epigenomics

Sept. 28th, 2020
Re: Submission Request – Colorectal Cancer Screening Guidelines

Submitted by:
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Date of request: Sept 28th, 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

Theo deVos, PhD
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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.

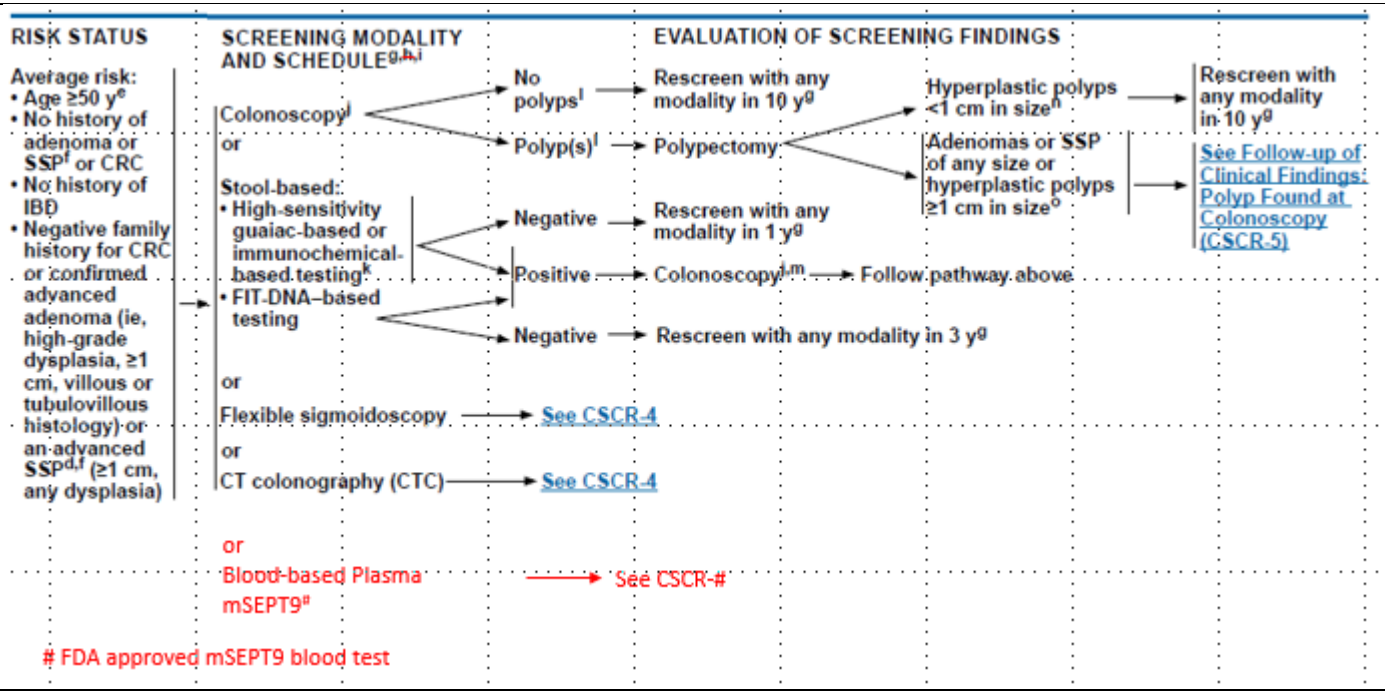
2. Liles EG, Coronado GD, Perrin N, et al. Uptake of a colorectal cancer screening blood test is higher than of a fecal test offered in clinic: a randomized trial. Cancer Treat Res Commun. 2017;10:27-31.

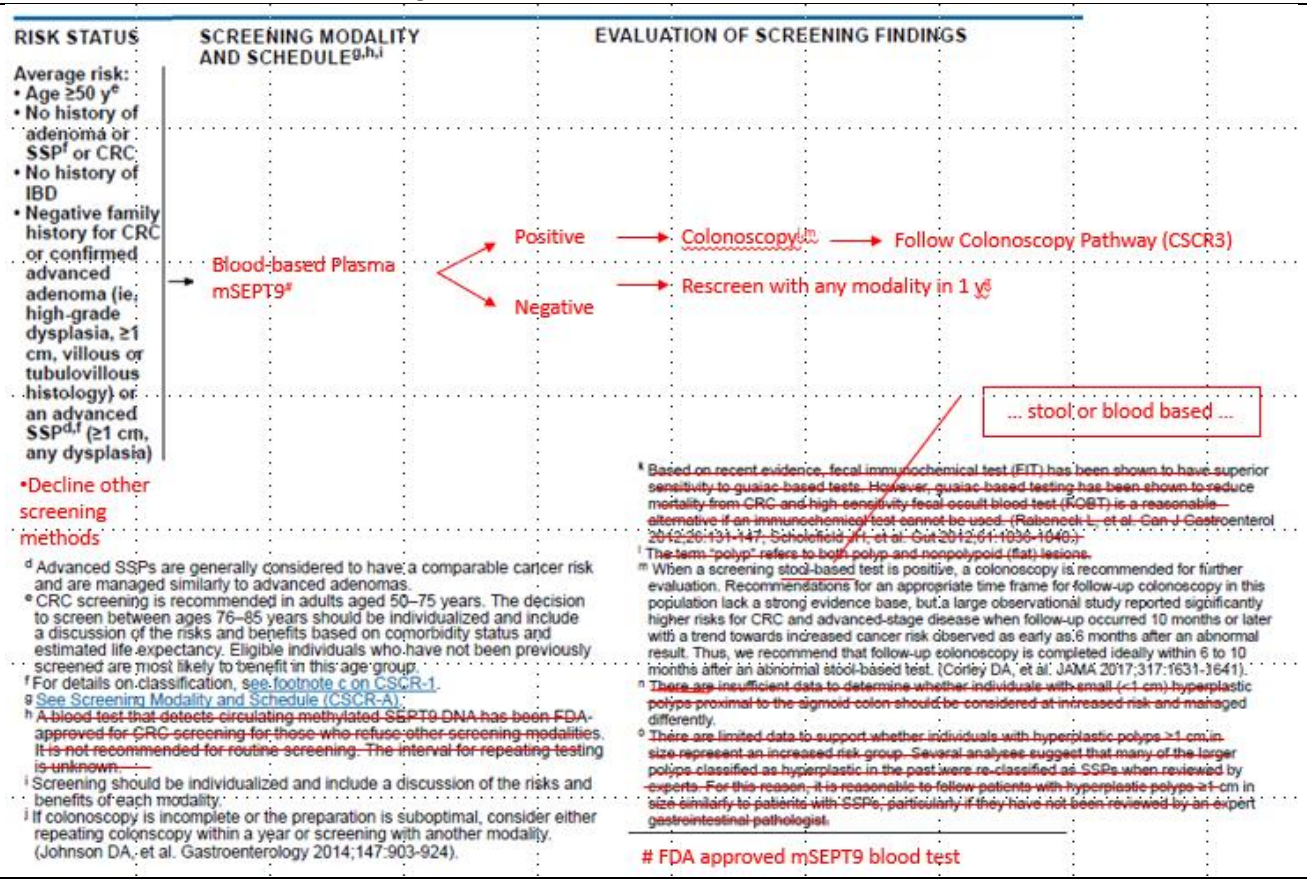
3. Peter S. Liang, Anika Zaman, Anne M. Kaminsky, Yongyan Cui, Gabriel Castillo, Craig T. Tenner, Scott E. Sherman, Jason A. Dominitz. Tu1828 - Offering a Blood Test Increases Colorectal Cancer Screening Uptake in Individuals who have declined colonoscopy and fecal immunochemical testing May 2020 Gastroenterology 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

NCCN Colorectal Cancer Screening Guidelines – Institutional Review

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	

Guideline Page	Comments / Request / References
Proposed Changes: New CSCR-# for non-compliant patients	1. New Proposed Screening Flow Chart a. Add 'decline other screening methods' to patient description b. Incorporate blood based path for 'non-compliant' patients c. Delete footnote h,k,l n,o for this page d. Add footnote # "FDA approved mSEPT9 blood test" e. Edit footnote M "When a screening stool or blood based test…"
New CSCR-#	

<table>
<tr><th>Guideline Page</th><th>Comments / Request / References</th></tr>
<tr><td>CSCR-A 2 of 5</td><td>Delete footnote referring to the mSEPT9 blood test.
Add the mSEPT9 blood test in the Screening Modality and Schedule Table:

<table>
<tr><th rowspan="2">Screening Test</th><th rowspan="2">Recommended Testing Interval</th><th colspan="2">Sensitivity</th><th rowspan="2">Specificity</th></tr>
<tr><th>Colorectal Cancer</th><th>Advanced Adenoma</th></tr>
<tr><td>mSEPT9 blood test</td><td>Annually</td><td>68%[1]</td><td>22%[1]</td><td>80%[1]</td></tr>
</table>
[1] 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.</td></tr>
<tr><td>CSCR-A 5 of 5</td><td>Update mSEPT9 blood test:

mSEPT9 blood test
• Recommended for patients declining other screening methods
• Annual Interval recommended
• Any positive test requires endoscopic evaluation
•</td></tr>
</table>

Guideline Page	Comments / Request / References
MS-14	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" 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: "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"