

Retrospective Cohort Study

Multitarget stool DNA tests increases colorectal cancer screening among previously noncompliant Medicare patients

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Abstract

AIM

To determine the uptake of noninvasive multitarget stool DNA (mt-sDNA) in a cohort of colorectal cancer (CRC) screening non-compliant average-risk Medicare patients.

METHODS

This cross sectional primary care office-based study examined mt-sDNA uptake in routine clinical practice among 393 colorectal cancer screening non-compliant Medicare patients ages 50-85 ordered by 77 physicians in a multispecialty group practice (USMD Physician Services, Dallas, TX) from October, 2014-September, 2015. Investigators performed a Health Insurance Portability and Accountability Act compliant retros-

pective review of electronic health records to identify mt-sDNA use in patients who were either > 10 years since last colonoscopy and/or > 1 year since last fecal occult blood test. Test positive patients were advised to get diagnostic colonoscopy and thereafter patients were characterized by the most clinically significant lesion documented on histopathology of biopsies or excisional tissue. Descriptive statistics were employed. Key outcome measures included mt-sDNA compliance and diagnostic colonoscopy compliance on positive cases.

RESULTS

Over 12 mo, 77 providers ordered 393 mt-sDNA studies with 347 completed (88.3% compliance). Patient mean age was 69.8 (50-85) and patients were 64% female. Mt-sDNA was negative in 85.3% (296/347) and positive in 14.7% (51/347). Follow-up colonoscopy was performed in 49 positive patients (96.1% colonoscopy compliance) with two patients lost to follow up. Index findings included: colon cancer (4/49, 8.2%), advanced adenomas (21/49, 42.9%), non-advanced adenomas (15/49, 30.6%), and negative results (9/49, 18.4%). The positive predictive value for advanced colorectal lesions was 51.0% and for any colorectal neoplasia was 81.6%. The mean age of patients with colorectal cancer was 70.3 and all CRC's were localized Stage I (2) and Stage II (2), three were located in the proximal colon and one was located in the distal colon.

CONCLUSION

Mt-sDNA provided medical benefit to screening non-compliant Medicare population. High compliance with mt-sDNA and subsequent follow-up diagnostic colonoscopy identified patients with clinically critical advanced colorectal neoplasia.

Key words: Multitarget stool DNA; Advanced adenoma; Screening compliance; Colonoscopy; Colorectal cancer screening; Preventive

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Core tip: The availability of multitarget stool DNA (mt-sDNA) colorectal cancer screening led to high screening compliance (88%) and diagnostic colonoscopy compliance on mt-sDNA positive cases (96%) in a cohort of previously screening non-compliant Medicare patients ages 50-85 years in a multi-specialty group practice setting.

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INTRODUCTION

Colorectal cancer (CRC) is among the top three causes of cancer related death in men and women in the United States^[1]. Despite the longstanding availability and recent broad third party coverage of screening tests without patient out-of-pocket expense (including fecal occult blood (FOBT/FIT), sigmoidoscopy, and colonoscopy) under the United States Affordable Care Act, a large percentage of Americans are not up to date with CRC screening^[2,3]. Given the reluctance of some patients to have an invasive structural screening test like sigmoidoscopy or colonoscopy or the required annual testing using FOBT/FIT, a high sensitivity noninvasive screening test with a longer screening interval may provide an effective alternative that could increase the participation in and performance of CRC screening programs^[4-7].

USMD (USMD, Dallas, TX) is an integrated health system in Dallas/Fort Worth, Texas and is focused on preventive care to improve population health. Patient compliance with colorectal cancer screening is a quality metric for USMD primary care physicians and is documented with the USMD electronic health record (EHR). Despite repeated efforts by clinicians, some patients continuously refuse CRC screening *via* colonoscopy and FOBT/FIT. We implemented mt-sDNA (mt-sDNA) screening in general clinical practice to provide a new strategy to increase colorectal cancer screening in our previously screening-non-compliant Medicare patients.

Mt-sDNA is an FDA approved, noninvasive, high-sensitivity CRC screening strategy (Cologuard[®], Exact Sciences Corporation, Madison WI) for patients at average risk for colorectal cancer. Average risk includes individuals 50 years of age and older who are asymptomatic and have no personal history of colorectal cancer or colorectal adenoma; no family history of a first degree relative developing colorectal cancer at age 60 or younger; or of any two first degree relatives with colorectal cancer developed at any age; or an inherited predisposition to colorectal cancer including adenomatous polyposis coli or Lynch syndrome (Hereditary non-polyposis colorectal cancer) or no other rare inherited CRC predispositions, or inflammatory bowel disease.

Mt-sDNA is a candidate test for increasing population based screening. It has documented superior sensitivity for CRC, high grade dysplasia, advanced adenoma, and sessile serrated adenoma/polyps compared to fecal immunochemical testing (FIT) alone, albeit with somewhat lower specificity^[8,9]. The CRC screening system which includes mt-sDNA was purposefully designed to address patient preference issues including the need for screening support, which is managed through an embedded nationwide patient navigation system. Mt-sDNA was recently included as a recommended routine CRC screening

test by the United States Preventive Services Task Force (2016) and is included in the American Cancer Society (2014) and National Comprehensive Cancer Network (2016) screening guidelines at three-year intervals^[10-12]. It is covered by Centers for Medicare and Medicaid Services (CMS) at three year intervals and described by test specific descriptive codes (HCPCS G0464, CPT code 81528)^[13]. The National Committee on Quality Assurance (NCQA) has added mt-sDNA to the 2017 Healthcare Employer Data Information Set (HEDIS 2017) which provides physicians the opportunity to receive quality credit for using mt-sDNA screening in the HEDIS effectiveness-of-care domain which covers preventive health measures^[14].

Mt-sDNA is a multi-analyte test with algorithmic analysis that provides a single qualitative dichotomous positive or negative test result for each patient^[15]. The test requires no preparation, change in medication, or dietary restrictions. The test result is based on a composite score derived from the quantitative values of the 11 biomarkers included in the test: 10 DNA markers [aberrantly methylated *NDRG4* and *BMP3* gene promoter regions, 7 *Kras* point mutations, β -*actin* (reference gene)] and fecal hemoglobin (immunochemical technique) analyzed as a group in a logistic regression algorithm^[8]. Scores exceeding the composite score threshold are reported qualitatively as "positive." Individual biomarker results are not reportable and are not associated with biomarker specific reference ranges for clinical evaluation.

This study evaluated mt-sDNA uptake in a cohort of screening non-compliant average-risk Medicare patients aged 50-85 and the subsequent diagnostic colonoscopy usage for those patients with a positive mt-sDNA result. We correlated positive mt-sDNA results with colonoscopy findings.

MATERIALS AND METHODS

Physicians at USMD began offering mt-sDNA routinely to patients as of October 2014 in an effort to improve CRC screening among previously non-compliant Medicare patients. We performed a Health Insurance Portability and Accountability Act compliant retrospective EHR-based medical records review (October, 2014-September, 2015) to identify mt-sDNA use in average-risk Medicare patients treated by USMD Physician Services (Dallas, Texas) who were not previously compliant with colorectal cancer screening. We offered mt-sDNA to patients who were either > 10 years since last colonoscopy and/or > 1 year since last fecal occult blood test. Follow-up colonoscopy was advised for all patients with a positive mt-sDNA result.

Mt-sDNA was ordered as part of the USMD physician's daily clinical practice without any modification. Providers ordered the test, patients engaged with the mt-sDNA patient navigation system, collection kits were shipped directly to patients' homes, samples

were collected by the patients, and the completed tests were returned to the laboratory using pre-paid shipping labels. The samples were then processed and analyzed and the results reported to the USMD ordering physicians. The kit and patient process is illustrated in Figure 1.

Mt-sDNA testing is provided by a single source clinical laboratory (Exact Sciences Laboratories, LLC, Madison, WI, United States) that is accredited by the College of American Pathologists and certified by the CMS Clinical Laboratory Improvement Amendments (CLIA '88) program for high complexity testing. It is supported by a patient navigation system that is available *via* telephone at all hours, every day and supports patients, ordering providers, and health systems to assure successful screening events. A laboratory report with an mt-sDNA qualitative "Positive" or "Negative" clinical result was the measure of a completed test that was used to calculate screening compliance with a test order (intent-to screen compliance). Data was compiled and analyzed using descriptive statistics.

USMD physicians referred the patients with positive results for diagnostic colonoscopy. Patients with negative results were returned to the screening pool to be screened again in three years.

Colonoscopy and pathology findings on all mt-sDNA positive patients were tabulated and included: histologic classification, size, location, and total number of adenomas and non-adenomatous polyps. Patients were categorized by the most advanced finding (index lesion) as described on pathologic analysis of colonoscopically directed biopsies and any subsequent surgical excisional tissues^[8]. Major categories of index lesions were CRC, advanced adenoma (AA), non-advanced adenoma (NAA), and negative findings. Advanced adenomas are further categorized as: tubular adenoma (TA) with high grade dysplasia or significant villous component of any size; and tubular adenoma or sessile serrated adenoma/polyp without other advanced features \geq 10 mm in greatest dimension. Non-advanced adenomas are further characterized as; 1-2 TA's > 5 mm but < 10 mm; > 3 TA's < 10 mm; 1-2 TA's \leq 5 mm. as these may have differing post-colonoscopy clinical surveillance intervals. Negative findings include absence of colorectal neoplasia but may include the presence of hyperplastic polyps (HP's) < 10 mm. High risk patients were excluded from this study including those patients who were symptomatic and/or had a significant personal or family history of colorectal neoplasia or inflammatory bowel disease.

RESULTS

Over 12 mo, 77 providers ordered mt-sDNA tests for 393 screening-noncompliant Medicare patients and 347 patients completed the test (88.3% intent-to-screen compliance). Successfully screened patients (347) had a mean age of 69.8 (range 50-85) and

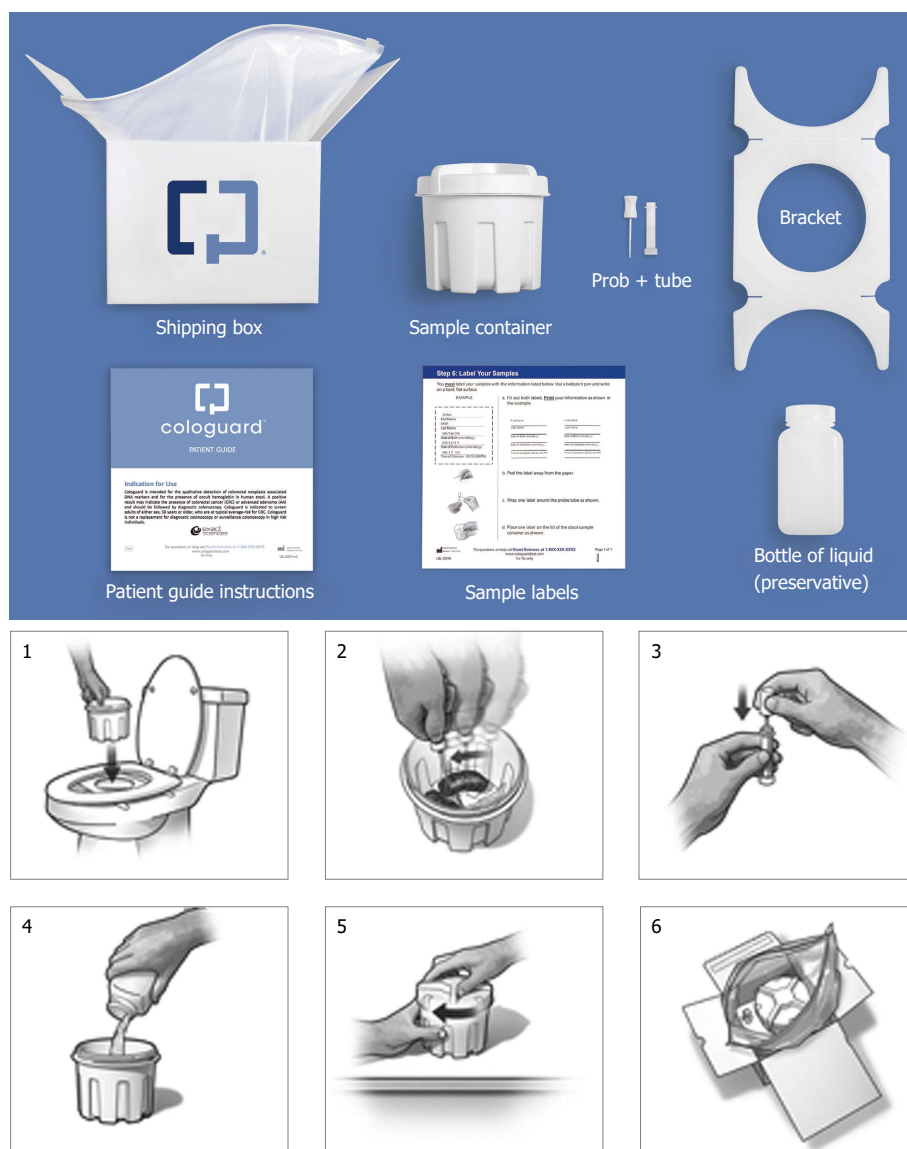


Figure 1 Multi-target stool DNA collection kit and collection process. A: Contents of Cologuard collection kit: Top row, left to right: collection kit/shipping box, stool collection container, hemoglobin sample tube, collection container support bracket for toilet; Bottom row - instructions for use, DNA preservative buffer; B: Collection process - 1, set up collection container; 2 and 3, sample for hemoglobin; 4, add DNA preservative buffer; 5, close container; 6, replace hemoglobin tube and sample container in box, seal and ship.

were 64% female. Unsuccessfully screened patients (46; 11.7%) had a mean age of 71.2 (range 61-83), and were 59% female. The mt-sDNA result was negative in 296 patients (85.3%), mean age 69.1 (range 50-85) and 61% female and positive in 51 patients (14.7%), mean age 71.8 (range 65-83), 49% female (Figure 2).

Diagnostic colonoscopy was subsequently performed on 49 mt-sDNA positive patients (96.1% diagnostic colonoscopy compliance) and two patients were lost to follow up. Index findings among 49 positive patients included: 4 patients with colorectal cancer (8.2%), 21 patients with advanced adenoma (42.9%), 15 patients with non-advanced adenoma (30.6%), and 9 patients with negative results (18.4%) (Table 1). The positive predictive value for advanced colorectal neoplasia was 51.0% (25/49) and for any colorectal

neoplasia was 81.6% (40/49).

The four CRC patients were ages 66, 68, 73, and 74 years and included 2 men and 2 women. All CRC's were localized, Stage I (2) and Stage II (2), and three were located in the proximal colon and one was located in the distal colon. The 21 advanced adenoma patients, median age 73 (65-83), 43% female (9/21), included: one with high-grade dysplasia in a 20 mm rectal tubulovillous adenoma in a 72-year-old female; 9 with tubulovillous or villous adenoma; 10 with tubular adenoma ≥ 10 mm without other advanced features; and one with a 10 mm sessile serrated adenoma/polyp. Index lesion location was specified in 20 advanced adenomas and 40% (8/20) were in the proximal colon.

The 15 non-advanced adenoma patients, mean age 70 (range 64-81) and 24% female (6/15),

Table 1 Distribution of most advanced findings on colonoscopy

Most advanced finding	n (%)
Colorectal cancer	4 (8.2)
Advanced adenoma ¹	21 (42.9)
Non advanced adenoma ²	15 (30.6)
1-2 adenomas, > 5 and < 10 mm	7
> 3 adenomas, any size < 10 mm	5
1-2 adenomas, ≤ 5 mm	3
No colorectal neoplasia	9 (18.4)
HP only	5
No findings	4
Total Patients	49 (100)

¹Includes adenoma with high grade dysplasia, villous adenoma, tubulovillous adenoma and tubular adenoma and sessile serrated adenoma/polyp ≥ 10 mm; ²Non advanced adenoma includes tubular adenomas < 10 mm with no advanced features. HP: Hyperplastic polyp.

included: 7 patients with 1-2 tubular adenomas > 5 mm but < 10 mm; 5 patients with > 3 tubular adenomas < 10 mm; and 3 patients with 1-2 tubular adenomas ≤ 5 mm. The specimen of one patient with a well described 8 mm polyp that was removed but not retrieved and is included in the non-advanced adenoma total. No sessile serrate adenomas/polyps were recorded that were < 10 mm. There were 9 patients without colorectal neoplasia, median age 71 (65-80) and 67% female (6/9), including 5 with hyperplastic polyps < 10 mm and 4 not requiring a biopsy. Figure 3 includes a summary of the findings.

The size distribution of CRC and advanced adenoma cases is provided in Table 2. The four CRCs were 14, 20, 25, and 40 mm in greatest dimension. Advanced adenoma index lesions include 5 at 10 mm, 9 at 11-19 mm, 5 at 20-29 mm, and 2 at ≥ 30 mm.

DISCUSSION

Preventing colorectal cancer morbidity and mortality primarily rests on the ability of providers to successfully screen patients for premalignant and malignant colorectal neoplasia and treat accordingly. Colonoscopy is the most widely used and effective screening tool for those who will take advantage of it and ensures the screening compliance of the vast majority of screening compliant Americans^[3]. However, there are millions of patients who remain unscreened or only intermittently screened using FOBT/FIT only and who will not use colonoscopic screening for a variety of reasons including risk, inconvenience, preparatory requirements and embarrassment^[1,2,4,16-21].

Consequently, in the United States, colorectal cancer remains the second leading cause of cancer related death overall and third leading cause of death for each sex. The age-adjusted incidence of new CRC cases reported by the US Surveillance, Epidemiology, and End Results Program for the period 2009-2013 was 47.1 and 36.0 per 100000 for men and women respectively. Incidence increases with age with 82.4%

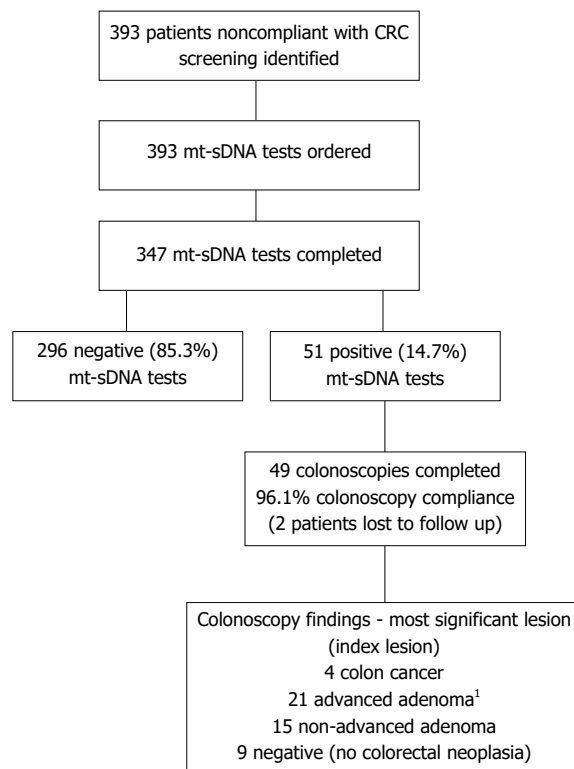


Figure 2 Enrollment outcomes. ¹Advanced adenoma: colorectal adenoma or sessile serrated adenoma/polyp ≥ 1.0 cm in diameter; or adenoma with high-grade dysplasia or ≥ 25% villous component, of any size. mt-sDNA: Multitarget stool DNA.

of new cases occurring patients age 45-84 years and with 21.8%, 24% and 21.8% of new cases seen in patients 55-64, 66-74, and 75-84 respectively^[22,23].

Our study documented the experience of an integrated multispecialty medical practice working to increase screening effectiveness in its screening-noncompliant Medicare age patients. This population is of critical importance; CRC incidence increases with age and CRC's that present with symptoms rather than being detected through asymptomatic screening are more likely to be of late stage with increased related morbidity and cost^[24].

We studied whether the availability of non-invasive CRC screening with mt-sDNA in USMD's general medical practice for routine use might encourage providers and patients to achieve successful screening. Our study did not address the discriminate features of mt-sDNA testing that led to increased patient uptake and compliance. Common patient preference issues that contribute to screening program performance include concerns around privacy, convenience, accuracy, extended screening intervals, and/or direct patient support through an embedded patient navigation system. Additionally, the long-term benefits of decreased patient and provider screening burden related to performing, tracking, administering, and navigating the mt-sDNA screening process on patient compliance were not assessed.

Our data demonstrate that mt-sDNA, with an

Group	Category	n	PPV			
Advanced colorectal neoplasia	CRC	4	8.2%	51%	82%	Any colorectal neoplasia
	Advanced adenoma	21	42.9%			
Nonadvanced colorectal neoplasia (adenoma < 10 mm)	NAA	15	30.6%			
HP's and no findings	Negative	9	18.4%			
Total positive		51	-			
Positives with colonoscopy		49	100%			
Colonoscopy compliance			96.1%			

Figure 3 Summary of colonoscopy findings in 49 mt-sDNA positive patients. PPV: Positive predictive value; CRC: Colorectal cancer; NAA: Non-advanced adenoma; HP's: Hyperplastic polyps.

Table 2 Features of the advanced colorectal neoplasms found in Cologuard positive patients on colonoscopy

Index lesion	Greatest dimension (mm)				Total	Proximal colon
	10	11-19	20-29	30+		
CRC ¹	0	1	2	1	4	75% (3/4)
HGD	0	0	1	0	1	0% (0/1)
TVA/VA ²	1	3	4	1	9	38% (3/8)
TA	3	6	0	1	10	40% (4/10)
SSA/P	1	0	0	0	1	100% (1/1)
Total	4	10	7	3	24	40% (8/20)

Index lesion only. ¹Stage I (2), Stage II (2); ²1 location not reported. Index lesion: Most clinically significant lesion found on colonoscopy; CRC: Colorectal cancer; HGD: High grade dysplasia; TVA/VA: Tubulovillous adenoma/villous adenoma; TA: Tubular adenoma \geq 10 mm with no HGD or villous features; SSA/P: Sessile serrated adenoma/polyp \geq 10 mm.

88.3% intent-to-screen compliance, provided an acceptable CRC screening strategy for previously screening-noncompliant Medicare patients. Further, there was almost universal compliance with follow-up diagnostic colonoscopy (96.1%) by mt-sDNA positive patients. Congruent with the purpose of CRC screening, mt-sDNA screening identified patients with early stage CRC (4/4) and advanced adenoma that were amenable to definitive surgical treatment and/or colonoscopic excision. Therefore, screening with mt-sDNA could reasonably be expected to contribute to CRC related mortality reduction and prevention respectively.

Because of the small size of the study, population based statistics are only somewhat informative. CRC incidence was elevated at 11.5/1000 (1.2%) which is likely consistent with population age and advanced adenoma incidence was unremarkable at 60.5/1000 (6%). The positive predictive value of mt-sDNA for CRC and advanced adenoma exceeded that seen in the much larger and more diverse DeeP-C mt-sDNA screening study, again likely more reflective of the

study population of unscreened and under-screened patients than changes in test performance^[24].

The study is limited by relatively small size (393) but it is strengthened by the diversity of the provider group participating (77); the use of mt-sDNA in routine daily clinical practice with a focus on shared decision making; and strong compliance data for both mt-sDNA screening and post-positive test colonoscopy. The findings may not be generalizable to non-Medicare-age patients and may reflect disease incidence particular to this geographic area.

In conclusion, the availability of mt-sDNA colorectal cancer screening provided significant medical benefit to Medicare patients cared for in a large multi-specialty group practice who were previously screening-noncompliant. Patients with clinically significant advanced colorectal neoplasia were identified as a result of high compliance with both mt-sDNA screening and subsequent diagnostic colonoscopy. Broader implementation of mt-sDNA screening into patients ages 50-65 should be evaluated to ascertain similar benefits in screening compliance in younger patients.

COMMENTS

Background

A significant percentage of Americans are not up-to-date with colorectal cancer (CRC) screening. A high sensitivity noninvasive screening test with a multi-year screening interval could provide a strategy to increase CRC screening program participation. The multitarget stool DNA (mt-sDNA) was recently included in the recommendations of the United States Preventive Services Task Force for average risk colorectal cancer screening. In this study, The authors determine the uptake of mt-sDNA screening in a cohort of previously screening non-compliant Medicare patients age 50-85 years.

Research frontiers

While several options are available to patients for screening for colorectal cancer and pre-malignant polyps, patient compliance has been lower than that seen on breast or cervical cancer screening. In the United States, a new screening strategy, multitarget stool DNA, provides a systems approach including high cancer and high-grade dysplasia sensitivity in a non-invasive format and an embedded national patient navigation system to support successful screening. Studies to evaluate the clinical uptake and compliance with this test will help inform decisions on applicability to national screening programs.

Innovations and breakthroughs

This is the first report of mt-sDNA use for routine average risk colorectal cancer screening in daily clinical practice by typical primary care clinicians. This medical-records-review based study demonstrates that clinicians using this system-based colorectal cancer screening strategy, combining high sensitivity mt-sDNA and a patient navigation system, achieved high levels of screening compliance (88%) in 393 patients age 50-85 years who were previously non-compliant with screening and who were participating in the United States Medicare program. Diagnostic colonoscopy compliance in 51 test positive cases was almost universal (96%) and revealed significant disease in 25 patients (4 colorectal cancers all Stage I or II, and 21 advanced adenomas). This first small but significant study reveals that mt-sDNA screening has the potential to enhance non-invasive screening success and performance in previously non-compliant individuals in daily practice.

Applications

The results of this study support the implementation of mt-sDNA in daily clinical practice, especially in patients that have been screening non-compliant. The article also demonstrates that compliance with a diagnostic colonoscopy in mt-sDNA positive patients was almost universal (96%) and that the positive predictive value for advanced colorectal neoplasia was high (51%), justifying the expenditure of colonoscopy resources in this group.

Terminology

Advanced colorectal neoplasia: includes patients with colorectal cancer or advanced adenoma, the lesions which are the primary targets of screening.

Advanced adenoma: the group of colorectal neoplasm most likely to progress to colorectal cancer over time. The group includes adenomas with high-grade dysplasia or $\geq 25\%$ villous component of any size and/or adenomas 1.0 cm in size or greater.

Affordable care act (ACA): United States regulation that includes a requirement for certain screening tests to be provided to individual participating in that program to be free of any costs to those individuals.

Average risk patient: Individuals age 50 and older who are asymptomatic and have no personal history of colorectal cancer or colorectal adenoma, no family history of a first degree relative developing colorectal cancer at age 60 or younger or any two first degree relatives with colorectal cancer developed at any age, or an inherited predisposition to colorectal cancer including adenomatous polyposis coli or Hereditary non-polyposis colorectal cancer (Lynch syndrome) or other rare inherited predispositions, or inflammatory bowel disease.

Medicare: The United States government based medical insurance system for persons 65 years of age and older and certain qualifying younger patients. Medicare pays the full expense for mt-sDNA tests for these patients ages 50-85 years once, every three years.

Mt-sDNA test: a stool based assay for colorectal cancer screening. It includes 11 biomarkers (10 DNA and 1 fecal hemoglobin) evaluated as a group in a logistic algorithm to provide a single composite result of "positive" or "negative".

Peer-review

This paper contains interesting results which merit publication. The mt-sDNA CRC screening seems to be helpful for colorectal cancer in average-risk population.

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