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Stool DNA Testing for Screening Detection of Colorectal Neoplasia in Alaska Native People

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Abstract

Objective: To assess the accuracy of a multitarget stool DNA test (MT-sDNA) compared with fecal immunochemical testing for hemoglobin (FIT) for detection of screening-relevant colorectal neoplasia (SRN) in Alaska Native people, who have among the world's highest rates of colorectal cancer (CRC) and limited access to conventional screening approaches.

Patients and Methods: We performed a prospective, cross-sectional study of asymptomatic Alaska Native adults aged 40-85 years and older undergoing screening or surveillance colonoscopy between February 6, 2012, and August 7, 2014.

Results: Among 868 enrolled participants, 661 completed the study (403 [61%] women). Overall, SRN detection by MT-sDNA (49%) was superior to that by FIT (28%; $P<.001$); in the screening group, SRN detection rates were 50% and 31%, respectively ($P=.01$). Multitarget stool DNA testing detected 62% of adenomas 2 cm or larger vs 29% by FIT ($P=.05$). Sensitivity by MT-sDNA increased with adenoma size (to 80% for lesions ≥3 cm; $P=.01$ for trend) and substantially exceeded FIT sensitivity at all adenoma sizes. For sessile serrated polyps larger than 1 cm (n=9), detection was 67% by MT-sDNA vs 11% by FIT ($P=.07$). For CRC (n=10), detection was 100% by MT-sDNA vs 80% by FIT ($P=.48$). Specificities were 93% and 96%, respectively ($P=.03$).

Conclusion: The sensitivity of MT-sDNA for cancer and larger polyps was high and significantly greater than that of FIT for polyps of any size, while specificity was slightly higher with FIT. These findings could translate into high cumulative neoplasm detection rates on serial testing within a screening program. The MT-sDNA represents a potential strategy to expand CRC screening and reduce CRC incidence and mortality, especially where access to endoscopy is limited.

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Alaska Native (AN) people have among the world's highest rates of colorectal cancer (CRC).[1,2] Based on a recent report of cancer trends,[3] the CRC incidence rate among AN people is more than twice that in US whites (90.9 vs 41.1 per 100,000 persons, respectively); likewise, the age-adjusted CRC mortality rate in AN people is more than 2-fold higher than that in US whites (35.4 vs 15.5 per 100,000 persons, respectively).[3] Although CRC incidence and mortality rates have been declining in the United States as whole since the 1980s, attributed largely to CRC screening,[4,5] it is not clear what the most effective or practical screening approach is in the AN population. With effective tools, screening has the potential to detect CRC at early, more curable stages, and to prevent CRC by detection and removal of precancerous polyps.[4,6,7]

Colorectal cancer screening rates among AN people fall well below the National Colorectal Cancer Roundtable's 80% by 2018 target. Conventional invasive screening approaches, including colon radiography, sigmoidoscopy, and colonoscopy, present logistic and access challenges for the AN population. More than half of all AN people reside in remote communities lacking endoscopic capacity.[8] Substantial resources, including time, travel expenses, and personnel, are required to administer these

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invasive screening tools within the Alaska Tribal Health System,[9,10] limiting their practicality. Furthermore, conventional screening tools are biased toward detection of distal disease,[11-17] and 41% of CRCs in AN people occur in the proximal colon.[1]

Stool testing represents a noninvasive screening alternative. However, widely used guaiac-based fecal occult blood tests (gFOBTs) are problematic in this population because of endemic gastrointestinal bleeding from *Helicobacter pylori* gastritis.[18] In AN people, we found test specificity to differ significantly between the gFOBT and the fecal immunochemical test (FIT) (76% vs 92%, respectively). Sensitivity for the aggregate of advanced adenomas (includes adenomas ≥1 cm and those containing tubulovillous or villous histologic features or high-grade dysplasia) and CRC was low and did not differ significantly between these 2 tests (29% vs 36%, respectively).[19] Such low neoplasm detection rates by fecal blood tests are consistent with findings from other reports.[17,20,21] As a consequence of these observations, gFOBTs are not recommended for CRC screening in AN people, whereas FIT is a recommended screening test. An additional issue is that fecal blood tests appear to miss nearly all sessile serrated adenomas and/or polyps, which tend to be flat and nonhemorrhagic.[22]

An ideal screening tool for the AN population would (1) effectively detect early-stage CRC and those precancers most likely to progress, (2) not be affected by tumor site, (3) be easy to use, and (4) be readily accessible. Next-generation stool DNA testing based on detection of exfoliated tumor-specific molecular markers may meet these criteria.[23,24] Such testing requires no bowel purgation and diet or medication restrictions and can be performed on samples collected at home. High neoplasm detection rates have been found across multiple studies.[25,26] In contrast to conventional screening approaches, neoplasm detection rates by stool DNA testing are comparable on both ends of the colorectum.[26,27]

A multitarget stool DNA test (MT-sDNA) exhibited high screening detection rates for both CRC and highest-risk precancers in a US multicenter validation study.[25] When the MT-sDNA was compared with a commercial FIT, MT-sDNA had a significantly higher sensitivity than FIT for CRC (overall, 92% vs 74%; stage I-II, 94% vs 70%) and advanced adenomas (42% vs 24%). For adenomas at greatest risk of progression (ie, those with high-grade dysplasia), MT-sDNA exhibited significantly higher sensitivity than FIT (69% vs 46%). For sessile serrated adenomas/polyps (precancers that are predominantly proximal and account for up to one-third of all CRCs[28]), MT-sDNA was substantially more sensitive than FIT (42% vs 5%). Point specificity was lower with MT-sDNA than with FIT (90% vs 96%). However, factoring in different screening frequencies translates to similar program specificities.[24] The MT-sDNA was approved in 2014 by the US Food and Drug Administration for general average-risk CRC screening and is covered by the Centers for Medicare and Medicaid Services for screening once every 3 years.

The purpose of this study was to evaluate MT-sDNA vs FIT for CRC screening in an AN population with elevated prevalence of adenomatous polyps and CRC. Findings from this study may have relevance for CRC screening in other populations with high CRC prevalence or in those living in rural/remote areas.

PATIENTS AND METHODS

Study Design

In this prospective cross-sectional study, we compared the accuracy of MT-sDNA and FIT for detection of screening-relevant colorectal neoplasia in AN people using colonoscopy as the reference standard. The study was approved by the Alaska Area Institutional Review Board, the Mayo Clinic Institutional Review Board, and the research review committees and governing boards of participating tribal health organizations. All participants were enrolled from February 6, 2012, through August 7, 2014, provided stool samples for MT-sDNA and FIT testing before prescheduled screening or surveillance colonoscopy, and gave written informed consent.

Study Participants

The target population comprised asymptomatic persons with any degree of self-reported AN heritage who were 40 through 85 years old, were scheduled for average-risk screening or surveillance colonoscopy at the Alaska Native Medical Center (ANMC) in Anchorage, Alaska, and were able to give informed consent.

We excluded patients if they (1) had undergone invasive screening tests in the previous 4 years or surveillance (ie, CRC or polyp follow-up) in the previous 2 years, (2) had a history of upper gastrointestinal cancer, (3) had overt hematochezia in the previous month, or (4) had inflammatory bowel disease or known hereditary CRC syndromes (eg, Lynch syndrome, familial adenomatous polyposis). Because the absolute number of CRCs in this cohort was expected to be low, patients referred with primary sporadic CRC were also recruited in a substudy. Participants completing all study elements received a $75 gift card.

Clinical Procedures

Stool Collection and Sampling. Stool samples were obtained before colonoscopy and before bowel purgation. Neither diet nor medication restriction was required. Participants collected a single stool using a container inserted under the toilet seat.[25,26] From this stool, 2 samples were taken for FIT testing using small probes (one as the FIT component of the MT-sDNA and the other for the commercial FIT comparator) that were then inserted into mailing tubes containing preservative buffer, as per manufacturers' instructions. For the DNA components of the MT-sDNA, a preservative buffer was added to the same whole stool, and a leakproof lid was screw-sealed onto the container for mailing. Samples were express shipped at ambient temperatures to a central laboratory and received within 3 days of defecation.

Colonoscopy and Pathology. All colonoscopies were performed at ANMC by certified endoscopists blinded to stool test results. Endoscopists were asked to confirm cecal intubation or describe the extent of insertion, assess quality of bowel cleansing, and record lesion size and site. Lesions were classified as proximal if located at or above the splenic flexure and as distal if located below this level. Histopathologic data were derived from final reports by pathologists at ANMC. Only the most advanced lesion per patient was used for analysis; if more than one similarly advanced lesion was present, only the largest lesion was used.

Stool Testing

All specimens were received at a central laboratory within the Mayo Clinic in Rochester, Minnesota, for initial processing and storage. Stool tests were performed in separate clinical laboratories by blinded technicians.

Multitarget Stool DNA Test. On receipt, buffered stool samples were homogenized, aliquoted, and stored at −80°C. Stool aliquots were subsequently sent in batches to Exact Sciences Corporation in Madison, Wisconsin, for performance of their commercial MT-sDNA (Cologuard). The MT-sDNA technical details have been described previously.[25,26] This automated molecular test quantifies *KRAS* mutations, 2 methylated genes (*NDRG4* and *BMP3*), and β-actin (a marker for total human DNA), as well as an immunochemical assay for human hemoglobin. The MT-sDNA results are called positive if an aggregate logistic score exceeds a predefined threshold.[26]

Fecal Immunochemical Test. On receipt of collection tubes, the commercial FIT (OC-Sensor Diana, PolyMedco, Inc, Portlandt, NY) was performed according to the manufacturer's instructions in a clinical laboratory at Mayo Clinic. Stools with more than 100 ng of hemoglobin per milliliter of buffer were considered positive.

Outcome Measures

The major outcome measure was test accuracy for screening-relevant neoplasia (SRN), defined as CRC or advanced adenoma (adenomatous polyp ≥1 cm or containing >25% villous component or high-grade dysplasia, or sessile serrated adenoma/polyp ≥1 cm) found on screening or surveillance colonoscopy.

Data Monitoring

Quality measures included (1) quarterly conference calls among investigators to review study execution and progress, (2) independent assessment of data entry accuracy by a Mayo Clinic monitor on 3 annual visits to the Alaska study site, and (3) independent review of polyps 1 cm or larger or containing high-grade dysplasia or more than 25% villous component by a Mayo Clinic pathologist before unblinding of stool results. A small number of polyps 1 cm or larger initially called hyperplastic were reclassified as sessile serrated adenoma/polyp; there were no other adjustments to SRN outcomes.

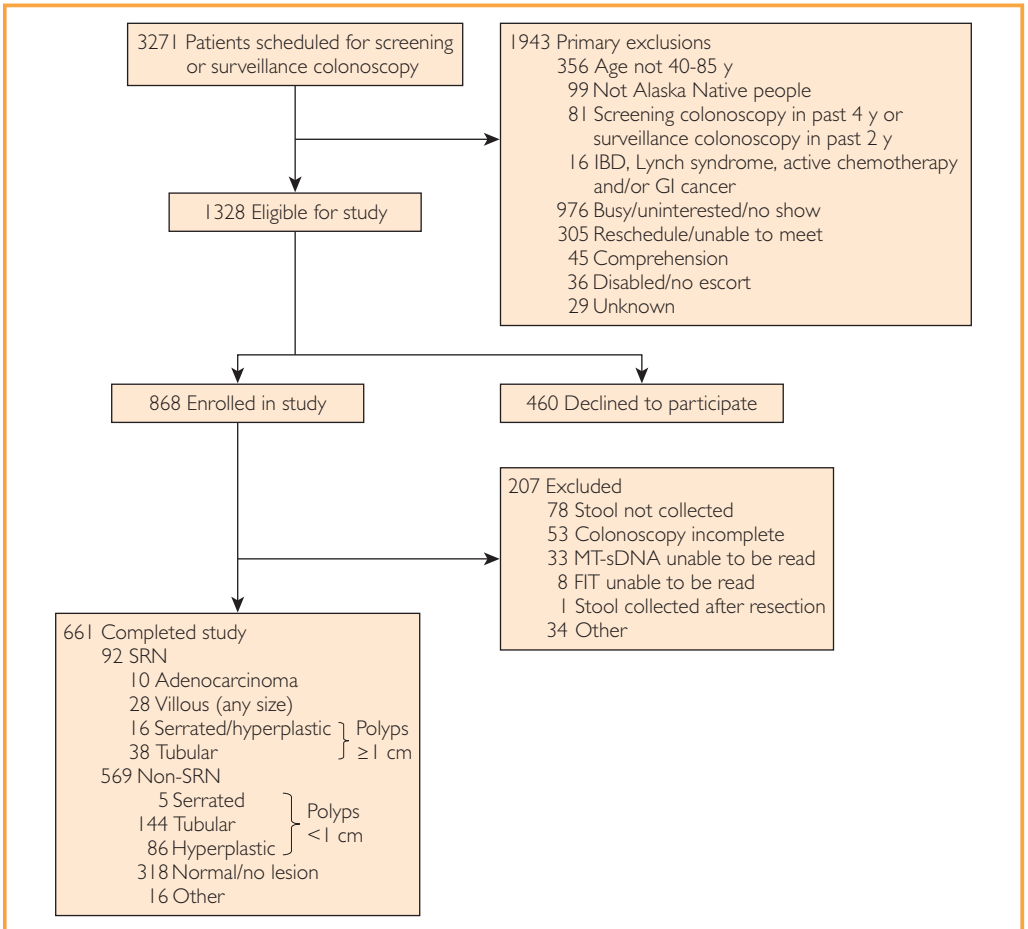

FIGURE 1. Study enrollment flow diagram. FIT = fecal immunochemical test; GI = gastrointestinal; IBD = inflammatory bowel disease; MT-sDNA = multitarget stool DNA test; SRN = screening-relevant colorectal neoplasia.

Sample Size Estimates and Statistical Analyses

Sample Size Justification. The study was powered at the 80% level to detect a difference in sensitivities of at least 20% between MT-sDNA and FIT assuming a 2-sided significance level of 5%. To achieve this goal, a total of 96 patients with SRN was required. Assuming that approximately 16% of the population harbored an SRN, the target sample size was set at 600 patients. In addition to the power assessment, having 96 subjects with SRN would ensure that the 2-sided 95% confidence bounds for MT-sDNA or FIT sensitivity estimates would not exceed 10%.

Statistical Considerations. Patient demographic characteristics are summarized as a median (25th-75th percentiles) for continuous variables and as a percentage of subgroup totals for categorical variables. The Wilcoxon rank sum test was used to compare continuous variables between groups, whereas the Fisher exact test was used to compare categorical variables between groups. Sensitivity and specificity were estimated with corresponding 95% CIs calculated using the exact binomial distribution. The number of AN patients needed to be screened for MT-sDNA or FIT was estimated as 1/(disease prevalence × test sensitivity) with corresponding 95% CIs calculated assuming the prevalence of disease as a known fixed quantity. Associations of clinical characteristics with test sensitivities and specificities were investigated using the Fisher exact test for categorical variables and the Spearman correlation coefficient

for continuous variables. The McNemar test was used to compare sensitivity and specificity between MT-sDNA and FIT. Positive and negative predictive values for each test were compared using the methods described by Moskowitz and Pepe.[29]

RESULTS

Study Population

Among the 3271 patients scheduled for screening or surveillance colonoscopy, 1328 met eligibility criteria, of which 868 (65%) agreed to participate (Figure 1). Among those enrolled, stool collections for either test were incomplete in 78, colonoscopy was incomplete or not done in 53, the MT-sDNA was unable to be read in 33, the FIT was unable to be read in 8, stool was collected after resection in 1, and there were 34 who were otherwise disqualified. The final study population comprised 661 patients (403 [60%] women) with a median age of 55 years (25th-75th percentiles, 50-61 years). Of these 661 patients, 435 (66%) were in the screening group, with 262 (60%) women and a median age of 52 years (25th-75th percentiles, 50-59 years); there were 226 in the surveillance group, with 141 (62%) women and a median age of 59 years (25th-75th percentiles, 54-64 years). Among the 667 patients who declined to participate or were excluded from the study, the median age was 58 years (25th-75th percentiles, 51-63 years) (P=.22 vs participant group), and 351 (52%) were women (P=.002 vs participant group). Among the 207 patients who signed consent to enroll in the study but who then were excluded or withdrew, 155 (75%) were scheduled for screening colonoscopy (P=.02 vs participant group).

The distribution of lesion types found on colonoscopy for the total group is summarized in Figure 1. Neoplasm detection rates for MT-sDNA and FIT are summarized in the Table. The prevalence of SRN in both the screening and surveillance groups was 14%.

Test Sensitivities

Screening-Relevant Neoplasia. Overall, MT-sDNA detected 49% (95% CI, 38%-60%) of SRN compared with 28% (95% CI, 19%-39%) by FIT (P<.001). In the screening group, MT-sDNA detected 50% (95% CI, 37%-63%) of SRN vs 31% (95% CI, 20%-44%) by FIT (P=.01). There were no significant covariate effects of age, sex, lesion site, or colonoscopy indication (screening vs surveillance) on SRN detection rates by either test.

Advanced Precancerous Lesions. Detection of advanced adenoma was higher by MT-sDNA than by FIT at all polyp sizes (Table). There was an appreciable increase in MT-sDNA sensitivity with slight changes in the polyp size cutoff around 1 cm, as detection rates increased from 41% for adenomas equal to or greater than 1 cm to 52% for those larger than 1 cm. For larger adenomas (≥2 cm) at

TABLE. Sensitivity and Specificity of Multitarget Stool DNA Test (MT-sDNA) and Fecal Immunochemical Test for Hemoglobin (FIT) for Colorectal Neoplasia in Alaska Native People[a]

Most advanced finding in 661 colonoscopies[b]	Sensitivity, % (95% CI) MT-sDNA	FIT	*P* value
Screening-relevant neoplasms[c]			
All participants (N=92)	49 (38-60)	28 (19-39)	<.001
Screening group (n=60)	50 (37-63)	31 (20-44)	.01
Colorectal cancer			
All participants (N=10)[d]	100 (69-100)	80 (44-97)	.48
Screening group (n=4)	100 (40-100)	75 (20-99)	.99
Advanced adenoma by size			
All participants			
≥1 cm (76)	41 (30-53)	22 (14-33)	.006
>1 cm (46)	52 (37-67)	30 (18-46)	.02
≥2 cm (21)	62 (38-82)	29 (11-52)	.05
≥3 cm (5)	80 (28-99)	40 (5-85)	.48
Screening group			
≥1 cm (53)	45 (31-60)	28 (17-42)	.05
>1 cm (33)	54 (37-71)	37 (21-55)	.15
≥2 cm (16)	63 (35-85)	38 (15-65)	.22
≥3 cm (4)	75 (19-99)	50 (7-94)	.99
Nonadvanced adenoma			
All participants (N=235)	12 (8-17)	10 (6-14)	.38
Screening group (n=130)	12 (7-18)	5 (2-11)	.06
	Specificity, % (95% CI)		
No screening-relevant neoplasms (n=569)[e]	91 (88-93)	94 (91-95)	.02
No neoplasms (n=334)[f]	93 (90-95)	96 (93-98)	.03

[a]Participants comprised 661 patients scheduled for screening (424) or surveillance (237) colonoscopy.
[b]Findings on colonoscopy and subsequent pathologic examination served as reference standard. Participants were classified according to the most advanced lesion found.
[c]Screening-relevant neoplasms included adenoma or sessile serrated adenoma/polyp ≥1 cm, any adenoma with ≥25% villous component, and cancer.
[d]Colorectal cancers included 7 referred patients.
[e]Colons harboring polyps <1 cm were considered "normal" in denominator for this calculation of specificity.
[f]Only colons with no polyps considered "normal" in denominator for this calculation of specificity.

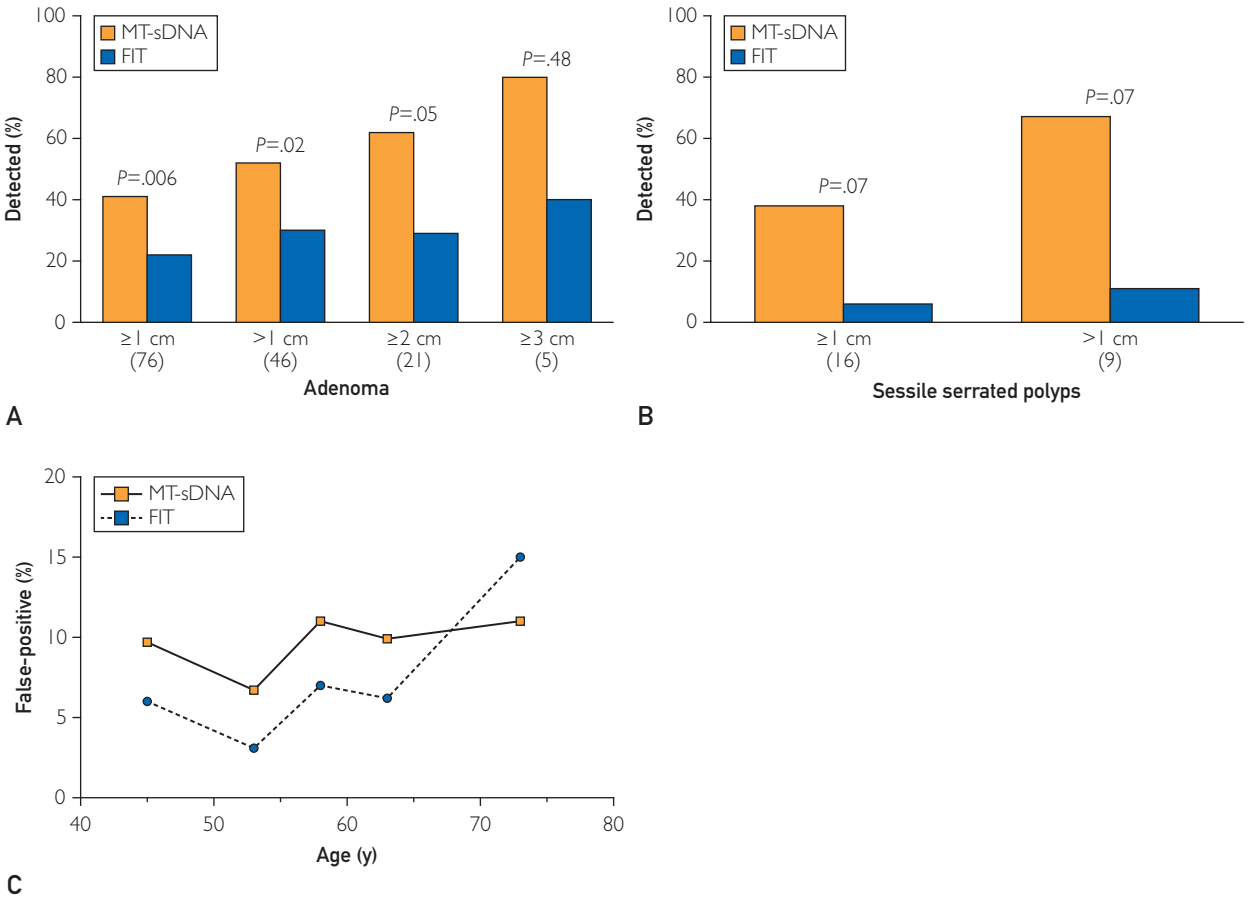

FIGURE 2. Effects of polyp size and patient age on test performances. A, Comparative detection rates of all advanced adenomas based on polyp size cutoff. Advanced adenomas included both adenomatous and sessile serrated adenoma/polyp types. B, Comparative detection rates of the sessile serrated adenoma/polyp subset based on size cutoff. C, Comparative false-positive rates by patient age. FIT = fecal immunochemical test; MT-sDNA = multitarget stool DNA test.

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high risk of progression, sensitivity was 62% by MT-sDNA and 29% by FIT (*P*=.05). Detection rates by MT-sDNA increased overall in proportion to polyp size, increasing to 80% for polyps 3 cm or larger (*P*=.01 for trend); the trend for increased FIT sensitivity with polyp size did not reach significance (Figure 2, A). For the subset of sessile serrated adenomas/polyps (Figure 2, B), detection rates were 38% by MT-sDNA and 6% by FIT for lesions equal to or greater than 1 cm or smaller (n=16; *P*=.07) and 67% and 11%, respectively, for lesions larger than 1 cm (n=9; *P*=.07).

Colorectal Cancer. Of the 10 patients with CRC, MT-sDNA detected all 10 CRCs (100%), and FIT detected 8 (80%) (*P*=.48) (Table). Within the screening group, 4 asymptomatic CRCs were found on colonoscopy (2 proximal, 2 distal); MT-sDNA detected all 4 (100%), and FIT detected 3 (75%) (*P*=.99).

Test Specificities

Specificities were calculated and compared in 2 different ways (Table). When all patients with no SRN are considered as normal (ie, colonoscopic findings of polyps <1 cm are classified as normal), overall specificities were 91% (95% CI, 88%-93%) for MT-sDNA and 94% (95% CI, 91%-95%) for FIT (*P*=.02). When only those patients without any polyps on colonoscopy were considered as normal, overall specificities were 93%

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(95% CI, 90%-95%) for MT-sDNA and 96% (95% CI, 93%-98%) for FIT (P=.03).

Colonoscopy indication significantly affected FIT but not MT-sDNA specificity. FIT specificity was 96% (95% CI, 93%-98%) in the screening group and 89% (95% CI, 84%-93%) in the surveillance group (P=.01); MT-sDNA specificities were 91% (95% CI, 88%-94%) and 90% (95% CI, 85%-94%), respectively (P=.94). The false-positive rate increased significantly with increasing patient age for FIT (P<.001) but not for MT-sDNA (P=.47) (Figure 2, C). Patient sex did not affect specificity for either test.

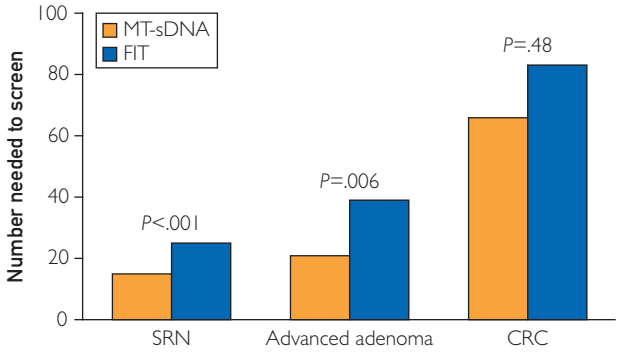

FIGURE 3. Test comparisons for number of patients who needed to be screened to detect one screening-relevant neoplasm (SRN), advanced adenoma, or colorectal cancer (CRC). FIT = fecal immunochemical test; MT-sDNA = multitarget stool DNA test.

Estimated Efficacy Metrics in a Screening Application

Based on the test accuracies and lesion prevalence observed in the present study, the estimated number of AN people who needed to be screened to detect a single SRN was 15 (95% CI, 12-19) by MT-sDNA compared with 25 (95% CI, 19-37) by FIT (P<.001). The number who needed to be screened to detect a single advanced adenoma was 21 (95% CI, 17-29) by MT-sDNA compared with 39 (95% CI, 26-64) by FIT (P=.006), and the number to detect a single CRC was 66 (95% CI, 65-96) by MT-sDNA vs 83 (95% CI, 68-149) by FIT (P=.48) (Figure 3).

Estimated positive predictive values for SRN were 46% (95% CI, 36%-56%) for MT-sDNA vs 41% (95% CI, 29%-54%) for FIT (P=.40). For advanced adenoma, these values were 32% (95% CI, 22%-41%) for MT-sDNA vs 27% (95% CI, 16%-38%) for FIT (P=.37), and for asymptomatic CRC, the values were 6% (95% CI, 0%-12%) for MT-sDNA vs 9% (95% CI, 0%-18%) for FIT (P=.29). Estimated negative predictive values for SRN were 92% (95% CI, 89%-94%) for MT-sDNA vs 89% (95% CI, 86%-91%) for FIT (P<.001), and for advanced adenoma, these values were 92% (95% CI, 89%-94%) for MT-sDNA vs 90% (95% CI, 90%-94%) for FIT (P=.01). For asymptomatic CRC, the estimated negative predictive values were 100% (95% CI, 99%-100%) for MT-sDNA vs 100% (95% CI, 99%-100%) for FIT (P=.16).

DISCUSSION

In the present study, we prospectively evaluated the performance of 2 tests for detection of asymptomatic SRN in AN people: (1) MT-sDNA and (2) FIT. The MT-sDNA detected significantly more SRNs than did FIT alone. The MT-sDNA had especially high sensitivities for CRC and large precancerous polyps at greatest risk of progression.

This investigation represents the second cross-sectional study evaluating the screening performance of MT-sDNA. Neoplasm detection rates by MT-sDNA observed in the present study corroborate those from the first—a multicenter study representative of the general US population (Figure 4).[25] These remarkably similar MT-sDNA findings suggest that there are no meaningful differences in the molecular biology of colorectal neoplasia between the 2 ethnically different populations. The screening specificity by MT-sDNA was higher in the present study at 93% compared with 90% in the US multicenter study, perhaps related to a younger median age in AN participants. FIT results observed in the AN study population were also very similar to FIT results from the US multicenter study.[25]

An ideal screening test would have a very high point-in-time sensitivity for CRC. Although the numbers were small in this study, MT-sDNA detected all (100%) of the CRCs, which is consistent with the very high (>92%) detection rates found in the US multicenter study.[25] Such high sensitivities by this noninvasive test are similar to those reported for screening colonoscopy.[30-34]

The MT-sDNA detected substantially more advanced precancers than did FIT. Importantly,

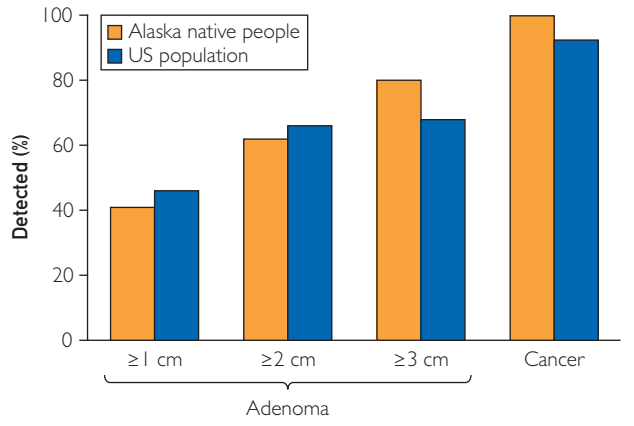

FIGURE 4. Comparison of colorectal neoplasm detection rates by MT-sDNA in Alaska Native people (present study) vs general US population.[25]

MT-sDNA sensitivity for advanced adenomas increased with polyp size and related risk of progression; MT-sDNA detected 62% of polyps 2 cm or larger and 80% of those 3 cm or larger, sizes in which most high-grade dysplasia occurs.[26,35,36] Consistent with earlier reports on MT-sDNA,[22,25] the important subset of sessile serrated adenomas/polyps was largely undetected by FIT, but MT-sDNA was positive in 67% of such lesions larger than 1 cm. Unlike CRC, precancerous polyps have a long dwell time, which permits a longer screening window for their detection.[37-39] As previously modeled,[40] these point-in-time polyp detection rates by MT-sDNA could translate into program sensitivities exceeding 90% for a cohort of advanced polyps by the second or third round of screening.

High specificity is important to minimize the expense and inefficiencies caused by false-positive results. Although the observed point-in-time specificity of 93% by MT-sDNA was slightly lower than that of 96% by FIT, these values applied to a program of MT-sDNA screening every 3 years would yield an annual false-positive rate of 2% compared with an annual false-positive rate of 4% by FIT done at the recommended frequency of every year. Thus, MT-sDNA may have higher program specificity than FIT when factoring in recommended screening interval.

Of practical relevance, the estimated number of screens by MT-sDNA needed to detect an SRN was only 15 and to detect an advanced adenoma only 21. Respective numbers needed for screening detection by FIT were roughly twice this high. Such high-yield screening detection by MT-sDNA in this population reflects both the higher sensitivity of MT-sDNA and the high prevalence of SRN in the AN population. The prevalence of SRN observed in this AN study was 14%, nearly twice as high as the 8% prevalence observed in the US multicenter study[25] and consistent with the well-established high CRC risk among AN people.[1,41]

A few study limitations must be emphasized. First, although we met our recruitment target and documented significantly superior SRN sensitivity by MT-sDNA over FIT, the sample size did not allow robust analysis of many covariates or various lesion subsets. Second, there was not an opportunity to repeat stool collections before prescheduled colonoscopy in the few instances of poor-quality stool samples, and these participants had to be disqualified (MT-sDNA, n=33; FIT, n=8). In practice, a repeated stool collection would be requested.

CONCLUSION

Based on MT-sDNA performance observed in this study, MT-sDNA applied in a screening program has potential to effectively detect SRN and thereby reduce both the incidence and mortality of CRC in the AN population. Given its test characteristics, MT-sDNA represents an attractive CRC screening strategy, particularly where colonoscopy access is limited. Further consideration and evaluation of the optimal test frequency, physician and patient acceptance, cost-effectiveness, and logistic algorithms for use and distribution within the Alaska Tribal Health System are warranted.

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Drs Redwood and Ahlquist reviewed analysis of unblinded data with the statisticians and take responsibility for the integrity and analyses of the data.

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Abbreviations and Acronyms: **AN** = Alaska Native; **ANMC** = Alaska Native Medical Center; **CRC** = colorectal cancer; **FIT** = fecal immunochemical test; **gFOBT** = guaiac-based fecal occult blood test; **MT-sDNA** = multitarget stool DNA test; **SRN** = screening-relevant colorectal neoplasia

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Potential Competing Interests: Mayo Clinic has licensed technology to Exact Sciences Corporation related to Cologuard. Drs Mahoney, Yab, and Ahlquist are coinventors of licensed technology and share in Cologuard royalties to Mayo Clinic in accordance with institutional guidelines. Drs Ahlquist and Yab serve as scientific advisors to and research collaborators with Exact Sciences Corporation.

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