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-
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®) 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. 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). 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.

Mt-sDNA is a multi-analyte test with algorithmic analysis that provides a single qualitative dichotomous positive or negative test result for each patient. 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. 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. 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/polypl without other advanced features ≥ 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 ≥ 5 mm. as these may have differing post-colonoscopy clinical surveillance intervals. Negative findings include absence of colorectal neoplasm 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 neoplasm 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
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              | 21 (42.9) |
| Non advanced adenoma          | 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[1,2,4,16-21]. 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% 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 multispeciality 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
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.

![Figure 3](image-url)

**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.

| Index lesion | Greatest dimension (mm) | Proximal colon |
|--------------|------------------------|---------------|
|              | 10  | 11-19 | 20-29 | 30+ | Total |
| CRC          | 0   | 1     | 2     | 1   | 4     | 75% (3/4) |
| HGDI         | 0   | 0     | 1     | 0   | 1     | 0% (0/1)  |
| TVA/VA       | 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. 2Stage I (2), Stage II (2); 3Location not reported. Index lesion: Most clinically significant lesion found on colonoscopy; CRC: Colorectal cancer; HGDI: High grade dysplasia; TVA/VA: Tubulovillous adenoma/villous adenoma; TA: Tubular adenoma ≥ 10 mm with no HGDI or villous features; SSA/P: Sessile serrated adenoma/polyp ≥ 10 mm.
Mt-sDNA testing: 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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