USPSTF Colorectal Cancer Screening Guidelines: An Extended Look at Multi-Year Interval Testing

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In its October 5, 2015, draft recommendation (draft statement) regarding colorectal cancer (CRC) screening, the US Preventive Services Task Force (USPSTF) assigned an "A" grade to CRC screening starting at age 50 and continuing until age 75.[1] In addition to the option of screening colonoscopy every 10 years (10y), the USPSTF recommended 3 screening options that include annual fecal occult blood testing: 1) annual fecal immunochemical test (FIT) alone, 2) annual FIT in combination with flexible sigmoidoscopy 10y, and 3) annual high-sensitivity fecal occult blood test (hsFOBT). These recommendations were made despite evidence that annual CRC screening test use across the United States is the least frequent strategy used by screen-eligible adults aged 50 to 75 years (10.4%),[2] and subject to poor year-over-year adherence in those patients that use it in routine clinical practice. Higher rates can be obtained in highly resourced screening environments focused on annual screening, although reported initial uptake remains less than 50%.[3,4] Further, FIT[5] and hsFOBT[6] demonstrate significantly inferior single application sensitivity (point sensitivity) to multi-target stool DNA testing (mt-sDNA).[4] Mt-sDNA—specifically, the Cologuard test—can be performed at 3-year (3y) intervals.[7,8]

Test sensitivity, patient preferences,[9,10] and access are key considerations for ensuring screening effectiveness and adherence. In view of the poor adherence to regular repeat testing, it is critical that the first opportunity we have in screening a patient should be with a test that has a high sensitivity for both CRC and significant precancerous lesions. This would maximize screening effectiveness in reducing CRC incidence and mortality.

Given the lack of adherence to annual testing and patient preference for longer intervals, a comparison of mt-sDNA 3y with biennial or triennial FIT/hsFOBT would be more clinically relevant than comparison with annual testing by the same methods. However, with minimal clinical rationale

ABSTRACT

Objectives: The US Preventive Services Task Force (USPSTF) released draft recommendations regarding colorectal cancer (CRC) screening in October 2015. Despite evidence that annual fecal blood testing test use is uncommon in screen eligible adults, with only 10.4% reporting the use of such a test in 2012, and features poor adherence over time, the USPSTF recommended only 3 noninvasive screening strategy options, all including annual fecal occult blood testing: 1) annual fecal immunochemical test (FIT) alone; 2) annual FIT in combination with flexible sigmoidoscopy every 10 years; and 3) annual high-sensitivity fecal occult blood test (hsFOBT). Mt-sDNA is the only FDA-approved CRC screening test, is covered by Medicare every 3 years, and is included as an every-3-year (3y) option in the American Cancer Society guidelines. We demonstrate that USPSTF modeling includes an embedded sensitivity analysis of less frequent than annual test adherence, which provides support for the inclusion of mt-sDNA 3y as a recommended test.

Study Design: A descriptive analysis of USPSTF modeling of the clinical impact of various stool based CRC screening strategies.

Methods: We analyzed the data generated by the USPSTF CRC screening models describing the impact of noninvasive CRC screening strategies on CRC incidence, CRC related mortality, life years gained (LYG), colonoscopy volume and associated complication, test efficiency (a measure of benefits (LYG) and harms (colonoscopies generated), and identified strategies that provide 90% or more of the LYG by screening with colonoscopy every 10 years. We compared mt-sDNA at 3y intervals and FIT and hsFOBT at 2-year (2y) and 3y intervals and did not consider annual testing.

Results: We found that only mt-sDNA 3y, FIT 2y, and FIT 3y were within 98% of the efficiency frontier. However, only mt-sDNA 3y generates more than 90% of the life-years gained with screening colonoscopy. These results meet the USPSTF criteria for a recommendation for mt-sDNA 3y for routine screening.

Conclusions: Given poor adherence to annual testing, any screening opportunity with a test, such as mt-sDNA, that has high sensitivity for CRC and for the most significant precancerous lesions would be an important screening option for patients for maximizing screening effectiveness in reducing CRC incidence and mortality.

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Take-Away Points

As of October 2015, US Preventive Services Task Force (USPSTF) draft recommendations for noninvasive colorectal cancer (CRC) screening depend on annual screening with fecal occult blood tests despite uncommon annual test use and poor adherence over time.

- CRC is the second leading US cause of cancer death with, annually, 133,000 new cases, 50,000 deaths (2015 estimate), and more than $14 billion in related costs.
- The multi-target stool DNA (mt-sDNA) test has significantly higher sensitivity for cancerous and precancerous lesions than fecal blood testing. This could be of great utility in irregularly screened patients and in allowing longer test intervals and lower health system screening-process burdens.
- USPSTF could recommend mt-sDNA screening every 3 years based on USPSTF modeling, providing support for appropriate medical policy.

and no expressed scientific rationale, and without accounting for patient preference factors, the Cancer Intervention and Surveillance Modeling Network (CISNET), which provided the model data to inform USPSTF recommendations, grouped "stool tests" together and ruled that only a single strategy could be "recommended" from that group.[11] By considering only annual strategies, the USPSTF recommended both annual FIT and hsFOBT for routine screening, but not mt-sDNA. Mt-sDNA was included in the draft statement as an "alternative test" that "may be useful in select clinical circumstances." Mt-sDNA is currently recommended for use at 3-year intervals, not annually.[6]

Mt-sDNA uses a single random stool sample to identify 11 biomarkers associated with CRC and precancerous lesions: 9 for altered DNA, 1 for the reference gene beta-actin, and 1 for hemoglobin. Biomarker results are algorithmically combined, provide a composite score, and generate a single "negative" or "positive" patient result. A prospective, cross-sectional, 90-site, 10,000-patient screening study demonstrated that mt-sDNA was significantly superior to FIT for detecting any class of colorectal neoplasia, including 92% versus 74% and 69% versus 46% sensitivity for CRC and high-grade dysplasia, respectively. Specificity (no lesions found during colonoscopy) was 90% for mt-sDNA versus 96% for FIT.[5]

Poor screening adherence can have grave consequences for patients. Although preventable and treatable, CRC is the second leading cause of cancer death in the United States, with an estimated 133,000 new cases and 50,000 deaths estimated for 2015.[12] Recent studies[2,13] indicate that screening rates plateaued in 2010, with an estimated 23 million Americans eligible for, but not participating in, CRC screening.[2]

The aim of this analysis was to demonstrate that the modeling performed by CISNET supports a recommendation of mt-sDNA 3y for routine screening based on the USPSTF's criteria, in light of data demonstrating that patients are unlikely to adhere to annual testing.

METHODS

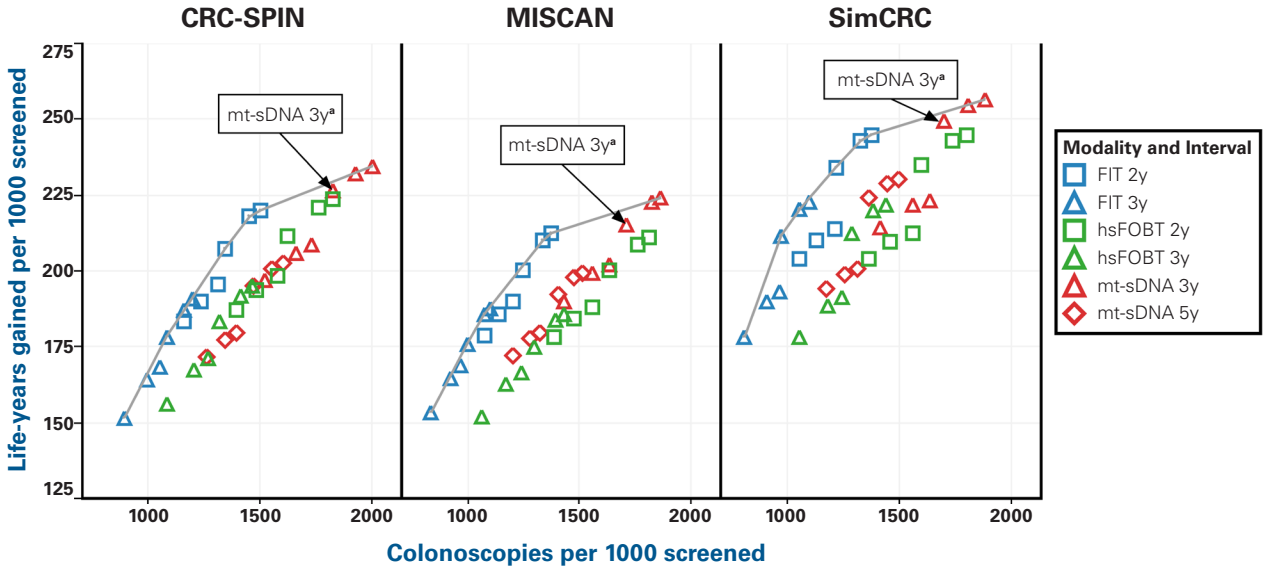
We reviewed the CISNET consortium modeling data in the technical report accompanying the draft statement[11] and identified an embedded sensitivity analysis of nonannual adherence by considering mt-sDNA 3y, FIT every 2 years (2y), FIT 3y, hsFOBT 2y, and hsFOBT 3y all as a group, and not considering data from annual testing. CISNET used 3 well-characterized CRC disease state models—Simulation Model of Colorectal Cancer (SimCRC), Microsimulation Screening Analysis (MISCAN) for Colorectal Cancer, and Colorectal Cancer Simulated Population Model for Incidence and Natural history (CRC-SPIN)—to provide screening outcomes under various stool-screening scenarios. These scenarios involved different modalities (hsFOBT, FIT, and mt-sDNA), intervals (2y, 3y, and every 5 years), and screening age groups (50-75, 50-80, 50-85, 55-75, 55-80, and 55-85 years). All scenarios assumed 100% adherence to the screening modality and interval.

Model screening outcomes included CRC incidence reduction, CRC mortality reduction, life-years gained (LYG), total colonoscopies performed, and screening complications, including adverse events related to follow-up colonoscopy. Screening scenarios were plotted against LYG and colonoscopies performed to create an "efficiency frontier," a line connecting the most efficient screening scenarios based on the trade-off between LYG and colonoscopies. By excluding annual stool tests, we recreated CISNET's analysis of the "efficiency frontier" and compared these screening scenarios with each other and with 10y colonoscopy screening. Per CISNET, tests were recommended if they were within 98% of the LYG at the equivalent point on the efficiency frontier and generated at least 90% of the LYG generated by 10y screening colonoscopy.

RESULTS

CISNET modeling showed that mt-sDNA 3y, FIT 2y, and FIT 3y were within 98% of the efficiency frontier, whereas hsFOBT 2y and hsFOBT 3y were not (**Figure**[11]). In comparison with FIT 2y and 3y and hsFOBT 2y and 3y, only mt-sDNA 3y generated greater than 90% of the LYG by screening colonoscopy 10y in at least 1 of the 3 models (SimCRC only) (**Table**[11]).

Figure. Efficiency Frontiers From CISNET Models[11]



2y, 3y, 5y indicate every 2, 3, or 5 years; CISNET, Cancer Intervention and Surveillance Modeling Network; CRC-SPIN, Colorectal Cancer Simulated Population Model for Incidence and Natural history; FIT, fecal immunochemical test; hsFOBT, high-sensitivity (guaiac) fecal occult blood test; MISCAN, Microsimulation Screening Analysis (MISCAN) for Colorectal Cancer; mt-sDNA, multi-target stool DNA test; SimCRC, Simulation Model of Colorectal Cancer.

[a]Each test modality for each interval is plotted for 6 age ranges (in years: 50-75, 50-80, 50-85, 55-75, 55-80, 55-85). For simplicity, only the US Preventive Services Task Force Grade A recommended age range (50-75 years) for mt-sDNA 3y is highlighted.

DISCUSSION

By considering only annual strategies, the USPSTF recommended both annual FIT and hsFOBT for routine screening, but not mt-sDNA. Mt-sDNA was included in the draft statement as an "alternative test" that "may be useful in select clinical circumstances" and is currently recommended for use at 3-year intervals, not annually. Screening test adherence is an important determinant of clinical effectiveness, but annual strategies are difficult to execute and are burdensome on patients, clinicians, and health systems. Biennial or triennial adherence more accurately reflect clinical experience with stool testing and provide a more realistic base for projecting outcomes using modeling. This critical issue was not reflected in the USPSTF's draft statement; however, the USPSTF modeling data itself provide a basis for the evaluation and recommendation of noninvasive screening strategies performed at intervals of more than 1 year.

Combining modeling data, empirically derived data, and clinical experience allows for reasonable clinical decisions on test strategies. We found that the CISNET modeling data support the use of mt-sDNA 3y for routine CRC screening using USPSTF criteria: mt-sDNA 3y lies within 98% of the efficiency frontier and provides greater than 90% of the LYG by screening colonoscopy (SimCRC). Further, the models show that hsFOBT 2y and hsFOBT 3y are not within 98% of the efficiency frontier and do not provide greater than 90% of the LYG by screening colonoscopy. Therefore, logically, the superior performance of mt-sDNA 3y over hsFOBT 2y allows the clinical utility inferred for hsFOBT 2y (from previous randomized controlled trials that showed CRC-related mortality reduction with biennial FOBT screening)[6] to be inferred as well for mt-sDNA 3y. Finally, clinical experience supports the use of high-sensitivity nonannual testing, and patient preference for high-sensitivity long-interval testing is known.[2,9]

Patient-level cost concerns are mitigated by coverage. The USPSTF-recommended screening tests are free of co-pays and deductibles under the Affordable Care Act, which will help increase access to more effective screening options by eliminating patient out-of-pocket expense. Medicare already covers mt-sDNA every 3 years for traditional Medicare beneficiaries without co-payments or deductible (Medicare cost $509). At a list price of $649, which includes a nationwide 24 hour, 7 day a week patient navigation/compliance system, mt-sDNA is less expensive than colo-

Table. Test Performance of Nonannual Adherence Strategies for Screening 1000 Patients Aged 50 to 75 Years[11]

Model	Modality (aged 50-75 years)	Total COLs, n	Complications,[a] n	LYG	CRC Incidence Reduction	CRC Mortality Reduction	% of the LYG by Screening with COL 10y	Distance From Efficiency Frontier
SimCRC	FIT 2y	1215	7	234	53.4%	72.1%	85.2%	100.0%
SimCRC	FIT 3y	971	6	212	44.5%	64.9%	77.0%	100.0%
SimCRC	hsFOBT 2y	1597	9	235	56.1%	73.2%	85.5%	94.0%
SimCRC	hsFOBT 3y	1286	7	212	47.2%	66.0%	77.3%	88.6%
SimCRC	mt-sDNA 3y	1701	9	245	62.7%	78.0%	90.8%	98.9%
MISCAN	FIT 2y	1243	8	200	34.6%	62.2%	80.9%	99.3%
MISCAN	FIT 3y	995	7	176	27.8%	55.0%	71.1%	100.0%
MISCAN	hsFOBT 2y	1636	9	200	37.2%	63.1%	80.9%	91.6%
MISCAN	hsFOBT 3y	1296	8	175	29.6%	55.4%	70.6%	84.7%
MISCAN	mt-sDNA 3y	1714	9	215	43.1%	67.5%	87.0%	97.6%
CRC-SPIN	FIT 2y	1346	9	207	58.3%	68.4%	76.9%	100.0%
CRC-SPIN	FIT 3y	1081	7	178	49.1%	58.9%	66.1%	100.0%
CRC-SPIN	hsFOBT 2y	1626	9	212	61.5%	70.3%	78.5%	94.7%
CRC-SPIN	hsFOBT 3y	1317	8	183	52.5%	61.4%	68.0%	89.8%
CRC-SPIN	mt-sDNA 3y	1827	10	226	68.2%	75.7%	83.9%	98.7%

2y and 3y indicate every 2 or 3 years; COL, follow-up colonoscopies; COL 10y, screening colonoscopy every 10 years; CRC, colorectal cancer; CRC-SPIN, Colorectal Cancer Simulated Population Model for Incidence and Natural history; FIT, fecal immunochemical test; hsFOBT, high-sensitivity fecal occult blood test; LYG, life-years gained; MISCAN, Microsimulation Screening Analysis (MISCAN) for Colorectal Cancer; mt-sDNA, multi-target stool DNA test; SimCRC, Simulation Model of Colorectal Cancer.
[a]Complications include those that occurred in both screening and follow-up procedures.

noscopy and more expensive than FIT/FOBT; at an average cost of $600, it has a cost effectiveness ratio of $11,313 per quality-adjusted life-year compared with not screening, which is well within an acceptable range.[8]

The first opportunity we have to screen a patient for CRC may be the last opportunity. Screening tests should have minimal opportunity for complications and high sensitivity for CRC and significant precancerous lesions to maximize screening effectiveness in reducing CRC incidence and mortality.

CONCLUSIONS

Three factors—CISNET modeling, relied on by the USPSTF in its draft statement; inferential clinical utility data supporting CRC mortality reduction; and clinical experience with lack of adherence to annual testing—all support a recommendation by the USPSTF for mt-sDNA 3y as a routine colorectal cancer screening test.

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