Personalizing the Future of Cancer Detection

In the past few years, advances in personalized medicine have opened up new avenues in cancer detection and monitoring.

Cancer doesn't look or behave the same way in any two people, posing tremendous challenges to screening, diagnosis, and treatment. But rather than taking a one-size-fits-all approach, personalized cancer detection technologies are fulfilling a pressing need for new strategies to determine which patients are at the highest risk for developing cancer, and who will respond to which treatments best.

Researchers and clinicians are training artificial intelligence (AI) models to predict an individual's disease risk, developing RNA-based blood tests for early diagnosis, and monitoring skin cancer treatment responses with more precision than ever before. Such innovations may catch cancer earlier than existing methods for screening and biopsies, offering patients more treatment options with better chances of survival.

"If you detect lung cancer early," says Florian Fintelmann, a physician and scientist at Massachusetts General Hospital (MGH), "the long-term outcome is significantly better. Your five-year survival rate is closer to 70%, whereas if you detect it when it's advanced, the five-year survival rate is just short of 10%."

Harnessing AI for cancer risk prediction

For radiologists, diagnosing cancer often begins with detecting something visible; for instance, a nodule on a lung scan or white area on a mammogram. These physical signs may indicate the presence of early-stage disease, requiring monitoring over time. But researchers are exploring the potential of AI to predict cancer even earlier — before it can be seen with the human eye.

At the MGH and Massachusetts Institute of Technology (MIT), a team of clinicians and scientists have developed an AI model, named Sybil, that is capable of using a single lung scan to predict the risk of a patient developing lung cancer six years before a diagnosis (Figure 1).

Lung cancer is the leading cause of cancer-related deaths worldwide. But screenings can help detect the disease before symptoms start, improving survival. Studies have shown that annual low-dose computed tomography (LDCT) scans, a type of imaging technique, can reduce lung cancer mortality by up to 24% in high-risk individuals, specifically smokers. This promising finding has led to clinical recommendations for yearly screenings in individuals over 50 with significant smoking histories.

Yet even with these screening recommendations in place, doctors still face significant challenges in detecting lung cancer in the earliest stages. Fewer than 10% of eligible, high-risk individuals receive an annual LDCT scan. Meanwhile, diagnoses among nonsmokers, who are considered low-risk, are rapidly rising.

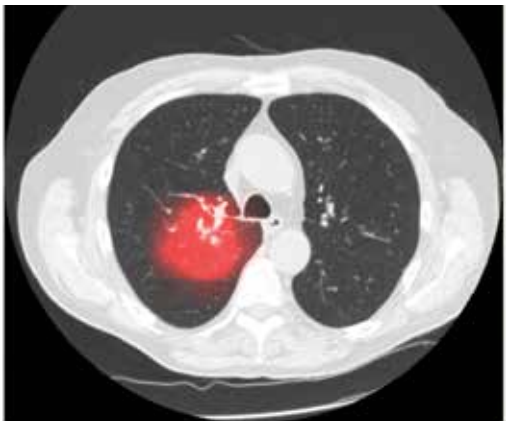
Sybil could help improve the lung cancer screening process by offering a more personalized approach. The AI model, which has been trained on thousands of LDCT scans, assesses an individual's risk level of developing cancer through the analysis of subtle, undefined features in their lung scan, bypassing the reliance on broad demographic categories or smoking history.

Researchers envision that Sybil could reduce unnecessary follow-up scans or biopsies for low-risk patients, prompt high-risk individuals to seek diagnostic screenings, and even detect missed cancers in ongoing screening programs.

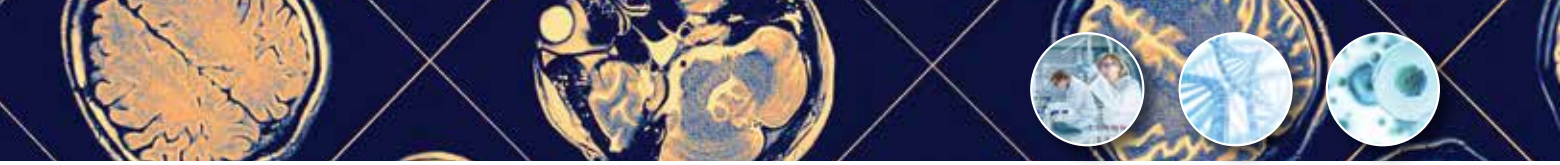
"In an ideal world," says Peter Mikhael, an MIT PhD student in electrical engineering and computer science who worked on the study, "you would use Sybil to say, 'You're at incredibly low risk, you don't need more tests.' Or, 'You're high risk and should come back sooner, in X number of years.'"

To determine a patient's individualized screening needs, Sybil generates annual probability scores for lung cancer development over a six-year period *(1)*. Researchers assessed the model's performance using a statistical measurement called area under the receiver operating characteristic curve, or AUC, in which the highest score is 1. Impressively, Sybil achieved AUC scores of 0.92 at one year, 0.86 at two years, and 0.75 at six years, showcasing its potential as an innovative new tool for lung cancer risk assessment.

"Lung cancer screening is not being deployed to its fullest potential



◀ **Figure 1.** Low-dose computed tomography (LDCT) scans can reduce lung cancer mortality if done every year for high-risk patients. However, fewer than 10% of eligible, high-risk individuals receive an annual LDCT scan. Now, a new AI-based tool could allow more accurate lung cancer diagnoses. In this image, a red glow indicates where cancer is likely to develop. Image courtesy of Alexandra Ouyang, Massachusetts Institute of Technology (MIT).



in the U.S. or globally," says coauthor Lecia V. Sequist, a medical oncologist and director of the Center for Innovation in Early Cancer Detection at MGH. "Sybil may be able to help us bridge this gap."

At the Univ. of Michigan, researchers are on a similar mission to improve the cancer screening process using machine learning. In this case, though, they've harnessed clinical and demographic data, rather than visual data, to predict future risk of two deadly forms of esophageal and stomach cancer — esophageal adenocarcinoma (EAC) and gastric cardia adenocarcinoma (GCA) — at least three years prior to a diagnosis *(2)*.

EAC and GCA are less prevalent than other cancers, making population-wide screening impractical. On top of that, current screening recommendation guidelines lack accuracy, only identifying up to 36% of people who go on to develop EAC and GCA, according to Joel Rubenstein, a research scientist and professor of internal medicine at Michigan Medicine, who led the study.

Rubinstein and team developed an AI tool, called Kettles Esophageal and Cardia Adenocarcinoma prediction tool, or K-ECAN for short, that fared significantly better. Utilizing data from patients' electronic health records — including demographic data, prescriptions, laboratory tests, and previous diagnoses — the AI model identified up to 66% of individuals who later developed the diseases.

In a clinical context, K-ECAN could be introduced at opportune moments to direct high-risk patients toward a diagnostic screening test like upper endoscopy, according to Rubinstein. For instance, electronic health records might alert a provider of their patient's increased risk of EAC or GCA when they're ordering a colon cancer screening, prompting an upper endoscopy to be performed easily at the same time as a colonoscopy.

Alternatively, a primary care provider could have access to a dashboard that listed all of their patients who have a high risk of EAC or GCA, highlighting those who need screenings the most.

"AI is going to have tremendous impact on the way we diagnose and treat everything," Rubinstein says. "Tools like machine learning are particularly adept at developing successful prediction tools, identifying associations and myriad interactions that humans can't easily identify with our traditional risk-modeling techniques."

Developing a single blood test for multi-cancer detection

Once a patient is identified as high risk, confirming the presence or absence of a specific cancer requires diagnostic tools. In most cases, doctors perform a surgical tissue biopsy to test suspicious cells or tissues in the laboratory. But these procedures are starting to be replaced by a quicker, cheaper, minimally invasive alternative.

Liquid biopsies, which rely on a simple blood test, may one day be able to screen for multiple cancers simultaneously, with earlier results than ever before. The technique involves sequencing a patient's DNA or RNA, enabling the identification of cancer-related genetic material, often before physical symptoms manifest.

While the majority of companies and researchers in the liquid biopsy field have focused on DNA analyses, a new study led by Daniel Kim at the Univ. of California, Santa Cruz is exploring RNA to obtain even earlier diagnoses *(3)*.

DNA-based blood tests work by analyzing cell-free DNA — the fragments of DNA that exist outside of cells in the bloodstream — to screen for genetic material from tumors. But cells must undergo apoptosis, or cell death, before this material can be released.

"DNA technologies work, particularly for later-stage cancers, like three or four," says Roman E. Reggiardo, a biomolecular engineering researcher and the study's first author. "But RNA is a really dynamic measurement of what cells and tissues are doing at any point in time. One of the things our work has found is that RNA is secreted from cells and tissues continuously."

At the earliest stages of cancer, or tumorigenesis, cells begin to manufacture a different RNA profile, explains Reggiardo. Some of this RNA leaves the cell and enters the bloodstream, making it detectable for analysis in techniques like liquid biopsies.

Specifically, researchers in Kim's lab are interested in profiling a class of cell-free RNA known as noncoding repetitive RNA, which is derived from repeat sequences of DNA. Although half of our genomic sequence is composed of these repeat elements, for various technical reasons, this class of RNA has rarely been included in conventional RNA analyses.

To address this knowledge gap, Kim's lab developed an advanced sequencing platform called COMPLETE-seq. The technology is specially designed to analyze cell-free RNA, with a novel focus on repetitive RNAs. To do this, researchers created a custom transcriptome annotation that incorporates over five million repeat element insertions across the human genome, in addition to the tens of thousands of RNAs that have already been well-documented.

"The idea behind COMPLETE-seq is utilizing a much broader collection of potential RNA identities to detect the complete transcriptome, which has coding, noncoding, and repetitive RNAs," says Reggiardo. "We're looking at all of these as potential biomarkers for this approach."

Researchers introduced COMPLETE-seq to analyze blood samples of patients with pancreatic cancer, known for being challenging to diagnose. They found that cancer samples

had significantly larger fractions of repetitive RNAs within their cell-free RNA profile compared to healthy controls. Furthermore, a distinct pattern of repetitive RNAs emerged that could be associated with the disease.

Next, Kim's lab went on to analyze the cell-free RNA profiles of individuals with five other types of cancers, including lung, liver, esophageal, colorectal, and stomach cancer. For each disease, the COMPLETE-seq analysis revealed a cancer-specific pattern in repetitive RNAs, highlighting the potential of this approach for sensitive and precise diagnosis.

This is a promising first step toward a multi-cancer detection test. But COMPLETE-seq will need larger and more varied datasets of cell-free RNA in order to improve diagnostic accuracy and pinpoint the exact tissue or organ in which the cancer originated. "The value of our study is that we've now shown the potential of these repeat elements for diagnosing disease," says Kim, "so hopefully there'll be a lot of interest in leveraging repetitive RNAs to boost the sensitivity of these multi-cancer early detection tests."

Personalized skin cancer monitoring

Personalized medicine isn't just changing the face of early cancer detection; it's also offering new strategies for individuals with later-stage cancers.

Although treatment options for melanoma, the most serious type of skin cancer, have been significantly improved by new immunotherapies, more than 50% of patients still do not respond to current immunotherapy treatments. And, among those who do respond, many become resistant to the treatment's effects over time.

Monitoring a patient's response to melanoma therapy could help lead to more personalized care, and subsequently, better outcomes. But existing techniques can be invasive, such as biopsy; time-consuming and expensive, such as PET-CT scans; or lack appropriate sensitivity and specificity. This leads to a pressing need for novel strategies to monitor melanoma treatment responses.

Researchers at the Wyss Institute at Harvard Univ., MIT, and Brigham and Women's Hospital in Boston have developed a new approach to skin cancer monitoring that is both minimally invasive and more sensitive than conventional methods *(4)*. It uses a painless microneedle that is capable of collecting biomarkers from deeper layers of the skin, in combination with an advanced sequencing technology.

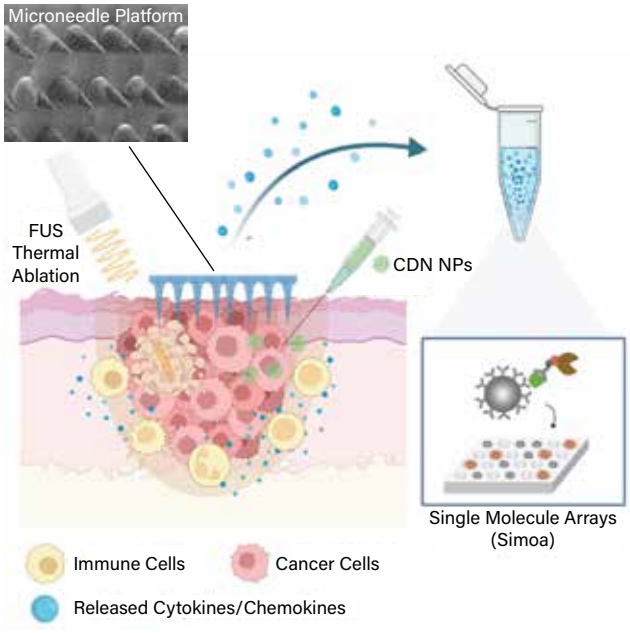
"Melanoma biomarkers can be used to guide patient stratification and help identify responders, saving patients from toxic and costly treatment they may not benefit from," says Natalie Artzi, an Associate Professor of Medicine at Harvard Medical School, who led the study. "Biomarkers can also be used during treatment to inform if treatment is working."

To access biomarkers, Artzi's lab has developed a novel microneedle platform, capable of drawing samples of skin interstitial fluid, a rich source of biomarkers that correlate with the ones in plasma, directly from the tumor site. This approach results in minimal discomfort for the patient while providing valuable information about the individual's health.

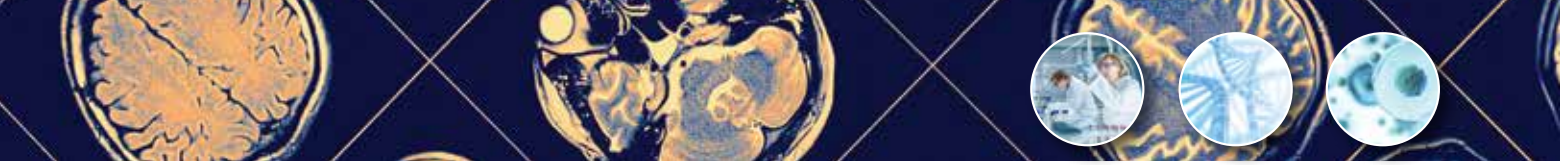
However, the microneedles only collect a few microliters of fluid, making biomarker detection challenging. To address this, Artzi's lab has employed an ultra-sensitive detection technology called Single Molecule Arrays (Simoa), developed with Wyss Core Faculty member David Walt. Simoa surpasses existing sensitivity limitations and works with very low sample concentrations. It can also quantify multiple disease biomarkers simultaneously, providing a comprehensive clinical visualization of a patient's response to therapy.

The researchers provided proof-of-concept for their melanoma monitoring approach in a mouse model in which they treated cancerous lesions with a novel two-stage immunotherapy that acts locally, also developed in Artzi's lab (Figure 2).

"Localized therapy for melanoma offers several advantages," explains Artzi, "particularly when combined



◀ **Figure 2.** Researchers have developed a strategy for monitoring immunological responses to a locally applied immunotherapy against melanoma. They tested their strategy in mice. The therapy acts on tumor lesions by combining focused ultrasound (FUS) with the delivery of an immune-stimulating nanoparticle (NP). After treatment, a painless microneedle platform samples interstitial skin fluid from the lesions, and then biomarkers contained in the fluid can be quantified with ultrasensitive Simoa assays. Image courtesy of Wyss Institute at Harvard Univ.



with the proposed monitoring strategy. One of the benefits is the ability to target the skin tumor cells directly while minimizing side effects on healthy tissues."

The novel immunotherapy consisted of two combined treatments, which Artzi describes as the "heat and wake-up approach." First, focused ultrasound waves are applied at a focal point to thermally kill cancer cells. Next, the delivery of nanoparticles carrying cyclic dinucleotides (CDNs) stimulate a protein known as stimulator of interferon genes (STING) and activate an immune response against the tumor.

Mice with melanoma received either the combined therapy, each therapy alone, or a no-treatment control. While survival rates differed between the monotherapies, all mice that received the combination therapy were tumor-free after the treatment.

Artzi's lab next tested their monitoring strategy on mice receiving the novel immunotherapy by applying microneedles atop local tumors and analyzing the samples with Simoa. It successfully provided real-time readouts. Researchers found that mice under treatment had higher pro-inflammatory biomarkers, indicating the desired immune response against the tumor, compared to control groups.

In the future, this could translate to the monitoring of responses in human patients undergoing immunotherapy, contributing valuable insights to treatment decision-making. But more safety and efficacy demonstrations are needed before the microneedle platform can move onto clinical trials.

"Ultimately, this approach can be used to create better personalized treatments by identifying early on which patients respond to which drug, and support patient stratification to maximize therapeutic benefits," says Artzi.

— *Stephanie Lee* CEP

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