May 10, 2024

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Director
Coverage and Analysis Group
Centers for Medicare & Medicaid Services
Mail Stop C1-09-06
7500 Security Boulevard
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Via email: NCDRequest@cms.hhs.gov

RE: **Request for Reconsideration of NCD for Screening for Colorectal Cancer – Stool DNA Testing (CAG-00440N) – sRNA ColoSense™ Test**

Dear Director Jensen:

Geneoscopy, Inc. is writing to formally request that the Centers for Medicare & Medicaid Services (CMS) open a reconsideration of the Medicare coverage requirements for Colorectal Cancer Screening Tests in section 210.3 of the National Coverage Determinations (NCD) Manual. This letter provides the agency with peer reviewed published clinical information and the recent approval of a new screening test by the Food and Drug Administration (FDA) and supplements.

On May 3, 2024, the FDA approved the pre-market approval (PMA) of our ColoSense multi-target stool RNA (mt-sRNA) screening test to detect colorectal cancer (CRC), advanced adenomas (AA), and serrated precancerous lesions (SPL). Additionally, the FDA granted ColoSense Breakthrough Device designation on January 10, 2020.

This reconsideration request is also supported by the publication in the Journal of the American Medical Association (JAMA), of the results of the CRC-PREVENT clinical validation study[1]

CMS has provided coverage for one Multi-target Stool DNA (sDNA) Test since October 9, 2014, nearly ten years ago. Based on the recent FDA approval of ColoSense and the enclosed clinical information, it is appropriate for the agency to update the NCD criteria to provide coverage for stool RNA (sRNA) tests that display similar analytical and clinical validity for sensitivity and specificity criteria that CMS considered in deciding to provide coverage for an sDNA test in 2014. In particular, Geneoscopy's ColoSense clinical data demonstrated the

[1] Erica K. Barnell, MD, PhD; Elizabeth M. Wurtzler, PhD; Julie La Rocca, MS; Multitarget Stool RNA Test for Colorectal Cancer Screening, JAMA. 2023;330(18):1760-1768. https://jamanetwork.com/journals/jama/fullarticle/2811133.

sensitivity and specificity measures that CMS determined in 2014 were sufficient to warrant coverage for a stool-based colorectal cancer screening test.

As part of this reconsideration request, below we provide recommended NCD Manual coverage criteria language for including ColoSense consistent with the current coverage criteria established for the sDNA test Cologuard. We respectfully request that CMS open the National Coverage Analysis for ColoSense by issuing a Proposed Decision Memorandum updating the NCD Manual to reflect the recent FDA approval, as was done in 2014 for Cologuard. We believe that a similar approach today will advance public health given the important role that stool-based tests play in supporting at-home specimen collection for CRC screening, particularly considering the significant number of missed CRC screenings that occurred due to the COVID-19 pandemic.

I. Background

A. Background on Geneoscopy and ColoSense

Geneoscopy's CAP/CLIA-certified laboratory located in St. Louis, Missouri developed and will perform the ColoSense multi-target sRNA CRC screening test. ColoSense is intended for the qualitative detection of colorectal neoplasia-associated RNA markers and for the presence of occult hemoglobin in human stool for the purpose of aiding in the detection of CRC, AA, and SPL. A positive ColoSense result may indicate the presence of colorectal cancer, AA, and/or SPL and should be followed by a diagnostic colonoscopy. ColoSense involves a proprietary RNA extraction method that amplifies the human signal and degrades bacterial noise in stool, allowing for sensitive extraction of human sRNA.

ColoSense is a stool-based test that detects sRNA biomarkers contained in the cells shed by individuals with CRC, AA, or SPL. The ColoSense test output is an aggregate quantification of testing and survey results for biomarkers, fecal immunochemical blood test (FIT/iFOBT), and smoking status. The biomarkers involve quantification of sRNA expression. The FIT/iFOBT test involves quantification of stool hemoglobin, which can be associated with colonic bleeding.

Stool samples are collected using the ColoSense Collection Kit, which includes patient instructions for use, a stool sample collection bucket, a toilet seat bracket, an absorbent sheet, an OC-Auto® sampling bottle, a ColoSense sample preservative, and a shipping box. The ColoSense Collection Kit is sent to the patient's residence after being prescribed by a healthcare provider. The patient deposits a stool sample into the ColoSense collection kit and ships the ColoSense Collection Kit to Geneoscopy's centralized laboratory. Once the stool sample is received, the stool sample is directed into parallel workflows for analysis of hemoglobin and RNA biomarkers. To assess the hemoglobin in stool, the OC-Auto® sampling bottle is analyzed using an FDA-cleared automated fecal immunochemical blood test (FIT/iFOBT) system with a modified threshold. The ColoSense test evaluates eight (8) RNA biomarkers. Isolation and analysis of RNA analytes requires three steps. First, the eukaryotic cells are isolated from the stool sample and a solution containing eukaryotic nucleic acids is

generated via lysis. Next, the RNA is isolated using EMAG protocols, DNase treatment, and a spin column-based cleanup kit per the manufacturers' instructions. Expression of the RNA biomarkers is quantified using the ColoSense Test Kit and the QXDx Droplet Digital PCR system.

The ColoSense software is used to aggregate data from the RNA biomarkers, smoking status, and FIT/iFOBT to generate a score. The score is compared to the predefined threshold, yielding a positive (abnormal) or negative result. The score is calculated by multiplying the patient's individual RNA expression, demographic information (smoking status), and stool hemoglobin (FIT/iFOBT) results by a marker-specific weighting factor. The aggregate of these individually weighted marker results determines the composite score, which is then compared to a cut-off to determine a positive (abnormal) or negative result.

ColoSense underwent clinical validation through the CRC-PREVENT clinical trial (NCT04739722). This study evaluated 8,920 subjects who completed ColoSense and a subsequent colonoscopy. Among all 8,920 subjects, 7,763 were considered average-risk for CRC and were eligible for the primary effectiveness analysis assessment performed by the FDA. Across all 8,920 subjects, 1,360 (15.2%) were 65 years or older, 781 were Medicaid beneficiaries (8.8%), 1,081 (12.1%) were Medicare beneficiaries, and 687 (7.7%) were Medicare Advantage enrollees. Results from CRC-PREVENT became available in December 2022 and were published in the Journal of the American Medical Association in October 2023 (DOI: 10.1001/jama.2023.22231).

The FDA granted ColoSense a Breakthrough Device Designation on January 10, 2020. Geneoscopy submitted a PMA application for ColoSense to the FDA on January 19, 2023. ColoSense was approved by the FDA on May 3, 2024.

B. **Medicare Coverage of Colorectal Cancer Screening**

CRC screening tests are covered by Medicare under § 1861(s)(2)(R) of the Social Security Act. The CRC test benefit category is established at § 1861(pp), and includes screening fecal-occult blood tests, screening flexible sigmoidoscopies, screening colonoscopies, and "[s]uch other tests or procedures, and modifications to tests and procedures under this subsection, with such frequency and payment limits, as the Secretary determines appropriate, in consultation with appropriate organizations."

In 2014, the Secretary of Health and Human Services extended Medicare coverage for CRC screening tests when CMS issued a Decision Memorandum 210.3 for "Stool DNA Testing" for CRC screening. This Decision Memorandum established national coverage for one sDNA CRC screening test, Cologuard, effective October 9, 2014. Notably, after Exact Sciences submitted its reconsideration request on May 9, 2014, the Cologuard NCA proceeded on an expedited timeline that aligned with the FDA's premarket review of Cologuard. CMS accepted this reconsideration request and issued a Proposed Decision Memo on August 11, 2014, the same day Cologuard

was approved by the FDA. The final Decision Memo was issued on October 9, 2014 (https://www.cms.gov/medicare- coverage-database/view/ncacal-decision-memo.aspx?proposed=N&NCAId=277). This expedited process had the effect of accelerating access to CRC screening for Medicare beneficiaries and dually eligible individuals.

Relevant to our NCD reconsideration request, the Manual language currently states, "All other indications for colorectal cancer screening not otherwise specified in the Act and regulations, or otherwise specified above remain nationally non-covered." The Manual continues by stating that non-coverage specifically includes "[a]ll screening sDNA tests, effective April 28, 2008, through October 8, 2014. Effective for dates of service on or after October 9, 2014, all other screening sDNA tests not otherwise specified above remain nationally non-covered." As an sRNA test, ColoSense does not fall under any of the indications specified as addressed in NCD 210.3. Thus, we are requesting a reconsideration of the NCD language to remove automatic non-coverage of ColoSense under the NCD. With ColoSense now approved by the FDA, CMS should open the National Coverage Analysis with a Proposed Decision Memo as soon as possible in order to expedite expanded access to CRC screening for Medicare beneficiaries and dually eligible individuals and demonstrate a consistent policy approach toward CRC screening tests of similar modalities.

II. Clinical Evidence in Support of Medicare Coverage

A. Summary of FDA Approval

The FDA granted ColoSense its Breakthrough Device Designation on January 10, 2020. Geneoscopy submitted a PMA application for ColoSense to the FDA on January 19, 2023. Geneoscopy's PMA application to the FDA's Center for Devices and Radiological Health (CDRH) described ColoSense as a multi-target stool RNA (mt-sRNA) test that is used to detect colorectal cancer, advanced adenomas, and serrated precancerous lesions in average-risk individuals 45 years or older. The FDA approved the PMA for ColoSense on May 3, 2024 with the following indication:

> *ColoSense is intended for the qualitative detection of colorectal neoplasia-associated RNA markers and for the presence of occult hemoglobin in human stool. ColoSense is for use with the ColoSense Collection Kit, the ColoSense Test Kit, the ColoSense Software, and the following instruments: Polymedco iFOBT Analyzer; bioMérieux EMAG Nucleic Acid Extraction System; and Bio-Rad QXDx ddPCR System. ColoSense is a single-site test performed at Geneoscopy, Inc.*
>
> *A positive ColoSense result may indicate the presence of colorectal cancer (CRC), advanced adenomas (AA), or serrated precancerous lesions (SPL) and should be followed by a colonoscopy. ColoSense is indicated as a screening test for adults, 45 years of age or older, who are at typical*

average-risk for developing CRC. ColoSense is not a replacement for diagnostic colonoscopy or surveillance colonoscopy in high-risk individuals.

Demonstration of safety and efficacy for ColoSense was based on PMA review of both analytical validation studies and a clinical validation study. Analytical validation studies assessed detection capabilities, precision, robustness, interfering substances, carryover, cross-contamination, cross reactivity, biocompatibility, human factors, and stability of the entire test system. These studies were designed to verify that the ColoSense design outputs met design inputs and were performed under the relevant Clinical and Laboratory Standards Institute (CLSI) guidelines. Each study conducted met the acceptance criteria defined in the protocol and/or design input(s).

The clinical validation study (CRC-PREVENT) was a pivotal prospective, cross-sectional clinical trial used to evaluate the sensitivity and specificity of the mt-sRNA test compared with a colonoscopy. As part of clinical validation, three co-primary endpoints were evaluated:

- Sensitivity for subjects with colorectal cancer (CRC), which is the percentage of individuals with a diagnosis of colorectal cancer that were detected as positive by ColoSense.
- Sensitivity for subjects with advanced adenomas (AA) and serrated precancerous lesions (SPL), which is the percentage of individuals with a diagnosis of advanced adenoma or serrated precancerous lesion that were detected as positive by ColoSense.
- Specificity for subjects with Non-advanced Precancerous Lesions (NAPL) or Negative Findings (NEG), which is the percentage of individuals without a diagnosis of CRC, AA, or SPL that were detected as negative by ColoSense.

Each subject in the CRC-PREVENT clinical trial completed a ColoSense test prior to completing a screening colonoscopy. Lesion subtypes were based on colonoscopy findings as described below:

	Test Result	**Colonoscopy Findings**
Colorectal Cancer (CRC)	Positive	Stage I-IV colorectal cancer, any size
Advanced Adenomas (AA)		High-grade dysplasia or ≥10 adenomas, any size
		Tubulovillous adenoma, any size
		Tubular adenoma, ≥10mm
Serrated Precancerous Lesions (SPL)		Sessile serrated lesions with dysplasia (SSLDs); Traditional serrated adenoma (TSA) (include size greater than 1 cm and/or presence of high-grade dysplasia); Conventional adenomas with serrated architecture; Sessile serrated lesions ≥10mm
Non-advanced Precancerous	Negative	5-9 adenomas or sessile serrated lesion, <10mm, non-advanced
		3-4 adenomas or sessile serrated lesion, <10mm, non-advanced

Lesions (NAPL)		1-2 adenomas or sessile serrated lesion, 5-9mm, non-advanced
		1-2 adenomas or sessile serrated lesion, <5mm, non-advanced
Negative Findings (NEG)		Hyperplastic polyps or negative lesions
		No lesions on colonoscopy

In the CRC-PREVENT clinical trial, a total of 8,920 subjects completed all study requirements. A subset of 7,763 subjects were determined by the FDA to be average-risk for CRC. The Average-risk Cohort (n = 7,763) served as the primary effectiveness cohort for the PMA review. In the Average-risk Cohort, ColoSense demonstrated 93% sensitivity for CRC, 45% sensitivity for AA, 22% sensitivity for SPL, and 86% sensitivity for all other findings, with 88% specificity for no findings on colonoscopy.

Sensitivity	**Ratio**	**Point Estimate**	**95% CI**
Colorectal Cancer (CRC)	25 / 27	92.6%	76% - 99%
Advanced Adenomas (AA)	231 / 514	44.9%	41% - 49%
Serrated Precancerous Lesions (SPL)	22 / 98	22.4%	15% - 32%
Specificity	**Ratio**	**Point Estimate**	**95% CI**
All other findings	6,097 / 7,124	85.6%	85% - 86%
Non-advanced adenomas / other lesions	3,206 / 3,821	83.9%	83% - 85%
No findings on colonoscopy	2,891 / 3,303	87.5%	86% - 89%

It was further stated by the Agency that, “ColoSense additionally demonstrated benefit over FIT, identifying 4 of 6 (67%) CRC cases that were not identified by FIT. Similarly, for AA detection, ColoSense identified 52 of 335 (16%) AA cases that were not identified by FIT. For SPL detection, ColoSense identified 12 of 88 (14%) SPL cases that were not identified by FIT.”

B. **Published Clinical Evidence Supports ColoSense Analytical and Clinical Validity**

The Analytical Validation studies that were part of the PMA application were summarized and submitted for peer review to the Journal of Molecular Diagnostics on November 13, 2023. This peer-reviewed manuscript was accepted for publication on May 2, 2024. We have been informed that these data will be available online and in print in July 2024. This manuscript assesses each component of the assay including limit of blank, limit of detection, limit of quantification, linearity, precision and reproducibility, interfering substances, cross-reactivity, carry-over, cross-contamination, and robustness of the mt-sRNA test system.

The clinical validation study (CRC-PREVENT) that was part of the PMA application was summarized and submitted to the Journal of American Medical Association. This peer-reviewed manuscript was published on October 23, 2023 (DOI: 10.1001/jama.2023.22231). As described above, the CRC-PREVENT clinical trial served as the pivotal study to demonstrate safety and efficacy of the ColoSense test. The CRC-PREVENT clinical trial utilized a novel decentralized clinical trial design that was launched through a digital campaign that enrolled 14,263 subjects, of whom 8,920 completed all study requirements (stool sample collection and subsequent

colonoscopy). This decentralized recruitment design resulted in a highly diverse and representative patient population that included many Medicare-aged individuals. The trial population self-identified as 11% Black, 4% Asian, and 1% Native American/Alaskan. Of the patients who completed all study requirements, 15% were enrollees aged 65 or older, totaling 1,360 subjects. Additionally, 1,768 participants, or 20%, identified themselves as Medicare beneficiaries. Within this subgroup, 1,081 were enrolled in traditional Medicare, and 687 were part of a Medicare Advantage plan. The subjects from the CRC-PREVENT trial were derived from 49 states in the U.S. and utilized more than 3,800 different endoscopy centers.

Across all eligible subjects (n = 8,920), a total of 36 eligible subjects were found to have colorectal cancer on colonoscopy (prevalence of 0.4%) and a total of 606 subjects were found to have advanced adenoma on colonoscopy (prevalence of 6.8%). ColoSense detected 34 of 36 subjects with colorectal cancer (94% sensitivity). ColoSense detected 278 of 606 subjects with advanced adenomas (46% sensitivity). The positive predictive value (PPV) for colorectal neoplasia (CRC or AA) was 21%. The average age for subjects with CRC was 58 years old with 50% (n = 16 / 36) being 60 years old or older. The average age for advanced adenomas was 57 years old with 37% (n = 227 / 606) being 60 years old or older. Importantly, ColoSense demonstrated 100% CRC sensitivity for Stage I cancer (n = 14 / 14). ColoSense also demonstrated 95% CRC sensitivity for individuals enrolled in Medicare and Medicaid programs (n = 18 / 19).

In addition to clinical validation supported by the CRC-PREVENT clinical trial, the use of a novel, decentralized recruitment strategy leveraged in this study points to novel mechanisms that could improve colorectal cancer screening rates in noncompliant cohorts. As noted above, 14,263 subjects were enrolled online using social media. Through this decentralized recruitment strategy, we observed that 64% of enrolled subjects were not actively participating in colorectal cancer screening (i.e., had never before been screened with a colonoscopy, FIT, or molecular test), and 68% of subjects did not have a colonoscopy scheduled at the time of enrollment. This contrasts with traditional site-based models whereby 100% of subjects already have a colonoscopy scheduled since intervention occurs at the endoscopy center. Across all 14,263 subjects enrolled in the study, ~80% completed the mt-sRNA test and ~80% of those completed a subsequent colonoscopy. Of subjects who completed a ColoSense test but did not complete a colonoscopy, 1,462 had a negative ColoSense score. Therefore, in a “real-world setting”, adherence to the program was 73.6% (completed ColoSense test and completed colonoscopy for those who had a positive noninvasive test). This was achieved in a cohort of subjects who were not actively participating in screening programs and required ultimate navigation to colonoscopy to complete study requirements. Of note, compliance rates were associated with minimal compensation for completing study requirements.

This study leads to several conclusions regarding enhanced adherence to colorectal cancer screening recommendations. First, digital patient engagement could effectively identify individuals who are not actively participating in colorectal cancer screening. Second, structured

patient navigation potentially leads to increased screening compliance. Finally, the infrastructure to support this navigation has already been developed as part of our clinical trial and will play a large role in ensuring broad and equitable access to alternative colorectal cancer screening options.

III. Update to NCD 210.3 Warranted for RNA Technologies

A. Advances in RNA CRC Screening Technologies Support Category-Wide Coverage Criteria

As suggested by the ColoSense clinical validation study, a CRC-specific RNA signature may outperform tumor-specific DNA alterations in such samples. RNA shows increased expression even in precancerous tissues, and RNA expression profiles allow for discrimination between a chronic inflammatory state and carcinoma. Notably, RNA expression profiles also expand beyond mutational alterations, reflecting molecular changes associated with neoplasia development and progression.

Specifically, research supports that stool-derived eukaryotic RNA biomarkers are the ideal platform for the detection of colorectal neoplasms because of the transcriptome's ability to provide a real-time snapshot of cellular activity using signals that are exponentially amplified relative to DNA markers. As indicated above, the sRNA test can detect advanced adenomas that have a high malignant transformation rate. These findings reinforce that an sRNA test can be a significant advancement in CRC screening by helping to reduce overall CRC cases and deaths.

These data support modifications to NCD 210.3 to eliminate the current framework of non-coverage for sRNA testing. The NCD is nearly ten (10) years old, with subsections B.2 and C(1) specifically limited to a single technology, the Cologuard sDNA test. Subsection C states that all "***other indications for colorectal cancer screening not otherwise specified in the Act and regulations, or otherwise specified above remain nationally non-covered***." The test-specific coverage requirement and rigid non-coverage provision governing all CRC screening tests that are not specifically covered are out of alignment with the significant advances in sRNA CRC screening technology over the past several years.

Furthermore, since issuing the October 2014 Decision Memo, CMS has moved away from the test-specific approach to NCDs. The most recent addition to the CRC screening NCD, issued in January 2021, establishes category-wide sensitivity and specificity conditions for blood-based biomarker screening tests, rather than covering a specific test. NCD 90.2 for Next Generation Sequencing, most recently updated in January 2020, similarly imposes category-wide coverage criteria. We believe that CMS should update the NCD for stool-based CRC screening to align with this more consistent, and less resource-intensive, approach.

By adopting category-wide coverage criteria that include RNA testing technologies, Medicare beneficiaries and dually eligible individuals will obtain access to additional and, we believe, more accurate non-invasive screenings that support the early detection of CRC,

enabling more immediate clinical intervention. The current, test-specific approach to stool-based testing outlined in subsections B.2 and C(1) of NCD 210.3, combined with the non-coverage language in subsection C, results in new stool-based CRC screening tests requiring an individual reconsideration to establish coverage. In particular, all sRNA tests are non-covered under the current NCD language. Given the considerable advances in CRC detection made using RNA technologies, it would be appropriate to establish category-wide coverage criteria that will provide coverage for newly FDA-approved sRNA tests that meet uniform specifications established by CMS.

B. **ColoSense Clinical Utility Comparable to 2014 Sensitivity and Specificity Benchmarks**

There is no need for separate clinical utility evidence to support coverage of an sRNA test that plays the same clinical role as Cologuard. The clinical utility of non-invasive, stool-based CRC screening tests has been well established. In October 2014, CMS expanded the CRC screening benefit to include coverage of Cologuard. In the Decision Memo for Cologuard, CMS reasoned that "[p]rimary prevention, early detection and early treatment have contributed to the observed reduction in mortality" in CRC. CMS noted that "Medicare currently covers several CRC screening tests, yet utilization rates are suboptimal. The Cologuard test is a technologically advanced, non-invasive CRC screening test, with test performance that has been shown to be significantly better in detecting advanced adenomas and cancers than current fecal immunochemical tests." The agency found that "[b]ased on a systematic review of the evidence…colorectal cancer screening in Medicare beneficiaries using the Cologuard test is appropriate for the prevention or early detection of illness or disability."

ColoSense's clinical pattern of use as a CRC screening test mirrors that of Cologuard, but uses sRNA biomarkers rather than sDNA. The agency's 2014 determination that Cologuard is appropriate for the prevention or early detection of illness or disability applies equally to ColoSense. Although no head-to-head comparison data exists, the ColoSense clinical data on which the FDA based its approval demonstrate comparable sensitivity and specificity test benchmarks as those underlying CMS's 2014 coverage determination. When looking at subjects in the CRC-PREVENT study who are eligible for health coverage under CMS (Medicare/Medicaid) (n = 2,549), ColoSense showed 95% sensitivity for detecting Colorectal Cancer (n = 19) and 56% sensitivity for detecting advanced adenomas (n = 242). This breakdown is not provided for individuals in the Deep-C study (Cologuard), but the ColoSense data metrics show sensitivity and specificity metrics that compare favorably to the performance data reported to support coverage of Cologuard across all participants. Although the trials involved different eligibility criteria and evaluated different-sized cohorts, if "colorectal cancer screening in Medicare beneficiaries using the Cologuard test is appropriate for the prevention or early detection of illness or disability," it follows that CRC screening using ColoSense is appropriate for this purpose as well.

IV. Expedited Reconsideration Timeline is Appropriate Given the Importance of Non-Invasive CRC screening and its Ability to Help Address Health Disparities

Geneoscopy respectfully requests that CMS open its National Coverage Analysis of ColoSense with a Proposed Decision Memo as soon as possible now that the FDA has approved ColoSense, just as the agency did with the NCD in 2014.

Non-invasive tests like ColoSense can help reduce preventable deaths. For instance, the ColoSense test can identify a patient who needs a diagnostic colonoscopy based on a high demonstrated sensitivity for CRC and AAs, thereby helping to identify cancers at an early (or precancerous) stage. This is particularly important for the Medicare-aged population, as nearly 70% of diagnosed cases of colorectal cancer are in individuals who are 65 years or older. That said, it is important to note that 19% of Medicare beneficiaries are individuals under age 65 who are dually eligible for Medicare and Medicaid, according to the January 2024 dual eligible data book. These beneficiaries are highly likely to have comorbidities or disabilities that make in-person care difficult, and they also have disproportionately high costs of care. A non-invasive test like ColoSense, with its effectiveness starting at age 45, can help younger beneficiaries have convenient access to CRC screening. Further, identifying cancers at an early or precancerous stage for these younger beneficiaries not only will improve their health and outcomes but will reduce long-term healthcare costs, allowing Medicare dollars for non-senior dual-eligibles to stretch further. Dually eligible beneficiaries aged 45-64 can benefit significantly from access to the ColoSense test.

Taking steps to improve the availability of non-invasive CRC screens—such as expediting reconsideration of the NCD to establish coverage of ColoSense—is warranted to help recover from the decline in CRC screening stemming from the COVID-19 pandemic. During the initial months of the pandemic (March to June 2020), there was a 90% drop in colonoscopies and biopsies relative to the same period in 2019. This is estimated to have resulted in 1.7 million missed colonoscopies and 18,000 missed or delayed CRC diagnoses. Altogether, delays in CRC screening during the COVID-19 pandemic are projected to result in a 12% increase in cancer deaths over the next five years. Improving the availability of well-validated, non-invasive CRC screening tests in an expeditious fashion may help mitigate the number of missed CRCs and preventable deaths, while ensuring that remote screening is more accessible if another public health emergency strikes.

Additionally, expedited reconsideration would align with the prominence the Biden Administration has given to its Cancer Moonshot and the findings of the Presidential Commission on Cancer. The Cancer Moonshot issued a call to action "to help ensure equitable access to screening and prevention through at-home screening, especially for colon cancer..."[1] Geneoscopy agrees with the Administration that at-home tests like ColoSense are critical to decreasing CRC mortality because they may reach "people who live long distances from medical facilities, have difficulty attending appointments, or are uncomfortable in medical

settings or with medical procedures used for other screening approaches."[2] Similarly, the Presidential Commission on Cancer reiterated the findings of several studies that the active distribution of stool-based tests increased the completion of colorectal cancer screening. Both the Moonshot and Commission emphasize the public health importance of increasing access to CRC screening. Opening reconsideration of the NCD as soon as possible with a Proposed Decision Memorandum best advances these federal government priorities and public health objectives.

V. Coverage Request and Recommendation

As set out above, Geneoscopy respectfully requests that CMS reconsider section 210.3.B.2 of the NCD Manual to establish coverage for the ColoSense test. Below Geneoscopy recommends the following revisions of the NCD to provide coverage for ColoSense (blue underlined text indicates recommended additions or changes to existing text):

2. ~~The Cologuard™ –~~ Multi-target Stool DNA (sDNA) and Stool RNA (sRNA) Testing (effective October 9, 2014)

Screening stool or fecal DNA (deoxyribonucleic acid, sDNA), or stool or fecal RNA (ribonucleic acid, sRNA) testing detects molecular markers of altered DNA or RNA that are contained in the cells shed by colorectal cancer and pre-malignant colorectal epithelial neoplasia into the lumen of the large bowel. Through the use of selective enrichment and amplification techniques, sDNA and sRNA tests are designed to detect very small amounts of DNA or RNA markers to identify colorectal cancer or pre-malignant colorectal neoplasia. The Cologuard™ – multi-target sDNA test is a proprietary in vitro diagnostic device that incorporates both sDNA and fecal immunochemical test techniques and is designed to analyze patients' stool samples for markers associated with the presence of colorectal cancer and pre-malignant colorectal neoplasia. The ColoSense – multi-target sRNA test is a proprietary in vitro diagnostic device that incorporates both sRNA and fecal immunochemical test techniques and is designed to analyze patients' stool samples for markers associated with the presence of colorectal cancer and pre-malignant colorectal neoplasia.

Effective for dates of service on or after October 9, 2014, The Cologuard™ test is covered once every three years for Medicare beneficiaries that meet all of the following criteria. Effective for dates of service on or after DATE, the ColoSense test, and other sRNA tests displaying similar performance to the ColoSense test for their FDA-approved labeled indications, are covered once every three years for Medicare beneficiaries that meet all of the following criteria:

- *Age 45 to 85 years, and,*
- *Asymptomatic (no signs or symptoms of colorectal disease including but not limited to lower gastrointestinal pain, blood in stool, positive guaiac fecal occult blood test (gFOBT) or fecal immunochemical test (iFOBT)), and,*
- *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 adenomatous polyps, familial adenomatous polyposis, or hereditary nonpolyposis colorectal cancer).

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Thank you for your consideration of this request. We welcome the opportunity to meet with you to review any of the clinical information and scientific data included in this request.

Please contact me if you have any questions or would like additional information. We look forward to hearing from you soon.

Finally, we request that this letter be treated as Confidential.

Respectfully submitted,

Andrew Barnell

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