MULTITARGET STOOL DNA COLORECTAL CANCER SCREENING TEST DOSSIER

EVIDENCE FOR COVERAGE

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LABORATORY INFORMATION

The Cologuard® (mt-sDNA) test is a proprietary test provided by Exact Sciences Laboratories, LLC. Cologuard is exclusively processed at Exact Sciences Laboratories, LLC and is not available through any other laboratory. There are no other labs that offer a comparable stool DNA test for colorectal cancer screening.

Exact Sciences Laboratories, LLC has a Clinical Laboratory Improvement Amendments (CLIA) Certification of Accreditation and is College of American Pathologists (CAP) accredited. It holds Clinical Laboratory Licenses/Permits in New York, Illinois, Maryland, Rhode Island, California and Pennsylvania.

Exact Sciences Laboratories, LLC is located in the state of Wisconsin, and services patients in all US states, territories, and the District of Columbia.

Full prescribing information is available at www.cologuardhcp.com.

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ABBREVIATIONS

ACG	American College of Gastroenterology	**Hs-FOBT**	High-Sensitivity Fecal Occult Blood Test
ACP	American College of Physicians	**HCP**	Health Care Provider
ACS	American Cancer Society	**HGD**	High-Grader Dysplasia
ACTB	Beta-actin	**iFOBT**	Immunochemical Fecal Occult Blood Test
AJCC	American Joint Committee on Cancer	**LYG**	Life-Year Gained
AMA	American Medical Association	**mt-sDNA***	Multitarget stool DNA (Cologuard)
BMP3	Bone morphogenetic protein 3	**MSTF**	United States Multi-Society Task Force
CAP	College of American Pathologists	**NCCN®†**	National Colorectal Cancer Network
CDC	Centers for Disease Control and Prevention	**NCD**	National Coverage Decision
CISNET	Cancer Intervention and Surveillance Modeling Network	**NCHS**	National Center for Health Statistics
CLIA	Clinical Laboratory Improvement Amendments	**NCI**	National Cancer Institute
CMS	Centers for Medicare and Medicaid Services	**NDRG4**	N-myc Downstream-regulated Gene 4
CRC	Colorectal Cancer	**QuARTS**	Quantitative Allele-specific Real-time Target and Signal
CTC	Computed Tomography Colonoscopy	**QALY**	Quality-adjusted Life-year
FIT	Fecal Immunochemical Test	**RCT**	Randomized Controlled Trial
FIT-DNA	Cologuard (as defined by USPSTF)	**sDNA**	Stool DNA Test
FIT-fecal DNA	Cologuard (as defined by MSTF)	**SEER**	Surveillance, Epidemiology, and End Results Program
FDA	United States Food and Drug Administration	**SRN**	Screening-relevant Colorectal Neoplasia
FS	Flexible Sigmoidoscopy	**SSA**	Sessile Serrated Adenoma
HEDIS®‡	Healthcare Effectiveness Data and Information Set	**USPSTF**	United States Preventive Services Task Force

* May be referred to as FIT-DNA, FIT-fecal DNA, or sDNA as indicated by third party publications
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1.0 EXECUTIVE SUMMARY

Cologuard, the first and only US Food and Drug Administration (FDA) approved multitarget stool DNA (mt-sDNA) test, is a noninvasive colorectal cancer (CRC) screening test developed by Exact Sciences Corporation, covered by Centers for Medicare and Medicaid Services (CMS), and available by prescription for use by adults aged ≥50 years at average risk for CRC. The mt-sDNA test was the first medical product to successfully navigate the joint FDA-CMS parallel review process; receiving premarket approval from the FDA on August 11, 2014, and a CMS National Coverage Decision (NCD) on October 9, 2014.[1-3]

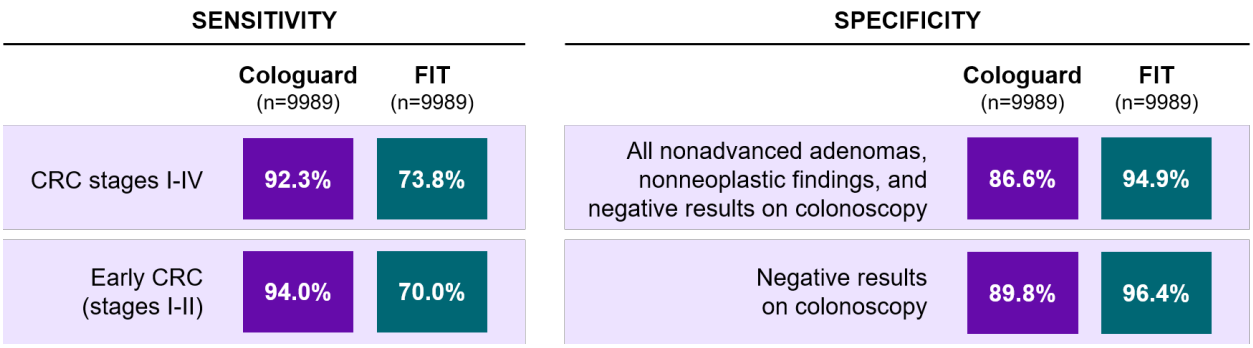
On September 20, 2019, the FDA expanded approval of the mt-sDNA test for use by adults ≥45 years at average risk for CRC. Test performance in patients ages 45 to 49 years was estimated by sub-group analysis of near-age groups and supported by retrospective data analysis. Expansion of the screening age for CRC is expected to have a substantial impact on the utilization of screening resources.[4, 5] Based on the current US population and available data regarding prevalence of risk factors in people aged 45 to 49 years, it is estimated that expansion of the CRC screening eligible population down to age 45 years will result in an additional 19 million adults at average risk.[§6]

1.1 Screening Test Performance

Results from the pivotal study, a prospective, 90-site, 10,000-patient cross-sectional randomized, controlled study were published in the *New England Journal of Medicine* in April 2014.[7] The "Multitarget Stool DNA Testing for Colorectal-Cancer Screening" study compared mt-sDNA (Cologuard) and fecal immunochemical test (FIT)[**], using colonoscopy as the reference standard in all cases. The study demonstrated that mt-sDNA was superior to FIT (Figure 1) for detecting CRC, especially early-stage CRC, as well as advanced and non-advanced adenomas. Mt-sDNA demonstrated sensitivity superior to FIT at 92% of that seen with colonoscopy in detecting CRC (74% for FIT). Specificity was 87% for findings other than CRC or advanced precancerous lesions (95% for FIT) and 89.8% relative to negative findings on colonoscopy (96.4% for FIT).

§ Estimate based on the US population aged 45-74 as of 2018, adjusted for the reported rates of high-risk conditions and prior screening history for CRC.
** OC FIT-CHEK, Polymedco, Inc.

Figure 1. Sensitivity and Specificity of mt-sDNA and FIT for Detecting CRC in the Pivotal Study, with Colonoscopy Used as Reference [8, 9]



1.1.1 Performance in Age Group 45 to 49

The Act Now study was a prospective, cross-sectional study to evaluate mt-sDNA (Cologuard) for CRC screening in individuals aged 45 to 49 and at average risk for development of CRC, using colonoscopy as the reference method.[10] The primary objective was to confirm the specificity of mt-sDNA (Cologuard) in an average risk population, aged 45 to 49. Secondary outcome measures included sensitivity of mt-sDNA (Cologuard) for CRC and advanced precancerous lesions (APL), positive and negative predictive values, positive and negative likelihood ratios, distribution of colorectal epithelial lesions among positive mt-sDNA (Cologuard) test, and the rate of no mt-sDNA (Cologuard) result.

A total of 983 participants were enrolled. The evaluable cohort included 816 individuals and was 47.7% female. The mean age was 47.8 years (SD 1.5). No CRC was found among the evaluable individuals. Fifty-three individuals (6.5%) had a positive mt-sDNA test result. Specificity was 95.2% (95% CI: 93.4-96.6%) among participants with non-advanced findings or negative colonoscopic findings, with 37 participants of 767 with a positive result. Specificity was 96.3% (CI: 94.3-97.8%) in those with negative colonoscopic findings, with 19 of 514 participants with a positive result. Specificity did not differ by sex or race among participants with non-advanced neoplasia or negative findings. Variations in specificity by age were not evaluated due to the narrow range of ages in this study.

Sensitivity for APL was 32.7% (CI: 19.9-47.5%) with mt-sDNA detecting 16/49 participants. Estimation of sensitivity by APL size or location was not possible due to the low prevalence of CRC and APL in this study. There was no specific pattern of APL detection based upon anatomic site, supporting the consistent detection of APL by mt-sDNA (Cologuard). The positive and negative predictive values (PPV, NPV) in this study were 30.2% and 95.7%, respectively, with a positive likelihood ratio of 6.77 (CI: 4.06-11.28) and a negative likelihood ratio of 0.71 (CI: 0.58-0.86). The area under the receiver operating characteristics curve (AUROC) was 0.72 (CI: 0.64-0.81) for distinguishing between APL and lesser findings, including non-advanced adenomas or negative findings, among participants aged 45 to 49 years old. This AUC is comparable to the AUC participants 50 years and older in the pivotal study for this test (0.73, CI: 0.69-0.74).[7, 11]

The low prevalence of advanced neoplasia (CRC and APL) in this patient population precludes a precise estimate of mt-sDNA and limits the interpretation of the APL sensitivity. To obtain a reasonable measure of sensitivity 20X more participants would be needed. Selection bias may have influenced study enrollees as they were self-selected, nonconsecutively, to complete a screening colonoscopy. It is unclear whether this represents the average-risk spectrum of adults who are 45-49 years of age. Additionally, most participants were white (83.9%) and the results of this study may not be generalizable to other racial and ethnic populations within the US. Further, the CRC screening adherence characteristics of the patients in this patient population are not well defined as guidelines have not previously included this age group. This study does not consider patient perspectives including preferences, uptake, adherence, and cost. Considering these perspectives is needed to understand real-world uptake of any CRC screening test.

Table 1. Test performance in the evaluable cohort[10]

	Overall Findings†				
	Total	CRC	APL	Non-advanced Neoplasia	Negative Findings
n (%)‡	816	0 (0.0%)	49 (6.0%)	253 (31.0%)	514 (63.0%)
mt-sDNA Positive	53	0	16	37	19

Most Advanced Finding	Colonoscopy (n=816)	mt-sDNA (n=816)§	
	n	Positive Results, n	Specificity, % (95% CI)
All non-advanced, non-neoplastic* findings, and negative results on colonoscopy	767	37	95.2 (93.4-96.6)
Negative results on colonoscopy	514	19	96.3 (94.3-97.8)

Retrospective data were collected to evaluate whether mt-sDNA performance in samples from patients ages 45 to 49 years is comparable to that achieved in samples obtained from patients ages 50 and older.[8] Through September 2018, there had been 2241 completed tests (through Exact Sciences Laboratories) aged 45 to 49 years. It is unknown if these patients were at average risk for CRC. Of these tests, 7.4% (165/2241) had a positive result and 92.6% (2076/2241) had a negative result, indicating the specificity in this age group is ≥92.6%, which is comparable to the specificity of patients ages 50 to 59 from the pivotal study.[7] Follow-up data were not available from the 2241 completed tests to confirm CRC outcomes for either positive or negative results.

1.2 Product Use in the Health Care System

Health care providers can order the mt-sDNA test for their patients using paper fax, eFax, HL7, or through the Exact Sciences Laboratories secure provider ordering portal. The mt-sDNA Collection Kit is shipped directly to the patient. Patients then provide a stool specimen at home, which is shipped directly to Exact Sciences Laboratories for processing. Mt-sDNA provides a single qualitative positive or negative test result based on the composite score generated by an algorithm that uses the quantitative values of ten DNA biomarkers and fecal hemoglobin present in the stool. There are no reportable individual biomarker results. A positive mt-sDNA result may indicate the presence of CRC or advanced adenomas and should be followed by diagnostic colonoscopy. A negative mt-sDNA result does not guarantee the absence of cancer or advanced adenoma. A negative test result means that the test did not detect abnormal DNA and/or blood in the sample. Following a negative result, a patient should continue participating in a screening program at an interval and with a method appropriate for the individual patient.[8] Mt-sDNA testing is supported by Exact Sciences Laboratories' 24/7 patient navigation system utilizing a US based call center that supports over 100 languages to ensure adherence with the CRC screening order.

Mt-sDNA coverage evaluation considerations may include:

PERFORMANCE: Mt-sDNA provides CRC screening with high sensitivity and good specificity as demonstrated in the pivotal study published in the *New England Journal of Medicine* (Figure 1).[7] The high sensitivity of mt-sDNA and good specificity were confirmed in the Redwood et al study published in the *Mayo Clinic Proceedings*.[7, 12] The mt-sDNA test is highly specific among average-risk 45 to 49-year-olds, supporting its usage as a noninvasive option for CRC screening in this age group (Table 1).[10]

PATIENT ACCEPTABILITY: Mt-sDNA is a noninvasive CRC screening test designed to help address some of the barriers to patient acceptance and promote high adherence rates. The mt-sDNA compliance rate of 66% represents the cumulative completed tests from kits shipped to patients during the 6-month period ending 12 months prior to June 30, 2020, excluding program orders,[13] which compares favorably with 43-48% compliance in a first round annual fecal occult blood testing.[14, 15] Additional studies have shown lower compliance rates with FIT in subsequent years.[16]

In a real-world analysis of a large, nationally representative population of Medicare beneficiaries, 71% of patients who were prescribed mt-sDNA (Cologuard) for CRC screening completed the test.[17] A majority (61.5%) of patients in the study population who completed the test did so within the first 30 days of receiving it, corresponding to when the mt-sDNA patient navigation program is most active. The study noted that patient factors such as age, sex, Medicare coverage type, geography, or test order date did not affect the rate of mt-sDNA test completion.

The mt-sDNA screening system is comprised of the test itself and the mt-sDNA Compliance Program, a 24/7 nationwide patient navigation system. The patient navigation system is a critical component supporting population health and mt-sDNA value. In large part, it addresses the burdens associated with patient instruction and

tracking, as well as providing providers with ad hoc access to patient status and reports through a dedicated portal.

ADHERENCE WITH CRC SCREENING: In a survey of 3,847 patients conducted by Exact Sciences Laboratories between June 2017 and June 2018, 48% indicated that they had never been screened for CRC prior to their mt-sDNA test.[13] Mt-sDNA adherence in 393 previously non-compliant Medicare beneficiaries (age 50-85) at a single multispecialty group practice (USMD Physician Services, Dallas, TX) was reported at 88%; follow-up diagnostic colonoscopies on mt-sDNA positive cases were completed in 96% of cases.[18]

THE IMPORTANCE OF CHOICE: Current guidelines from ACS and USPSTF emphasize the importance of shared decision making, including consideration of patient preferences and practical implications.[19, 20] Data from a trial by Inadomi demonstrated a significant improvement in patient adherence when patients are offered a choice between a noninvasive screening option (FOBT) or a screening colonoscopy (68%) versus a screening colonoscopy only (38%) (*P*<.001).[††21] An extension of the Inadomi study illustrated that patients offered a choice between FOBT and colonoscopy continue to have high adherence over 3 years while adherence in the FOBT only arm fell significantly (67% in year 1, 27% in year 2, and 14% in year 3).[22]

1.2.1 CRC Screening Guidelines and Recommendations

In the 2018 update, the American Cancer Society Colorectal Cancer Screening Guideline lowered the recommended age to start CRC screening from 50 to 45 for patients at average risk for CRC and included the use of the multi-target stool DNA test (Cologuard) for cancer screening within that recommendation, along with other stool-based non-invasive tests and structural (visual) examination options, depending on patient preference and test availability.[23] The ACS based their qualified recommendation on CRC incidence and mortality rates, results from microsimulation modeling that demonstrate a favorable benefit-to-burden balance of screening beginning at age 45, and the expectation that screening will perform similarly in adults ages 45 to 49 as it does in adults ages 50 and older.

Since June 2016, mt-sDNA[‡‡] has been recognized by the US Preventive Services Task Force (USPSTF) under their “A” rating for CRC screening as one of several equally positioned screening strategies.[24] In 2021, the USPSTF released an updated recommendation statement on screening for CRC.[20] With this update, the USPSTF continues to recommend screening for CRC in all adults ages 50 to 75 (Grade A).[§§] The USPSTF also recommends that clinicians selectively offer screening for CRC in adults ages 76 to 85 years based on a patient’s overall health and prior screening history (Grade C).[***] New within this update is the recommendation to

[††] FOBT-only compliance was not statistically different vs choice arm.
[‡‡] Guidelines may refer to mt-sDNA by different names including FIT-Fecal DNA, sDNA and sDNA-FIT.
[§§] Grade A: The USPSTF recommends the service. There is high certainty that the net benefit is substantial.
[***] Grade C: The USPSTF recommend selectively offering or providing this service to individual patients based on professional judgement and patient preferences. There is at least moderate certainty that the net benefit is small.

screen for CRC in adults ages 45 to 49 (Grade B).††† Mt-sDNA continues to be recognized as one of the recommended CRC screening modalities. This recommendation statement applies to asymptomatic adults age 45 years and older who are at average risk of CRC (ie, no prior diagnosis of CRC, adenomatous polyps, or inflammatory bowel disease or a family history of known genetic disorders that predispose them to a high lifetime risk of CRC [such as Lynch syndrome or familial adenomatous polyposis]).

The USPSTF recommendation includes stool-based tests with high sensitivity, colonoscopy, computed tomography (CT) colonography, and flexible sigmoidoscopy. Positive results on stool-based screening tests require follow-up with colonoscopy for the screening benefits to be achieved. The USPSTF recognizes that the benefits of screening can only be fully achieved when follow-up of abnormal screening test results is performed.

"Because no direct evidence compares different screening tests, and because local resources or patient factors may influence feasibility of different screening strategies, the USPSTF is unable to determine which tests are unequivocally 'better' or 'worse'."

The recommendation statement also recognizes the different considerations that apply to each CRC screening test that can impact patient adherence. Where the screening test is performed, who performs the screening procedure, the need for pre-procedure bowel preparation, the need for anesthesia or sedation during the test, and follow-up procedures for abnormal findings on a screening test may all influence patient adherence. The USPSTF recommends discussion of screening considerations between health care providers and patients to identify the screening test that is more likely to be completed.

The March 2021 update to the NCCN guidelines for colorectal cancer screening updated the recommended age to begin screening to 45 years.[25] This is based on data from modeling studies and the relative increase in CRC incidence in 40 year olds. The guidelines note that data is lacking to support screening in those <50 years largely due to screening studies focusing on the over 50 population. Race/ethnicity, patient preference, and available resources should all be considered when determining the age to initiate CRC screening, according to the NCCN, and the choice of a particular screening modality should include a conversation between the patient and provider to ensure that testing characteristics algin with patient preferences. The use of mt-sDNA is also recommended in several other guidelines regarding CRC screening (Table 2).

††† Grade B: The USPSTF recommends this service. There is high certainty that the net benefit is moderate or there is moderate certainty that the net benefit is moderate to substantial.

Table 2. Current Screening Recommendations for Stool-based DNA Tests

Organization	Recommendations
National Comprehensive Cancer Network®‡‡‡ (NCCN®) (2021)	mt-sDNA-based testing for average risk screening at 3-year intervals[25]
American College of Gastroenterology (ACG)(2021)	mt-sDNA suggested at 3-year intervals for patients unwilling or unable to undergo colonoscopy or FIT[26]
United States Preventive Services Task Force (USPSTF) (2021)	sDNA-FIT for average risk screening at 1 to 3 year intervals[20]
American Cancer Society (ACS) (2018)	mt-sDNA for average risk screening at 3-year intervals[23]
United States Multi-Society Task Force (MSTF) (2017)	FIT-fecal DNA every 3 years (Tier 2)[27]

The National Committee for Quality Assurance (NCQA®) includes stool DNA (mt-sDNA, Cologuard) in the Health Effectiveness Data and Information Set (HEDIS®)§§§ of quality measures for CRC screening****. The inclusion of mt-sDNA in the HEDIS® measures allows payers, health systems, and providers the opportunity to receive quality credit for a three-year lookback period during HEDIS® audits (the HEDIS® audit credit period for mt-sDNA includes the measurement year or the two years prior to the measurement year). To the extent that organizations utilize HEDIS® measures to track CRC screening performance and outcomes, mt-sDNA is included for quality credit.[28]

Based on data from the National Health Interview Survey, the Centers for Disease Control and Prevention (CDC) calculates that in 2018, the most recent data available, only 67% of Americans aged 50-75 were up-to-date with the recommended CRC screening guidelines.[29] Less than half of adults aged 50-54 years and only 21% of adults aged 45-49 years report recent screening for CRC.

A longitudinal study of more than 150,000 patients demonstrated that one-third of eligible adults over 50 failed to be adherent with CRC screening recommendations of the USPSTF over a ten-year period. The study, published in *American Journal of Managed Care*, further shows that only three in a thousand people (0.3 percent) were adherent with annual CRC screening using either FIT or FOBT during a continuous ten-year observation period.[30]

1.3 Economic Benefits

CLINICAL UTILITY: Peer-reviewed papers discussing the clinical utility of mt-sDNA include the following:

- *Real world healthcare impact on adherence*: A twelve-month study of mt-sDNA use demonstrated that 77 providers from the USMD Health System in Texas, ordered mt-sDNA tests for 393 Medicare patients noncompliant with CRC screening and 347 patients

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**** Third-party guidelines and quality measures do not specifically "endorse" commercial products, and inclusion in same does not imply otherwise.

completed mt-sDNA for an adherence rate of 88%. The mt-sDNA result was negative for 296 patients (85%) with 51 (15%) testing positive. Of those 51 positive-result patients, 49 completed their diagnostic colonoscopies resulting in an adherence rate of 96%.[18] A study by McCarthy et al. evaluated timely follow-up of abnormal FOBT/FIT tests compared to abnormal mammograms by race/ethnicity. For FOBT/FIT tests, timely follow-up was defined as a colonoscopy within 3 months of a positive test result. Data showed that only 68% of the subjects who had a positive FIT/FOBT test result pursued a timely follow-up colonoscopy.[31]

- *Improving the value of diagnostic colonoscopy*: A matched cohort study measured the impact that knowledge of a positive mt-sDNA test result has on colonoscopy yield and quality. A group of unblinded, retrospectively-identified patients who underwent colonoscopy following a positive mt-sDNA test result (n=172) was matched with a group of blinded, positive mt-sDNA test patients participating in a clinical trial (n=72). The study determined that knowledge of positive mt-sDNA test results can have a beneficial impact on the value of the subsequent follow-up diagnostic colonoscopy, resulting in twice the median number of polyps detected (*P*=0.0007) and significantly higher rates of total adenomatous/sessile serrated polyps detected (*P*=0.013).[32] In a retrospective, consecutive series cohort study evaluating the real-world performance characteristics of mt-sDNA at multiple Mayo Clinic sites, mt-sDNA demonstrated a high positive predictive value (PPV) for any colorectal neoplasia (CRN; colorectal cancer, advanced precancerous lesions, or sessile serrated polyps) regardless of prior screening colonoscopy.[33] Among the cohort of patients who completed the mt-sDNA test, 14% (2326/16,469) had a positive test result. Adherence to follow-up colonoscopy after a positive mt-sDNA test result in average risk patients was high, at 87% (1,558/1,801). Of the 1,558 mt-sDNA test positive patients who underwent a follow-up colonoscopy, CRN was identified in 1,067, resulting in a PPV of 67%. The majority (79%) of patients with neoplastic lesions detected by mt-sDNA had at least 1 right-sided lesion. The overall PPV for right-sided CRN was 53%. The proportion of patients with positive colonoscopy findings following a positive mt-sDNA result was high regardless of colonoscopy screening history (73% vs 63% in those with prior screening colonoscopy).

- *Follow-up colonoscopy completion:* A retrospective cohort study within a vertically integrated healthcare system demonstrated that adherence to follow-up colonoscopy after a positive mt-sDNA test was higher than for those with a positive FIT.[34] Patients with a positive mt-sDNA test also completed a colonoscopy in less time than those with a positive FIT. Of 631 identified patients, 308 had a positive FIT and 323 had a positive mt-sDNA result. Patients with a positive FIT completed a follow-up colonoscopy within 6 months 46.7% of the time (144/308 patients) compared to 71.5% of the time (231/323 patients) for patients with a positive mt-sDNA result. The median time to follow-up for a patient with a positive FIT was >6 months compared to a median time of 2.2 months (95% CI, 1.80-2.52 months) for patients with a positive mt-sDNA result. Patients with a positive mt-sDNA test were nearly twice as likely to have a follow-up COL within six months (hazard ratio, 1.83; 95% CI 1.48-2.25). The study also evaluated barriers to follow-up colonoscopy and identified barriers at multiple levels (patient-, provider-, and system-level). Reasons for lack of follow-up were generally similar between the two modalities, and included prior recent colonoscopy, assumed false positive/positive result associated with other colorectal pathology, and colonoscopy refusal or appointment cancellation. In some cases, the reason for nonadherence was not known. Of those who did not complete a colonoscopy after a positive

FIT, colonoscopy was not ordered in 82.3% of patients compared to 49% of patients with a positive mt-sDNA result. Among the 144 patients with a positive FIT who underwent colonoscopy, precancerous or malignant lesions were found in 48.6% of patients. In the 231 patients with positive mt-sDNA testing, precancerous or malignant lesions were found in 77.1% of patients.

- *No need for further evaluation of mt-sDNA-positive/colonoscopy-negative patients*: A retrospective cohort study of the pivotal trial evaluated the incidence of aerodigestive cancers in 1216 patients who had negative colonoscopy findings to determine if those with positive (discordant) mt-sDNA test results were at an increased risk. Those patients with negative colonoscopy and negative (concordant) mt-sDNA test results served as the reference group. The study found that the rate of aerodigestive cancer was similar between the two groups and both were lower than the expected rate for this population based on SEER data. The authors concluded that false-positive mt-sDNA results does not warrant further testing.[35]

- *Mt-sDNA is cost effective vs. not screening*: Modeling is particularly important when assessing the clinical utility and economic value of a non-pharmaceutical product. A study using the Archimedes cost-effectiveness model, created by the ACS and Archimedes Inc., provided data supporting the clinical effectiveness and cost effectiveness of a three-year testing interval for mt-sDNA. The model demonstrates that mt-sDNA used every three years compares favorably to colonoscopy every 10 years. The analysis shows a CRC incidence reduction of 57% and mortality reduction of 67%, compared to 65% and 73% respectively, for colonoscopy every 10 years. The cost per quality adjusted life year (QALY) of screening every 3 years with mt-sDNA resulted in $11,313/QALY compared to no screening.[36]

- *Modeling data is often used to inform guidelines*, including those for CRC screening.[24] Key assumptions that may impact the outcomes of CRC screening modeling estimates include assumptions of 100% adherence to screening and follow-up, screening start age, delays in screening, and alignment of screening interval. Real-world data suggest that actual adherence to stool-based testing is well below 100%.[17] Real-world evidence-based adherence values used in comparative effectiveness models more accurately assess the impact of CRC screening on health system populations. Data from a recently developed Colorectal Cancer and Adenoma Incidence and Mortality Microsimulation Model (CRC-AIM) using real-world data for adherence of stool-based testing and for colonoscopy follow-up of a positive initial CRC screening illustrate the comparative effectiveness of CRC screening strategies. When modeling real-world adherence rates of 40% for annual FIT and 70% for triennial mt-sDNA derived from a critical assessment of meta-analyses and retrospective cross-sectional data in systems using FIT without a navigation program, the number of life years gained (LYG) as well as reductions in CRC incidence and mortality were higher for triennial mt-sDNA than annual FIT.[17, 37, 38] Adherence to stool-based CRC screening tests appears to be an important, yet under-appreciated, factor when assessing the relative comparative-effectiveness of CRC screening.

- *Mt-sDNA three-year interval and mortality benefit supported by analysis of USPSTF Technical Data*: A study analysis using the data from the CISNET modeling group which used three models (MISCAN, SIMCRC, CRC-SPIN) to provide data from the USPSTF

evidence review, demonstrate that mt-sDNA used at a three-year interval is within 98% of the USPSTF's efficiency frontier and is the only multi-year interval, noninvasive test to generate greater than 90% of the LYG by screening colonoscopy at 10-year interval in at least one model.[39]The use of the “efficiency ratio” and the performance calculated above, support the inference of the mt-sDNA test’s positive CRC related mortality and incidence reduction, from five randomized control trials of gFOBT every two years, which show a mortality benefit.[40]

- *Mt-sDNA used every three years has the best ratio of hazards (complications) to benefits (LYG) of all USPSTF recommended options*: Analysis of the USPSTF Technical Report CISNET modeling data demonstrates the efficacy of mt-sDNA at three-year intervals and demonstrates across 1000 screened individuals, age 50-74, that it yields a median of 226 life-years gained, averts 20 CRC deaths, reduces CRC mortality by 76%, and produces the most benefit (LYG) per complication. The data further demonstrates that the number of colonoscopies per LYG generated by mt-sDNA at three-year intervals is equivalent to annual FIT and lower than high sensitivity (hs)FOBT.[39]

MT-SDNA EXTERNAL REVIEW: UpToDate®, an online, evidence-based, physician-authored clinical decision support resource accessed by over one million clinicians references the use of mt-sDNA every 3 years as a CRC screening option for average-risk patients.[41]

MT-SDNA HAS BROAD PAYER COVERAGE: Based on the pivotal mt-sDNA study and the positive decisions of the FDA and CMS, numerous commercial health plans have extended coverage to mt-sDNA as the data describing its performance compares well with technology assessment criteria and conditions for coverage by commercial health plans. As a result, mt-sDNA has achieved a broad coverage footprint of over 289 million Americans in the Medicare program and commercial health plans.[13]

As of December 2020, over 95% of all Americans ages 50 and older have coverage for mt-sDNA as a CRC screening test.[13]

- CMS: Since October 9, 2014, CMS has extended coverage to mt-sDNA through NCD 210.3 (Colon Cancer Screening Tests). Mt-sDNA is covered as frequently as every three years for use in asymptomatic patients age 50-85 who are at average risk for CRC, independent of the use of any other CRC screening test.[2]

- The number of screening eligible patients with preventive services coverage may continue to grow as payers, providers, professional societies and guideline organizations weigh the decision to follow the ACS’ qualified recommendation to begin screening at age 45.[23]

- State mandated coverage: As of March 2020, CRC screening is mandated for fully insured commercial plans in approximately 29 states and the District of Columbia with rules requiring coverage of mt-sDNA.

INCORPORATING MT-SDNA INTO A CRC SCREENING PROGRAM: Colonoscopy costs are heavily burdened by the effects of poor preparation and screening overuse. Poor bowel preparation alone accounts for 15-25% of failed colonoscopies,[42] resulting in significant additional costs to

payers, employers, and patients due to time lost from work. Published claims data from a national commercial health plan shows that the average cost of colonoscopy is $2,146 while the CDC Colorectal Cancer Control Program averages the cost of colonoscopy programs to be $3,153 over a 5-year timeframe, compared with $1,057 for noninvasive tests.[42, 43] Mt-sDNA is not only less costly than colonoscopy as a non-invasive test, but as a single-source testing method via Exact Sciences Laboratories, can monitor all users within a secure patient database reducing the number of unnecessary or duplicate tests provided.

Furthermore, even a lower negotiated rate for colonoscopy does not alleviate the cost of colonoscopy overuse for payers; 34% of colonoscopies are repeated too early, typically between five and six years after initial screening.[44] Claims for reimbursement are only filed for mt-sDNA tests that have an actionable positive or negative result. There is no additional billing for repeat testing required due to patient or technical issues. Also, mt-sDNA pricing includes the cost for the dedicated patient navigation system.[13]

MT-SDNA HAS A UNIQUE CURRENT PROCEDURAL TERMINOLOGY (CPT) CODE (81528): This allows for easy unequivocal utilization and quality report tracking. On January 1, 2016, a new Category I CPT code became effective for mt-sDNA: “Oncology (colorectal) screening, quantitative real-time target and signal amplification of 10 DNA markers (KRAS mutations, promoter methylation of NDRG4 and BMP3) and fecal hemoglobin, utilizing stool, algorithm reported as a positive or negative result.” Mt-sDNA (Cologuard) is the only test that fits the long description at the present time. Category I codes are only assigned to products that have FDA approval or clearance (if such approval is required), are widely used by physicians in a manner that is consistent with current medical practice, and which have documented clinical efficacy. Specific coding for mt-sDNA (Cologuard) has been in effect since January 1, 2015.[45]

CENTERS FOR MEDICARE AND MEDICAID SERVICES (CMS) NATIONAL COVERAGE DETERMINATION FOR MT-SDNA CRC SCREENING TOOL: This affects both traditional Medicare and Medicare Advantage patients. On August 8, 2016, CMS issued an updated Evidence of Coverage notice for Medicare Advantage plans that affirms that such plans must include coverage of mt-sDNA every three years without patient coinsurance, copayments, or deductibles. This is significant because it reflects recognition from CMS that mt-sDNA is included among A-graded preventive services under the recently updated USPSTF CRC screening recommendations.[46]

1.4 Conclusions

In summary, mt-sDNA is an evidence-based, validated, noninvasive screening test for CRC and advanced colorectal precursor lesions. Mt-sDNA is supported by a nationwide patient navigation system that promotes high test completion rates and successful screening events. Mt-sDNA obtained FDA approval through the rigorous FDA/CMS parallel review process, an industry first, and is supported by significant peer-reviewed publications in high quality scientific journals documenting its sensitivity and specificity.

In addition to being covered by most commercial health plans, mt-sDNA is covered through a mt-sDNA-specific Medicare NCD, which requires coverage in traditional Medicare and Medicare Advantage health plans nationwide. Mt-sDNA has achieved coverage of 95% of the addressable 50 and older clinical population since its launch.[13, 47]

The 2021 USPSTF recommendations for CRC screening include mt-sDNA testing every one to three years, with a rating of “A” for screening average-risk patients ages 50 to 75 and a rating of “B” for screening average-risk patients ages 45-49, as one of several equally positioned screening tests.[48] The ACS Colorectal Cancer Screening Guidelines (2018) and the NCCN®†††† Guidelines (2021) support mt-sDNA testing every three years.[23, 25]

The list price of mt-sDNA is US $681 as of April 1, 2021.

Extending coverage to mt-sDNA and incorporating it into an established screening program is an important step toward limiting the population burden of CRC. For all the above reasons, payer stakeholders should review the data presented in this dossier and consider extending coverage and a network agreement for mt-sDNA.

†††† NCCN® makes no representations or warranties of any kind regarding their content, use or application and disclaims any responsibility for their application or use in any way.

2.0 PRODUCT INFORMATION AND DISEASE DESCRIPTION

2.1 Product Description

INDICATIONS

Cologuard is intended for the qualitative detection of colorectal neoplasia associated DNA markers and for the presence of occult hemoglobin in human stool. A positive result may indicate the presence of CRC or advanced adenoma and should be followed by diagnostic colonoscopy. Cologuard is indicated to screen adults of either sex, 45 years or older, who are at typical average-risk for CRC. Cologuard is not a replacement for diagnostic colonoscopy or surveillance colonoscopy in high risk individuals.[8]

CONTRAINDICATIONS

Cologuard is intended for use with patients, age 45 years and older, at average risk who are typical candidates for CRC screening. Cologuard was not clinically evaluated for the following types of patients[8]:

- Patients with a history of colorectal cancer, adenomas, or other related cancers
- Patients who have had a positive result from another colorectal cancer screening method within the last 6 months
- Patients who have been diagnosed with a condition that is associated with high risk for colorectal cancer. These include but are not limited to:
    - Inflammatory Bowel Disease (IBD)
    - Chronic ulcerative colitis (CUC)
    - Crohn's disease
    - Familial adenomatous polyposis (FAP)
    - Family history of colorectal cancer
- Patients who have been diagnosed with a relevant familial (hereditary) cancer syndrome, such as:
    - Hereditary non-polyposis colorectal cancer syndrome (HNPCC or Lynch Syndrome)
    - Peutz-Jeghers Syndrome
    - MYH-Associated Polyposis (MAP)
    - Gardner's syndrome
    - Turcot's (or Crail's) syndrome
    - Cowden's syndrome
    - Juvenile Polyposis
    - Cronkhite-Canada syndrome
    - Neurofibromatosis
    - Familial Hyperplastic Polyposis

WARNINGS AND PRECAUTIONS*

- The performance of Cologuard has been established in a cross-sectional study (i.e., single point in time). Programmatic performance of Cologuard (i.e., benefits and risks with repeated testing over an established period of time) has not been studied. Performance has not been evaluated in adults who have been previously tested with Cologuard. Non-inferiority or superiority of Cologuard programmatic sensitivity as

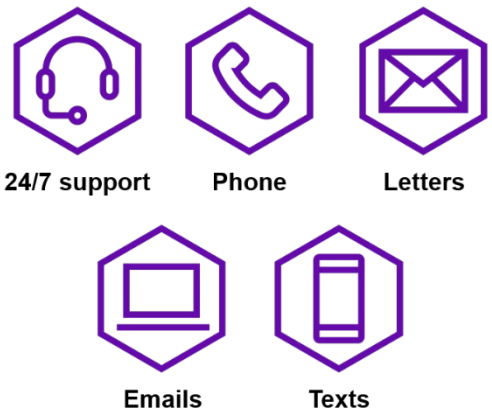
compared to other recommended screening methods for CRC and AA has not been established.

- The clinical validation study was conducted in patients 50 years of age and older. ACS Guidelines recommend screening begin at age 45. Cologuard performance in patients ages 45 to 49 years was estimated by sub-group analysis of near-age groups.
- CRC screening guideline recommendations vary for persons over the age of 75. The decision to screen persons over the age of 75 should be made on an individualized basis in consultation with a healthcare provider. Cologuard test results should be interpreted with caution in older patients as the rate of false positive results increases with age.
- A negative Cologuard test result does not guarantee absence of cancer or advanced adenoma. Patients with a negative Cologuard test result should be advised to continue participating in a colorectal cancer screening program with another recommended screening method. The screening interval for this follow-up has not been established.
- Cologuard may produce false negative or false positive results. A false positive result occurs when Cologuard produces a positive result, even though a colonoscopy will not find cancer or precancerous polyps. A false negative result occurs when Cologuard does not detect a precancerous polyp or colorectal cancer even when a colonoscopy identifies the positive result.
- Patients should not provide a sample for Cologuard if they have diarrhea or if they have blood in their urine or stool (e.g., from bleeding hemorrhoids, bleeding cuts or wounds on their hands, rectal bleeding, or menstruation).
- To ensure the integrity of the sample, the laboratory must receive the patient specimens within 72 hours of collection. Patients should send stool samples to the laboratory according to the instructions stated in the Cologuard Patient Guide.
- Patients should be advised of the caution listed in the Cologuard Patient Guide. Patients should NOT drink the preservative liquid.
- The risks related to using the Cologuard Collection Kit are low, with no serious adverse events reported among people in a clinical trial. Patients should be careful when opening and closing the lids to avoid the risk of hand strain.

* Rx Only

TEST ORDERING, COLLECTION, AND REPORTING

An mt-sDNA (Cologuard) test is ordered by a patient's health care provider (HCP) through the Exact Sciences Laboratories provider ordering portal at www.cologuard.com or through paper requisition. Upon prescribing the test, there is timely contact between the patient and the mt-sDNA (Cologuard) nationwide 24/7 US-based (Madison, WI) patient navigation system, and the following cascade of activities are initiated:



- Welcome call to the patient, which is designed to promote a greater understanding of CRC screening and the mt-sDNA (Cologuard) test
- The patient's shipping address is validated
- The sample collection kit is shipped to the patient via UPS overnight delivery
- Reminder calls to the patient are made if the sample collection kit is not returned. Patients may opt-in to reminder texts and emails.
- A welcome and reminder letter is sent via traditional mail

Once an mt-sDNA (Cologuard) test has been ordered, the collection kit is delivered via UPS to the patient's home, where the patient collects the specimen. The collection kit includes instructions, sample labels, a stool sample collection container, a support bracket for the toilet, a fecal hemoglobin sample tube, a buffer solution for DNA stabilization during sample transport, and a pre-paid UPS return shipping label. All materials are returned in the original sample collection kit box (2). The patient then arranges for the completed kit to be picked up by UPS at the home or leaves it at a drop-off station for transport to Exact Sciences Laboratories where sample analysis occurs. No return office visit is needed.[8]

Patients should not collect their stool for sampling if they have acute diarrhea or are known to have blood in the urine or stool from actively bleeding hemorrhoids, bleeding cuts or wounds on the hands, rectal bleeding, or during a menstrual period. Results are reported directly to the ordering HCP who will communicate the findings to the patient. All positive results are flagged and communicated directly to the ordering HCP in addition to the routine distribution of reports (HCPs may choose to opt out of this service).

In addition, the mt-sDNA (Cologuard) Customer Care Center is available 24 hours per day, 7 days per week, 365 days per year, to answer questions about the test, sample collection, and shipping details in over 100 languages (https://www.cologuard.com/contact). HCPs can access information regarding billing and reimbursement. Patients can also call the Customer Care Center for billing questions and support (eg, if they receive a bill with out-of-pocket responsibilities after using mt-sDNA [Cologuard]).

Figure 2. mt-sDNA (Cologuard) Sample Collection Kit and the Home Sample Collection Process[18]

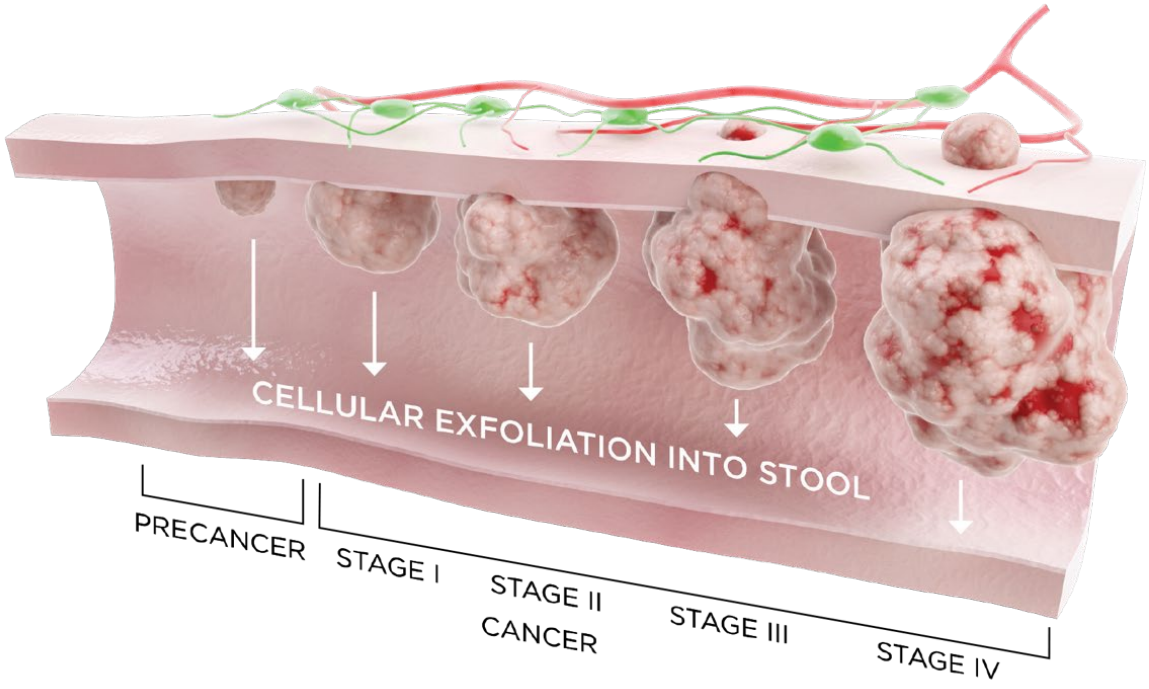
Rx only. Complete product labeling available at Cologuard.com.

TEST AND ASSAY TECHNOLOGY

For the complete description of the mt-sDNA (Cologuard) test and the pertinent assay technology, please see the Summary of Safety and Effectiveness Data (SSED).[49]

The mt-sDNA (Cologuard) test utilizes a multi-target approach to detect eleven distinct biomarkers that are associated with CRC and precancerous lesions. The targeted biomarkers are from three independent categories and provide an additive association with precancerous lesions and CRC.[8] As cancerous lesions and precancerous polyps undergo cellular exfoliation, they shed altered DNA and/or blood into the stool which are then detectable by the mt-sDNA (Cologuard) test (Figure 3). Mt-sDNA (Cologuard) incorporates detection of fecal occult hemoglobin using the mt-sDNA (Cologuard) FIT component, enabling it to detect hemoglobin in the stool samples and enhance overall assay performance. Results from the methylation, mutation, and hemoglobin assays are combined during analysis to determine a single qualitative result, which is either positive or negative.[8]

Figure 3. Shedding of cells from colorectal tumors into stool[9]



The patient stool samples are processed at the laboratory to isolate the DNA for testing. Amplification and detection of methylated target DNA (N-myc downstream-regulated gene 4 [*NDRG4*], bone morphogenetic protein 3 [*BMP3*]), Kirsten Rat Sarcoma 2 Viral gene Homolog (*KRAS*) point mutations, and beta-actin (*ACTB*; a reference gene for quantitative estimation of total amount of human DNA in each sample) is performed using the Quantitative Allele-specific Real-time Target and Signal Amplification (QuARTS™) technology. Multiplexed QuARTS reactions are processed using a real-time cycler with each marker (*NDRG4, BMP3, KRAS*, and *ACTB*) monitored separately through independent fluorescent detection channels. The

hemoglobin stool sample is prepared and analyzed in a quantitative enzyme-linked Immunosorbent Assay (ELISA) that determines the concentration of hemoglobin in the sample.[8]

Run control samples for both the QuARTS and hemoglobin assay are tested along with the patient samples to show that the process has been performed appropriately. Results from the methylation, mutation, and hemoglobin assays are combined during analysis to determine a positive result, negative result, or no result.[8]

2.2 Place of the Product in Therapy

2.2.1 Disease Description

Colorectal Cancer Epidemiology

CRC is the third most commonly diagnosed cancer and the second leading cause of cancer death among men and women combined in the US.[50] Although the highest incidence of CRC is observed in persons aged 50 years and over, over the past decade the frequency of CRC in persons younger than 50 has steadily risen,[51] and individuals younger than 50 years of age currently account for roughly 10% of new CRC cases in the US.[52] Data from The American Cancer Society SEER Database from 2014-2018 shows CRC incidence rates in adults aged <50 increased by 2.3% annually and by 0.3% annually in those ages 50-64, which is a sharp contrast to declines of 3.1% per year in adults ages 65 and older.[54] In addition, CRC incidence has slowed or decreased among adults 55 years and older.[23] Along with increasing incidence, younger adults are more likely to present with a more advanced stage of CRC.[55] A survey of the National Cancer Database in 2015 found 51.6% of patients under age 50 were diagnosed with stage III/IV CRC as compared to 40.0% of patients over 50. Most CRC develops from precancerous growths in the colon and rectum through a well-established progression process that, in most cases, takes several years to occur. CRC is frequently surgically curable, especially if diagnosed at an early stage (per AJCC, Stage I and IIa or IIb). However, symptoms are generally non-specific, which can lead to delays in presentation and diagnosis.[56] As a result, 60% of patients are diagnosed after the cancer has already spread beyond the colon wall (per AJCC Stage IIc and III [regional spread with five-year survival 71.3%] and IV [distant metastases with 5-year survival 14.2%]). However, if CRC is caught before it spreads, the five-year survival in patients is as high as 90%. The five-year survival rate for CRC overall, regardless of stage, is 64.4%.[50] Many patients with early-stage CRC have no symptoms and are diagnosed through screening.[57] As a result, emphasis has been placed on detecting CRC at the earliest possible stage through systematic, universal CRC screening programs.

With the concerning CRC trends in adults younger than 50 years and the mortality benefit from detecting CRC early, efforts are being made to expand the recommended CRC screening population.[53] The ACS updated their CRC screening guidelines in 2018 with a *qualified recommendation* (defined as one for which there is clear evidence of benefit or harm, with less certainty about the balance of benefits and harms or the values and preferences of patients, which can lead to different individual decisions) to initiate CRC screening in average risk adults at age 45 years. The recommendation was designated as qualified since there is limited data on screening outcomes in adults aged 45-49 years as a result of the long-standing recommendation to initiate screening at age 50.[23] Due to the disproportionally high incidence of CRC in African Americans less than 50 years old,[52] MSTF has an exception in their guidelines recommending that African Americans begin CRC screening at age 45 years.[27] In 2021, USPSTF released an updated recommendation statement for colorectal cancer screening.[20] New within the update is the recommendation to screen for CRC in adults ages 45 to 49 (Grade B).‡‡‡‡ In addition to the ACS guidelines and the updated USPSTF recommendations, in 2021

‡‡‡‡ Grade B: The USPSTF recommends this service. There is high certainty that the net benefit is moderate or there is moderate certainty that the net benefit is moderate to substantial.

the American College of Gastroenterology (ACG) and the National Comprehensive Cancer Network (NCCN) updated their guidelines to recommend CRC screening begin at age 45.[25, 26]

Based on the current US population and available data regarding prevalence of risk factors in people aged 45 to 49 years, it is estimated that expansion of the CRC screening eligible population down to age 45 years will result in an additional 19 million adults at average risk.[§§§§6]

2.2.2 Approaches to Screening

The Work-Up and Treatment of Colorectal Cancer

A variety of screening tests allow for the examination of the colon and rectum to detect and diagnose CRC. Once diagnosed numerous factors such as staging, damage to the colon, patient's overall health status, and if it's a recurrence are used to determine the patient's prognosis and appropriate care plan.[58] There are seven different standard treatment options available for CRC with surgery being the most common and utilized across all stages.[58] Late stage and advanced cancers typically require more intensive treatment strategies including chemotherapy, radiation, and/or biologics.

Current Screening Approaches

The stage at which CRC is detected has a dramatic effect on survival;[59] this fact underlies the unanimous support for population-based CRC screening in all guidelines issued by professional medical and public health societies. The majority of guidelines recommend a universal, comprehensive screening program for individuals aged 50-75 and, based on patient specific factors, appropriate patients up to age 85 at average risk for developing CRC.[24, 25, 27] Screening begins at an earlier age for individuals at above-average risk of developing CRC.[24, 25, 27] As this strategy has been employed for a number of years, there is considerable direct and indirect evidence showing that screening programs have been successful in identifying CRC at an earlier stage (known as stage shifting) as well as reducing CRC-attributable morbidity and mortality. An analysis of data from a large insurance health plan showed that there was an initial rise in CRC incidence due to greater detection of early-stage cancers with increased implementation of CRC screening, and then a steady decrease was observed. CRC mortality decreased by more than 50% between 2000 and 2015.[60]

Guideline recommendations also recognize that patient CRC screening test preference and test related issues can hinder progress towards successful universal CRC screening. Two 2021 studies by Zhu, et al investigated patient awareness, preference, and utilization by employing a

§§§§ Estimate based on the US population aged 45-74 as of 2018, adjusted for the reported rates of high-risk conditions and prior screening history for CRC.

likely to prefer stool-based tests (mt-sDNA, FIT/FOBT) over colonoscopy. Participants who had previously heard of, had a healthcare provider recommend (within the last 12 months), or previously had a stool-based CRC screening test preferred stool-based testing, but stool-based testing preference was significantly lower among those who had previously heard of, had a healthcare provider recommend (within the last 12 months), or previously had a colonoscopy. In this study, a higher percentage of older participants (65-75 years old) preferred colonoscopy over stool-based tests compared to those aged 45-64. Half of Hispanic and non-Hispanic Black respondents expressed a preference for stool-based testing over colonoscopy, and specifically mt-sDNA over FIT/gFOBT.[62] There are limitations to these studies as they are survey-based, and rely upon self-reported responses which may be inaccurate due to memory recollection. In addition, only 31.3% of participants contacted provided survey replies. It is possible that there was a non-response bias and the participants who did complete the surveys had an interest in, or felt comfortable with, discussing their opinions regarding CRC screening. However, the findings reported in these studies are in agreement with other studies demonstrating that employment and insurance status, socio-economic status, race/ethnicity, age, and previous experience influence patient awareness, knowledge, preference, and utilization of various screening modalities. Current guidelines include a broad portfolio of validated screening modalities and encourage discussion between healthcare providers and patients regarding the pros and cons of all available CRC screening options; a process known as shared decision-making. Patients can then make informed decisions and choose between more invasive or radiation associated tests (colonoscopy, sigmoidoscopy and CT colonography) or noninvasive stool-based tests like mt-sDNA (Cologuard), FOBT, and FIT[23] based on their personal preferences.

A colonoscopy is one of the direct visualization test options that involves doctors using a colonoscope to examine the entire length of the colon and rectum. This test requires the patient to empty their colon and rectum prior to the procedure by undergoing bowel prep. A sigmoidoscopy is a similar procedure that captures pictures of the colon and rectum, but instead of using a colonoscope it utilizes a sigmoidoscope. The sigmoidoscope is a shorter device that allows the doctors to see the rectum and the lower or distal side of the colon. A computed tomography (CT) colonography, also known as a virtual colonoscopy, uses a CT scanner to take multiple pictures of the colon and rectum as it rotates around you. This test is less invasive than the previous two, but still requires bowel prep.[63]

Mt-sDNA (Cologuard) is a noninvasive test that analyzes a stool sample to detect if abnormal sections of DNA and/or hemoglobin are present. These biomarkers are associated with CRC and precancerous lesions. FIT is another noninvasive test that examines stool for occult blood. Similarly, gFOBT detects occult blood in the stool, however it uses a different chemical reaction than FIT. None of these noninvasive tests require prior bowel preparation and can be performed at home.[63]

Shared decision making between patients and HCPs has been shown to lead to more successful patient adherence with provider recommendations.[21] This patient-centered approach results in patients that are more likely to identify a screening test that aligns with their own preferences. This concept is captured well in the 2021 USPSTF recommendation that states, “Each screening test has different considerations for implementation that may facilitate patient uptake of and adherence to screening or serve as a barrier to screening.” “Discussion of implementation considerations with patients may help better identify screening tests that are more likely to be completed by a given individual.”[20] In 2021, NCCN updated their CRC

screening guidelines and included a discussion of the importance of choice and shared decision making. NCCN noted that there is data to demonstrate that screening rates improve when options are offered that align test characteristics with patient preferences.[25]

Table 3 shows the 2018 ACS colorectal cancer screening recommended testing interval. The tests listed are those recommended for individuals ages 45-75 with average risk of developing CRC.[23]

Table 3. ACS Recommended Testing Intervals

(hs)-gFOBT	FIT	mt-sDNA	Flex Sig	CT colonography	Colonoscopy
•Every Year	•Every Year	•Every 3 Years	•Every 5 Years	•Every 5 Years	•Every 10 Years

For most of these screening tests, a randomized, controlled study could not be performed because it would be unethical to have a control group with CRC screening at less than the recommended level of intensity. As such, numerous tests have been added to the recommendations over the years based on sensitivity in detection of CRC and advanced adenomas in large clinical studies and extrapolation of the impact of the screening test, as defined in an Agency for Healthcare Research and Quality (AHRQ) Technical Report using a modeling approach.[64]

Challenges to Screening – Non-adherence

Non-adherence is the Achilles' heel of systematic, universal CRC screening programs. The CDC reported that, in 2018, the most recent year for which data are available, only 68.8% of Americans age 50–75 were compliant with the recommended screening guidelines.[29] Using 2018 National Health Interview Survey data, Shapiro and colleagues examined CRC screening test use for adults aged 50-75 years as well as time trends in CRC screening test use from 2010-2018. From this analysis, the percentage of participants up-to-date with CRC screening increased from 61.2% in 2015 to 65.3% in 2018; the authors state this increase was driven by the increased use of stool testing.[65]Using Medicare claims data from 2014-2018, Limburg and colleagues also assessed trends in the utilization of stool-based CRC screening modalities. The authors analyzed CPT code frequency for colonoscopy, flexible sigmoidoscopy, FIT, FOBT, and mt-sDNA. Mt-sDNA test utilization increased significantly (166% annually), flexible sigmoidoscopy use increased modestly (10.3% annually), FIT and colonoscopy (the most commonly used screening modality) use remained stable, and FOBT utilization decreased (-11.75% annually).[66] The current portfolio of readily available and broadly covered CRC screening tests has not yet achieved a greater level of adherence with the recommendations of the screening guidelines. As a result, organizations such as the National Colorectal Cancer Roundtable, ACS, and the CDC are advocating for better adherence with the guidelines aiming to achieve 80% adherence (or better) in every community.[67]

There are a number of patient-reported barriers to CRC screening, including:[68]

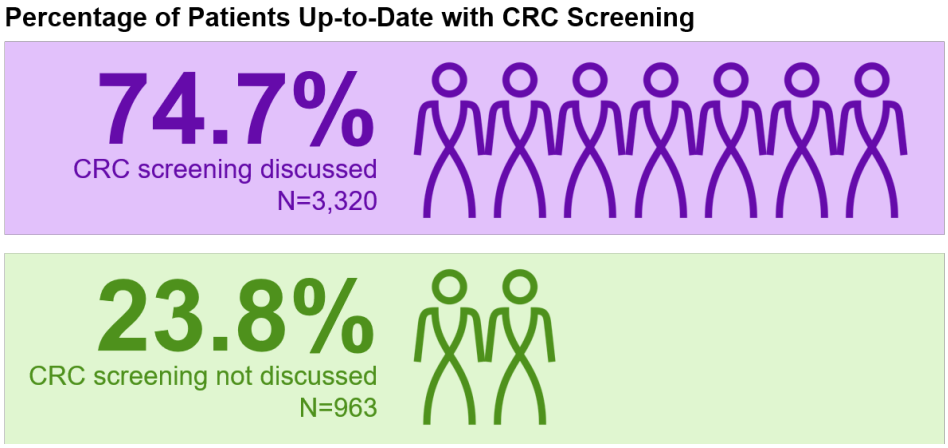
- Lack of social support

- Fearfulness
- Apprehension about bowel preparation
- Lack of knowledge or information provided
- Pain/discomfort associated with the procedure
- Concerns about insurance/cost
- Afraid of the results
- Inconvenience
- Embarrassment
- Asymptomatic
- Procedural anxiety

Mt-sDNA (Cologuard) allows patients to undertake screening at home, with delivery and pickup of the test kit, thereby obviating the need for additional healthcare appointments and many of the other barriers listed above, and at no additional cost to them.

Discussing CRC screening with patients can also increase adherence. In one study, the percentage of patients with up-to-date CRC screening was 23.8% when it was not discussed during healthcare-provider visits but increased to 74.7% when the topic was included in the consultation (Figure 4).[69]

Figure 4. The Importance of Discussing CRC Screening with Patients[69]



Multivariate OR (95% CI): 8.83 (7.20-10.84).

A systematic review of published literature has found that patient navigation, encompassing guidance through complex healthcare systems, addressing social, cultural, educational, and logistical barriers enhances CRC screening completion by 2-fold as compared to usual care.[70] This demonstrates why providing a test supported by a navigation system is critical for driving the high patient adherence that has been seen with mt-sDNA (Cologuard), especially in previously unscreened and non-compliant patients. A separate randomized controlled trial compared usual practice to tailored navigation in patients aged 50-74 years across 21 practices in Canada. The tailored navigation intervention included provision of information regarding CRC screening, discussion of the different tests, their risks and CRC detection rates, and elicitation of the individual patient's preference. Within the following 12 months 35% of patients who received the intervention underwent screening compared with 20% of patients who received usual care.[71]

A number of system-level barriers are also perceived by healthcare providers who have no screening protocol. Specifically, lack of a reminder system and lack of support staff.[72]

While patient and HCP preference, test cost, and cultural considerations likely play a large role in screening rates, certain characteristics of the available tests themselves may contribute to low adherence. For instance, gFOBT and FIT require yearly testing, which can present a challenge with poor long-term adherence.[23] Colonoscopy offers the longest testing interval and is considered the "gold standard" in terms of sensitivity and specificity.[73] However, colonoscopy is an invasive procedure that requires extensive and uncomfortable bowel preparation, and comes with a generally higher cost per test.[23] These factors all may serve as detractors to some patients and may account for the low adherence rates for colonoscopy.[21]

One study of patient adherence and type of test ordered demonstrated that adherence was best when the patient was offered a choice between invasive screening using colonoscopy and noninvasive screening with gFOBT. Over the first year, a significantly lower proportion of patients completed colonoscopy (38%) compared with the proportion completing FOBT (67%) (P<0.001) or patients who were allowed to choose the screening strategy (69%) (P<0.001).[21]

In a 2021 study, Miller-Wilson and colleagues

Participants (n = 1,420,460) included individuals ages 50 years and older with commercial insurance or Medicare, with a valid mt-sDNA test shipped by Exact Sciences Laboratories between January 1, 2018, and December 31, 2018.

O

In a survey of 3847 patients conducted by Exact Sciences between June 2017 and June 2018, 48% of patients who completed Cologuard testing during that period indicated that they had never been screened prior to their screening with Cologuard.[13] A noninvasive, stool-based CRC screening test like mt-sDNA (Cologuard), with no requirement for preparation or change in medication or diet, may provide an opportunity to achieve gains in the total number of individuals being screened. Increasing CRC screening rates may result in avoidance of colorectal cancer related costs from downstream morbidity and costs from CRC treatment itself.[36, 39]

3.0 CLINICAL EVIDENCE

3.0 Pivotal Mt-sDNA Study

Study Design

The pivotal mt-sDNA study was a prospective, blinded, cross-sectional, multi-center study that began enrollment of study participants on June 30, 2011. A total of 12,776 patients were enrolled from 90 sites in the US and Canada, including both colonoscopy centers and primary care sites, with study participation concluding on February 4, 2013. Subjects were provided with a collection kit, which they used to collect a stool sample for mt-sDNA testing and comparator FIT. Subjects subsequently underwent colonoscopy within 90 days of study enrollment. Colonoscopists were blinded to mt-sDNA and FIT results.[7]

Each stool sample was divided reserving some for the analysis with the mt-sDNA test and some for the comparator FIT. Samples for mt-sDNA analysis were sent to a central biorepository for batch testing at one of three laboratories while the remainder of the stool sample was sent for the comparator FIT (automated Polymedco OC FIT-CHEK) to a single laboratory for testing. The comparator FIT was completed prior to the mt-sDNA analysis. Mt-sDNA samples were assayed by laboratory technicians blinded to the results of colonoscopy and the FIT results. All data were collected by a contract research organization and preparation of the summary data tables was provided by an independent biostatistician. Results from mt-sDNA and FIT testing were compared to the results of an optical colonoscopy examination, and histopathological diagnosis of all significant lesions discovered during the colonoscopy were either biopsied or surgically removed.[49]

Colonoscopy findings were recorded per site specific standard of practice. Subjects with no colorectal neoplastic findings were categorized as negative by colonoscopy. Patients were placed in a single category based on the histopathological results from biopsied tissue or excised lesions, categorized based on the most clinically significant lesion present (“index lesion”) by a blinded central pathologist according to the pre-specified standards outlined in Table 4.

Table 4. Histopathological Category Definitions[49]

Category	Findings
1	CRC, all stages (I-IV)
2	Advance adenoma, including the following subcategories: 2.1 – Adenoma with carcinoma *in situ*/high grade dysplasia, any size 2.2 – Adenoma, villous growth pattern (≥25%), any size 2.3 – Adenoma ≥ 1.0 cm in size, or 2.4 – Serrated lesion, ≥ 1.0 cm in size
3	1 or 2 adenoma(s), > 5 mm in size, or < 10 mm in size, non-advanced
4	≥ 3 adenomas, < 10 mm in size, non-advanced
5	1 or 2 adenoma(s), ≤ 5 mm in size, non-advanced
6	Negative – No neoplastic findings 6.1 – negative upon histopathological review 6.2 – no findings on colonoscopy, no histopathological review

*This table is a recreation of Table 6 from the SSED.[49]

Inclusion and Exclusion Criteria

Subjects eligible for enrollment in the study were of both sexes between the ages of 50 and 84 years (inclusive), who were at average risk for development of colorectal cancer and asymptomatic for gastrointestinal symptoms warranting diagnostic colonoscopy. In addition, subject enrollment was age-weighted toward a slightly older population to increase the point prevalence of colorectal cancer in this study. An effort was made to enroll the majority of subjects of age 65-84 given the increased age-related prevalence of colorectal cancer; 64% of subjects in the actual study population were of age 65-84.[49]

Clinical Performance Measures

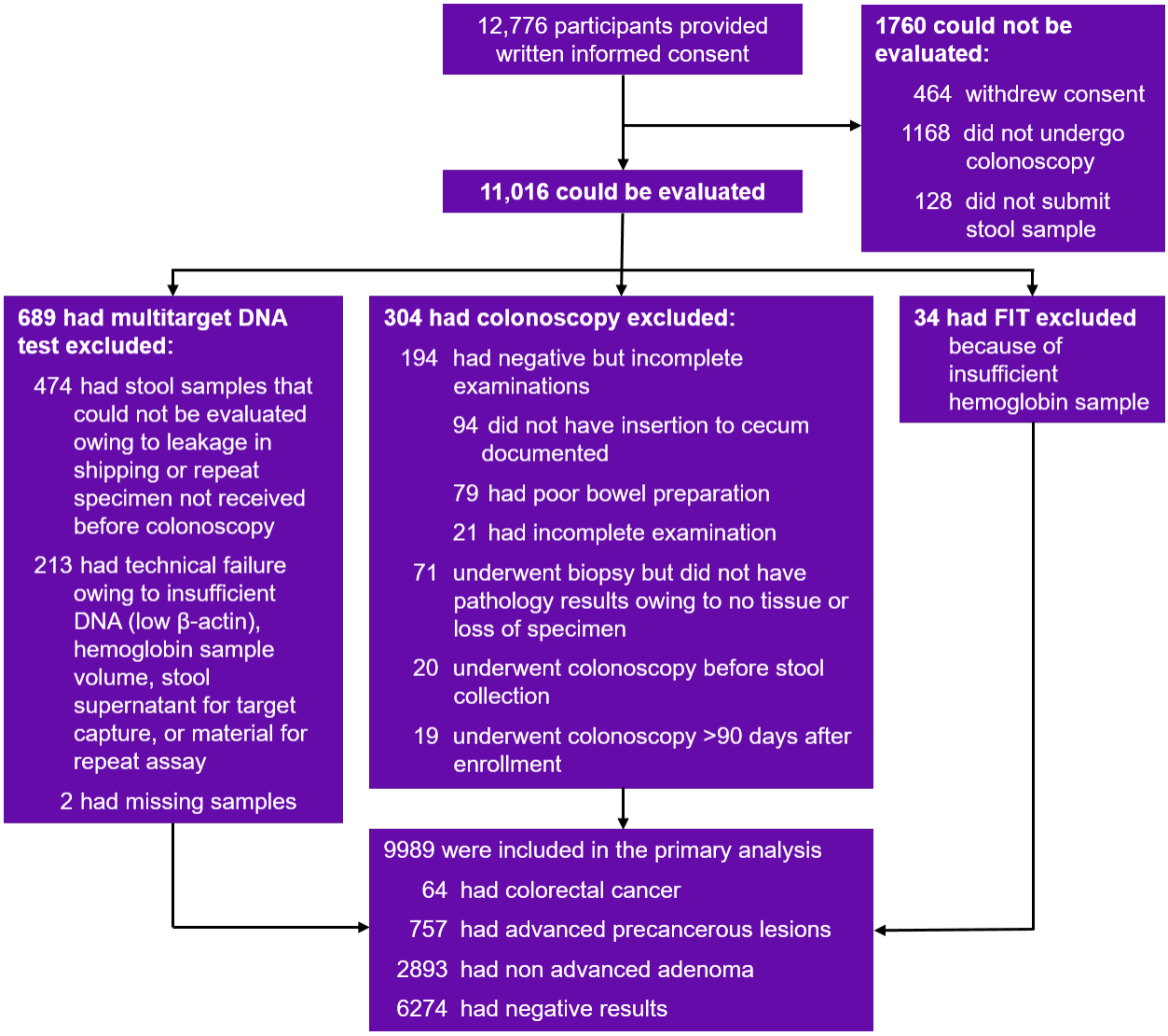
The performance of mt-sDNA was evaluated based on comparison of the test result with the histopathological category (Table 4).[49]

The primary outcome was mt-sDNA sensitivity for CRC, with disease stage determined with the use of the American Joint Committee on Cancer (AJCC) staging system. The secondary outcome was the ability of the mt-sDNA test to detect advanced precancerous lesions, including advanced adenomas (high-grade dysplasia or with ≥25% villous histologic features or measuring ≥1 cm in the greatest dimension) and sessile serrated polyps measuring ≥1 cm in diameter.[7]

Study Cohort

The study enrolled a total of 12,766 average risk subjects at 90 sites, including both primary care sites and colonoscopy referral centers. A total of 9,989 subjects were included in the primary analysis population (Figure 5). This population included 65 subjects with CRC found on study colonoscopy.

Figure 5. Enrollment and Outcomes of the Pivotal Study[7]



Study Population Demographics and Baseline Parameters

The baseline demographic characteristics for the primary effectiveness population are presented in Table 5. As shown in the table, the average age of subjects was 64.2 years old, and there was a slightly higher percentage of female subjects (5378/10,023; 53.7%) as compared with male subjects (4645/10,023; 46.3%). The majority of subjects were White (8422/10,017; 84.1%), and 10.7% (1,071/10,017) were Black or African American. Nearly 10% of subjects self-identified as Hispanic or Latino (991/10,019; 9.9%). Average BMI was 28.83 and the majority of subjects never smoked (5531/10,019, 55.2%). It should be noted that two 49-year-old subjects and one 44-year-old subject were included in the study, which is inconsistent with the intended use population. Each of these subjects was a true negative and their inclusion did not notably impact data analyses.[75]

Table 5. Demographics of the Pivotal Study[75]

Demographics (evaluable group, n=9989)	
Average age, years (range)	64.2 (44-84)
Gender, n (%)	
Male	4625 (46.3)
Female	5364 (53.7)
Mean BMI, kg/m^2 (SD)	28.83 (5.836)
Ethnicity, n (%)	
Hispanic/Latino	991 (9.9)
Not Hispanic/Latino	9028 (90.1)
Race, n (%)	
White	8392 (84.0)
Black or African American	1068 (10.7)
Asian	259 (2.6)
American Indian/ Alaska Native	36 (0.4)
Native Hawaiian or Other Pacific Islander	23 (0.2)
Other	206 (2.1)
Missing	6
Smoking History	
Never Smoked	5531 (55.2)
Former Smoker	3589 (35.8)
Smoker	903 (9.0)

The study demonstrated that the mt-sDNA test has an overall sensitivity of 92.3% for CRC and a specificity of 86.6%, with patients having non-advanced adenomas (Category 3-5) and no neoplastic findings (Category 6) considered false positives (Table 6). Mt-sDNA testing exhibits superior sensitivity to FIT for CRC and advanced adenomas, 92.3% vs. 73.8%, and 42.4% vs. 23.8% respectively. Importantly, for the adenomas most at risk for progression to CRC, those with high-grade dysplasia, the sensitivity of mt-sDNA was superior to that of FIT: 69.2% vs 46.2%, respectively. FIT had a slightly higher overall specificity than mt-sDNA: 94.9% vs 86.6%, respectively, for all nonadvanced adenomas and no neoplastic findings.[7]

Table 6. Summary of Findings from the Pivotal Study[7, 8]

Sensitivity (n=9989)	**Colonoscopy findings,** n detected	**Mt-sDNA,** % detected	**FIT,** % detected
Colorectal cancer (Stages I-IV)	65	92.3% (83.0-97.5)	73.8% (61.5-84.0)
Early stage colorectal cancer (Stage I/II)	50	94.0%	70.0%
Advanced adenoma	757	42.4% (38.9-46.0)	23.8% (20.8-27.0)
High-grade dysplasia	39	69.2%	46.2%
Sessile Serrated Adenoma/Polyp ≥1.0 cm	99	42.4%	5.1%
Specificity (n=9989)			
All nonadvanced adenomas, non-neoplastic findings, and negative results on colonoscopy (CRC and advanced adenomas excluded)	9167	86.6% (85.9-87.2)	94.9% (94.4-95.3)
Negative results on colonoscopy (no adenomas, no biopsy done)	4457	89.8% (88.9-90.7)	96.4% (95.8-96.9)

The study also demonstrated that mt-sDNA provides a highly sensitive screening test for CRC with a strong negative predictive value (NPV) to ensure sound clinical decision-making. The NPV of a diagnostic test represents the percentage of patients with negative test results that truly do not have the disease. The NPV for both mt-sDNA and FIT were calculated for colorectal cancer and advanced colorectal neoplasia. Mt-sDNA was found to have an NPV of 99.94% for colorectal cancer and 94.79% for advanced colorectal neoplasia. In contrast, FIT has an NPV of 99.8% for colorectal cancer and 93.6% for advanced colorectal neoplasia.[11] Compared with mt-sDNA, the NPV of FIT does not provide the same level of confidence in deferral of negative results post-screening—particularly for a disease with significant morbidity and mortality risk if found in later stages. Mt-sDNA achieved a high specificity (87%; 13% false-positive rate) for ages 50-85, and even higher specificity (91.5%; 8.5% false-positive rate) for ages 50-65. The overall specificity of FIT for patients 50-85 years was slightly higher than that of mt-sDNA at 94.9%.[7] Given that the purpose of a screening test is to find patients with early stage and high-risk precursors to CRC, the sensitivity of the test is the most appropriate comparator for test selection. As colonoscopy itself is used as a screening test, then the trade-off for mt-sDNA testing is modestly higher false-positive single-application specificity than FIT-only moderate single application sensitivity for the target lesions of screening, is clinically reasonable.[18] Finally, given that the adherence with annual screening with FIT is low,[16] patients may be inclined to be screened only with noninvasive tests with the most sensitive test as the single application. These results emphasize the clinical advantage of mt-sDNA to commercially available FIT.

3.1 Specificity of mt-sDNA in patients age 45 to 49

Study Design

The Specificity of the Multi-target Stool DNA test for Colorectal Cancer Screening in Average-risk 45-49 Year Olds: A Cross-sectional Study (Act Now) was a prospective, cross-sectional study evaluating individuals at average risk for CRC, between the ages of 45 and 49 years old, and interested in a screening colonoscopy. Study participants were self-selected through advertisement. Enrollment occurred between November 2018 and June 2019 at 31 sites in the US.

Subjects were provided with a collection kit, which they used to collect a stool sample for mt-sDNA testing. Subjects subsequently underwent colonoscopy within 60 days of study enrollment. The stool sample for the mt-sDNA test was collected before the bowel preparation for colonoscopy and shipped to Exact Sciences Laboratories for processing; standard bowel preparations were performed according to usual practice at each clinical site with endoscopists blinded to mt-sDNA results.

Histopathology was analyzed from biopsy and surgical specimens according to each site's local surgical pathologist. Index lesions were categorized as colorectal cancer (CRC), advanced precancerous lesion (APL) [high-grade dysplasia/carcinoma in situ of any size, villous growth pattern (≥25%) of any size, adenomas ≥10 mm, and serrated lesion ≥10 mm], non-advanced adenoma (NAA), nonneoplastic findings (hyperplastic polyps, lymphoid aggregates, others), and negative (no colorectal neoplasia, no findings on colonoscopy, no biopsy taken). Diagnoses of advanced colorectal neoplasia (CRC or APL) required confirmation a central pathologist, with discrepant findings adjudicated through review and interpretation by a second central pathologist. All pathologists were blinded to mt-sDNA test results.

Inclusion and Exclusion Criteria

Inclusion and exclusion criteria, other than age, were identical to those of the mt-sDNA pivotal study.[7] The population included in this study were participants at average-risk for CRC, 45 years of age and older, and considered typical candidates for CRC screening.

Clinical Performance Measures

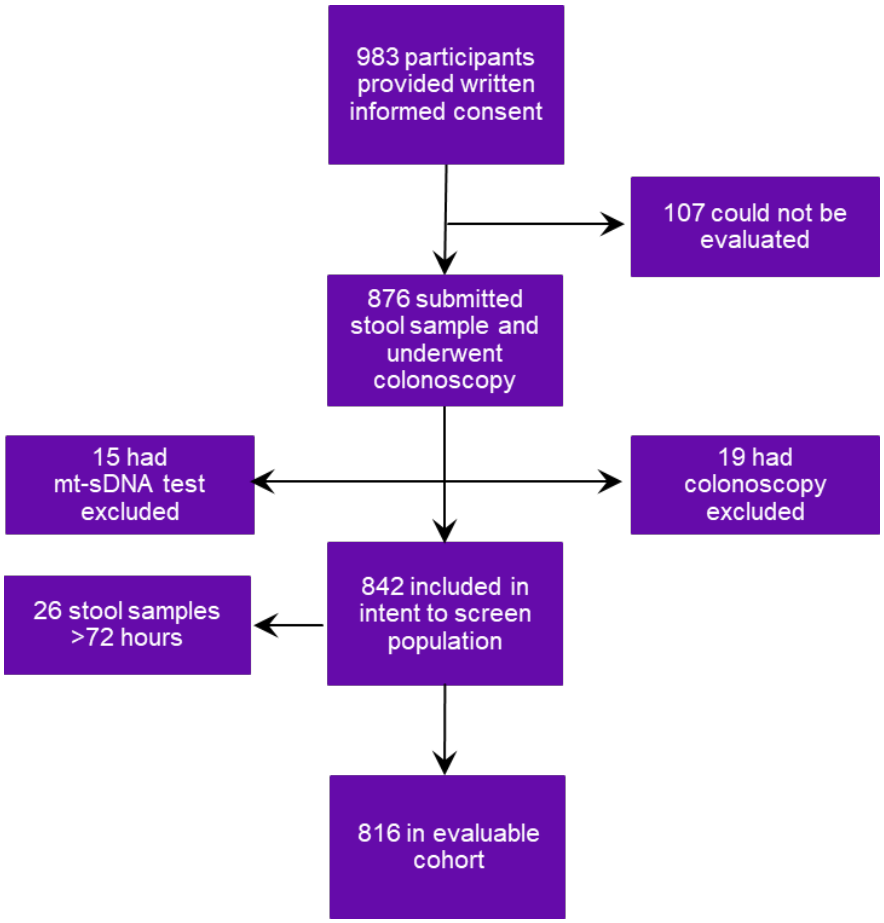
The primary outcome was to determine the specificity of mt-sDNA for advanced colorectal neoplasia using colonoscopy was used as the reference standard. Additional measurements included specificity for any precancerous lesion, advanced or non-advanced.

The secondary outcome was to determine the sensitivity of the mt-sDNA test for CRC and APL, including receiver operating characteristics (ROC) and area under the curve (AUC) analyses. Additional measurements included lesion location (proximal, distal, or rectal) and size (mm) and were recorded for all CRCs and APLs; characterization was based on the histopathologic diagnosis of the index lesion (most clinically significant lesion), with pathologists blinded to mt-sDNA test results.

Study Cohort

The study enrolled a total of 983 average risk patients. A total of 816 subjects were included in the primary analysis population (Figure 6).

Figure 6. Enrollment of the Act Now Study[10]



Study Population Demographics and Baseline Parameters

The baseline demographic characteristics for the primary effectiveness population are presented in Table 7. As shown in the table, the average age of subjects was 47.8 years old, and there was a slightly higher percentage of male subjects (518/816; 52.7%) as compared with female subjects (465/816; 47.3%). The majority of subjects were white (803/816; 81.7%), and 12.9% (127/816) were Black or African American. Nearly 7% of subjects self-identified as Hispanic or Latino (67/816; 6.8%).

Table 7 Demographics of the Act Now Study[10]

Demographics (evaluable cohort n=816)	
Mean age, years (SD)	47.8 (1.5)
Sex, n (%)	
Male	518 (52.7)
Female	465 (47.3)
Ethnicity, n (%)	
Hispanic/Latino	67 (6.8)
Not Hispanic/Latino	916 (93.2)
Race, n (%)	
White	803 (81.7)
Black or African American	127 (12.9)
Asian	41 (4.2)
American Indian/ Alaska Native	1 (0.1)
Native Hawaiian or Other Pacific Islander	1 (0.1)
Other	10 (1.0)

The study demonstrated that the mt-sDNA test has a high specificity of 95.2% (95% CI: 93.4-96.6%) among participants with non-advanced findings or negative colonoscopic findings, with 37 participants of 767 with a positive result (Table 8). Specificity was 96.3% (CI: 94.3-97.8%) in those with negative colonoscopic findings, with 19 of 514 participants with a positive result. Specificity did not differ by sex or race among participants with non-advanced neoplasia or negative findings and variations in specificity by age were not evaluated due to the narrow range of ages in this study.

Table 8. Summary of Findings from the Act Now Study

Overall Findings†					
	Total	CRC	APL	Non-advanced Neoplasia	Negative Findings
n (%)‡	816	0 (0.0%)	49 (6.0%)	253 (31.0%)	514 (63.0%)
mt-sDNA Positive	53	0	16	37	19

Most Advanced Finding	**Colonoscopy (n=816)**	**mt-sDNA (n=816)§**	
	n	Positive Results, n	Specificity, % (95% CI)
All non-advanced, non-neoplastic* findings, and negative results on colonoscopy	767	37	95.2 (93.4-96.6)
Negative results on colonoscopy	514	19	96.3 (94.3-97.8)
Colorectal Cancer	0	NA	NA
Advanced precancerous lesions	49	16	32.7 (19.9-47.5)
High-grade dysplasia	0	NA	NA
Adenoma, villous growth pattern	10	6	60.0 (26.2-87.8)
Adenoma ≥10 mm	32	7	28.1 (13.7-46.7)
Serrated lesion ≥10 mm	7	1	14.3 (0.4-57.9)
Nonadvanced adenoma	253	18	7.1 (4.3-11.0)

Sensitivity for APL was 32.7% (CI: 19.9-47.5%) with mt-sDNA detecting 16/49 participants. Estimation of sensitivity by APL size or location was not possible due to the low prevalence of CRC and APL in this study. There was no specific pattern of APL detection based upon anatomic site, underscoring the detection of APLs by the mt-sDNA test is agnostic to colorectal location. The positive and negative predictive values (PPV, NPV) in this study were 30.2% and 95.7%, respectively, with a positive likelihood ratio of 6.77 (CI: 4.06-11.28) and a negative likelihood ratio of 0.71 (CI: 0.58-0.86). The area under the receiver operating characteristics curve (AUROC) was 0.72 (CI: 0.64-0.81) for distinguishing between APL and lesser findings, including non-advanced adenomas or negative findings, among participants aged 45 to 49 years old. This AUC is comparable to the AUC participants 50 years and older in the pivotal study for this test (0.73, CI: 0.69-0.74).[7, 11]

This study demonstrates that the mt-sDNA test is highly specific among average-risk 45 to 49-year-olds, supporting its use as a noninvasive option for CRC screening in this age group. Specificity was the primary outcome of the study due to the expected lower prevalence of CRC and APLs in this age group. Low prevalence makes it difficult to estimate sensitivity as a primary endpoint because the required sample size is not feasible. This low prevalence necessitates a

high-specificity screening test for this population to minimize the costs and risks of avoidable diagnostic procedures. The performance of mt-sDNA in persons aged 45-49 is comparable to persons aged ≥50 years. The AUROC and 32.7% APL sensitivity reported in this study is consistent with that of participants aged 50 years and older in the pivotal study, suggesting performance of mt-sDNA in patients aged 45-49 years old is similar.[7]

3.2 Mt-sDNA use in an Alaska Native population

To further document the clinical validity of the mt-sDNA test and study the effect in a rural population, Redwood et al. carried out a prospective, blinded, cross-sectional clinical study: "Stool DNA Testing for Screening Detection of Colorectal Neoplasia in Alaska Native People". This study evaluated 661 Alaska Native people and was led by researchers at the Mayo Clinic.[12] Alaska Native people have limited access to conventional screening approaches particularly due to their location. The Alaska Native people have among the world's highest rates of colorectal cancer, more than twice the rate of US Caucasians. Colorectal cancer is the most commonly diagnosed cancer among this population.[53]

The study demonstrated a higher rate of sensitivity for CRC and pre-cancer and an increased specificity with mt-sDNA compared to that observed in the pivotal study. The mt-sDNA test detected 100% of colorectal cancers and 52% of significant premalignant lesions (adenomas > 1 cm) in people between the ages of 40-85. The sensitivity of mt-sDNA was 80% for the largest pre-cancers (> 3 cm), which are most likely to progress to cancer. FIT detected 80% of colorectal cancers and only 30% of significant premalignant lesions (advanced adenomas ≥ 1 cm).[12]

The mt-sDNA test was found to have 49% sensitivity for screening-relevant neoplasms (includes adenoma or sessile serrated adenoma/polyp ≥1 cm, any adenoma ≥25% villous component, and cancer), versus 28% with FIT (*P*<.001). Mt-sDNA exhibits greater sensitivity than FIT in detection of advanced adenomas at all polyp sizes; the sensitivity of mt-sDNA for detecting advanced adenomas increased directly with larger polyp size, reaching 80% for polyps 3 cm or larger (*P*=0.01 for trend). By comparison, FIT only had a sensitivity of 40% for similarly sized polyps (*P*=.48) and its trend for increased sensitivity with larger polyp size did not reach significance. The overall specificity of mt-sDNA (defined as no polyps on colonoscopy) was 93% versus 96% with FIT (*P*=.03).[12]The specificity of mt-sDNA for screening-relevant neoplasms (adenoma or sessile serrated adenoma/polyp ≥1 cm, any adenoma with ≥25% villous component, and cancer) was 91%, compared with 94% for FIT. These results are summarized in Table 9.

Table 9. Sensitivity and Specificity of Mt-sDNA and FIT for Colorectal Neoplasia in Alaska Native People[12]

Most advanced finding in 661 colonoscopies	Sensitivity, % (95% CI)		*P* value
	Mt-sDNA	FIT	
Screening-relevant neoplasms			
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)	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 (30-35)	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
Non-advanced 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)	91 (88-93)	94 (91-95)	.02
No neoplasms (n=334)	93 (90-95)	96 (93-98)	.03

3.3 False-positive Mt-sDNA Results

Other studies have assessed whether significant long-term outcomes are associated with false-positive mt-sDNA results.

3.3.1 Pivotal Study Retrospective Cohort

A retrospective cohort study was conducted to determine if patients with false-positive mt-sDNA test results were at increased risk for aerodigestive cancer. Five sites from the pivotal study were selected to analyze follow-up data of patients with negative colonoscopy findings and either positive (discordant) or negative (concordant) mt-sDNA test results. Among the 1216 patients included in the primary analysis aerodigestive cancer was diagnosed in 2.4% of the discordant group and 1.1% of the concordant group. The incidence of aerodigestive cancer was similar between the groups and fell below the SEER-derived expected rates for this population. These findings indicate that further testing beyond a high-quality colonoscopy is not warranted in patients with false-positive mt-sDNA test results.[35]

3.3.2 Single-center Studies

A study conducted in Calgary, Canada, analyzed data from the pivotal study. A total of 118 patients had a positive mt-sDNA result and negative colonoscopy. At a median follow-up of 2.9 years, none had been diagnosed with a post-colonoscopy CRC.[76]

A separate study conducted at the Indiana University School of Medicine assessed the long-term follow-up of 37 patients who had a false-positive mt-sDNA result. After 3.1-5.1 years of follow-up none had CRC or another digestive tract cancer.[77]

A further study prospectively identified 30 patients with an apparent false-positive mt-sDNA result. Patients were invited to repeat the mt-sDNA test at 11-29 months after the initial test, followed by repeat colonoscopy and upper endoscopy. A total of 12 patients were restudied: 7 patients had a negative second mt-sDNA and normal second colonoscopy and upper endoscopy and 5 patients had a positive second mt-sDNA test. Three of the 5 patients had positive findings on repeat colonoscopy, giving a positive predictive value of 0.60 and a negative predictive value of 1.00 for the second mt-sDNA test.[78]

The results of these studies are consistent with data published in the 2014 FDA Summary of Safety and Effectiveness Data and support that no additional clinical evaluation or work-up is recommended for asymptomatic individuals with false-positive mt-sDNA results.[75]

3.4 Positive Test Follow-up

An effective noninvasive CRC screening strategy requires patients with positive screening test results to follow-up with a diagnostic colonoscopy. A study conducted at USMD Health System in Texas demonstrated that over twelve months, 77 providers ordered mt-sDNA tests for 393 screening non-compliant Medicare patients; 347 patients completed mt-sDNA for an adherence rate of 88%. The mt-sDNA result was negative for 296 patients (85%) with 51 (15%) testing positive. Of those 51 positive-result patients, 49 completed their diagnostic colonoscopy resulting in a colonoscopy adherence rate of 96%.[18] Studies demonstrate that the colonoscopy adherence rate for FIT positive patients, within 12 months, is 78.4%.[14]

Mt-sDNA test results may prompt gastroenterologists to have a higher index of suspicion, leading to more productive colonoscopies. A Mayo Clinic (Rochester, MN) study compared colonoscopic findings and withdrawal times between two groups of patients. A group of unblinded, retrospectively-identified patients who underwent colonoscopy following a positive mt-sDNA test result (n=172) was matched with a group of blinded, positive mt-sDNA test patients participating in a clinical trial (n=72). The study determined that knowledge of positive mt-sDNA test results can have a beneficial impact on the value of the subsequent follow-up diagnostic colonoscopy, resulting in twice the median number of polyps detected (P=0.0007) and significantly higher rates of total adenomatous/sessile serrated polyps detected (P=0.013).[32]

All positive stool-based screening tests should be followed-up with a colonoscopy.[23] Adherence to this follow-up is important to completing CRC screening. A retrospective cohort study within a vertically integrated healthcare system demonstrated that adherence to follow-up colonoscopy after a positive mt-sDNA test was higher than for those with a positive FIT.[34] Patients with a positive mt-sDNA test also completed a colonoscopy in less time than those with a positive FIT. Of 631 identified patients, 308 had a positive FIT and 323 had a positive mt-sDNA result. Patients with a positive FIT completed a follow-up colonoscopy within 6 months 46.7% of the time (144/308 patients) compared to 71.5% of the time (231/323 patients) for patients with a positive mt-sDNA result. The median time to follow-up for a patient with a positive FIT was >6 months compared to a median time of 2.2 months (95% CI, 1.80-2.52 months) for patients with a positive mt-sDNA result. Patients with a positive mt-sDNA test were nearly twice as likely to have a follow-up COL within six months (hazard ratio, 1.83; 95% CI 1.48-2.25). The study also

evaluated barriers to follow-up colonoscopy and identified barriers at multiple levels (patient-, provider-, and system-level). Reasons for lack of follow-up were generally similar between the two modalities, and included prior recent colonoscopy, assumed false positive/positive result associated with other colorectal pathology, and colonoscopy refusal or appointment cancellation. In some cases, the reason for nonadherence was not known. Of those who did not complete a colonoscopy after a positive FIT, colonoscopy was not ordered in 82.3% of patients compared to 49% of patients with a positive mt-sDNA result. Among the 144 patients with a positive FIT who underwent colonoscopy, precancerous or malignant lesions were found in 48.6% of patients. In the 231 patients with positive mt-sDNA testing, precancerous or malignant lesions were found in 77.1% of patients.

4.0 ECONOMIC VALUE AND MODELING REPORT

4.1 Modeling Overview

4.1.1 Use of modeling for decision-making

While the sensitivity and specificity of a CRC screening test can be documented in a clinical study, the clinical utility of a CRC screening test is typically determined using a model that determines the performance of a CRC screening program utilizing different testing methodologies.

The Cancer Intervention and Surveillance Modeling Network (CISNET) models are commonly used to evaluate the impact of CRC screening modalities on a large population and include three individual microsimulation models: MISCAN, SimCRC, and CRC-SPIN.[79] The models range in age from 10-20 years old (first developed in 1999) and each is based on a different set of assumptions. There are several limitations to the current models used to conduct cost-effectiveness analyses:

- Models assume perfect adherence over lifetime of screening including 100% adherence to follow-up colonoscopy for positive initial non-invasive screening tests
- Alternating modalities or hybrid screening strategies were not considered
- Test sensitivity (efficacy) after multiple rounds of repeat testing has not been widely studied, therefore the rescreening efficacy is based on one-time screening (carried over)
- Accuracy of diagnostic colonoscopy is assumed the same as screening colonoscopy
- Colonoscopy does not result in complications if there is no polypectomy
- No consideration for alternate disease pathways such as sessile serrated polyps or high-grade dysplasia
- Disease progression does not account for sojourn time when a precancerous lesion is developing into neoplasia

4.2 CISNET Modeling

Zauber and colleagues have used USPSTF Technical Report CISNET data to compare the utility of mt-sDNA testing every 3 years with annual FIT, hsFOBT every year, and colonoscopy every 10 years. In the CRC-SPIN model, mt-sDNA yields a median of 226 life-years gained, averts 20 CRC deaths, reduces CRC mortality by 76%, and produces the most benefit (LYG) per complication. The data further demonstrates that the number of colonoscopies per LYG generated by mt-sDNA at 3-year intervals is equivalent to colonoscopies generated by annual FIT and lower than those generated by hsFOBT.[64]

In addition, a peer-reviewed analysis of the CISNET modeling data, relied upon by the USPSTF when developing its 2016 colorectal cancer screening guidelines, concludes that screening with mt-sDNA on a 3-year interval is equal or superior to screening with fecal blood tests on a 2- or 3-year interval.[64] These extended FIT/FOBT intervals, while still overly optimistic based on the evidence of repeat testing with FIT/FOBT,[14, 16] better reflect the clinical impact of FIT/FOBT screening than using annual screening in models. The USPSTF only recommended fecal blood tests on an annual basis and did not consider adherence or the availability of five positive RCTs

using two-year CISNET modeling, with three independent models (MISCAN, SIMCRC and CRC-SPIN) providing data showing that only mt-sDNA (3-year schedule as opposed to FIT 2- or 3-year schedule and hsFOBT 2- or 3-year schedule), generated >90% of the LYG by colonoscopy every 10 years in at least one of the models.[64]

4.3 Colorectal Cancer and Adenoma Incidence and Mortality (CRC-AIM) Microsimulation Model[80]

The Colorectal Cancer and Adenoma Incidence and Mortality Microsimulation (CRC-AIM) Model was developed to model the natural sequence of adenoma detection to carcinoma progression in unscreened patients as well as to evaluate the contribution of test-related attributes, such as patient adherence to both initial screening and follow-up colonoscopy, when indicated. Insights regarding the effectiveness, rather than the efficacy, of CRC screening strategies necessitate assumptions using reported real-world data.

The CRC-AIM microsimulation model is a validated model based on previously reported parameters from the Colorectal Cancer Simulated Population model for Incidence and Natural history (CRC-SPIN). CRC-AIM has demonstrated substantial cross-model validity when comparing natural history, screening outputs and probability curves to those from other CISNET models, particularly CRC-SPIN. Within this model, adenomas may grow and transition to preclinical cancer, which in turn may progress to symptomatic CRC. The screening strategies modeled then potentially detect an adenoma or preclinical CRC, as a function of their test performance and patient adherence.

4.3.1 Impact of screening and follow-up colonoscopy adenoma sensitivity on colorectal cancer screening outcomes in the CRC-AIM microsimulation model[81]

The objective of this analysis was to explore the impact on CRC screening outcomes when assuming different adenoma sensitivities between screening and combined follow-up/surveillance colonoscopies using the Colorectal Cancer and Adenoma Incidence and Mortality Microsimulation (CRC-AIM) model. Adenoma sensitivity may be lower in a screening colonoscopy compared to a follow-up colonoscopy after a positive result from a stool-based CRC screening test based on real-world evidence demonstrating lower adenoma detection rates (ADR)***** when endoscopists are blinded to stool-based CRC screening results.[32] Previous CRC microsimulation models, used to inform CRC screening guidelines, assume identical sensitivities between screening and follow-up colonoscopies after positive stool-based CRC screening tests.[82]

Outcomes were simulated for 4 million individuals born in 1975 and reported per 1000 individuals free of diagnosed CRC at age 40. CRC screening strategies modeled included colonoscopy every 10 years, mt-sDNA every 3 years, or FIT annually among an average-risk screening period between 50 and 75 years of age. Outcomes evaluated included number of stool tests, complications from colonoscopies, estimated CRC incidence and mortality, life-years with CRC, life-years gained (LYG), ADR, and adenoma miss rate (AMR).

Modeled natural history was through the adenoma-carcinoma development pathway in unscreened patients and among screened patients 100% adherence was assumed for both the

***** ADR: proportion of patients with ≥1 detected adenoma at a given age. Calculated for the first follow-up colonoscopy after a positive stool-based test.

CRC screening test and follow-up colonoscopy. To account for uncertainty and variability of real-world colonoscopy performance, ranges of adenoma sensitivity values were developed using different slopes of odds ratio (OR) adjustments; designated as small, medium, or large impact scenarios. Large adenoma (>10 mm) sensitivity values between screening and follow-up/surveillance colonoscopies were fixed with a log(OR)= 0.00 (“small impact”), 1.00 (“medium impact”), or 2.00 (“large impact”). A constant increase in the slope of 0.15, 0.30, or 0.60 was assumed between large and medium adenomas and between medium and small adenomas. Base-case (“no impact”, scenario 1) adenoma sensitivity values were identical for screening and combined follow-up/surveillance colonoscopy and were used in previous models4: 75% (small adenoma; 1-5 mm), 85% (medium adenoma; 6-9 mm), 95% (large adenoma; ≥10 mm).

In the base-case scenario, LYG were higher for colonoscopy every 10 years (351.9 years) vs. triennial mt-sDNA (299.5) and annual FIT (317.8). Reductions in CRC-related incidence and mortality were higher for colonoscopy (83.1%, 85.7%, respectively) vs. mt-sDNA (64.5%, 72.2%) and FIT (68.3%, 76.2%). Total number of colonoscopies associated with every 10-year colonoscopy screening strategy were 4167 compared to 1958 for mt-sDNA and 2036 for FIT. The weighted mean AMR was 21.3% for colonoscopy every 10 years, 18.9% for triennial mt-sDNA, and 19% for annual FIT. ADR was 30.3% for triennial mt-sDNA and 31.7% for annual FIT.

Increased differences in modeled adenoma sensitivity for screening vs. follow-up/surveillance colonoscopy resulted in improved LYG, reductions in CRC-related incidence and mortality, decreased AMRs, increased ADRs for triennial mt-sDNA and annual FIT, and a decline in evaluated outcomes for screening colonoscopy, compared with no screening.

Colonoscopy LYG decreased to 320.2 LYG (-31.7) and the reductions in incidence and mortality decreased ~8% to 74.7% and 78%, respectively. LYG with triennial mt-sDNA increased to 310.1 LYG (+10.5) and reductions in incidence and mortality improved approximately 3-4% to 68.3% and 75.3%, respectively. LYG using annual FIT increased to 328.3 LYG (+10.5) and reductions in incidence and mortality improved approximately 3-4% to 72.5% and 79.4%, respectively. The weighted mean AMR increased to 52.7% for colonoscopy every 10 years, and decreased to 5.1% for triennial mt-sDNA and 5.1% for annual FIT. ADR increased for triennial mt-sDNA and annual FIT to 33.8% and 35.7% respectively.

There are several limitations to this analysis. The surveillance colonoscopy adenoma sensitivity is set equal to the follow-up colonoscopy adenoma sensitivity. This is due to limited published evidence reporting adenoma sensitivity for surveillance colonoscopy after a positive stool-based CRC screening test compared to a screening colonoscopy. Additionally, the current analysis does not account for the serrated polyp pathway, which may account for up to 30% of all CRC cases. Similar to other models, this model assumed 100% adherence for both CRC screening and any resultant follow-up colonoscopy after a positive stool-based screening test, which is not reflective of real-world adherence and clinical scenarios. This may alter sensitivity values for CRC screening modalities with varying adherence rates.

In the present study, the “medium impact” scenario demonstrated a relative difference in ADR ~32% for mt-sDNA. This scenario may be the most reflective of real-world clinical practice colonoscopy sensitivities as previous reports indicate endoscopists who were unblinded to patients’ CRC screening test results detected relatively 32% more adenomas than blinded endoscopists.[32] Real-world evidence also demonstrates non-advanced colorectal neoplasia (<1

cm in size) was detected in 39% of patients during follow-up colonoscopy after a positive stool-based test.[33]

These data support the impact of differing sensitivities on evaluated outcomes. Microsimulation models should consider incorporating a range of different sensitivities between screening and follow-up/surveillance colonoscopies to provide a more accurate simulation of the benefits to CRC screening using stool-based strategies. The potential benefits of stool-based CRC screening strategies are underestimated when equal adenoma sensitivities for both screening and follow-up/surveillance colonoscopies are used, while the benefits for colonoscopy are overestimated. The relationship between realistic modeling inputs and resultant benefits/harms for respective CRC screening strategies is important to capture, most importantly when informing CRC screening guidelines and policy.

4.3.2 Estimating the impact differential adherence on the comparative effectiveness of stool-based colorectal cancer screening using the CRC-AIM microsimulation model[38]

Using the CRC-AIM microsimulation model, this study simulated the impact of imperfect adherence on the relative benefits and burdens of guideline-endorsed, stool-based CRC screening modalities.

Using a simulated population of 4 million average-risk adults, born in 1975, between ages 45-85 and free of diagnosed CRC, mt-sDNA, FIT, HSgFOBT were modeled using cross-sectional, first-round participation rates. Positive results are followed-up with a colonoscopy with 100% adherence assumed, in accordance with CISNET models. Three separate analyses were performed including evaluation of the comparative effectiveness of screening strategies using a spectrum of adherence rates, estimation of the comparative impact of differential adherence to the stool tests, and evaluation of the comparative effectiveness of screening strategies using varying numbers of completed tests.

The findings demonstrated that at imperfect adherence rates, mt-sDNA provides more LYG than FIT or HSgFOBT at an acceptable tradeoff in screening burden. All stool-based screening strategies decreased CRC-related incidence and mortality compared with no screening, regardless of adherence assumptions. When imperfect real-world adherence rates were assumed for each stool-based test used amongst individuals screened between 50-75 years of age, the LYG from mt-sDNA screening was 19.1% greater than FIT, and 25.4% greater than HSgFOBT. CRC incidence and mortality reductions were also higher for mt-sDNA compared with FIT and HSgFOBT. A similar pattern was observed for individuals screened between 45-75 years of age.

Assuming imperfect adherence, mt-sDNA screening strategies are efficient/near-efficient (by LYG relative to number of colonoscopies and patient burden), have efficiency ratios below accepted thresholds, and offer more LYG than FIT or HSgFOBT. When screening adherence scenarios ranged from 10%-100%, the predicted LYG increased from 133.1 to 300.0 for triennial mt-sDNA, 96.3 to 318.1 for annual FIT, and 99.8 to 320.6 for annual HSgFOBT. The LYG from FIT screening was more sensitive to changes in adherence rates than mt-sDNA.

When assuming random adherence to an equal number of stool-based screening tests, 21 FIT tests would be needed to match the LYG with 9 mt-sDNA tests. A similar pattern was observed for individuals screened between 45-75 years of age (25 FIT vs 11 mt-sDNA tests).

There are limitations to this study. This analysis modeled cross-sectional, first-round participation rates and assumes a fixed probability of adherence longitudinally. As such, for stool-based tests with lower reported real-world adherence rates coupled with the potential for adherence to decline over time, the imperfect adherence scenarios used in this analysis may be overestimating outcomes. Adherence to follow-up colonoscopy was set to 100%, identical to CISNET model inputs, which may not be reflective of real-world adherence. The CRC-AIM model also does not incorporate the real-world colonoscopy performance for either endoscopist variance or differences in sensitivity between screening and follow-up colonoscopy. Retrospective analyses were used to determine imperfect adherence rates and the populations in those databases may not be generalizable across the population adherent in the first-round, or subsequent rounds, of CRC screening. The analyzed population data did not indicate age-related trends for mt-sDNA or patterns related to the type of Medicare coverage.

4.3.3 Budget impact and cost-consequence model[83]

The objective of the budget impact and cost-consequence model developed by Hathway et al was to evaluate the total costs and health consequences of a CRC screening program with colonoscopy, fecal immunochemical test (FIT), and expanded use of multi-target stool DNA (mt-sDNA, Cologuard) from the perspectives of integrated delivery networks (IDNs, sometimes referred to as health systems) and payers.[83]

A 10-year Markov cohort model with annual cycles was developed. CRC screening was simulated for eligible, average-risk individuals aged 50 to 75 years, and included a scenario analysis to look at individuals aged 45 to 75 years as well. A status quo scenario using a screening mix of colonoscopy (83%), FIT (11%), and mt-sDNA (6%), as well as an increased mt-sDNA (Cologuard) scenario using an increasing mt-sDNA (Cologuard) utilization of up to 28% over 10 years were modeled. One million adults enter the model based on the size of common US payer populations. Calculations from US Census data indicate that 38% of covered lives would be eligible for CRC screening based on age 50-75 years. An assumed 80% of those would be considered average risk for CRC based on family history. The simulated screening-eligible population was 302,000 adults aged 50-75 years, and in the scenario analysis 360,000 adults aged 45-75 years. The screening algorithm was based on the 2016 USPSTF CRC screening recommendations. Eligible individuals (screeners) in the model were screened with mt-sDNA (Cologuard), FIT, or colonoscopy. Flexible sigmoidoscopy and CT colonography were not included in the model as they are not commonly utilized in the US.

Model Framework

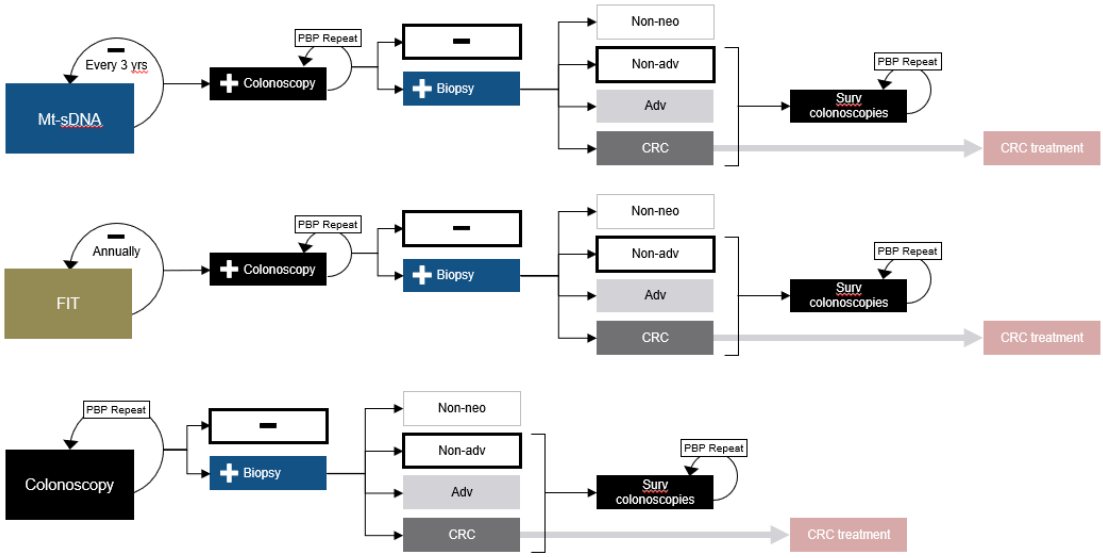
For a negative test, mt-sDNA (Cologuard) screeners enter a non-screening state and are eligible for screening again in 3 years according to guideline recommendations. Negative FIT screeners are eligible for rescreening annually, and colonoscopy screeners with negative results enter a non-screening state for the remainder of the time horizon (guidelines recommend rescreening at 10 years).

Positive stool-based screening results are referred to diagnostic colonoscopy. If a polyp or colorectal neoplasia is detected during a diagnostic or screening colonoscopy, a biopsy is performed and the pathology is determined to be either a non-neoplastic finding, a

nonadvanced adenoma, an advanced adenoma, or cancer (Conceptual Model Framework, Figure 8). Post-polypectomy surveillance is based on polyp categorization and the 2012 AGA guidelines. Individuals with a negative diagnostic or surveillance colonoscopy enter a non-screening state for the remainder of the model horizon.

The model allows stool-based screeners to change screening modalities during each eligible cycle over the 10-year period. Additionally, 16% of all colonoscopies were required to be repeated due to poor bowel preparation and AE rates due to colonoscopy were assumed to be based on whether or not a polypectomy is performed.

Figure 8. Conceptual Model Framework



FIT=Fecal immunochemical test; - =negative test result; + =positive test result; Non-neo=non-neoplastic finding; Non-adv=non advanced adenoma detected; Adv=advanced adenomas detected; CRC=colorectal cancer; PBP Repeat=repeat due to poor bowel prep; Surv colonoscopies= surveillance colonoscopies

Age-specific risk profiles for incidence and prevalence of CRC, adenoma, and death are assigned according to 5-year age bands at the beginning of each cycle. Within each cycle, 20% of each surviving population ages into the subsequent age group while those above 75 years age out of the model.

Modeling Results

Budget impact modeling suggests that increased mt-sDNA utilization leads to fewer screening and surveillance colonoscopies, less adverse events, and lower overall costs for both payers and IDNs (health systems), reducing overall screening program costs while maintaining screening adherence rates over 10 years.

Compared with the status quo, increased mt-sDNA use resulted in an additional 7,038 total CRC screenings and 4 CRC cases detected over the 10-year time horizon in the 45-75 age group as compared to the status quo.

Among a hypothetical cohort of 1 million individuals, the estimated 10-year cost-savings of increased mt-sDNA use was $19.1 million for the health systems perspective (IDN, Table 8) and $4.2 million for payers (Table 9) for eligible patients aged 45-75 years. The incremental savings per-person-per-month (PMPM) was $0.16 for the health system perspective and $0.03 for payers. For both perspectives, increased diagnostic colonoscopy costs were offset by reductions in screening colonoscopy costs and costs of adverse events.

For health systems, total savings were attributable to decreases in the cost of surveillance colonoscopies, screening colonoscopies, adverse events, and direct non-medical costs.

For payers, total savings were attributable to decreases in the cost of surveillance colonoscopies, across all screening modalities and adverse events.

Table 10. Incremental economic outcomes for the IDN perspective, ages 45-75 years

	Status Quo (6% mt-sDNA/11% FIT/83% CY)	**Increased mt-sDNA** (28% mt-sDNA/9% FIT/63% CY)	**Incremental Costs**
CRC screenings	$376,362,864	$392,018,192	−$15,655,327
Surveillance colonoscopies	$18,662,285	$18,935,870	−$273,586
Diagnostic colonoscopies	$8,234,466	$5,888,874	$2,345,592
Adverse events	$70,688,413	$73,020,075	−$2,331,663
CRC treatment	$183,248,638	$182,730,298	$518,340
Aggregate costs	**$**1,103,226,070	**$**1,122,409,102	**−$**19,183,032
Average PMPM costs	$9.19	$10.01	-$0.16

Table 11. Incremental economic outcomes for the payer perspective, ages 45-75 years

Costs	**Status Quo** (6% mt-sDNA/11% FIT/83% CY)	**Increased mt-sDNA** (28% mt-sDNA/9% FIT/63% CY)	**Incremental Costs**
CRC screenings	$444,144,314	$439,518,233	−$4,626,081
Surveillance colonoscopies	$20,767,798	$20,467,915	−$299,883
Diagnostic colonoscopies	$6,451,959	$9,020,673	$2,568,714
Adverse events	$73,020,075	$70,688,413	−$2,331,663
CRC treatment	$182,730,298	$183,248,638	$518,340
Aggregate costs	**$**727,114,444	**$**722,943,871	**−$**4,170,573
Average PMPM costs	$6.06	$6.02	-$0.03

Abbreviations. mt-sDNA, multi-target stool DNA; FIT, Fecal Immunochemical Test; CY, colonoscopy; CRC, Colorectal cancer; PPPM, per-person-per-month.

While this model aimed to address multiple limitations of other CRC screening models, some limitations remain. The model did not simulate the natural history of CRC. CRC and adenoma epidemiology estimates for this analysis were based on models, published in the peer-reviewed literature, which simulated underlying disease. Direct non-medical and indirect costs were applied on a per-person per modality basis, whereas in real case scenarios some of these costs may be fixed. Surveillance colonoscopy compliance was assumed to be 100% which may not reflect real-world rates.

4.3.4 Lowering the Colorectal Cancer Screening Age Improves Predicted Outcomes in Pre-Medicare and Medicare Populations in the CRC-AIM Microsimulation Model[84]

Using the validated CRC-AIM microsimulation model, this study estimated the impact of lowering the CRC screening initiation age on outcomes for triennial mt-sDNA or annual FIT screening strategies.

Screening strategies were simulated for individuals free of diagnosed CRC at age 40 and screened from ages 50–75 or 45–75. CRC incidence, mortality, and LYG were assessed. Adherence rates were assumed to be as previously reported (71% for mt-sDNA, 43% for FIT) or perfect (100%). Predicted outcomes of screening vs no screening were evaluated per 1000 individuals.

For individuals who initiated CRC screening at age 45 with reported adherence, triennial mt-sDNA and annual FIT resulted in 23.9 and 24.4 more predicted LYG, respectively, versus starting screening at age 50. With reported adherence, reductions in CRC incidence with mt-sDNA were 64.5% and 61.1% at screening start ages of 45 and 50, respectively, and with FIT were 53.7% and 49.9% (both $p< 0.0001$). Reductions in CRC mortality with mt-sDNA were 71.7% and 68.7% at screening start ages of 45 and 50, respectively, and with FIT were 62.7% and 59.0% (both $p< 0.0001$). With reported adherence, the number of CRC cases and deaths were lower with triennial mt-sDNA than annual FIT regardless of screening start age. Improvement in outcomes with earlier screening initiation were greater when assuming reported versus perfect adherence.

4.4 Cost-effectiveness analyses

Several cost-effectiveness analyses have been conducted on CRC screening modalities. Not all analyses use the same inputs and assumptions, and they may approach the question of cost-effectiveness from different perspectives.

An analysis by D'Andrea et al focused on the impact of adherence on the cost-effectiveness of CRC screening modalities.[85] Effectiveness was defined in terms of CRC incidence and mortality, incremental LYG, number of colonoscopies required, and adverse events. Under the perfect (100%) adherence scenario, noninvasive CRC screening strategies (hs-gFOBT, FIT, mt-sDNA, methylated *SEPT9* (m*SEPT9*)) averted similar numbers of CRC cases (42-45) and CRC deaths (25-26) per 1000 individuals. In the same scenario, colonoscopy averted 46 cases and 26 deaths, computed-tomography colonoscopy averted 39 cases and 23 deaths, and flexible

sigmoidoscopy averted 32 cases and 19 deaths per 1000 individuals. The authors concluded that adherence rates higher than 65%-70% are needed for stool-based CRC screening modalities to match the benefits of colonoscopy.

When assuming reported adherence rates, m*SEPT9* annually averted 37 CRC cases and 23 CRC deaths, colonoscopy averted 34 cases and 20 deaths, and stool-based tests (mt-sDNA, FIT, hs-gFOBT) averted 16-25 cases and 10-16 deaths per 1000 individuals. At the same reported adherence (42.6%), mt-sDNA averted more cases of CRC and more CRC deaths than FIT, likely due to the increased performance of the test.

There are limitations to the analysis by D'Andrea et al. The modeled benefit associated with annual m*SEPT9* screening may be due to the higher rate of false positives (20%) requiring more patients to undergo diagnostic colonoscopy (>1500 colonoscopies per 1000 screened). Adherence to the mt-sDNA test was assumed to be the same as FIT due to a lack of published evidence on mt-sDNA adherence at the time the study was conducted. Data suggest that adherence to FIT is not static and likely declines over time.[16] Lastly, the model assumes 85% adherence with the m*SEPT9* blood test based on studies in colonoscopy nonadherent patients. Adherence with m*SEPT9* as a noninvasive CRC screening test prior to colonoscopy is unknown and this use would be off-label.

A separate analysis by Naber et al aimed to evaluate whether mt-sDNA testing is a cost-effective alternative to other CRC screening strategies that are currently reimbursed by CMS.[86] The patient population studied in this analysis was strictly those individuals eligible for Medicare (previously unscreened US 65-year-olds). Using the established CISNET models, mt-sDNA testing was cost-effective compared to no screening but was not found to be cost-effective compared to annual FIT or colonoscopy every 10 years. Compared to no screening, triennial mt-sDNA screening resulted in 82 (range: 79-88) life-years gained (LYG) per 1000 simulated individuals. This was more than for five-yearly sigmoidoscopy (80 [range: 71-89] LYG), but fewer than for every other simulated strategy. Additionally at its 2017 CMS reimbursement rate of $512, mt-sDNA was the most costly strategy evaluated. The Naber study concludes that mt-sDNA testing adherence would need to be 31-53% higher than other screening modalities to be cost-effective relative to the other tests. Further, if patients complete mt-sDNA testing who were not adherent to other screening modalities, its effectiveness would increase. This underscores the importance of patient adherence and its impact on cost-effectiveness of CRC screening modalities.

There are limitations to the analysis by Naber et al. The model assumes 100% adherence to screening and diagnostic follow-up, which does not reflect real-world screening behaviors. This study modeled unscreened 65-year-olds that, in a real-world setting, likely would have already declined screening colonoscopy, making the 100% adherence assumption unrealistic. The CISNET models also assume that the result from one round of testing is independent from the result of subsequent rounds. This may underestimate the rate of false negative results. Costs of each test were based on Medicare reimbursement rates, and the rates used are from two different fee schedule years that do not reflect current fees or real-world costs. The authors also do not consider the indirect costs of patient navigation programs. Robust navigation programs have been shown to improve adherence rates and may require additional financial resources outside of the costs of CRC screening tests themselves.

Modeling data from Ladabaum and Mannalithara shows that over the course of 30 years, a person screened with mt-sDNA will incur 1.4 colonoscopies, whereas each person screened with FIT or colonoscopy will incur 1.5 and 3.8 colonoscopies, respectively.[4] Over time, it is projected that the overall colonoscopies generated from mt-sDNA and FIT will be very similar. This is further demonstrated by the CISNET modeling from USPSTF around lifetime number of colonoscopies performed per 1000 asymptomatic individuals ages 50 to 75. Mt-sDNA generates 1714 colonoscopies, FIT generates 1757 colonoscopies, and colonoscopy generates 4049 colonoscopies.[24]

Ladabaum and Mannalithara also found that "mt-sDNA every 3 years could be cost effective at current mt-sDNA test costs if the patient support program that is included in its test cost could yield participation rates higher than 1.7-fold relative to the participation rates with FIT."[4]

Real-world evidence-based adherence values used in comparative effectiveness models more accurately assess the impact of colorectal cancer screening on health system populations. The recently developed CRC-AIM model uses real-world data for adherence of stool-based testing and for colonoscopy follow-up of a positive initial colorectal cancer screen illustrate the comparative effectiveness of colorectal cancer screening strategies. When modeling real-world adherence rates of 40% for annual FIT and 70% for triennial mt-sDNA derived from a critical assessment of meta-analyses and retrospective cross-sectional data in systems using FIT without a navigation program, the number of LYGand reductions in CRC incidence and mortality were higher for triennial mt-sDNA than annual FIT.[17, 37, 87] Adherence to stool-based colorectal cancer screening tests appears to be an important, yet under-appreciated, factor when assessing the relative comparative-effectiveness of colorectal cancer screening.

4.4.1 Cost-Effectiveness of mt-sDNA as compared to no screening

The objective of the cost-effectiveness analysis conducted by Berger and colleagues was to evaluate the cost-effectiveness and economic impact of the mt-sDNA test for CRC screening in the context of current screening guidelines and use of colonoscopy. The patient population and characteristics of CRC and its natural history were taken into account. The study used the Archimedes cost-effectiveness model, created by the ACS and Archimedes Inc., and provided data supporting the clinical effectiveness and cost effectiveness of a three-year testing interval for mt-sDNA. The model demonstrates that mt-sDNA used every three years compares favorably to colonoscopy every 10 years. The analysis shows a CRC incidence reduction of 57% and mortality reduction of 67%, compared to 65% and 73% respectively, for colonoscopy every 10 years. The cost per quality adjusted life year (QALY) of screening every 3 years with mt-sDNA resulted in $11,313/QALY compared to no screening.[36]

Table 12. Modeled Reductions in CRC Incidence and CRC Mortality with Mt-sDNA Compared with No Screening Using the Archimedes Model[36]

Screening Approach	Modeled reduction in CRC incidence (%)	Modeled reduction in CRC mortality (%)	QALY gained relative to no screening	Cost per QALY
No screening	0	0	-	-
Colonoscopy every 10 years	65	73	0.1330	
Mt-sDNA every year	63	72	0.1290	$20,178

Mt-sDNA every 3 years	57	67	0.1160	$11,313
Mt-sDNA every 5 years	52	62	0.1050	$7,388

A 2021 study by Fendrick et al used CRC-AIM microsimulation modeling to study adherence to initial stool-based screening (FIT and mt-sDNA]) and follow-up colonoscopy (after a positive stool test) in average risk individuals on CRC outcomes (LYG) and CRC incidence and mortality reductions (per 1000 individuals) versus no screening. Primary analyses incorporated published mt-sDNA (71%) or FIT (43%) screening adherence, with follow-up colonoscopy adherence ranging from 40%-100%. Three secondary adherence modeling simulations were assessed: 100% adherence for stool-based screening and colonoscopy follow-up (S1), published adherence for stool-based screening with 100% adherence to colonoscopy follow-up (S2) and published adherence for both stool-based screening and colonoscopy follow-up after positive mt-sDNA (73%) or FIT (47%) (S3). S1 (100% adherence for stool screening and colonoscopy follow-up) favored FIT versus mt-sDNA; LYG 316 vs. 297; CRC incidence reduction 68% vs. 64%; CRC mortality reduction 76% vs.72%. Using published adherence for stool-based screening with 100% adherence to colonoscopy follow-up (S2), mt-sDNA resulted in 284 LYG vs. 245 for FIT, a CRC incidence reduction of 61% vs. 50%, as well as CRC mortality reduction 69% vs. 59% (mt-sDNA vs. FIT). S3 also favored mt-sDNA over FIT, with LYG 203 vs. 113, CRC incidence reduction 43% vs. 23%, CRC mortality reduction 49% vs. 27%.[88] There are limitations associated with this study. It relies on published reported adherence rates, which may not be generalizable across the population of people eligible for screening, and a paucity of data evaluating the rate of adherence to follow-up colonoscopy after a positive mt-sDNA test.

4.4.2 Real-world cost-effectiveness of stool-based colorectal cancer screening in a Medicare population[89]

This cost-effectiveness analysis from the perspective of Medicare as a primary payer used CRC–AIM to estimate cost and clinical outcomes for triennial mt-sDNA, annual FIT and annual FOBT screening strategies in a simulated cohort. The cohort consisted of one million, average risk US adults aged 65 years, who were assumed to either be previously unscreened or initiating screening upon entry to Medicare. The primary outcome was the incremental cost effectiveness ratio (ICER) using QALYs. Secondary analyses evaluated other cost and clinical outcomes including incidence and mortality reduction, total lifetime screening costs, and QALYs gained.

Test performance (sensitivity and specificity) are identical to those used in previous CISNET modeling analyses. including those used to inform the 2016 USPSTF recommendation statement. Reported real-world adherence rates for initial stool-based screening and follow-up colonoscopy were defined as 71.1% and 73.0% for mt-sDNA, 42.6% and 47.0% for FIT, and 33.4% and 47.0% for FOBT, respectively. Only direct medical costs were included in the analysis. This included the cost of mt-sDNA, screening costs associated with FIT and FOBT, the cost of surveillance colonoscopy, colonoscopy complication costs, and CRC-related direct medical costs stratified by stage and time since diagnosis.

Three scenarios were considered to evaluate the impact of reported real-world screening adherence.

Table 13. Reported test-specific adherence rates

	mt-sDNA	FIT	FOBT	Follow-up colonoscopy

Scenario 1	100%	100%	100%	100%
Scenario 2	71.1%	42.6%	33.4%	100%
Scenario 3	71.1%	42.6%	33.4%	mt-sDNA: 73.0% FIT: 47.0% FOBT: 47.0%

When 100% adherence is assumed for all stool-based screening strategies and follow-up colonoscopies (scenario 1), the total number of screening tests per 1,000 patients was highest for FIT (6,704) and the total number of colonoscopies per 1,000 patients were highest for FOBT (1,248). Assuming 100% adherence to all stool-based screening and follow-up colonoscopies, mt-sDNA was dominated (i.e. costs more and is less effective) by both FIT and FOBT. When reported real-world adherence inputs were used for initial stool-based screening, and 100% adherence was assumed for follow-up colonoscopies (scenario 2), the total number of screening tests per 1,000 patients remained highest for FIT (3,296) compared to other screening strategies, while the total number of colonoscopies per 1,000 patients was highest for mt-sDNA (850). When considering reported real-world adherence rates for stool-based screening, mt-sDNA becomes cost-effective versus both FIT ($62,814/QALY) and FOBT ($39,171/QALY) at a WTP threshold of $100,000/QALY.

When reported real-world adherence rates were included for both initial stool-based screening and follow-up colonoscopy scenario 3), the total number of screening tests per 1,000 patients were highest for FIT (3,300) and exceeded the total number of screening tests for any strategy in Scenario 2. While the total number of colonoscopies decreased across all screening strategies compared to Scenario 2, mt-sDNA still reported the highest total number of colonoscopies per 1,000 patients (632). As in Scenario 2, reductions in CRC incidence and mortality were highest for mt-sDNA (27.0% and 33.5%, respectively), though the magnitude of reduction was decreased. Total costs and QALYs remained highest for mt-sDNA under this scenario ($6,525 and 9,3694 QALYs, respectively) When considering reported real-world adherence rates for all initial stool-based screening and follow-up colonoscopies, the cost-effectiveness of mt-sDNA vs. FIT and FOBT is improved ($31,725/QALY and $28,465/QALY, respectively) as compared to Scenario 2.

As has been previously reported, all stool-based screening modalities were cost-effective compared to no screening. When reported real-world adherence rates were considered, mt-sDNA was the more cost-effective option and resulted in greater reductions in CRC incidence and mortality.

5.0 ADDITIONAL SUPPORTING EVIDENCE

5.1 Clinical Practice Guidelines

Table 14. Summary of CRC Screening Recommendations

Organization	USPSTF[20]	ACS[23]	NCCN®[25,a,b]	US MSTF[27c]

Most recent update	May 18, 2021 (online) Published in *JAMA*	May 30, 2018 (online) Published in *CA Cancer J Clin*	March 25, 2021 Published on *nccn.org*	June 6, 2017 (online) Published in *Am J of Gastroenterol*
Age to begin screening (Average Risk)	50 years *(Grade A recommendation)*[e] 45 years *(Grade B recommendation)*[f]	50 years *(strong recommendation)*[i] 45 years *(qualified recommendation)*[h]	45 years	50 years overall; *(strong recommendation*[j]*, high-quality evidence)* 45 years for African Americans *(weak recommendation*[k]*, very-low-quality evidence)*
Age to end screening	75 years *(Grade C recommendation)*[g]	75 years *(qualified recommendation)*[h]	75 years	75 years or when life expectancy is <10 years *(weak recommendation*[k]*, low-quality evidence)*
Screening after 75 years	Individualized decision for screening *(Grade C recommendation)*[g]	Individualized decision for screening at ages 76-85 years *(qualified recommendation)*[h]	Individualized decision for screening at ages 76-85 years (include a discussion of the risks & benefits based on comorbidity status and estimated life expectancy)	Stop screening when life expectancy is <10 years; recommendation to stop screening can be based on patient age and comorbidities *(weak recommendation*[k]*, low-quality evidence)*
Choice of test	Clinicians and patients may consider a variety of factors in deciding which test may be best for each person	• High-sensitivity stool-based test or a structural (visual) exam, depending on patient preference & test availability *All positive results on non-colonoscopy screening tests should be followed up with a timely colonoscopy*	• Multiple modalities exist, and the choice should be based on patient preference and resource availability Any screening is better than none	Recommend colonoscopy every 10 years or annual FIT as first-tier options for screening *(strong recommendation*[j]*, moderate quality evidence)*
gFOBT or hs-FOBT	Annual hs-gFOBT	• Annual hs-gFOBT	• Annual guaiac-based test (hs-gFOBT)	No recommendation

Organization	USPSTF[20]	ACS[23]	NCCN®[25,a,b]	US MSTF[27c]
Colonoscopy	Every 10 years	Every 10 years	Every 10 years	Every 10 years (Tier 1) *(strong recommendation[j], moderate-quality evidence)*
FIT	Annual	Annual	Annual	Annual (Tier 1) *(strong recommendation[j], moderate-quality evidence)*
mt-sDNA†††††	Every 1 to 3 years	Every 3 years	Every 3 years	Every 3 years (Tier 2) *(strong recommendation[j], low-quality evidence)*
CT colonography	Every 5 years	Every 5 years	Every 5 years	Every 5 years (Tier 2) *(strong recommendation[j], low-quality evidence)*
Flex Sig	Every 5 years	Every 5 years	Every 5-10 years	Every 5 or 10 years (Tier 2) *(strong recommendation[j], high-quality evidence)*
FS with FIT	FS every 10 years with annual FIT	No recommendation	FS every 10 years with annual FIT is an alternate strategy	No recommendation
Capsule colonoscopy	No recommendation	No recommendation	No recommendation	Every 5 years (Tier 3) *(weak recommendation[k], low-quality evidence)*

CRC: colorectal cancer; gFOBT: guaiac fecal occult blood test; hs-FOBT: high sensitivity fecal occult blood test; mt-sDNA: multi-target stool DNA test; FS: flexible sigmoidoscopy.

b. NCCN® makes no warranties of any kind regarding their content, use, or application and disclaims any responsibility for their application or use in any way.
c. All recommendations are category 2A unless otherwise indicated. Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
d. MSTF includes the American College of Gastroenterology (ACG), the American Gastroenterological Association (AGA), and the American Society for Gastrointestinal Endoscopy (ASGE).
e. Joint guidelines from ACS, the MSTF, and the American College of Radiology.
f. Grade A: The USPSTF recommends the service. There is high certainty that the net benefit is substantial.
g. Grade B: The USPSTF recommends this service. There is high certainty that the net benefit is moderate or there is moderate certainty that the net benefit is moderate to substantial.
h. Grade C recommendation indicates selectively offering to individuals based on professional judgment and patient preferences; at least moderate certainty that net benefit is small.
i. Qualified Recommendation indicates there is clear evidence of benefit (or harm) but less certainty either about the balance of benefits and harms or about patients' values and preferences, which could lead to different individual decisions.
j. Strong recommendation conveys the consensus that the benefits of adherence to the intervention outweigh the undesirable effects and the most patients would choose the intervention.
k. Strong recommendation includes those that would be chosen by most informed patients.
l. Weak recommendation is that where patient values and preferences might play a larger role than evidence quality.
m. Tier 1: Screening tests recommended as cornerstones of screening regardless of how screening is offered.
n. Tier 2: Appropriate screening tests that have disadvantages relative to the Tier 1 tests.
Tier 3: Screening tests with limited evidence and obstacles to use.

††††† Guidelines may refer to mt-sDNA by different names including FIT-Fecal DNA, sDNA and sDNA-FIT

5.2 Health Technology Assessments and Systematic Reviews

None presented.

5.3 Compendia

mt-sDNA (Cologuard) is included in the NCCN® guidelines and UpToDate® (part of Wolters Kluwer/Lexi-Drugs). NCCN® guidelines recommend mt-sDNA testing (Cologuard) for CRC screening in average risk adults aged 45 years and older at three-year intervals.[25]

UpToDate®, an online, evidence-based, physician-authored clinician decision support resource accessed by over one million clinicians references the use of mt-sDNA (Cologuard) every 3 years as a CRC screening option for average-risk patients.[41]

5.4 Other Economic or Outcomes Evidence

None presented.

5.5 Impact on Quality

None presented.

5.6 Other Evidence or Information

In previous sections of this dossier, the assertion is made that the case for extending coverage for mt-sDNA (Cologuard) is strong. In this section of the dossier, the strength of this assertion is made evident by a listing of government health programs and commercial health plans that have already extended coverage to mt-sDNA (Cologuard) based on the clinical data, the numerous large medical groups that had adopted mt-sDNA (Cologuard) as their standard of care, and, finally, the numerous coverage mandates at a state level that supersede medical policy and further compel coverage.

Medicare National Coverage Determination

The Medicare National Coverage Determination (NCD) 210.3 for mt-sDNA (Cologuard) has been in effect since October 9, 2014 and states as follows:

"After considering public comments and consulting with appropriate organizations, the Centers for Medicare & Medicaid Services (CMS) has determined that the evidence is sufficient to cover Cologuard™ - a multitarget stool DNA test - as a colorectal cancer screening test for asymptomatic, average risk beneficiaries, aged 50 to 85 years."[90]

And continues:

"Medicare Part B will cover the Cologuard™ test once every three years for beneficiaries who meet all of the following criteria:

Age 50 to 85 years,

Asymptomatic (no signs or symptoms of colorectal disease including but not limited to lower gastrointestinal pain, blood in stool, positive guaiac fecal occult blood test or fecal immunochemical test), and

At average risk of developing colorectal cancer (no personal history of adenomatous polyps, colorectal cancer, or inflammatory bowel disease, including Crohn's Disease and ulcerative colitis; no family history of colorectal cancers or adenomatous polyps, familial adenomatous polyposis, or hereditary nonpolyposis colorectal cancer)."[90]

This NCD, which is specific to mt-sDNA (Cologuard), has impact throughout the Medicare program including Part B and Medicare Advantage (or Part C). The 2019 CMS Program Data has identified this to include approximately 61.5 million beneficiaries, 38.6 million in Medicare and 22.9 million in Medicare Advantage and other Health Plan Enrollment.[91]

Commercial Health Plans

More than 94% of commercial health plans have extended coverage to mt-sDNA (Cologuard) through positive medical policies put in place since in its initial FDA approval in August of 2014. In addition, most national and key regional health plans consider Exact Sciences Laboratories to be an in-network provider. More information on mt-sDNA (Cologuard) coverage is available at the following website address: https://www.cologuard.com/insurance.

State Medicaid programs

There are currently 33 state Medicaid programs that cover mt-sDNA (Cologuard); they are: Arizona, California, Colorado, Connecticut, Delaware, Georgia, Hawaii, Idaho, Illinois, Indiana, Kentucky, Maine, Maryland, Massachusetts, Michigan, Minnesota, Mississippi, Missouri, Montana, New Hampshire, New Jersey, New Mexico, New York, North Carolina, North Dakota, Ohio, Oklahoma, Pennsylvania, South Dakota, Vermont, West Virginia, Virginia, and Wisconsin.

States with Mandated Coverage

As of January 2019, 29 states and the District of Columbia have colorectal cancer screening mandates that require coverage of mt-sDNA (Cologuard) for fully-insured members. These states provide coverage to 61% of the total US population according to the 2010 census.[47] These jurisdictions and references to their mandate citations are listed in Table 13.

While each of these mandates may differ somewhat, the most common mandate is that health plans operating in the specified state must extend coverage to all CRC screening services recommended in the most recent ACS recommendations. In such cases, mt-sDNA (Cologuard),

as a specifically named test in the 2018 update of the ACS recommendations and the USPSTF Recommendation Statement, would be mandated for coverage once every three years.[20, 23, 24]

Coding

On January 1, 2016, a new Category I CPT code became effective for mt-sDNA (Cologuard): "Oncology (colorectal) screening, quantitative real-time target and signal amplification of 10 DNA markers (*KRAS* mutations, promoter methylation of *NDRG4* and *BMP3*) and fecal hemoglobin, utilizing stool, algorithm reported as a positive or negative result." Mt-sDNA (Cologuard) is the only test that fits the long description at the present time. Category I codes are only assigned to products that have FDA approval or clearance (if such approval is required), are widely used by physicians in a manner that is consistent with current medical practice, and which have documented clinical efficacy. Specific coding for mt-sDNA (Cologuard) has been in effect since January 1, 2015.[45]

Table 15. List of Jurisdictions with Mandates for Coverage of CRC Screening

	Jurisdiction	Citation
1	Alabama	Ala. Code § 27-57-2
2	Alaska	AS21.42.377
3	Arkansas	Ark. Code Ann. § 23-79-1202
4	California	Health & Safety Code 1367.665
5	Colorado	Section 10-16-104 (18), C.R.S.
6	Connecticut	Conn. Gen. Stat. Ann. § 38a-492k (Ind) and 38a-518k
7	Delaware	18 DE Code § 3562 (2012 through 146th Gen Ass)
8	District of Columbia	DC Code § 31-2931
9	Georgia	GA Code § 33-24-56.3
10	Hawaii	HI Rev Stat § 432:1-617 (2013)
11	Illinois	215 ILCS 5/356x
12	Indiana	Ind. Code § 27-8-14.8-3
13	Kentucky	KRS § 304.17A-257
14	Maine	24-A MRS §§ 2763, 2847-N, 4254
15	Maryland	MD Ins. Code § 15-837
16	Minnesota	MN Code 62A.30
17	Missouri	MO Rev. Stat. 376.1250
18	Nebraska	Neb. Rev. Stat. § 44-7,102
19	Nevada	NRS 695G.168
20	New Jersey	NJ Stat. 17B:26-2.1u
21	New Mexico	NM Stat § 59A-23-7.6
22	North Carolina	NCGS §58-3-179
23	Oklahoma	OK Stat. §36-6060.8a
24	Oregon	OR Rev Stat § 743A.124 (2015)
25	Rhode Island	RI Gen. L. § 27-18-58
26	Tennessee	Tenn. Code Ann. § 56-7-2363
27	Texas	TIC Ch. 1363.001-1363.005; TIC Comm Bull #B-0006-09
28	Washington	WA Rev Code § 48.43.043 (2014)
29	Wisconsin	WIC bulletin dated June 8, 2016
30	Wyoming	WY Stat. § 26-19-107(j)

On August 8, 2016 CMS issued an updated Evidence of Coverage notice for Medicare Advantage plans that affirms that such plans must include coverage of mt-sDNA (Cologuard) every three years without patient coinsurance, copayments, or deductibles. This is significant because it reflects recognition from CMS that mt-sDNA (Cologuard) is included among A-graded preventive services under the recently updated USPSTF CRC screening recommendations.[46]

Pricing

The list price for mt-sDNA (Cologuard) is currently $681.[92]

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