No area of cancer medicine has advanced as rapidly as molecular-based diagnostics, which have become so sensitive and specific that we now have the capacity to identify bits of tumor DNA circulating in the bloodstream (ctDNA). One such assay, Signatera (Natera), is informed by whole-exome sequencing of an individual's primary tumor, so its specificity is nearly certain.

Theoretically, in patients who become disease free, surveillance with this test could herald cancer recurrence at the stage of minimal residual disease (MRD), thus offering the opportunity for earlier and possibly more effective interventions. Unfortunately, the study by Fakih et al in *JAMA Network Open* suggests that finding MRD in a subset of patients with colorectal cancer may be both unachievable and—worse—not helpful.

This retrospective, single-institution study reported on the results of surveillance of 48 patients with stage II to IV colorectal cancer who had completed curative therapy and were believed to be disease free. Patients were followed up for recurrence with serial imaging and measurement of carcinoembryonic antigen levels per the National Comprehensive Cancer Network guidelines. In addition to those tests at specific intervals, serial ctDNA measurements were also obtained. Although the risk of recurrence was not uniform among this heterogeneous patient population (15 patients with stage II cancer, 16 with stage III cancer, and 17 with resected metastatic cancer), all patients were followed up with similar intensity. In only 5 of the 15 patients who developed recurrent cancer was the ctDNA assay result the first evidence of recurrence, whereas imaging identified 7 cancer recurrences in patients with negative ctDNA assay findings at that time.

The Signatera ctDNA assay was recently granted a breakthrough device designation by the US Food and Drug Administration (FDA) for the detection of molecular residual disease (the 2022 version of MRD) in a variety of solid cancers, including colorectal cancer. Such a designation by the FDA neither imputes clinical utility nor endorses the device (although companies usually do not put the wording in context when they announce such a designation in press releases). Instead, it represents a confirmation by the FDA that it agrees that the assay could provide important information for patient treatment and is a commitment by the agency to work with the sponsor in the development of necessary trials and to expedite the review of a formal application for approval.

The preliminary data that prompted both the application to the FDA and the belief that detection of MRD was possible included numerous studies across a variety of cancers. However, the data specific to colorectal cancer are not substantial, consisting of 2 prospective studies, including only 230 patients with resected stage I to III colon cancer. In those studies, patients with a positive ctDNA assay finding at postoperative day 30—which represented persistent rather than recurrent disease—had a universally poor prognosis. The assay result apparently prompted the administration of adjuvant therapy when it would otherwise not have been used, and the disappearance of ctDNA in some of those patients correlated with long-term disease-free survival.

The report from Fakih et al adds to the data in support of the association between ctDNA Signatera positivity and recurrent cancer in that the assay finding was positive in 14 of 15 patients with cancer recurrence. However, more often than not, ctDNA did not detect recurrence sooner than imaging in the surveillance setting. Even when it did so, as in 2 of the 3 patients in this series who underwent a curative operation and remain disease-free with long-term follow-up, it could not be argued that it triggered the curative intervention. Because the curative intervention in recurrent colorectal cancer is extirpation of oligometastatic disease, ctDNA positivity is an intermediate finding that likely results in further imaging, because the site of recurrence must be identified before it can...
be surgically addressed. Notably, 1 patient did not develop radiographic evidence of cancer until 28 months after the positive ctDNA finding, at which time incurable diffuse metastatic disease was identified.

The actionability of ctDNA-based MRD determination is best exemplified in patients with lymphoid or hematologic malignant neoplasms. In such patients, MRD represents a crucial juncture, where an early warning can accelerate an intervention such as marrow-ablative therapy, which is more likely to be curative when used in less symptomatic or asymptomatic patients with lower tumor burden. In a similar vein, MRD as characterized in the preliminary colorectal cancer data in support of Signatera could be seen as upstaging a patient with, for example, stage II colon cancer who would otherwise not receive adjuvant chemotherapy. That is the premise of ongoing prospective studies that use the assay in risk-adaptive decision algorithms for patients with early-stage colon cancer.5

In other words, MRD has different implications in different cancers and circumstances. Whether it is called molecular residual disease or minimal residual disease, discovering MRD via ctDNA in a patient with colorectal cancer before the site of recurrence can be localized does not open the window of opportunity. Instead, it gives advanced notice that a patient has cancer recurrence when the only practical intervention is repeated imaging. In other words, patients receive bad news that is not actionable. Arguably, patients similar to those who participated in the surveillance study by Fakih et al1 might be harmed rather than helped by the earliest discovery of recurrence, learning of inevitable cancer recurrence with nothing to do but wait.

Although this small study is by no means definitive regarding the capability of the Signatera assay's ability to find MRD in patients with colorectal cancer, it shines a light on the conundrum created if it could reliably find MRD after adjuvant therapy. Mature data from rigorous clinical trials, such as the BESPOKE study currently under the sponsorship of Natera,4 are needed to settle the issue of the role of ctDNA in colorectal cancer surveillance. If ctDNA can indeed detect MRD sooner than imaging, then interventional trials with molecular response as an end point are warranted to determine whether ctDNA detection is an actionable finding or merely advanced notice that the cancer is destined to recur.

ARTICLE INFORMATION
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REFERENCES