Hopes and Hurdles for Liquid Biopsy Technology

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In 2016, the U.S. Food and Drug Administration (FDA) approved the first liquid biopsy test, Roche's cobas® EGFR Mutation Test v2, which can detect certain mutations in the DNA of non-small cell lung cancer (NSCLC) cells circulating in the bloodstream. The test helps oncologists select the best first-line treatment for patients with NSCLC without needing to surgically collect tumor samples — a major advance that ushered in a wave of liquid biopsy innovations designed to help oncologists tailor treatments to individual patients and improve them over time to prevent recurrences.

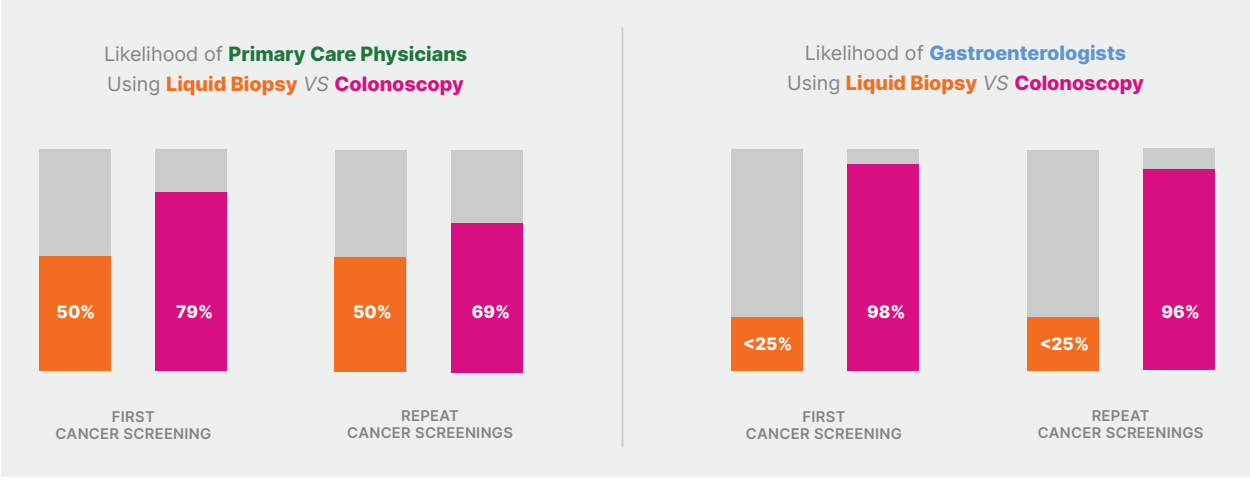
Since then, four additional FDA-approved liquid biopsy tests have come to market, including, most recently, Guardant Health's Shield™, a blood test that, in clinical trials, detected colon cancers with 83 percent sensitivity. The FDA approved Shield as a primary screening option, with Medicare agreeing to cover its cost for beneficiaries to be tested every three years. As private insurers also agree to cover the test, people who are reluctant to undergo colonoscopies or to take an at-home stool test may opt for the liquid biopsy instead.

Dozens more liquid biopsies are in pipelines. One recent estimate values the size of the global market for liquid biopsy technology at $5.4 billion, growing at a compound annual rate of 14.2 percent. At that rate, the market for liquid biopsies could hit more than $20 billion in annual revenues by 2033. While approved tests primarily aid in the treatment of patients with lung, breast, colorectal or prostate cancer, the pipeline includes several multi-cancer early detection tests (MCEDs), designed to find several different types of tumors in their earliest stages, when they can be most easily treated and, ideally, eradicated.

But for the liquid biopsy market to meet those optimistic projections, developers will need to overcome hurdles that are hampering physician uptake, including concerns about the tests' accuracy compared to other available technologies, and difficulties obtaining insurance coverage.

For more than two years starting in 2022, the Deerfield Institute, a division of Deerfield Management Company, an affiliate of Cure, surveyed hundreds of general practitioners and oncologists about their use of liquid biopsies, hurdles faced incorporating these tests into patient care and their predictions about how the evolving technology will change medical practice during the next five years. The key takeaways from that research are revealed here for the first time.

Attitudes Toward a New Liquid Biopsy Test for Colon Cancer Detection



Concerns About Accuracy

In a survey of 112 primary care physicians and 79 gastroenterologists, respondents were asked to imagine that a liquid biopsy test was FDA approved for the early detection of colon cancer.

The hypothetical test would be less sensitive at detecting advanced precancerous lesions and colorectal cancer than the stool test Cologuard, which has 90% sensitivity for colorectal cancer.

The survey revealed that if the hypothetical test were approved and commercially available, half of primary care physicians would be unlikely to use it for first-time or repeat screening, as would more than 75 percent of gastroenterologists. For first-time screening, colonoscopy was the first choice of 79 percent of primary care physicians and 98 percent of gastroenterologists. For repeat screening, 69 percent of primary care physicians preferred colonoscopy, as did 96 percent of gastroenterologists.

In a survey done later in 2022, one gastroenterologist explained the reluctance to use liquid biopsies to screen for colorectal cancer, even if their sensitivity were similar to that of Cologuard: "Firstly, it will miss 10 percent of colon cancer and will give patients a false sense of security. Second, it will de-emphasize the preventive nature of colon cancer screening that colonoscopy so deftly addresses."

Several survey participants also noted that a major advantage of colonoscopies is that the physicians performing them can remove precancerous lesions on the spot—something noninvasive options cannot offer.

A Hunger for Treatment Guidelines

In addition to improving early detection efforts, liquid biopsies could help oncologists select treatments for patients with cancer based on their tumor mutations, monitor treatment progress by measuring minimal residual disease (MRD), and detect recurrences aftertreatments are complete. The problem is, for many cancers, major medical organizations have yet to issue clear guidelines on the use of liquid biopsies for these purposes.

For example, current guidelines from the National Comprehensive Cancer Network (NCCN) favor the use of tumor tissue samples for genomic profiling in NSCLC patients and say the use of liquid biopsy should be limited. One oncologist surveyed by Deerfield commented that using liquid biopsies for therapy monitoring in lung cancer is "not in NCCN guidelines," while another stated that there are "no data supporting its use."

As for monitoring MRD in lung cancer, one oncologist commented that there is "no science to support it now in lung cancer," and that it is "not proven to improve outcomes." Another expressed a need for more data on the impact of MRD testing on overall survival before they would consider using liquid biopsies for that purpose.

Oncologists surveyed by Deerfield reported that they had ordered liquid biopsy testing for MRD in less than 2 percent of their NSCLC patients over the previous three months, across all stages of the disease. They did predict, however, that MRD monitoring with liquid biopsies will be more prevalent three to five years from now, forecasting that 23 percent of patients with stage 0 or 1 NSCLC would undergo liquid biopsy for detecting MRD.

23%

Patients with stage 0 or 1 NSCLC forecasted to undergo liquid biopsy in three to five years.

In a separate Deerfield survey of oncologists who treat a range of solid tumor types, respondents indicated several uses for monitoring MRD with liquid biopsies. Some use the technology now to help determine whether or not they should continue drug therapies for patients who have had surgery, radiation or another type of intervention. Others have started using liquid biopsies to measure MRD, so they can determine how well patients are responding to immunotherapy.

Respondents also predicted that the overall use of liquid biopsy for MRD monitoring in the treatment of patients with solid tumors would rise from 32 percent now to 57 percent five years from now.

Overcoming Reimbursement Hurdles

The shortage of efficacy data and professional guidelines for liquid biopsies directly impacts another major concern for the physicians who Deerfield surveyed: insurance coverage. Many respondents reported pushback from payers in some instances — an issue they said could only be addressed with data proving best-use practices and positive results.

Between 40 percent and 60 percent of respondents said the current reimbursement environment has an impact on their decisions about whether or not to use liquid biopsies for mutation identification, MRD monitoring or therapy monitoring. The biggest concern was expressed by current users of liquid biopsies for MRD monitoring: 60 percent cited reimbursement as impacting their decisions.

Insurer Pushback of Liquid Biopsies

"MRD is a newer concept for [colorectal cancer] and if it is too costly. I will pass," said one respondent.

Among oncologists who treat NSCLC, 62.8 percent of respondents reported no pushback for the use of liquid biopsies for mutation identification. But 75 percent of respondents said insurers balked at using liquid biopsies for therapy monitoring and 86 percent reported pushback in using the tests for MRD monitoring.

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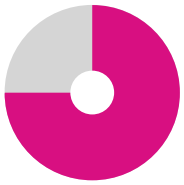
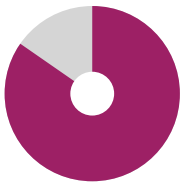


75% of respondents said insurers balked at using liquid biopsies for therapy monitoring



86% reported pushback in using the tests for MRD monitoring.

"The payers will not approve [liquid biopsy] without an adversarial conference, and even then, it is prone to denial for lack of actionable evidence as they see it," one oncologist said.

A top goal of many liquid biopsy innovators is to develop MCED tools that can be used as part of everyone's annual physical to detect early-stage cancers before they cause symptoms. But Deerfield's research showed that physicians are skeptical about this emerging technology — largely because of reimbursement concerns.

In the 2022 survey of primary care physicians and gastroenterologists, respondents were asked to consider data from studies of two investigational MCED tests. One achieved more than 99 percent specificity for breast, colon, lung and pancreatic cancers but only 55 percent sensitivity overall. The other showed 90 percent specificity for colon and lung cancers, 95 percent for pancreatic and bladder cancers, and 93 percent sensitivity overall.

Deerfield also asked respondents about two scenarios: one in which insurance would cover all but $190 of the full retail cost of $950 for either test, and the other in which the patient would bear the full cost out-of-pocket. Just half of surveyed physicians said they would complete either test under the first scenario. And if the patient had to cover the full retail cost, only 28 percent would complete the first test and 15 percent the second test.

A Bright Future

First-generation liquid biopsy tests have received a mixed reception from physicians who treat patients with cancer— but optimism for the future of the technology is high.

Doctors surveyed by Deerfield expressed enthusiasm about using liquid biopsies to detect more early-stage cancers than they can today, and to improve how they tailor treatments to individual patients and track progress over time. But they expressed the need for more data showing the effectiveness of liquid biopsies in extending patient survival, as well as for better guidelines on incorporating the technology into patient care. Data and guidelines would improve not just physicians' confidence, but also willingness among payers to cover liquid biopsy use.

As one primary care physician said, liquid biopsy has "GREAT potential.

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