INLAND EMPIRE HEALTH PLAN

IEHP UM Subcommittee Approved Authorization Guidelines
Colorectal Cancer Screening with Cologuard™ for Medicare Beneficiaries

Policy:
Based on our review of the available evidence, the IEHP UM Subcommittee adopts the use of Cologuard™ - a multi-target stool DNA test – as a colorectal cancer screening test for asymptomatic, average risk Medicare beneficiaries, aged 50 to 85 years. The current recommendation is to perform the test at 3 year intervals.

Criteria:
1. Age 50 to 85 years
2. 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 or fecal immunochemical test), and
3. 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 cancer or adenomatous polyps, familial adenomatous polyposis, or hereditary nonpolyposis colorectal cancer).
4. Medicare beneficiary; not a covered benefit for all other lines of business.

CPT Code: 81528

Centers for Medicare & Medicaid Services (CMS):
Decision Memo for Screening for Colorectal Cancer – Stool DNA Testing (CAG-00440N), October 9, 2014[5]:

"The Centers for Medicare & Medicaid Services (CMS) has determined that the evidence is sufficient to cover Cologuard™ – a multitarget stool DNA test – as a colorectal cancer screening test for asymptomatic, average risk beneficiaries, aged 50 to 85 years."

"Overall, the Cologuard™ test is a suitable screening test for CRC, as demonstrated primarily in a large well conducted study (Imperiale, 2014) and has significantly higher sensitivity compared to the other currently covered fecal screening tests. As a suitable screening test likely to lead to improvements in health outcomes, the evidence is sufficient to conclude that CRC screening in Medicare beneficiaries using the Cologuard™ test is appropriate for prevention or early detection. This is consistent the United States Multi-Society Task Force (2008), American

College of Radiology and American Cancer Society (2008) who have already added sDNA testing to their list of recommended CRC screening tests based on a predecessor test. The American College of Gastroenterology (2009) and USPSTF (2008) have an insufficient grading, but are likely to reconsider based on the new data from Imperiale (2014)."

Medi-Cal:

Procedure Code Inquiry performed by provider: PHP305306 on Friday, April 29, 2016 at 2:41:14 PM

81528 ONCOLOGY COLORECTAL SCR		
Procedure Level : **CPT4 code**	Procedure Type : **Pathology**	
Effective Date : **01/01/2016**	End Date : **12/31/2069**	Follow Up Days : **0**
Gender : **Both**	Min Age : **0**	Max Age : **99**
Medi-Cal Max Allowable Amount : **$0.00**	Split Bill professional percentage : **0.0%**	
This procedure is not a covered benefit. No TAR or medi-reservation required.		

Professional Society Recommendations:

1. **USPSTF, November 4, 2008**[11]
    a. The USPSTF screening for colorectal cancer using fecal occult blood testing, sigmoidoscopy, or colonoscopy in adults, beginning at age 50 years and continuing until 75 years. (Grade A recommendation)
    b. The USPSTF recommends against routine screening for colorectal cancer in adults 76 to 85 years of age. There may be consideration that support colorectal cancer screening in an individual patient (Grade C recommendation)
    c. The USPSTF recommends against screening for colorectal cancer in adults older than age 85 years (Grade D recommendation)
    d. The USPSTF concludes that evidence is insufficient to assess the benefits and harm of computed tomographic colonography and fecal DNA testing as screening modalities for colorectal cancer (Grade I statement). CMS notes this recommendation was specific to a predecessor test. The Cologuard™ test was not evaluated.
2. **American College of Gastroenterology Guidelines for Colorectal Cancer Screening 2008, March 2009**[4]

a. Preferred CRC screening recommendations
    i. Cancer prevention tests should be offered first. The preferred CRC prevention test is colonoscopy every 10 years, beginning at age 50. (Grade 1B) Screening should begin at age 45 years in African Americans (Grade 2C)
    ii. Cancer detection tests should be offered to patients who decline colonscopy or another cancer prevention test. The preferred cancer detection test is annual FIT for blood (Grade 1B)
b. Alternative CRC prevention tests
    i. Flexible sigmoidoscopy every 5-10 years (Grade 2B)
    ii. CT Colonography every 5 years (Grade 1C)
c. Alternative cancer detection tests
    i. Annual Hemoccult Sensa (Grade 1B)
    ii. Fecal DNA testing every 3 years (Grade 2B). CMS notes that this recommendation was based on a predecessor test. The Cologuard™ test was not evaluated.

3. **American Cancer Society Colorectal Cancer Advisory Group; US Multi-Society Task Force; American College of Radiology Colon Cancer Committee. Screening and surveillance for the early detection of colorectal cancer and adenomatous polyps, May 2008**[3]
    a. Specifically for fecal DNA testing: "sDNA-Conclusions and Recommendations. In previous assessments of the performance of sDNA, both the ACS and the USPSTF concluded that data were insufficient to recommend screening with sDNA for average-risk individuals. Based on the accumulation of evidence since the last update of these guidelines, the panel concluded that there now are sufficient data to include sDNA as an acceptable option for CRC screening.
4. **Smith RA, et al. Cancer screening the United States, 2014: a review of current American Cancer Society guidelines and current issues in cancer screening, January-February 2014**[10]
    a. Stool DNA testing is listed as a recommendation starting at age 50, interval uncertain.
    b. Smith notes that the stool DNA test approved for colorectal cancer screening in 2008 was no longer commercially available. He continues that new stool DNA tests are presently undergoing evaluation and may become available at some future time. Again, CMS notes that this recommendation was based on a predecessor test. The Cologuard™ was not evaluated.

Studies:

Reference	Study Type	Treatment	N	Results	Conclusions
Ahlquist, et al, 2008[2]	Blinded, multi-center, Cross-sectional	Three Fecal blood cards (Hemoccult and Hemoccult Sensa) were compared with one fecal DNA card using a precommercial 23-marker assay (SDT-1) and one fecal DNA card using a novel test targeting 3 markers (SDT-2).	4, 482	Sensitivity for screen-relevant neoplasms was 20% by SDT-1, 11% by Hemoccult (P = 0.020), 21% by HemoccultSensa (P = 0.80). Specificity was 96% by SDT-1, compared with 98% by Hemoccult (P < 0.001) and 97% by HemoccultSensa (P = 0.20). Stool DNA test 2 detected 46% of screen-relevant neoplasms, compared with 16% by Hemoccult (P < 0.001) and 24% by HemoccultSensa (P < 0.001). Stool DNA test 2 detected 46% of adenomas 1 cm or larger, compared with 10% by Hemoccult (P < 0.001) and 17% by HemoccultSensa (P < 0.001). Among colonoscopically normal patients, the positivity rate was 16% with SDT-2, compared with 4% with Hemoccult (P = 0.010) and 5% with HemoccultSensa (P = 0.030).	Stool DNA test 2 detects significantly more neoplasms than does Hemoccult or HemoccultSensa, but with more positive results in colonoscopically normal patients. Higher sensitivity of SDT-2 was particularly apparent for adenomas.
Ahlquist, et al, 2011[1]	Blinded, multi-center, Case-Control	Archived stool samples collected from 252 patients with colorectal cancer, 133 with adenomas > 1 cm, and 293 with normal colonoscopies; Samples were tested using a sDNA that detected 4 methylated genes,	385 (cases); 293 (controls)	The sDNA test identified 85% of patients with CRC and 54% of patients with adenomas ≥1 cm with 90% specificity. The test had a high rate of detection for all nonmetastatic stages of CRC (aggregate 87% detection rate for CRC stages I-III). Detection rates increased with	Early-stage CRC and large adenomas can be detected throughout the colorectum and with high levels of accuracy by the sDNA test. Neoplasm size, but not anatomical site, affected detection rates.

Reference	Study Type	Treatment	N	Results	Conclusions
		mutant KRAS form, and alpha-actin gene, and quantified hemoglobin.		adenoma size: 54% ≥ 1 cm, 63% >1 cm, 77% >2 cm, 86% >3 cm, and 92% >4 cm (P < .0001). Sensitivities for detection of CRC and adenoma did not differ with lesion site.	
Imperiale, et al, 2014[7]	Cross-sectional	Comparison of a stool DNA test with FIT in persons at average risk for colorectal cancer. The DNA test includes *KRAS* mutations, aberrant *NDRG4* and *BMP3* methylation, and β-actin, plus a hemoglobin immunoassay. Results were generated with the use of a logistic-regression algorithm. Tests were processed independently of colonoscopic findings	9,989	65 (0.7%) had colorectal cancer and 757 (7.6%) had advanced precancerous lesions (advanced adenomas or sessile serrated polyps measuring ≥1 cm in the greatest dimension) on colonoscopy. The sensitivity for detecting colorectal cancer was 92.3% with DNA testing and 73.8% with FIT (P=0.002). The sensitivity for detecting advanced precancerous lesions was 42.4% with DNA testing and 23.8% with FIT (P<0.001). The rate of detection of polyps with high-grade dysplasia was 69.2% with DNA testing and 46.2% with FIT (P=0.004); the rates of detection of serrated sessile polyps measuring 1 cm or more were 42.4% and 5.1%, respectively (P<0.001). Specificities with DNA testing and FIT were 86.6% and 94.9%, respectively (P<0.001). The numbers of persons who would need to be screened to detect one cancer were 154 with colonoscopy, 166 with DNA testing, and 208	In asymptomatic persons at average risk for colorectal cancer, multitarget stool DNA testing detected significantly more cancers than did FIT but had more false positive results.

Reference	Study Type	Treatment	N	Results	Conclusions
				with FIT.	
Lidgard, et al, 2013[8]	Blinded, multi-center, Case-Control	Cases included CRC (n = 93), advanced adenoma (AA) (n = 84), or sessile serrated adenoma ≥1 cm (SSA) (n = 30); controls included nonadvanced polyps (n = 155) or no colonic lesions (n = 641). Samples were analyzed by using an automated multi-target sDNA assay to measure β-actin (a marker of total human DNA), mutant KRAS, aberrantly methylated BMP3 and NDRG4, and fecal hemoglobin. Data were analyzed by a logistic algorithm to categorize patients as positive or negative for advanced colorectal neoplasia.	207 (cases); 796 (controls)	At 90% specificity, sDNA analysis identified individuals with CRC with 98% sensitivity. Its sensitivity for stage I cancer was 95%, for stage II cancer it was 100%, for stage III cancer it was 96%, for stage IV cancer it was 100%, and for stages I-III cancers it was 97% (nonsignificant P value). Its sensitivity for advanced precancers (AA and SSA) ≥1 cm was 57%, for >2 cm it was 73%, and for >3 cm it was 83%. The assay detected AA with high-grade dysplasia with 83% sensitivity.	We developed an automated, multi-target sDNA assay that detects CRC and premalignant lesions with levels of accuracy previously demonstrated with a manual process. This automated high-throughput system could be a widely accessible noninvasive approach to general CRC screening.
Skally, et al, 2011[9]	Systematic Review	Studies included undertook an economic evaluation of fDNA compared with other relevant screening modalities and/or no screening.	7 articles	fDNA was cost-effective when compared with no screening in six studies. Compared with other screening modalities, fDNA was not considered cost-effective in any of the base-case analyses; in five studies it was dominated by all alternatives considered. Sensitivity analyses identified cost, compliance, and test	On the basis of the available (albeit limited) evidence, while fDNA is cost-effective when compared with no screening, it is currently dominated by most of the other available screening options. Cost and test performance appear to be the

Reference	Study Type	Treatment	N	Results	Conclusions
				parameters as key influential parameters. In general, poor presentation of "study design" and "data collection" details lowered the quality of included articles.	main influences on cost-effectiveness.

Background:

Colorectal cancer (CRC) is the fourth most common cancer and the second leading cause of cancer deaths in the United States. In 2013 the National Institutes of Health (NIH) National Cancer Institute (NCI) estimated the incidence of CRC at over 140,000 in the United States with a median age at diagnosis of 68 years. Overall mortality rates have declined over the past decade. Primary prevention, early detection and early treatment have contributed to the reduction in mortality, however, CRC was estimated to account for over 50,000 deaths in 2013, with a median age at death of 74 years.

Medicare currently covers several screening methods for colorectal cancer, although utilization of these methods is suboptimal. Cologuard™ provides another option that is technologically advanced, non-invasive and recommended to occur at less frequency than other methods, which may result in higher compliance. The Cologuard™ test performance has been shown to be significantly better in detecting advanced adenomas and cancers than the current fecal immunochemical test (Imperiale, 2014). Based on a systematic review of the evidence, CMS found that colorectal cancer screening in Medicare beneficiaries using the Cologuard™ test is appropriate for the prevention or early detection of illness or disability.

Cologuard™ is a stool DNA (sDNA) test that detects molecular markers of altered DNA that are contained in the cells shed by CRC and pre-malignant colorectal epithelial neoplasia. It evaluates specific DNA markers (methylation of NDRG4 and BMP3, point mutations of K-ras, and quantitative B-actin) and fecal hemoglobin (Fecal Immunochemical Test (FIT)) using a propriety algorithm that produces a composite score that is interpreted as positive or negative. A positive result needs to be followed by a diagnostic colonoscopy. The current recommended frequency of screening using Cologuard™ is every 3 years.

The Cologuard™ benefit will be limited to Medicare beneficiaries at this time. This is due to the inconsistent current recommendations among the professional societies, as well as the availability of alternative methods for colon cancer screening, including colonoscopy, which is the gold standard. Questions remain, also, regarding the optimal frequency of interval screening with Cologuard™. The manufacturer has committed to conducting a follow-up post approval

study, as required by the FDA, to generate additional evidence to address longer term outcomes and frequency.

Effective Date: *June 09, 2015* **Reviewed Annually:** *November 9, 2016*

Revised:
May 18, 2015 May 11, 2016

Bibliography:

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