New tool mines whole-exome sequencing data to match cancer with best drug

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A University of Colorado Cancer study published today in the *Journal of the American Medical Informatics Association* (*JAMIA*) describes a new tool that interprets the raw data of whole exome tumor sequencing and then matches the cancer's unique genetics to FDA-approved targeted treatments.

"Whole exome sequencing is becoming more available to patients and this tool will help them distill the sequencing data to candidate genes and link them with therapies," says Aik Choon Tan, PhD, investigator at the CU Cancer Center, associate professor of Bioinformatics at the CU School of Medicine, and the paper's senior author.

The tool, called Integrating Molecular Profiles with Actionable Therapeutics, or IMPACT, starts with the data generated by whole-exome sequencing - a string of A, T, C and G hundreds of millions of letters long. IMPACT then maps this string onto the human genome to partition the raw data into segments that correspond to the body's approximately 20,000 genes. The tool then compares the code of these genes to "normal" gene patterns to discover which genes differ in ways that could guide the development of cancer. (In a second step, IMPACT also counts the number of gene repeats, which when adjusted higher or lower can also drive the growth of cancer.)

"Now we have a list of candidate genes," Tan says. "The next step is to link candidate genes with therapeutics."

IMPACT does this by mining publicly available data including that of the NCI-MATCH clinical trial and the database at MyCancerGenome.org to discover which FDA-approved therapies target these candidate genes.

The Tan lab tested the tool by inputting whole-exome sequencing data for patients known to have EGFR-mutated non-small cell lung cancer from The Cancer Genome Atlas. Sure enough, IMPACT successfully identified the gene EGFR as a driving mutation and recommended FDA-approved EGFR inhibitors.

In collaboration with the laboratory of CU Cancer Center investigator William A. Robinson, MD, PhD, Tan and colleagues then used the tool to retrospectively analyze a series of exome-sequences from patients diagnosed with melanoma, validating the tool's ability to discover a patient's activating mutation and pair it with useful treatment.

"For example, a patient was found to have a BRAF mutation and was put on a clinical trial of the drug vemurafenib, which targets BRAF alterations," Tan says.

The drug controlled the patient's tumor. However, two years later the tumor relapsed. At this point, the group resequenced the tumor and found that in addition to BRAF mutation, the patient had developed NRAS mutation.

"Taking tumor samples over time, we could see the cancer cell figuring out how to become resistant," Tan says.

However, drugs also exist to disrupt cells that depend on NRAS mutation. The combination of dabrafenib (for BRAF) and trametinib (for NRAS) controlled the patient's melanoma for another two years. When the cancer relapsed, it was again resequenced and evaluated using

IMPACT. Analysis showed loss of the gene CDKN2a, a known tumor suppressor gene that keeps in check cells that have learned to speed through the process of replication. Currently there are no inhibitors of the CDK family of genes approved by the FDA to treat melanoma. However, the drug palbocicilib recently earned FDA approval to treat a subset of breast cancers.

"We are trying to see if we can treat this melanoma with a CDK inhibitor. Will this drug overcome the cancer's resistance to the previous combination?" Tan says.

The IMPACT tool works in four steps: 1) identify possible cancer-causing mutations; 2) identify possible cancer-causing gene copy number alterations; 3) match cancer's genetic causes with the most likely therapeutic controls; 4) evaluate the ongoing evolution of cancer to continue matching controls with emerging causes.

"We hope that IMPACT proves to be an important tool in empowering the shift toward precision medicine," Tan says.

More information: *Journal of the American Medical Informatics Association* , jamia.oxfordjournals.org/conte … 6/03/28/jamia.ocw022

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