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Mount Sinai to Test Cancer Network Modeling Approach in Two Clinical Trials

by Julia Karow

RESEARCHERS AND CLINICIANS at Mount Sinai School of Medicine have started to use cancer network models to analyze genomic data from patient tumors and are planning to test the ability of their approach to help doctors make treatment decisions and improve patient outcomes in two clinical trials.

Many clinical cancer sequencing programs focus on panels of known oncogenes that can be targeted by specific drugs. Mount Sinai's approach, on the other hand, analyzes the entire genome and transcriptome of a patient's tumor, maps the mutations onto a network model for that cancer type, and tries to predict the most suitable therapy based on the results.

"We are taking a more data-driven approach" that provides a complete view of a tumor's biology, said Joel Dudley, an assistant professor of genetics and genomic sciences at Mount Sinai School of Medicine.

So far, the researchers have completed their analysis for about 10 patients with recurrent late-stage cancers, including glioblastoma, head and neck cancer, and pancreatic cancer, and have returned the results to the treating physicians.

The next step will be to test in clinical trials whether the network-based genomic analysis improves patients' outcomes.

The process starts with obtaining a tumor sample, preferably fresh because the RNA degrades quickly, although the scientists have also used frozen and fixed material. Dudley said close

collaboration with pathologists is critical to obtain adequate and well-annotated samples.

The tumor then undergoes genome-wide transcriptome sequencing as well as whole-genome sequencing, along with WGS of a matched germline control.

Sequencing is performed at Mount Sinai's CLIA-certified genomics core facility (*IS 1/8/2013*) on Illumina's HiSeq 2500. The researchers are considering sequencing on both the Illumina and Pacific Biosciences platforms in the future, at least for some patients, in order to take advantage of the PacBio's long reads, Dudley said. Gene fusions and chromosomal rearrangements, in particular, are difficult to detect with short read technology alone, he added.

The researchers then call somatic mutations in the tumor RNA and DNA and put them on a probabilistic network model they have previously built for that type of cancer. "We want to organize the information on a network because we think that's the best way to interpret the biology," said Dudley, who is also director of biomedical informatics. In addition, they identify specific epitopes present in the tumor DNA, which is important for cancer vaccine approaches.

The network models, which are "pretty complex to build," are based on large datasets for a specific tumor type, for example RNA, DNA, copy number variant, and methylation data from the *Cancer Genome Atlas*.

By projecting an individual patient's data onto the network, the researchers can identify sub-networks that are enriched for mutations and "determine what's really unique about the biology of their tumor," Dudley explained. From that, they can identify "key driver" genes in the sub-networks that could potentially be targeted by drugs.

In the cases they have analyzed so far, none of the mutated sub-networks had known cancer drug targets, he said. In the meantime, they have been gleaning insights into tumor biology. For example, they have identified some cancers with "lots of



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mutations” in genes connected to an oncogene but not the oncogene itself, and others where hypermutations in certain genes relate to the tumor’s escape from prior therapy.

In addition to assessing known drug targets, the scientists perform *in silico* drug screens, where they look through thousands of approved drugs in order to find one that might down-regulate the mutated sub-network of a patient’s tumor. “The target for that drug might not necessarily be in that sub-network, it’s just that we know from the transcriptional pattern of the drug that it’s going to downregulate that network,” Dudley said. The screen might yield non-obvious results, he added, for example drugs used in other types of cancers or other diseases altogether, such as autoimmune drugs.

Currently, the researchers are further developing the pipeline for creating the tumor networks and performing the drug screens. “The pieces of the pipeline exist; we are just now making it more automated,” Dudley said.

The result of the analysis is a report for physicians, which is also still evolving. “That’s the big challenge, the challenge everybody is trying to solve right now,” he said.

“The current form represents a series of slides where we summarize our findings, but we’re working actively on how to deliver that as a clinical report,” he said. “You can’t show doctors networks, they don’t care about networks.” Rather, the report will include information about the genes in the patient-specific networks, their functions and relation to cancer, and clinical actionability regarding further tests or drugs.

The researchers are targeting turnaround times of one to two weeks for sequencing and data analysis, Dudley said. While they have provided results from the drug screens back to clinicians, they do not know yet whether doctors have actually prescribed those drugs. “We have had some say, ‘I would have never considered this drug in a million years, but now this drug is on the table to be considered,’” he said.

He and his colleagues are now preparing two clinical trials to see whether the network analysis helps doctors make treatment

decisions and improve patients’ outcomes.

The first trial, to be launched within the next few months, will involve at least 50 multiple myeloma patients from Mount Sinai. Doctors have “a toolbox of drugs” available to treat this cancer, but patients eventually become resistant to all of them, Dudley said. The network analysis could help doctors decide in which order to prescribe the existing therapies.

While the exact trial design has not been finalized yet, one possibility is that patients who have developed resistance to their first treatment enter the trial, and the network analysis will help decide which drug should be next. “Then, we should know within months whether the choice was a good one or not,” Dudley said.

The trial would compare the outcomes of patients whose doctors were informed by the network results with the outcomes of those whose doctors did not have that information.

Prior to the trial, the scientists will build a multiple myeloma network model, for which they are currently sequencing the RNA and DNA of at least 100 bone marrow transplant samples from a large tissue collection.

For the second clinical trial, scheduled to launch later this year, they have not yet decided the cancer type but are considering several, including melanoma and prostate cancer. The ultimate choice will depend on the number of patients available and whether the cancer provides “the right endpoints that let us show that early on, we’re having an effect,” Dudley said.

Key to the success of the entire program is that computational biologists have been working hand in hand with clinicians who have been involved from the beginning, he said. “Researchers at other places who can do the network modeling are not necessarily as close to the clinical side.” Clinicians at Mount Sinai have been “amazingly open to this approach,” he added, noting that given that many patients are still dying of cancer, “they are desperately hungry for innovations in this area.”