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Promise and Perils of Blood-based Signatures for Detecting Early-Onset Colorectal Cancer

Siddharth Singh, MD, MS[1,2], **Samir Gupta, MD, MSCS**[1,3,4]

[1]Division of Gastroenterology, Department of Medicine, UC San Diego, La Jolla, California, USA

[2]Division of Biomedical Informatics, Department of Medicine, UC San Diego, La Jolla, California, USA

[3]Jennifer Moreno Veterans Affairs Medical Center, San Diego, CA

[4]Moores Cancer Center, University of California San Diego, La Jolla, CA

The incidence and mortality of early-onset colorectal cancer (EOCRC) is rising.[1] Efforts to identify and address the causes of EOCRC are underway but have not yet offered opportunities for risk reduction. In the meantime, efforts to reduce incidence and mortality must focus on screening and early detection, including with identification of high-risk populations. Two widely endorsed approaches for early detection and prevention include initiation of screening at age 45y for average-risk individuals, and early initiation of screening based on family history.[2–4] However, some average risk individuals may find current options for screening, such as colonoscopy and stool-based tests burdensome, many average risk individuals develop EOCRC before they are eligible for age-based initiation of screening at age 45y, and only a fraction of individuals at risk for EOCRC have a family history.[5] Novel, non-invasive options for screening, applicable to a broader age range of individuals under 50y, have potential to address these clinical practice gaps in early detection and prevention. Specifically, a blood-based screening test for EOCRC could be an ideal strategy for improving early detection and prevention.

In this issue of *Gastroenterology*, Nakamura, Hernández, Sharma, *et al*, present a novel approach for developing blood-based screening test that could be applicable to EOCRC, using a two-phase design with an initial biomarker discovery phase followed by independent

Corresponding author: Siddharth Singh, MD, MS Associate Professor of Medicine, Division of Gastroenterology, and Division of Biomedical Informatics, Department of Medicine, University of California San Diego, 9452 Medical Center Drive, ACTRI 1W501, La Jolla, CA 92037, U.S.A., sis040@ucsd.edu, Phone: 858-246-2352, Fax: 858-657-7259.

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validation in multiple clinical groups.[6] In the first phase, the investigators conducted genome-wide transcriptomic profiling to identify miRNA signatures increased in colonic tissue from patients with stage I/II EOCRC, compared with late-onset CRC and healthy controls. They identified a panel of 7 miRNAs that were uniquely and significantly overexpressed in EOCRC. To translate these findings into a blood-based liquid biopsy signature, these 7 miRNA tissue-based markers were tested for detectability in plasma samples, and a unique 4 miRNA liquid biopsy signature (hsa-miR-513a-5p, hsa-miR-628–3p, hsa-miR-193a-5p and hsa-miR-210) for detection of EOCRC was identified. These miRNAs serve as transcripts of several key genes associated with pathogenesis of various solid organ cancers. A training set of blood samples from 72 EOCRC cases and 45 non-cancer controls from Japan was used to optimize the signature, including with selection of positivity cutoffs, and subsequently applied to a validation set of 77 EOCRC cases and 65 non-cancer controls from Spain. In the training and validation cohorts, the estimates for area under the receiver operating curve (AUC) were 0.92 and 0.88, sensitivity were 90% and 82%, and specificity were 80% and 86%, respectively. Performance estimates were qualitatively similar for identifying early and late stage EOCRC, compared with non-disease controls. In a group of 10 patients who had the marker measured before and 3 months after surgical resection, miRNA marker levels decreased significantly, suggesting that the source of marker expression was the resected cancer, though expression values did not normalize.

Strengths of this study include the systematic biomarker discovery and validation approach taken in diverse groups, their focus on a high priority condition and longitudinal evaluation of biomarkers after surgery. As with most early discovery and validation efforts, several limitations must be considered in interpreting this work. First, test performance is invariably optimistic due to spectrum bias. Spectrum bias is of particular concern for case-control studies, which tend to overestimate sensitivity and specificity because they artificially exclude patients typically seen in the general population, such as asymptomatic patients with EOCRC in the pre-diagnostic period. Indeed, in the current study, patients included either had early and late stage EOCRC or were non-disease controls, and it is unclear the extent to which these groups represent the general population of adults at risk for EOCRC. Further, patients with advanced adenomas or low-risk adenomas were not included, and it is unclear whether adenomas secrete miRNAs detectable in serum, and what the discriminative ability of this signature would be for patients along the disease spectrum. There was limited clinical information on the cases and controls utilized for test development and validation. Absence of additional clinical characteristics leaves open the possibility that the miRNA expression signatures are associated with other factors driving EOCRC risk, such as smoking or obesity. While the observation that signatures decreased in a small sample of post-surgical patients argues against this possibility, variables such as smoking and obesity can also change before and after a major surgery.

Even if we assume that the impact of spectrum bias was limited, the available test characteristics need to be viewed through the lens of potential translation to clinical practice. Real-world test performance is closely linked to disease state prevalence – applying this test to patients with low pre-test probability of EOCRC will result in high rates of false positives. Let’s examine the impact of applying a screening test with the performance reported to a theoretical population of 100,000 individuals younger than age 50y (Table 1). The reported

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prevalence of EOCRC for this group is 0.013%.[7] With the current test characteristics, an estimated 14% of the population would have a positive test, yet the positive predictive value would be only 0.08%. Corresponding rates for fecal immunochemical test would be 4% test positivity, with a positive predictive value of 0.25%, assuming FIT performance in patients younger than 50 is at least as good as for older age groups.[8] These data demonstrate that an opportunity remains to optimize the specificity of the miRNA approach for EOCRC screening, and are consistent with the principle that high specificity is critically important to achieve for a population-based screening test.

This thought exercise brings up a common challenge. Basic and translational science are evolving at an incredible pace, with an ever increasing array of biologically plausible, mechanistically rational, and practically measurable candidate markers for cancer screening emerging. How can we frame and evolve early discoveries to strategies that can be viable for clinical practice? For a low prevalence condition such as EOCRC that requires an invasive, expensive follow up diagnostic test such as colonoscopy, we recommend that marker panels be optimized putting a higher emphasis on achieving a target specificity that is acceptable at a population level, rather than putting the biggest emphasis on sensitivity or the combination of sensitivity and specificity, often assessed as accuracy. Specific to the promising approach of measuring miRNA as reported by Nakamura, Hernández, Sharma and colleagues, one strategy could be to set the specificity threshold for cutoffs at 95%, or to work to select markers with this goal in mind. This will come at the expense of sensitivity, but the issue of sensitivity could be addressed by utilizing other complementary biologic markers that fill sensitivity gaps associated with miRNA. We anticipate that multi-omic, multi-marker panels, set with cutoffs to achieve high specificity, will ultimately provide opportunities to test sufficiently sensitive and specific blood tests in large cohort studies of populations at risk for EOCRC.

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REFERENCES

1. Burnett-Hartman AN, Lee JK, Demb J, et al. An Update on the Epidemiology, Molecular Characterization, Diagnosis, and Screening Strategies for Early-Onset Colorectal Cancer. Gastroenterology 2021;160:1041–1049. [PubMed: 33417940]
2. USPSTF, Davidson KW, Barry MJ, et al. Screening for Colorectal Cancer: US Preventive Services Task Force Recommendation Statement. JAMA 2021;325:1965–1977. [PubMed: 34003218]
3. Patel SG, May FP, Anderson JC, et al. Updates on Age to Start and Stop Colorectal Cancer Screening: Recommendations From the U.S. Multi-Society Task Force on Colorectal Cancer. Gastroenterology 2022;162:285–299. [PubMed: 34794816]
4. Rex DK, Boland CR, Dominitz JA, et al. Colorectal Cancer Screening: Recommendations for Physicians and Patients From the U.S. Multi-Society Task Force on Colorectal Cancer. Gastroenterology 2017;153:307–323. [PubMed: 28600072]
5. Gupta S, Bharti B, Ahnen DJ, et al. Potential impact of family history-based screening guidelines on the detection of early-onset colorectal cancer. Cancer 2020;126:3013–3020. [PubMed: 32307706]
6. Nakamura K, Hernandez G, Sharma GG, et al. A Liquid Biopsy Signature for the Detection of Patients with Early-Onset Colorectal Cancer. Gastroenterology 2022.

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7. Sinicrope FA. Increasing Incidence of Early-Onset Colorectal Cancer. N Engl J Med 2022;386:1547–1558. [PubMed: 35443109]
8. Gupta S Screening for Colorectal Cancer. Hematol Oncol Clin North Am 2022;36:393–414. [PubMed: 35501176]

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Table 1.

Test performance of the novel liquid biopsy signature vs. fecal immunochemical test in clinical practice in a theoretical population of 100,000 individuals under age 50y being screened for EOCRC.

Screening test	**Novel liquid biopsy signature**		**Fecal immunochemical test**	
Test performance	Sensitivity: 82%	Specificity: 86%	Sensitivity: 74%	Specificity: 96%
EOCRC prevalence	13 per 100,000 (0.013%)			
Number of individuals	**EOCRC +**	**No EOCRC**	**EOCRC +**	**No EOCRC**
Test positive	11	13998	10	3999
Test negative	2	85989	3	95988
Number of patients with a positive test needing follow up colonoscopy	14009		4009	
Percent of population with a positive test	14.01%		4.01%	
Positive predictive value	0.08%		0.25%	