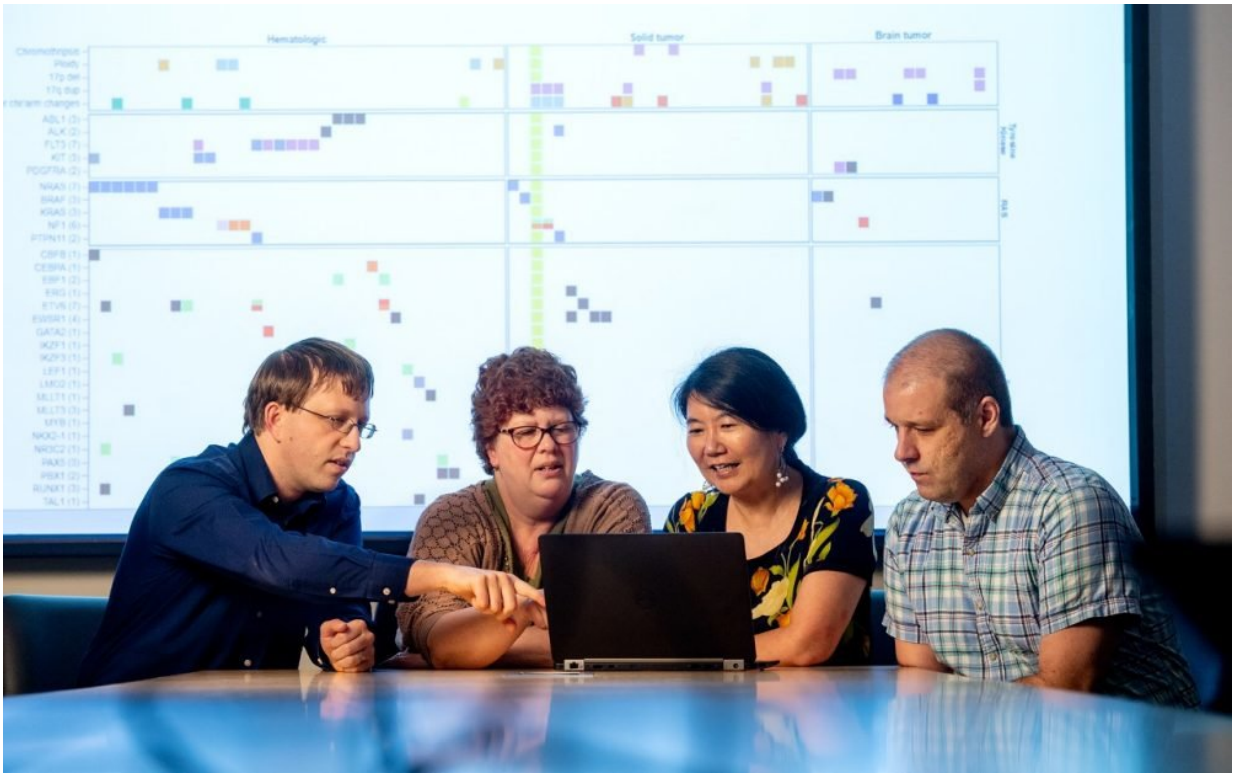
Researchers find a 'critical need' for whole genome sequencing of young cancer patients

October 12 2018



St. Jude investigators (from left) Michael Rusch, Sheila Shurtleff, Ph.D., Jinghui Zhang, Ph.D., and Scott Newman, Ph.D. Credit: St. Jude Children's Research Hospital

St. Jude Children's Research Hospital has re-defined the gold standard for diagnostic testing of childhood cancer patients in the precision-

medicine era and has implemented the testing for new cancer patients. The findings appeared online recently in the scientific journal *Nature Communications*.

Researchers showed that incorporating whole-genome sequencing into clinical genomic testing led to identifying additional cancer-driving mutations in almost half of patients in a recent study. These mutations could not be identified by sequencing just the protein-coding regions of the genome (exome) and gene expression (transcriptome).

The pilot study included 78 children and adolescents with a wide variety of cancers who were treated at St. Jude and had undergone extensive diagnostic testing. The research laid the foundation for the clinical genomic testing now offered to every new St. Jude cancer patient. The effort included developing a clinical pipeline for analyzing, validating and identifying clinically significant results in a timely manner.

"This research offers a new gold standard for clinical genomic testing and emphasizes the critical need for incorporating whole-genome sequencing into clinical testing and treatment of pediatric cancer patients," said James R. Downing, M.D., St. Jude president and chief executive officer. Downing; Jinghui Zhang, Ph.D., chair of the St. Jude Department of Computational Biology; and David Ellison, M.D., Ph.D., chair of the St. Jude Department of Pathology, are the study's corresponding authors.

Whole-genome sequencing involves determining the exact order of the 3 billion chemical bases that make up human DNA, the molecule that encodes the instructions for assembling and sustaining life. Although whole-genome sequencing offers the most comprehensive assessment of differences between patients' normal and cancer genomes, the method is not in widespread clinical use, in part due to cost and timeliness of test results.

Currently, clinical testing with next-generation sequencing often involves integrated analysis of more limited sequencing of the whole exome and whole transcriptome, also known as RNA sequencing. The exome is the 1 to 2 percent of the genome that encodes instructions for assembling proteins. The transcriptome identifies genes that are being expressed.

Findings

This study compared results of clinical tests that integrated whole-genome and whole-exome sequencing of patients' tumors and normal DNA plus the whole transcriptome of tumor DNA, with results when the analysis was limited to the exome and transcriptome. The testing was done in a CLIA-certified and CAP-accredited St. Jude clinical diagnostic laboratory.

For 47 percent of patients, clinical tests that included whole-genome sequencing identified known or likely cancer-causing mutations that were not picked up in tests with just whole exome and whole transcriptome sequencing.

Testing that included all three next-generation sequencing methods detected 99 percent of known or suspected cancer-causing mutations compared to 78 percent of mutations from tests with whole exome and whole transcriptome alone.

"This really showed the value of whole-genome sequencing, at least for childhood cancer," Zhang said.

The genomic alterations that give rise to and fuel cancer vary widely. Cancer mutations include single base changes (point mutations) in the genetic code, structural variations caused by chromosomal rearrangements and deletion or addition of DNA segments. "Different sequencing methods are better for identifying different alterations,"

Zhang said, adding that whole-genome sequencing is the best approach for finding certain mutations that are widely seen in childhood cancer. "It is not surprising that incorporating whole-genome sequencing in the analysis discovered high-risk mutations that whole-exome sequencing or whole-transcriptome sequencing did not," she said.

Ellison added, "We expect the combined sequencing methods to provide a comprehensive view of the genetic alterations in a child's cancer that matter most for treatment decisions and also to serve as a discovery engine for the genetic basis of uncommon childhood cancers."

The study builds on the St. Jude—Washington University Pediatric Cancer Genome Project. Launched in 2010, the Pediatric Cancer Genome Project sequenced the normal and cancer genomes of more than 800 young patients with some of the least understood and most aggressive cancers. The project has produced groundbreaking discoveries in a number of cancers as well as computational algorithms that have improved genomic sequencing analysis.

For this study, researchers developed an analytic pipeline to detect, compare and validate variations in tumor and germline DNA identified in whole genome, exome and transcriptome sequencing. Likely or suspected pathogenic variants were identified. The rankings and clinical importance were then reviewed by a committee of experts with bioinformatics, genetic and clinical expertise before the findings were reported to clinicians and included in patient medical records.

Today the pipeline provides reported results in an average of 31 days. That is comparable to the turnaround time for returning results of tumor exome sequencing or similar genomic testing. Per patient costs of sequencing and storing whole genome, exome and transcriptome data have declined since the study began in 2013.

A key feature of the clinical pipeline was software developed by co-first author Michael Rusch of the St. Jude Computational Biology Department and his colleagues. The pipeline streamlined integration and validation of genomic variants picked up by the different sequencing platforms. "Validating the results across all three sequencing platforms improved the accuracy and sensitivity of the results," Rusch said.

Sequenced data used in this study, both raw and processed, are available to researchers worldwide via the St. Jude PeCan (pediatric cancer) data portal in St. Jude Cloud. St. Jude researchers hope the access will fuel future research and development or clinical applications involving whole-genome sequencing.

Provided by St. Jude Children's Research Hospital