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Correspondence
Address correspondence to: Jeffrey K. Lee, MD, MPH, Division of Research, Kaiser Permanente Northern California, 2000 Broadway, Oakland, California 94612. e-mail: Jeffrey.K.Lee@kp.org.

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Blood-Based Liquid Biopsies: A Noninvasive and Cost-Effective Tool for Improved Risk Assessment and Identification of Lymph Node Metastasis in Patients With Submucosal T1 Colorectal Cancer

See "A liquid biopsy assay for noninvasive identification of lymph node metastases in T1 colorectal cancer," by Wada Y, Shimada M, Murano T, et al, on page 151.

Liquid biopsy–based assays are increasingly gaining momentum for the management of cancer patients, primarily for more robust and earlier disease detection, as well as for disease monitoring after the initiation of treatment.[1,2] These technologies are based on their ability to detect circulating tumor cells (CTCs), circulating tumor DNA (ctDNA), and circulating tumor RNA (ctRNA), as well as on the development of highly sensitive and high-throughput technologies such as digital droplet polymerase chain reaction and next-generation sequencing, that can trace circulating nucleic acids in a variety of body fluids.[3–6] In the context of colorectal cancer (CRC), several studies used liquid biopsy–based assays, which prompted the National Cancer Institute to establish a task force that issued a whitepaper addressing potential applications. These include the detection of minimal residual disease, the management of patients with rectal cancer, monitoring responses to therapy, and tracking clonal dynamics in response to targeted and systemic treatments.[7] The development of liquid biopsy–based cell-free DNA and RNA panels for specific applications requires rigorous experimental design, appropriate patient cohorts, and relevant specimen selection. Many biomarker panels have gone through such rigorous interrogations (eg, ColoGuard), which led to approvals by the US Food and Drug Administration for specific clinical applications.[8]

In this issue of the *Gastroenterology*, Wada et al,[9] describe the process through which they developed a transcriptomic signature that consisted of both mRNA and microRNAs (miRNAs) for the identification of patients with T1 CRCs and presence of lymph nodes metastasis (LNM). This has potential eventual clinical application for helping to reduce overtreatment in those who are deemed to be lymph node negative.

Discussion

Wada et al's work is a logical extension of their previous findings, where they reported a panel of miRNAs[10] and mRNAs[11] for the identification of LNM in T1 CRCs. These markers were first established in surgically resected tissue specimens and endoscopic biopsies taken during colonoscopy. The present article builds on those previous studies and evaluates the expression of 4 miRNAs (miR-181b, miR-193b, miR-195, and miR-411) and 5 mRNAs (AMT, FOXA1, PIGR, MMP1, and MMP9) in the plasma specimen–based liquid biopsy assay. The authors demonstrated that these noninvasive biomarkers were superior in their ability to detect presence of LNM in T1 lesions compared with currently used pathologic risk factors, even when the pathologic features (depth of submucosal invasion >1000 μm, presence of lymphatic or vascular invasion, high-grade tumor budding, and poorly differentiated histology) suggested a high-risk tumor and a likelihood of LNM. The authors successfully integrated their miRNA and mRNA biomarkers into a combined transcriptomic panel for potential clinical application for a liquid biopsy assay. This work has important clinical significance and implications. It sets the groundwork for the

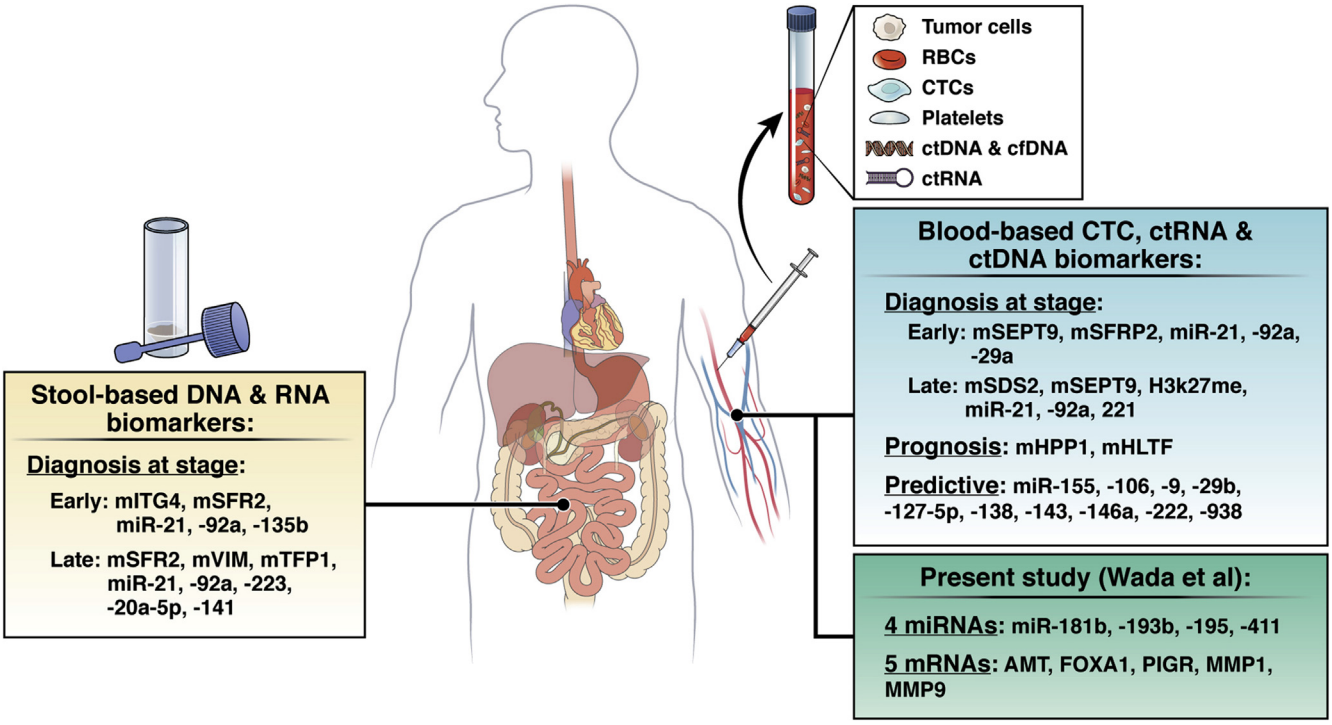

Figure 1. Blood- and stool-based DNA/RNA biomarkers for diagnosis, prognosis, and predictive of CRC.

development of a noninvasive assay for LNM detection in the submucosal T1 CRCs, of which a majority are currently overtreated, when such clinical decisions are based solely on pathologic features of the tumor. The authors developed and confirmed their findings in training and validation cohorts, where both tissue specimens and matched blood samples were available. Even though the number of LNM-positive cases was small, the study reported a remarkable area under the receiver operating characteristic curve of 0.90. Pending successful validation in independent studies, these findings hold the promise of improving the management of patients with T1 CRC through a more accurate LNM risk assessment. Although it is a retrospective study that was performed primarily in Japanese CRC patients, it nonetheless provides a proof of concept that liquid biopsy assays based on tissue-established biomarkers could have translational and clinical applicability (Figure 1). The authors acknowledge that their findings need to be further investigated in larger and more diverse cohorts to assess generalizability of their findings.

Summary and Future Directions

Pathology features suggestive of potential LNM in invasive submucosal T1 CRC should be used as a first step in assessing metastatic potential and deciding subsequent steps in the patient's management. Because of intratumor heterogeneity and molecular evolution, not all similar-looking tissue specimens have the same invasive and metastatic potential. Personalized medicine based on biomarker data should allow for a much better stratification of patients' risks. Initially used to refer to CTCs, the term liquid biopsy has now expanded to include ctDNA and ctRNA. Although ctDNA is still used primarily to detect somatic mutations that might originate from CTCs, ctRNA seems to be more informative as it reflects the dynamics of gene expression in circulating nucleic acids.

Overall, Wada et al,[9] made a case for a transcriptomic liquid biopsy assay to tease apart LNM-positive from LNM-negative T1 CRCs. Such biomarker panels were also proposed to assess the emergence of therapy resistance, residual disease, and recurrence.[12] However, rigorous large multicenter studies are needed to assess these liquid biopsy–based biomarkers before their use in the clinic. Ignatiadis et al have suggested 10 priority areas for liquid biopsy research.[1] There are many markers for CRC patients with multiple metastases and advanced disease but not many for stage I or II patients. A combination of different methylation targets in cell-free DNA may be an effective biomarker for early diagnosis of CRC. The most studied epigenetic marker for CRC screening in cell-free DNA is methylated Septin-9 (mSEPT9) in plasma and fecal specimens, which was found to be cost-effective when screening colonoscopy was not available.[13] A recent study on tumor liquid biopsies, investigating mSEPT9 in CRC patients' plasma, resulted in the diagnosis of 72% of stage I–III cancers with 93% specificity.[14] According to detection rates of each miRNA, the entire sensitivity was 50%, and the specificity was 80% for diverse diagnostic miRNAs in CRC with the use of plasma or fecal samples.[15] These results further highlight the potential of the panel developed by Wada et al for the accurate assessment of metastatic potential in submucosal invasive T1 CRCs.

HASSAN ASHKTORAB
HASSAN BRIM
Cancer Center and Pathology Department
Howard University College of Medicine
Washington, DC

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Correspondence
Address correspondence to: Hassan Ashktorab, Howard University Medicine, 2041 Georgia Avenue, Washington, DC 20817. e-mail: hashktorab@howard.edu.

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The Race to Resolution of Benign Biliary Strictures: Slow and Steady vs Pedal to the Covered Metal?

See "Fully Covered Self-Expanding Metal Stent vs Multiple Plastic Stents to Treat Benign Biliary Strictures Secondary to Chronic Pancreatitis: A Multicenter Randomized Trial," by Ramchandani M, Lakhtakia S, Costamagna G, et al, on page 185.

Benign extrahepatic biliary strictures (BBSs), including those seen in patients with chronic pancreatitis (CP) after postoperative injury and liver transplantation or due to autoimmune diseases, can be treated definitively in most patients during endoscopic retrograde cholangiopancreatography (ERCP). A robust experience describing the serial placement of multiple plastic stents (MPSs) in sequentially increasing numbers with or without concomitant balloon dilation has shown success in the majority of patients, with fairly low recurrence.[1] Therapy is applied to palliate the symptoms of cholestasis and to prevent secondary biliary cirrhosis and usually requires 3 or more ERCP sessions spread out over 1 year. It has been suggested that strictures associated with CP are more difficult to treat, with a lower response rate and higher recurrence, compared to other etiologies.[1]

Self-expanding metal stents (SEMSs) placed during ERCP have been shown to provide more durable palliation of extrahepatic malignant obstruction compared to single plastic stents, and their use in selected patients has become the standard of care.[2] Initially developed as bare metal stents with interstices that allowed for epithelial ingrowth and anchoring, these devices are extremely difficult to remove once placed, have a defined patency, and are not