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New 'liquid biopsy' blood test improves breast cancer diagnostics

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Muhammed Murtaza, M.B.B.S., Ph.D., Assistant Professor and Co-Director of TGen's Center for Noninvasive Diagnostics. He also holds a joint appointment on the Research Faculty at Mayo Clinic in Arizona, and is one of the study's senior authors. Credit: TGen

A new type of blood test for breast cancer could help avoid thousands of

unnecessary surgeries and otherwise precisely monitor disease progression, according to a study led by the Translational Genomics Research Institute (TGen) and Mayo Clinic in Arizona.

TGen is an affiliate of City of Hope, which along with The Cancer Research UK Cambridge Institute at Cambridge University and the Biodesign Institute at Arizona State University (ASU) also contributed to this study.

Published today in the premier journal *Science Translational Medicine*, the study suggests that the test called TARDIS—TARgeted DIgital Sequencing—is as much as 100 times more sensitive than other blood-based cancer monitoring tests.

TARDIS is a "liquid biopsy" that specifically identifies and quantifies small fragments of cancer DNA circulating in the patient's bloodstream, known as circulating tumor DNA (ctDNA). According to the study, TARDIS detected ctDNA in as low as 2 parts per 100,000 in patient blood.

"By precisely measuring ctDNA, this test can detect the presence of residual cancer, and inform physicians if cancer has been successfully eradicated by treatment," said Muhammed Murtaza, M.B.B.S., Ph.D., Assistant Professor and Co-Director of TGen's Center for Noninvasive Diagnostics. He also holds a joint appointment on the Research Faculty at Mayo Clinic in Arizona, and is one of the study's senior authors.

For example, Dr. Murtaza explained, TARDIS is precise enough to tell if early stage breast cancer patients have responded well to pre-operative drug therapy. It is more sensitive than the current method of determining response to drug therapy using imaging.

"This has enormous implications for women with breast cancer. This test

could help plan the timing and extent of surgical resection and radiation therapy after patients have received pre-operative therapy," said Dr. Barbara A. Pockaj, M.D., a surgical oncologist who specializes in breast and melanoma cancer patients at Mayo Clinic in Arizona, and is the study's other senior author. Dr. Pockaj is the Michael M. Eisenberg professor of surgery and the chair of the Breast Cancer Interest Group (BIG), a collaboration between researchers at Mayo, TGen and ASU.

Unlike traditional biopsies, which only produce results from one place at one time, liquid biopsies use a simple blood draw, and so could safely be performed repeatedly, as often as needed, to detect a patient's disease status.

This study was performed in collaboration with Carlos Caldas, M.D., Professor of Cancer Medicine at the University of Cambridge and Director of the Breast Cancer Programme at the Cancer Research UK Cambridge Cancer Centre.

"TARDIS is a game changer for response monitoring and residual disease detection in early breast cancer treated with curative intent. The sensitivity and specificity of patient-specific TARDIS panels will allow us to tell very early, probably after one cycle, whether neo-adjuvant (before surgery) therapy is working and will also enable detecting micro-metastatic disease and risk-adapted treatment after completing neo-adjuvant therapy," said Dr. Caldas, who also is Senior Group Leader at the Cancer Research UK Cambridge Institute, and one of the study's contributing authors.

Following further clinical testing and trials, TARDIS could someday be routinely used for monitoring patients during cancer treatment, and discovering when patients are essentially cured and cancer free.

"The results of these tests could be used to individualize cancer therapy

avoiding overtreatment in some cases and under treatment in others," Dr. Murtaza said. "The central premise of our research is whether we can develop a blood test that can tell patients who have been completely cured apart from patients who have residual disease. We wondered whether we can see clearance of ctDNA from blood in patients who respond well to pre-surgical treatment."

Current tests and imaging lack the sensitivity needed to make this determination.

"Fragments of ctDNA shed into blood by tumors carry the same cancer-specific mutations as the tumor cells, giving us a way to measure the tumor," said Bradon McDonald, a computational scientist in Dr. Murtaza's lab, and the study's first author.

"The problem is that ctDNA levels can be so low in non-metastatic cancer patients, there are often just not enough fragments of ctDNA in a single blood sample to reliably detect any one mutation. This is especially true in the residual disease setting, when there is no obvious tumor left during or after treatment," McDonald said. "So, instead of focusing on a single mutation from every patient, we decided to integrate the results of dozens of mutations from each patient."

The study results suggest that personalized ctDNA analysis, using TARDIS, is a promising approach to identifying patients with a curative response following pre-surgical drug therapy.

"Together with imaging and tissue-based predictive biomarkers, ctDNA is rapidly becoming a useful diagnostic test to determine individualized decisions about additional treatment," Dr. Murtaza said.

Dr. Pockaj affirmed: "We are excited that TARDIS has the potential to really individualize clinical management of patients with non-metastatic

cancer."

Thomas Slavin, M.D., Assistant Clinical Professor at City of Hope National Medical Center, and a contributing author of the study, noted that "reliably identifying, often multiple, circulating tumor mutations in the plasma of patients with non-metastatic breast cancer also holds promise that ctDNA may one day be a great tool for early breast cancer detection."

TGen is now focused on evaluating the best partners to work with to automate and scale TARDIS, so it can be made available broadly to benefit patients in need.

"This data represents an exciting strategy to improve the sensitivities of liquid biopsies, which have been challenging for breast cancer," said Karen Anderson, M.D., Ph.D., a researcher at the Biodesign Institute, a medical oncologist at Mayo Clinic in Arizona, and one of the study's contributing authors. "This work represents highly collaborative efforts across multiple institutions, and with the generosity and foresight of our patients who have contributed to this study."

More information: B.R. McDonald el al., "Personalized circulating tumor DNA analysis to detect residual disease after neoadjuvant therapy in breast cancer," *Science Translational Medicine* (2019). stm.sciencemag.org/lookup/doi/ … scitranslmed.aax7392

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