MedicalXpress

Genetic sequencing could help match patients with biomarker-driven cancer trials, treatments

November 30 2011

As cancer researchers continue to identify genetic mutations driving different cancer subtypes, they are also creating a catalog of possible targets for new treatments.

The University of Michigan Comprehensive Cancer Center and Michigan Center for Translational Pathology (MCTP) recently completed a pilot study aimed at solving the practical challenges involved in quickly and systematically sequencing genetic material from patients with advanced or treatment-resistant cancer in order to match them with existing clinical trials based on the biomarkers identified.

"We're talking about more than just examining a few genes where mutations are known to occur, or even about a hundred genes," says co-lead investigator Dan Robinson, Ph.D., a post-doctoral fellow at MCTP. "We're talking about the ability to sequence more than 20,000 genes and look not just for individual genetic mutations, but at combinations of mutations."

The exploratory study, known as the Michigan Oncology Sequencing Project (MI-ONCOSEQ), found that identifying a patient's "mutational landscape" provides a promising approach for identifying which trials may best help a patient, the researchers say. Their findings were published today in Science Translational Medicine.

"High-throughput sequencing harnesses the latest technological advances to process millions of pieces of genetic information, allowing us to map a cancer's genetic aberrations," says co-lead investigator Sameek Roychowdhury, M.D., Ph.D., a clinical lecturer in hematology and oncology at the U-M Medical School. "Using this technique to identify biomarker-driven treatment options really opens the door for personalized oncology, but it also presents a number of logistical challenges, chief among them making the results available cost-effectively and in a clinically relevant timeframe."

"A decade or two ago, this type of sequencing would have cost many millions or even billions of dollars, but the technology is advancing so rapidly, we're now talking in terms of thousands – which makes widespread use a real possibility," he adds.

Cancer can arise from a variety of genetic alterations including rearrangements, additions, deletions and substitutions within the genetic code.

"Different sequencing processes are required to find different types of alterations," Roychowdhury says. "But to be cost-effective, there must be a balancing act between a broad analysis and a deep analysis."

The study began by testing the researchers' sequencing strategy on prostate cancer tumors that had been grown in mice. Later, two patients were enrolled in a clinical pilot: one with colorectal cancer and one with melanoma. Potential clinical trials were identified for both patients.

However, the researchers caution, not all patients will match an existing study. Some patients with a given mutation may be excluded because they have, for example, prostate cancer, but a trial is only enrolling breast cancer patients. The researchers believe that this approach also provides an opportunity to approach clinical trials in a new way, moving

from a tissue-specific focus toward genetic aberrations shared across cancer types.

Still, enrolling in a trial does not guarantee a patient will benefit from the treatment, the researchers caution.

Hurdles to widespread implementation include the need for a multidisciplinary Sequencing Tumor Board to interpret the complex sequencing results, management of the necessary computational resources, and a process for dealing with incidental genetic findings revealed by the sequencing – such as a risk for hemochromatosis, a genetic disorder that causes the body to absorb too much iron.

Achieving a four-week turnaround time for results is important because that's how long patients are usually required to wait for unsuccessful treatments to leave their systems before starting a clinical trial.

"Once some of the practical and technological hurdles are cleared, we envision an array of mutation and pathway-based trials for available targeted therapies, with eligibility based on molecular assessment," says senior investigator Arul Chinnaiyan, M.D., Ph.D., director of MCTP, Howard Hughes Medical Institute Investigator, and S.P. Hicks Professor of Pathology at the U-M Medical School. "Moreover, if patients are treated with matching targeted therapies and develop secondary resistance, it could also help reveal the mechanisms of resistance and inform future trials for combination therapies."

Chinnaiyan says the work was made possible only by collaboration and teamwork. U-M physicians Moshe Talpaz, M.D., Stephen Gruber, M.D., Ph.D., and Kenneth Pienta, M.D. played key roles in the clinical implementation of this exploratory protocol, he notes.

Researchers hope this type of sequencing will become more widely

available over the next 5 to 10 years. Cancer patients are encouraged to speak to their doctors about clinical trial opportunities.

More information: "Personalized Oncology Through Integrative High-Throughput Sequencing: A Pilot Study," *Science Translational Medicine*, Nov. 30.

Provided by University of Michigan Health System