A Step Closer to Realizing the Promise of Precision Medicine in Cancer

New findings just published in *Scientific Reports* (a *Nature* research journal) may prove to be an important solution to one of the more difficult problems faced in the field of precision medicine when it comes to treating cancer. A novel statistical approach developed by J. Sunil Rao, Ph.D., professor and co-leader of the Cancer Control Research Program at Sylvester Comprehensive Cancer Center at the University of Miami Miller School of Medicine, and recent UM Ph.D. graduate Hongmei Liu, may better help physicians match the right drugs to the right patient.


The idea is simple: determine a patient’s cancer genomic profile, and then, using knowledge of other patients with similar profiles, prescribe treatments that target this patient’s set of unique cancer mutations. High-throughput pharmacogenomics studies — in which drugs are screened against panels of cancer cell lines — have been proposed as a strategy to enable these prescriptions.

While cancer researchers and clinicians around the world strategize to find appropriate drug matches, the challenge remains being able to replicate and validate findings.
“You have to prove these things are reproducible,” says Rao, who is also interim chair of the Department of Public Health Sciences and division head for biostatistics at UM. “If I go to another dataset, I should be able to validate my findings. That is, I should see reproducible patterns emerge. That’s the benchmark for discovery in medicine and science.”

The two largest studies currently are the Genomics of Drug Sensitivity in Cancer (GDSC) project from the Sanger Institute/Massachusetts General Hospital consortium and the Cancer Cell Line Encyclopedia (CCLE) study from Broad Institute. Validation using these two datasets together has proven elusive. Attempts to better analyze and harmonize experimental protocols have not alleviated the problem. Other groups have tried to replicate the experimental design and generated additional data — again with only limited improvements in reproducibility of found gene-drug interactions. Additionally, very few new interactions were detected. It got to the point where some prominent researchers were questioning the very usefulness of such pharmacogenomic assays.

To overcome this obstacle, Rao and Liu developed an entirely new analysis paradigm. They derived an estimator for the gene-drug interaction effects that accounted for potential discordancies or inconsistencies across datasets. If there were differences, their methodology, which is termed “discordancy partitioning,” identified them and separated them from the true signal. If differences were not present, then the model adapted accordingly. This allowed any reproducible true effects across datasets to come through and not be masked.
With this new approach, the GDSC and CCLE datasets started to match up. The UM research team found large numbers of new and consistently reproducible biomarkers for all drugs examined, which could be valuable information for oncologists, helping them identify the best drugs for each cancer patient. Even better, the model is built to handle more data.

“You don’t have to limit it to just two datasets,” said Rao. “As we get more and more pharmacogenomic information, the methodology will scale naturally. The potential to finally validate these studies is significant. It opens up a bottleneck for understanding how to better match patients to drugs. It is also crucial for drug development, because promising new compounds can more readily be identified and then verified.”