

Multitarget stool DNA for colorectal cancer screening: A review and commentary on the United States Preventive Services Draft Guidelines

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Abstract

Multitarget stool DNA (mt-sDNA) testing was approved for average risk colorectal cancer (CRC) screening by the United States Food and Drug Administration and thereafter reimbursed for use by the Medicare program (2014). The United States Preventive Services Task Force (USPSTF) October 2015 draft recommendation for CRC screening included mt-sDNA as an "alternative" screening test that "may be useful in select clinical circumstances", despite its very high sensitivity for early stage CRC. The evidence supporting mt-sDNA for routine screening use is robust. The clinical efficacy of mt-sDNA as measured by sensitivity, specificity, life-years gained (LYG), and CRC deaths averted is similar to or exceeds that of the other more specifically recommended screening options included in the draft document, especially those requiring annual testing adherence. In a population with primarily irregular screening participation, tests with the highest point sensitivity and reasonable specificity are more likely to favorably impact CRC related morbidity and mortality than those depending on annual adherence. This paper reviews the evidence supporting mt-sDNA for routine screening and demonstrates, using USPSTF's modeling data, that mt-sDNA at three-year intervals provides significant clinical net benefits and fewer complications per LYG than annual fecal immunochemical testing, high sensitivity guaiac based fecal occult blood testing and 10-year colonoscopy screening.

Key words: Colorectal cancer screening; Multitarget stool DNA; Stool DNA; The United States Preventive Services Task Force; Cancer Intervention Surveillance Modeling Network; Fecal immunological technique; Modeling; Interval

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Core tip: Multi-target stool DNA (mt-sDNA) testing was approved for average risk colorectal cancer (CRC) screening by the United States Food and Drug Administration (2014). The evidence supporting mt-sDNA for routine screening use is robust. The clinical efficacy of mt-sDNA every three years, measured by life-years gained, and CRC deaths averted, is similar to that of other screening strategies more specifically recommended by the United States Preventive Services Task Force. In an irregularly screened population, however, tests with the highest point sensitivity and reasonable specificity like mt-sDNA are more likely to reduce CRC related morbidity and mortality than less sensitive tests that depend on annual adherence to achieve high programmatic sensitivity.

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INTRODUCTION

In its October 5, 2015 draft recommendation statement for colorectal cancer (CRC) screening, the United States Preventive Services Task Force (USPSTF) includes multi-target stool DNA (mt-sDNA) as an “alternative” screening test that “may be useful in select clinical circumstances”^[1]. However, the evidence supporting mt-sDNA for routine screening use is robust. The clinical efficacy of mt-sDNA as modeled for life-years gained (LYG), and CRC deaths averted is similar to other options more specifically recommended in the draft statement. This paper reviews the evidence supporting mt-sDNA clinical validity^[2-4], analytical validity^[5-7], and the USPSTF CRC screening modeling^[8-10]. This body of evidence supports the use of mt-sDNA at three-year intervals (mt-sDNA3y) to provide significant clinical net benefits and fewer complications per LYG than annual fecal immunochemical testing (FIT), annual high sensitivity guaiac based fecal occult blood testing (hsFOBT), and screening colonoscopy every 10 years (Colo10y). In comparison to biennial or triennial FIT (FIT2y, FIT3y) or hsFOBT (hsFOBT2y, FSFOBT3y), both of which are adherence intervals more typically achieved in clinical practice^[11,12], only mt-sDNA3y is at or within 98% of the screening test efficiency frontier^[10] as measured by the ratio of LYG to colonoscopies generated. Additionally, mt-sDNA3y generates greater than 90% of the LYG by Colo10y in the simulation model of colorectal cancer (SimCRC)^[10].

CRC is the second leading cause of cancer death in the United States. In 2015, an estimated 133000

people will be diagnosed with the disease and about 50000 will die from it^[13]. When detected early, CRC can be treated with positive outcomes. The Centers for Disease Control and Prevention estimate that 42% of Americans are not currently up to date with colon cancer screening, including millions of Americans who have avoided screening completely, and that if everyone age 50 or older was regularly screened, at least 60% of CRC deaths could be avoided^[14]. These statistics leave much room for improvement in routine CRC screening; effective, broad implementation of a non-invasive high sensitivity, low risk screening strategies like mt-sDNA could immediately help to address this serious public health issue.

THE mt-sDNA TEST

mt-sDNA uses a single random stool sample, collected by patients at home, without requiring any preparation, or change in medications or diet. The test identifies 10 biomarkers known to be associated with CRC and pre-cancerous lesion, including altered human DNA and hemoglobin. The test combines all biomarker results with the normalizing gene beta-actin in an algorithm that generates a composite, single, “Negative” or “Positive” patient result. Several detailed reviews describing the biology that underlies this screening approach and the design features of the test have been published^[5-7]. The test was systematically designed to lower patient burdens with respect to ease of sample collection and specimen handling with a custom-designed collection kit. High CRC, high-grade dysplasia, and large adenoma point sensitivity and the prolonged pre-malignant phase of colorectal carcinogenesis allow for longer screening intervals between screening tests with mt-sDNA, which significantly lowers the burdens of annual testing. The American Cancer Society currently recommends mt-sDNA at three-year intervals^[15]. Burdens on patients, providers and health care systems are further reduced through an included United States 24 h, 7 d-a-week telephonic patient navigation system. This system assists patients throughout the testing process to maximize the number of successful screening events and reports results to directly to ordering medical providers.

The mt-sDNA analytic process and biomarker selection were used to create a test with greater sensitivity for CRC and significant premalignant lesions than fecal hemoglobin as a single marker. All tests based on fecal hemoglobin alone are biologically limited in their ability to detect colorectal neoplasia, especially precancerous lesions and early stage CRC, which may bleed intermittently or not at all. The random sampling and small sample size used in FIT and hsFOBT tests contribute to sampling error and further limits detectability. In contrast, mt-sDNA detects DNA alterations, both mutations and aberrant methylation, in DNA released from cells that are constantly shed from premalignant lesions and early and late stage cancers, enhancing their detectability by mt-sDNA. Stool sampling error with mt-sDNA is significantly diminished through the

use of an aliquot of the entire stool sample homogenate and the laboratory's automated, uniform processing protocol^[2].

mt-sDNA is primarily being used in the United States and has been approved by the United States Food and Drug Administration for average risk CRC screening^[16] and is reimbursed by the United States Centers for Medicare and Medicaid Services once every three years^[17]. It was awarded a unique Clinical Procedural Terminology code of 81528 by the American Medical Association. Cologuard® (multi-target sDNA) has been CE marked for use in Europe, though there is limited availability to date through laboratories in England and Dubai. Additional studies to determine local efficacy in a number of Asian countries are under discussion and studies are ongoing in Italy, the United Kingdom and the Netherlands. The test cost is USD649 (USD509 for Medicare), which includes a United States patient navigation/compliance system supporting over 70 languages.

In the United States, mt-sDNA is used in both opportunistic and local invitational settings. The test, requiring no change in diet, medication or any preparation and a specimen collection at home, is appropriate for population-based use. However, the size of the specimen container, allowable 72 h transit time back to the laboratory, and cost may mitigate use in that manner, especially in low resource countries. Countries with limited colonoscopy capacity for evaluating positive tests may be challenged by somewhat lower specificity (90%) of mt-sDNA compared to FIT, measured in patients requiring no biopsies when examined with colonoscopy, in any given year. However, overall, mt-sDNA3y results in fewer negative colonoscopic follow-up examinations for a positive screening test than result from the compounded programmatic specificity failure of annual FIT or hsFOBT at 95% specificity^[8].

mt-sDNA PERFORMANCE IN SCREENING POPULATIONS

Three studies in screening populations show consistent results. Studies demonstrate significant greater single test application sensitivity of mt-sDNA over FIT for advanced colorectal neoplasia detection, though at lower specificity.

DeeP-C study

Results from this pivotal, prospective 90-site, 10000 patient cross-sectional clinical study were published in the New England Journal of Medicine in April 2014^[2]. The DeeP-C study compared mt-sDNA and FIT, using colonoscopy as the reference standard on all cases. The study demonstrated that mt-sDNA was significantly more sensitive than FIT (Table 1) for detecting CRC, especially early stage CRC and advanced and non-advanced adenomas. Specificity in the target screening age of 50-74 years was 92.3% compared to 97.0% for FIT in patients where no biopsy was required during

colonoscopy. Matching FIT specificity to that of the mt-sDNA test only increases FIT sensitivity 2 percentage points. Thus the lower specificity of mt-sDNA did not account for the increased sensitivity of the mt-sDNA assay over FIT.

Alaska study: This prospective study of 661 Alaska native people compared mt-sDNA to FIT with colonoscopy as the reference, the same design as DeeP-C^[3]. In the overall study population ($n = 661$), which included both higher risk and average risk individuals for routine screening (screen subgroup) mt-sDNA detected 49% of advanced colorectal neoplasms (colorectal cancer plus advanced adenoma) vs 28% for FIT ($P < 0.001$), including the identification of 100% (10/10) colorectal cancers vs 80% (8/10) for FIT. In the screen sub-group ($n = 464$), mt-sDNA detected 50% advanced colorectal neoplasia vs 31% for FIT ($P = 0.01$), including the detection of 100% (4/4) of colorectal cancers vs 75% (3 of 4) for FIT. In subjects with no adenomas detected on colonoscopy, specificity was 93% for mt-sDNA vs 96% for FIT ($P = 0.034$). mt-sDNA may provide an attractive approach to provide high sensitivity screening for populations where routine travel for colonoscopy is challenging or where colonoscopy capacity itself is limited. Similarly, individuals participating only irregularly in screening care may accrue a greater benefit using a higher sensitivity tests when provided with an opportunity for screening.

Netherlands study: mt-sDNA was compared to FIT (OC Sensor) in prospectively collected frozen archived samples ($n = 1047$)^[4] from an invitational screening cohort (COCOS) collected in the Netherlands^[18]. The study compared the performance of mt-sDNA and FIT to colonoscopy on all subjects for the detection of advanced colorectal neoplasia. mt-sDNA detected 49% (50/102) and FIT 25% (26/102) of cases of advanced colorectal neoplasia ($P < 0.001$) at specificities of 89% and 96% respectively. The findings are consistent with those of the DeeP-C and Alaska studies.

PATIENT PREFERENCES AND TEST PERFORMANCE IN DIFFERENT POPULATIONS AFFECT SCREENING PROGRAM EFFICACY

The effectiveness of a test is a function of its performance, its availability, and patient adherence. The USPSTF noted in their draft statement that "clinicians should consider engaging patients in informed decision-making about the screening strategy that would most likely result in completion, with high adherence over time, taking into consideration both the patient's preferences and local availability"^[1]. Data has begun to accrue from studies that the mt-sDNA performance and process may appeal to previously unscreened patients

Table 1 Findings from the DeeP-C cross-sectional study^[5], comparing multitarget stool DNA with fecal immunological test using colonoscopy as the reference standard on all cases (*n* = 9989 subjects)

	Colonoscopy findings <i>n</i> detected	mt-sDNA % detected	FIT % detected
Sensitivity			
Colorectal cancer (stages I-IV)	65	92.3%	73.8%
Early stage colorectal cancer (stage I and II)	50	94.0%	70.0%
AA	757	42.4%	23.8%
High grade dysplasia	39	69.2%	46.2%
Sessile serrated adenoma/polyp ≥ 1.0 cm	99	42.4%	5.1%
Specificity			
Specificity (only CRC and AA excluded)	9167	86.6%	94.9%
Specificity, no adenomas, no biopsy done	4457	89.8%	96.4%
Age-adjusted (50-74 yr) ^[31]	4032	92.3%	97.0%

FIT: Fecal immunological test; AA: Advanced adenoma.

and lead to increased screening rates. A study by Berger *et al.*^[19] surveyed a random sample of almost 3000 average-risk patients (99% participation rate) who had been prescribed mt-sDNA (Cologuard) by their physician and found that 42% of the patients, aged 50-74 years had not been previously screened.

A second study by Cole *et al.*^[20] of 675 average-risk patients, aged 50-75 years who had never been screened for CRC showed that when patients were informed regarding screening alternatives they preferred the noninvasive, mt-sDNA option by more than 50% over colonoscopy or FIT. The study went on to note that educating patients about the noninvasive mt-sDNA option and involving the patient in the shared decision-making process about test choice can increase the likelihood that noncompliant patients will get screened.

A third study by Abola *et al.*^[21] of 423 individuals (617 invited, 69% participation rate) found that 75% considered mt-sDNA more suitable for screening than colonoscopy with no significant difference between Caucasian and African American respondents. The authors concluded that "intervention to increase the uptake of sDNA (mt-sDNA) testing may reduce racial disparities in CRC".

The availability of mt-sDNA allows patients who would be screened but who will not use colonoscopy for personal or cultural reasons or who reside in rural areas where there is less access to colonoscopy, to have a high sensitivity noninvasive test option. This is especially relevant for those who will not adhere to an annual screening regime.

Addressing disparities resulting from test access and patient preference are important. Studies show that multiple screening choices increase the overall level of screening and that patients will gravitate to their preferred option. Inadomi *et al.*^[11] showed that offering colonoscopy alone was less effective (38% screened) than offering a choice of colonoscopy or gFOBT screening (69% screened) for obtaining a successful screening event within 12 mo of a physician's recommendation for screening. A large prospective randomized screening study comparing FIT to colonoscopy, conducted in Spain, by Quintero *et al.*^[22], allowed post-randomization cross-

over. Approximately 23% (1706/7355) of patients randomized to colonoscopy crossed over to FIT, with 1.2% (117/9353) of patients randomized to FIT crossing over to colonoscopy. This demonstrates a preference for non-invasive testing in a significant number of subjects. If this occurred in a clinical situation outside of a clinical trial, 23% of patients would be selecting a screening approach with much less sensitivity and a more burdensome screening requirement. These issues could be significantly mitigated by using high sensitivity mt-sDNA as a routine non-invasive choice. Additional studies have shown that test preferences for non-invasive screening over invasive screening are most attractive to certain populations related to cultural preferences, a population area where high sensitivity non-invasive screening may also improve screening efficacy.

Finally, for patients who do choose non-invasive testing, sensitivity for CRC and its precursors in the proximal colon are key to screening efficacy. African American patients and elderly patients in general have an increased prevalence of proximal colorectal neoplasia^[23-25]. In contrast to FIT which is more sensitive for lesions in the distal colon, mt-sDNA has equivalent sensitivity for CRC in the proximal and distal colon. Importantly, and key for decreasing proximal CRC incidence when using noninvasive screening, mt-sDNA has significant sensitivity for sessile serrated adenoma/polyps, the pre-cursor lesion for approximately 25% of CRC and a common cause of missed or interval cancers arising in the proximal colon. In the DeeP-C study, mt-sDNA identified 42.4% of patients with sessile serrated adenomas ≥ 1 cm in diameter whereas FIT detected only 5.1% ($P < 0.001$) as these lesions are non-hemorrhagic whereas they exfoliate aberrantly methylated DNA in the stool^[2].

MODELING mt-sDNA PERFORMANCE AS AN APPROACH FOR SETTING AN INITIAL INTER-TEST INTERVAL

Establishing an initial inter-test interval using vetted, well designed and calibrated CRC screening models is recommended for new tests^[8]. Modeled intervals can be

tempered over time to accommodate accumulating clinical experience, patient preferences and medical delivery system impacts. Comparative prospective randomized longitudinal studies with mortality endpoints are large, complex, lengthy, and expensive. Currently, only screening with low sensitivity guaiac FOBT and flexible sigmoidoscopy are supported by prospective randomized control trials (RCT's) with mortality endpoints. The use of models allows for virtual prospective studies to be done on large cohorts. These provide comparative performance of multiple tests simultaneously. Such modeling and its limitations are described below.

The predictive power of modeling has limitations related to the degree that the biology of colorectal cancer, clinical practice related factors, test uptake, and performance assumptions accurately reflect the clinical screening "ecosystem". One concern is establishing a comparative baseline by only using 100% uptake and adherence for each screening test. The USPSTF technical report^[8] assumes 100% compliance and adherence for each strategy, despite strong evidence that initial uptake of FIT/FOBT in the United States is low (10.4%)^[26,27] and adherence for FIT and FOBT declines significantly over time^[28]. A recent review of a large cohort of patients continuously insured for ten years showed that of patients who were screened according to guidelines, only 0.3% (268/97518) were current with screening as a result of completing ten consecutive annual FIT/FOBT tests^[29]. Patients who were non-adherent with colonoscopy and non-adherent to annual test use completed an average of 2.6 FIT/FOBT during the 10-year study period. Forty-six percent completed only a single FOBT/FIT test during the 10-year study period. Ninety-nine point six percent (97801/97518) of patients who were current with screening had received a colonoscopy during the 10-year study period. In a three-year follow-up^[28] of the Inadomi study^[11] reported by Liang *et al.*^[28], the annual adherence for patients in the group assigned to FOBT screening fell from 67% the first year to 27% at year two, and to 14% by year three. In the group that chose FOBT over colonoscopy, adherence dropped from 38% in the first year to 19% at year two and to 12% at year three. In highly resourced integrated health system with patient navigation infrastructure, improved programmatic adherence with annual FIT has been shown, though initial uptake remains < 50%^[30]. Despite evidence of poor year-over-year adherence, the USPSTF continues to recommend routine screening with annual FIT, hsFOBT, or annual FIT with flexible sigmoidoscopy every 10 years, based on modeling 100% adherence while acknowledging that "In practice, such high adherence is not observed either for initial or repeat screening^[8]" and considers high sensitivity mt-sDNA an "alternative test" only for use in selected patients.

This USPSTF draft CRC screening recommendation^[1] is informed by the results of three independently-developed microsimulation models of CRC that are funded by the National Cancer Institute's Cancer Intervention and Surveillance Modeling Network (CISNET) - SimCRC,

microsimulation screening analysis (MISCAN) for CRC, and colorectal cancer simulated population model for incidence and natural history. The performance of the various CRC screening tests were evaluated using these models to predict LYG, decreases in CRC incidence, CRC related mortality, number of screening tests required, and complications arising from screening^[8].

For comparative purposes, CISNET assumed 100% perfect adherence to all screening and surveillance procedures and performed no sensitivity analysis around adherence that would more accurately reflect actual test use. Further, their analysis grouped FIT, gFOBT, and mt-sDNA together because they are "exclusively stool-based screening modalities with comparable burden"^[8]. However, mt-sDNA has higher single-event CRC, and advanced adenoma sensitivity, including sensitivity for sessile serrated adenomas. It has significantly lower patient burdens given the need for far fewer test events with the recommended three-year screening schedule, a specifically designed patient collection process to minimize sample handling, and an embedded patient navigation support system. Based on the lower patient burden and the great biological differences in the test approach, mt-sDNA could have been considered in its own category for interval effect analysis, similar to all other non-stool based strategies. At the least, mt-sDNA3y could have been grouped with FIT2y and FIT 3y and hsFOBT2y and hsFOBT3y as a more clinically representative grouping for evaluation. This is an important consideration as, under CISNET modeling rules, only one strategy per "group" could ultimately be "recommended" for routine screening^[8].

This grouping and arbitrary rule led to the finding that "annual mt-sDNA" was less efficient with respect to the number of colonoscopies generated per LYG than annual FIT and hsFOBT and precluded a consideration of the multi-year interval (3 years) for which the test is already recommended by others^[9,15]. According to the draft recommendation statement, the CISNET modeling of mt-sDNA at a one-year interval (mt-sDNA1y) would "potentially yield approximately the same number of life-years gained as the recommended strategies previously listed" but when "compared with other stool-based screening tests and screening with colonoscopy every 10 years, FIT-DNA (mt-sDNA) requires a larger number of lifetime colonoscopies (a proxy for the harms of screening) per LYG"^[1]. When calculating lifetime colonoscopies using the intervals for each screening test as recommended by the American Cancer Society (Table 2)^[15], the data shows that mt-sDNA3y has the fewest lifetime colonoscopies (COL) and an equivalent number of colonoscopies per LYG compared to FIT and hsFOBT at one-year intervals (FIT1y and hsFOBT1y) (Table 3)^[8]. Colonoscopy itself generates approximately twice as many colonoscopies per LYG as any of the non-invasive strategies.

Overall, mt-sDNA3y is associated with less burdens and harms than FIT1y and gFOBT1y. In clinical practice the comparative benefits of mt-sDNA may be even greater given the lack of adherence to annual FIT or

Table 2 American Cancer Society recommended colorectal cancer screening test frequency intervals for average risk individuals

Test	Frequency (yr)
Colonoscopy	10
CT colonography	5
Flexible sigmoidoscopy	5
Multi-target stool DNA test (Cologuard, mt-sDNA)	3
High sensitivity guaiac-based fecal occult blood test	1
Fecal immunochemical test	1

CT: Computed tomography.

hsFOBT screening^[11,28-30]. A comparison reflecting actual clinical practice experience would have included a comparison of mt-sDNA3y with FIT/FOBT at 2y and 3y, which is detailed below.

A sensitivity analysis exploring non-annual adherence demonstrated more clinically relevant benefits and harms for stool-based strategies. The CISNET modeling data on FIT and hsFOBT at two-year intervals^[8] (FIT2y and hsFOBT2y) and mt-sDNA3y (Table 4), show mt-sDNA3y to be the only strategy generating greater than 90% LYG by screening colonoscopy 10y (% of COL 10y LYG) (SimCRC) in any of the models. While the colonoscopies per LYG are similar for hsFOBT and somewhat lower for FIT2y, overall LYG, CRC incidence, and related deaths are notably lower and more lives will be saved with mt-sDNA3y than with either FIT2y or gFOBT2y^[8].

The CISNET modeling data on FIT and gFOBT at three-year intervals^[8] (FIT3y, hsFOBT3y) reflects a second scenario supported by clinical experience^[8-10]. Compared to FIT3y and hsFOBT3y, mt-sDNA benefits are notably better with 19-22 CRC deaths averted, 43%-68% CRC incidence reduction, and 68%-78% mortality reduction across the three models (Table 5)^[8]. At three-year intervals, FIT and hsFOBT generate only 68%-77% of the life years gained by Colo10y vs 84%-91% for mtsDNA3^[8,10].

BALANCING BENEFITS AND HARMS

The specific harms associated with the non-invasive testing process are held to be minimal. Paradoxically, the USPSTF^[1] uses colonoscopies as a proxy for harms for the non-colonoscopy screening tests, but not for colonoscopy based screening itself. If colonoscopy related harm is a greater concern than screening benefit, especially where differences in the balance of harms and benefits is very small among non-invasive tests, mt-sDNA3y appears favorable when compared to Colo10y. mt-sDNA3y generates far fewer colonoscopies per 1000 people screened (1701-1827) across the three CISNET models^[8] than Colo10y (4007-4101) or annual hsFOBT (2230-2287) and similar numbers to annual FIT (1739-1899) (Table 3)^[8].

There are no direct harms or complications from mt-sDNA beyond those associated with a follow-up colonoscopy for a positive mt-sDNA screening test. No additional investigation is indicated for a positive mt-

sDNA test outside a careful structural examination of the colon in a well prepared patient, generally by optical colonoscopy. The aggregate contribution of other cancers of the aerodigestive tract and inflammatory diseases to the mt-sDNA false positive rate is two cases per 10000 screened patients, precluding the need for additional studies in an otherwise asymptomatic patient on the basis of a positive mt-sDNA test alone^[31]. Like all tests, mt-sDNA may be associated with false positive results and false negative results, wherein advanced colorectal neoplasia is not identified on a single screening event. Colonoscopy, however, may be associated, though rarely, with significant adverse events^[31].

The USPSTF technical report calculated complications for all model outputs. These complications are based on the serious adverse event rates summarized in the USPSTF evidence synthesis^[25] and are dependent on patient age and type of lesion removed. Table 3 shows the complications per 1000 patients screened, the LYG, the CRC deaths averted and screening related complications across the three models. mt-sDNA3y has the lowest rate of complications per LYG (0.036-0.044) vs annual FIT (0.038-0.045), annual hsFOBT (0.042-0.047) or colo10y (0.051-0.060). With respect to complications per death averted, mtsDNA3y (0.41-0.50) outperforms colonoscopy (0.58-0.68) and in two of three models, annual FIT (0.43-0.50) and annual hsFOBT (0.48-0.55)^[8].

Finally, the total number of screening tests required itself is an indicator burden. Fewer stool tests and clinical encounters are required for mt-sDNA3y than with FIT1-3y or hsFOBT1-3y (Tables 3-5). mt-sDNA3y provides significantly fewer burdens on patients, physicians, and healthcare systems than other fecal tests. Notably, this factor was not accounted for as a "burden" in the USPSTF analysis^[8].

mt-sDNA CLINICAL UTILITY CAN BE INFERRED FROM PREVIOUS RCT'S OF FOBT

The clinical utility of mt-sDNA3y with respect to reducing both CRC related mortality and CRC incidence can be inferred from previous RCT's of annual and biennial screening with the less sensitive FOBT test. No CRC screening test recommended by the USPSTF has been shown empirically to decrease CRC related mortality^[25]. Only low sensitivity guaiac based FOBT (gFOBT, *e.g.*, Hemoccult II), used annually or biennially, and flexible sigmoidoscopy alone have been shown to decrease CRC mortality in well-designed RCTs, but these are no longer widely used in the United States for screening, nor recommended by the USPSTF^[1,8,25]. However, the USPSTF infers decreases in CRC related mortality and the CRC incidence for both FIT and hsFOBT from the mortality benefit demonstrated for Hemoccult II gFOBT in these RCT's^[8]. These benefits can also be applied to mt-sDNA similarly through the same logical inference, as given mt-sDNA's superior sensitivity over FIT (Table 1) and by

Table 3 Burdens, harms, benefits, and efficiencies for 100% perfect adherence for colorectal cancer screening tests at current recommended intervals, ages 50-75, per 1000 people screened

CISNET model	Test	Burdens and harms			Benefits							
		Stool tests	Total COL	Complications	LYG	CRC DA	CRC incidence reduction	CRC mortality reduction	% of COL 10y LYG	COL per LYG	Complications per LYG	Complications per DA
SimCRC	COL 10y	0	4007	14	275	24	81%	87%	100%	15	0.051	0.58
	FIT1y	15778	1739	10	260	23	67%	81%	95%	7	0.038	0.43
	hsFOBT1y	12914	2230	11	261	23	69%	82%	95%	9	0.042	0.48
	mt-sDNA3y	5990	1701	9	250	22	63%	78%	91%	7	0.036	0.41
MISCAN	COL 10y	0	4101	15	248	22	62%	79%	100%	17	0.060	0.68
	FIT1y	15843	1757	10	231	20	47%	72%	93%	8	0.043	0.50
	hsFOBT1y	12927	2287	11	232	20	49%	73%	94%	10	0.047	0.55
	mt-sDNA3y	5779	1714	9	215	19	43%	68%	87%	8	0.042	0.47
CRC-SPIN	COL 10y	0	4049	15	270	24	88%	90%	100%	15	0.056	0.62
	FIT1y	15444	1899	11	244	22	72%	81%	90%	8	0.045	0.50
	hsFOBT1y	13026	2253	11	247	22	75%	82%	92%	9	0.045	0.50
	mt-sDNA3y	5927	1827	10	226	20	68%	76%	84%	8	0.044	0.50

CISNET: National Cancer Institute's Cancer Intervention and Surveillance Modeling Network; SimCRC: Simulation model of colorectal cancer; MISCAN: Microsimulation screening analysis; CRC-SPIN: Colorectal cancer simulated population model for incidence and natural history; COL: Colonoscopies; LYG: Life-years gained; DA: Deaths averted; COL 10y: Colonoscopy at a 10-year interval.

Table 4 Burdens, harms, benefits, and efficiencies at 2-year adherence rates for fecal immunological technique/fecal occult blood testing compared to recommended intervals for colonoscopy and mt-sDNA, ages 50-75, per 1000 people screened

CISNET model	Test	Burdens and harms			Benefits							
		Stool tests	Total COL	Complications	LYG	CRC DA	CRC incidence reduction	CRC mortality reduction	% of COL 10y LYG	COL per LYG	Complications per LYG	Complications per DA
SimCRC	COL 10y	0	4007	14	275	24	81%	87%	100%	15	0.051	0.58
	FIT2y	9326	1215	7	234	20	53%	72%	85%	5	0.030	0.35
	hsFOBT2y	8388	1597	9	235	21	56%	73%	86%	7	0.038	0.43
	mt-sDNA3y	5990	1701	9	250	22	63%	78%	91%	7	0.036	0.41
MISCAN	COL 10y	0	4101	15	248	22	62%	79%	100%	17	0.060	0.68
	FIT2y	9342	1243	8	200	17	35%	62%	81%	6	0.040	0.47
	hsFOBT2y	8408	1636	9	200	18	37%	63%	81%	8	0.045	0.50
	mt-sDNA3y	5779	1714	9	215	19	43%	68%	87%	8	0.042	0.47
CRC-SPIN	COL 10y	0	4049	15	270	24	88%	90%	100%	15	0.056	0.62
	FIT2y	9241	1346	9	207	18	58%	68%	77%	6	0.043	0.50
	hsFOBT2y	8448	1626	9	212	19	62%	70%	78%	8	0.042	0.47
	mt-sDNA3y	5927	1827	10	226	20	68%	76%	84%	8	0.044	0.50

CISNET: National Cancer Institute's Cancer Intervention and Surveillance Modeling Network; CRC: Colorectal cancer; SimCRC: Simulation model of CRC; MISCAN: Microsimulation screening analysis; CRC-SPIN: Colorectal cancer simulated population model for incidence and natural history; COL: Colonoscopies; LYG: Life-years gained; DA: Deaths averted; COL 10y: Colonoscopy at a 10-year interval; FIT: Fecal immunological test.

inference, superiority to low sensitivity gFOBT^[2]. CISNET modeling supports the proposition that mt-sDNA3y is more efficient^[10] and efficacious than hsFOBT2y and therefore similar clinical utility can be ascribed to mt-sDNA3y as the four RCTs of low sensitivity gFOBT2y provide for the clinical utility of hsFOBT2y^[8]. Using comparable clinical efficiency^[10] to allow clinical utility to be inferred from the RCTs of biennial FOBT obviates concern around small differences in specificity between the tests. In practical terms, even if patient uptake of mtsDNA is the same as that of FIT or hsFOBT, patients are more likely to see a greater net benefit from higher sensitivity mt-sDNA screening than from intermittent FIT/FOBT use, especially given the low rate of serious colonoscopy related complications.

CONCLUSION

CRC is the second leading cause of cancer mortality in

the United States with nearly 50000 deaths per year. mt-sDNA provides a colorectal cancer screening test with high sensitivity for the detection of CRC and the most significant pre-malignant lesions in a non-invasive format. It is approved as safe and effective for routine screening of asymptomatic individuals by the United States FDA, CE marked in Europe, and vetted and approved for coverage by the United States Centers of Medicare and Medicaid Services at three year intervals. mt-sDNA at three-year intervals is included in the American Cancer Society guidelines. Clinical experience demonstrates that patients formerly non-compliant with screening, ages 50-74, comprise a significant proportion (42%) of mt-sDNA users, which is consistent with patient screening preference studies.

Multiple studies support the superior point sensitivity of mt-sDNA over FIT, an important attribute of a screening test with limited harms that appeals to patients hesitant to pursue screening by other methods. The data

Table 5 Burdens, harms, benefits, and efficiencies for fecal immunological technique and fecal occult blood testing at 3-year adherence rates compared to recommended intervals for colonoscopy and mt-sDNA, ages 50-75, per 1000 people screened

CISNET model	Test	Burdens and harms			Benefits							
		Stool tests	Total COL	Complications	LYG	CRC DA	CRC incidence reduction	CRC mortality reduction	% of COL 10y LYG	COL per LYG	Complications per LYG	Complications per DA
SimCRC	COL 10y	0	4007	14	275	24	81%	87%	100%	15	0.051	0.58
	FIT3y	6887	971	6	212	18	45%	65%	77%	5	0.028	0.33
	hsFOBT3y	6456	1286	7	212	18	47%	66%	77%	6	0.033	0.39
	mt-sDNA3y	5990	1701	9	250	22	63%	78%	91%	7	0.036	0.41
MISCAN	COL 10y	0	4101	15	248	22	62%	79%	100%	17	0.060	0.68
	FIT3y	6795	995	7	176	15	28%	55%	71%	6	0.040	0.47
	hsFOBT3y	6302	1296	8	175	15	30%	55%	71%	7	0.046	0.53
	mt-sDNA3y	5779	1714	9	215	19	43%	68%	87%	8	0.042	0.49
CRC-SPIN	COL 10y	0	4049	15	270	24	88%	90%	100%	15	0.056	0.62
	FIT3y	6857	1081	7	178	16	49%	59%	66%	6	0.039	0.44
	hsFOBT3y	6498	1317	8	183	16	53%	61%	68%	7	0.044	0.50
	mt-sDNA3y	5927	1827	10	226	20	68%	76%	84%	8	0.044	0.50

CISNET: National Cancer Institute's Cancer Intervention and Surveillance Modeling Network; COL: Colonoscopies; COL 10y: Colonoscopy at a 10-year interval; LYG: Life-years gained; CRC: Colorectal cancer; MISCAN: Microsimulation screening analysis; CRC-SPIN: Colorectal cancer simulated population model for incidence and natural history; SimCRC: Simulation model of colorectal cancer; DA: Deaths averted; FIT: Fecal immunological test.

provided by the USPSTF technical report^[8] from three separate models supports the efficacy of mt-sDNA3y and demonstrates across 1000 screened individuals, age 50-74, that it yields a median of 226 life-years gained (range 215-250), averts 20 CRC deaths (range 19-22), reduces CRC mortality by 76% (range 68%-78%, and produces the most benefit (LYG) per complication (harm). The three CISNET models demonstrate that in terms of the number of colonoscopies per LYG, mt-sDNA3y (7-8) is equivalent to annual FIT (7-8) and lower than hsFOBT (9-10)^[8].

The USPSTF draft recommendation states "Screening for CRC is a substantially underused preventive health strategy in the United States... Accordingly, the best screening test is the one that gets done" and that maximizing the total proportion of the eligible population that receives screening will "result in the greatest reduction in deaths due to CRC"^[1]. As such, the clinical and modeling evidence and societal need for improved noninvasive screening strategies support a USPSTF recommendation for mt-sDNA for routine screening at three-year intervals, a conclusion consistent with the recommendations of others.

Failure to include a clear recommendation of mt-sDNA3y in the final USPSTF guideline may limit access to mt-sDNA for Americans not covered by Medicare. By only recommending the same tests as were recommended in 2008, the USPSTF draft recommendation limits significant progress in improving United States screening rates^[13,14] by affirming the current approaches only. In order to increase the screening rate, we must offer more efficacious choices. mt-sDNA3y for routine screening provides an opportunity to expand the pool of screened patients and to increase the quality of screening among those choosing non-invasive approaches.

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