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First WGS of multiple pancreatic cancer patients outlined in new study

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Whole genome sequencing—spelling out all 3 billion letters in the human genome—"is an obvious and powerful method for advancing our understanding of pancreatic cancer," according to a new study from TGen, Mayo Clinic and Scottsdale Healthcare published today.

The Translational Genomics Research Institute (TGen) demonstrated that the use of WGS "represents a compelling solution to obtaining detailed molecular information on tumor biopsies in order to provide guidance for therapeutic selection," concluded the study published by the journal PLOS ONE.

Examining three patients, the study spelled out the DNA of normal cells and compared that to the DNA of cells from biopsies of pancreatic adenocarcinoma (PAC), which makes up 95 percent of all pancreatic cancer tumors. Pancreatic cancer is the fourth leading cause of cancer death in the U.S.

Using next-generation sequencing, the study generated an average of 132 billion mappable bases, or data points, for each patient, resulting in the identification of 142 cellular genetic coding events, including mutations, insertions and deletions, and chromosomal copy number variants.

"This study is the first to report whole genome sequencing findings in paired tumor/normal samples collected from (three) separate PAC patients," said the report, which also was compiled with the collaboration of Mayo Clinic in Arizona, Arizona State University, and the Virginia G.

Piper Cancer Center Clinical Trials at Scottsdale Healthcare, which is a partnership between TGen and Scottsdale Healthcare.

In all three case studies, the report found multiple potential therapeutic targets, highlighting the need to study the full spectrum of the genome and re-emphasizing the need to develop multiple avenues of therapeutics to match the specific medical challenges of each patient.

"Cancer, and specifically here pancreatic cancer, is a highly complex disease that ultimately will require a variety of treatment methods to control, and ultimately to cure," said Dr. Daniel Von Hoff, TGen's Physician-In-Chief, and Chief Scientific Officer for the Virginia G. Piper Cancer Center at Scottsdale Healthcare.

"This study shows that, as we continue to generate more information by sequencing the whole genomes of patients, we will continue to discover—with ever more confidence—the specific mechanisms that cause this cancer," said Dr. Von Hoff, one of the study's senior authors and one of the world's leading authorities on pancreatic cancer.

"We are very pleased to be working together with TGen in bringing hope and state of the art therapy to our patients at the Mayo Clinic Comprehensive Cancer Center," said Keith Stewart, M.B., Dean of Research at Mayo Clinic in Arizona, and the study's other senior author.

In the case of Patient 1, for example, genes previously associated with PAC were identified, including BRCA2, TP53, CDKN2A, MYC, SMAD4 and KRAS. But the study also made new discoveries. "Although BRCA2 mutations have been identified in PAC, the deletion we identify here in exon 10 of BRCA2 has not been previously reported," the study said.

Multiple therapeutics based on these findings were applied to Patient 1,

who initially "showed a complete response," but developed drug resistance after six months.

"The BRCA2 deletion is likely the driving mutation in this patient as the loss of DNA repair functions permits the occurrence of mutations," the study said. "This finding and association provides evidence of the utility of performing whole genome analysis of patients in order to identify less common mutations that may be relevant for therapeutic selection."

WGS for Patient 2 and Patient 3 also uncovered multiple potential therapeutic targets through the identification of mutations and copy-number changes. In addition, RNA sequencing, or whole transcriptome analysis, of Patient 2 and Patient 3 revealed gene expression data that provided more information about likely affected biological processes.

Cellular pathway analysis of all sequencing data was also performed to identify processes that may be the most heavily impacted by cellular and gene expression alterations.

"As we continue to sequence patients, we will acquire a better understanding of the compendium of events that have a role in the disease, and strengthen our knowledge base for identifying and developing improved therapeutics," said Winnie Liang, Ph.D., Assistant Director of TGen's Collaborative Sequencing Center and one of the co-lead authors of the study.

"This study has demonstrated the feasibility of applying genome sequencing approaches toward eventual personalization and precision of therapy for patients with pancreatic cancer," said Dr. Mitesh Borad, hematologist/oncologist at Mayo Clinic in Arizona and co-author of the study. "Current studies are focusing on application of this approach in the clinical setting in a real time fashion."

Co-author Dr. Michael Demeure, Clinical Professor of TGen's Rare Cancer Unit and Scientific Director of the Endocrine and Rare Tumors Program at the Virginia G. Piper Cancer Center at Scottsdale Healthcare, said, "Whole genome sequencing provides us with the genetic blueprint and knowledge that is needed to crack the complex mysteries surrounding pancreatic cancer. For rare cancers where the data pool is relatively small, the potential for progress is particularly encouraging."

This groundbreaking study—Genome-wide characterization of pancreatic adenocarcinoma patients using next generation sequencing—was funded by: the National Foundation for Cancer Research, the Randy Pausch Scholarship Fund, and the Seena Magowitz Foundation. Additional support was provided by the Mayo Clinic Comprehensive Cancer Center, the U.S. Department of Health and Human Services, and supercomputing resources funded by the National Institutes of Health.

"This study represents a major step forward in the quest to find a cure for this cancer, which took the life of my mother, Seena. We are working harder than ever with TGen and others to continue this fight," said Roger Magowitz, President and co-founder of the Seena Magowitz Foundation.

"Whole genome sequencing is a new approach toward finding better treatments and to making these treatments available to cancer patients who need them now. We cannot emphasize enough the need for this kind of research," said Franklin C. Salisbury Jr., President of the NFCR.

More information: dx.plos.org/10.1371/journal.pone.0043192

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