The impact of increasing multitarget stool DNA use among colorectal cancer screeners in a self-insured US employer population

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**ABSTRACT**

**Background:** In the United States (US), colorectal cancer (CRC) is the second leading cause of cancer-related deaths. With the majority of the US population covered by employer-based health plans, employers can play a critical role in increasing CRC screening adherence, which may help avert CRC-related deaths. Therefore, it is important for self-insured employers to consider the impact of appropriate utilization of CRC screening options.

**Objective:** To evaluate the impact of increasing multitarget stool DNA [mt-sDNA (Cologuard®)] use among CRC screeners from the perspective of a US self-insured employer.

**Methods:** A 5-year Markov model was developed to quantify the budget impact of increasing mt-sDNA from 6% to 15% among average-risk screeners using colonoscopy, fecal immunological test, and mt-sDNA. Data on direct medical costs were obtained from published literature, Medicare CPT codes, and the Healthcare cost and Utilization project. Indirect costs included productivity loss due to workplace absenteeism for CRC screening and treatment.

**Results:** With a hypothetical population of 100,000 employees with screeners aged 50–64 years, compared to status quo, increased mt-sDNA utilization resulted in no differences in the numbers of cancers detected and the overall direct and indirect cost savings were ~$214,000 ($0.04 per employee-per-month) over 5 years. Most of the savings were due to a reduction in the direct medical expenditure related to CRC screening, adverse events, and productivity loss due to colonoscopy screening. Similar results were observed in the model simulation among screeners aged 45–64 years.

**Conclusion:** Increased utilization of mt-sDNA for CRC screening averts direct and indirect medical costs from a self-insured US employer perspective.

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**INTRODUCTION**

Colorectal cancer (CRC) is the second-leading cause of cancer-related deaths in the United States (US) in both women and men [1,2]. In 2020 alone, 53,000 deaths were expected from CRC [2]. While CRC is most frequently diagnosed in those aged 65–75 years, its incidence is increasing among younger populations [2]. Nearly 18,000 CRC cases are diagnosed annually in individuals younger than age 50 years [2]. Colorectal cancer screening reduces both morbidity and mortality, yet national screening rates are estimated at only 68% [3]. The screening rate in commercially insured individuals aged 50–75 years is 62%, but only 48% in individuals aged 50–54 years [3]. It is therefore imperative to adopt effective screening practices to increase uptake and adherence to screening guidelines.

In addition to clinical and humanistic burden, CRC also imposes significant economic implications for patient caregivers, family members, and employers [4–7]. More than half of the US population is covered under employer-based health insurance of which about 60% are covered by a self-insured employer [8,9]. Thus, it is important for employers and their third-party insurers to consider the impact of appropriate utilization of evidence-based preventive screenings including CRC screening. Self-insured employers incur not only direct medical costs, but also indirect medical costs, such as productivity loss as a result of CRC screening procedures and CRC diagnoses. According to a population-based survey, only 55% of stage III CRC-survivors were able to retain their jobs, and about 34% became disabled or unemployed [10]. In the US, lost productivity – calculated as earning loss alone – due to CRC was estimated to be $9.4 billion in 2015 [11]. Therefore, screening can help in reducing not only CRC-related morbidity and mortality, but also CRC-related direct medical costs and indirect costs related to lost productivity due to employee workplace absenteeism.

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and disability (wage-replacement benefits). Despite significant clinical and economic benefits, screening rates—especially among the younger populations—have been sub-optimal for several reasons, including limited policy coverage, inconvenience, and adverse events (AE) associated with invasive procedures such as colonoscopy [12–15].

The US Preventive Services Task Force (USPSTF) and the American Cancer Society (ACS) recommend CRC screening for average-risk individuals beginning at age 50 and 45 years, respectively [16,17]. It is estimated that screening all the individuals in the guideline-recommended age groups could avert more than 60% of the CRC deaths [1]. These guidelines note that the uptake may increase as individuals are offered more screening modality options, including colonoscopy, fecal immunochemical tests (FIT), and multi-target stool DNA (mt-sDNA [Cologuard®]). Fecal screening tests, such as FIT and mt-sDNA, require neither bowel preparation nor sedation, are non-invasive, and can be done privately and conveniently in the home, thereby potentially increasing adherence to screening recommendations.

The choice of screening modality is primarily driven by provider-patient shared decision-making discussions about the varying degrees of preparation, time requirements, and invasiveness as well as test performance characteristics [18,19]. However, it is important to assess the economic impact of utilization of various CRC screening modalities on direct healthcare and indirect costs. While such evaluations have been conducted from the payer and integrated delivery network (IDN) perspectives [20], no studies have evaluated the employer perspective. Therefore, we sought to quantify the impact of increasing mt-sDNA use among CRC screeners from the perspective of the US self-insured employer.

Methods
Model overview
We developed a 5-year Markov state transition model to quantify the budget impact of increasing mt-sDNA use among commercially-insured, average-risk CRC screeners from the perspective of a self-insured US employer (Figure 1). We chose a five-year time horizon because, according to the Bureau of Labor Statistics, employees remain with a given employer for an average of 4.2 years [21]. The model assesses the direct medical and indirect costs associated with different CRC screening modalities with varying levels of utilization and adherence. Individuals in the modeled population can be screened with colonoscopy, FIT or mt-sDNA according to the USPSTF and ACS recommended screening intervals for each modality. Negative colonoscopy screeners enter a tunnel (non-screening) state for the remainder of model horizon as guidelines recommend screening.

![Figure 1. Conceptual model framework.](image-url)

FIT, fecal immunological test; Adv, advanced; Surv, surveillance; PBP Repeat, repeat colonoscopy due to poor bowel preparation; Det, detected. Green negative and red positive signs refer to negative and positive test results, respectively.
again after 10 years following a negative screening [20]. Individuals with negative FIT results are eligible for another screening after 1 year. Individuals with a negative mt-sDNA result enter a tunnel state and are eligible to screen again after 3 years. The model allows eligible screeners to change screening modalities during each eligible cycle throughout the 5-year model horizon.

In cases of positive stool-based screening results, individuals are referred to diagnostic colonoscopy. Detection of a polyp or colorectal neoplasia during any colonoscopy is followed by a biopsy to determine whether the finding is non-neoplastic, non-advanced adenoma, advanced adenoma, or cancer. Individuals with non-neoplastic findings or non-advanced adenomas enter a tunnel state for rest of the model horizon. If a biopsy finds an advanced adenoma, the individual is referred to a surveillance colonoscopy in 3 or 5 years, depending on histology and adenoma size [22]. A small proportion of screening colonoscopies (16%) need to be repeated due to poor bowel preparation [23]. The assumed rates of colonoscopy-related AE depends on whether or not a polypectomy is performed [24].

Model population
A hypothetical population of 100,000 individuals enter the self-insured employer-based model, assuming a population ≤65 years of age. Of these, based on the US Census data, 31% (ages 45–64) and 21% (ages 50–64) of covered lives were eligible for CRC screening based on the population age. The USPSTF and ACS recommendations apply only to average-risk individuals [16,17]. The model assumed that 80% of the screening eligible individuals were at average risk for CRC [25], thereby leading to ~25,000 and ~17,000 individuals in the 45–64 year old and 50–64 year old cohorts, respectively, in the self-insured employer population. We applied published estimates of adherence to determine the proportion of the screening-eligible individuals who were non-screeners and potential-screeners, i.e., those who never screen and those who screen at least once during the model time horizon. The model approach is further explained in a previously published study [20].

Model inputs
Adenoma and CRC epidemiology
The model is driven by observable epidemiological and clinical parameters. Model inputs regarding age-specific estimates on adenoma incidence and size were based on published literature (Appendix Tables). For CRC incidence, we used relevant data from the National Cancer Institute’s Surveillance, Epidemiology, and End Results (SEER) Program. For individuals who never screen, we used SEER estimates from 1975 to 1979, i.e., prior to the guidelines being established for CRC screening. The baseline SEER CRC estimates were used for potential screeners [5]. We then applied relative risk reduction estimates from the Cancer Intervention and Surveillance Modelling Network Simulation Model for Colorectal Cancer (CISNET SimCRC) for each screening modality to reflect the number of detected cancers among individuals undergoing screening [5]. These estimates were 63% for mt-sDNA (reflecting a 3-year screening interval), 67% for FIT (reflecting an annual screening interval), and 81% for colonoscopy (reflecting a 10-year screening interval). The SimCRC model assumes 100% adherence, and therefore overestimates detection of pre-cancerous lesions and, consequently, underestimates CRC incidence. To generate more precise approximations of overall CRC incidence in real-world scenarios, we weighted the risk reduction among compliant (to whom the full SimCRC reduction per modality are applied) and non-compliant (to whom the 1975–1979 SEER CRC incidence rates are applied) potential screeners per annual cycle.

Test sensitivity and specificity per screening modality were extracted from published sources and FDA safety and effectiveness data [20]. For probabilities of clinical events, we assigned 5-year age-band specific risk profiles for incidence and prevalence of CRC, adenoma and death to individuals at the beginning of each model cycle (Appendix Table A1).

Cost data
The cost burden for employers includes both direct and indirect costs of CRC screening. The direct costs associated with colonoscopy procedures and complications were obtained from the Center for Medicare and Medicaid Services (CMS), and CRC treatment costs were based on published literature (Appendix Table A2) [20]. Cost indices were calculated in order to convert Medicare costs to Commercial costs. The details on the model inputs for the direct medical costs are explained in a previously published study as well as in Appendix Table A2 [20].

To assess employer-specific indirect costs of productivity loss (measured as workplace absenteeism) associated with CRC screening and treatment, we used estimates from the published literature [26,27]. Regarding workplace absenteeism, the model assumes an average hourly wage of $28.05 (Table 1) [26].

All costs were either extracted from 2019 data or were updated to 2019 USD based on the medical Consumer Price Index [28]. This modelling study is based on publicly-available data, and did not require an ethical approval.
**Primary analysis**

We compared the direct medical and indirect costs for a status quo scenario, in which current modality utilization was based on manufacturer data, to an ‘increased mt-sDNA’ utilization scenario. In the status quo, the model assumes a constant screening modality utilization mix throughout the time horizon, with a utilization mix of 83% colonoscopy, 11% FIT and 6% mt-sDNA. In the increased mt-sDNA scenario, the model assumes that the proportion of screeners utilizing mt-sDNA increases from 6% to 15%, and the proportions utilizing colonoscopy and FIT reduce from 83% to 75% and from 11% to 10% by year 5.

Regarding workplace absenteeism for CRC screening, no productivity loss was assumed for home-based FIT and mt-sDNA tests. The primary analysis assumes that an individual is absent from work for 12 hours (i.e., 4 hours for bowel preparation and 8 hours for the day of the colonoscopy procedure), yielding a total of $337 in lost productivity per colonoscopy for the employer (Table 1a).

**Sensitivity analyses**

We conducted several sensitivity analyses to assess the impact of varying durations of productivity loss due to bowel preparation, the model time horizon, and absenteeism due to colonoscopy procedures. In the first sensitivity scenario, we calculated the 5-year model outcomes under the assumption that colonoscopy bowel preparation and procedure require employees to take a total of either (1) 8 hours (0 hours for preparation and 8 hours for the day of the procedure) or (2) 16 hours (8 hours each for preparation and day of the procedure) (Table 1a). To assess the uncertainty around the duration of employee tenure, we implemented a 3-year and a 10-year time horizon. The status quo utilization estimates remain the same for the 3- and 10-year horizons as in the primary analysis. In the increased mt-sDNA scenario for the 3-year time horizon however, the model simulates a peak mt-sDNA utilization of 15% and minimum colonoscopy and FIT utilizations of 75% and 10% by year 3. In the increased mt-sDNA scenario for the 10-year time horizon, the model simulates a peak mt-sDNA utilization of 28% and minimum colonoscopy and FIT utilizations of 63% and 9% by year 10. To account for the extended duration of the 10-year time horizon, we applied a 3% annual discount rate to relevant cost outcomes. Furthermore, we calculated the employer cost associated with annual wage replacement paid by the employer to those employees who take short- and long-term disability leave upon CRC diagnosis (Table 1b) [12,29,30].

To understand parameters to which the model was most sensitive, we conducted a deterministic sensitivity analysis (DSA) on the primary analysis for the 50–64 and 45–64 year old cohorts. Clinical inputs related to prevalence of advanced and non-advanced adenomas present during screening, and related to screening test performance characteristics, were individually varied according to 95% confidence intervals from published estimates. Adverse event costs were varied according to

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**Table 1.** Indirect cost of productivity loss (workplace absenteeism) due to CRC screening procedure and disability.

| Cost category | Hourly wage | Hours required for bowel preparation | Hours required for colonoscopy | Total work hours lost per colonoscopy | Opportunity cost per colonoscopy |
|---------------|-------------|--------------------------------------|--------------------------------|---------------------------------------|---------------------------------|
| Colonoscopy   | $28.05*     | 4^b                                  | 8^b                            | 12                                   | $337                            |
| FIT           | Productivity loss was not applied to stool-based screening tests as they do not require sedation nor time off work | $0 |
| Mt-sDNA       | Productivity loss was not applied to stool-based screening tests as they do not require sedation nor time off work | $0 |

**B. Disability cost among patients diagnosed with CRC**

| CRC stage | Proportion seeking disabilitybenefit among CRC diagnosed employees  | Weighted wage replacement for short-term disability (STD) | Percent of STD claims that convert to long term disability (LTD) | Weighted wage replacement for LTD | Total disability cost per patient |
|-----------|----------------------------------------------------------------|----------------------------------------------------------|---------------------------------------------------------------|---------------------------------|---------------------------------|
| Stage I   | 13.38%                                                       | $1,202                                                    | 21%                                                          | $709                            | $1,911                          |
| Stage II  | 13.38%                                                       | $1,202                                                    |                                                              | $709                            | $1,911                          |
| Stage III | 26%                                                          | $2,335                                                    |                                                              | $1,378                          | $3,713                          |
| Stage IV  | 81.17%                                                       | $7,290                                                    |                                                              | $4,302                          | $11,592                         |

Notes:

*aAverage hourly and weekly earnings of all employees on private non-farm payrolls by industry sector, seasonally adjusted, June 2019 average national hourly wage [28].

^bThe primary model scenario assumes that 4 hours as time off work was required for preparation and 8 hours were required for the procedure itself.

^cBased on a US population-based survey, 26% individuals with stage III CRC (Georgia and Detroit region) were disabled due to their cancer diagnosis and treatment [10]. We interpolated this data to compute percentage disabled among CRC Stages I, II, and IV based on hazard ratio reported by Hauglann et al. 2013 [30].

^dAverage wage replacement data for short- and long-term disability were obtained from an Integrated Benefits Institute report [29]. We weighted these wage replacement data based on distribution of CRC stage at diagnosis among those disabled.
95% confidence intervals calculated from standard errors provided by the Healthcare Cost and Utilization Project (HCUP) data [31]. Other cost estimates for which confidence intervals could not be obtained or calculated were varied ±20%.

The model was developed using Excel 2016 software (Microsoft Corp., Redmond, WA, USA).

Results

Primary analysis

Among screeners aged 50–64 years, compared to the status quo, 2 more screenings (all modalities combined) occurred during the 5-year horizon in the increased mt-sDNA utilization scenario. There were no differences in the numbers of cancers detected and there was a small decrease (<1.0%) in advanced adenomas detected. In the increased mt-sDNA utilization scenario, the number of diagnostic colonoscopies increased by 8.0% and surveillance screening decreased by 0.1%. The number of non-neoplastic findings – including non-advanced and advanced adenomas – detected declined by 1.3%, and 0.04% additional screeners were diagnosed with CRC. In the screeners aged 45–64 years, increased mt-sDNA utilization led to similar changes in clinical outcomes. See Table 2.

Among screeners aged 50–64 years, the estimated total employer cost was $29.7 million ($4.94 per-employee per month (PEPM)) in the status quo and $29.4 million ($4.91 per-employee per month (PEPM)) in the increased mt-sDNA utilization scenario. This resulted in total cost savings of ~$214,000, which equates to savings of $0.04 PEPM with increased mt-sDNA utilization. A large proportion (62.5%, i.e. ~$133,500) of the total cost savings is due to reduction in the direct medical expenditure for CRC screening (0.7%) and adverse event costs (1.3%). Furthermore, compared to the status quo, the indirect cost of productivity loss due to absenteeism for CRC screening (1.5 days for bowel preparation and the colonoscopy procedure) declined by 1.3% (~$63,000).

Similar changes in economic outcomes were observed among screeners aged 45–64 years (Table 3).

Sensitivity analyses

Compared to the primary analysis, there was no impact on clinical outcomes and direct medical costs in the sensitivity analyses that assumed different durations of colonoscopy preparation and procedure (i.e., 1 or 2 days combined). Overall, the productivity loss (indirect cost) was directly proportional to the length of absenteeism from colonoscopy procedures; however, as in the primary analysis, the percent reduction in these costs when increasing mt-sDNA utilization remained at ~1.1% for 45–64 year olds and ~1.3% for 50–64 year olds in these sensitivity analyses (Appendix Table A3).

Among the 50–64 year old cohort, when assuming different employee tenure durations, the 3-year and 10-year time horizons resulted in overall cost savings of $33,000 (0.2% decrease) and $89,000 (1.7% decrease) compared to $214,000 (0.7% decrease) in the 5-year primary analysis time horizon. The increase in the number of detected CRC cases in the increased mt-sDNA scenario was 0.02% and 0.6% in the 3- and 10-year time horizons, compared to a 0.4% increase in cases in the primary 5-year horizon. These simulations led to similar results for age group 45–64 years. See Appendix Table A4–A6 and Appendix Figure A1 for details.

Incorporating CRC disability wages did not change the percent cost savings with increased mt-sDNA utilization. Disability wages paid to CRC employees resulted in a negligible increase in overall spending (~$77 over 5 years) among cohort aged 50–64 years in the increased mt-sDNA scenario, compared to the status quo.

Table 2. Change in clinical outcomes in scenario with increased mt-sDNA usage compared to status quo over 5-year model horizon.

| Clinical outcomes                        | Status quo | Increased mt-sDNA utilization | Change in increased mt-sDNA scenario compared to Status quo |
|-----------------------------------------|------------|-------------------------------|----------------------------------------------------------|
| Number of colonoscopy screenings        | Ages 50–64 included | 13,975 | 19,732 | Ages 50–64 included | 13,770 | 19,492 | -206 (-1.5%) | -240 (-1.2%) |
| Number of FIT screenings                | Ages 45–64 included | 2,081 | 2,881 | Ages 45–64 included | 2,053 | 2,848 | -32 (-1.3%) | -33 (-1.1%) |
| Number of mt-sDNA screenings           | Ages 50–64 included | 1,145 | 1,565 | Ages 50–64 included | 1,378 | 1,642 | 236 (20.6%) | 277 (17.7%) |
| Number of diagnostic colonoscopies     | Ages 45–64 included | 221 | 299 | Ages 45–64 included | 239 | 320 | 18 (8.0%) | 21 (6.9%) |
| Number of surveillance colonoscopies   | Ages 50–64 included | 203 | 281 | Ages 50–64 included | 203 | 280 | 0 (-0.1%) | 0 (-0.1%) |
| Number of non-neoplastic findings detected | Ages 45–64 included | 1,854 | 2,642 | Ages 45–64 included | 1,829 | 2,612 | -25 (-1.3%) | -29 (-1.1%) |
| Number of non-Advanced Adenomas detected | Ages 50–64 included | 663 | 850 | Ages 50–64 included | 655 | 842 | -8 (-1.2%) | -6 (-0.9%) |
| Number of Advanced Adenomas detected   | Ages 45–64 included | 266 | 310 | Ages 45–64 included | 263 | 308 | -2 (-0.8%) | -2 (-0.7%) |
| Number of detected CRC cases           | Ages 50–64 included | 25 | 29 | Ages 50–64 included | 25 | 29 | -0.01 (0.04%) | 0.02 (0.07%) |
quorum. Nevertheless, the employer still experienced savings. See Table 3 and Appendix Table A4.

The deterministic sensitivity analysis indicated that the model results for both cohorts were most sensitive to the following parameters: proportion of covered lives at average risk, cost of anesthesia, and the specificity of mt-sDNA. See Appendix Figure A2.

Discussion

The US Centers for Disease Control and Prevention (CDC) notes that employers can play a critical role in increasing CRC screening levels by offering employees healthcare benefits that cover CRC screening, and by adopting leave policies that allow time-off required for screening [32]. In addition to having clinical benefits for employees, paid time off for CRC screening over a screening lifetime could pay for itself for self-insured employers in terms of direct medical cost savings as well as indirect cost savings associated with employees’ work time-off and sick leaves for CRC diagnosis and treatment [33,34].

Our model found that increased utilization of mt-sDNA, while reducing the use of colonoscopy and FIT, compared to the status quo, for CRC screening among an average risk population of individuals 50–64 years old would lead to a total cost savings of $214,000, equating to $0.04 PEPM savings over a 5-year horizon for self-insured employers. The same number of cancers would be detected in the increased mt-sDNA scenario compared to the status quo. While both the home-based tests mt-sDNA and FIT are less expensive than colonoscopy screening, mt-sDNA screeners with negative test result do not require screening for another 3 years compared to 1 year for FIT, thus contribute to lower healthcare resource utilization. The cost savings in our model are primarily driven by the reduction in the number of screening colonoscopies performed due to the increase in mt-sDNA use. Colonoscopy is a more expensive screening modality, and is also associated with the risk of adverse events (such as myocardial infarction and GI bleeding) that add to the overall healthcare costs [13–15,35]. Increased utilization of mt-sDNA results in diagnostic colonoscopy referrals for those patients with a positive screening test. This indicates a higher likelihood of CRC or related precancerous findings (e.g., advanced adenomas).

The literature notes that work productivity loss associated with CRC diagnosis and treatment is a major indirect cost to employers; on average, employees diagnosed with CRC miss about 7 days of work annually, and about 14% take employment disability [12]. According to the Integrated Benefits Institute, the overall cost of a short-term disability (STD) among CRC patients is $8,900, and 21% of the STD claims convert to long-term disability (LTD) that costs up to $25,000 [29]. It is important to note that there are no published data that describe the differences in STD and LTD for Stage I, II, III, and IV CRC; however, the 5 year survival rates for stage I and IV are 90% and 10%. In the US private sector, about 40% employees are offered employment disability benefits by their employers, who pay all or a portion of the cost of insurance premiums [36]. For the purpose of the model from the self-insured employer perspective, we assumed that the cost of CRC-related disability benefit (wage replacement) is paid completely by the employer. Furthermore, the model calculates the indirect cost incurred by the employer for lost productivity due to employee workplace absenteeism for

### Table 3. Change in economic outcomes in scenario with increased mt-sDNA usage compared to status quo over 5-year model horizon.

| Cost                          | Status quo  | Increased mt-sDNA scenario | Change (%) compared to Status quo |
|------------------------------|-------------|----------------------------|-----------------------------------|
| **Clinical outcomes**        | Ages 50-64 included | Ages 45-64 included | Ages 50-64 included | Ages 45-64 included | Ages 50-64 included | Ages 45-64 included |
| Primary analysis             |             |                           |                                  |                    |                         |                         |
| CRC screening                | $17,831,055 | $25,128,284               | $17,697,525                     | $24,973,124        | $-133,530 (-0.7%)       | $-155,160 (-0.6%)      |
| Surveillance colonoscopies   | $250,120    | $345,761                  | $249,849                       | $345,430           | $-272 (-0.1%)           | $-331 (-0.1%)          |
| Diagnostic colonoscopies     | $272,387    | $369,058                  | $294,383                       | $394,443           | $21,996 (8.1%)          | $25,385 (6.9%)         |
| Adverse events               | $2,867,853  | $4,020,050                | $2,830,728                     | $3,976,867         | $-37,125 (-1.3%)        | $-43,183 (-1.1%)       |
| Colorectal cancer treatment  | $3,587,481  | $4,156,723                | $3,585,986                     | $4,158,715         | $-1,496 (0.04%)         | $1,993 (0.05%)         |
| Productivity loss (bowel preparation and procedure) | $4,946,755 | $6,837,023               | $4,783,484                   | $6,762,980         | $-63,271 (-1.3%)        | $-74,045 (-1.1%)       |
| Total costs (Primary analysis) | $29,655,652 | $40,856,899               | $29,441,954                  | $40,611,560        | $-213,698 (-0.7%)       | $-245,339 (-0.6%)      |
| PEPM (primary analysis)      | $4.94       | $6.81                     | $4.91                          | $6.77              | $-0.04 (-0.7%)          | $-0.04 (-0.6%)         |
| **Sensitivity analysis**     |             |                           |                                  |                    |                         |                         |
| Disability cost due to CRC   | $137,494    | $160,150                  | $137,421                       | $160,183           | $-73 (-0.05%)           | $33 (0.02%)            |
| Total costs inclusive disability cost | $29,793,146 | $41,017,049               | $29,579,371                    | $40,771,743        | $-213,775 (-0.7%)       | $-245,306 (-0.6%)      |
| PEPM cost inclusive of disability cost | $4.97 | $6.84 | $4.93 | $6.80 | $-0.04 (-0.80%) | $-0.04 (-0.60%) |

PEPM, per employee per month
colonoscopy screening. By increasing the utilization of mt-sDNA, the overall employer productivity loss would decline by 1.3% ($63,000). As FIT is also home-based test that does not require screeners to take time off from work, the reduction in productivity loss in both the scenario and status quo was partly driven its use (11% to 10% by year 5). Note that the model assumes that all employees earn the US average wage, but that would not be true for employees working at companies large enough to be self-insured. Therefore, the model calculations provide a conservative estimate of the potential decline in productivity loss with increased mt-sDNA utilization.

The sensitivity analyses show that the assumption about absenteeism for bowel preparation and colonoscopy procedures (i.e., 1, 1.5, or 2 days) will have a direct effect on the total cost and, therefore, on cost savings due to productivity loss. Nevertheless, productivity loss declined 1.3% (i.e., saving of $42-84 K) for each of these durations when utilization of mt-sDNA was increased. We also assessed the impact of varying time horizons on model outcomes. With increased mt-sDNA utilization, the employer cost savings were about 0.2% (i.e., $32,793) and 1.7% (i.e., $893,310) in the 3- and 10-year horizons, compared with 0.7% ($213,698) for the 5-year horizon. These variations reflect the increased number of screening opportunities in the longer time horizon.

The 2016 USPSTF guidelines recommend starting CRC screening at age 50, compared to age 45 in the 2018 ACS guidelines. Overall, we found a similar impact of increased mt-sDNA utilization in the CRC 50–64 year old and 45–64 year old screening cohorts. By extending screening to a younger age group to 45–64 years, the status quo base-case scenario had higher clinical and economic burden compared to the 50–64 year old cohort. However, increasing mt-sDNA utilization had similar impact, in terms of percent changes, in the two age groups. With longer screening intervals compared to FIT, mt-sDNA offers the opportunity for employers to increase screening uptake and adherence. The model had a time horizon of 5 years, which is relevant for US employers. The model also accounts for a variety of real-world situations such as imperfect screening adherence rates, patients’ ability to switch screening modalities, and incorporates the costs of productivity loss as well as disability costs.

The key limitations of the model are described in a previously published study and include the fact that the natural history of CRC development was not modeled [20]. Nevertheless, epidemiological parameters were based on published literature estimates [5,20,25,37]. An additional limitation of the employer perspective model is the assumption that individuals diagnosed with CRC remain in the model (and, therefore incur CRC treatment costs) until the pertinent CRC stage-specific life expectancy ends, whereas in real life a significant proportion of employees either become unemployed or are disabled within a year after CRC diagnosis [12]. We have also limited the age group of employees to maximum age of 64 years due to complexities associated with dual eligibility for Medicare and commercial insurance in older populations. Costs and outcomes have been omitted for employees above this age, which likely underestimates the results because of increasing incidence and prevalence of CRC beyond age 64. Furthermore, the model is based on a fixed employee cohort over time. Therefore, we do not account for employee attrition or new hires over time, and follow the same individuals until their natural or CRC-related death or the end of model horizon, whichever is earlier.

Conclusion
The model suggests that increased utilization of mt-sDNA would avert direct and indirect medical costs from a US self-insured employer perspective and would result in a similar number of detected CRCs. With a hypothetical population of 100,000 employees, the model projects that the incremental direct medical cost savings were ~$150,000 from fewer screening and surveillance colonoscopies, and fewer adverse events due to colonoscopies. The indirect cost savings from reduced productivity loss due to CRC screening would be ~$63,000. Overall, the incremental direct medical and indirect costs would yield a cumulative savings of ~$214,000 and PEMP savings of $0.04.

These findings suggest that increasing mt-sDNA utilization and decreasing utilization of colonoscopy and FIT, compared to status quo, among the average-risk adult population would lead to cost savings in terms of direct medical expenses and indirect costs (i.e., lost productivity and CRC-related disability) for self-insured employers.

Author Contribution
All authors contributed to the conception and design of the study, data acquisition and analysis, and interpretations of the results. Hathway J and Sharma A drafted the first draft of the manuscript. All authors critically revised the manuscript to its final stages, approved the final version of the manuscript, and take responsibility for all aspects of the study.

Disclosure statement
Hathway J, Sharma A, Jensen IS, Yao W and Raza S are employees of PRECISIONhealth, which provides consulting services to the biopharmaceutical industry, including Exact
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