November 13, 2020

Tamara Syrek Jensen, Director
Coverage and Analysis Group
Centers for Medicare & Medicaid Services
7500 Security Blvd,
Baltimore, MD 21244

Re: Proposed Decision Memorandum for Screening for Colorectal Cancer - Blood-Based Biomarker Tests (CAG-00454N)

Dear Ms. Syrek Jensen,

Epigenomics appreciates this opportunity to comment on the Proposed Decision Memorandum for Screening for Colorectal Cancer – Blood-Based Biomarker Tests. Epigenomics develops and commercializes patient-friendly, blood-based diagnostic tests across multiple cancer indications with high medical need. Using blood as a liquid biopsy can improve patient access to cancer screening and thereby contribute to eradicating today's deadliest cancers. By leveraging our product pipeline and strong intellectual property, we aim to become a global leader in blood-based cancer detection and revolutionize cancer diagnostics using our unique, proprietary DNA methylation biomarker technology.

Thank you for addressing this particularly important topic as colorectal cancer (CRC) continues to be a major cause of death and morbidity among Medicare beneficiaries. In fact, the chance of developing CRC increases significantly with age. CRC is most frequently diagnosed among people aged 65–74 with a median age of 67 at diagnosis (https://seer.cancer.gov/statfacts/html/colorect.html). According to the American Cancer Society (ACS), the probability of developing CRC before age 50 is about 0.4%, but it more than doubles to 1% for those 60 – 69 years of age and from there it triples to 3.2% for those 70 and older (https://cancerstatisticscenter.cancer.org/?_ga=2.34148001.1285459708.1604865539-2118789323.1604865539#!/cancer-site/Colorectum).

Although we are encouraged by the proposed coverage of certain blood-based biomarker tests for CRC, as described in the Proposed Decision Memorandum released on October 16, 2020, the Proposed Decision Memorandum fails to consider important evidence regarding the benefits of screening using Epi proColon®. We request that this evidence be considered and that the Centers for Medicare & Medicaid Services (CMS) cover annual CRC screening using the Epi proColon blood test. We also urge CMS to modify the blood-based biomarker screening test requirements to more adequately align with the clinical performance measures of existing and future Food and Drug Administration (FDA)-approved tests with an indication for screening. Rather than using arbitrarily assigned point estimates, the test performance criteria should be based on longstanding scientifically accepted decision modeling methods developed by the

Cancer Intervention and Surveillance Modeling Network (CISNET) that are presently and broadly used to evaluate the long-term clinical benefits and harms associated with recommended and newly proposed screening strategies.

The development and validation of the CISNET models over the past twenty years has been sponsored by the National Cancer Institute (NCI) in an effort to provide tools for assessing the clinical effectiveness of new and innovative screening modalities. This includes determining the optimal interval for implementation of test strategies based on a prediction of the clinical outcomes of incidence and mortality reduction, along with the potential harms. For non-invasive procedures like blood tests, harms are primarily limited to those adverse events resulting from completion of the screening process via follow-up colonoscopy after a positive non-invasive test.

The CISNET models have been used by a multitude of experts, including the United States Preventive Services Task Force (USPSTF) and the ACS, to generate consensus statements on CRC screening recommendations (see: *Screening for Colorectal Cancer US Preventive Services Task Force Recommendation Statement*, JAMA, 2016 & *Colorectal Cancer Screening for Average-Risk Adults: 2018 Guideline Update From the American Cancer Society*, CA CANCER J CLIN, 2018). These models have also served as the primary health economic analysis method for determining cost effectiveness. CMS also has recognized the utility of these models and in fact has co-authored CISNET studies and/or commissioned this group to perform microsimulation analysis for new CRC screening methods (see: Goede et al. *Cost-savings to Medicare from Pre-Medicare Colorectal Cancer Screening*, MED CARE, 2015 & Naber et al. *Cost-effectiveness of a multitarget stool DNA test for colorectal cancer screening of Medicare beneficiaries*, PLOS ONE, 2019).

We therefore note that setting arbitrary sensitivity and specificity threshold requirements for coverage is inappropriate and scientifically unsound given that a robust methodology has been firmly established in this field by CISNET. The use of point estimates in isolation has led CMS to the erroneous assumption that Epi proColon is an inferior test as compared to stool-based alternatives. This is, of course, not accurate. In fact, the latest independent NCI-CISNET analysis demonstrates Epi proColon is at least as beneficial, or better than, fecal immunochemical test (FIT) and Cologuard®. We urge CMS not to break away from the established methodology accepted by experts for decades for assessing benefits and harms (clinical utility) associated with proposed CRC screening methods.

We urge CMS to cover a CRC screening test when the following requirements are met:

- **The test must be FDA approved for any CRC screening indication,**
- **Published CISNET data demonstrates that the test is at least as beneficial in reducing the mortality and incidence of CRC as an existing and available medically appropriate alternative at the optimal testing interval demonstrated by the NCI-sponsored analysis, and**

- **The test must be performed in a Clinical Laboratory Improvement Amendments (CLIA) certified high complexity laboratory.**

We do not agree with the requirement for inclusion in clinical guidelines for reasons that are outlined elsewhere in this comment letter. However, if CMS believes that inclusion of a new test in professional society guidelines is required as a condition for coverage, then the criterion should be as follows:

- The test is included as a CRC screening test in at least one professional society guideline or consensus statement or USPSTF recommendation in accordance with the FDA intended use labeling for the product.

CMS inappropriately ignored the data from the inclusion of Epi proColon in CISNET decision modeling analysis, which reveals that the Epi proColon blood test achieves greater reductions in CRC mortality and incidence than FIT and Cologuard.

The FDA-approved Epi proColon test, also referred to as the Septin9 (*mSEPT9*) test, was included in the latest CISNET decision modeling analysis, and the results of this study were published in the Journal of the National Cancer Institute in August, 2020 (Peterse EFP, Meester RGS, de Jonge L, et al. Comparing the cost-effectiveness of innovative colorectal cancer screening tests. J Natl Cancer Inst. 2020 Aug 6:djaa103. doi: 10.1093/jnci/djaa103). While CMS listed this key study as a reference in the proposed decision memorandum, the methodology and data generated by the decision modeling experts were not included as part of the evidence review or the framework for test assessment. We believe this is a serious oversight. This kind of modeling is essential for the assessment of new test methods because data based on sufficiently powered clinical utility studies is typically not available at the time of FDA approval. Instead of using this analysis, CMS has instead randomly selected point estimates for sensitivity and specificity and an arbitrary three-year interval as the standard for assessing the clinical effectiveness of all present and future blood tests in CRC screening. This proposed national coverage determination (NCD) in its current form would therefore determine coverage of blood-based biomarker tests based not on a scientifically-validated and peer-reviewed model, such as the CISNET MISCAN model, but on randomly selected test performance characteristics and inferred clinical outcomes with no supporting evidence or validated analytical tools. The proposed decision by CMS not only lacks scientific rigor by ignoring the published CISNET literature, but it will ultimately be a disservice to Medicare patients, failing to reduce the number of deaths due to this disease. Finalizing these criteria also would set a dangerous precedent for future coverage determinations by not relying on validated analytical tools.

Overview of the 2020 NCI-sponsored CISNET decision modeling results

No new test will have direct evidence on outcomes or testing interval, therefore we need to generate indirect evidence to make the assessment of clinical benefit. This need has been fulfilled by decision modeling tools, which have now become the longstanding standard for USPSTF, ACS, CMS, NCI and other experts. The CISNET decision analysis tools use data on disease prevalence, the natural progression of CRC, and treatment options in conjunction with point estimates on clinical performance (sensitivity and specificity for both pre-cancerous lesions and cancer) for a full range of screening methods to generate indirect evidence on the harms and benefits of new and existing screening modalities. **These models have been validated over 20 years** using direct evidence from large government-sponsored longitudinal outcome studies (NORCAPP, SEER data, Minnesota, Nottingham, and Funen randomized trials, UKFSST, PLCO, & many others).

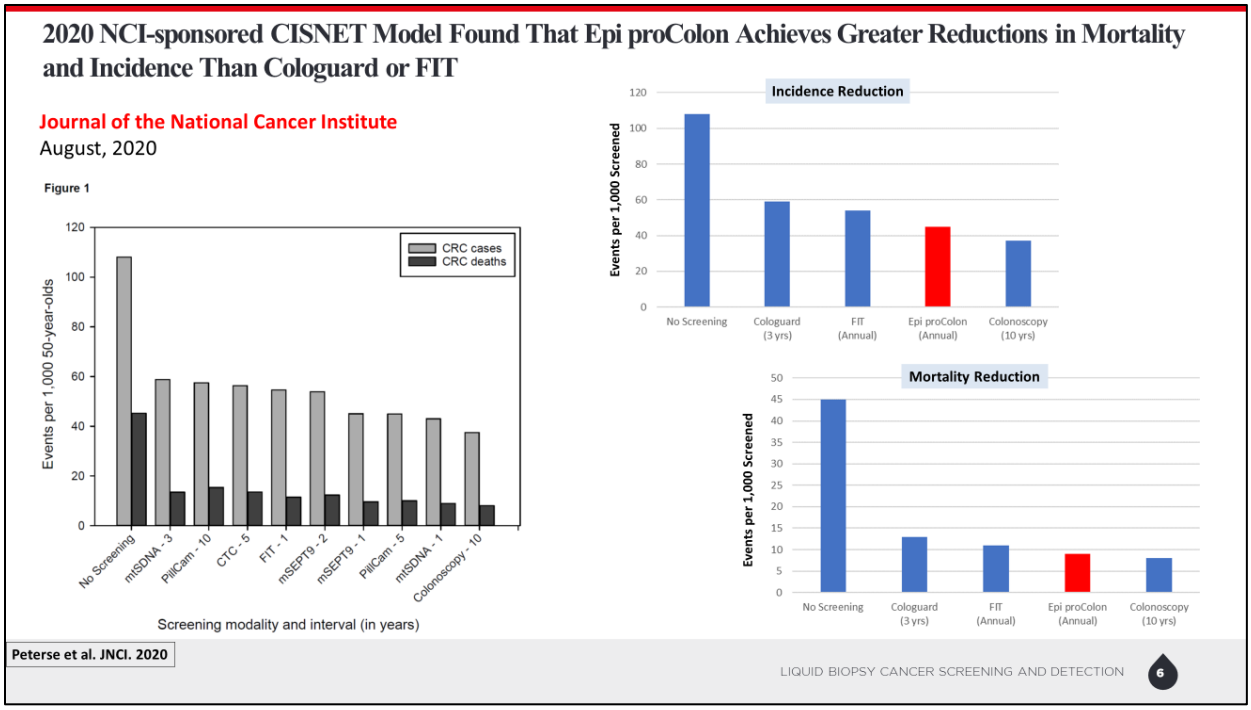
Benefits of Epi proColon compared to FIT and Cologuard

CISNET modeling as published in August, 2020 in the Journal of the National Cancer Institute demonstrated that Epi proColon led to greater clinical benefit than both FIT and Cologuard.

- **Screening annually with Epi proColon results in:**
  - **4% fewer CRC deaths than annual FIT**
  - **9% fewer CRC deaths than triennial Cologuard**

- **Epi proColon performed annually results in:**
  - **8% fewer CRC cases than annual FIT**
  - **13% fewer CRC cases than triennial Cologuard**

- Most important, **Epi proColon results in approximately 80% fewer CRC deaths and nearly 60% fewer CRC cases when compared to no screening.**



Harms of Epi proColon compared to Colonoscopy, FIT and Cologuard

The CISNET data also analyzed harms for Epi proColon and compared them to other methods. The only harms associated with non-invasive screening methods (blood- and stool-based tests) are the adverse events (AEs) resulting from the colonoscopy burden associated with each method. That is, the total number of colonoscopies associated with each screening modality over a lifetime of screening is used as a proxy for the harms and burden of screening. The AEs associated with colonoscopy can include serious gastrointestinal events such as perforations, gastrointestinal bleeding or transfusions, and other gastrointestinal events such as paralytic ileus, nausea, vomiting, dehydration, and abdominal pain. Cardiovascular events may include myocardial infarction or angina, arrhythmias, congestive heart failure, cardiac or respiratory arrest, syncope, hypotension, or shock. These are rare events, and the AE rate also varies with age. Based on the CISNET modeling analysis published in JNCI:

- **Epi proColon results in nearly 20% fewer harms (colonoscopy burden) than the gold standard method of CRC screening, which is to screen using colonoscopy alone at a ten-year interval.**

- The harms to benefit ratio for Epi proColon as compared to no screening was 19 (colonoscopies required per quality-adjusted-life-years-gained or QALYG). The same ratio for the gold-standard method as compared to no screening was 22. That is, using colonoscopy once every ten years as the gold standard CRC screening method, the medical community has determined that 22 colonoscopies per QALYG is an

acceptable ratio. Epi proColon requires only 19 colonoscopies per QALYG, which is favorable to the threshold of 22 set by the gold standard.

- The AE rates associated with screening 1,000 individuals over a lifetime using different modalities would be as follows (using AE rates for a typical 65-year old Medicare beneficiary):

			95% CI			95% CI	
METHOD	AE/QALYG	AE rate per 1000 screened	Lower Bound	Upper Bound	Serious AE rate per 1000 screened	Lower Bound	Upper Bound
Cologuard (3yr)	0.13	2.35%	1.58%	3.49%	0.87%	0.45%	1.66%
FIT (1yr)	0.13	2.43%	1.64%	3.58%	0.90%	0.47%	1.70%
Epi proColon (1yr)	0.20	3.95%	2.91%	5.35%	1.46%	0.88%	2.41%
Colonoscopy (10yr)	0.23	4.89%	3.72%	6.41%	1.81%	1.15%	2.84%

  - The serious AE rates statistically overlap between all methods.
  - The overall AE rates statistically overlap between all non-invasive methods analyzed.
  - Epi proColon demonstrates a nearly 20% decrease in AE rate over a lifetime of screening as compared to the gold-standard (colonoscopy every ten years).
  - Despite the higher AE rates for colonoscopy, it remains the gold-standard because it yields the greatest benefit over the other methods. In the same manner, the AE rates associated with Epi proColon are not statistically different than those of FIT and Cologuard, yet Epi proColon yields greater benefits.

Cost-Effectiveness of Epi proColon

The CISNET analysis also concluded that Epi proColon was more cost-effective than Cologuard (a CRC screening method already approved for coverage by CMS).

Optimal Testing Interval for Epi proColon

CMS states in its Proposed Decision Memorandum that it did not find evidence on the frequency of CRC screening using a blood-based biomarker test. **In fact, the latest decision modeling published in JNCI by CISNET in August 2020 also analyzed different testing intervals for Epi proColon and concluded that annual Epi proColon was the optimal choice for CRC screening.** Annual testing maximizes the benefits of Epi proColon. When comparing the efficiency ratio (ER) between annual and biennial Epi proColon, administering the test annually yields 19 additional QALYG and results in 626 additional colonoscopies. Therefore, the ER

between annual and biennial Epi proColon is 33 (626/19) and favors annual over biennial testing.

- **CMS' proposal for a default three-year testing interval is arbitrary and inappropriate.** CMS proposes that the evidence is sufficient to cover a blood-based biomarker test as an appropriate CRC screening test once every three years or at the interval designated in the FDA label if the FDA indicates a specific test interval.

- Testing Interval is not and will not be indicated in the FDA label of any newly approved CRC screening test. The FDA requires completion of long-term post-approval studies before making any labeling recommendations on testing interval. This takes years and is not the appropriate methodology, as CMS has previously recognized.

    - Cologuard's FDA label states: "Patients with a negative Cologuard test result should be advised to continue participating in a colorectal cancer screening program with another recommended screening method. The screening interval for this follow-up has not been established."

    - CMS' NCD for Cologuard states: "As discussed in the proposed decision memorandum, the frequency of CRC screening with the Cologuard test has not been definitively established. Since cross-sectional studies usually provide evidence at one point in time (one screening in this case), these studies do not provide direct evidence on how often any particular test should be performed. The manufacturer of the current FDA-approved sDNA test has suggested CRC screening once every three years with Cologuard. The post approval study required by the FDA is designed to evaluate the validity of screening once every three years to ensure that clinically important findings are not missed...CMS will re-evaluate the screening interval after the completion of the post approval study and modify coverage if appropriate."

    - Post-approval studies take three to five years to complete, further delaying coverage for new and innovative screening alternatives.

    - CISNET decision modeling has been used to determine the optimal interval for different screening tests. **Only one test is recommended every three years.** One, three, five, and ten-year intervals have been assigned to different screening methods. Tests with higher sensitivity typically have longer testing intervals. Tests with lower sensitivity are not inferior tests, but instead require shorter testing intervals as for example FIT vs. Cologuard.

CMS's proposed approach of using point estimates for sensitivity and specificity as acceptance criteria for coverage is arbitrary and flawed.

- The Proposed Decision Memorandum compares point estimates for cancer sensitivity, specificity, and positive predictive value (PPV) and assigns minimum acceptance cut-offs based on the sensitivity of FIT and the specificity of Cologuard (tests already covered by CMS). The Proposed Decision Memorandum also arbitrarily assigns a three-year testing interval based on Cologuard or as designated by the FDA for a new test. There are major flaws in this approach:

    - **This method has not been tested or validated in any way unlike CISNET models, which have been developed and validated for over 20 years.**

    - **A 74% sensitive / 90% specific test based on the acceptance criteria proposed performed at a three-year interval will actually generate less benefit (life-years gained (LYG), mortality reduction, incidence reduction) as compared to FIT annually, Cologuard every three years, and Epi proColon annually.**

- **Point estimates alone have erroneously led CMS to the assumption that Epi proColon is an inferior test** as compared to stool-based alternatives. **This is, of course, not accurate.** In fact, the latest independent NCI-CISNET analysis (the longstanding scientific standard for assessing the clinical utility of CRC screening methods) demonstrates **Epi proColon is at least as beneficial or better than FIT and Cologuard.**

- **Point estimates alone fail to capture the long-term clinical benefits and harms of newly proposed screening programs.** This is because point estimates do not tell the entire story. Decision modeling has been developed to account for the multitude of factors (disease prevalence, demographics, dwell times and disease progression, polyp size and distribution, test performance, test interval, clinical management, etc.) that influence the overall success of a screening program by making accurate predictions on clinical outcomes over time such as mortality and incidence rates along with anticipated harms.

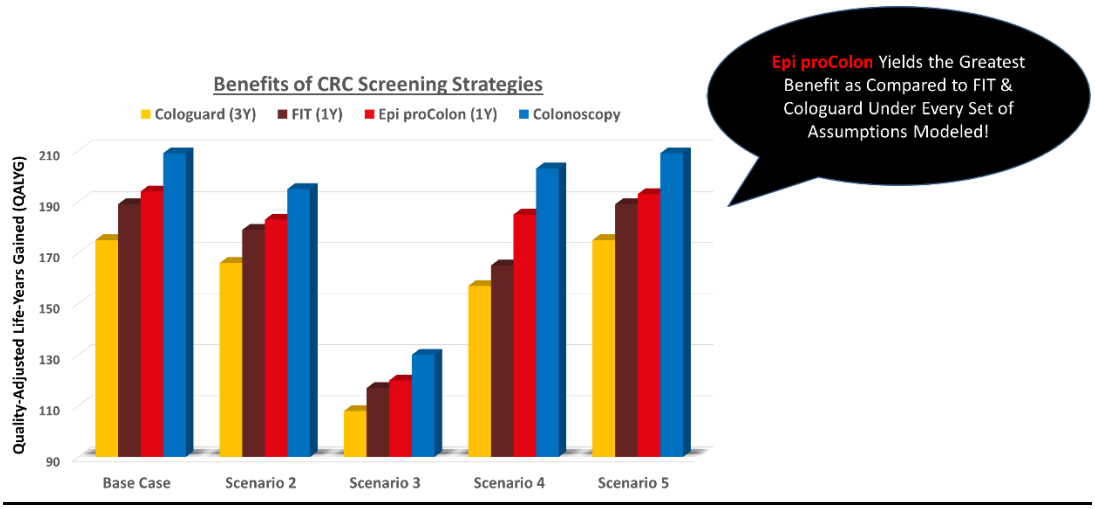
The CISNET decision model was rigorously tested under a multitude of varying assumptions, and Epi proColon consistently ranked as a "test of choice."

The model results were extensively evaluated using rigorous sensitivity analysis under five different scenarios, and Epi proColon generated greater benefits than stool-based methods (FIT and Cologuard) under all conditions analyzed. In each scenario, annual screening with Epi proColon generated more QALYG than screening every three years with Cologuard, or annual FIT. The only screening method with higher QALYG was colonoscopy.

- While the results of the CISNET modeling may seem counterintuitive and to the dislike of some critics, the data are the data!

- **In the process of making critical CMS coverage decisions and other consensus screening recommendations, it is inappropriate and harmful to our clinical field to cherry-pick only those subset of outcomes from decision modeling that align with our predetermined thinking and to ignore the subset of data that inconveniently challenge it.**

Analysis	Description
Base Case	**2020 NCI-sponsored MISCAN Model:** Screening from age 50 through 75 years in an-average risk population
Scenario 2	**2018 ACS Model:** Screening from age 45 through 75 years in an-average risk population
Scenario 3	**2016 USPSTF Model:** Based on lower CRC Incidence inputs
Scenario 4	**Imperfect adherence MISCAN Model:** Adherence estimates in line with current CRC participation rates including colonoscopy follow-up and surveillance
Scenario 5	**Handicap Epi proColon Clinical Performance:** Assume 12% of advanced adenomas and 18% of colorectal cancers are systematically missed by *mSEPT9*



The CISNET decision modeling data also is supported by another independent study out of Harvard Medical School (D'Andrea et al. Cancer Med. 2019). This study was mentioned in the Proposed Decision Memorandum, but the key message of this study (outside of adherence) appears to have also been ignored by CMS. **The outcomes of this study illustrate that Epi proColon provides equivalent benefit to stool-based tests without accounting for any differences in adherence.** Beyond that initial base case analysis, the authors then looked at how adherence would impact their base case outcomes and found that by incorporating differences in the initial uptake between different screening modalities (as reported in the literature), Epi proColon led to much greater long-term benefits as compared to all stool-based alternatives.

Based on these critical data, which were not discussed in the Proposed Decision Memorandum, we request that these important points be re-evaluated, and in so doing we request that CMS cover annual CRC screening using the Epi proColon blood test.

Below we address numerous errors in the Proposed Decision memorandum

The Proposed Decision Memorandum includes various inaccurate statements or proposed requirements. We have listed the statements and provided clarifications below. We request that these important points be re-evaluated, and in so doing we request that CMS cover annual CRC screening using the Epi proColon blood test.

- The Proposed Decision Memorandum states, “There is no evidence that shows screening for colorectal cancer with Epi proColon® is more effective than fecal immunochemical tests (FIT). Compared to FIT, there is no indirect evidence that using Epi proColon® is as effective for colorectal cancer screening among Medicare beneficiaries.” This statement is inaccurate.

    - Epi proColon sensitivity is equivalent to FIT based on a direct head-to-head comparison study conducted in the United States. Johnson et al. Plasma Septin 9

versus fecal immunochemical testing for colorectal cancer screening: a prospective multicenter study. Plos One. 2014.

- The Johnson et al. study reported that the sensitivity point estimate for Epi proColon was equal to or greater than that for FIT for all cancer stages. The Johnson et al. study compared both FIT and Epi proColon against CRC cases identified using the recognized standard (colonoscopy) and was based on the pivotal studies included in the FDA labeling for Epi proColon. It should therefore not be ignored as part of the clinical evidence in support of the robust clinical sensitivity performance of Epi proColon as directly compared to FIT.

- Advanced Adenoma (AA) Detection:
  - Imperiale et al. 2014 (NEJM) reported FIT sensitivity of 23.8% for AA based on 757 colonoscopy confirmed cases.
  - Potter et al. 2014 (Clin Chem) reported Epi proColon sensitivity of 22% for AA based on 621 colonoscopy confirmed cases.
  - Johnson et al. 2014 (Plos One) reported 15% of AA (95%CI: 0.06-0.32) had positive Epi proColon tests, compared with 7% of AA (95%CI: 0.02-0.23) detected by OC-FIT in the head to head comparison in the same patients.

- Positive Predictive Value (PPV)
  - The PPVs reported for Cologuard® and FIT by Imperiale et al. (2014) were 3.7% (95% CI: 2.85%-4.76%) and 6.9%, respectively. The PPV reported for Epi proColon by Potter et al. (2014) was 2.5% (95% CI: 2.0%-3.0%). The PPVs between Cologuard and Epi proColon statistically overlap.

- CISNET Decision Modeling
  - CISNET modeling has recently demonstrated that Epi proColon is more effective than both FIT and Cologuard in the reduction of both CRC incidence and mortality (JNCI, August 2020). This analysis is discussed in detail elsewhere in this comment letter.

- The Proposed Decision Memorandum states, "It is difficult to identify an appropriate population for the Epi proColon® test based on the available evidence." Additionally, the Proposed Decision Memorandum states, "Yet even given this narrow indication, there is unclear evidence if a patient who has refused all other tests (patients needs to be willing to undergo screening and then diagnostic testing) or believes they cannot undergo a fecal based test that they will agree to the colonoscopy since they refused screening to begin with." These statements are inaccurate.

  - The appropriate population has been clearly addressed by the FDA in the indication for use for the test. The Epi proColon test is indicated to screen adults of either sex, 50 years or older, defined as average risk for CRC, who have been

offered and have a history of not completing CRC screening. The test is intended for CRC screening, but excludes those willing to undergo screening by other methods. This exclusion should not be misinterpreted as a lack of test performance or inappropriateness. It is simply an exclusion for a subset of Medicare beneficiaries who are currently up to date with their CRC screening. In this way, the Epi proColon test provides another option for the millions of Medicare beneficiaries who have been resistant to other screening methods, for whom blood tests have been shown to improve screening uptake. It is not uncommon for FDA labels to highlight exclusions. For example, the FDA label for various CRC screening tests highlights numerous contraindications, precautions, and warnings that may exclude certain patient populations from the tests.

- The argument that it would be administratively burdensome or costly to document that a patient has been offered and declined other screening options has no merit. Tracking as has been discussed with CMS can easily be done as part of routine clinical practice through the use of existing ICD10 codes. Most important, saving lives should not be viewed as an administrative burden.

- The argument that those resistant to colonoscopy will not complete their screening process by refusing to undergo a diagnostic colonoscopy following a positive Epi proColon test is inaccurate. There is direct evidence that patients unwilling to undergo a screening colonoscopy will in fact participate in diagnostic colonoscopies following either a positive Epi proColon or FIT test. The colonoscopy follow-up rate is similar between FIT and Epi proColon, and in the range of 67% – 80% as reported by Liles et al. Cancer Treatment and Research Communications (2017); Corley et al. JAMA. (2017); and Jensen et al. Ann Intern Med. (2016).

- The proposed requirement for inclusion in clinical guidelines is unnecessary and inconsistent with previous CRC NCDs. If CMS ultimately decides to incorporate a guideline-inclusion requirement for coverage, it should be aligned with the intended use of the FDA approved product.

    - Requiring clinical guideline inclusion will delay coverage of new technology innovation by five to eight years. Why? Many clinical guideline groups have long cycles for review, inclusion of new methods, and publication of new screening recommendations.
        - One approach to address this would be that once the final NCD is issued, CMS would cover any test for four years after that test meets all the other final NCD requirements to allow for guideline inclusion in future years. This aligns directly with CMS's proposal to cover FDA approved breakthrough technologies under the Medicare Coverage for Innovative Technology (MCIT) pathway.

- Cologuard was not included in USPSTF or other guidelines prior to CMS coverage. This is an appropriate precedent for future coverage decisions. At the time CMS granted national Medicare coverage for Cologuard:
    - NCD (CAG-00440N) for Cologuard: " The USPSTF concludes that the evidence is insufficient to assess the benefits and harms of...fecal DNA testing as screening modalities for colorectal cancer."
    - Under Section 5 entitled Professional Society Recommendations/Consensus Statements of the Cologuard Decision Memorandum, every guideline summary is followed by the following statement: "This recommendation was based on a predecessor test. The Cologuard test was not evaluated." The predecessor test called PreGen-Plus™ used in this justification was totally unrelated to the Cologuard test. PreGen-Plus had no FIT component and out of the four DNA markers used, only *KRAS* was common to both tests.

- Should guideline inclusion be considered essential, it should be in line with the FDA-labeling for the product, which may not always include routine screening. For example,
    - Inclusion as a colorectal cancer screening test in at least one professional society guideline or consensus statement or USPSTF recommendation per the product's FDA intended use.
    - National Comprehensive Cancer Center Network (NCCN) has included Epi proColon in its CRC guidelines according to its FDA-approved labeling as a test to be considered for patients unwilling to use other methods.

- CMS inappropriately applies the "reasonable and necessary" standard to CRC screening. Although CMS correctly notes that CRC screening is covered under sections 1832, 1861(s)(2)(R) and 1861(pp) of the Social Security Act (SSA), CMS also discusses application of the "reasonable and necessary" standard under section 1862(a)(1)(A), which applies to diagnostic and therapeutic services, not to preventive services. As CMS acknowledged in its decision memoranda on screening occult fecal occult blood tests and screening computed tomography colonography, "Subject to frequency limits, certain Colorectal Cancer Screening Tests are payable under the Medicare statute even if the tests would not satisfy the "reasonable and necessary" provision of section § 1862(a)(1)(A)." CMS thus is applying a different standard for coverage of blood-based biomarker tests than it applied to other CRC screening methods.

- Considering Commercial Payer Coverage is not appropriate. CMS is the largest health insurance provider in the United States, and CRC is most impactful for Medicare beneficiaries. CRC rates are highest among the Medicare population.
    - The Medicare population accounts for 40 percent of all average-risk individuals eligible for CRC screening. No commercial payer has such a significant number of covered lives impacted by this disease, by far.

- Commercial payers have been waiting for CMS coverage prior to making an assessment on coverage of Epi proColon.

- An assessment of the commercial market for coverage by private payers was not mentioned anywhere in the Cologuard NCD (CAG-00440N) and blood-based biomarker tests should be treated equally.

- Table 10 is inaccurate and misleading. The outcomes of benefits and harms attributed to the Epi proColon test should be based on CISNET modeling results. Assessment based on one-time point estimates of sensitivity and specificity, as proposed, do not represent the impact of a comprehensive screening program. Therefore, Table 10 of the Proposed Decision Memorandum contains two major misrepresentations:

    - The statement that one test misses more cancer than another test based on single point estimates of one-time testing is not applicable here. *The number of false negatives for a single test is not an appropriate interpretation of the benefits of long-term screening.* In fact, microsimulation data shows that the small gaps in the point estimates for sensitivity are easily overcome and are often outweighed by the testing interval. *For example, the point estimate of sensitivity for one Cologuard test versus one FIT test is inappropriate.* The correct method for test comparison would be to measure the sensitivity of three FIT tests performed annually over three years and contrast that to the sensitivity of Cologuard performed once over that same three-year period.

        - Modeling analysis extrapolates benefits over a lifetime of testing based on point estimates of performance and other factors. This is exactly what these models have been designed to do over the last two decades.

    - The statement that "excess positives tell more patients that they have cancer" is also not accurate.
        - Non-invasive screening methods are not diagnostic tests for CRC. This applies to FIT, Cologuard, and Epi proColon. Excess positives tell more patients that they will need a colonoscopy to complete their screening process and NOT that they have cancer.
        - Because Epi proColon is indicated for patients who refused a screening colonoscopy (the gold standard for screening) and other screening methods, any colonoscopies that result from excess positives should be viewed as a benefit of bringing more patients into compliance with CRC screening, not a harm.
        - The recent decision modeling published in JNCI by CISNET (August, 2020) indicates that Epi proColon performed annually would lead to fewer harms than the gold-standard.

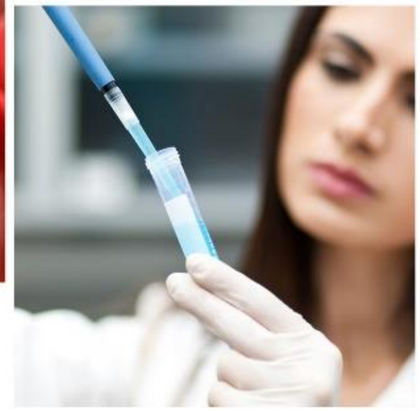
Again, we request that these important points be re-evaluated, and in so doing we request that CMS cover annual CRC screening using the Epi proColon blood test.
Epigenomics appreciates this opportunity to comment on the Proposed Decision Memorandum. We would be happy to discuss any questions you have. Please feel free to contact us with any questions.

Sincerely,

Jorge Garces Ph.D.
President & Chief Scientific Officer
Epigenomics AG

Theo deVos Ph.D.
Vice President Clinical & Scientific affairs
Epigenomics Inc

Ensuring Medicare Beneficiaries Access to Colorectal Cancer Screening through Blood Testing



Epigenomics Discussion with CMS

October 27, 2020

Our Collective Goal is to Save Lives!

The goal of any CRC screening program is to improve population health outcomes:

- Decrease mortality associated with CRC
- Decrease the incidence of the disease

One important consideration is whether covering the screening method proposed will result in more harm than good:

- Existing methods can answer this question, particularly if there is a gold standard for comparison

How do we assess that the test is "at least as beneficial as an existing and available medically appropriate alternative"?

No new test will have direct evidence on outcomes or testing interval, therefore how do we generate indirect evidence to make the assessment of clinical benefit?

- **Longstanding USPSTF, ACS & NCI standard:**
  - Use data on disease prevalence, the natural progression of CRC, and treatment options in conjunction with point estimates on clinical performance (sensitivity and specificity for both pre-cancerous lesions and cancer) for a full range of screening methods to generate indirect evidence on the harms and benefits of new and existing screening modalities. i.e., Microsimulation Modeling

  - Models have been validated over 20 years using direct evidence from large government-sponsored longitudinal outcome studies (NORCAPP, SEER data, Minnesota, Nottingham, and Funen randomized trials, UKFSST, PLCO, & many others)

- **CMS proposal:**
  - Compare point estimates for cancer sensitivity, specificity, and PPV
  - Assign minimum acceptance cut-offs based on sensitivity of FIT and Specificity of Cologuard (tests already covered)
  - Arbitrarily assign a three-year testing interval based on Cologuard or as designated by the FDA for a new test

Decision Models Provide a Tool to Address Which Screening Strategies and Interval of Screening is Optimal

Colorectal Cancer Screening for Average-Risk Adults: 2018 Guideline Update From the American Cancer Society

CA CANCER J CLIN, 2018

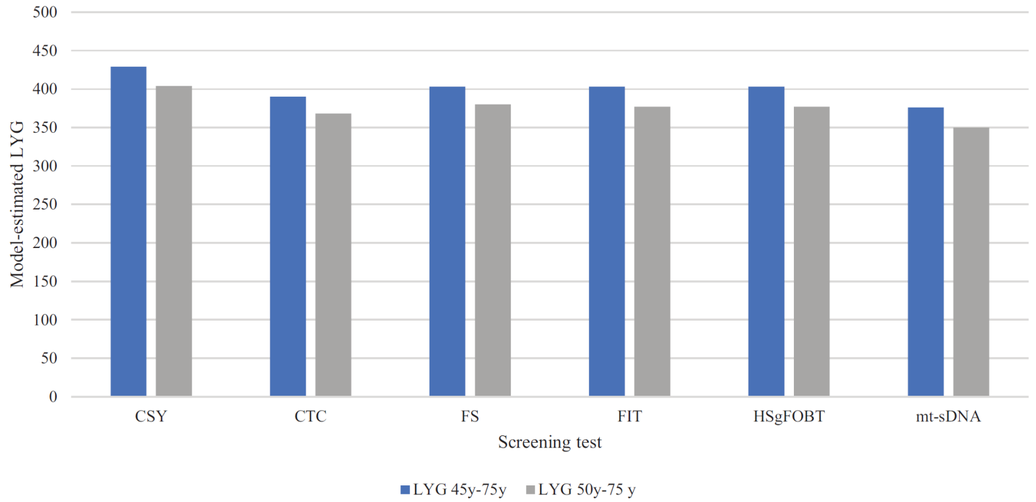
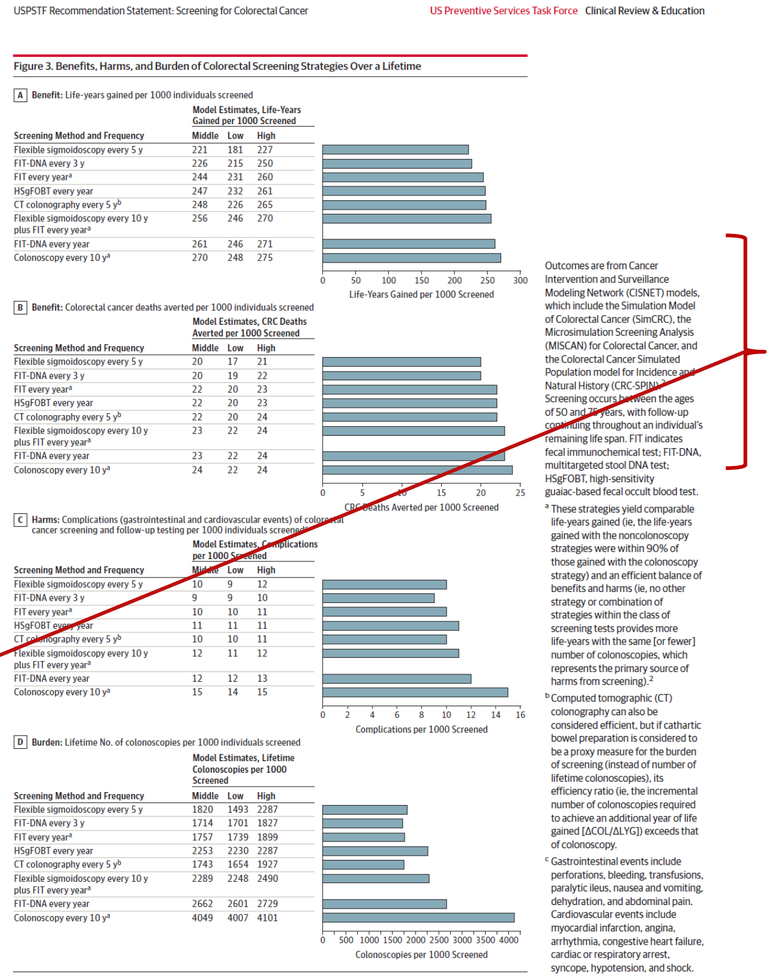


FIGURE 5. Model-Estimated Life-Years Gained (LYG) from Colorectal Cancer Screening Starting at Age 45 Years Versus 50 Years, per 1000 Screened Over a Lifetime. CSY indicates colonoscopy; CTC, computed tomography colonography; FSIG, flexible sigmoidoscopy; FIT, fecal immunochemical test; gFOBT, guaiac-based fecal occult blood test; LYG, life-years gained; mt-sDNA, multitarget stool DNA. Adapted from: Peterse EFP, Meester RGS, Siegal RL, et al. The impact of the rising colorectal cancer incidence in young adults on the optimal age to start screening: microsimulation analysis I to inform the American Cancer Society colorectal cancer screening guideline. *Cancer*. 10.1002/cncr.31543 [epub ahead of print].[34]

Screening for Colorectal Cancer US Preventive Services Task Force Recommendation Statement

JAMA, 2016



Both of these analyses use microsimulation models to identify effective screening methods and intervals . This was the key analytical method used by ACS to alter their starting age recommendation for CRC Screening and for USPSTF to set their clinical guidelines.

Decision Models Have Been Used as a Standard for Determining Benefits and Health Economics by CMS

NCI, NIH, CDC, CMS Collaboration
MED CARE, 2015

Cost-savings to Medicare from Pre-Medicare Colorectal Cancer Screening

S. Lucas Goede, Msc[1], **Karen M. Kuntz, ScD**[2], **Marjolein van Ballegooijen, MD, PhD**[1], **Amy B. Knudsen, PhD**[3], **Iris Lansdorp-Vogelaar, PhD**[1], **Florence K. Tangka, PhD**[4], **David H. Howard, PhD**[5], **Joseph Chin, MD, MSc**[6], **Ann G. Zauber, PhD**[7], and **Laura C. Seeff, PhD**[4]

[1]Department of Public Health, Erasmus University Medical Center, Rotterdam, The Netherlands [2]Division of Health Policy and Management, University of Minnesota, Minneapolis, MN [3]Institute for Technology Assessment, Department of Radiology, Massachusetts General Hospital, Boston, MA [4]Division of Cancer Prevention and Control, Centers for Disease Control and Prevention, Atlanta, GA [5]Department of Health Policy and Management, Emory University, Atlanta, GA [6]Coverage and Analysis Group, Centers for Medicare and Medicaid Services, Baltimore, MD [7]Department of Epidemiology and Biostatistics, Memorial Sloan Kettering Cancer Center, New York, NY

Abstract

Background—Many individuals have not received recommended colorectal cancer (CRC) screening before they become Medicare eligible at age 65. We aimed to estimate the long-term implications of increased CRC screening in the pre-Medicare population (50–64 years) on costs in the pre-Medicare and Medicare populations (65+ years).

Methods—We used two independently developed microsimulation models (MISCAN and

CMS requested an analysis of mtSDNA screening of Medicare enrollees from the MITRE Corporation. MITRE commissioned investigators from the Cancer Intervention and Surveillance Modeling Network (CISNET)...
PLOS ONE, 2019

RESEARCH ARTICLE

Cost-effectiveness of a multitarget stool DNA test for colorectal cancer screening of Medicare beneficiaries

Steffie K. Naber[1☯]*, **Amy B. Knudsen**[2☯], **Ann G. Zauber**[3], **Carolyn M. Rutter**[4], **Sara E. Fischer**[3¤a], **Chester J. Pabiniak**[5], **Brittany Soto**[3¤b], **Karen M. Kuntz**[6], **Iris Lansdorp-Vogelaar**[1]

1 Erasmus MC, University Medical Center Rotterdam, Department of Public Health, Rotterdam, The Netherlands, **2** Institute for Technology Assessment, Massachusetts General Hospital, Boston, Massachusetts, United States of America, **3** Department of Epidemiology and Biostatistics, Memorial Sloan Kettering Cancer Center, New York, New York, United States of America, **4** RAND Corporation, Santa Monica, California, United States of America, **5** Kaiser Permanente Washington Health Research Institute, Seattle, Washington, United States of America, **6** Division of Health Policy and Management, School of Public Health, University of Minnesota, Minneapolis, Minnesota, United States of America

☯ These authors contributed equally to this work.
¤a Current address: Georgetown University, Washington, D.C., United States of America
¤b Current address: CVS Health, Woonsocket, Rhode Island, United States of America
* s.naber@erasmusmc.nl

Abstract

Background

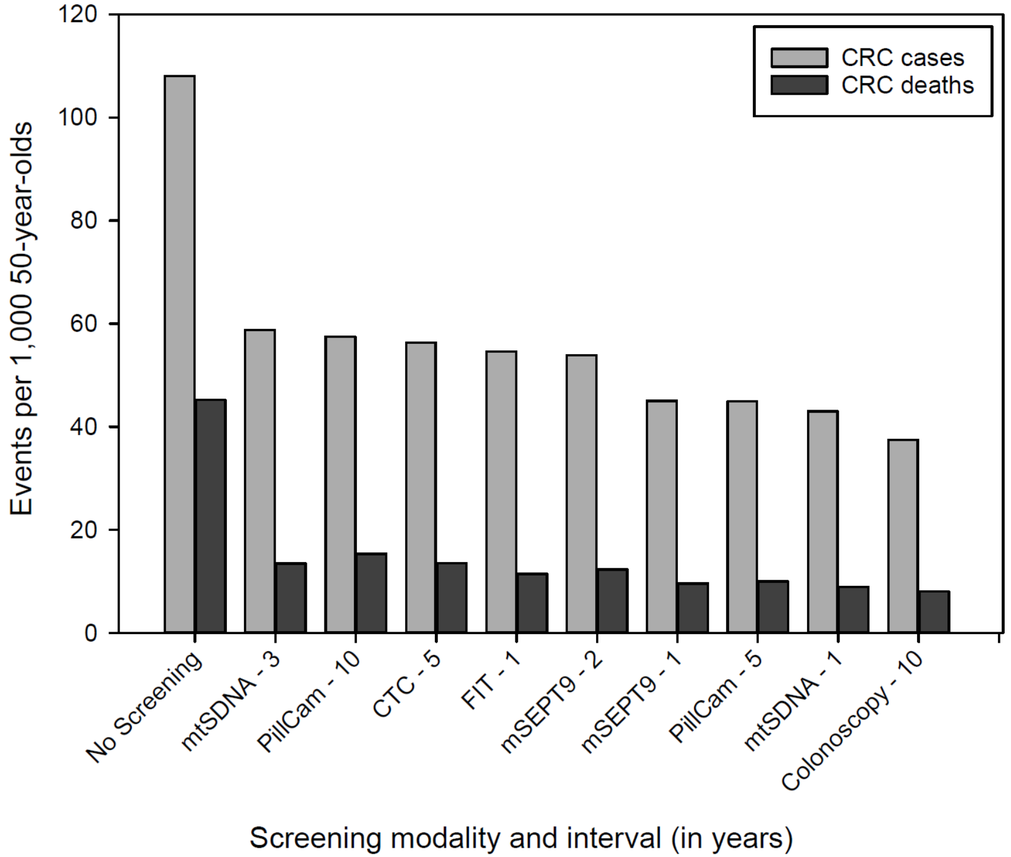
In 2014, the Centers for Medicare and Medicaid Services (CMS) began covering a multitar-

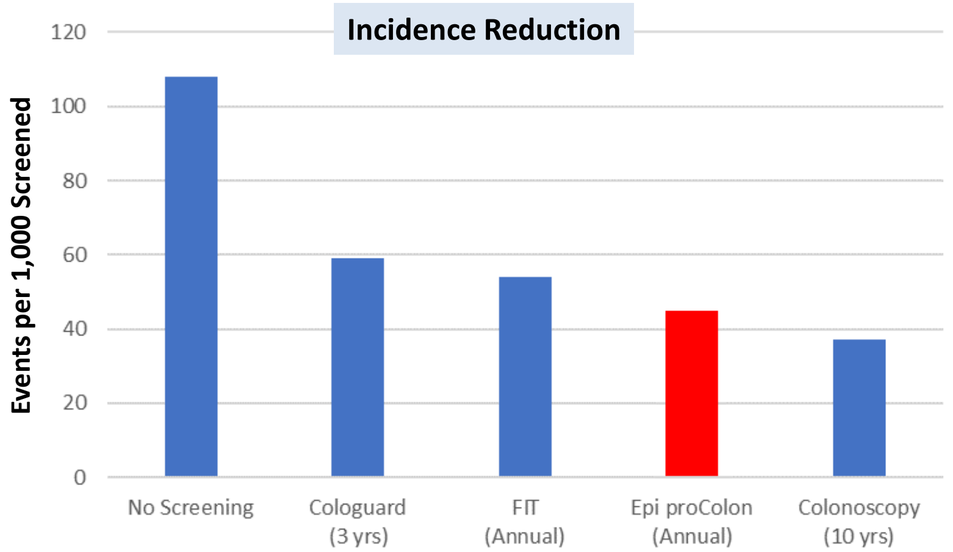
2020 NCI-sponsored CISNET Model Found That Epi proColon Achieves Greater Reductions in Mortality and Incidence Than Cologuard or FIT

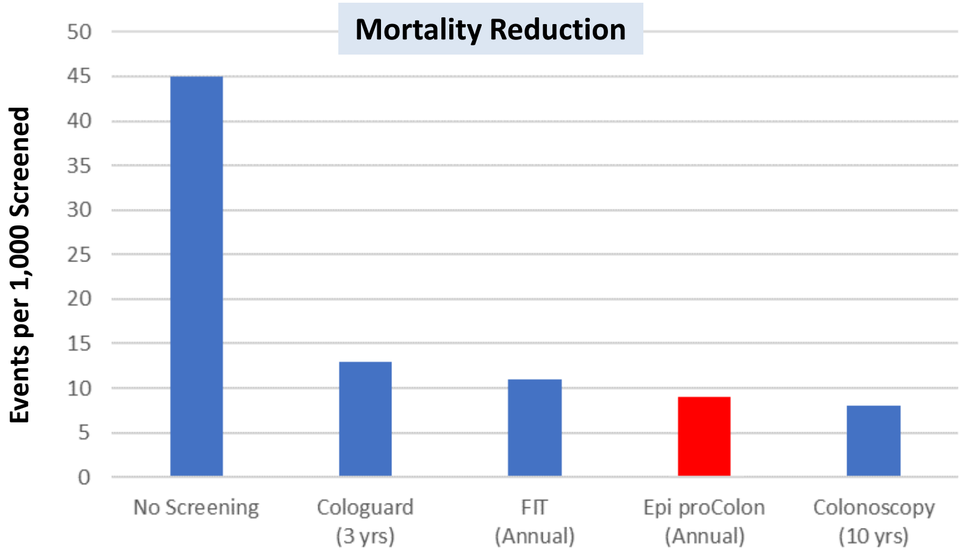
Journal of the National Cancer Institute

August, 2020

Figure 1

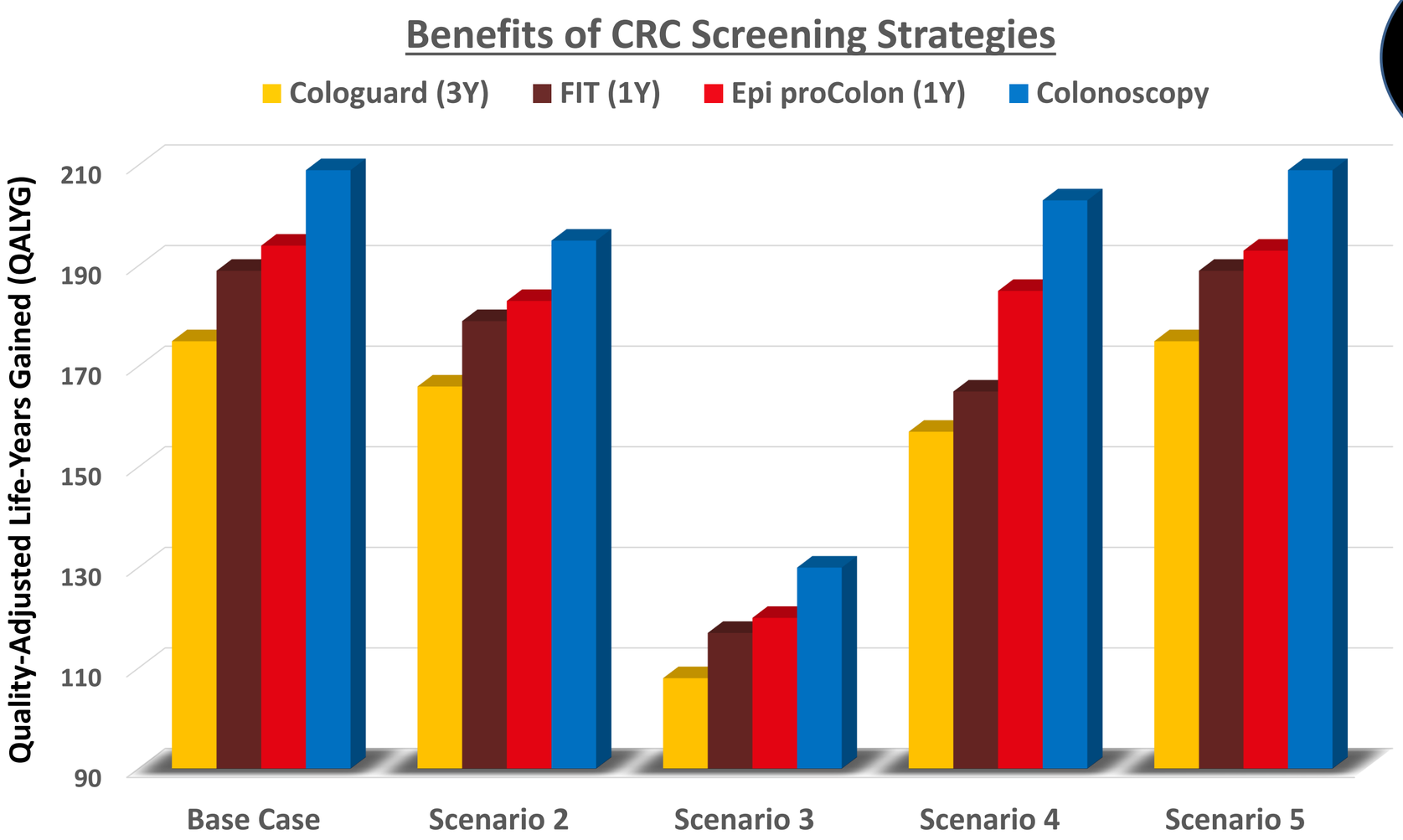






Peterse et al. JNCI. 2020

Extremely Robust Analysis: Screening Methods Evaluated Under Multiple Scenarios

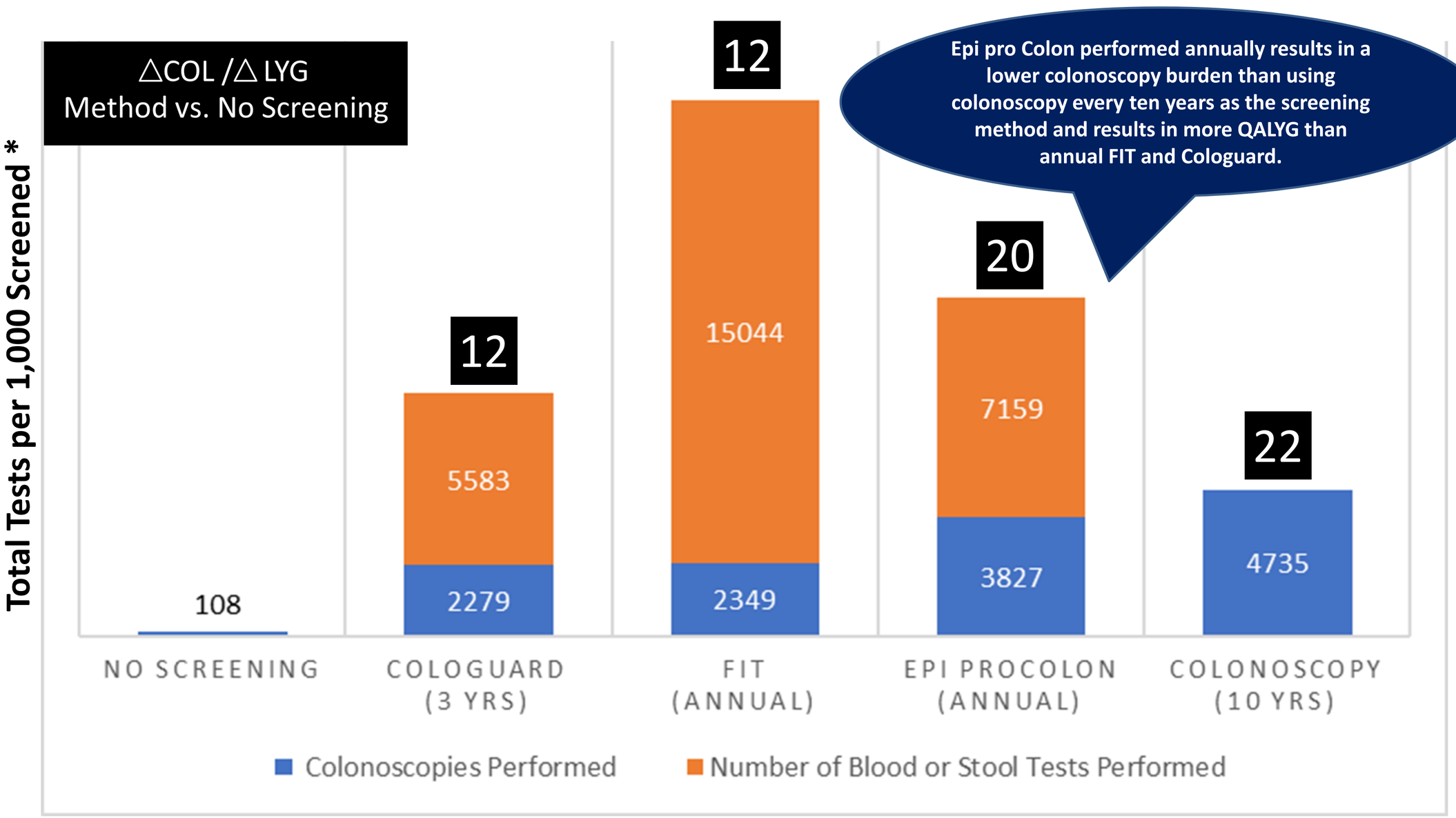


Epi proColon Yields the Greatest Benefit as Compared to FIT & Cologuard Under Every Set of Assumptions Modeled!

Analysis	Description
Base Case	**2020 NCI-sponsored MISCAN Model:** Screening from age 50 through 75 years in an-average risk population
Scenario 2	**2018 ACS Model:** Screening from age 45 through 75 years in an-average risk population
Scenario 3	**2016 USPSTF Model:** Based on lower CRC Incidence inputs
Scenario 4	**Imperfect adherence MISCAN Model:** Adherence estimates in line with current CRC participation rates including colonoscopy follow-up and surveillance
Scenario 5	**Handicap Epi proColon Clinical Performance:** Assume 12% of advanced adenomas and 18% of colorectal cancers are systematically missed by *mSEPT9*

Peterse et al. JNCI. 2020

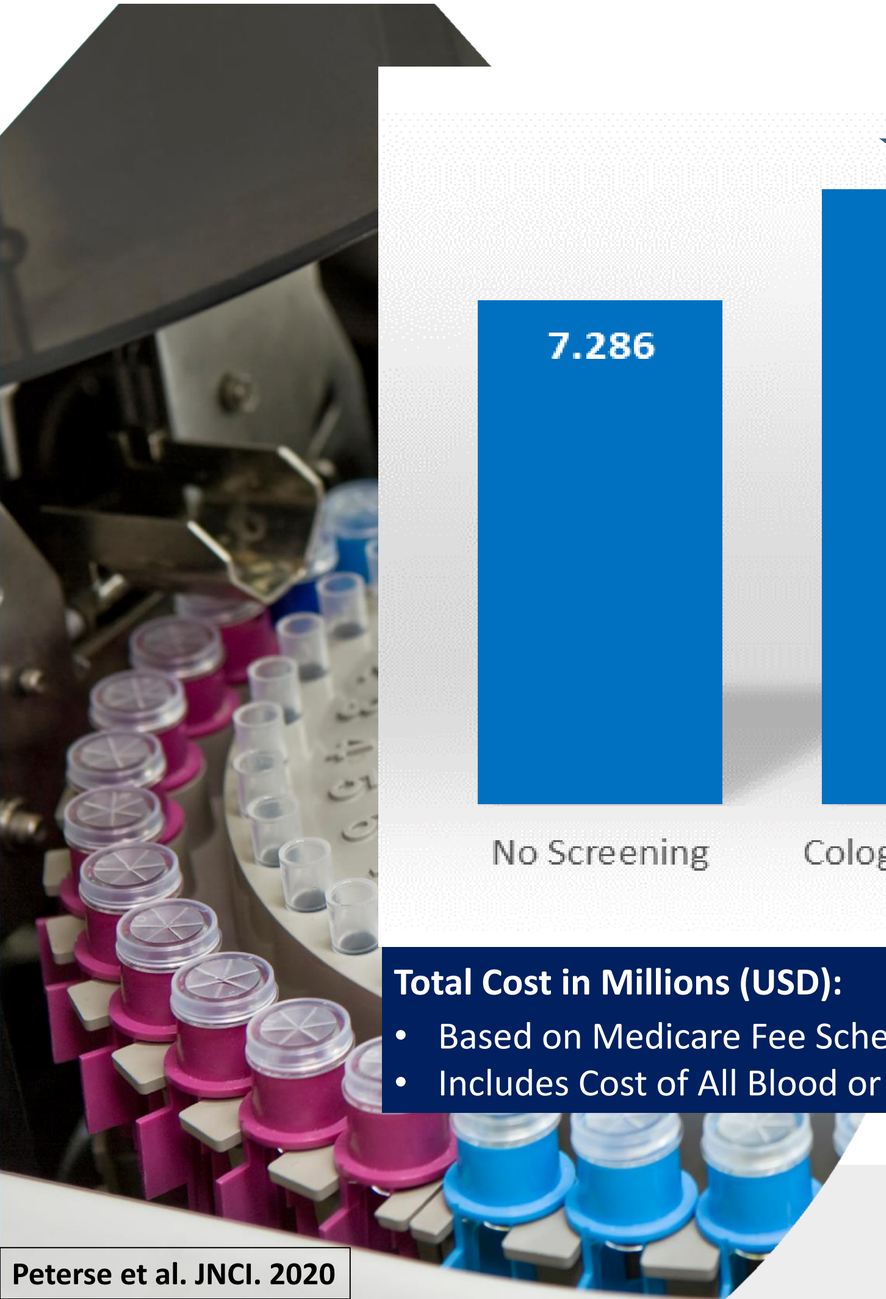
Total Number of Tests and Colonoscopies Performed

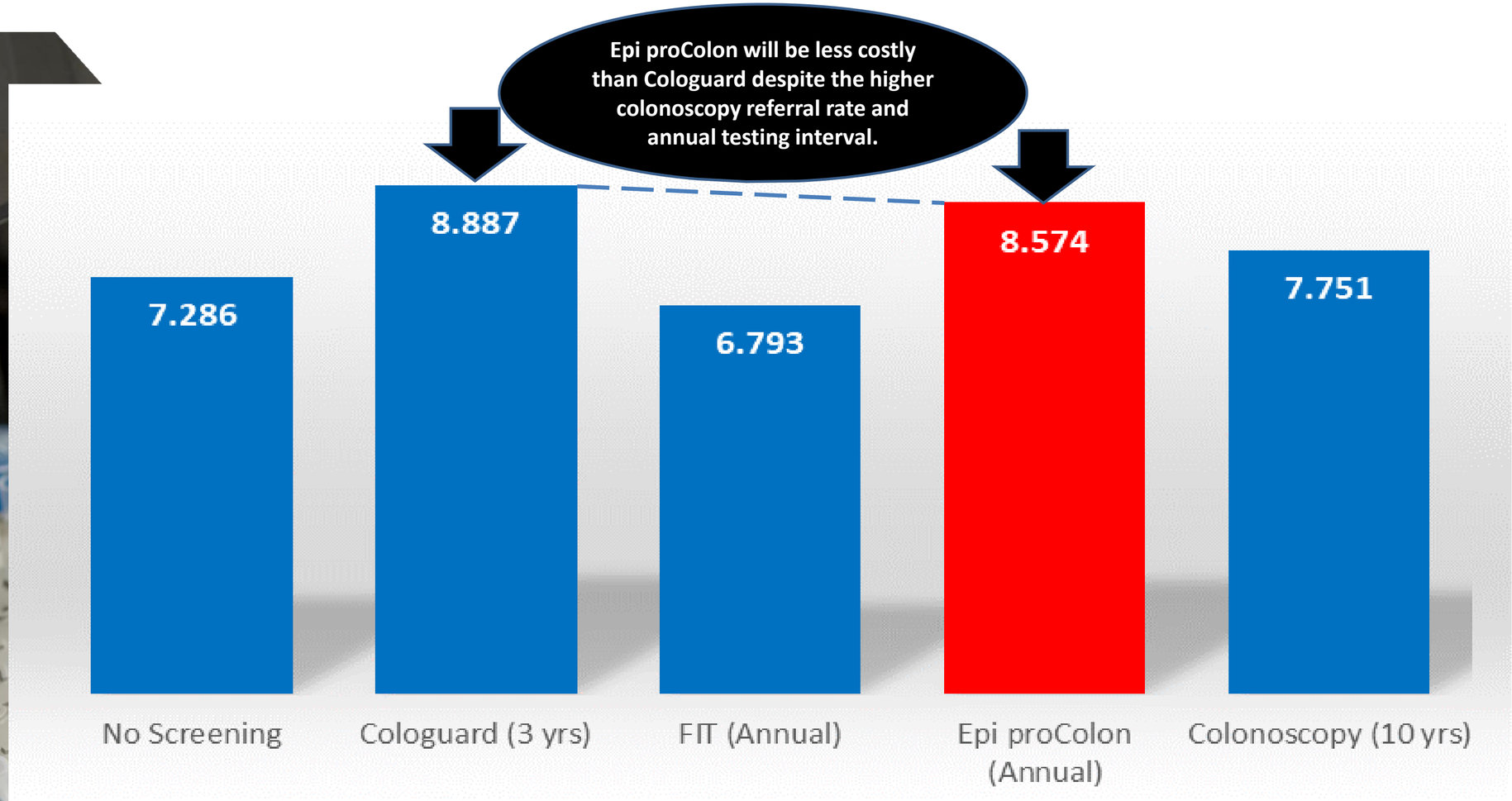


***Note: Total Number of Tests Administered Over a Lifetime**

Peterse et al. JNCI. 2020

Total Cost (Screening, Diagnosis, Treatment) By Screening Method



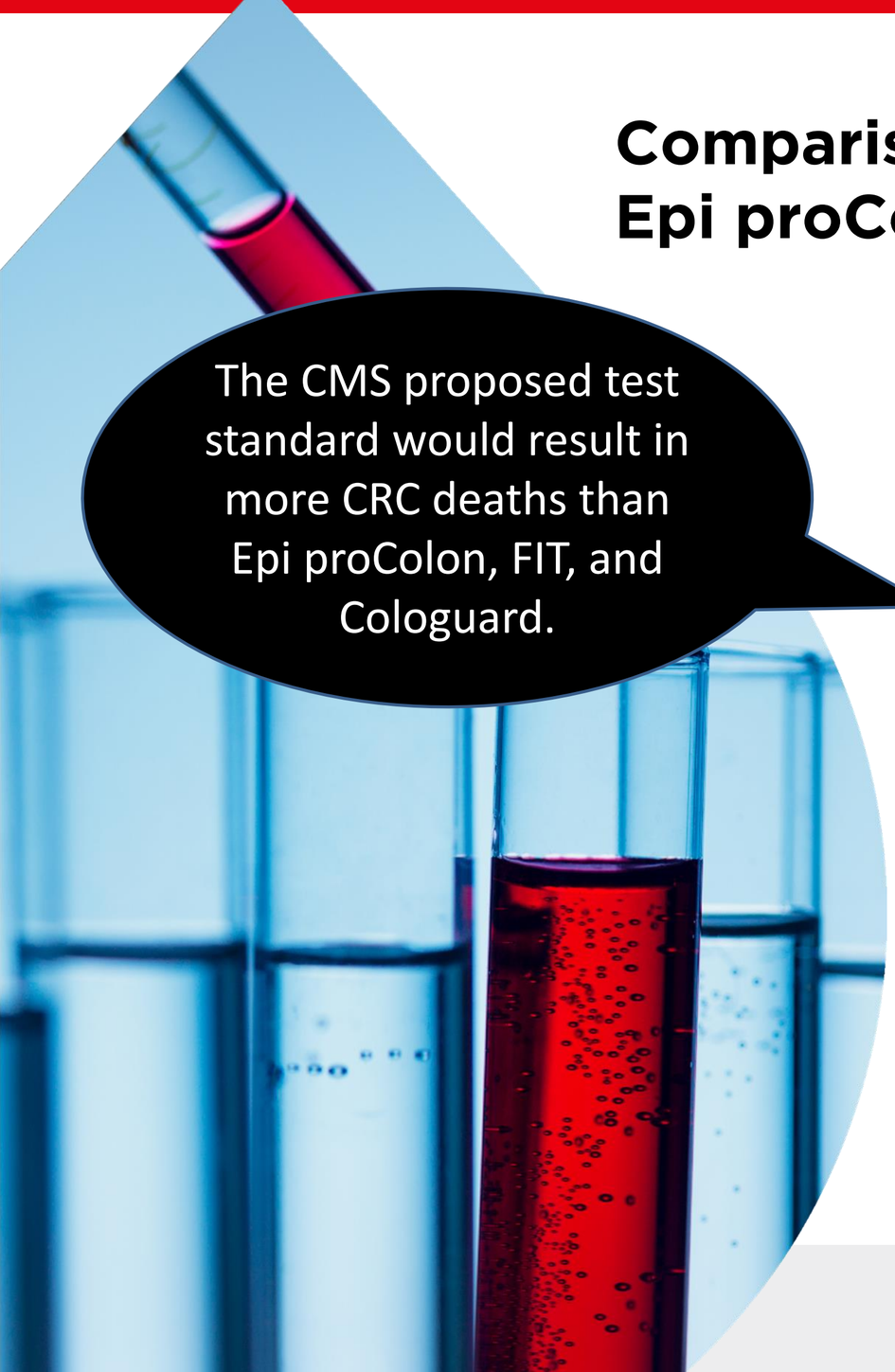


Total Cost in Millions (USD):

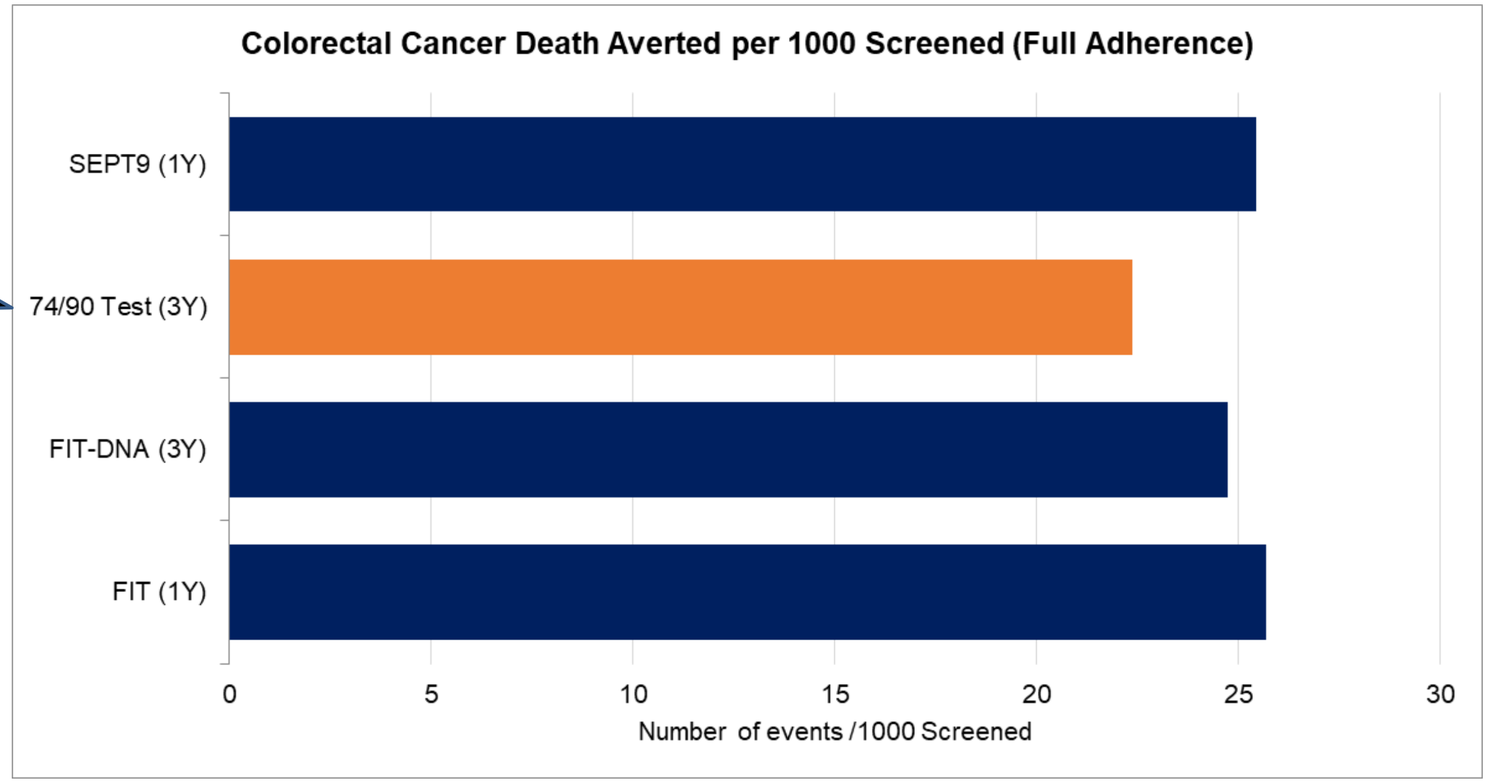
- Based on Medicare Fee Schedule, and
- Includes Cost of All Blood or Stool Tests + All Colonoscopies + All Treatments Over a Lifetime of 1,000 patients

Peterse et al. JNCI. 2020

Comparison of CMS Proposed NCD Test Standard to Epi proColon, FIT-DNA, and FIT



The CMS proposed test standard would result in more CRC deaths than Epi proColon, FIT, and Cologuard.



Predict Microsimulation Model (Harvard)

The Epi proColon test is at least as beneficial as an existing and available medically appropriate alternative

- Microsimulation is the longstanding scientifically accepted standard used to assess the indirect benefits associated with different CRC screening strategies
- The latest independent NCI-CISNET microsimulation analysis demonstrates **Epi proColon is at least as beneficial or better than FIT and Cologuard**
- Health economic modeling demonstrates Epi proColon costs less than Cologuard

Points of Clarification

- **Epi proColon Sensitivity is Equivalent to FIT Based on Direct Head to Head Comparison**
  - Only US side by side comparison study : Johnson et al. Plasma Septin 9 versus fecal immunochemical testing for colorectal cancer screening: a prospective multicenter study. Plos One. 2014
    - **Demonstrated that the point estimate for sensitivity was equal to or better for Epi proColon across all cancers!**

Epi proColon				
Test Result	CRC	Non-CRC	**Sensitivity**	**Specificity**
Epi proColon Positive	70	37	**72%**	
Epi proColon Negative	27	156		**81%**
Total	97	193		

FIT				
Test Result	CRC	Non-CRC	**Sensitivity**	**Specificity**
OC FIT-CHEK Positive	66	5	**68%**	
OC FIT-CHEK Negative	31	188		**97%**
Total	97	193		

CRC Stage	Epi proColon Sensitivity	95% CI	FIT Sensitivity	95% CI
Stage 0/I	64.3%	45.8 - 79.3%	60.7%	42.4 -76.4%
Stage II	80.0%	58.4 - 91.9%	80.0%	58.4 - 91.9%
Stage III/IV	75.0%	58.9 - 86.3%	74.3%	57.9 - 85.8%
Unknown	76.5%	52.7 - 90.4%	50.0%	26.8 - 73.2%
All Stages	73.3%	63.9 - 80.9%	68.0%	58.2 - 76.5%

In another independent side by side comparison by Jin et al. (J Gastroenterol Hepatol. 2015), the authors concluded that SEPT9 showed better performance in CRC detection than FIT and similar for advanced adenomas.

- Advanced Adenoma Detection
  - **FIT reported at 23.8%** by Imperiale et al. 2014 (NEJM) based on 757 colonoscopy confirmed cases
  - **Epi proColon reported at 22%** by Potter et al. 2014 (Clin Chem) based on 621 colonoscopy confirmed cases
  - Epi proColon detected 15% of AA (95%CI: 0.06-0.32) and FIT detected 7% of AA (95%CI: 0.02-0.23) in head to head comparison by Johnson et al. 2014 (Plos One)

- PPV
  - The PPV reported for Cologuard and FIT by Imperiale et al. (2014) was 3.7% (95% CI: 2.85%-4.76%) and 6.9%, respectively. The PPV reported for Epi proColon by Potter et al. (2014) was 2.5% (95% CI: 2.0%-3.0%). **The PPV between Cologuard and Epi proColon statistically overlap.**

Points of Clarification

- **Table 10 of the proposed decision memorandum contains two major misunderstandings**

  - **Number 1:** The statement that one test misses more cancer than another test based on single point estimates of one-time testing is not applicable here. *The number of false negatives for a single test is not an appropriate interpretation of the benefits of long-term screening.* In fact, microsimulation data shows that the small gaps in the point estimates for sensitivity are easily overcome and in fact often outweighed by testing interval.
    - *For example: The point estimate of sensitivity for one Cologuard test versus one FIT test is inappropriate.* The correct way to compare these tests is to measure the sensitivity of three FIT tests performed annually over three years and contrast that to the sensitivity of Cologuard performed once over that same three-year period.
    - **Modeling analysis extrapolates benefits over a lifetime of testing based on point estimates of performance. This is exactly what these models have been designed to do over the last two decades.**

  - **Number 2:** The statement that "Excess positives tell more patients that they have cancer" is again not accurate.
    - **Non-invasive screening methods are not diagnostic tests for colorectal cancer.** This applies to FIT, Cologuard, and Epi proColon. **Excess positives tell more patients that they will need a colonoscopy to complete their screening process.**
    - Because Epi proColon is indicated for patients who refused a screening colonoscopy (the gold standard for screening) and other screening methods, any colonoscopies that result from excess positives should be viewed as a benefit of bringing more patients into compliance with CRC screening, not a harm.

An Appropriate Population for Testing with Epi proColon Has Been Identified

CMS states that "It is difficult to identify an appropriate population for the Epi proColon® test based on the available evidence."

- **This has been answered by the FDA**
  - The Epi proColon test is indicated to screen adults of either sex, 50 years or older, defined as average risk for CRC, who have been offered and have a history of not completing CRC screening.
  - Patients unwilling to undergo a screening colonoscopy will in fact participate in diagnostic colonoscopies (Liles et al. 2017). The colonoscopy follow-up rate is similar between FIT and Epi proColon, and in the range of 67% – 80% as reported by Liles et al. Cancer Treatment and Research Communications (2017); Epi proColon FDA-post approval study data; Corley et al. JAMA. (2017); and Jensen et al. Ann Intern Med. (2016).

- **Inclusion in Clinical Guidelines**
  - NCCN has included Epi proColon according to its FDA-approved labeling
  - ACS explicitly stated that the lack of microsimulation modeling data was the reason for exclusion in the past
    - These data are now available
  - USPSTF did not consider Potter et al. (2014) data in their analysis and Epi proColon had not yet been included in CISNET microsimulation models
  - Cologuard was not included in USPSTF or any other guidelines prior to CMS coverage, and we should follow that precedent
    - NCD (CAG-00440N) for Cologuard: " The USPSTF concludes that the evidence is insufficient to assess the benefits and harms of...fecal DNA testing as screening modalities for colorectal cancer."
    - Under Section 5 entitled Professional Society Recommendations/Consensus Statements of the NCD, every guideline summary is followed by the following statement. "This recommendation was based on a predecessor test. The Cologuard test was not evaluated." The predecessor test was totally unrelated to Cologuard.

- **Considering Commercial Payer Coverage Is Not Appropriate**
  - CMS is the largest payer, and CRC is most impactful among Medicare beneficiaries
    - CRC rates are highest among the Medicare population
    - The Medicare population accounts for 40% of all average-risk individuals eligible for CRC screening. No other payer has such a significant number of covered lives impacted by this disease, by far.
  - Commercial payers have been waiting for CMS coverage prior to making an assessment on coverage of Epi proColon
  - **An assessment of the commercial market for coverage by private payers was not mentioned anywhere in the Cologuard NCD (CAG-00440N)**

Testing Interval is Not Indicated in the FDA Label

CMS proposes that "the evidence is sufficient to cover a blood-based biomarker test as an appropriate colorectal cancer screening test once every 3 years, or at the interval designated in the Food and Drug Administration (FDA) label if the FDA indicates a specific test interval."

- **Cologuard FDA Label States:** "Patients with a negative Cologuard test result should be advised to continue participating in a colorectal cancer screening program with another recommended screening method. The screening interval for this follow-up has not been established."

- **CMS NCD for Cologuard:** "As discussed in the proposed decision memorandum, **the frequency of CRC screening with the Cologuard test has not been definitively established**. Since cross-sectional studies usually provide evidence at one point in time (one screening in this case), these studies do not provide direct evidence on how often any particular test should be performed. The manufacturer of the current FDA-approved sDNA test has suggested CRC screening once every three years with Cologuard. The post approval study required by the FDA is designed to evaluate the validity of screening once every three years to ensure that clinically important findings are not missed...CMS will re-evaluate the screening interval after the completion of the post approval study and modify coverage if appropriate."

- **Post-approval studies take 3 – 5 years to complete further delaying coverage for new and innovative screening alternatives**

- **Microsimulation modeling has been used to determine the optimal interval for different screening tests. Only one test is recommended every three years. One, three, five, and ten-year intervals have been assigned to different screening methods.**

We urge CMS to Nationally Cover CRC Screening with Blood–Based Biomarker Tests when the Following Requirements are Met

The Patient:

- Age 50 to 85 years,
- Asymptomatic (no signs or symptoms of colorectal disease),
- At average risk of developing colorectal cancer (no personal history of adenomatous polyps, colorectal cancer, or inflammatory bowel disease, including Crohn's Disease and ulcerative colitis; no family history of colorectal cancers or an adenomatous polyp, familial adenomatous polyposis, or hereditary nonpolyposis colorectal cancer), and
- Meet the specific indication for use criteria of the FDA-approved colorectal cancer screening blood-based test, as defined in the test's premarket approval (PMA).

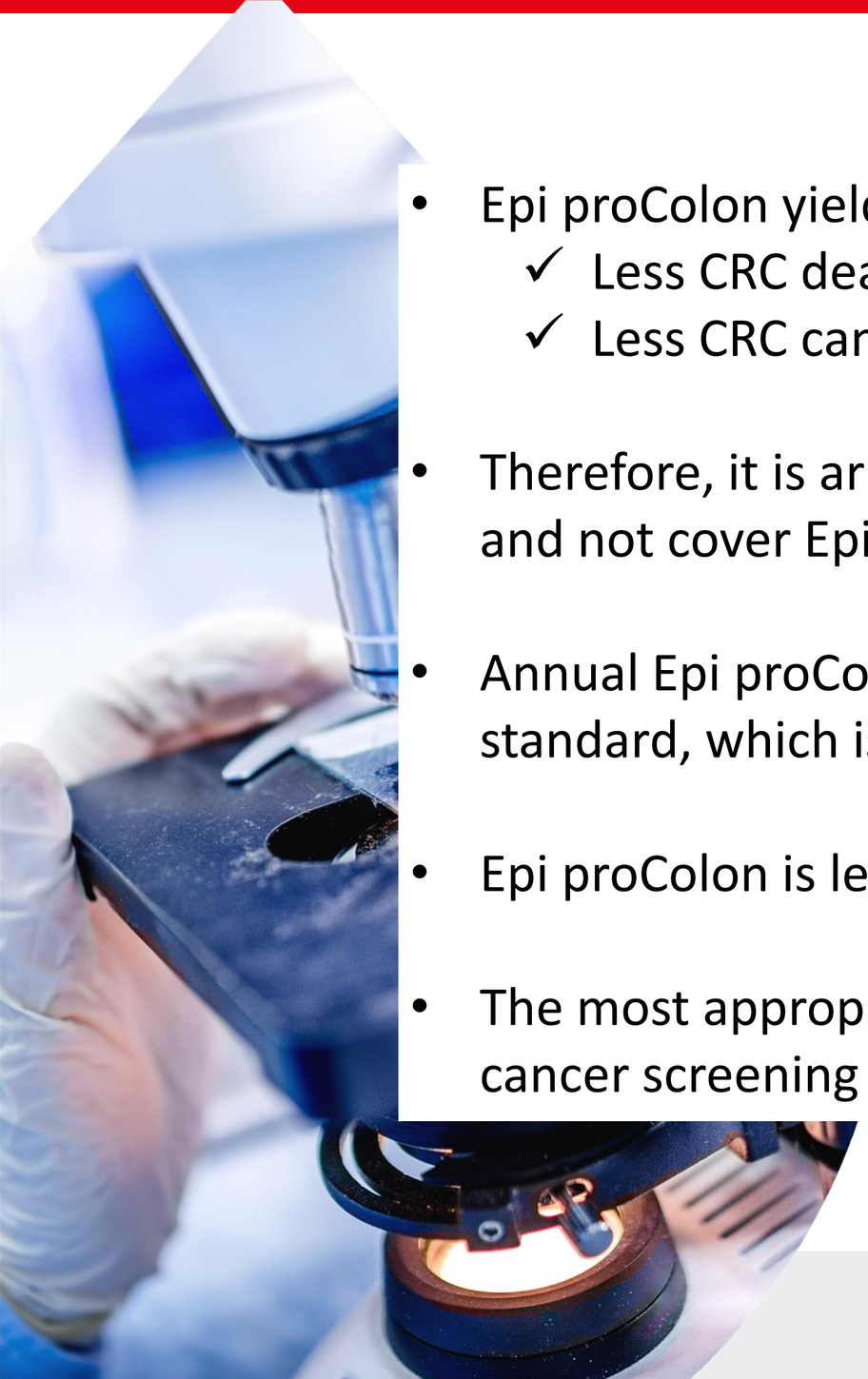
The Screening Test:

16

- FDA approved for a colorectal cancer screening indication,
- Published NCI-sponsored microsimulation data demonstrating that the test will reduce the incidence and mortality of CRC in a manner equal to or better than other CRC screening methods already covered by CMS at the optimal testing interval demonstrated by the NCI-sponsored analysis,
- Is performed in a Clinical Laboratory Improvement Amendments (CLIA) certified high complexity laboratory.

Requiring clinical guideline inclusion will delay coverage of new technology innovation by 5 – 8 years. One approach would be to cover the test for the first five years after the conditions above are fulfilled to allow for guideline inclusion in the future. The guideline inclusion should be in line with the FDA-labeling for the product, which may not always include routine screening.

Brief Synopsis



- Epi proColon yields greater benefits as compared to Cologuard and FIT:
  - ✓ Less CRC deaths
  - ✓ Less CRC cancer cases

- Therefore, it is arbitrary and not scientifically defensible to cover FIT and Cologuard and not cover Epi proColon.

- Annual Epi proColon screening has a lower colonoscopy burden than the gold standard, which is to screen using colonoscopy every 10 years.

- Epi proColon is less costly than Cologuard despite the higher positivity rate.

- The most appropriate metric to provide indirect evidence of clinical effectiveness for cancer screening strategies is NCI sponsored microsimulation modeling.

Automatic Coverage for FDA-Designated Breakthrough Technologies

"The lag time between FDA approval and Medicare coverage has been called the "valley of death" for innovators. Our MCIT proposal seeks to eliminate the valley of death, potentially giving seniors just the opposite – another chance at life."

Epi proColon was designated as a Breakthrough Technology by the FDA in Feb, 2013 and yet it still remains without Medicare Coverage in 2020!

- "For new technologies, CMS coverage approval has been a chicken and egg issue. Innovators had to prove their technologies were appropriate for seniors, but that was almost impossible since the technology was not yet covered by Medicare and thus not widely used enough to demonstrate their suitability for Medicare beneficiaries,"
- "These efforts will ensure seniors get access to the latest technologies while lowering costs for innovators. **Arcane bureaucratic requirements have no business preventing seniors' access to a technology that might save their lives."**

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Centers for Medicare & Medicaid Services

42 CFR Part 405

[CMS–3372–P]

RIN 0938–AT88

Medicare Program; Medicare Coverage of Innovative Technology (MCIT) and Definition of "Reasonable and Necessary"

AGENCY: Centers for Medicare & Medicaid Services (CMS), HHS.

ACTION: Proposed rule.

SUMMARY: This proposed rule would establish a Medicare coverage pathway to provide Medicare beneficiaries nationwide with faster access to new, innovative medical devices designated as breakthrough by the Food and Drug Administration (FDA). After the final rule is effective, the Medicare Coverage of Innovative Technology (MCIT) pathway would begin national Medicare coverage on the date of FDA market authorization and would continue for 4 years. We are also proposing regulatory standards to be used in making reasonable and necessary determinations under section

All statements in Quotes made by CMS Administrator Dr. Seema Verma.

Concluding Remarks

- We agree that the goal of any CRC screening program is to improve patient outcomes
    - Outcomes include reduced cancer incidence and mortality in the population which go far beyond point estimates on cancer detection.

- How do we assess that the test is "at least as beneficial as an existing and available medically appropriate alternative"?
    - Decision modeling has been developed over the last two decades to help us answer this precise question.

- Does the testing result in more harm than good?
    - Obviously not when you consider the ratio of harms to benefit of the blood test as compared to no screening versus the ratio of harms to benefit of the current gold standard as compared to no screening.

- Finally as stated by USPSTF, a significant portion of *"eligible adults in the United States have never been screened for colorectal cancer and offering* ***choice*** *in colorectal cancer screening strategies may increase screening uptake."*
    - Our collective goal is to Save Lives!