

Sept. 28<sup>th</sup>, 2020

Re: Submission Request – Colorectal Cancer Screening Guidelines

Submitted by:

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Date of request: Sept 28<sup>th</sup>, 2020

NCCN Guidelines Panel: Colorectal Cancer Screening Panel

On behalf of Epigenomics, we respectfully request the NCCN Colorectal Cancer Screening Panel consider:

- Adapting the CRC screening guideline to formally incorporate Epi proColon (methylated SEPT9) as a CRC screening option for patients who refuse other screening modalities and remove the ‘not recommended’ language.
- Updating the guideline to indicate an annual interval for use of the test.
- Modifying the flowcharts to include testing with blood-based mSept9 as an option for patients refusing other screening modalities (suggested flow chart updates attached)

Supporting Evidence & Rationale:

Peterse E., Meester R., de Jonge L., Omidvari A., Alarid-Escudero F., Knudsen A., Zauber A., & I. Lansdorp-Vogelaar - JNCI in press. <https://pubmed.ncbi.nlm.nih.gov/32761199/> (attached)

- This CISNET study used the MISCAN-Colon model to assess both the clinical utility and cost-effectiveness of different CRC screening tests in comparison to FIT and colonoscopy
- An annual interval for mSEPT9 was determined to be optimal for clinical and health economic benefits
- Annual mSEPT9 showed clinical benefits superior to annual FIT and Cologuard every three years as exemplified by the number of CRC cases and deaths averted.
- For those resistant to screening by FIT or colonoscopy, annual mSEPT9 was the “test of choice” over all other non-invasive methods analyzed including Cologuard, CTC, and the pill cam
- Epi proColon performed annually results in less colonoscopies administered to a screening population as compared to the gold-standard of colonoscopy once every ten years.

D'Andrea E, Ahnen DJ, Sussman DA, Najafzadeh M. Quantifying the impact of adherence to screening strategies on colorectal cancer incidence and mortality. *Cancer Med* 2020; 9(2): 824-36. (attached)

- In this study, the impact of CRC screening on cancer incidence and mortality were characterized using another independent and strenuously validated microsimulation model. In addition, the study analyzed the impact of uptake /adherence to testing strategies on long-term clinical outcomes. Epi proColon was found to deliver benefits

equivalent to those of other currently guideline-recommended screening strategies assuming perfect adherence for all testing modalities.

- At uptake / adherence levels closer to those observed in real clinical practice (non-perfect adherence), Epi proColon outperformed all the other methods
- Based on a harms to benefits analysis using thresholds set by ACS and USPSTF, an annual interval was determined to be optimal for Epi proColon.
- All non-invasive methods had significant clinical impact compared with no screening
- Epi proColon performed annually results in less total colonoscopies (less harms) administered to a population as compared to the gold-standard of colonoscopy once every ten years.

In further support of the microsimulation data, a number of studies in the US and Europe have shown the positive impact of blood-based screening uptake amongst patients unwilling to be screened by colonoscopy or stool-based testing. For German patients refusing colonoscopy, Adler et.al. (1) showed that 83% of patients were willing to have a blood test, and that in combination with an offer of FIT they achieved a 97% screening rate. Similarly, in a study in two large US health systems (Kaiser-Permanente and Geisinger) Liles et. al. (2) reported that for patients previously non-compliant with screening, nearly all (99%) accepted blood testing when offered. More recently, in a study of patients in the VA population who had a history of non-compliance, Liang et.al.(3) showed that including an offer of blood-based testing increased screening rates. Finally, in an ongoing study of care delivery through Health Fairs in Miami, Ioannou et.al. (4) showed that offering a blood test substantially increased CRC screening rates. In combination, these reports provide direct evidence for the value of blood-based screening using mSEPT9.

The 2020 guideline indicated that the mSEPT9 test could be considered for patients refusing other screening modalities. We request that the committee incorporate this in the flow diagram, indicating this option for the unscreened (that is, those resistant to other recommended screening methods). We consider this an appropriate approach to reflect the FDA-approved labeling of the test, which explains that the test is indicated for those patients who are not completing CRC screening.

With best regards,



Theo deVos, PhD  
VP Clinical & Scientific Affairs



Jorge Garces, PhD  
President & CSO

Additional References:

1. Adler A, Geiger S, Keil A, et al. Improving compliance to colorectal cancer screening using blood and stool based tests in patients refusing screening colonoscopy in Germany. *BMC Gastroenterol.* 2014;14:183.
2. Liles EG, Coronado GD, Perrin N, et al. Uptake of a colorectal cancer screening blood test is higher than of a fecal test offered in clinic: a randomized trial. *Cancer Treat Res Commun.* 2017;10:27-31.
3. Peter S. Liang, Anika Zaman, Anne M. Kaminsky, Yongyan Cui, Gabriel Castillo, Craig T. Tenner, Scott E. Sherman, Jason A. Dominitz. Tu1828 - Offering a Blood Test Increases Colorectal Cancer Screening Uptake in Individuals who have declined colonoscopy and fecal immunochemical testing May 2020 *Gastroenterology* 158(6):S-1178
4. Ioannou S, Sutherland K, Iyengar R, et al. Su1667 – Increasing uptake of colon cancer screening in a medically underserved population with the addition of blood-based testing. *Gastroenterology* 2019;156:S-604–4

Name: Institution: Epigenomics Inc.

Guideline Page	Comments / Request / References																																			
2020 CSCR-3 Proposed Changes	1. New Proposed Screening Flow Chart. a. Delete comment H. Replace with footnote # “#FDA approved mSEPT9 blood test.” b. Incorporate path for ‘non-compliant’ patients																																			
New CSCR3	<table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th style="width: 20%;">RISK STATUS</th> <th style="width: 30%;">SCREENING MODALITY AND SCHEDULE<sup>g,h,i</sup></th> <th colspan="2" style="width: 50%;">EVALUATION OF SCREENING FINDINGS</th> </tr> </thead> <tbody> <tr> <td rowspan="10">                     Average risk:                      • Age ≥50 y<sup>e</sup>                      • No history of adenoma or SSP<sup>f</sup> or CRC                      • No history of IBD                      • Negative family history for CRC or confirmed advanced adenoma (ie, high-grade dysplasia, ≥1 cm, villous or tubulovillous histology) or an advanced SSP<sup>d,f</sup> (≥1 cm, any dysplasia)                 </td> <td>Colonoscopy<sup>j</sup></td> <td>No polyps<sup>l</sup></td> <td>Rescreen with any modality in 10 y<sup>g</sup></td> <td rowspan="2">                     Hyperplastic polyps &lt;1 cm in size<sup>n</sup> → Rescreen with any modality in 10 y<sup>g</sup>                      Adenomas or SSP of any size or hyperplastic polyps ≥1 cm in size<sup>o</sup> → <a href="#">See Follow-up of Clinical Findings: Polyp Found at Colonoscopy (CSCR-5)</a> </td> </tr> <tr> <td>or</td> <td>Polyp(s)<sup>l</sup></td> <td>Polypectomy</td> </tr> <tr> <td>Stool-based: • High-sensitivity guaiac-based or immunochemical-based testing<sup>k</sup> • FIT-DNA-based testing</td> <td>Negative</td> <td>Rescreen with any modality in 1 y<sup>g</sup></td> <td rowspan="2">                     Follow pathway above                 </td> </tr> <tr> <td>or</td> <td>Positive</td> <td>Colonoscopy<sup>m</sup></td> </tr> <tr> <td>or</td> <td>Flexible sigmoidoscopy</td> <td>→ <a href="#">See CSCR-4</a></td> <td></td> </tr> <tr> <td>or</td> <td>CT colonography (CTC)</td> <td>→ <a href="#">See CSCR-4</a></td> <td></td> </tr> <tr> <td>or</td> <td>Blood-based Plasma mSEPT9<sup>a</sup></td> <td>→ <a href="#">See CSCR-#</a></td> <td></td> </tr> <tr> <td colspan="4">                     # FDA approved mSEPT9 blood test                 </td> </tr> </tbody> </table>	RISK STATUS	SCREENING MODALITY AND SCHEDULE <sup>g,h,i</sup>	EVALUATION OF SCREENING FINDINGS		Average risk: • Age ≥50 y <sup>e</sup> • No history of adenoma or SSP <sup>f</sup> or CRC • No history of IBD • Negative family history for CRC or confirmed advanced adenoma (ie, high-grade dysplasia, ≥1 cm, villous or tubulovillous histology) or an advanced SSP <sup>d,f</sup> (≥1 cm, any dysplasia)	Colonoscopy <sup>j</sup>	No polyps <sup>l</sup>	Rescreen with any modality in 10 y <sup>g</sup>	Hyperplastic polyps <1 cm in size <sup>n</sup> → Rescreen with any modality in 10 y <sup>g</sup> Adenomas or SSP of any size or hyperplastic polyps ≥1 cm in size <sup>o</sup> → <a href="#">See Follow-up of Clinical Findings: Polyp Found at Colonoscopy (CSCR-5)</a>	or	Polyp(s) <sup>l</sup>	Polypectomy	Stool-based: • High-sensitivity guaiac-based or immunochemical-based testing <sup>k</sup> • FIT-DNA-based testing	Negative	Rescreen with any modality in 1 y <sup>g</sup>	Follow pathway above	or	Positive	Colonoscopy <sup>m</sup>	or	Flexible sigmoidoscopy	→ <a href="#">See CSCR-4</a>		or	CT colonography (CTC)	→ <a href="#">See CSCR-4</a>		or	Blood-based Plasma mSEPT9 <sup>a</sup>	→ <a href="#">See CSCR-#</a>		# FDA approved mSEPT9 blood test			
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Guideline Page	Comments / Request / References
<p>Proposed Changes: New CSCR-# for non-compliant patients</p>	<p>1. New Proposed Screening Flow Chart</p> <ol style="list-style-type: none"> <li>Add 'decline other screening methods' to patient description</li> <li>Incorporate blood based path for 'non-compliant' patients</li> <li>Delete footnote h,k,l,n,o for this page</li> <li>Add footnote # "FDA approved mSEPT9 blood test"</li> <li>Edit footnote M "When a screening stool or blood based test..."</li> </ol>
<p>New CSCR-#</p>	<p><b>RISK STATUS</b></p> <ul style="list-style-type: none"> <li>Average risk:             <ul style="list-style-type: none"> <li>• Age ≥50 y<sup>e</sup></li> <li>• No history of adenoma or SSP<sup>f</sup> or CRC</li> <li>• No history of IBD</li> <li>• Negative family history for CRC or confirmed advanced adenoma (ie, high-grade dysplasia, ≥1 cm, villous or tubulovillous histology) or an advanced SSP<sup>d,f</sup> (≥1 cm, any dysplasia)</li> </ul> </li> <li>• Decline other screening methods</li> </ul> <p><b>SCREENING MODALITY AND SCHEDULE<sup>g,h,i</sup></b></p> <p>Blood-based Plasma mSEPT9<sup>#</sup></p> <p><b>EVALUATION OF SCREENING FINDINGS</b></p> <ul style="list-style-type: none"> <li>Positive → Colonoscopy<sup>h</sup> → Follow Colonoscopy Pathway (CSCR3)</li> <li>Negative → Rescreen with any modality in 1 yr</li> </ul> <p>... stool or blood based ...</p> <p><b>Footnotes:</b></p> <p><sup>d</sup> Advanced SSPs are generally considered to have a comparable cancer risk and are managed similarly to advanced adenomas.</p> <p><sup>e</sup> CRC screening is recommended in adults aged 50–75 years. The decision to screen between ages 76–85 years should be individualized and include a discussion of the risks and benefits based on comorbidity status and estimated life expectancy. Eligible individuals who have not been previously screened are most likely to benefit in this age group.</p> <p><sup>f</sup> For details on classification, see footnote c on CSCR-1.</p> <p><sup>g</sup> See Screening Modality and Schedule (CSCR-A).</p> <p><sup>h</sup> A blood test that detects circulating methylated SEPT9 DNA has been FDA approved for CRC screening for those who refuse other screening modalities. It is not recommended for routine screening. The interval for repeating testing is unknown.</p> <p><sup>i</sup> Screening should be individualized and include a discussion of the risks and benefits of each modality.</p> <p><sup>j</sup> If colonoscopy is incomplete or the preparation is suboptimal, consider either repeating colonoscopy within a year or screening with another modality. (Johnson DA, et al. Gastroenterology 2014;147:903-924).</p> <p><sup>k</sup> Based on recent evidence, fecal immunochemical test (FIT) has been shown to have superior sensitivity to guaiac-based tests. However, guaiac-based testing has been shown to reduce mortality from CRC and high-sensitivity fecal occult blood test (FOBT) is a reasonable alternative if an immunochemical test cannot be used. (Rabeneck L, et al. Can J Gastroenterol 2012;26:131-147; Scholefield JH, et al. Gut 2012;61:1036-1040).</p> <p><sup>l</sup> The term "polyp" refers to both polyp and nonpolypoid (flat) lesions.</p> <p><sup>m</sup> When a screening stool-based test is positive, a colonoscopy is recommended for further evaluation. Recommendations for an appropriate time frame for follow-up colonoscopy in this population lack a strong evidence base, but a large observational study reported significantly higher risks for CRC and advanced-stage disease when follow-up occurred 10 months or later with a trend towards increased cancer risk observed as early as 6 months after an abnormal result. Thus, we recommend that follow-up colonoscopy is completed ideally within 6 to 10 months after an abnormal stool-based test. (Corley DA, et al. JAMA 2017;317:1631-1641).</p> <p><sup>n</sup> There are insufficient data to determine whether individuals with small (&lt;1 cm) hyperplastic polyps proximal to the sigmoid colon should be considered at increased risk and managed differently.</p> <p><sup>o</sup> There are limited data to support whether individuals with hyperplastic polyps ≥1 cm in size represent an increased risk group. Several analyses suggest that many of the larger polyps classified as hyperplastic in the past were re-classified as SSPs when reviewed by experts. For this reason, it is reasonable to follow patients with hyperplastic polyps ≥1 cm in size similarly to patients with SSPs, particularly if they have not been reviewed by an expert gastrointestinal pathologist.</p> <p><b># FDA approved mSEPT9 blood test</b></p>

Guideline Page	Comments / Request / References												
CSCR-A 2 of 5	<p>Delete footnote referring to the mSEPT9 blood test. Add the mSEPT9 blood test in the Screening Modality and Schedule Table:</p> <table border="1" data-bbox="430 394 1988 542"> <thead> <tr> <th data-bbox="430 394 743 467" rowspan="2">Screening Test</th> <th data-bbox="743 394 1052 467" rowspan="2">Recommended Testing Interval</th> <th colspan="2" data-bbox="1052 394 1675 467">Sensitivity</th> <th data-bbox="1675 394 1988 467" rowspan="2">Specificity</th> </tr> <tr> <th data-bbox="1052 467 1365 505">Colorectal Cancer</th> <th data-bbox="1365 467 1675 505">Advanced Adenoma</th> </tr> </thead> <tbody> <tr> <td data-bbox="430 505 743 542">mSEPT9 blood test</td> <td data-bbox="743 505 1052 542">Annually</td> <td data-bbox="1052 505 1365 542">68%<sup>1</sup></td> <td data-bbox="1365 505 1675 542">22%<sup>1</sup></td> <td data-bbox="1675 505 1988 542">80%<sup>1</sup></td> </tr> </tbody> </table> <p><sup>1</sup> Potter NT, Hurban P, White MN, et al. Validation of a real-time PCR-based qualitative assay for the detection of methylated SEPT9 DNA in human plasma. Clinical chemistry 2014; 60(9): 1183-91.</p>	Screening Test	Recommended Testing Interval	Sensitivity		Specificity	Colorectal Cancer	Advanced Adenoma	mSEPT9 blood test	Annually	68% <sup>1</sup>	22% <sup>1</sup>	80% <sup>1</sup>
Screening Test	Recommended Testing Interval			Sensitivity			Specificity						
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mSEPT9 blood test	Annually	68% <sup>1</sup>	22% <sup>1</sup>	80% <sup>1</sup>									
CSCR-A 5 of 5	<p>Update mSEPT9 blood test:</p> <p>mSEPT9 blood test</p> <ul style="list-style-type: none"> <li>• Recommended for patients declining other screening methods</li> <li>• Annual Interval recommended</li> <li>• Any positive test requires endoscopic evaluation</li> <li>•</li> </ul>												

Guideline Page	Comments / Request / References
MS-14	<p>Current Text: “The interval for repeat testing is uncertain and the NCCN Guidelines for CRC Screening (see CSCR-3 and CSCR-4 in the algorithm) do not recommend the SEPT9 DNA test for routine screening”</p> <p>Comment: Based on the two Microsimulation Studies (Peterse et.al. and D’Andrea et.al.) the optimal interval is annual testing. In addition, these studies indicate that this test is optimal for patients not completing endoscopic or stool based testing. Therefore we propose to modify this language to:</p> <p>“An annual interval for repeat testing is recommended. The NCCN Guidelines for CRC Screening (see CSCR-3 and CSCR-# in the algorithm) recommend the SEPT9 DNA test as an option for non-compliant patients”</p>