

## A blood test could predict who benefits from immunotherapy

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A test which detects changing levels of tumor fragments in the blood may be an easy, non-invasive and quick way to predict who will benefit from immunotherapy, a treatment option for advanced cancers.

Although immunotherapy has been shown to shrink tumors and prolong survival for <u>patients</u> for whom other treatments have failed, about 20-30% of patients benefit from it. Clinicians don't yet know ahead of



time who this subset of patients is.

Understanding this is crucial, since immunotherapy can have severe side effects in a small percentage of patients, and knowing whether to begin or continue would be helpful for patients weighing different treatment options.

A team of Princess Margaret Cancer Centre scientists and clinicians addressed this question with a novel study evaluating various cancer patients' response to a specific immunotherapy drug via a customized test based on each patient's tumor profile.

They found that individual response to treatment can be predicted within weeks, based on increasing or decreasing levels of DNA fragments which are shed from the tumor into the blood.

Genomic testing with powerful new technologies can detect the same <u>genetic mutations</u> in the fragments circulating in the blood as in the actual tumor. These fragments are called circulating DNA or ctDNA.

Specifically, the study found that a decrease in these circulating tumor DNA fragments at six—seven weeks after treatment with the immunotherapy drug pembrolizumab was associated with a beneficial response to the drug and longer survival.

The study, "Personalized circulating tumor DNA analysis as a predictive biomarker in solid tumor patients treated with pembrolizumab", is published in *Nature Cancer*, August 3, 2020.

Dr. Lillian Siu, a Senior Scientist and medical oncologist at the Princess Margaret, BMO Chair in Precision Cancer Genomics, and a co-senior author, noted that the study is one of the first studies across a broad spectrum of tumors to show that measuring levels of ctDNA could be



useful as a predictor of who responds well to immunotherapy.

"It's like a molecular CT scan that gives us a molecular dimension, an added layer of information to know whether a tumor is growing or not, " she says, "That's why this is so exciting. It helps to predict early on what may happen over time.

"Although important, computerized tomography (CT) and other scans alone will not tell us what we need to know quickly or accurately enough."

Dr. Scott Bratman, who is first author and a radiation oncologist and Senior Scientist at Princess Margaret and Associate Professor of Radiation Oncology and Medical Biophysics, University of Toronto, points out that it may take many months to detect whether a tumor is shrinking with various imaging scans.

"New next-generation sequencing technologies can detect and measure these tiny bits of cellular debris floating in the blood stream accurately and sensitively, allowing us to pinpoint quite quickly whether the cancer is active."

The prospective study analyzed the change in ctDNA from 74 patients, with different types of advanced cancers, being treated with pembrolizumab.

In order to customize or personalize the test, all the genes from the <u>tumor</u> biopsy tissue of each patient were sequenced or decoded at Princess Margaret, with specific attention to the mutations that occur in cancer. These cancer mutations ranged from dozens to tens of thousands of mutations per tissue sample, differing according to cancer type.

Sixteen genetic mutations for each patient were then selected for a



specific test to be developed and customized to detect personalized ctDNA of each patient via a simple blood sample.

"When we looked at all 20,000 genes in each cancer, the range of mutations in different individuals was huge due to the many different cancer types in the study," says Dr. Trevor Pugh, a co-senior author, Senior Scientist at Princess Margaret and Associate Professor, Dept. of Medical Biophysics, University of Toronto, and Director of Genomics, Ontario Institute for Cancer Research.

"The novelty is that, rather than taking a one-size-fits-all approach, we designed a personalized blood test for each person based on their own cancer's mutation list."

Of the 74 patients, 33 had a decrease in ctDNA levels from their original baseline levels to week six to seven after treatment with the drug. These patients had better treatment responses and longer survival. Even more striking was that all 12 patients who had clearance of the ctDNA to undetectable levels during treatment were still alive at a median follow-up of 25 months.

Conversely, a rise in ctDNA levels was linked to a rapid disease progression in most patients, and poor survival.

"Few studies have used a clinical biomarker across different types of cancers," says Dr. Siu, who is also the Clinical Lead for the Tumor Immunotherapy Program at the Princess Margaret and Professor of Medicine, University of Toronto, adding that "the observation that ctDNA clearance during treatment and its link to long-term survival is novel and provocative, suggesting that this biological marker can have broad clinical impact."

Mr. Azim Jamal, 71, was part of the study, and one of the patients who



benefited from immunotherapy. He was diagnosed with throat cancer in 2016, and received radiation and targeted molecular therapy.

With limited response and the <u>cancer</u> spreading to his lungs, he then received immunotherapy over two years, beginning in 2017. As of July 2020, his disease is in remission, with no evidence of progression.

"It was a last resort, but I said yes immediately," he says when asked if he would like to participate in the immunotherapy clinical trial. "I want to enjoy life, I want to see my grandchildren, participate in my community and church. And I also appreciate the opportunity to participate in important research that could help others."

Serena Jamal-Esmail, his daughter who is also a nurse, says that seeing her father respond so well to the immunotherapy was "like a light...It had been so emotional, so scary. My kids will be able to remember their granddad. I can breathe again."

The prospective study is part of a larger flagship clinical trial, INSPIRE, which has enrolled more than 100 patients with head and neck, breast, ovarian, melanoma and other advanced solid tumors. Launched at Princess Margaret in 2016, the trial follows and tests patients at various stages of their treatment to pembrolizumab, a commonly used type of <u>immunotherapy</u>.

It also brings together researchers from many disciplines to investigate if specific genomic and immune biomarkers in patients may predict for response or resistance to the drug.

**More information:** Personalized circulating tumor DNA analysis as a predictive biomarker in solid tumor patients treated with pembrolizumab, *Nature* (2020). DOI: 10.1038/s43018-020-0096-5, www.nature.com/articles/s43018-020-0096-5



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