Double Jeopardy: Gene-Sequencing Test Uncovers New Clues about a Defect Seen in Many Tumors

By Julie Grisham, **Wednesday, July 18, 2018**

Computational biologist Barry Taylor studies genetic abnormalities that contribute to cancer.

Summary

MSK-IMPACT™ has led to many important findings about cancer genomics. In a recent study, researchers found that a genetic state in tumors called whole-genome doubling is connected with worse outcomes for people with cancer.

Healthy cells contain two copies of each gene: one from your mother and one from your father. But cancer cells don't play by the rules, and they can disrupt that arrangement.

A collaborative team of researchers from Memorial Sloan Kettering has found that a genetic state called whole-genome doubling is more common in cancer than expected. In addition, they were able to show a connection between this phenomenon and worse outcomes in people with cancer. The findings were **published online** July 16, 2018, in *Nature Genetics*. This research helps set the stage for a new way to categorize cancer and could ultimately help guide treatment decisions.

"This was a big surprise," says senior author **Barry Taylor**, Associate Director of the **Marie-Josée and Henry R. Kravis Center for Molecular Oncology** (CMO). "It turns out that almost 30% of all cancers have this change, across all different types of cancer. That makes whole-genome doubling the second most common feature of cancer after mutations in the *p53* gene."

Unexpected Discoveries from Genetic Testing

Whole-genome doubling is just what it sounds like. It means that a cell has gone from having two copies of every gene in its genome to four. It's one of the many different types of genetic errors that can enable cancer cells to grow out of control. Until now, it was unknown how often it occurs.

> Researchers found that almost 30% of cancers have whole-genome doubling, a much higher number than expected.

The new discovery was uncovered thanks to MSK-IMPACT™. This diagnostic test of tumor tissue looks for mutations in 468 genes that are known to drive cancer. The test is available to people being treated at MSK for advanced cancer. It helps doctors determine which therapies are most likely to offer a benefit, including experimental new drugs in clinical trials.

To ensure that the mutations detected by MSK-IMPACT are part of the cancer, pathologists also test some of the person's normal tissue. This is usually a blood sample. Directly comparing the tumor genome to the inherited genomes in normal

blood allowed the researchers in this study to tell the whole-genome doubling apart from other changes specific to the cancer.

Sequencing with MSK-IMPACT began in 2014. Since then, discoveries about genetic changes in normal blood have led to other important results. These include findings about **how common inherited cancer genes are** and the presence of a blood condition known as **clonal hematopoiesis**.

MSK-IMPACT also anonymously links the genomic data for each person to their clinical records. Investigators are then able to find connections that they wouldn't be able to make with the genomic information alone.

"We looked to see whether people whose tumors had whole-genome doubling had different outcomes than those whose tumors did not," Dr. Taylor explains. "It turns out they did. This genetic change was associated with lower survival rates in the people who had it, regardless of cancer type and other clinical and molecular features."

Validating the Findings in Future Research

Because MSK-IMPACT testing is performed on advanced cancers, the researchers used another set of data to confirm their findings. They looked at **The Cancer Genome Atlas** (TCGA), a database of tumor information from more than 10,000 people with cancer. TCGA includes information on cancers that are newly diagnosed and at all stages, from I to IV. The researchers found that the rate of whole-genome doubling in these tumors was about the same as what was seen in the MSK-IMPACT data.

"This suggests that whole-genome doubling happens sooner in the development of cancer rather than later," Dr. Taylor says. "We don't think it's an event that initiates cancer, but it occurs early in a tumor's evolution."

He adds that the findings help explain why people with advanced cancer that has spread often fare differently from one another. Some survive for years after their cancer has spread, while others do not. The variation in outcomes may be due to whole-genome doubling in the tumors. However, the causes behind these differences are not yet known.

More research is needed to validate the study's findings before they can be used to influence patient care. But in the future, genome doubling could help guide

personalized medicine, directing doctors to the people who need the most-aggressive treatment.

The co-authors on this study included MSK Physician-in-Chief José Baselga as well as CMO Director **David Solit** and Associate Director **Michael Berger**. The first author was **Craig Bielski**, a computational biologist in Dr. Taylor's lab.

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