Detection of Postcolonoscopy Colorectal Neoplasia by Multi-target Stool DNA

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INTRODUCTION: **Significant variability between colonoscopy operators contributes to postcolonoscopy colorectal cancers (CRCs). We aimed to estimate postcolonoscopy colorectal neoplasia (CRN) detection by multi-target stool DNA (mt-sDNA), which has not previously been studied for this purpose.**

METHODS: **In a retrospective cohort of patients with +mt-sDNA and completed follow-up colonoscopy, positive predictive value (PPV) for endpoints of any CRN, advanced adenoma, right-sided neoplasia, sessile serrated polyps (SSP), and CRC were stratified by the time since previous colonoscopy (0–9, 10, and ≥11 years). mt-sDNA PPV at ≤9 years from previous average-risk screening colonoscopy was used to estimate CRN missed at previous screening colonoscopy.**

RESULTS: **Among the 850 studied patients with +mt-sDNA after a previous negative screening colonoscopy, any CRN was found in 535 (PPV 63%). Among 107 average-risk patients having +mt-sDNA ≤9 years after last negative colonoscopy, any CRN was found in 67 (PPV 63%), advanced neoplasia in 16 (PPV 15%), right-sided CRN in 48 (PPV 46%), and SSP in 20 (PPV 19%). These rates were similar to those in 47 additional average risk persons with previous incomplete colonoscopy and in an additional 68 persons at increased CRC risk. One CRC (stage I) was found in an average risk patient who was mt-sDNA positive 6 years after negative screening colonoscopy.**

DISCUSSION: **The high PPV of mt-sDNA 0–9 years after a negative screening colonoscopy suggests that lesions were likely missed on previous examination or may have arisen *de novo*. mt-sDNA as an interval test after negative screening colonoscopy warrants further study.**

SUPPLEMENTARY MATERIAL accompanies this paper at http://links.lww.com/CTG/A641

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INTRODUCTION

Despite effective population-level screening strategies, colorectal cancer (CRC) remains the second leading cause of cancer-related deaths for men and women in the United States (1). The US Preventive Services Task Force recommends CRC screening for average-risk adults aged 50–75 years (2). Among CRC screening strategies, colonoscopy is most frequently used (3); however the well-established operator-dependent nature of screening colonoscopy quality remains a concern. Most notable is the variability in detection/prevention of right-sided colon cancer by colonoscopy and related cancer death (4–10). Most postcolonoscopy cancers (PCCRC) (CRC after previous negative colonoscopy (11)) occur in the proximal colon (12) or harbor molecular features associated with right-sided neoplasms (5,10,13). Variability among operators is felt to be a leading cause in the 3.5%–9% rate of PCCRC (12,14) and lower impact of screening/surveillance colonoscopy in preventing right-sided CRC (5,15,16). Although some have argued that the disparity in protection from right-sided CRC may be closing (17–19), recent data show that the relative risk reduction in proximal CRC is durable for only 7 years after colonoscopy (20). Although this study also showed a relative risk reduction for CRC beyond 12 years from colonoscopy, absolute CRC incidence reached the same threshold as for average risk individuals aged 50 to 54, 7 years postnegative colonoscopy (20). Conversely, a recent report from Poland showed reductions in incidence/mortality for up to 17 years among those with a negative screening colonoscopy compared with the general population (21). Although encouraging, these observations were

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in a population with a much greater CRC incidence and lower screening colonoscopy rate than the United States. Furthermore, fewer than one-third of those patients received an examination of sufficient quality to reduce proximal CRC mortality (21).

The role of missed colorectal neoplasia (CRN) at screening is also of particular concern. Previous pooled prospective analysis suggested PCCRC was a result of missed CRN in more than 50% of cases (22), and based on previous estimates, 3.5 cancers per 1,000 persons would be anticipated within 5 years of screening colonoscopy (23). Notably, a recent meta-analysis of same-day tandem colonoscopies revealed that CRN miss rates are even higher than previously reported (24). Aside from PCCRC, missed CRN also threatens appropriate risk stratification after colonoscopy, which is invaluable for reducing CRC incidence (25).

Could the combination of structural and stool-based screening address this critical gap? Multi-target stool DNA (mt-sDNA) is approved by the Food and Drug Administration (FDA) for CRC screening in average-risk persons aged 45–84. The test quantifies methylated *BMP3* and *NDRG4*, mutant *KRAS*, *β-actin*, and fecal hemoglobin, with the results reported as positive or negative based on a validated, multiparameter algorithm (26). In the pivotal DeeP-C trial leading to FDA approval, mt-sDNA was found to be significantly more sensitive than fecal immunochemical testing (FIT) in the detection of advanced CRN and sessile serrated polyps (SSPs) (27). Several real-world evidence studies are also available now. Roughly, twice as many polyps overall and 4 times more right-sided lesions were discovered when the colonoscopists were unblinded to the +mt-sDNA results in comparison to the same group when blinded (28). Furthermore, mt-sDNA increases the rates of SSP diagnosis, which has not been demonstrated after +FIT (29,30).

However, the yield of CRN with a +mt-sDNA test in patients who have had a recent negative screening colonoscopy is not known. Our group previously demonstrated that mt-sDNA performance among average-risk patients was preserved independent of the history of colonoscopy; however, most of these patients had mt-sDNA use ≥10 years from previous colonoscopy (31). We therefore evaluated the PPV of mt-sDNA stratified by time since the last colonoscopy and CRC risk (average and high) among the same population, which was not previously analyzed. To estimate postcolonoscopy missed CRN, the analysis focused on average-risk persons who underwent mt-sDNA sooner than indicated based on the guideline recommendations after negative screening colonoscopy (2,32,33).

METHODS

Study population

Data were generated from an institutional review board-approved retrospective cohort study of all patients who underwent mt-sDNA testing between October 1, 2014, and December 31, 2017, at Mayo Clinic (Minnesota, Arizona, and Florida sites) and the surrounding Mayo Clinic Health System community practices in Minnesota, Wisconsin, and Iowa.

All patients with +mt-sDNA results were included in the initial study cohort. Because colonoscopy is not conducted on those with a negative mt-sDNA, these patients were not studied further. Patients were identified by the Department of Biomedical Statistics and Informatics by using diagnostic and procedure billing codes (see Supplementary Table 1, Supplementary Digital Content 1, http://links.lww.com/CTG/A641). This list was corroborated with 2 separate systems, one by the test manufacturer (Exact Sciences Corporation, Madison, WI) and the second was generated from the Mayo Clinic Enterprise Data Warehouse. Those without signed authorization for chart review research were excluded, in accordance with Minnesota Health Records Act, 144.295. The trained data extraction team then collected study endpoints through detailed chart review of each patient with a +mt-sDNA test. All data were entered into a secure online database built using REDCap (Vanderbilt University, Nashville, TN).

For patients with a +mt-sDNA test, extracted variables included sex, age, race, tobacco use, and history of previous colonoscopy. A single reviewer (D.W.E.) extracted colonoscopy metrics (cecal intubation, bowel prep quality, and withdrawal time) for the colonoscopy before mt-sDNA testing to determine the adequacy of previous assessment. The single reviewer also extracted the date and neoplasia (polyp number, size, and pathology) for all available previous colonoscopies. The baseline colonoscopy findings and subsequent surveillance colonoscopy were used, in part, to determine patient risk for subsequent advanced CRN in accordance with the guidelines (32). Findings enumerated at post-mt-sDNA colonoscopy included polyp number, size, location, histopathology, and dysplasia grade. Documentation of cecal intubation and reported bowel preparation quality were also collected for the post-mt-sDNA diagnostic colonoscopy.

Similar to the FDA pivotal study (27), patients with increased risk for CRC were identified based on any of the following: personal history of advanced CRN, inflammatory bowel disease, polyposis or CRN syndrome, family history of CRC ≤60 years of age, positive fecal blood testing within the previous 6 months, overt rectal bleeding or anemia of unknown etiology, or known cancer of the aerodigestive tract (lung and gastrointestinal) within the 5 years before mt-sDNA.

Interval CRN

For patients with +mt-sDNA who had undergone previous screening colonoscopy, the date of previous colonoscopy and highest risk CRN were recorded. For those with previous CRN identified outside of our institution, lesions were characterized as per the US Multi-Society Task Force on CRC (32) by availability of data sources ranked in the order of (i) pathology reports, (ii) the reported size at colonoscopy, or (iii) the interval recommended for surveillance at colonoscopy. Patients were first stratified by time since last colonoscopy (0–5, 6–9, 10 or ≥11 years) and then underwent additional chart review to discern the indication for mt-sDNA ordering if less than 10 years from the most recent colonoscopy.

Indications fell into 3 categories, which were then further stratified by patient CRC risk (average versus increased) (Figure 1). The first category, early screen, included mt-sDNA use for the indication of screening an average-risk patient, and mt-sDNA use was at an interval 9 or fewer years after previous colonoscopy. Importantly, the indication for early screen could not be for signs or symptoms (bleeding, anemia, abdominal pain, change in bowel habit, and unintentional weight loss) that otherwise required a diagnostic colonoscopy or raised CRC risk. The previous colonoscopy also needed to be adequate for screening (by colon preparation, extent reached, and withdrawal time). In the event these quality markers were not known or reported, the quality of colonoscopy was inferred from chart review or based on the suggested

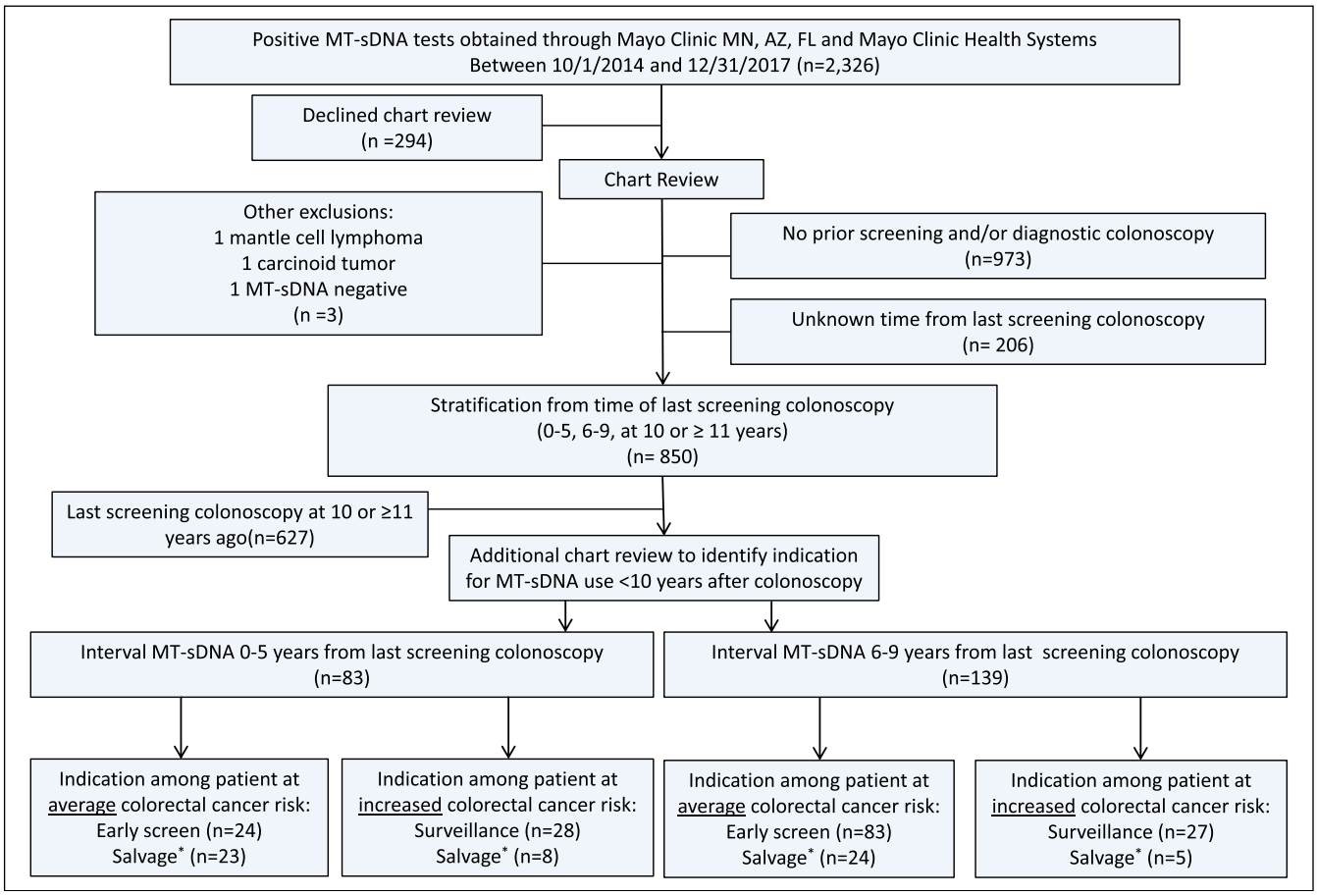

Figure 1. Study flow diagram. *Previous colonoscopy was not adequate for screening purposes. mt-sDNA, multi-target stool DNA.

time for subsequent colonoscopy. Importantly, in the absence of high-risk factors for CRC, average-risk patients may have had a history of previous neoplasia. However, the individual must have returned to average risk based on previous surveillance colonoscopy frequency/findings or had neoplasia that suggested surveillance at a 7- to 10-year interval. This risk assessment for CRC is in accordance with the current guidelines as the risk for advanced CRN is similar for those with 1–2 adenomas <10 mm when compared with no history of adenoma (32). The second category was mt-sDNA use for an indication of surveillance. These patients had increased CRC risk or a history of previous CRN warranting surveillance colonoscopy at an interval of 5 or fewer years but may have refused surveillance colonoscopy. The third category included mt-sDNA used to salvage incomplete previous colonoscopy that was aborted for inadequate prep or difficult anatomy (34); thus, the CRC screening opportunity was preserved by a noninvasive strategy, similar to the precedent uses of CT colonography and capsule colonoscopy (35). This salvage group with previous incomplete colonoscopy was also stratified based on CRC risk. Because average-risk patients within the salvage group were not up-to-date with screening (given the previous incomplete screening), they were studied as a positive control arm within each time interval of mt-sDNA testing for the average-risk early screen groups. Salvage mt-sDNA use among those with increased CRC risk served as the positive control for those who had mt-sDNA for increased risk surveillance.

The detection of CRN at a diagnostic colonoscopy for +mt-sDNA 0–5 and 6–9 years after previous colonoscopy was used to estimate potentially missed lesions at previous colonoscopy. Hyperplastic polyps were excluded from all analyses, irrespective of the size. Between the early screening and the salvage groups, we also compared the percentage of examinations with any neoplasia, advanced neoplasia (CRC or adenoma/SSP ≥1 cm or with high-grade dysplasia or villous elements), right-sided neoplasia (at least one neoplasm proximal to the splenic flexure), and SSPs for each time range.

Statistical analysis

With minimal *a priori* information regarding the percent of interval findings of CRN, sample size assessments were performed at the most variable point of the binomial distribution (percent positive = 50%) to derive adequate power across the entire range of PPV. To test trends in CRN across ordinal time intervals, a simulation of multinomial distributions was performed, assuming equal sample sizes per time interval and the percent positive increasing by 5% per group starting at 40% and ending at 60% (mean of 50% with a 20% difference between the lowest to highest ordinal group). With a 2-sided alpha of 0.05 and 80% power, the minimum sample size per group was estimated to be 85 patients. To detect a 20% difference in CRN between the screening and salvage groups, the minimum sample size per group was estimated to be 91. The same power to detect a 20% difference is

Table 1. Characteristics of patients having mt-sDNA testing 9 or fewer years after previous colonoscopy

Group[a]	Average risk			Increased risk[b]			Overall[c]
Variable	Early screening (n = 107)	Salvage (n = 47)	*P*	Surveillance (n = 55)	Salvage (n = 13)	*P*	*P*
Time since last colonoscopy							
0–5 yr, n (%)	24 (22)	23 (49)	0.002	28 (51)	8 (62)	0.55	0.003
6–9 yr, n (%)	83 (78)	24 (51)		27 (49)	5 (38)		
Median age, yr (IQR)	74 (68–79)	69 (62–72)	<0.0001	78 (70–83)	73 (63–78)	0.14	0.003
Men, n (%)	57 (53)	12 (26)	0.002	29 (53)	5 (38)	0.54	0.56
White race, n (%)	102 (95)	46 (98)	0.67	51 (93)	13 (100)	1.00	1.00
Current or former tobacco,[d] n (%)	48 (45)	19 (41)	0.72	36 (67)	8 (62)	0.75	0.03

IQR, interquartile range; mt-sDNA, multi-target stool DNA.
[a]Early screen includes mt-sDNA use before the anticipated interval screen based on previous colonoscopy findings. Salvage mt-sDNA use was conducted after an aborted colonoscopy; previous colonoscopy screen was therefore incomplete.
[b]History of digestive cancer, advanced colorectal neoplasia, inflammatory bowel disease, overt rectal bleeding, iron deficiency anemia within 90 days, + fecal blood testing within 6 months to mt-sDNA, family history of colorectal cancer ≤60 years of age, and/or previous colorectal neoplasia conferring increased risk for future advanced adenoma.
[c]Comparison between average risk and increased risk regardless of indication.
[d]Missing tobacco use for 2 patients in average risk (1 salvage and 1 screening) and 1 patient in increased risk (surveillance).

maintained with 59 subjects per group for endpoints with either a lower average positivity rate of 20% or a higher average positivity rate of 80%. All sample size calculations were performed using PASS 2020 (Power Analysis and Sample Size Software [2020]; NCSS, LLC, Kaysville, UT) (36).

Comparisons of clinical characteristics were made using the Wilcoxon Rank Sum test for continuous variables (summarized as a median with corresponding 25th and 75th percentiles), whereas the proportions were compared by the Fisher exact test. The Cochran-Mantel-Haenszel test was used to test for trends in percentages regarding predefined time intervals. Statistical comparisons and corresponding nominal *P* values of finely stratified CRN endpoints that are less than the required sample sizes are reported and considered as hypothesis generating.

RESULTS

Study population

The formative data pull for the cohort identified 2,326 +mt-sDNA tests during the study period. Authorization for chart review was not provided by 294 patients, and 3 additional patients did not pass the inclusion criteria. The study flow overview is provided in Figure 1.

Of the 2,029 eligible patients with +mt-sDNA, 1,056 had previous screening colonoscopy and diagnostic colonoscopy after +mt-sDNA. Findings at previous screening colonoscopy could only be confirmed from medical records for 850 of 1,056 (80%). Among the final cohort of 850 patients analyzed, 83 of these (10%) had mt-sDNA testing 0–5 years from previous colonoscopy and 139 (16%) at 6–9 years. Among the patients with mt-sDNA use between 0 and 9 years, 154 (69%) were at average CRC risk and the complete clinical characteristics for this cohort are shown (Table 1).

mt-sDNA PPV for CRN across all patients

Any CRN (advanced/nonadvanced CRN, excluding hyperplastic polyps) was found in 535 of 850 patients with +mt-sDNA (PPV 63%), with PPV of 60% at 0–5 years, 65% at 6–9 years, 65% at 10 years, and 62% at ≥11 years ($P = 0.95$) for cohort trend, Figure 2a). Composite PPV by risk is provided (see Supplementary Table 2, Supplementary Digital Content 1, http://links.lww.com/CTG/A641). For the 850 patients, adequate bowel prep and cecal intubation was documented for 697 (82%), whereas cecal intubation but inadequate or no reporting of prep was found in 129 (15%). For the entire cohort, advanced neoplasia was identified in 195 patients (23%). Advanced neoplasia was identified in 15 of 83 (18%) persons 0–5 years from previous colonoscopy and 23 of 139 (17%) persons at 6–9 years from previous colonoscopy, independent of CRC risk or mt-sDNA indication. In the 528 patients with CRN site documented, at least one right-sided CRN was found in 442 (84%); these patients included 46 of 50 (92%) at 0–5 years and 70 of 87 (80%) at 6–9 years.

CRC was identified in 8 patients (1%), with a range of 6–19 years since screening colonoscopy. The 1 patient with CRC at year 6 was stage I, whereas the cancer stages for the 4 patients diagnosed at 10 years from previous colonoscopy ranged from *in situ* to stage IV (see Supplementary Table 3, Supplementary Digital Content 1, http://links.lww.com/CTG/A641).

mt-sDNA detects postcolonoscopy CRN among average-risk patients

Among 154 average-risk patients with mt-sDNA testing between 0 and 9 years, CRN was detected for 96 patients (62%). Among average-risk patients undergoing early screening with mt-sDNA 0–9 years after previous screening, any CRN, advanced CRN, and right-sided neoplasia was detected for 67 of 107 (63%), 16 of 107 (15%), and 48 of 107 (46%), respectively. When those neoplasia endpoints are compared with average risk mt-sDNA salvage use (in whom previous colonoscopy was inadequate for CRC screening), there were no significant differences. When any neoplasia is compared between those at increased risk undergoing surveillance, there was greater detection in comparison to those at high-risk with a previous incomplete examination ($P = 0.05$). However, there were no other differences in study endpoints for the high-risk surveillance group compared with positive control and no differences among groups by CRC risk overall across all endpoints (Table 2).

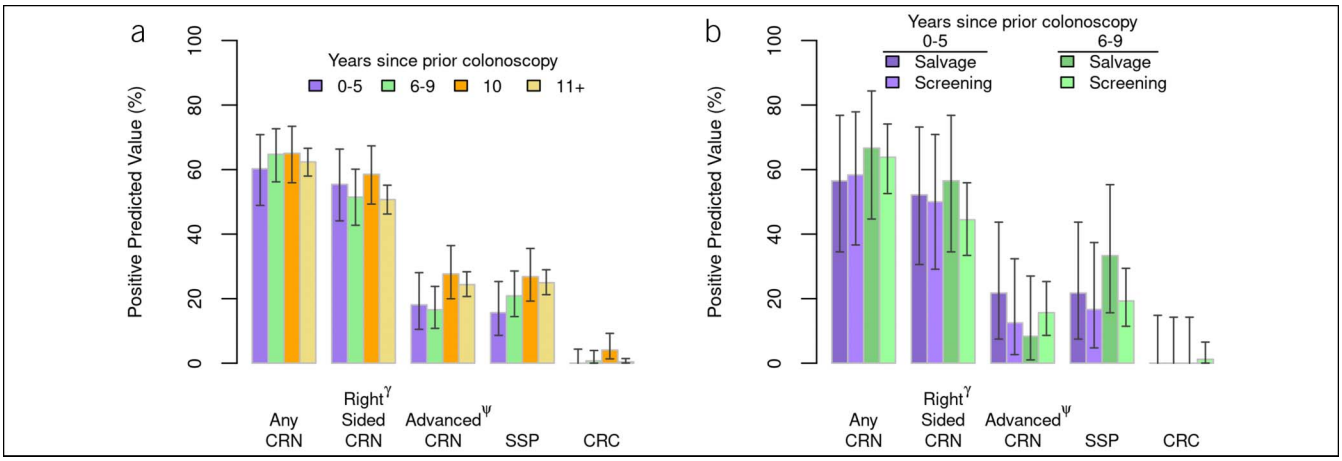

Figure 2. Positive predictive value and 95% confidence intervals of mt-sDNA for colorectal neoplasms is shown. (**a**) When stratified by time since previous colonoscopy for all patients, confidence intervals overlap, and *P* values by Cochran-Armitage trend test for proportions were 0.95 for any CRN, 0.42 for right-sided CRN, 0.06 for advanced CRN, 0.07 for SSP, and 0.76 for CRC. (**b**) When stratified by ordering indication and interval among only average risk patients, the confidence intervals overlap; detailed statistical comparisons are provided in Table 2. ϒPatients with at least 1 colorectal neoplasm proximal to the splenic flexure (missing location for 7 patients with CRN across all year intervals; 1 was missing for salvage 6–9; 2 for screen 6–9). ΨCRC or adenoma/sessile serrated polyps ≥1 cm or with high-grade dysplasia or villous elements. CRC, colorectal cancer; CRN, colorectal neoplasia; mt-sDNA, multi-target stool DNA; SSP, sessile serrated polyp.

Hypothesis generating secondary observations were made within the 0–9 year group. Among average-risk patients only, there was no significant difference in the PPV for advanced neoplasia with mt-sDNA testing 0–5 years from previous screening colonoscopy, 3 of 24 (13%) compared with 13 of 83 (16%) at 6–9 years ($P = 1.00$). There was no difference in PPV for right-sided neoplasia at screening 0–5 (12/24 [50%]) versus 6–9 years (36/81 [44%]) ($P = 0.65$) (Figure 2b). Polyp size and number among average-risk patients are shown in Supplementary Table 4 (see Supplementary Digital Content 1, http://links.lww.com/CTG/A641).

DISCUSSION

In this real-world retrospective observational study of patients at average risk undergoing early mt-sDNA testing, CRN was detected at substantial rates and were similar to those observed in average-risk persons positive control salvage group, who were essentially unscreened. Although most patients evaluated in our overall cohort had mt-sDNA conducted 10 or more years after the time of their last colonoscopy, the PPV for any CRN, right-sided CRN, CRC, or sessile serrated polyps were similar when mt-sDNA testing was performed 9 or fewer years from previous colonoscopy. Importantly, the findings among the 0–9 year group were the same between those assessed early by mt-sDNA for screening or surveillance. Thus, our observations cannot be accounted for by known risk factors for CRC. These findings indicate that CRN was missed at previous colonoscopy and support recent tandem colonoscopy reports in which even advanced CRN was missed at a rate of 9% (24). The prevalence of advanced CRN by colonoscopy is estimated to be 6.3% among average-risk White patients (37). In this study, the PPV for advanced CRN was 17% for average risk patients with +mt-sDNA within 5 years of previous colonoscopy.

Table 2. Findings at diagnostic colonoscopy of patients having mt-sDNA testing 9 or fewer years after previous colonoscopy

Group[a]	Average risk			Increased risk[b]			Overall[c]
Variable	Early screening (n = 107)	Salvage (n = 47)	*P*	Surveillance (n = 55)	Salvage (n = 13)	*P*	*P*
Any colorectal neoplasia, n (%)	67 (63)	29 (62)	1.00	39 (71)	5 (38)	0.05	0.77
Advanced colorectal neoplasia, n (%)	16 (15)	7 (15)	1.00	12 (22)	3 (23)	1.00	0.25
Right-sided neoplasia, n (%)	48 (46)[d]	25 (54)[d]	0.38	38 (69)	5 (38)	0.06	0.06
Sessile serrated polyp, n (%)	20 (19)	13 (28)	0.29	8 (15)	1 (8)	1.00	0.19

mt-sDNA, multi-target stool DNA.
[a]Early screen includes mt-sDNA use before the anticipated interval screen based on previous colonoscopy findings. Salvage mt-sDNA use was conducted after an aborted colonoscopy; previous colonoscopy screen was therefore incomplete.
[b]History of digestive cancer (n = 2), advanced colorectal neoplasia (n = 27), inflammatory bowel disease (n = 3), overt rectal bleeding (n = 3), iron deficiency anemia within 90 days (n = 11), + fecal blood testing within 6 months to mt-sDNA (n = 3), family history of colorectal cancer ≤60 years of age (n = 15), and/or previous neoplasia conferring risk for future high-risk adenoma (n = 38). Criteria are not mutually exclusive.
[c]Comparison between average risk and increased risk regardless of indication.
[d]Lesion location not reported in 2 average risk screening and 1 average risk salvage patients.

FIT has also been shown to detect CRN after negative screening (38) and is the other predominant noninvasive screening modality in the United States. These investigators observed the rates of advanced CRN similar for those <3 and 3–10 years from previous screening, concluding that screen-relevant adenomatous neoplasia was missed at previous colonoscopy (38); serrated lesions were not enumerated, consistent with expectations on FIT performance for SSPs and right-sided polyps (27,39–41). There are only 3 studies that have evaluated mt-sDNA and FIT performance in reference to concurrent colonoscopy (27,39,40); mt-sDNA had significantly greater detection for advanced neoplasia and sessile serrated lesions across all studies and may offer increased sensitivity as an interval test. In this study, right-sided CRN accounted for most neoplasia detected among the entire cohort (442/528, 84%) and the PPV of SSP detection at early screening (<9 years) was 19%. Our study used retrospective, real-world data and was not designed to estimate the sensitivity and specificity of early mt-sDNA testing because colonoscopy was not conducted after a negative mt-sDNA. Because no cancers were observed ≤5 years after previous negative screening colonoscopy, and the rates of advanced adenoma ≤5 years were the same as seen 6–9 years after colonoscopy, we propose that mt-sDNA be studied in the future as an interval screening test 5 years after negative screening colonoscopy with or without comparison to FIT. Although not yet available in the United States, there are other methylated stool-based tests in development (42) and in commercial use (43,44). Although these tests will require validation and approval in the United States, prospective comparison between the stool-based tests with concurrent colonoscopy will be invaluable for assessing differences in test performance and potential use as an adjunct to colonoscopy.

As reviewed by Rabeneck et al. (11), PCCRC is largely the result of missed neoplasia (23), rapid *de novo* growth (45), and/or incomplete polypectomy (22,46). Interval noninvasive testing is hypothesized to provide a safety net in the face of variable screening colonoscopy quality. This may be especially applicable to persons diagnosed with low-risk colorectal neoplasms for whom recent guidelines suggest lengthening surveillance colonoscopy to an interval of 7–10 years from previous guidance of 5–10 years (47). The risks/benefits of this approach will need to be carefully addressed by natural history models that account for the cost of noninvasive interval assessment and potential complications of additional diagnostic colonoscopies. Before mt-sDNA availability, microsimulation adjusting for variable adherence to FIT and colonoscopy had been evaluated among those with a history of negative colonoscopy and found noninvasive assessment cost effective and with fewer complications (25). The cost effectiveness of mt-sDNA has been modeled to support the use for routine screening at an interval of every 3 years (48) and has demonstrated better adherence compared with annual FIT (49,50). To best inform the future use of stool-based testing after colonoscopy, modeling should also account for the likelihood for missed neoplasms as colonoscopy is currently practiced (51).

The study has several limitations, importantly a retrospective design. There was no control over which patients and providers opted for early screening or used mt-sDNA for surveillance. The salvage groups with previous incomplete colonoscopies that served as positive controls could have amplified the study effect, but this difference was not observed. The early screen and surveillance groups were older than their respective salvage groups, and those at increased CRC risk had higher rates of tobacco use. However, it is unlikely that these numerical differences would have significantly influenced the main findings, given the marked similarity in neoplastic findings among all groups and that advancing age would be anticipated to bias in the direction of false-positive mt-sDNA test results (27). mt-sDNA diagnostic yield may have been influenced by the variability among proceduralists preforming the previous screening; this phenomenon requires further detailed study, beyond the intended scope of this work. We also note that although the quality of previous colonoscopy was assessed, certain markers, particularly withdrawal time, where often not noted; however, detailed chart review was conducted in these instances to determine whether previous colonoscopy was adequate. This limitation is one often faced in clinical practice where additional quality metrics (such as colonoscopist adenoma detection rate) is otherwise not known. The colonoscopy quality as reported exclusively from the original colonoscopy report, before mt-sDNA testing, for the 0–9 years intervals is provided (see Supplementary Table 5, Supplementary Digital Content 1, http://links.lww.com/CTG/A641). Although this study raises important questions, the use of mt-sDNA as an interval test to complement colonoscopy would be best studied prospectively to avoid these and other potential biases.

In summary, our study demonstrates that mt-sDNA testing in patients who have had a previous negative screening colonoscopy has a high yield for CRN. Importantly, most mt-sDNA detected lesions are right-sided. We do not overlook that interval *de novo* development of metachronous CRN can occur after an adequate colonoscopy. However, the PPV for advanced CRN detection by mt-sDNA was observed within 5 years of negative colonoscopy, was similar in incompletely screened patients, and was independent from risk status. These factors argue that (i) a portion of postcolonoscopy advanced neoplasms were missed at previous screening colonoscopy and (ii) prospective studies to evaluate mt-sDNA as an interval test between screening colonoscopies are warranted.

CONFLICTS OF INTEREST

Guarantor of the article: John B. Kisiel, MD.

Specific author contributions: D.W.E.: data curation, investigation, writing—original draft, and lead. J.D.E.: data curation, investigation, writing—review and editing, and supporting. K.N.B.: data curation, formal analysis, project administration, writing—review and editing, and supporting. D.W.M.: formal analysis, methodology, validation, writing—review and editing, and supporting. J.B., A.K., and E.A.R.: data curation, writing—review and editing, and supporting. D.O.P., M.B.W., S.V.K., L.J.F.R., and S.R.G.: writing—review and editing, and supporting. J.B.K.: conceptualization, funding acquisition, methodology, supervision writing—review and editing, and equal.

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Potential competing interests: J.B.K. and D.W.M. are listed as inventors on joint intellectual property of Mayo Clinic and Exact Sciences (Madison, WI) and may receive royalties in accordance with Mayo Clinic policy. L.J.F.R. receives compensation from Exact Sciences through a contract established between Mayo Clinic and Exact Sciences. Other authors have no potential conflicts to disclose.

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The authors dedicate this work to the memory of Dr. David A. Ahlquist (1951–2020).

Study Highlights

WHAT IS KNOWN

- ✓ Variable detection of sessile serrated polyps and advanced precancerous lesions, especially on the right side of the colon, contribute to postcolonoscopy colorectal cancer.
- ✓ Multi-target stool DNA (mt-sDNA) testing is sensitive for precancerous lesions in the screening setting but has not been specifically studied to detect postcolonoscopy neoplasia.

WHAT IS NEW HERE

- ✓ mt-sDNA ≤9 years from previous colonoscopy detects a significant number of proximal and advanced neoplasms.
- ✓ mt-sDNA detection of advanced neoplasia at short intervals after negative colonoscopy suggests neoplasia had been missed.
- ✓ Prospective study of mt-sDNA after negative colonoscopy is warranted.

TRANSLATIONAL IMPACT

- ✓ The exfoliation of aberrantly methylated or mutant nucleic acids and/or hemoglobin by the operator-independent mt-sDNA assay may augment the early detection of advanced colorectal neoplasms by the operator dependent criterion standard, colonoscopy.

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