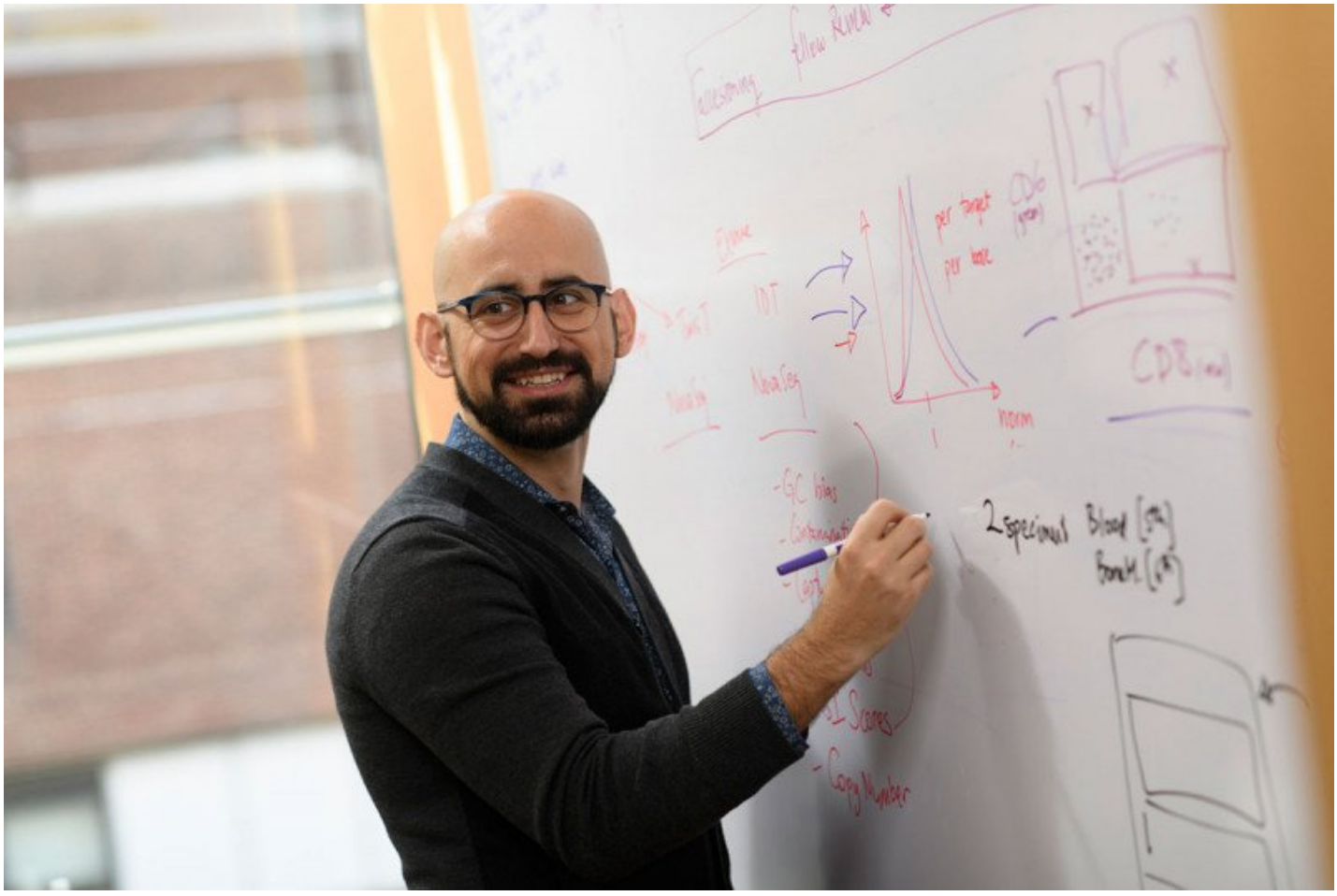
Gene Mutations in the Blood Can Complicate Findings from Tumor Sequencing

By Julie Grisham, **Tuesday, June 5, 2018**



Bioinformatician Ahmet Zehir says his latest study findings show "there's lots to consider when matching patients to the right treatment."

Summary

MSK researchers have found that clonal hematopoiesis (CH) can be misinterpreted as tumor mutations in sequencing tests. CH is a blood condition related to aging that can cause mutations in the blood. Misreading such results could affect treatment decisions.

MSK-IMPACT™ is a diagnostic test that looks for mutations in more than 450 cancer-causing genes in people's tumors. It has led to major advances in precision medicine. Based on the mutations that are found, people with cancer may receive treatment with an approved targeted therapy or immunotherapy that's matched to their cancer. Some people may enroll in a clinical trial based on the results.

When Memorial Sloan Kettering experts — including pathologist **Marc Ladanyi** and geneticist **Michael Berger** — built the test, they also included the analysis of an individual's blood sample in addition to the tumor sample. This component is not part of most other tumor-sequencing tests. That's what makes it possible to determine which mutations are part of a tumor and likely to be driving the cancer and which may be present in other parts of the body.

Today at the American Society of Clinical Oncology (ASCO) annual meeting, a new study illustrates a major benefit of that approach. The findings show if data about the blood are not part of test results, mutations specific to the blood may be misread as mutations in the tumor. This can potentially affect the therapy that someone gets.

"These findings add another layer of complexity to precision medicine," says MSK bioinformatician **Ahmet Zehir**, who presented the study at the ASCO meeting. "They show us that there's lots to consider when matching patients to the right treatment."

The Consequences of a Blood Condition

Cancer mutations may be present in a person's blood, even if they don't have blood cancer, due to a condition called clonal hematopoiesis (CH). Hematopoietic stem cells give rise to all types of blood cells. In CH, those stem cells form a group of cells that is genetically distinct from the rest of the blood stem cells. MSK physician-scientist **Ross Levine** was part of the research team that first identified the genetic basis of CH and its connection to blood cancer.

Learn more about clonal hematopoiesis and MSK's recently opened clinic to monitor people who have this blood condition.

CH is most commonly found in older people, especially those who have a history of smoking. Having CH doesn't mean that someone has or will get blood cancer. In fact, most people with CH will not: Experts estimate that between 0.1% and 4% of people

with CH will develop cancer within ten years of diagnosis, depending on their medical history. MSK **recently opened a clinic** for people with CH, to study the condition and monitor them for the development of blood cancer as well as heart disease, which is also linked to CH.

The reason CH-related mutations show up in tumor analysis is simple. Tumors have a blood supply, so some DNA from the blood is mixed with the tumor DNA.

A Potential to Influence Treatment Decisions

"We already have some examples of how this situation could directly affect patient care," Dr. Zehir says. In one case, a person was found to have a mutation in *BRCA2*, suggesting that he could benefit from a class of drugs called poly (ADP-ribose) polymerase (PARP) inhibitors. But that *BRCA2* mutation was due to CH, not genetic changes that were driving tumor growth, so a PARP inhibitor would not have been effective.

> "The findings show that you also need to analyze a blood sample if you want to be 100% confident in choosing the right therapy."

Ahmet Zehir
bioinformatician

This study, which is being published today in *JAMA Oncology*, outlines this case and others. "The findings show that you also need to analyze a blood sample if you want to be 100% confident in choosing the right therapy," Dr. Zehir says. He adds that misinterpreted sequencing results could alter the outcomes of clinical trials for new drugs if patients are assigned to a trial for a drug targeting a mutation their tumor doesn't have. The study's first author was MSK bioinformatician Ryan Ptashkin.

"Our findings show that this phenomenon could affect up to 5% of people with advanced cancer," Dr. Zehir concludes. "That may not sound like a high percentage, but it's still a large number of people. I hope that after doctors at other hospitals learn about our findings, they will be more aware of this issue when they're interpreting tumor-only sequencing results and deciding which treatments to give patients."

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