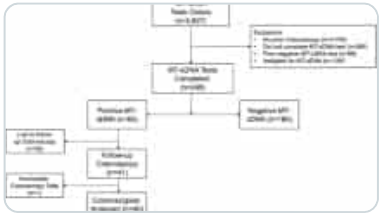
Recent Findings

MT-sDNA has been included in major society guidelines as an option for colorectal cancer screening, and has seen exponentially increasing use in clinical practice. MT-sDNA appears to be attracting new patients to CRC screening, and patient adherence to diagnostic colonoscopy after a positive MT-sDNA test is high. Approximately two-thirds of these patients are found to have colorectal neoplasia (CRN), 80% of whom have at least one right-sided lesion; 1 in 3 will have advanced CRN. High yield of CRN is due not only to post-screening increase in probability but also likely improved endoscopist attention. In those with a negative high-quality colonoscopy after positive MT-sDNA test ("false positive MT-sDNA"), further interventions do not appear to be necessary.

Summary

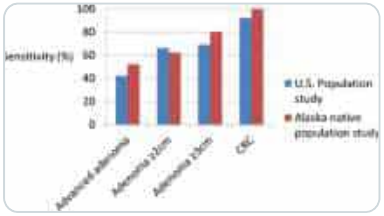
MT-sDNA is a promising tool to improve rates and quality of CRC screening. Further investigation should examine MT-sDNA performance in populations at increased risk for CRC, and as an interval test after colonoscopy to detect potentially missed lesions.

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Introduction

Colorectal cancer (CRC) is a major cause of cancer-related death in the USA [1], with approximately 150,000 new diagnoses and 50,000 deaths from CRC projected in 2019 alone [2]. With widespread screening initiatives to detect CRC and pre-cancerous polyps, CRC-related morbidity and mortality have decreased in recent years [2]. The US Preventive Services Task Force (USPSTF) recommends screening for CRC in average-risk adults between the ages of 50 and 75 [3], while more recent recommendations from the American Cancer Society (ACS) suggest initiating screening at age 45 in light of the increasing rate of CRC diagnosed in younger patients [4•,5,6,7,8]. However, despite these guidelines and extensive public health initiatives, approximately one-third of screen-eligible adults in the USA remain unscreened [9, 10•].

Several methods are recommended for CRC screening [3, 4•, 11•]. Colonoscopy is the most widely used modality in the USA [9] and permits simultaneous diagnostic and therapeutic intervention for colorectal neoplasia (CRN). However, screening colonoscopy has several notable drawbacks, including reduced sensitivity in the proximal colon [12,13,14,15,16,17,18•] and inter-operator variability in colonoscopy quality [19,20,21,22]. Furthermore, its invasive nature; risk of complications; and the inconvenience of preparation, sedation, and time away from work are recognized barriers to patients considering screening [23]. Several non-invasive screening modalities are endorsed as an alternative to colonoscopy for use in average-risk patients. Guaiac-based fecal occult blood testing (gFOBT) has the strongest body of evidence demonstrating a reduction in CRC-related mortality [24,25,26,27]. However, dietary and medication interactions, poor performance in the proximal colon, and issues with adherence to the recommended yearly screening interval have led to decreased utilization of this test [28,29,30]. The introduction of fecal immunochemical testing (FIT) addressed some of these limitations, with FIT included as a first-line option in major society screening guidelines [3, 11•]. A recent meta-analysis suggested moderate-to-high sensitivity and specificity for CRC and advanced adenoma (AA) in a single-use setting, but performance varied by assay and positivity cutoff [31]. Concerns remain regarding reduced sensitivity for right-sided and sessile serrated

precursor lesions [28, 29, 32•] in addition to persistent poor adherence to required annual testing [30, 33,34,35,36].

Multi-target stool DNA testing

Multi-target stool DNA (MT-sDNA) is a newer stool-based screening modality, with one commercial product available to patients in the USA (Cologuard™, Exact Sciences, Madison, WI). This test detects abnormal DNA markers (aberrantly methylated *BMP3* and *NDRG4*, mutant *KRAS*) shed from neoplastic cells in the gastrointestinal tract. Another marker, *β-actin*, serves as a control to ensure adequate quantity of DNA in the sample, while an immunochemical assay for hemoglobin detects evidence of gastrointestinal bleeding. These components are measured quantitatively and incorporated into a logistic regression algorithm containing mathematical interaction variables for each marker. These interaction terms result in numerous marker combinations that can trigger a pre-specified threshold score, resulting in a positive or negative test result that is more than the sum of its individual components [37].

MT-sDNA testing is performed by the patients in the comfort of their own home. Following a provider order, a manufacturer-based patient navigation office contacts the patient and arranges sample collection via a courier-delivered kit [38]. This system also provides patient education and test completion reminders which have been shown to result in adherence to testing of over 70% in Medicare beneficiaries [38]. Following delivery of the MT-sDNA kit, patients collect a whole stool sample, swab a portion to collect the FIT sample, add a preservative buffer to the whole stool, seal the container, and mail the samples in one box back to the laboratory for analysis.

MT-sDNA testing was approved for screening in average-risk adults by the US Food and Drug Administration (FDA) in 2014, following a large screen–setting trial by Imperiale et al. (DeeP-C trial), comparing MT-sDNA and FIT. Overall, the sensitivity of MT-sDNA for detecting CRC in this study was 92% (vs 74% for FIT, $p = 0.002$), and 42% for advanced pre-cancerous lesions (vs 24% for FIT, $p < 0.001$) [39]. A second study performed in an Alaska Native cohort confirmed these findings, and re-demonstrated increasing sensitivity by adenoma size, with 80% sensitivity for lesions > 3 cm, and 100% sensitivity for CRC [40••]. Specificity was 87–94% across these two studies, and increased in younger patients (Table

1) [39, 40••]. MT-sDNA appears to have similar performance for the detection of both conventional adenomas and sessile serrated polyps (SSPs). Large SSPs and hyperplastic polyps (≥1 cm) were included in the sensitivity estimate for advanced pre-cancerous lesions in the DeeP-C study [39]. For greater clarity, a post hoc analysis of DeeP-C data was performed on all lesions ≥1 cm with histology confirmed for SSP. The median size was 1.2 cm (range 1–3), and the majority (28/29 (93%)) were located proximal to the splenic flexure; only one SSP contained dysplasia. In this setting, MT-sDNA had a sensitivity of 55% (95% CI, 36–74%) and a specificity of 91% [41]. MT-sDNA performance characteristics for the individual endpoint category of large hyperplastic polyp have not been estimated and traditional serrated adenomas were not identified by screening colonoscopy in the DeeP-C study; these endpoints are deserving of future study.

Table 1 Multi-target stool DNA demonstrates higher specificity in younger patients with normal colonoscopy

Population modeling studies performed as part of a USPSTF review suggest that programmatic use of MT-sDNA would result in fewer lifetime colonoscopies than FIT and a stronger benefit-to-harms ratio than colonoscopy (Table 2) [3]. As a result of the above findings, MT-sDNA testing was subsequently endorsed by the USPSTF in their 2016 guidelines for CRC screening [3]. Utilization of MT-sDNA has been increasing exponentially since then, with nearly 3 million screens performed to date [42].

Table 2 Screening with multi-target stool DNA testing results in fewer lifetime colonoscopies than FIT, and has a superior benefit-to-harm ratio compared to colonoscopy

Outcomes in patients undergoing multi-target stool DNA testing

Since the introduction of MT-sDNA in 2014, data have begun to emerge regarding its "real-world" performance. MT-sDNA appears to be attracting new patients to screening. One recent study demonstrated high utilization of MT-sDNA in almost 400 previously non-adherent average-risk Medicare patients, with 51% harboring advanced neoplastic lesions; fewer than 20% had no neoplastic findings at diagnostic colonoscopy [43•]. Furthermore, we recently presented data from a cohort of over 2000 MT-sDNA-positive patients showing that approximately 25% had never been screened for CRC and were > 10 years overdue [44]. While there may be many reasons for patients to go without screening, these findings suggest that MT-sDNA is attracting previously non-adherent patients, a critical outcome in the ongoing long-term fight to reduce CRC-attributable mortality.

Of all patients screened with MT-sDNA, 14–16% will have positive results [39, 44, 45]. Following a positive MT-sDNA test, it is imperative that patients undergo diagnostic colonoscopy to evaluate for CRN. While previous estimates of adherence to diagnostic colonoscopy ranged from 75 to 96% [43•, 45], our recent analysis showed a diagnostic colonoscopy completion rate of ~ 90% in a large multi-practice setting [44]. Reasons for non-adherence to recommended diagnostic colonoscopy vary, but are commonly related to a wish to avoid colonoscopy, in addition to medical comorbidities that preclude sedation and procedural intervention [45]. These factors illustrate the importance of both provider and patient education prior to pursuing MT-sDNA testing in order to ensure selection of appropriate patients for screening with this test.

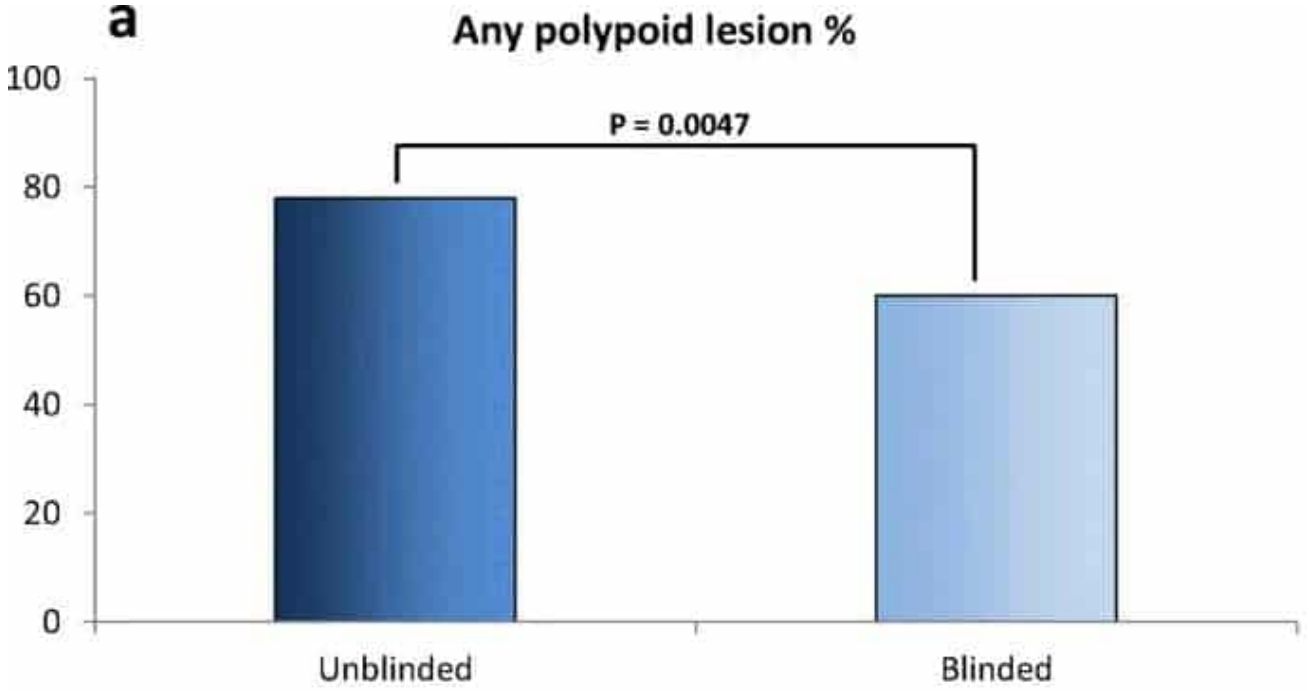
In patients with positive MT-sDNA testing who undergo diagnostic colonoscopy, our data show that approximately two-thirds will be found to have at least one neoplastic lesion [44]. Among patients with CRN, 40% will have at least one advanced lesion (defined as CRC, adenomas, or SSPs with at least one of the following characteristics: ≥1 cm in size, high-grade dysplasia, or having ≥25% villous elements), and ~ 1% will have CRC. SSPs will be detected in about half of patients with positive tests.

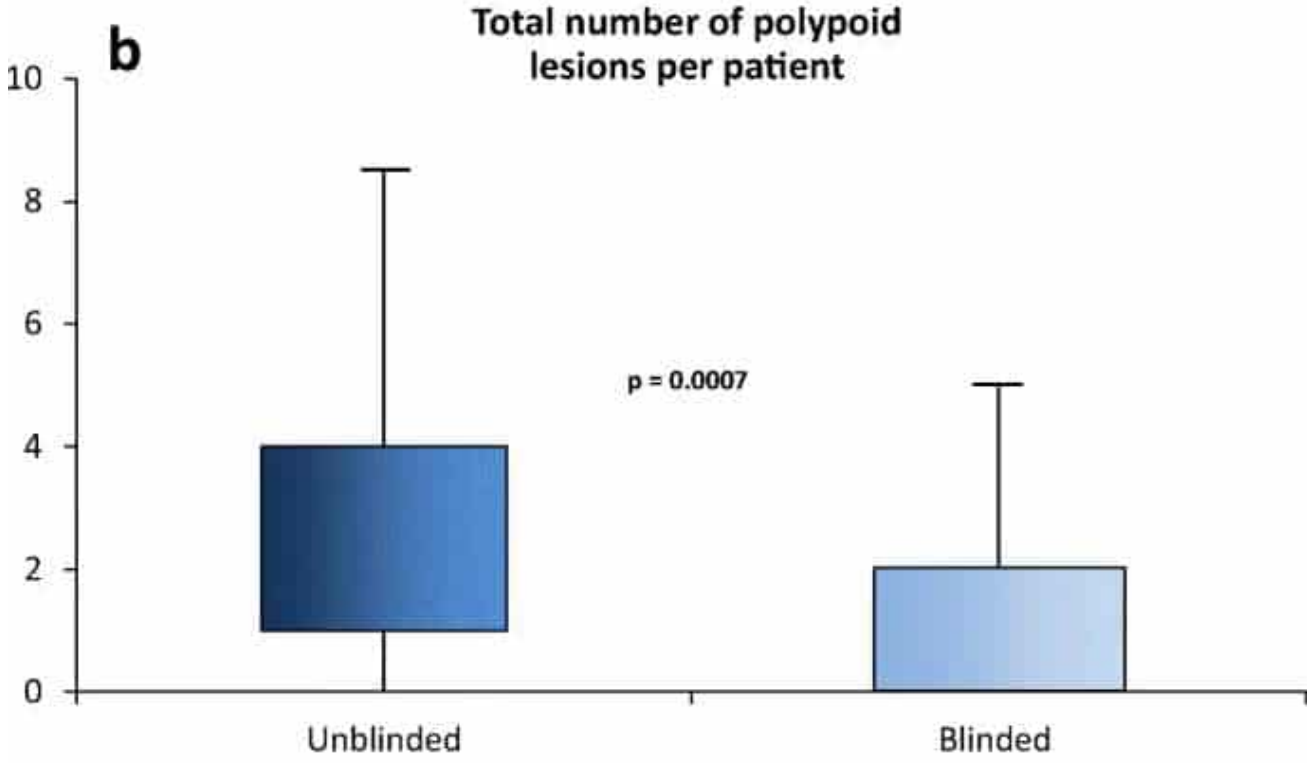
Importantly, MT-sDNA testing appears to perform well in detecting right-sided (proximal) neoplasia. In our multi-site cohort of patients with positive MT-sDNA tests, over 50% of patients overall (and 80% of those with neoplastic lesions) were found to have proximal CRN [44]. The reason for the high yield of proximal CRC is likely multifactorial, although

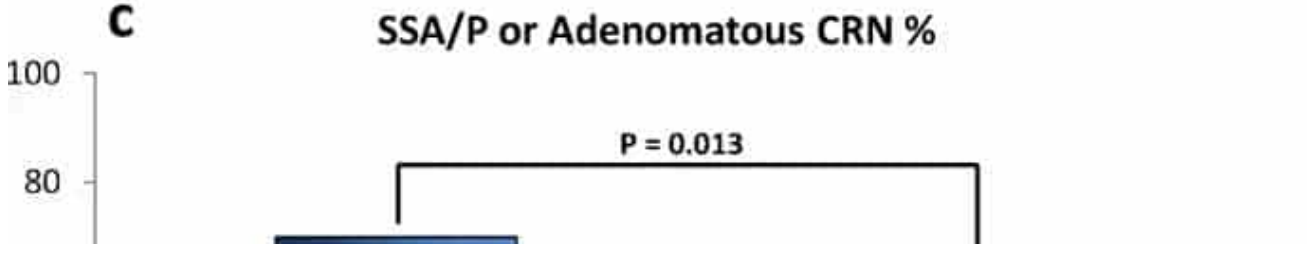
improved detection resulting from the multiple markers in MT-sDNA offers one potential explanation. Right-sided lesions tend to be flat and less likely to bleed [46], and exfoliation of DNA markers is more consistent throughout the colon [47]; therefore, MT-sDNA has an advantage over other non-invasive methods for the detection of right-sided neoplasia.

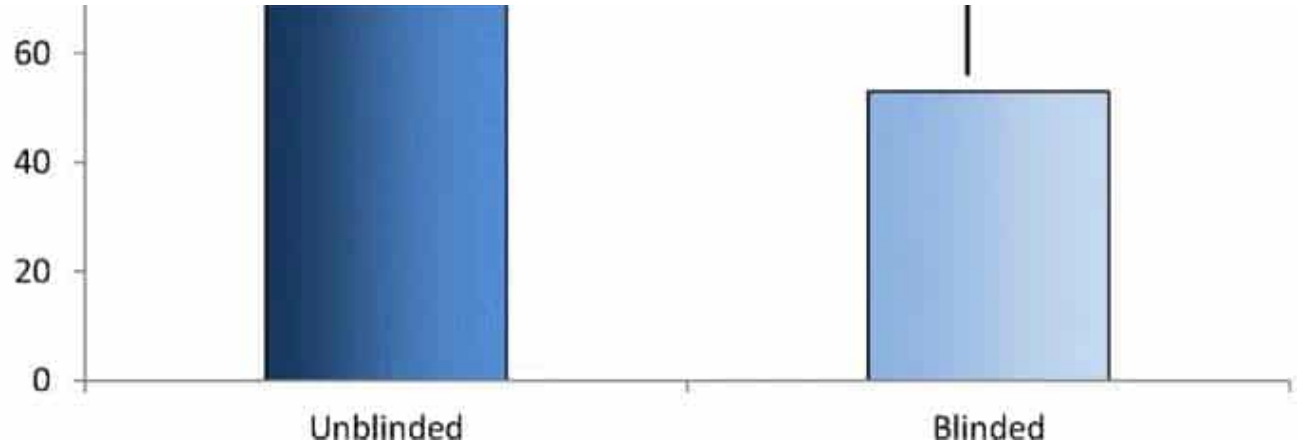
These point estimates for positive predictive value appear higher than reported in the pre-FDA approval trial, where advanced lesions were found in 24% of those with positive MT-sDNA tests [39]. This is likely in part due to underlying differences in the populations being studied, or in differences in those opting to use the test in clinical practice versus the clinical trial setting. However, there are several other factors that likely contribute to the high yield of MT-sDNA for CRN, both proximal and distal. First, by screening an average-risk population with MT-sDNA and performing further testing only in those with positive results, this creates an enriched population in whom the pre-test probability of CRN at diagnostic colonoscopy is increased. Furthermore, studies have shown that endoscopist knowledge of a positive MT-sDNA test significantly increases quality metrics such as ADR at diagnostic colonoscopy compared with blinded endoscopists, likely related to longer withdrawal time and increased attention to subtle lesions (Fig. 1) [48••]. Moreover, recent data suggest that while improvement in quality and yield of diagnostic colonoscopy is observed in all endoscopists in a large academic practice, the greatest improvement in polyp detection is seen in gastroenterologists with lower baseline detection rates [49].

Fig. 1


a
Any polypoid lesion %
100
80
60
40
20
0
P = 0.0047
Unblinded
Blinded


b
Total number of polypoid lesions per patient
10
8
6
4
2
0
p = 0.0007
Unblinded
Blinded


c
SSA/P or Adenomatous CRN %
100
80
P = 0.013



The **a** proportion of patients with polyps, **b** number of polyps per patient, and **c** proportion of patients with sessile serrated and adenomatous polyps found at diagnostic colonoscopy after positive multi-target stool DNA test is higher in unblinded endoscopists compared with blinded endoscopists. Used with permission from Elsevier.

"False positive" MT-sDNA tests

A common question among physicians and other health care providers is what should be done in the setting of a positive MT-sDNA test followed by a negative colonoscopy (a "false positive" MT-sDNA test). However, before addressing this question, negative colonoscopy needs to be more clearly defined. The original studies investigating MT-sDNA testing labeled true positive tests as those in which only advanced neoplasia or CRC was detected [39]. However, we have shown that approximately 40% of lesions detected by MT-sDNA are non-advanced [44]; a positive MT-sDNA test in these situations is therefore unlikely to be biologically false, but rather to have detected exfoliated DNA from a neoplasm not meeting arbitrary size-based criteria. With this in mind, knowing that 14% of all MT-sDNA tests are positive and that 67% of these patients have CRN found at diagnostic colonoscopy, less than 5% of all patients screened with MT-sDNA would have no polyps found at colonoscopy (14.1% × (100% − 67%) = 4.7%). Even when including only advanced CRN and CRC, 10% (14.1% × (100% − 28%)) would have false positive results.

In the clinical situation of a false positive MT-sDNA test, the next step is to ensure that a diagnostic colonoscopy of sufficient quality was performed. In clinical trials of MT-sDNA, only those with high-quality colonoscopy, defined as having good or excellent bowel preparation, photographic evidence of cecal intubation, and withdrawal time of ≥ 6 min, were included in primary study outcomes [21, 39, 40••, 50]. Assuming a high-quality

colonoscopy, current guidelines suggest that no further testing be performed [11•]. These recommendations are based on several studies that found no increased risk of CRC in this specific population. One such study prospectively evaluated 30 patients with initial false positive MT-sDNA testing (evaluated by both colonoscopy and esophagogastroduodenoscopy (EGD)), who underwent repeat MT-sDNA and colonoscopy/EGD 1 year later. In this cohort, only two advanced lesions were found on repeat testing; however, information on initial colonoscopy quality was not reported [51•]. Another study retrospectively analyzed approximately 1000 patients with either false positive or true negative MT-sDNA tests, and found no increased rate of aerodigestive cancers in a per-protocol analysis at a median follow-up of 4 years [52•]. More recently, a multi-site retrospective cohort study performed by Berger et al. evaluated approximately 1200 patients with negative colonoscopy over a median of 5 years, and stratified patients by concordant (negative) or discordant (positive) MT-sDNA results. They found no increased incidence of aerodigestive cancers in either group, with rates that were equivalent to the general population based on Surveillance, Epidemiology, and End Results (SEER) Program data [53•]. Therefore, based on currently available evidence, clinicians should not recommend repeat colonoscopy, EGD, or other further testing in patients with positive MT-sDNA, a negative high-quality diagnostic colonoscopy, and no localizing signs or symptoms that would mandate evaluation.

Future directions

Even with increasing utilization of MT-sDNA and the emergence of post-approval performance data, several opportunities for further study remain. While the current recommended testing interval for MT-sDNA is 3 years, this is based on manufacturer's recommendations and computer modeling, and further investigation is needed into MT-sDNA performance with different testing frequencies. Additional study of patient adherence to both the testing schedule and diagnostic colonoscopy in other populations would also help to further inform test performance in the real world.

MT-sDNA testing may benefit additional patient populations. In response to the ACS recommendation to begin screening for CRC at age 45, studies conducted in archival tissue specimens demonstrated that MT-sDNA markers in primary CRC tumors among those 45–49 years old at diagnosis are similar to those seen in tumors of patients aged 50–64 [54]; methylated DNA markers were all substantially higher than observed in control tissues

across these age ranges. As a result of these data and those expected from a clinical trial utilizing MT-sDNA in patients age 45–49 (ClinicalTrials.gov Identifier: NCT03728348), the FDA recently expanded the label for MT-sDNA to include those age 45–84.

The FDA's current labeling excludes those at increased risk for CRC due to conditions such as inflammatory bowel disease (IBD), personal history of advanced CRN, family history of early CRC, and signs of blood loss, among others. Initial data from our group's evaluation of off-label use of MT-sDNA testing (~ 10% of tests) in patients with these risk factors show that test performance is similar to those at average risk [55]. Furthermore, in a research study of 192 patients with IBD undergoing MT-sDNA testing for surveillance, the test demonstrated similar sensitivity for both CRC and CRN when compared with the general population [56•]. However, further study is needed before extending MT-sDNA use into these increased-risk populations.

Finally, MT-sDNA may have important utility as an interval test following apparently negative colonoscopy. In our group's analysis of data in patients undergoing MT-sDNA testing within 5 years of a negative colonoscopy, the yield of all CRN and most CRN subtypes was the same as in those undergoing testing 10 or more years after colonoscopy. When these patients were further stratified by whether their prior colonoscopy was complete or incomplete (e.g., poor prep, no cecal intubation), neoplastic yield remained similar between groups [57]. Advanced neoplasms were found in 16–17% of those screened early with MT-sDNA; these findings could not be explained by known elevations in baseline risk. Taken together, these findings suggest that lesions are likely being missed at screening colonoscopies. MT-sDNA should therefore be studied as a tool between colonoscopies to identify those in which polyps were likely to have been missed, and thereby reduce the risk of interval CRC.

Conclusion

MT-sDNA is a stool-based screening test with high sensitivity and specificity for both CRN and CRC. As its use has increased over the past 5 years after FDA approval, it has attracted a large population of previously non-adherent patients to screening. A majority of patients with a positive test are found to have CRN at diagnostic colonoscopy, with most harboring right-sided lesions. While further investigation is necessary into additional potential uses,

MT-sDNA has firmly cemented itself as a convenient, non-invasive, and effective tool for widespread screening in the ongoing fight against CRC.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as: • Of importance •• Of major importance

1. Cronin KA, Lake AJ, Scott S, Sherman RL, Noone AM, Howlader N, et al. Annual Report to the Nation on the Status of Cancer, part I: national cancer statistics. Cancer. 2018;124(13):2785–800. https://doi.org/10.1002/cncr.31551.

Article PubMed PubMed Central Google Scholar

2. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. CA Cancer J Clin. 2019;69(1):7–34. https://doi.org/10.3322/caac.21551.

Article Google Scholar

3. Bibbins-Domingo K, Grossman DC, Curry SJ, Davidson KW, Epling JW Jr, Garcia FAR, et al. Screening for colorectal cancer: US Preventive Services Task Force recommendation statement. JAMA. 2016;315(23):2564–75. https://doi.org/10.1001/jama.2016.5989.

Article CAS PubMed Google Scholar

4. • AMD W, ETH F, Church TR, Flowers CR, Guerra CE, SJ LM, et al. Colorectal cancer screening for average-risk adults: 2018 guideline update from the American Cancer Society. CA Cancer J Clin. 2018;68(4):250–81. https://doi.org/10.3322/caac.21457 Guideline update from the American Cancer Society in 2018 recommending screening for colorectal cancer starting at age 45 in average-risk individuals, with MT-sDNA supported as a non-invasive screening modality.

Article Google Scholar

5. Ward EM, Sherman RL, Henley SJ, Jemal A, Siegel DA, Feuer EJ, et al. Annual Report to the Nation on the Status of Cancer, featuring cancer in men and women age 20–49 years. JNCI: Journal of the National Cancer Institute. 2019. https://doi.org/10.1093/jnci/djz106.

Article Google Scholar

6. Bailey CE, Hu CY, You YN, Bednarski BK, Rodriguez-Bigas MA, Skibber JM, et al. Increasing disparities in the age-related incidences of colon and rectal cancers in the United States, 1975-2010. JAMA surgery. 2015;150(1):17–22. https://doi.org/10.1001/jamasurg.2014.1756.

Article PubMed PubMed Central Google Scholar

7. Hessami Arani S, Kerachian MA. Rising rates of colorectal cancer among younger Iranians: is diet to blame? Curr Oncol. 2017;24(2):e131–e7. https://doi.org/10.3747/co.23.3226.

Article CAS PubMed PubMed Central Google Scholar

8. Troeung L, Sodhi-Berry N, Martini A, Malacova E, Ee H, O'Leary P, et al. Increasing incidence of colorectal cancer in adolescents and young adults aged 15-39 years in Western Australia 1982-2007: examination of colonoscopy history. Front Public Health. 2017;5:179. https://doi.org/10.3389/fpubh.2017.00179.

Article PubMed PubMed Central Google Scholar

9. Control CD. Vital signs: colorectal cancer screening test use--United States, 2012. MMWR Morb Mortal Wkly Rep. 2013;62(44):881–8.

Google Scholar

10. • Joseph DA, King JB, Richards TB, Thomas CC, Richardson LC. Use of colorectal cancer screening tests by state. Prev Chronic Dis. 2018;15:E80. https://doi.org/10.5888/pcd15.170535 CDC report showing large proportion of Americans are not up to date with colorectal cancer screening, with significant geographic variation in screening rates.

Article PubMed PubMed Central Google Scholar

11. • Rex DK, Boland RC, Dominitz JA, Giardiello FM, Johnson DA, Kaltenbach T et al. Colorectal cancer screening: recommendations for physicians and patients from the U.S. Multi-Society Task Force on colorectal cancer. Am J Gastroenterol. 2017;112(7):1016–1030. doi:https://doi.org/10.1038/ajg.2017.174. Multi Society Task Force recommendations for colorectal cancer screening which include multi-target stool DNA as an option in average-risk patients. This guideline also recommends against additional testing in patients with negative colonoscopy after a positive MT-sDNA test.

Article Google Scholar

12. Nishihara R, Wu K, Lochhead P, Morikawa T, Liao X, Qian ZR, et al. Long-term colorectal-cancer incidence and mortality after lower endoscopy. N Engl J Med. 2013;369(12):1095–105. https://doi.org/10.1056/NEJMoa1301969.

Article CAS PubMed Google Scholar

13. Xiang L, Zhan Q, Zhao XH, Wang YD, An SL, Xu YZ, et al. Risk factors associated with missed colorectal flat adenoma: a multicenter retrospective tandem colonoscopy study. World J Gastroenterol. 2014;20(31):10927–37. https://doi.org/10.3748/wjg.v20.i31.10927.

Article PubMed PubMed Central Google Scholar

14. Singh H, Nugent Z, Demers AA, Kliewer EV, Mahmud SM, Bernstein CN. The reduction in colorectal cancer mortality after colonoscopy varies by site of the cancer.