# Artificial intelligence analysis of DNA fragmentomes and protein biomarkers noninvasively detects ovarian cancer

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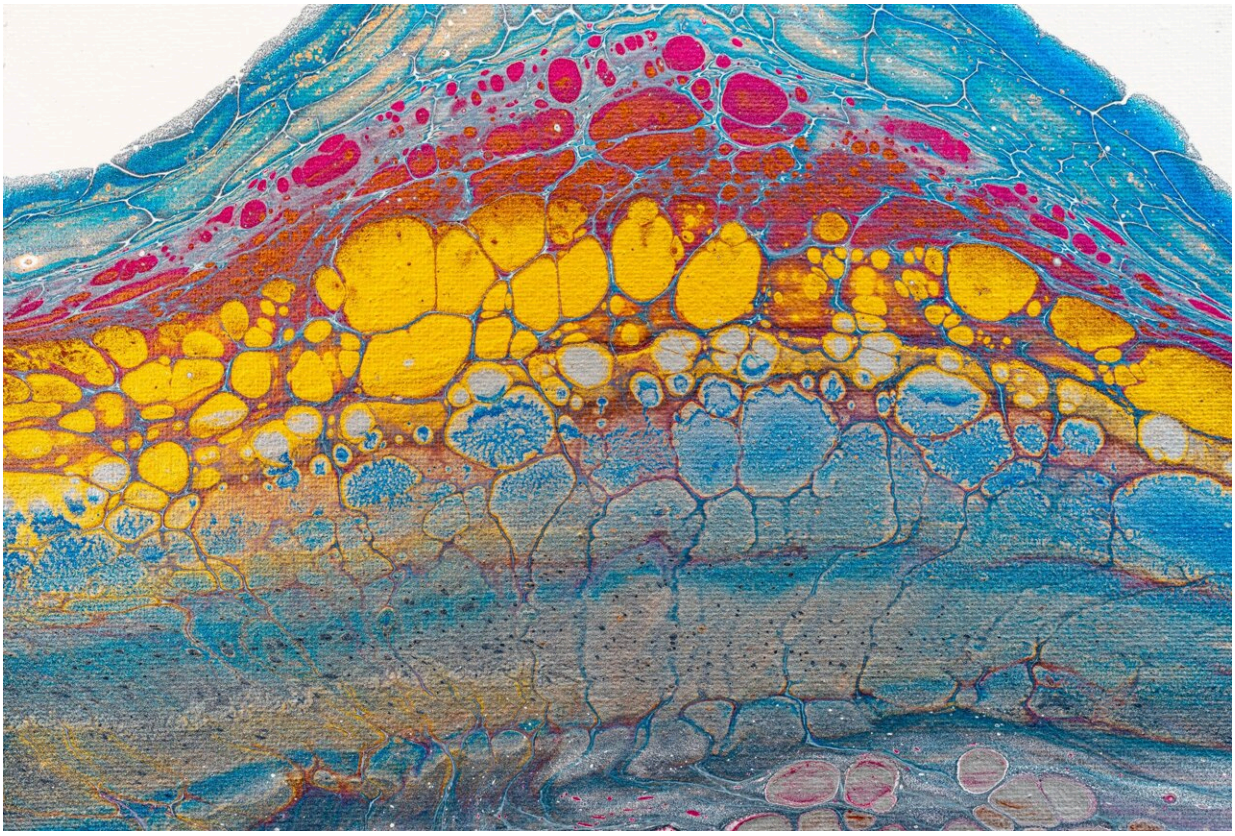

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A blood-based machine learning assay that combines cell-free DNA (cfDNA) fragment patterns and levels of the proteins CA125 and HE4 could differentiate patients with ovarian cancer from healthy controls or patients with benign ovarian masses, according to a retrospective study presented at the American Association for Cancer Research (AACR) Annual Meeting 2024, held April 5-10.

Federal statistics list ovarian cancer as the fifth-most common cause of cancer deaths among women in the United States, with a five-year survival rate of approximately 50%. Part of what makes ovarian cancer so deadly is that it does not typically cause symptoms in the early stages of disease, explained Jamie Medina, Ph.D., a postdoctoral fellow at the Johns Hopkins Kimmel Cancer Center.

"The lack of efficient screening tools, combined with the asymptomatic development of ovarian cancer, contributes to late diagnoses when effective treatment options are limited," said Medina, who presented the study alongside co-first author Akshaya Annapragada, an MD/Ph.D. student at the Johns Hopkins University School of Medicine. "A cost-effective, accessible detection approach could change clinical paradigms of ovarian cancer screening and potentially save lives."

Liquid biopsy technologies, in which researchers analyze patients' blood for evidence of tumor-derived DNA, have been explored as a way to noninvasively detect a variety of cancers; however, they have not always been useful in ovarian cancer, Medina explained. DELFI (DNA Evaluation of Fragments for early Interception), utilizes a newer method of liquid biopsy analysis, called fragmentomics, that has shown promise in improving the accuracy of such tests. The approach is based on detecting in the circulation changes in the size and distribution of cfDNA fragments across the genome, or the fragmentome.

"Because cancer cells are rapidly growing and dying and have chaotic genomes as compared to healthy cells, patients with cancer have different patterns of DNA fragments in their blood than patients without cancer," Medina said. "By carefully analyzing these fragments across the entire human genome, we can detect subtle patterns indicating the presence of cancer."

Medina, Annapragada, and colleagues analyzed fragmentomes from individuals with and without ovarian cancer using DELFI. They trained a machine learning algorithm to integrate the fragmentome data with plasma levels of two known biomarkers of ovarian cancer: the proteins CA125 and HE4.

"Ovarian cancer is an incredibly deadly disease with no great biomarkers for screening and early intervention," said Victor Velculescu, MD, Ph.D., FAACR, senior author of the study, a professor of oncology, and codirector of the Cancer Genetics and Epigenetics Program at the Johns Hopkins Kimmel Cancer Center. "Our goal was to overcome this challenge by combining genome-wide cell-free DNA fragmentation with protein biomarkers to develop a new high-performance approach for early detection of ovarian cancer."

The researchers analyzed plasma from 134 women with ovarian cancer, 204 women without cancer, and 203 women with benign adnexal masses. They used the data to develop two models: one to examine ovarian cancer screening in an asymptomatic population and the other to noninvasively differentiate benign masses from cancerous ones.

At a specificity of over 99% (nearly no false positives), the screening model identified 69%, 76%, 85%, and 100% of ovarian cancer cases staged I-IV, respectively; the area under the curve (a measure of accuracy that increases as the value approaches 1) was 0.97 across all stages, much higher than the performance of current biomarkers. For

comparison, an analysis of CA125 levels alone identified 40%, 66%, 62%, and 100% of cases staged I-IV, respectively.

The diagnostic model was able to differentiate ovarian cancer from benign masses with an area under the curve of 0.87.

The group intends to validate their models in larger cohorts to strengthen the associations observed here, Velculescu said, but he found the current data encouraging. "This study contributes to a large body of work from our group demonstrating the power of genome-wide cell-free DNA fragmentation and machine learning to detect cancers with high performance," he said. "Our findings indicate that this combined approach resulted in improved performance for screening compared to existing biomarkers."

Limitations of this study include a relatively small sample size, a study population primarily comprised of American and European patients, and the retrospective nature of the analysis.

Provided by American Association for Cancer Research

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