# Serrated Polyp Yield at Colonoscopy in Patients with Positive FIT, Positive mt-sDNA, and Colonoscopy Only: Data from the New Hampshire Colonoscopy Registry

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## ABSTRACT

**Background:** Stool-based screening with fecal immunochemical (FIT) or multitarget-stool DNA (mt-sDNA) tests is associated with increased colonoscopy polyp yield. mt-sDNA includes methylated markers, which improve detection of serrated polyps (SP) versus FIT. We compared SP detection in colonoscopies performed for positive FIT or mt-sDNA tests, as well as in colonoscopies without a preceding stool test, using the New Hampshire Colonoscopy Registry, a comprehensive statewide population-based registry.

**Methods:** Across the three groups, we compared the frequency of clinically relevant SPs (CRSP: sessile SPs, hyperplastic polyps ≥10 mm, and traditional serrated adenomas). We also compared SP size, histology, number, and bulk (combined sizes).

**Results:** Our sample included 560 mt-sDNA+ (age ± SD: 66.5 ± 7.9), 414 FIT+ (age ± SD: 66.3 ± 8.8), and 59,438 colonoscopy-only patients (age ± SD: 61.7 ± 8.0). mt-sDNA+ patients were more likely to have a higher yield of CRSPs and CRSP bulk than FIT+ (*P* < 0.0001) or colonoscopy-only patients (*P* < 0.0001). More mt-sDNA+ patients had CRSPs without large adenomas or colorectal cancers (17.9% vs. 9.9% of FIT+ and 8% of colonoscopy-only patients). After adjusting for synchronous large adenomas, colorectal cancers, and other risk factors, mt-sDNA+ patients were more likely (OR, 1.82; 95% CI, 1.18–2.85) than FIT+ patients to have CRSPs.

**Conclusions:** mt-sDNA+ patients had a higher SP yield than FIT+ or colonoscopy-only patients, particularly in the absence of synchronous large adenomas or colorectal cancer.

**Impact:** Our results suggest that screening with mt-sDNA tests could improve colorectal cancer screening by identifying more patients at increased risk from the serrated pathway.

## Introduction

Colorectal cancer screening for average-risk adults starting at age 45 is recommended by the American Cancer Society (ACS), the US Multi-Society Task Force (USMSTF) on colorectal cancer, and the US Preventive Services Task Force (USPSTF; refs. 1–3). Recommended screening methods include colonoscopy as well as stool-based tests, such as the fecal immunochemical test (FIT) and the multitarget-stool DNA (mt-sDNA) test. Use of these stool based tests for initial screening, the mt-sDNA in particular, has increased in the past few years (4).

Stool tests were developed to detect early stages of colorectal cancer as well as precancerous polyps, which can then be removed during subsequent colonoscopy, which should be performed for all patients with positive stool tests. Past research has found that patients with either positive FIT or positive mt-sDNA tests are more likely to have polyps found during colonoscopy than those without preceding stool tests (5). Thus, the use of these tests for screening can increase the number of individuals referred for colonoscopy who have important lesions which need to be resected.

Both FIT and mt-sDNA stool tests include the use of an antibody specific to the globin moiety of human hemoglobin (HgB) to detect colorectal polyps, especially large adenomas and cancer, which may bleed intermittently (6–8). Serrated polyps are much less likely to bleed than adenomas and as a result, FIT, which relies solely upon the HgB antibody, has been shown to have a low sensitivity for detecting serrated polyps (9, 10). This has implications for screening since serrated polyps are present in a high proportion of asymptomatic individuals (11–13) and the serrated pathway may account for 15% to 30% of all colorectal cancer (14, 15).

Unlike FIT, the mt-sDNA test detects molecular markers, which may be shed by serrated (and large nonserrated) colorectal neoplasia, including mutated (*KRAS*) and methylated (*BMP3, NDRG4)* DNA (16). Previous studies have found mt-sDNA to have a higher sensitivity for colorectal polyps as compared with both the guaiac-based fecal occult blood and FIT tests (16, 17). mt-sDNA has also been found to have increased sensitivity for serrated polyps in particular compared with FIT in both a large randomized trial (16) as well as in an analysis of stool specimens and subsequent colonoscopy from individuals in a screening program (18).

To date, few studies have closely examined the distribution of serrated polyps by size, histology, and number in patients with positive FIT and mt-sDNA stool tests in community clinical practice. The New Hampshire Colonoscopy Registry (NHCR) is a statewide population-based registry, which has collected comprehensive data on over 250,000 colonoscopies. Our focus was to provide real-world evidence on the implications of positive stool tests for primary care doctors or endoscopists who might be seeing patients following those tests rather than on determining the optimal test from a broader or systemic

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perspective. Thus, our study aims to describe the distribution of serrated polyp findings, classified by histology, size, and polyp bulk, in patients with preceding positive FIT (FIT+) and mt-sDNA (mt-sDNA+) tests, to compare those outcomes with a reference population of patients presenting for colonoscopy, the gold standard for detecting polyps, without a preceding positive stool test, and to determine whether our evidence is consistent with the idea that colonoscopies in patients with positive mt-sDNA tests are more likely to find serrated polyps.

## Materials and Methods

### Population

Patients complete an NHCR Patient Information Form prior to colonoscopy, providing demographic, health behavior, and personal and family history data. Colonoscopy data are collected through NHCR Procedure Forms, which are completed by endoscopists and/or endoscopy nurses during or immediately after colonoscopy and include exam indication, completion status, withdrawal time, bowel preparation quality, recommended follow-up, and the location, size, and treatment method for all findings. Pathology outcomes are abstracted by trained NHCR staff who match data from pathology reports to polyp-level findings recorded on the Procedure Form (19).

As approved by our Institutional Review Board (IRB), through 2018, all patients provided separate written informed consent; since 2018, to indicate consent patients complete and return the Patient Information Form, which, for this minimal risk study was determined by the IRB to be "acceptable to indicate consent and authorization to participate." All data collection and study procedures were approved by the IRB of the NHCR (the Committee for the Protection of Human Subjects at Dartmouth College, CPHS#00015834) in accordance with the Belmont Report and the US Common Rule.

### Study cohorts

Exact Sciences Laboratories, LLC, under an IRB-approved protocol, provided the NHCR with identifiers of all patients with positive mt-sDNA tests in the NHCR catchment area. This cohort included 560 individuals with an mt-sDNA+ result as part of usual clinical care and a subsequent colonoscopy in the NHCR database. A second cohort of 414 individuals had positive FIT tests during the same time interval and a subsequent colonoscopy. A third cohort of 59,438 individuals with screening or surveillance colonoscopy only, with no indication of a prior positive stool test, was used as a reference group to represent the population using colonoscopy as their initial (and only) colorectal screening test. Patients with mt-sDNA+ and FIT+ results were referred by their primary care providers to endoscopists throughout NH who performed their colonoscopies. All mt-sDNA, FIT tests, and colonoscopies were conducted in the course of routine clinical practice. To avoid any potential bias due to increases in polyp detection rates over time, colonoscopies for all cohorts occurred during the same time period from 2015 to 2021. Although all patients were asymptomatic, some had stool tests for off label indications, including a personal or family history of colorectal cancer or a personal history of polyps (Table 1).

**Table 1.** Patient characteristics.

| | Mt-sDNA+ N = 560 | | FIT+ N = 414 | | Colonoscopy only N = 59,438[a] | | |
|---|---|---|---|---|---|---|---|
| | N/Mean | %/SD | N/Mean | %/SD | N/Mean | %/SD | P |
| Age (continuous) | 66.5 | 7.9 | 66.3 | 8.8 | 61.7 | 8.0 | <0.001 |
| Patient sex | | | | | | | <0.001 |
| Male | 216 | 38.6 | 201 | 48.6 | 29,094 | 48.9 | |
| Female | 344 | 61.4 | 213 | 51.4 | 30,344 | 51.1 | |
| BMI (continuous) | 29.3 | 7.3 | 28.8 | 7.6 | 28.8 | 7.2 | 0.163 |
| Smoking status | | | | | | | <0.001 |
| Never smoker | 216 | 45.8 | 161 | 45.5 | 28,274 | 55.5 | |
| Former smoker | 201 | 42.6 | 149 | 42.1 | 18,941 | 37.2 | |
| Current smoker | 55 | 11.7 | 44 | 12.4 | 3,707 | 7.3 | |
| Aspirin/NSAIDs use at least once/week | 158 | 37.5 | 148 | 45.1 | 19,571 | 40.6 | 0.109 |
| Blood thinner use | 37 | 8.1 | 27 | 7.5 | 1,205 | 2.3 | <0.001 |
| Patient colonoscopy history[b] | | | | | | | <0.001 |
| No prior exam | 268 | 47.9 | 158 | 38.2 | 18,807 | 31.6 | |
| Prior exam | 292 | 52.1 | 256 | 61.8 | 40,631 | 68.4 | |
| Patient risk[c] | | | | | | | <0.001 |
| Average risk | 442 | 78.9 | 307 | 74.2 | 30,776 | 51.8 | |
| Increased risk | 118 | 21.1 | 107 | 25.8 | 28,662 | 48.2 | |
| Patient history of neoplastic findings | | | | | | | <0.001 |
| No prior neoplastic findings | 489 | 87.5 | 354 | 85.5 | 37,070 | 62.4 | |
| Prior neoplastic findings | 70 | 12.5 | 60 | 14.5 | 22,368 | 37.6 | |
| First-degree family history of colorectal cancer | | | | | | | <0.001 |
| No first-degree family history of colorectal cancer | 390 | 87.1 | 275 | 82.1 | 39,042 | 76.5 | |
| First-degree family history of colorectal cancer | 58 | 12.9 | 60 | 17.9 | 11,982 | 23.5 | |

Note: All tests are chi squared tests except age and BMI, which are Kruskal–Wallis tests.
[a]Colonoscopy-only group includes 70 patients with no outcome data who are excluded from further analyses.
[b]History of colonoscopy as per patient self-report, surveillance indication, and prior exams in the NHCR database.
[c]Increased risk includes patients with prior neoplasia (including colorectal cancer) and/or a family history of colorectal cancer in a first degree relative.
Percent missing: indication for exam (8%), BMI (22%), smoking status (14%), aspirin/NSAIDs (19%), blood thinners (12%), first degree family history of colorectal cancer (14%).

Patients <50 years of age and those with inflammatory bowel disease (IBD) or a genetic syndrome such as Lynch syndrome were excluded. Colonoscopy outcomes were merged and treated as a single exam if two or more colonoscopies were performed within 12 months of each other and the initial exam was incomplete or had poor bowel preparation or the subsequent exam was indicated for polypectomy or completion of polypectomy of a known polyp. After this merge, patients with no complete exam with adequate bowel preparation were excluded.

### Outcomes

Study outcomes were serrated polyps detected through each of the three screening methods: mt-sDNA+ or FIT+ followed by colonoscopy, or colonoscopy alone. Exams were categorized by (i) the presence of CRSPs, including all traditional serrated adenomas (TSA), all sessile SPs (SSP), and large hyperplastic polyps (HP; ≥10 mm) with or without synchronous large (≥10 mm) adenomas or cancers; (ii) by size of the largest serrated polyp (including all HPs; 0–5, 5–<10, 10–<20, and 20 mm+); (iii) by serrated polyp histology (TSA/SSP, HP, or serrated not otherwise specified); (iv) by number of CRSPs; and (v) by CRSP bulk [sum of CRSP diameters; (0–4, 5–9, 10–19, 20–29, 30+)]. We stratified CRSPs by the presence or absence of large adenomas and/or cancers, because both positive FIT and mt-sDNA tests in those patients may have been due to hemoglobin (HgB) shed by the adenomas or colorectal cancer, rather than through specific detection of the CRSPs by methylated markers in the mt-sDNA test. Our analysis included all colorectal cancer and other neoplasia detected during colonoscopy or from surgical resections, incorporating colorectal cancer diagnosis data available through linkage with the New Hampshire State Cancer Registry. We excluded patients with missing outcome data from our comparison of findings across the three groups (0 from the mt-sDNA+ and FIT+ groups; 70 from the colonoscopy-only group).

### Covariates

Patient variables were derived from the NHCR Patient Information Form and included demographic factors (e.g., age, sex, race) health behaviors (e.g., smoking status, Body Mass Index, overall health status), aspirin/nonsteroidal anti-inflammatory drug (NSAID), or blood thinner use, and history of prior colonoscopy.

### Statistical and analytic approach

We performed several analyses to compare differences across the mt-sDNA+, FIT+, and colonoscopy-only groups. First, we compared patient characteristics in the three cohorts using chi-squared tests and Kruskal–Wallis tests, shown in **Table 1**. Second, we compared the frequency of CRSPs using chi-squared tests. We then stratified those findings by the presence/absence of colorectal cancer or large (≥10 mm) adenomas using Monte Carlo simulations of Fisher exact test with 50,000 replications (**Table 2**), to account for the possibility that bleeding lesions triggered a positive test in patients who also had serrated polyps, obscuring our estimates of the ability of the mt-sDNA and FIT tests to detect serrated polyps specifically. We also stratified this analysis by patient sex (**Table 2B** and **C**). We used logistic regression to further explore the impact of co-incident colorectal cancer or large adenomas on the odds of finding a CRSP in mt-sDNA+ and FIT+ patients while also adjusting for a wide range of other known potential confounding characteristics, that is, age, sex, aspirin or NSAID use, blood thinner use, smoking history, BMI, baseline risk status, and history of prior colonoscopy (**Table 3**). We also compared size and histology of serrated polyps (**Table 4**) and the number and bulk (defined as the sum of polyp diameters) of CRSPs

(**Table 5**) using Monte Carlo simulations of Fisher exact test with 50,000 replications to better examine whether serrated polyp findings in our three cohorts differed not only in frequency, but also in kind.

### Data availability

Data were generated by the authors but are not publicly available because confidentiality of endoscopists and patients might be compromised but the non protected health information data used in the analyses are available upon reasonable request.

## Results

After exclusions, 60,412 patients with colonoscopy remained: 560 after positive mt-sDNA (average age ± SD: 66.5 ± 7.9), 414 after positive FIT (average age ± SD: 66.3 ± 8.8), and 59,438 with colonoscopy with no prior stool test (average age ± SD: 61.7 ± 8.0; **Table 1**). More mt-sDNA+ patients were female (61.4%) than were male, whereas the FIT+ group was more evenly split by sex, similar to the colonoscopy-only group (51.4% and 51.1% female, respectively). Fewer mt-sDNA+ patients had known prior colonoscopies (52.1%) than did FIT+ patients, who were again more similar to colonoscopy-only patients (61.8% and 68.4%, respectively). However, both mt-sDNA+ and FIT+ patients were unlikely to be at increased risk for colorectal cancer (21.1% and 25.8%, respectively), compared with nearly half (48.2%) of the colonoscopy-only cohort. For the colonoscopy only group, the indications were surveillance for 35.5% ($n = 21,119$) of all patients and screening for 64.5% ($n = 38,319$).

A higher proportion of CRSPs were detected in the mt-sDNA+ patients compared with FIT+ (chi squared $P < 0.0001$, **Table 2**). To account for tests that were positive due to conventional adenomas or cancers that were large enough to bleed, we stratified by size of these lesions. Our results show that even after stratifying CRSP findings by the presence of large adenomas or colorectal cancers, a higher proportion of CRSPs were detected in the mt-sDNA+ patients compared with FIT+ (chi squared $P < 0.0001$, **Table 2**). **Table 2B** and **C** present the data as stratified by sex.

A logistic regression model demonstrated that mt-sDNA+ patients were still more likely than FIT+ patients to have CRSP detected in subsequent colonoscopy (OR, 1.82; 95% CI, 1.18–2.85), even after adjusting for potentially confounding differences in both cohorts. These results are shown in **Table 3**.

The largest serrated polyps found in mt-sDNA+ patients tended to be larger than the largest found in FIT+ patients, who more closely resembled colonoscopy-only patients; the mt-sDNA+ group had a higher percentage of exams with largest serrated polyp in all categories greater than 5 mm than the other two groups (**Table 4**). mt-sDNA+ patients also had a higher prevalence of both TSA/SSPs and HPs than the FIT+ group, which again had proportions similar to the colonoscopy-only cohort (**Table 4**). Patients with mt-sDNA+ tests were more likely to have both a higher number and higher bulk, or total combined diameter, of CRSPs than both FIT+ ($P < 0.001$ as shown in **Table 5**) or colonoscopy-only patients (Fisher test $P < 0.001$), particularly in CRSP bulk categories ≥10 mm.

## Discussion

Positive stool tests prior to colonoscopy are known to enrich polyp findings at colonoscopy (5). However, the likelihood of specific polyp findings at colonoscopy may not be the same for different stool tests, which employ single (FIT, FOBT) or multiple (mt-sDNA) markers to

**Table 2.** Colonoscopy outcomes: CRSPs (all TSAs, all sessile serrated polyps, and those HPs ≥ 10 mm) with and without large adenomas or colorectal cancer.

| A. All patients | Mt-sDNA+ (N = 560) | | FIT+ (N = 414) | | Colonoscopy only (N = 59,368) | | P value | |
|---|---|---|---|---|---|---|---|---|
| Colonoscopy findings | N | % | N | % | N | % | All groups | mt-sDNA vs. FIT |
| Detection of CRSPs (unstratified) | | | | | | | | |
| CRSP | 117 | 20.9 | 47 | 11.4 | 5124 | 8.6 | <0.0001 | <0.0001 |
| No CRSP | 443 | 79.1 | 367 | 88.6 | 54,244 | 91.4 | | |
| CRSPs with and without large adenomas/colorectal cancer | | | | | | | | |
| CRSP and large conventional adenoma/colorectal cancer | 17 | 3 | 6 | 1.4 | 388 | 0.7 | | |
| Large conventional adenoma/colorectal cancer and no CRSP | 88 | 15.7 | 56 | 13.5 | 2,463 | 4.1 | <0.0001 | 0.0003 |
| CRSP and no large conventional adenoma/colorectal cancer | 100 | 17.9 | 41 | 9.9 | 4,736 | 8 | | |
| No CRSP or large conventional adenoma/colorectal cancer | 355 | 63.4 | 311 | 75.1 | 51,781 | 87.2 | | |

| B. MALE | Mt-sDNA+ (N = 216) | | FIT+ (N = 201) | | Colonoscopy only (N = 29,059) | | P value | |
|---|---|---|---|---|---|---|---|---|
| Colonoscopy findings | N | % | N | % | N | % | All groups | mt-sDNA vs. FIT |
| Detection of CRSPs (unstratified) | | | | | | | | |
| CRSP | 38 | 17.6 | 22 | 10.9 | 2,543 | 8.8 | <0.001 | 0.05 |
| No CRSP | 178 | 82.4 | 179 | 89.1 | 26,516 | 91.2 | | |
| CRSPs with and without large adenomas/colorectal cancer | | | | | | | | |
| CRSP and large conventional adenoma/colorectal cancer | 7 | 3.2 | 2 | 1.0 | 237 | 0.8 | | |
| Large conventional adenoma/colorectal cancer and no CRSP | 50 | 23.1 | 30 | 14.9 | 1,556 | 5.4 | <0.0001 | 0.0112 |
| CRSP and no large conventional adenoma/colorectal cancer | 31 | 14.4 | 20 | 10.0 | 2,306 | 7.9 | | |
| No CRSP or large conventional adenoma/colorectal cancer | 128 | 59.3 | 149 | 74.1 | 24,960 | 85.9 | | |

| C. Female patients | Mt-sDNA+ (N = 344) | | FIT+ (N = 213) | | Colonoscopy only (N = 30,309) | | P value | |
|---|---|---|---|---|---|---|---|---|
| Colonoscopy findings | N | % | N | % | N | % | All groups | mt-sDNA vs. FIT |
| Detection of CRSPs (unstratified) | | | | | | | | |
| CRSP | 79 | 23.0 | 25 | 11.7 | 2,581 | 8.5 | <0.0001 | <0.001 |
| No CRSP | 265 | 77.0 | 188 | 88.3 | 27,728 | 91.5 | | |
| CRSPs with and without large adenomas/colorectal cancer | | | | | | | | |
| CRSP and large conventional adenoma/colorectal cancer | 10 | 2.9 | 4 | 1.9 | 151 | 0.5 | | |
| Large conventional adenoma/colorectal cancer and no CRSP | 38 | 11.0 | 26 | 12.2 | 907 | 3.0 | <0.0001 | 0.0087 |
| CRSP and no large conventional adenoma/colorectal cancer | 69 | 20.1 | 21 | 9.9 | 2,430 | 8.0 | | |
| No CRSP or large conventional adenoma/colorectal cancer | 227 | 66.0 | 162 | 76.1 | 26,821 | 88.5 | | |

Note: In this analysis, colorectal cancers and large adenoma were combined due to their combined potential contributions to fecal occult bleeding. Colorectal cancers by group: mt-sDNA 9 (1.6%), FIT+ 8 (1.9%), colonoscopy only 156 (0.3%).

screen-detect relevant colorectal neoplasia. This consideration may be important in selecting screening options, depending on patient risk factors and family history. Therefore, we investigated colonoscopy outcomes for patients having a preceding positive mt-sDNA or FIT, and for patients with colonoscopy only, specifically investigating the

**Table 3.** Risk of CRSP (all TSAs, all sessile serrated polyps, and those HPs ≥10 mm) by patient demographic and stool assay results (FIT+ as reference).

| Variable | OR | 95% CI Lower bound | 95% CI Upper bound | P value |
|---|---|---|---|---|
| mt-sDNA+ (vs. FIT+) | 1.82 | 1.18 | 2.85 | 0.008 |

Note: Regression included the following covariates: age (years over 50), patient sex, use of aspirin or NSAIDs, use of blood thinners, smoking status (never vs. former or current), BMI (centered on 25), increased risk of colorectal cancer, prior history of colonoscopy).

yield of serrated polyps. Recognizing the ability of each colorectal cancer stool test option to detect serrated polyps is particularly useful for those patients with risk factors that increase the likelihood of those polyps (such as smoking or obesity; ref. 20). Because serrated polyps progress through methylation, it would be reasonable to expect that colonoscopies after a positive mt-sDNA test, with two methylated markers, might have a higher yield of serrated polyps compared with those after positive FIT (5, 21).

We found that patients in our population with preceding mt-sDNA+ stool tests were more likely to have serrated polyps at colonoscopy than patients with preceding FIT+ tests or patients who had a colonoscopy without a preceding stool test. Specifically, nearly 1 in 5 (17.9%) mt-sDNA+ patients had CRSPs with no synchronous large (≥ 1 cm) adenomas or colorectal cancer detected at colonoscopy, compared with 1 in 10 (9.9%) FIT+ patients and 8.0% of colonoscopy-only patients. Because both mt-sDNA and FIT look for blood, but only mt-sDNA detects molecular markers that are shed by some serrated polyps, we compared patients with CRSPs and no synchronous large

**Table 4.** Precancerous serrated polyps (including TSAs, sessile serrated polyps, and HPs) by largest size and most advanced histology.

| | Mt-sDNA+ N = 560 | | FIT+ N = 414 | | Colonoscopy only N = 59,368 | | Fisher test P values | |
|---|---|---|---|---|---|---|---|---|
| | N | % | N | % | N | % | Overall | mt-sDNA vs. FIT |
| Largest precancerous serrated polyp found | | | | | | | <0.0001 | <0.0001 |
| >20 mm | 5 | 0.9 | 1 | 0.2 | 170 | 0.3 | | |
| 10–20 mm | 42 | 7.5 | 10 | 2.4 | 1,313 | 2.2 | | |
| 5–<10 mm | 95 | 17.0 | 34 | 8.2 | 4,639 | 7.8 | | |
| 0–<5 mm | 118 | 21.1 | 67 | 16.2 | 10,088 | 17.0 | | |
| Serrated polyp, unknown maximum size | 6 | 1.1 | 12 | 2.9 | 522 | 0.9 | | |
| No serrated polyp | 294 | 52.5 | 290 | 70.0 | 42,636 | 71.8 | | |
| Most advanced precancerous serrated histology | | | | | | | <0.0001 | <0.0001 |
| TSA/SSP | 115 | 20.5 | 42 | 10.1 | 4,740 | 8.0 | | |
| HP | 149 | 26.6 | 73 | 17.6 | 11,639 | 19.6 | | |
| Serrated—not otherwise specified | 2 | 0.4 | 9 | 2.2 | 353 | 0.6 | | |
| None | 294 | 52.5 | 290 | 70.0 | 42,636 | 71.8 | | |

adenomas or colorectal cancers, thereby removing the possibility that either stool test was positive due to the presence of blood shed by those polyps. This allowed us to focus our investigation on detection of serrated polyps specifically.

Although some patients with positive results on either stool test had normal or insignificant findings, our results show that patients with either positive test, and with positive mt-sDNA in particular, had higher prevalence of clinically significant lesions than those who had colonoscopy without preceding stool tests. Because mt-sDNA is less likely to be positive for small polyps than for larger polyps (5, 16), it is unlikely that mt-sDNA is detecting polyps for which colonoscopic removal would not have been recommended, with or without a preceding stool test. The same would be true for FIT, although the sensitivity of FIT for advanced polyps is less than that of mt-sDNA (16).

In addition to accounting for the potential impact of synchronous large adenomas on the probability of CRSP detection in our logistic regression comparing yield of CRSP in FIT+ to mt-sDNA+ patients, we also adjusted for patient characteristics associated with an increased risk for serrated polyps. Both the FIT+ and mt-sDNA+ cohorts were older, more likely to report former or current smoking, more likely to take blood thinners, and less likely to report good/excellent health than

the colonoscopy-only cohort. The increase in patients with these factors in the stool test groups could reflect primary care providers more frequently recommending stool tests (rather than more invasive colonoscopy) for their older patients. However, the mt-sDNA+ and FIT+ groups were similar to one another in terms of most risk factors for neoplastic findings, with the exception of patient sex, where the mt-sDNA+ group was more female than the FIT+ group. Despite the increased prevalence of polyps in males in general, in our sample we had a higher rate of polyps in the mt-sDNA+ group. To account for potential differences in these patient risk characteristics between the mt-sDNA+ and FIT+ cohorts, we included covariates for age, sex, use of NSAIDs, aspirin or blood thinners, smoking, BMI, patient risk status, and history of prior colonoscopy (**Table 3**) in our logistic regression (20). Even after adjusting for these factors, we observed that patients with positive mt-sDNA tests in our population were nearly twice as likely as FIT+ patients to have CRSPs at colonoscopy.

Our comparisons of serrated polyps by histology, size, number, and bulk across the three cohorts also yielded useful results. We found that patients with positive mt-sDNA tests in our population were more likely to harbor serrated polyps of all histology types, including TSA/SSPs and HPs, compared with patients with positive FIT tests. In addition, NHCR patients with positive mt-sDNA tests were twice as

**Table 5.** CRSPs (all TSAs, all sessile serrated polyps, and those HPs ≥10 mm) by study cohort: number and bulk.

| | Mt-sDNA+ N = 560 | | FIT+ N = 414 | | Colonoscopy only N = 59,368 | | Fisher test P values | | |
|---|---|---|---|---|---|---|---|---|---|
| | N | % | N | % | N | % | Overall | mt-sDNA vs. FIT | mt-sDNA vs. colo only |
| Total number of precancerous CRSPs | | | | | | | <0.0001 | <0.0001 | <0.0001 |
| 4 or more | 19 | 3.4 | 2 | 0.5 | 329 | 0.6 | | | |
| 3 | 20 | 3.6 | 2 | 0.5 | 380 | 0.6 | | | |
| 2 | 20 | 3.6 | 8 | 1.9 | 925 | 1.6 | | | |
| 1 | 58 | 10.4 | 35 | 8.5 | 3490 | 5.9 | | | |
| No CRSP found | 443 | 79.1 | 367 | 88.6 | 54244 | 91.4 | | | |
| Total precancerous CRSP bulk | | | | | | | <0.0001 | <0.0001 | <0.0001 |
| 30 mm+ | 5 | 0.9 | 2 | 0.5 | 237 | 0.4 | | | |
| 20 mm–<30 mm | 21 | 3.8 | 4 | 1.0 | 530 | 0.9 | | | |
| 10–<20 mm | 42 | 7.5 | 10 | 2.4 | 1645 | 2.8 | | | |
| 5–<10 mm | 22 | 3.9 | 20 | 4.8 | 1583 | 2.7 | | | |
| 0–<5 mm | 7 | 1.3 | 7 | 1.7 | 643 | 1.1 | | | |
| CRSP, missing size | 20 | 3.6 | 4 | 1.0 | 486 | 0.8 | | | |
| No CRSP | 443 | 79.1 | 367 | 88.6 | 54244 | 91.4 | | | |

likely to have serrated polyps ≥5 mm than NHCR patients in the FIT+ or colonoscopy-only groups (**Table 4**). These polyps are important as they are likely to pose an increased risk for more advanced polyps in the future (21). This finding is consistent with the idea that polyps that are ≥5 mm may be more likely to shed the methylated markers detected by mt-sDNA. We also examined the yield for multiple CRSPs (≥2) in each group. Compared with FIT+ NHCR patients, those with positive mt-sDNA tests were more than three times as likely (10.5% versus 2.9%) to have multiple CRSPs. These results have implications for identifying patients with multiple serrated polyps, a proportion of whom may have undiagnosed serrated polyposis syndrome, which is associated with an increased risk for colorectal cancer (22). Finally, to assess whether an increased overall burden of serrated polyps, rather than just individual polyp size, is associated with positive mt-sDNA tests, we examined CRSP bulk by adding the diameters of all detected CRSPs at the exam level. We observed that positive mt-sDNA tests were associated with an increased detection of CRSP bulk, especially a bulk of 10 mm or more. Thus, in addition to the size of the largest individual serrated polyp, combined bulk of all CRSPs may impact the detection of serrated polyps by mt-sDNA testing.

Our results have implications for colorectal cancer screening because CRSPs are important colorectal cancer precursors, thought to account for about 15% to 30% of colorectal cancer (22). This category includes all SSPs and TSAs as well as large HPs, which are considered SSP-equivalent findings (23). We found that NHCR patients with positive mt-sDNA tests are more likely than patients in the FIT+ or colonoscopy-only group to have these CRSPs, all of which have been shown to be associated with an increased risk for colorectal cancer (14, 24, 25). Our observation that all subtypes of serrated polyps—not just TSAs and SSPs, but also large HPs—had a higher frequency in mt-sDNA+ NHCR patients may be related to previously published data, suggesting that many large HPs may in fact be misclassified SSPs (23). Our results suggest that size and combined polyp bulk related to multiplicity of serrated polyps may be factors that affect detection by mt-sDNA tests, which may have implications for patients with multiple serrated polyps.

Although previous studies have compared the sensitivity and specificity for mt-sDNA and FIT, this study expands the evidence on differences in serrated polyp detection by these two tests, by focusing on both the positive predictive value of serrated polyps and on the distribution of the size and location of serrated polyps detected during colonoscopies following these tests. Specifically, we stratified serrated polyps by histology, size, and bulk, and also focused on CRSPs, which are important colorectal cancer precursors. With data derived from clinical practice, we demonstrated the yield of positive stool tests in community practice. In this real-world study, we adjusted for all known differences in patient risk characteristics between the mt-sDNA+ and FIT+ groups in a logistic regression. All study patients received their stool tests and colonoscopies in the course of usual clinical care and the results may be more generalizable to that of general practice than previous studies which used data from clinical trials. Although one limitation of our results is that the population of New Hampshire is predominantly white, there is considerable ethnic, urban/rural and socioeconomic diversity in the population that is captured within the NHCR (26). Confirmation of our results in more racially diverse populations is needed. This study is based within the data of the NHCR and as such does not collect data on patients who do not receive colonoscopy following their FIT+ or mt-sDNA+ tests, or on negative mt-sDNA and FIT tests in NHCR patients. Therefore, we offer evidence on findings in patients who tested positive in both stool test groups and we cannot provide information on the sensitivity and specificity of the stool tests. The NHCR is a voluntary registry. Patients are invited to participate when they arrive for colonoscopy at endoscopy practices throughout New Hampshire. Although rare, some patients decline participation in the registry. Although the vast majority of NH endoscopy practices participate in the NHCR, a small number of practices were not participating during the time of this study.

Our results do not address cost–benefit trade-offs due to differences in the costs of the two tests or in the costs of performing colonoscopies on patients with false-positive results. In addition, the results of this observational study do not represent a head-to-head comparison of different tests in the same study population. Although we adjust for many known colorectal neoplasia risk factors, it is possible that some differences could be due to sampling of different cohorts. One additional concern is that there may have been differences with respect to endoscopic evaluation of patients with positive stool tests. However, a previously published study of our population demonstrated no significant differences for quality measures such as withdrawal time or endoscopist adenoma detection rates between the three cohorts which are also used in this article (27).

In summary, we observed that in NHCR patients receiving screening tests in the course of routine practice, those with positive mt-sDNA tests were more likely to have serrated polyps detected on subsequent colonoscopy than those with preceding positive FIT tests. Our findings are consistent with prior evidence, suggesting that mt-sDNA tests are more likely to identify patients with serrated polyps than FIT tests, and expand on prior work by providing evidence on the types of serrated polyps found in patients after both types of stool tests. Patients in our population with positive mt-sDNA tests tended to have larger serrated polyps as well as a greater combined bulk of all CRSPs than patients in the FIT+ group or in the colonoscopy-only group. These results are consistent with the idea that the differences between mt-sDNA and FIT tests are clinically meaningful and have practical implications for improving CRC prevention through increased detection of serrated polyps. However, more data examining head-to-head comparisons of tests for CRC incidence and mortality outcomes could confirm these outcomes. Our data suggest that positive mt-sDNA stool tests are associated with a higher yield of serrated polyps; as always, the choice of screening tests should also consider cost, capacity, and feasibility.

## Authors' Disclosures

## Authors' Contributions

**J.C. Anderson:** Conceptualization, formal analysis, supervision, validation, writing–original draft, writing–review and editing. **W.M. Hisey:** Conceptualization, resources, data curation, software, formal analysis, validation, investigation, visualization, methodology, writing–original draft, writing–review and editing. **C.M. Robinson:** Conceptualization, resources, data curation, software, formal analysis, supervision, funding acquisition, validation, investigation, visualization, methodology, writing–original draft, project administration, writing–review and editing. **P.J. Limburg:** Writing-review and editing. **B.L. Kneedler:** Data curation, writing–review and editing. **L.F. Butterly:** Conceptualization, resources, data curation, software, formal analysis, supervision, funding acquisition, validation, investigation, visualization, methodology, writing–original draft, project administration, writing–review and editing.

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