Research tests cost-effective approach to early-cancer detection from cell-free DNA in blood samples

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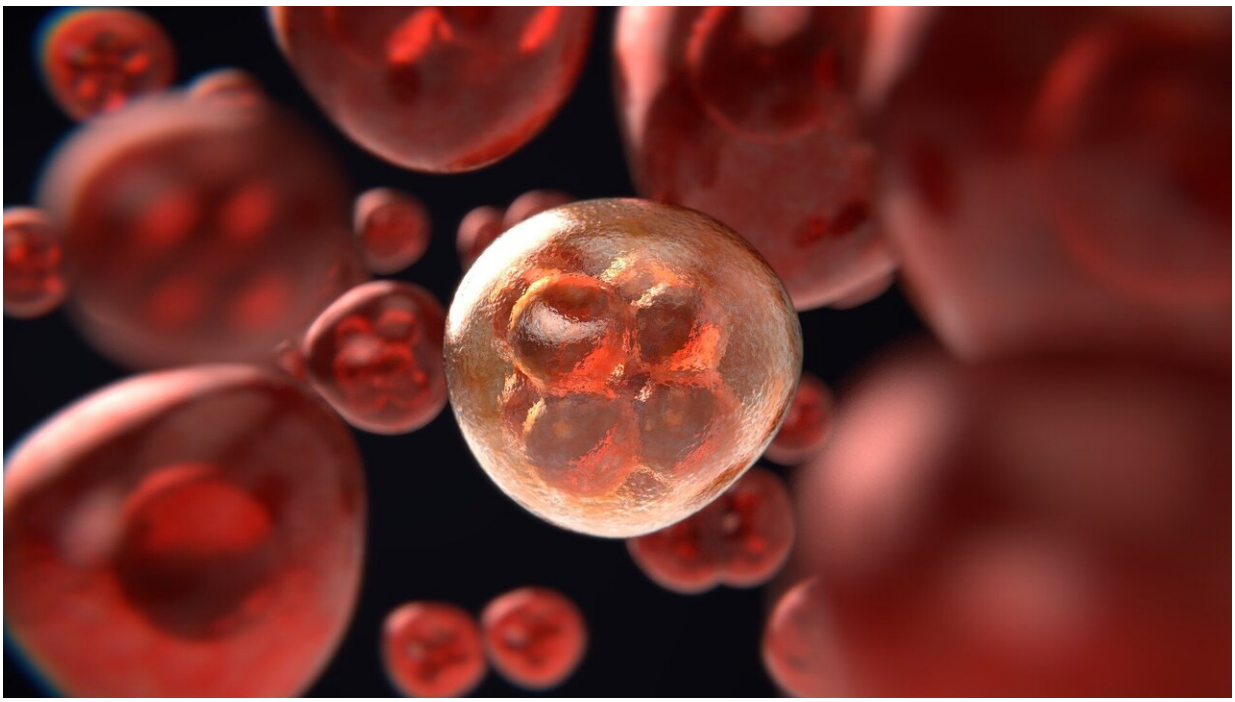

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Early detection remains key to successfully treating many cancers, and early detection via cell-free DNA (cfDNA) circulating in the bloodstream—the so-called "liquid biopsy"—has become a research focal point. But using this method to detect cancer at its early stages has

been challenging due to low tumor concentrations in DNA blood fragments and the genetic diversity of cancer.

Now, researchers at UCLA's Jonsson Comprehensive Cancer Center and collaborating organizations report successful results from an experimental cancer-detection system that appears to have overcome these challenges in a novel, cost-effective way.

Their work, published in the journal *Nature Communications*, highlights an approach that offers more than 12-fold cost-savings over conventional methods to sequence cfDNA methylome, along with a computational model to extract information from this DNA sequencing to aid early detection and diagnosis.

Cell-free DNA methylation has been shown to be one of the most promising biomarkers for early cancer detection. However, the signatures of cfDNA aberrations from diverse cancer types, subtypes, stages and etiologies are heterogeneous, leading to challenges in identifying methylation markers suitable for early detection. This is especially of concern that the currently available sample sizes are small compared to the diversity of diseases and the patient population (age, gender, ethnicity, and comorbidity). Profiling cfDNA methylome can address this challenge, as it retains the genome-wide epigenetic profiles of cancer abnormalities, thereby permitting the classification models to learn and exploit newly significant features as training cohorts grow, as well as expanding their scope to more cancer types. However, the conventional way of profiling the cell-free DNA methylome (whole-genome bisulfite sequencing) is cost-prohibitive for clinical use.

"Our method, cfMethyl-seq, makes cfDNA methylome sequencing a viable option for clinical use", says Xianghong "Jasmine" Zhou, professor of pathology and laboratory medicine at UCLA and a corresponding author for the study. "Despite the inherent challenges, our

study shows tremendous potential for accurate early diagnosis of certain cancers from a single blood test."

Zhou and colleagues in her UCLA lab focus on precision medicine—the use of patients' genomic information to develop more personalized, targeted treatments—and big biodata analysis to integrate complex data from various platforms and modalities into practical methods that can be used in clinical settings.

For this study, Zhou and collaborators put their novel approach to the test to see if it could accurately detect four commonly diagnosed cancers—colon, liver, lung and stomach cancer –and do so at early stages.

The researchers collected blood samples from 408 study participants and applied their methylome-based blood test, which can identify a broad range of markers for different cancer types and possible causes. Of those, 217 were cancer patients and 191 were cancer-free control subjects. Samples were collected at UCLA's hospitals or purchased from commercial laboratories to achieve cross-source validation. Researchers also performed cross-batch validations, age-matched validations, and independent validations to prevent bias in the study.

Following collection and validation measures, researchers entered the data into their sophisticated computer model to measure its accuracy not only at detecting cancer, but also the tumor's specific location, referred to as "tissue of origin."

Their model was 80.7% accurate in detecting cancers across all stages and about 74.5% accurate in detecting early-stage cancers—those at stages I or II—with just under 98% specificity. There was only one incorrectly classified normal sample (false positive).

For tissue-of-origin accuracy, the model correctly identified tumor location with an average accuracy of 89.1% percent for all cancer stages and about 85% percent in early-stage patients.

"The key to early cancer detection is to identify the true cancer biomarkers, which requires a large cohort of training samples to cover the heterogeneity of cancer and population, especially for pan-cancer detection. Our cfDNA methylome approach allows the inclusion of new markers and the better weighting of existing markers as training cohorts grow. Indeed, our data show that as training sample sizes increase, the detection power of our method continues to increase," said Zhou, who is a member of the UCLA Jonsson Comprehensive Cancer Center's Gene Regulation Program. "With its cost-effective methylome sequencing, cfMethyl-seq can truly facilitate a big data approach for cancer detection."

The team is currently pursuing funding for large clinical trials to validate the technology in hopes of bringing it to use to benefit patients.

More information: Cost-effective Methylome Sequencing of Cell-free DNA for Accurately Detecting and Locating Cancer, *Nature Communications* (2022). DOI: 10.1038/s41467-022-32995-6

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