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NCCN Guidelines Panel: On behalf of Exact Sciences Corporation, we respectfully request that the NCCN Colorectal Cancer (CRC) Screening Panel for Detection, Prevention, and Risk Reduction review the enclosed data and other considerations below for FIT-DNA-based testing (mt-sDNA; Cologuard®) to inform updates to the NCCN Guidelines for CRC Screening and incorporate the changes noted below.

FDA Approval: The mt-sDNA test is indicated to screen adults of either sex, ages 45 years or older, who are at average risk for CRC.

Specific Changes: We would like to respectfully request one change to the Algorithm section for Average Risk screening and two changes to the Discussion section under CRC Screening Modalities: FIT-DNA-based or Multi-target Stool DNA Test for the panel's consideration:

1. Algorithm section: Replace the name 'FIT-DNA-based testing' in the Algorithm (*see CSCR-3*) and all corresponding text with 'mt-sDNA test', which is a unique FDA-approved screening method.

   Rationale: Use of the terminology 'FIT-DNA' is inaccurate and confusing for providers, implying that results are expected for each test marker rather than a single, composite result based on algorithmic analysis of the test components; however, reporting a single, qualitative test result is required by the FDA label, which does not permit separate reporting of individual quantitative DNA molecular and protein-based FIT results.

2. Discussion section: Include the 89.8% specificity for the mt-sDNA test as compared to negative colonoscopy findings (in addition to 86.6% specificity, *see MS-13*).

   Rationale: It is important to note that the pivotal study for the mt-sDNA test also includes the specificity for the test at 89.8% as compared to negative colonoscopy; therefore, including this 89.8% specificity for negative colonoscopy in the Discussion section allows for objective comparison and is consistent with mt-sDNA specificity referenced by other guideline-making bodies, such as the American Cancer Society 2018 CRC Screening Guideline and the modeling underlying the 2016 USPSTF CRC Screening Recommendation.

3. Discussion section: Reconsider the statement, "many more patients were excluded because of problems with mt-sDNA testing than because of problems with FIT," (*see MS-14*) given that the clinical experience with mt-sDNA testing, which includes robust patient and provider navigation support to facilitate test completion, is markedly different than the approach used in the 2014 pivotal research study.

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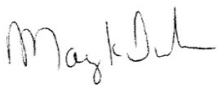
Rationale: Inclusion of this statement gives an inaccurate impression that mt-sDNA testing has a lower adherence rate than FIT, which is not supported by recently published literature demonstrating high adherence rates with the mt-sDNA test; further, assessing test completion was not part of the study design or endpoints for Imperiale et al, and real-world collection and shipping conditions for FIT are markedly different than the collection processes executed by Imperiale et al.

The following articles are submitted in support of these proposed changes.

1. Imperiale TF, Ransohoff DF, et al. Multitarget stool DNA testing for colorectal-cancer screening. N Engl J Med. 2014;371(2):187-188.
2. Wolf AMD, Fontham ETH, et al. Colorectal cancer screening for average-risk adults: 2018 guideline update from the American Cancer Society. CA Cancer J Clin. 2018 Jul;68(4):250-281.
3. Bibbins-Domingo K, Grossman DC, et al. Screening for Colorectal Cancer: US Preventive Services Task Force Recommendation Statement. JAMA. 2016;315(23):2564-2575.
4. Weiser E, Parks PD, et al. Cross-sectional adherence with the multi-target stool DNA test for colorectal cancer screening: Real-world data from a large cohort of older adults. J Med Screen. 2020 Feb 13:969141320903756.
5. Finney Rutten LJ, Jacobson DJ, et al. Colorectal cancer screening completion: An examination of differences by screening modality. Prev Med Rep. 2020 Sep 11;20:101202.
6. Limburg PJ, Mahoney DW, et al. Comparison of Tissue-Based Molecular Markers in Younger versus Older Patients with Colorectal Neoplasia. Cancer Epidemiol Biomarkers Prev. 2020 May 28.
7. Olson JE, Kirsch EJ, et al. Colorectal cancer outcomes after screening with the multi-target stool DNA assay: protocol for a large-scale, prospective cohort study (the Voyage study). BMJ Open Gastroenterol. 2020 Feb 19;7(1):e000353.
8. Eckmann JD, Ebner DW, et al. Multitarget Stool DNA Screening in Clinical Practice: High Positive Predictive Value for Colorectal Neoplasia Regardless of Exposure to Previous Colonoscopy. Am J Gastroenterol. 2020 Apr;115(4):608-615.
9. Prince M, Lester L, et al. Multitarget stool DNA tests increases colorectal cancer screening among previously noncompliant Medicare patients. World J Gastroenterol. 2017 Jan 21;23(3):464-471.

We would be happy to discuss any of these requests in further detail.

Sincerely,



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