No one doubts the value of diagnosing cancer at the earliest possible stage. Sometimes, though, the magnitude of the impact is underappreciated. Pharmacologist David Crosby, head of prevention and early detection research at Cancer Research UK, and his colleagues emphasized the early-detection effect on treatment results: “57% of people with lung cancer survive their disease for 5 years or more when diagnosed at stage I compared with only 3% of those diagnosed at stage IV” (1).

Existing cancer-screening tools help, but only when people get them. As an example, low-radiation computer tomography (CT) scans can reveal lung cancer, but as Sam Cykert, professor at the University of North Carolina School of Medicine, points out, “By far, the highest lung-cancer death rates in Americans are among black men, and they hardly ever get CT screening.”

With a simple blood test, possibly part of a regular exam every few years, more people might get screened for colon and other cancers. “Today, the majority of cancers are found too late, when outcomes are often fatal, because most deadly cancers have no available screening tests,” says Josh Ofman, chief medical officer and head of external affairs at GRAIL, a biotechnology company based in Menlo Park, California. “Current guideline-recommended screenings are critical, but in the United States they cover only five cancers and screen for a single cancer at a time.”

Catching cancer as early as possible promises much better outcomes, but that depends on easy and accurate screening methods. How close is oncology to that goal?

**Markers at miniscule levels**

For blood cancers, cancerous cells are relatively easy to access and identify—as easy as looking under a microscope, at least for a seasoned pathologist. The same cannot be said for solid tumors, but the blood does carry signs of these cancers as well.

Tumors lose pieces of DNA, but they’re hard to find in the blood. Of the cell-free DNA in the blood of someone with cancer, the circulating tumor DNA (ctDNA) might account for just 0.1%. Once extracted, that ctDNA can be analyzed—usually with next-generation sequencing (NGS)—for modifications, such as single-nucleotide variants, insertion-deletion mutations, and copy-number variations. Those changes in ctDNA carry information...
about the kind of cancer that created it. That's what most advanced cancer-screening tests look for in blood samples.

For example, Singlera Genomics developed the PanSeer assay, which looks for tumor-specific patterns of methylation in ctDNA with NGS. Geneticist Li Jin and his colleagues at Fudan University in Shanghai applied PanSeer to blood samples of 605 asymptomatic people, which included 191 patients diagnosed with cancer within 4 years of sample collection. The scientists reported: "PanSeer detects cancer in 95% ... of asymptomatic individuals who were later diagnosed. These results demonstrate that cancer can be noninvasively detected up to four years before current standard of care" (2).

That's the kind of early detection that oncologists would like to see on a regular basis. Many companies hope to make that a reality.

Colon-cancer challenges

Cyker noted that people without insurance can't easily get a colonoscopy. Maybe a blood-based test for colon cancer could be easier to obtain and less expensive. That's what Guardant Health hopes to provide.

An electrical engineer and one of Guardant Health's co-founders and president, AmirAli Talasaz, says that they've tested blood samples from more than 150,000 patients and "looked at tumor DNA shed from solid tumors." From this work, Guardant Health has recently introduced a test for early-stage colorectal cancer.

"The front end of our chemistry is homebrewed technology," Talasaz says. "We take a tube of blood and isolate the plasma and circulating free DNA, and then— in one assay—we find the sequence and methylation signature." This analysis utilizes tagging methylated DNA with barcodes and then applying NGS. As Talasaz says, "The beauty of our technology is our assay." He adds that the homebrewed technology "increases accuracy of NGS by orders of magnitude."

This is a yes or no test. Either a patient’s sample is positive for ctDNA or it's not. Talasaz says that the company's data indicate that this test specificity is 91%.

Multiplexing screens

Tests for specific kinds of cancer certainly have a place in oncology. These blood tests follow the tradition of prostate-specific antigen (PSA) tests for prostate cancer and mammograms for breast cancer. Some companies, though, want to test for many cancers in one assay.

Isaac Kinde, vice president, technology assessment and co-founder at Thrive, an Exact Sciences company based in Cambridge, Massachusetts, says its blood test analyzes mutations in about 2,000 base pairs of ctDNA to screen for multiple cancers. Kinde calls these among "the most commonly mutated regions within cancer." The company's test, CancerSEEK, also looks for several cancer-related proteins.

As Kinde explains, "A prototype version of our test was used in real-time to detect cancers [in 10,000 women not previously known to have cancer] and then led to interventions earlier than what could have been done before." He adds, "The sensitivity for various cancer types will vary due to biology." That is, some solid cancers shed more ctDNA than others, or less will reach the blood, which will impact the sensitivity of any ctDNA-based test.

Bending the curve

Other multicancer screening tools are also in development. One of them is GRAIL's Galleri test. "In clinical studies, an earlier version of Galleri showed the ability to detect more than 50 types of cancers—over 45 of which lack recommended screening today—with a low false-positive rate of less than 1%," Ofman says. "When a cancer signal is detected, the Galleri test also pinpoints where the cancer signal originated in the body with high accuracy, all from a single blood draw."

GRAIL's technology uses artificial intelligence (AI) and machine learning (ML) to analyze data from cell-free DNA in a patient's blood. Ofman says that the analysis "examines these patterns of DNA methylation to identify signatures that distinguish cancer from noncancer and help to distinguish different cancer types from each other."

By detecting so many cancers at an early stage, Ofman believes "we can bend the cancer mortality curve." There's some evidence that this might be possible.

For example, GRAIL's PATHFINDER study is evaluating the use of its technology in clinical practices. At the study sites, oncologists used GRAIL technology to detect signals in the blood for more than 50 cancers. Intermountain Healthcare's precision medicine program, Intermountain Precision Genomics, in Utah, served as one test site in that study. As Lincoln Nadauld, oncologist and chief of precision health and academics at Intermountain explains: "When a positive signal was detected, we worked those patients up, and we found cancers in patients who were previously asymptomatic. We wouldn't have found those cancers otherwise."

Increasing computation

The enormous amount of data collected in cancer screening and the need to analyze it quickly create significant challenges. To address these issues, some companies collaborate with computation experts.

In China, Ningbo Konfoong Bioinformation Tech (KFBio), a digital pathology company, set up a collaboration with Intel, a technology company based in Santa Clara, California, to screen for cervical cancer. Instead of using blood samples, KFBio uses slides of liquid-based cytology specimens obtained from Pap smears into images. Intel is helping with the image analysis. These slides are scanned at 40,000 by 40,000 pixels, and the resulting 1.6 gigapixels include lots of information, says Prashant Shah—global head of artificial intelligence for health and life sciences at Intel, and an advisor on AI for the U.S. National Institutes of Health.

The objective is to analyze the slides as quickly and accurately as possible. Using Intel's technology and expertise, the company increased the speed of analysis 8.4 times. In addition to being speedy, the AI-based model must run on various computers. Running the model that analyzes the slides takes hundreds of gigabytes of computer memory. "Using our Xeon --
Based servers and optimizing neural-network algorithms using OpenVINO, we created a solution that can run efficiently on small- and large-footprint hardware,” Shah says. That’s necessary for the screening tool to be used around the world.

When data from patients is being used, issues beyond screening must be considered. Intel is also working with the Perelman School of Medicine at the University of Pennsylvania (UPenn) to train an AI-based model on brain tumors. Doing that with high accuracy requires masses of data pooled across institutions, but security and privacy concerns reduces the number of clinics and hospitals that will participate. That’s because traditional ML models collect data in one centralized location for the computing, but there’s a better way to do it. “Federated learning splits up part of the training so it happens on each owner’s data, shares the learning, or the model, to a central location, and combines all the models in a single aggregate view,” explains Jason Martin, principal engineer in the Security Solutions Lab and manager of the Secure Intelligence Team at Intel Labs. “Then, the global trained model goes back out to the sites, and it’s done in an ongoing cycle.” So, the clinic or hospital that collected the data never needs to let anyone else see it.

Martin notes that his research with UPenn reaches “99% of the accuracy of a traditional approach.” It also makes it possible to use far more data to train the model. With a traditional approach, UPenn can provide data from around 500 patients with brain tumors; by taking the federated approach, 29 institutions are set up to provide data from more than 1,000 patients each. Ultimately, this AI-driven model could look at a patient’s brain data, scan it for areas of concern, and quickly direct a pathologist to any cells that need expert attention.

Added approaches

No matter how much screening improves, it’s not the only tool that can be used against cancer. Changes in behavior must also be encouraged.

According to the U.S. National Cancer Institute (NCI), “Smoking, poor nutrition, and physical inactivity are just some of the human behaviors that have been linked to the development of many common cancers.” Although NCI notes that smoking causes 30% or more of the cancer deaths in the United States, it also reports that “cigarette smoking prevalence among adults has declined steadily since 1992,” and that “initiation of the use of cigarettes among children and adolescents aged 12–17 started falling more rapidly in 2010” (4).

Even though the general population is decreasing cancer-causing behaviors, that cannot prevent all cancer. So despite the most advanced prevention programs, screening remains crucial—but participation could be improved. As the American Cancer Society puts it, “Research on barriers related to cancer screening shows that multiple factors—public policy, organizational systems and practice settings, clinicians, and the patients themselves— influence cancer screening and that a diverse set of interventions targeted at each of these can improve cancer screening rates” (5).

Steps ahead

Nadauld sees cancer screening as a standard part of future health care. He says, “I foresee patients coming in for their well-patient visit, and while they’re getting their cholesterol checked, for example, they will also get a blood test to see if they have one of dozens of different kinds of cancer.”

To him and many of his colleagues, the promise of screening tests in development is amazing. Nadauld says, “As a medical oncologist, I have longed for this kind of test.”

Undoubtedly, sophisticated cancer screening offers many benefits, but follow-up matters as well. “Even people who get screened for cancer today can fall through the cracks on the path to treatment,” Cykert explains. “That takes a system—running the tests, training people to explain the tests and the treatment options, and getting patients treated.”

Overall, combating cancer effectively depends on the integration of many factors. From expanding efforts on prevention to developing more accurate and available screening and treatment, it takes the entire health care system to reduce the incidence of cancer and improve the outcomes. And no matter how lifestyles improve, and no matter how much environmental exposure to carcinogens is reduced, cancer screening will maintain a fundamental role in health care. The promise of making these tests much more effective will impact people in every age group worldwide.

References


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