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# **Multitarget Stool DNA Testing for the Prevention of Colon Cancer: Outcomes in a Large Integrated Healthcare System**

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## Background and Aims

Multitarget stool DNA (MT-sDNA) testing is used in primary care as a screening test for colon cancer. Test effectiveness and patient compliance were examined in clinical practice.

## Methods

We assessed outcomes of MT-sDNA testing in a cohort study conducted in a large integrated healthcare system comprising 15 hospitals and 150 outpatient clinics using advanced electronic data capture (Clarity2 [Epic, Verona, Wisc, USA] and REDCap [Encinitas, Calif, USA]) followed by manual chart review to confirm MT-sDNA test results and to monitor the outcomes of subsequent colonoscopy.

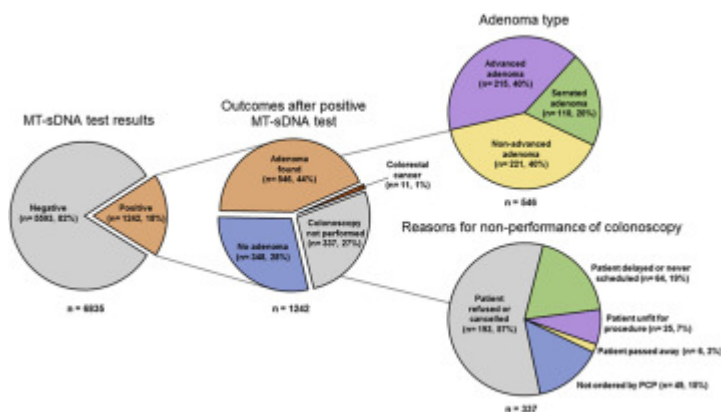
## Results

A total of 6835 MT-sDNA tests were performed over 1 year between 2017 and 2018. Of 1242 patients (18%) who tested positive, 1109 (89%) were referred for colonoscopy, and 905 of them (73%) underwent colonoscopy. Eleven patients (<1%) with a positive test had colorectal cancer, 215 (17%) had advanced adenomas, 110 (9%) had serrated adenomas, and 546 (60%) patients had an adenoma. Of the 6835 patients tested, adenoma or cancer was found in 557 patients (8%). An advanced adenoma or cancer was found in 226 of 1242 patients with a positive test (18%). Nonadherence with colonoscopy after a positive test was high (21%), and the cost to detect 1 advanced adenoma or cancer was \$38,849.

## Conclusions

The frequency of adenoma detection by an MT-sDNA screening strategy is low, and many positive tests are not associated with significant findings at colonoscopy. Failure to follow a positive test with colonoscopy is a significant problem that needs to be considered when this screening strategy is adopted.

## Graphical abstract



## Abbreviations

MT-sDNA, multitarget stool DNA; SD, standard deviation

The multitarget stool DNA (MT-sDNA) test is a widely used screening test for colorectal cancer in primary care. The test incorporates MT DNA testing and fecal immunochemical testing for blood, and a proprietary algorithm is used to determine whether the test is positive.<sup>1,2</sup> The MT-sDNA test is mentioned as an option in all current U.S. guidelines, but the U.S. Multi-Society Task Force ranks colonoscopy and fecal immunochemical testing in the first tier of tests, whereas the American College of Gastroenterology recommends colonoscopy.<sup>3,4</sup> According to the manufacturer of the MT-sDNA test (Cologuard; Exact Sciences Corp, Madison, Wisc, USA), a positive result

may indicate the presence of colorectal cancer or advanced adenoma and should be followed by diagnostic colonoscopy.<sup>5</sup> The test is indicated to screen adults of either sex, 45 years or older, who are at typical average risk for colorectal cancer. In a clinical study funded by Exact Sciences Corp, patients of average risk underwent screening.<sup>6</sup> Of the 9989 participants who could be evaluated, 65 (.7%) had colorectal cancer and 757 (7.6%) had advanced precancerous lesions (advanced adenomas or sessile serrated polyps measuring  $\geq 1$  cm in the greatest dimension) at colonoscopy. Few large studies have evaluated the performance of this test in routine clinical practice and provided data on follow-up rates of colonoscopy after a positive test. Compliance with follow-up colonoscopy is an important variable for a sequential screening strategy because the initial test does not provide a curative solution for the underlying problem.

The principal aims of our study were to determine the frequency of cancers and adenomas detected in a cohort undergoing the MT-sDNA test in a large integrated healthcare system, the frequency of positive MT-sDNA tests without a significant adenoma or cancer and the frequency of positive MT-sDNA tests without any adenoma or cancer. The secondary objectives were to determine the frequency with which adenomas are detected using the MT DNA test, the compliance rate with colonoscopy after a positive test, and the cost and return on investment for a healthcare system using an MT-sDNA screening strategy for cancer detection or prevention.

## Methods

### Healthcare system

Aurora Health Care is a not-for-profit integrated healthcare system headquartered in Milwaukee and serving Eastern Wisconsin. The system has 15 hospitals, more than 150 clinics, and 70 pharmacies. It has 32,000 employees, including 1800 employed physicians, and is Wisconsin's largest home care organization. Since its formation in 1984, Aurora has had affiliations with private physician groups. Aurora Health Care is a teaching affiliate of the University of Wisconsin School of Medicine and Public Health.

### Sample size calculation

We chose a 1-year time frame based on MT-sDNA test statistics from the previous year. We anticipated more than 5000 cases, which would make our study size the largest cohort reported with the new test that incorporates DNA testing with fecal immunochemical testing for blood in routine practice.

### Data collection and validation

Aurora Health Care has a single electronic medical record (Epic, Verona, Wisc, USA). All completed MT-sDNA tests are electronically recorded in the medical record. The Epic reporting environment Clarity2 was used to identify all MT-sDNA (Cologuard; Exact Sciences Corp) test results system-wide from June 2017 to June 2018. Discrete data elements for patients with positive MT-sDNA test results, including demographics, MT-sDNA testing orders and results, colonoscopy orders, and billing codes, were extracted using Clarity2 and uploaded into our electronic data capture tool, REDCap Cloud (REDCap Cloud Research Electronic Data Capture, Encinitas, Calif, USA). REDCap Cloud is a secure web-based data capture system that allows automated import of discrete data from electronic health record reports, manual data entry, real-time validation rules, audit trails, and automated export of data sets to statistical software. All uploaded data elements were manually checked for accuracy by review of the patient's medical record. Historical and contemporaneous colonoscopy procedure details, results, and pathologic data were tracked through the electronic medical record, and data were manually entered into REDCap Cloud. The outcomes were tracked without interventions from the investigators to alter compliance or to influence decisions regarding referral for further testing. Quality assurance was performed on 100% of the data set by manual review of the patient record.

## Endoscopists and primary care physicians

Twenty-nine gastroenterologists and surgeons employed by Aurora Health Care performed the colonoscopies. In addition, an affiliated private group of 15 gastroenterologists also performed some of the procedures in this study. The adenoma detection rate of endoscopists was calculated as the percentage of patients aged  $\geq 50$  years undergoing first-time screening colonoscopy who had 1 or more conventional adenomas detected and removed and proven by histology. Adenoma detection rates were calculated from  $\geq 100$  colonoscopies tracked through our system as an ongoing quality measure over a consecutive 8-month period. We used 100 procedures as the benchmark for calculating the adenoma detection rate based on similar large multicenter studies and the recommendation that maintenance of colonoscopy skills requires 100 colonoscopies a year.<sup>7,8</sup> All endoscopists were aware of the results of the MT-sDNA test.

## Cost analysis

We used cost-effectiveness to evaluate the economics of this test. The Centers for Disease Control and Prevention describe cost-effectiveness analysis as a comparison of the cost of an intervention with its outcome in terms of effectiveness.<sup>9</sup> Total net costs are divided by the net effects to generate a cost for each outcome. Cost-effectiveness analysis helps planners choose among different approaches to achieve a desired outcome by quantifying the value each proposed intervention is likely to produce.<sup>10</sup>

The total cost of the MT-sDNA screening strategy was determined by multiplying the number of tests by the published retail price of the test. The cost of colonoscopy was the median of published charges for the procedure at the 15 participating hospitals.<sup>11</sup> The cost per adenoma detected, significant adenoma detected, or cancer detected is obtained by dividing this figure by the number of patients with relevant lesions identified after colonoscopy.

## Statistical analysis

Adenomas, serrated adenomas, and cancers were defined by histopathology. An advanced adenoma was defined as an adenoma measuring  $\geq 10$  mm, containing a substantial villous component, or exhibiting high-grade dysplasia. A significant adenoma was defined as an adenoma  $\geq 10$  mm. Adherence was defined as the degree to which the patient correctly followed medical advice. We used an evidence-based definition of the event rate to calculate the rate of events in this trial. A standard textbook of evidence-based medicine defines an event rate as the proportion of patients in a group in whom the event is observed.<sup>12</sup> Cancers, adenomas, significant adenomas, and advanced adenomas were all events that were measured in this study, and their frequencies are reported as event rates.

All categorical variables were described as count and percentage. All continuous numeric variables were described as mean and standard deviation (SD). The frequency for adenoma + cancer detection was calculated as the fraction of patients with a positive MT-sDNA test and with an adenoma or cancer. The equation used to construct the 95% confidence intervals for the positive predictive value of the MT-sDNA test is  $CI_{PPV} = PPV \pm 1.96 \times SE$  (where CI is the confidence interval, PPV the positive predictive value, and SE the standard error). For all statistical tests an alpha of .05 was used. All statistical analysis was performed using SAS version 9.4 (SAS Institute, Cary, NC, USA). The Institutional Review Board of Aurora Health Care approved the protocol on March 23, 2018.

## Results

A total of 6835 MT-sDNA tests were completed between June 1, 2017 and June 1, 2018: 1242 (18%) were positive and 5593 (82%) negative. Characteristics of the patients with a positive MT-sDNA test are shown in Table 1. The mean age of the positive MT-sDNA test cohort was 65 years (SD, 8). Seven hundred eighty-one

patients (63%) had Medicare as insurance, 397 (32%) had private insurance, 46 (4%) had Medicaid, and 18 (1%) had no insurance. No patient previously had an MT-sDNA test.

Table 1. Characteristics of the MT-sDNA test positive cohort

| Characteristic                          | No. of patients (%) |             |             |             |            |
|---|---------------------|-------------|-------------|-------------|------------|
|   | Total               | Ages 50-59  | Ages 60-69  | Ages 70-79  | Ages 80-89 |
| Age                                     | 1242 (100)          | 299 (24.07) | 568 (45.73) | 342 (27.54) | 33 (2.66)  |
| Sex                                     |                     |             |             |             |            |
| Male                                    | 523 (42.11)         | 143 (27.34) | 233 (44.55) | 135 (25.81) | 12 (2.29)  |
| Female                                  | 719 (57.89)         | 156 (21.7)  | 335 (46.59) | 207 (28.79) | 21 (2.92)  |
| Race/ethnicity                          |                     |             |             |             |            |
| White                                   | 1170 (94.20)        | 276 (23.59) | 535 (45.73) | 326 (27.86) | 33 (2.82)  |
| African American                        | 55 (4.43)           | 15 (27.27)  | 25 (45.45)  | 15 (27.27)  | 0 (0)      |
| Hispanic/Latino                         | 27 (2.17)           | 9 (33.33)   | 12 (44.44)  | 6 (22.22)   | 0 (0)      |
| Native American                         | 4 (.32)             | 1 (25.00)   | 2 (50.00)   | 1 (25.00)   | 0 (0)      |
| Asian                                   | 6 (.48)             | 2 (33.33)   | 4 (66.67)   | 0 (0)       | 0 (0)      |
| Unknown                                 | 7 (.56)             | 5 (71.43)   | 2 (28.57)   | 0 (0)       | 0 (0)      |
| Colonoscopy within previous 5 y         | 93 (7.49)           | 15 (16.13)  | 35 (37.63)  | 36 (38.71)  | 7 (7.53)   |
| Colonoscopy after positive MT-sDNA test |                     |             |             |             |            |

| Characteristic        | No. of patients (%) |                |                |                |            |
|-----------------------|---------------------|----------------|----------------|----------------|------------|
|                       | Total               | Ages 50-59     | Ages 60-69     | Ages 70-79     | Ages 80-89 |
| Performed within 1 y  | 905<br>(72.87)      | 213<br>(23.54) | 411<br>(45.41) | 255<br>(28.18) | 26 (2.87)  |
| Performed within 6 mo | 857<br>(69.00)      | 202<br>(23.57) | 391<br>(45.62) | 241<br>(28.12) | 23 (2.68)  |

*MT-sDNA*, Multitarget stool DNA.

### Colonoscopy rates in patients with a positive *MT-sDNA* test

Of the 1242 patients with a positive *MT-sDNA* test, 1109 (89%) had a colonoscopy ordered; 905 (73%) completed a colonoscopy within 1 year of the positive *MT-sDNA* test result and 857 (69%) had a colonoscopy within 6 months of a positive *MT-sDNA* test. Of those undergoing colonoscopy, 888 patients (98%) had a complete colonoscopy as determined by cecal intubation.

### Quality of bowel preparation at colonoscopy

The quality of the bowel preparation was good in 847 of 904 patients (93.6%). The validated Boston Bowel Preparation Scale was used for reporting in 686 patients (73%).<sup>13</sup>

### Adenoma detection rates for endoscopists performing colonoscopy

Twenty-nine gastroenterologists and surgeons employed by Aurora Health Care performed 616 colonoscopies. Their mean adenoma detection rate was 48% (SD, 16%). The frequency of adenoma detection of the same physicians when calculated for the enriched cohort with a positive *MT-sDNA* was 66% (SD, 15%). An additional 15 gastroenterologists from a private group that tracks adenoma detection rate performed 100 colonoscopies. The mean adenoma detection rate of this group was 37% (SD, 10%). The frequency of adenoma detection of the same physicians when calculated for the enriched cohort with a positive *MT-sDNA* was 51% (SD, 32%). The remaining 189 procedures (21%) were performed by individuals for whom reliable adenoma detection rates were not available, primarily because of low procedural volumes.

### Findings at colonoscopy

Findings at colonoscopy are shown in Table 2. Of the 1242 patients with a positive *MT-sDNA* test, 905 (73%) underwent diagnostic colonoscopy. Eleven of 1242 patients had cancers (.89%). Of these, 8 (.64%) cancers were stage 1, 2 (.16%) were stage IIA, and 1 (.08%) was a breast cancer metastatic to the colon. Of 1242 patients, 215 (17%) had advanced adenomas (191 [15%] with adenomas  $\geq 10$  mm, 76 [6%] with villous components, and 25 [2%] with high-grade dysplasia). Seventy-seven patients (6%) had more than 1 advanced feature; 110 patients (9%) had serrated adenomas. Five hundred forty-six of the 1242 patients with a positive *MT-sDNA* test (44%) had an adenoma. Adenomas were detected in 247 of 523 men (47%) and 299 of 719 women (42%) (Table 1). Relative frequencies of adenoma detection per decade of age are shown in Table 2.

Table 2. Findings at colonoscopy in patients with a positive multitarget stool DNA test (n = 905) stratified by age

| Finding                            | No. of patients (%) |             |             |             |            |
|------------------------------------|---------------------|-------------|-------------|-------------|------------|
|                                    | Total               | Ages 50-59  | Ages 60-69  | Ages 70-79  | Ages 80-89 |
| <b>Cancer</b>                      | 11 (1.2)            | 5 (45.45)   | 3 (27.27)   | 1 (9.09)    | 2 (18.18)  |
| <b>Significant adenoma (≥1 cm)</b> | 191 (21.1)          | 43 (22.51)  | 88 (46.07)  | 55 (28.8)   | 5 (2.62)   |
| <b>Any polyp</b>                   | 711 (78.5)          | 166 (23.35) | 326 (45.85) | 200 (28.13) | 19 (2.67)  |
| <b>Adenoma of all sizes</b>        | 546 (60.3)          | 115 (21.06) | 252 (46.15) | 165 (30.22) | 14 (2.56)  |
| <b>Adenoma .5-.9 cm</b>            | 190 (20.9)          | 35 (18.42)  | 93 (48.95)  | 60 (31.58)  | 2 (1.05)   |
| <b>Other findings</b>              |                     |             |             |             |            |
| <b>Hemorrhoids</b>                 | 110 (12.1)          | 26 (23.64)  | 51 (46.36)  | 27 (24.55)  | 6 (5.45)   |
| <b>Ulcerations</b>                 | 7 (.77)             | 2 (28.57)   | 5 (71.43)   | 0 (.00)     | 0 (.00)    |
| <b>Arteriovenous malformation</b>  | 2 (.22)             | 0 (.00)     | 2 (100)     | 0 (.00)     | 0 (.00)    |
| <b>Colitis</b>                     | 1 (.11)             | 0 (.00)     | 1 (100)     | 0 (.00)     | 0 (.00)    |

Of the 711 patients with any type of polyp, 226 (32%) had 1 polyp, 174 (24%) had 2 polyps, 117 (16%) had 3 polyps, 68 had 4 polyps (10%), and 126 (18%) had 5 or more polyps. Of the 6835 patients undergoing MT-sDNA testing, any adenoma or cancer was detected in 8%. An advanced adenoma (n = 215) or cancer (n = 11) was found in 226 of 1242 patients with a positive MT-sDNA test (18%). If we consider only the 905 patients undergoing colonoscopy after a positive MT-sDNA test, 226 of them had an advanced adenoma or cancer (24.9%); therefore, 75% of patients with a positive MT-sDNA test did not have an advanced adenoma or a cancer. Similarly, 546 of 1242 patients testing positive with the MT-sDNA test were found to have any adenoma (44%). If we consider only the 905 patients undergoing colonoscopy after a positive MT-sDNA test, 546 of those patients undergoing colonoscopy had any adenoma (60%); therefore, 40% of patients with positive tests had no precancerous lesions at colonoscopy.

### Endoscopist volume and outcome

Twenty-nine physicians within the Aurora system had 100+ screening colonoscopies over an 8-month period. Table 3 shows their adenoma detection rates and the numbers of procedures they performed. There was no significant difference between them for the baseline adenoma detection rate. These physicians



performed 616 of procedures after the MT-sDNA test. Table 4 shows the frequency of adenoma detection after MT-sDNA testing, with no significant difference between the groups.

Table 3. Procedural volume (screening colonoscopies only over an 8-month period) and baseline adenoma detection rate

| No. of screening colonoscopies | No. of endoscopists | Total no. of screening colonoscopies | Mean no. of screening colonoscopies | Adenoma detection rate % mean (standard deviation) | P value analysis of variance |
|--------------------------------|---------------------|--------------------------------------|-------------------------------------|--|------------------------------|
| 100-199                        | 8                   | 972                                  | 122                                 | 47 (22)  | .830                         |
| 200-299                        | 9                   | 2189                                 | 243                                 | 46 (13)  |                              |
| 300-399                        | 9                   | 3112                                 | 346                                 | 49 (16)  |                              |
| ≥400                           | 3                   | 1657                                 | 552                                 | 56 (6)   |                              |

Table 4. Procedure volume (screening colonoscopies only over an 8-month period used for baseline adenoma detection rate calculation) and frequency of adenoma detection after MT-sDNA test

| No. of screening colonoscopies | No. of endoscopists | Total no. of colonoscopies after MT-sDNA test | Mean no. of colonoscopies after MT-sDNA test | Frequency of adenoma detection % mean (standard deviation) | P value analysis of variance |
|--------------------------------|---------------------|---|--|--|------------------------------|
| 100-199                        | 8                   | 120   | 15   | 70 (15)  | .732                         |
| 200-299                        | 9                   | 222   | 25   | 66 (15)  |                              |
| 300-399                        | 9                   | 160   | 18   | 62 (15)  |                              |
| ≥400                           | 3                   | 114   | 38   | 64 (25)  |                              |

MT-sDNA, Multitarget stool DNA.

### Failure to obtain colonoscopy

Three hundred thirty-seven patients (27%) failed to obtain a colonoscopy within 1 year of their positive MT-sDNA test result. Colonoscopy was never ordered in 49 patients (4%). Twenty-five patients (2%) were deemed unfit for colonoscopy for medical reasons, 6 (.5%) died before the procedure could be scheduled, 257 patients (21%) were nonadherent with recommendation for colonoscopy despite the positive MT-sDNA test, 183 (15%)

refused colonoscopy, and 10 (.8%) canceled the procedure after scheduling it. Sixty-four patients (5%) postponed repeatedly or never scheduled the procedure so that it was not performed during the 1-year follow-up period of this study.

### Predictive values of a positive test

The positive predictive value of the MT-sDNA test was 18.20% (95% confidence interval, 16.05-20.35) for an endpoint of advanced adenoma or cancer (226/1242 positive tests).

### Cost analysis

The published cost for the MT-sDNA test is \$649. The total retail cost of screening 6835 subjects was \$4,435,915 (6835 × \$649). The median cost of colonoscopy at the 15 hospitals within our system was \$4800. The total cost of colonoscopy in 905 patients who underwent colonoscopy was \$4,344,000 (905 × \$4900). The total costs are therefore \$8,779,915. Each outcome measure can then be used to generate a cost per outcome. The cost to detect at least 1 adenoma is \$16,080 ( $\$8,779,915 \div 546$ ). The cost to detect 1 cancer is \$798,174 ( $\$8,779,915 \div 11$ ) and to detect 1 advanced adenoma or cancer is \$38,849 ( $\$8,779,915 \div 226$ ). Figure 1 shows the cost of the MT-sDNA test strategy for the detection of adenomatous polyps or cancer.

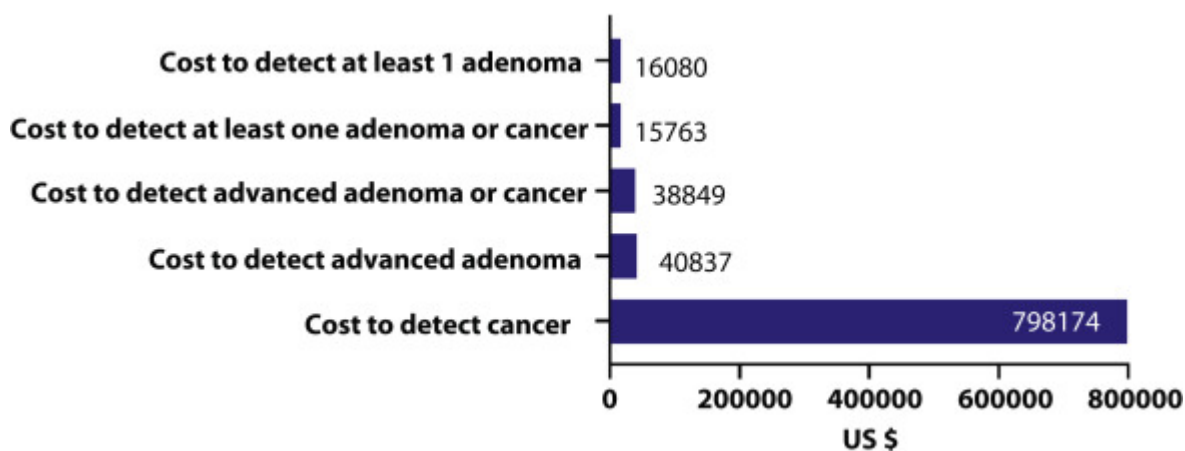


Figure 1. Cost in U.S. dollars of the multitarget stool DNA test for the detection of adenomatous polyps or cancer.

### Discussion

This is one of the largest studies of MT-sDNA testing in routine clinical practice. Our study demonstrates that the frequency of adenoma detection with the MT-sDNA test is less than that of colonoscopy performed by well-trained gastroenterologists (including those who performed colonoscopy in this study) and is lower than the cutoff for adenoma detection rates (overall, 25%; 30% in men and 20% in women) recommended by national societies for screening colonoscopy.<sup>14</sup> Our study demonstrates that a substantial number of patients fail to obtain colonoscopy despite a positive test, suggesting a need for careful patient selection and adequate education of both patients undergoing the test and providers ordering it.

The frequency of cancer and advanced adenoma in our study is comparable with a large validation study.<sup>6</sup> Other substantially smaller studies have shown higher cancer and advanced adenoma detection rates. In a cross-sectional, retrospective study in a multispecialty practice, colon cancer was found in 8.2% of patients with a positive MT-sDNA test and advanced adenomas in 43%, but the number of patients undergoing colonoscopy in that study was small.<sup>2</sup> In a retrospective study, Johnson et al<sup>1</sup> found that the rate of polyp detection was significantly higher in endoscopists who performed colonoscopy with knowledge of the MT-sDNA results and was 70% in a cohort of 172 subjects. In another study, MT-sDNA testing detected 49% of screening-related

neoplasia (defined as cancers, adenomas >1 cm, or villous adenomas) and was superior to a fecal immunochemical test.<sup>15</sup>

Some studies have suggested that hemorrhoids can affect the outcome of the immunochemical test for blood and cause a false-positive result.<sup>16</sup> Other studies have suggested that hemorrhoids are an infrequent cause of false-positive screening tests.<sup>17</sup> The prevalence of hemorrhoids was low in our study and does not explain the number of positive MT-sDNA tests with no underlying pathology identified at colonoscopy. Imperiale et al<sup>6</sup> extrapolated data from their study to a hypothetical cohort of 10,000 persons and calculated that with cancer or advanced adenoma endpoint, 76.4% would be false positives with DNA testing and 67.2% with fecal immunochemical testing. These results are comparable with the results in our study.

Our results also cannot be explained by the quality of the bowel preparation, completeness of the colonoscopy, or quality of the endoscopists or their procedural volume. The average adenoma detection rates of our endoscopists placed them in the fifth quintile, where the highest rates of advanced adenoma detection and the lowest rate of subsequent cancer detection have been shown to occur.<sup>18,19</sup> Other markers of high-quality colonoscopy within our study include high cecal intubation rates and high rates for serrated adenoma detection.<sup>20,21</sup>

In our study, 89% of patients with a positive MT-sDNA test were referred for colonoscopy, and only 73% had a colonoscopy within a year of the MT-sDNA test. Several causes were identified for the lack of a referral, including comorbid illnesses that precluded colonoscopy and death from other causes before the test was performed, but a substantial number of patients had no follow-up action after a positive test. Methods to track and educate patients about a positive test are essential for an MT-sDNA test to be successful long term.

Another troubling aspect of our data is the lack of compliance with colonoscopy in patients with a positive MT-sDNA test who were appropriately referred for the procedure. Some patients simply refused to have the test, others scheduled and canceled, and still others failed to schedule the procedure. Experience with fecal immunochemical testing suggests that patients who fail to follow-up on a positive screening test have a higher risk of death from colon cancer.<sup>22</sup> A personalized approach to screening for colon cancer has been proposed and may be useful in identifying patients who are well suited to sequential strategies (eg, stool test followed by colonoscopy).<sup>23</sup> An evaluation of compliance in the English colon cancer screening program suggests that patient behavior may vary and that some patients may be consistent screeners and others consistent nonscreeners; also, some patients drop out after the initial test despite the need for further evaluation.<sup>24</sup> The latter group may simply not be suited to sequential strategies, which require a follow-up test after the initial screening test and may be best served by a single test (eg, colonoscopy).

Lack of patient education in primary care may also play a role in noncompliance with follow-up procedures after a positive test, and many patients may simply not understand the significance of a positive test. As with most screening programs, appropriate selection of patients and adequate follow-up are essential for the success of the program. The significant lack of compliance with colonoscopy after a positive MT-sDNA test raises concerns for the cohort that tested negative. These individuals may be falsely reassured and may not understand or comply with the requirement to repeat an MT-sDNA test in 3 years. This should be an important aspect of education for patients who choose MT-sDNA testing as their strategy for colon cancer screening. Navigators that contact patients and educate and enhance follow-up on positive tests could improve compliance, although these strategies also add to cost.<sup>25</sup>

Cost and insurance coverage are important considerations in making a decision regarding a screening test. Most patients (99%) in our study were insured, and colonoscopy is generally covered as a screening procedure in Wisconsin; therefore, the cost of the procedure is unlikely to have been the reason for the choice of the MT-

sDNA test. Cost-effectiveness analysis is a method used to provide estimates of the cost of a strategy to achieve a certain outcome and to measure a return on investment for a payor. It can provide a guide for the investment required for a screening project based on MT-sDNA testing. Published costs of the test are used while recognizing that discounted prices may be available to insurance companies or healthcare systems. Our analysis suggests that the cost of implementing a screening strategy based on the MT-sDNA test is high. A recent cost-analysis suggested that MT-sDNA testing is cost-effective compared with no screening but is more expensive than other screening strategies.<sup>26</sup>

With regard to the effectiveness of the MT-sDNA test, the frequency of adenoma detection with a MT-sDNA strategy was lower than the minimum of 25% recommended by national societies and was substantially lower than the adenoma detection rate of the endoscopists in our study. In a large study of colonoscopy in California, Corley et al<sup>19</sup> reported the adenoma detection rates of 136 gastroenterologists and found that the rate varied from 7.4% to 52.5%. The frequency with which adenomas are identified with the MT-sDNA test in our study places its performance at the low end of this range. On the other hand, the MT-sDNA test did detect many advanced adenomas and cancers and is clearly better than no screening at all. The number of positive MT-sDNA tests with no underlying pathology at colonoscopy was high.

The primary limitations of our study are its retrospective nature and the lack of information regarding whether the positive test was driven by the detection of blood or by abnormal DNA (the manufacturer does not make this information available with the report). We did not perform interventions to enhance compliance with recommendations for colonoscopy after a positive MT-sDNA test, which could be considered a limitation of our study. On the other hand, our desire was to evaluate the performance of the MT-sDNA test in routine practice, and noncompliance with a sequential testing strategy is an important variable that deserves measurement. The advantages of our study are the use of a validated cloud-based data capture system followed by manual confirmation of the results. Other advantages of our study design are that it measures test performance in a diverse area of community practice, with colonoscopy quality parameters available for most endoscopists performing the procedures (adenoma detection rates, quality of the bowel preparation, and cecal intubation rates). An important advantage of our study is that it was not externally funded. A Cochrane review shows that sponsorship of drug and device studies by the manufacturing company leads to more favorable efficacy results and conclusions than sponsorship by other sources.<sup>27</sup> Further work will help determine the place of the MT-sDNA test in screening strategies for colorectal cancer when compared with lower cost tests such as the fecal immunochemical test for blood.

## Acknowledgments

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