Liquid biopsy predicts early disease progression, potential survival in patients with advanced breast cancer

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A novel, automated liquid biopsy test in development by researchers at the Johns Hopkins Kimmel Cancer Center can be used to predict early

disease progression and potential survival among patients with metastatic breast cancer in as little as one month after starting treatment, according to a recent study.

The test—so far, a prototype for research use only—was able to identify the presence of cancer DNA in one or more of nine genes commonly altered in breast cancers in blood samples from women actively undergoing breast cancer treatment. Methylation is a type of chemical tag associated with cancer development and progression for its ability to turn off tumor suppressor genes.

Patients with high cumulative methylation at week four of treatment had a significantly shorter progression-free survival (the length of time in which the disease does not worsen) and worse overall survival than those who had low cumulative methylation.

Researchers used methylation levels measured at week four to develop a new model to predict risk of early disease progression in women with metastatic breast cancer. Study results were published in the journal *Clinical Cancer Research*.

Predictive clinical biomarkers to identify early disease progression are needed for women with metastatic breast cancer given how heterogeneous the condition is, explains lead study author Kala Visvanathan, M.D., M.H.S., director of the Cancer Genetics and Prevention Service at the Johns Hopkins Kimmel Cancer Center. Biomarkers could help oncologists minimize the negative impacts on patients' quality of life from drug combinations by optimizing the use of available and effective therapies, she says.

"It looks promising that we can detect methylation in the first four weeks of treatment," she says. "Currently, we wait until we see symptomatic or clinical changes, usually within three months, before adjusting

treatments. If we could detect changes earlier, we could adjust treatments earlier, if necessary, with the goal of achieving better clinical outcomes and prolonging survival."

The assay, called the Liquid Biopsy for Breast Cancer Methylation (LBx-BCM), was developed in the laboratory of Saraswati Sukumar, Ph.D., professor of oncology at the cancer center and a co-lead author in the study.

The assay is compatible with a commercially available molecular testing platform called GeneXpert, and in under five hours can detect methylation in the following genes altered in the four subtypes of breast cancers: AKR1B1, TM6SF1, ZNF671, TMEFF2, COL6A2, HIST1H3C, RASGRF2, HOXB4, and RASSF1. The current study also looked for methylation in the gene ZNF671, associated with estrogen receptor (ER)-negative breast cancer. The assay requires less than 15 minutes of hands-on time by a laboratory technician.

Investigators evaluated the assay using plasma samples collected from 144 patients with metastatic breast cancer before starting treatment, and at four and eight weeks into treatment. The median age of patients was 56. Nineteen percent were Black and 87% were postmenopausal. The median follow-up time of the group was about six years.

Median progression-free survival for patients with high cumulative methylation at week four was found to be 2.88 months versus 6.66 months for those with low methylation. Median overall survival for those with high cumulative methylation at week four was found to be 14.52 months versus 22.44 months for those with low methylation.

Investigators also looked at the association between cumulative methylation and disease status at the first cancer re-staging, approximately three months later. In 77% of patients, cumulative

methylation levels decreased in the first four weeks and then remained stable through time to the first re-staging.

In 18% of patients with stable disease and 37% of patients with progressive disease, an increase in cumulative methylation was observed from baseline to week four. There was no further increase in cumulative methylation among those who responded to treatment, with levels remaining stable from week four to week eight.

High versus low cumulative methylation at week four was associated with progressive disease at first re-staging. The association between week four cumulative methylation levels at first restaging and progressive disease remained significant even in the presence of other circulating markers used to monitor disease progression, such as circulating tumor cells.

Researchers used results from cumulative methylation levels measured at week four to develop and evaluate a new model to predict disease progression as early as three months after initiating treatment.

"To our knowledge, this is the first methylation-based prediction model focused on early disease progression in patients with metastatic breast cancer," says Sukumar. "The model was robust when tested under many different statistical assumptions," adds Leslie Cope, Ph.D., associate professor of oncology and the biostatistician and second co-lead author on the study.

The next steps in research are to study patterns of methylation seen each week after starting treatment to identify the optimum time to measure cumulative methylation, and to validate and refine the model in similar patient populations as well as in patients with early-stage disease, Visvanathan says.

More information: Kala Visvanathan et al, Evaluation of a Liquid Biopsy-Breast Cancer Methylation (LBx-BCM) Cartridge Assay for Predicting Early Disease Progression and Survival: TBCRC 005 Prospective Trial, *Clinical Cancer Research* (2022). DOI: 10.1158/1078-0432.CCR-22-2128

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