May 6, 2014

VIA FedEx and Electronic Mail submission to: cms_caginquiries@cms.hhs.gov

Tamara S. Syrek-Jensen, JD
Acting Director, Coverage and Analysis Group
Centers for Medicare and Medicaid Service
Mail Stop C1-09-06
7500 Security Boulevard
Baltimore, MD 21244-1850

RE: A Formal Request for a National Coverage Determination – Reconsideration of the National Coverage Determination for Colorectal Cancer Screening Tests (210.3)

Dear Ms. Syrek-Jensen:

By this letter Exact Sciences Corporation ("Exact Sciences") formally requests a reconsideration of the National Coverage Determination ("NCD") for Colorectal Cancer Screening Tests (210.3).

NCD development track chosen: Track #1 (68 *Fed. Reg.* 55638, IV E.)

Benefit category of the Medicare program to which the service applies: colorectal cancer screening tests (Soc Sec Act § 1861(pp)(1)).

Exact Sciences is participating in the Food and Drug Administration ("FDA") – Centers for Medicare and Medicaid Services ("CMS") Parallel Review Pilot Program (the "Pilot Program"). The Premarket Approval ("PMA") application has been submitted to the FDA and is under review by that agency. At a recent meeting of the Molecular and Clinical Genetics Panel of the FDA's Medical Device Advisory Committee (the "Panel"), the Panel unanimously determined that Exact Sciences has demonstrated the safety, effectiveness, and favorable risk benefit profile of Cologuard®, the company's multi-target stool-based DNA (sDNA), non-invasive colorectal cancer screening test.. We are submitting this formal request for an NCD to the CMS to meet the requirements of the Pilot Program.

Exact Sciences has developed Cologuard® as a multi-target sDNA colorectal cancer screening test involving two DNA methylation markers (*NDRG4, BMP3*), seven point mutations on *KRAS* (codons 12 and 13), quantitative DNA (β-actin) and fecal hemoglobin (immunochemical method [FIT]) ("multi-target sDNA test"). Insofar as the Exact Sciences' multi-target sDNA test is not a screening fecal-occult blood test (FOBT), a screening flexible sigmoidoscopy, or a screening colonoscopy, it does not currently qualify as a covered colorectal cancer screening test. The Secretary of the Department of Health and Human Services, however, has the authority to provide coverage for innovative new tests that are also designed for early detection of colorectal cancer.

In the Physician Fee Schedule Final Rule for CY 2003[1], CMS amended the colorectal cancer screening test regulation in 42 CFR § 410.37(a)(1)(v) to provide that in addition to the screening tests already covered under the regulation, it could include coverage for "other tests or procedures **established by a national coverage determination"** (emphasis added). Therefore, we are submitting this request for an NCD to provide coverage for the Exact Sciences multi-target sDNA test.

[1] 67 *Fed. Reg.* 79,966 (December 31, 2002)

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As part of the National Coverage Analysis process, Exact Sciences has previously submitted a letter to CMS that contained a complete description of the service, a description of the proposed use of the service, supporting medical and scientific information, an explanation of the design/purpose/method of the item, and the current status of the FDA regulatory review. We have also submitted to CMS the Panel briefing materials and a recent publication of the pivotal trial results from the *New England Journal of Medicine*.

To complete the formal NCD reconsideration request, we are currently submitting the following materials:

1. List of references previously submitted to CMS as part of the NCA process.

2. Proposed NCD text

3. Poster presentation by Ligard GP, Domanico MJ, Bruinsma JJ, *et al*. An optimized stool DNA (sDNA) multi-target test for colorectal cancer screening: initial clinical appraisal.

Maneesh Arora, Chief Operating Officer, Exact Sciences, and Barry Berger, M.D., Chief Medical Officer, are the primary requestors for the reconsideration of the NCD. Paul Radensky, M.D., J.D., counsel to Exact Sciences, will serve as the principal point of contact and may be reached as shown below for additional information or clarification.

Sincerely,

Paul Radensky
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202.756.8794
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cc: Maneesh Arora
Barry Berger, M.D.

Appendix A: List of references submitted
Appendix B: Proposed NCD text
Appendix C: Ligard, et al. poster

Appendix A: List of Reference Materials

1. Ahlquist DA, Zou H, Domanico M, Mahoney DW, Yab TC, Taylor WR, Butz ML, Thibodeau SN, Rabeneck L, Paszat LF, Kinzler KW, Vogelstein B, Bjerregaard NC, Laurberg S, Sørensen HT, Berger BM, Lidgard GP. Next-generation stool DNA test accurately detects colorectal cancer and large adenomas. *Gastroenterology*. 2012 Feb;142(2):248-56; quiz e25-6. Epub 2011 Nov 4.

2. Ahlquist DA, Taylor WR, Mahoney DW, Zou H, Domanico M, Thibodeau SN, Boardman LA, Berger BM, Lidgard GP. The stool DNA test is more accurate than the plasma septin 9 test in detecting colorectal neoplasia. *Clin Gastroenterol Hepatol.* 2012 Mar;10(3):272-7.e1.Epub 2011 Oct 20.

3. Ahlquist DA, Sargent DJ, Loprinzi CL, Levin TR, Rex DK, Ahnen DJ, Knigge K, Lance MP, Burgart LJ, Hamilton SR, Allison JE, Lawson MJ, Devens ME, Harrington JJ, Hillman SL. Stool DNA and occult blood testing for screen detection of colorectal neoplasia. *Ann Intern Med*. 2008 Oct 7; 149(7):441-50, W81.

4. Diehl F, Schmidt K, Durkee KH, Moore KJ, Goodman SN, Shuber AP, Kinzler KW, Vogelstein B. Analysis of mutations in DNA isolated from plasma and stool for colorectal cancer patients. *Gastroenterology*. 2008 Aug;135(2):489-98. Epub 2008 May 15.

5. Imperiale TF, Ransohoff DF, Itzkowitz SH, Levin TR, Lavin P, Lidgard GP, Ahlquist DA, Berger BM. Multitarget stool DNA testing for colorectal-cancer screening. *N Engl J Med.* 2014;370(14):1287-97.

6. Lee JK, L.E. Accuracy of fecal immunochemical tests for colorectal cancer: systematic review and meta-analysis. *Ann Intern Med*. 2014;160(3):171-81.

7. Lidgard GP, Domanico MJ, Bruinsma JJ et al. Clinical performance of an automated stool DNA assay for detection of colorectal neoplasia. *Clin Gastroenterol Hepatol*. 2013 Oct;11(10):1313-8. Epub 2013 April 29.

8. Melotte V, Lentjes MH, van den Bosch SM, Hellebrekers DM, de Hoon JP, Wouters KA, Daenen KL, Partouns-Hendriks IE, Stessels F, Louwagie J, Smits KM, Weijenberg MP, Sanduleanu S, Khalid-de Bakker CA, Oort FA, Meijer GA, Jonkers DM, Herman JG, de Bruïne AP, van Engeland M. N-Myc downstream-regulated gene 4 (NDRG4): a candidate tumor suppressor gene and potential biomarker for colorectal cancer. *J Natl Cancer Inst*. 2009 Jul 1;101(13):916-27. Epub 2009 Jun 17.

9. Onouchi S, Matsushita H, Moriya Y, et al. New method for colorectal cancer diagnosis based on SSCP analysis of DNA from exfoliated colonocytes in naturally evacuated feces. *Anticancer Res*. 2008 Jan;28(1A):145-50.

10. Zou H, Allawi H, Cao X, et al. Quantification of methylated markers with a multiplex methylation-specific technology. *Clin Chem.* 2012;58(2):375-383

Appendix B: Proposed NCD for Colorectal Cancer Screening Tests (210.3)

National Coverage Determination (NCD) for Colorectal Cancer Screening Tests (210.3)

Tracking Information

Publication Number

100-3

Manual Section Number

210.3

Manual Section Title

Colorectal Cancer Screening Tests

Version Number

~~3~~ 4

Effective Date of this Version

~~5/12/2009~~ [Insert Effective Date]

Implementation Date

~~9/8/2009~~ [Insert Implementation Date]

Description Information

Benefit Category

Colorectal Cancer Screening Tests

Note: This may not be an exhaustive list of all applicable Medicare benefit categories for this item or service.

Item/Service Description

A. General

Section 4104 of the Balanced Budget Act of 1997 provides for coverage of screening colorectal cancer procedures under Medicare Part B. Medicare currently covers: (1) annual fecal occult blood tests (FOBTs); (2) flexible sigmoidoscopy over 4 years; (3) screening colonoscopy for persons at average risk for colorectal cancer every 10 years, or for persons at high risk for colorectal cancer every 2 years; (4) barium enema every 4 years as an alternative to flexible sigmoidoscopy, or every 2 years as an alternative to colonoscopy for persons at high risk for colorectal cancer; (5) stool DNA multi-target tests using an FDA-approved device every 3 years; and (~~5~~6) other procedures the Secretary finds appropriate based on consultation with appropriate experts and organizations. Coverage of ~~the above~~ screening examinations (1) through (4), above, was implemented in regulations through a final rule that was published on October 31, 1997 (62 FR 59079), and was effective January 1, 1998. At that time, based on consultation with appropriate experts and organizations, the definition of the term "FOBT" was defined in 42 CFR §410.37(a)(2) of the regulation to mean a "guaiac-based test for peroxidase activity, testing two samples from each of three consecutive stools." In the 2003 Physician Fee Schedule Final Rule (67 FR 79966) effective March 1, 2003, the Centers for Medicare & Medicaid Services (CMS) amended the FOBT screening test regulation definition at 42 CFR §410.37(a)(2) to provide that it could include either: (1) a guaiac-based FOBT, or, (2) other tests determined by the Secretary through a national coverage determination.

Indications and Limitations of Coverage

B. Nationally Covered Indications

Fecal Occult Blood Tests (FOBT) (effective for services performed on or after

January 1, 2004)

Stool DNA multi-target tests using an FDA-approved device (effective for services performed on or after [insert effective date])

[Insert code and descriptor, such as (Molecular pathology descriptor): Stool DNA multi-target tests using an FDA-approved device (effective for services performed on or after [insert effective date] (NDRG4/BMP3/KRAS/ACTB (*NDRG family member 4/bone morphogenetic protein 3/v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog/actin, beta) (eg, colorectal cancer), methylation/mutation analysis; quantitative test for fecal hemoglobin*)]

1. History

The FOBTs are generally divided into two types: immunoassay and guaiac types. Immunoassay (or immunochemical) fecal occult blood tests (iFOBT) use "antibodies directed against human globin epitopes. While most iFOBTs use spatulas to collect stool samples, some use a brush to collect toilet water surrounding the stool. Most iFOBTs require laboratory processing. Guaiac fecal occult blood tests (gFOBT) use a peroxidase reaction to indicate presence of the heme portion of hemoglobin. Guaiac turns blue after oxidation by oxidants or peroxidases in the presence of an oxygen donor such as hydrogen peroxide. Most FOBTs use sticks to collect stool samples and may be developed in a physician's office or a laboratory. In 1998, Medicare began reimbursement for guaiac FOBTs, but not immunoassay type tests for colorectal cancer screening. Since the fundamental process is similar for other iFOBTs, CMS evaluated colorectal cancer screening using immunoassay FOBTs in general.

The Exact Sciences Cologuard® Assay is a next-generation stool-based test that detects complementary DNA biomarkers known to be associated with colorectal cancer and its precursor lesions as well as fecal hemoglobin. The Cologuard® Assay utilizes three families of biomarkers that are independent, exhibiting an additive association with colorectal cancer and premalignant neoplasms. The first DNA family targets epigenetic changes in the form of gene promoter region methylation. The second DNA family targets specific point mutations. The third family of biomarkers is non-DNA based and detects hemoglobin in the fecal sample (FIT). The Cologuard® Assay received premarket approval from the FDA on [insert date of PMA].

2. Expanded Coverage

Medicare covers one screening FOBT per annum for the early detection of colorectal cancer. This means that Medicare will cover one guaiac-based (gFOBT) or one immunoassay-based (iFOBT) at a frequency of every 12 months; i.e., at least 11 months have passed following the month in which the last covered screening FOBT was performed, for beneficiaries aged 50 years and older. The beneficiary completes the existing gFOBT by taking samples from two different sites of three consecutive stools; the beneficiary completes the iFOBT by taking the appropriate number of stool samples according to the specific manufacturer's instructions. This screening requires a written order from the beneficiary's attending physician. ("Attending physician means a doctor of medicine or osteopathy (as defined in §1861(r)(1) of the Social Security Act) who is fully knowledgeable about the beneficiary's medical condition, and who would be responsible for using the results of any examination performed in the overall management of the beneficiary's specific medical problem.)

C. Nationally Non -Covered Indications

All other indications for colorectal cancer screening not otherwise specified above remain non -covered. Non-coverage specifically includes:

~~(1) Screening DNA (Deoxyribonucleic acid) stool tests, effective April 28, 2008,~~

~~and,~~

~~(2)~~ Screening computed tomographic colonography (CTC), effective May 12, 2009.

D. Other

N/A

(This NCD last reviewed ~~May 2009~~ [insert date last reviewed].)

Cross Reference

Also see NCD for Fecal Occult Blood Test (§190.34).

Transmittal Information

Transmittal Number

105

Coverage Transmittal Link

http://www.cms.gov/transmittals/downloads/R105NCD.pdf

Revision History

12/2003 - Expanded Medicare coverage for screening for early detection of colorectal cancer by adding additional fecal occult blood test (iFOBT, immunoassay-based) that can be used as alternative to existing gFOBT, guaiac-based test. Medicare coverage continues to allow one FOBT per year for beneficiaries aged 50 and over. Effective date 1/01/04. Implementation date

1/05/2004 for coverage & HCPCS codes and 4/05/2004 for frequency edits. (TN 5) (CR 2996)

08/2008 - Following reconsideration of the current national coverage determination (NCD) for colorectal cancer screening, CMS proposes not to expand the colorectal cancer screening benefit to include coverage of PreGen-Plus, a commercially available screening DNA stool test. The FDA determines that this test requires premarket review and approval. A subsequent request for reconsideration will be considered once FDA approval is obtained. Effective date 04/28/2008. Implementation date 08/25/2008. (TN 92) (CR6145)

08/2009 - CMS determines that the current evidence is inadequate to conclude that CTC is an appropriate colorectal cancer screening test under section 1861(pp)(1) of the Social Security Act. Therefore, effective May 12, 2009, CTC for colorectal cancer screening remains nationally non-covered. Effective date 05/12/2009. Implementation date 09/08/2009. (TN 105) (CR6578)

[Insert revision date] – Following reconsideration of the current NCD for colorectal cancer screening, CMS proposes to expand the colorectal cancer screening benefit to include coverage of screening stool DNA multi-target tests, including:

[Insert code and descriptor, such as (Molecular pathology descriptor): Stool DNA multi-target tests using an FDA-approved device (effective for services performed on or after [insert effective date] (NDRG4/BMP3/KRAS/ACTB (*NDRG family member 4/bone morphogenetic protein 3/v-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog/actin, beta) (eg, colorectal cancer), methylation/mutation analysis; quantitative test for fecal hemoglobin*)]

Effective date [enter date]. Implementation date [enter date]. (TN XX) (CRXXXX)

National Coverage Analyses (NCAs)

This NCD has been or is currently being reviewed under the National Coverage Determination process. The following are existing associations with NCAs, from the National Coverage Analyses database. Original consideration for Screening DNA Stool Test for Colorectal Cancer (CAG-00144N)

Original consideration for Screening Immunoassay Fecal-Occult Blood Test

(CAG-00180N)

Coding Analyses for Labs (CALs)

This NCD has been or is currently being reviewed under the National Coverage Determination process. The following are existing associations with CALs, from the Coding Analyses for Labs database.

Original consideration for Prothrombin Time and Fecal Occult Blood (Revision

of ICD-9-CM Codes for Injury to Gastrointestinal Tract) (CAG-00187N)

Additional Information

Other Versions

Colorectal Cancer Screening Tests - Version 2, Effective between 4/28/2008

- 5/12/2009

Colorectal Cancer Screening Tests - Version 1, Effective between 1/1/2004 -

4/28/2008

An Optimized Stool DNA (sDNA) Multi-Target Test for Colorectal Cancer Screening: Initial Clinical Appraisal

Graham P. Lidgard[1], Michael J. Domanico[1], Janelle J. Bruinsma[1], Zubin D. Gagrat[1], Rebecca L. Oldham-Haltom[1], Keith D. Fourrier[1], Tracy C. Yab[2], Julie A. Simonson[2], Russell I. Heigh[3], Barry M. Berger[1], and David A. Ahlquist[2]

Exact Sciences Corporation[1], Madison WI and Division of Gastroenterology and Hepatology, Mayo Clinic, Rochester MN[2] and Scottsdale AZ[3]

BACKGROUND AND OBJECTIVES

Colorectal cancer (CRC) is a leading cause of cancer death in the United States, yet with screening, is one of the most preventable cancers. CRC screening, using an advanced sDNA multi-target test approach has potential for high detection sensitivity of both CRC and precursor lesions. In previous studies, we reported on the detection of methylated DNA or mutated DNA in stool. Here we report the clinical performance for CRC and precursor detection for a sDNA multi-target test in a case control setting. We have now developed a test that is comprised of a stool collection kit, sample processing and assay reagents, protocols and automated instruments. The targets consist of a molecular assay for exfoliated DNA markers (methylated *BMP3* and *NDRG4*, mutant *KRAS*, and ß-actin (*ACTB*)) plus fecal immunochemical testing (FIT) for hemoglobin (Figure 1).

ABSTRACT

This study represents the first clinical assessment of a stool DNA (sDNA) multi-target screening test for colorectal cancer (CRC) and advanced adenomas. Previous studies presented specific component parts of the test (Next Generation Stool DNA Testing for Detection of Colorectal Neoplasia: Early Marker Evaluation. Presented at: Colorectal Cancer - Biology to Therapy. AACR Special Conference, 2010 Oct. 27– 30 Philadelphia PA; Sensitive Detection of Mutant KRAS in Colorectal Tissue using the Multiplex QuARTS™ Assay, Poster presented at: Frontiers in Cancer Prevention Research, 10th AACR International Conference, 2011 Oct. 22-25 Boston MA; Zou H. et al, Clinical Chemistry, 2012, 58:2, p.375-383). This study presents the results of the combined multi-target panel that detects specific methylation and mutation DNA markers and hemoglobin in stool. The data demonstrates high yield for the detection of both CRC and precursor lesions using a multi-target approach. We corroborate our previous findings that polyp size but neither site nor CRC stage affects detection rates (Ahlquist D. et al, Gastroenterology, 2012, 142:2, p.248-256). The test is currently being validated in a screening population, the large multicenter clinical study, Deep-C (clinicaltrials.gov, NCT01397747).

METHODS

We recruited 356 subjects from 20 sites: 78 cases (46 with CRC and 32 with precursor lesions ≥ 1 cm (adenomas or serrated lesions)) and 278 average-risk controls with normal findings or non-advanced polyps on colonoscopy (Table 1). Median age was 64 years old (range: 38-87 years) for cases and 65 years old (range: 44-84) for controls. Stools were collected from screen-detected cases and controls prior to screening colonoscopy and from referred cases ≥7 days post-colonoscopy and prior to chemo-radiation or surgery. Subjects used the provided collection kit and removed a small sample for FIT prior to adding a DNA preservative buffer to the specimen (Figure 2).

The optimized sDNA multi-target test combines the quantitative detection of methylated DNA sequences of the *NDRG4* and *BMP3* genes, 7 *KRAS* DNA mutations (codon 12 and 13), the reference gene *ACTB* and fecal hemoglobin.

In the lab, stool samples were homogenized, aliquoted, and frozen for subsequent blinded analyses. Following centrifugation of solids and inhibitor removal, DNA was isolated and purified using target-specific magnetic particles. Eluted DNA was split into two aliquots. One aliquot was treated with bisulfite conversion reagents to prepare the DNA for the methylation assay. The other aliquot was used for the mutation assay. Individual QuARTS™ (quantitative allele-specific real-time target and signal amplification) reaction master mixes were prepared for DNA methylation or DNA mutation assays. Both QuARTS™ reactions were performed using the ABI 7500 Real Time PCR System. The fecal hemoglobin sample was analyzed in a sandwich ELISA assay to determine the concentration of hemoglobin per gram of stool.

Analytic values for each marker were used to evaluate discrimination between normal and positive samples. Cutoffs for individual markers were used to determine positive or negative results from the methylation, mutation and hemoglobin assays before combining results to determine a multi-target result.

FIGURE 1. Stool DNA (sDNA) Multi-Target Test

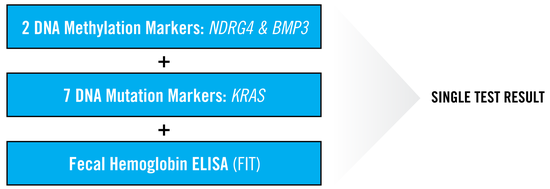

TABLE 1. Study Parameters – 2010 and 2011

	2010 Prototype	2011 Optimized Assay Configuration

SPECIMEN COLLECTION	• 678 samples
	• Stool collection at multiple sites over 7 years
	• Various sample processing methods
		• 356 samples
		  • 278 Normal
		  • 46 CRC
		  • 32 Adenoma ≥1 cm
		• Stool collection over 12 months
		• Consistent sample processing with fecal hemoglobin assay on all samples

ASSAY	• R&D reagents utilized	• Development lots reagents

MARKERS	• Prototype assay configuration
	  • 4 methylation markers + *ACTB*
	  • Singleplex *KRAS*
	  • Hemoquant
		• Final assay configuration
		  • Methylation Assay: 2 methylation markers + *ACTB*
		  • Mutation Assay: Multiplex *KRAS* + *ACTB*
		  • High sensitivity FIT

FIGURE 2. Patient Sample Collection Kit

Components
Bracket
Stool Collection Container
FIT Sampler
Stabilization Buffer

FIGURE 4a. Sensitivity by Cancer Stage

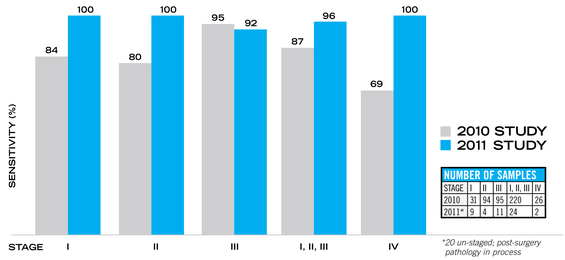

FIGURE 4b. Sensitivity by Lesion Site

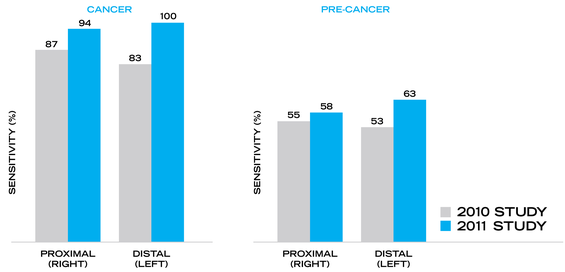

TABLE 2. Improved Assay Performance

	2010	2011
Number of Samples	678	356
Cancer Detection	85%	98%
Adenoma Detection ≥ 1 cm	54%	59%
Observed Specificity	89%	91%
Right-Sided Cancer	87%	94%
Left-Sided Cancer	83%	100%
Right-Sided Adenoma ≥ 1 cm	55%	58%
Left-Sided Adenoma ≥ 1 cm	53%	63%

FIGURE 3. ASSAY PERFORMANCE IN THIS STUDY

98% Sensitivity Cancer

59% Sensitivity Pre-Cancer (Advanced Adenoma ≥ 1cm)

91% Specificity

RESULTS

- The sDNA multi-target test detected 98% of CRC (45/46), 59% of precursor lesions ≥1.0 cm (19/32) at a specificity of 91% (251/277) (Figure 3).
- By CRC stage, the sDNA multi-target test detected 100% of stages I and II CRC, 92% of stage III CRC, 96% of the most curable stages I-III CRC, and 100% of stage IV CRC cases (Figure 4a).
- The sDNA multi-target test was comparably sensitive for proximal (94%) and distal (100%) CRC, and for proximal (58%) and distal (63%) advanced precursor lesions (Figure 4b).

CONCLUSIONS

This study represents the first clinical assessment of an optimized sDNA multi-target screening test for colorectal cancer (CRC) and advanced adenomas. Compared to previous studies (Table 2), these data demonstrate higher yield of an optimized sDNA multi-target approach for the detection of both CRC and precursor lesions (advanced adenoma). We corroborate our previous findings that polyp size but neither site nor CRC stage affects detection rates. These data established initial cutoff specifications that will be used in further verification and validation studies, including the Deep-C validation study.