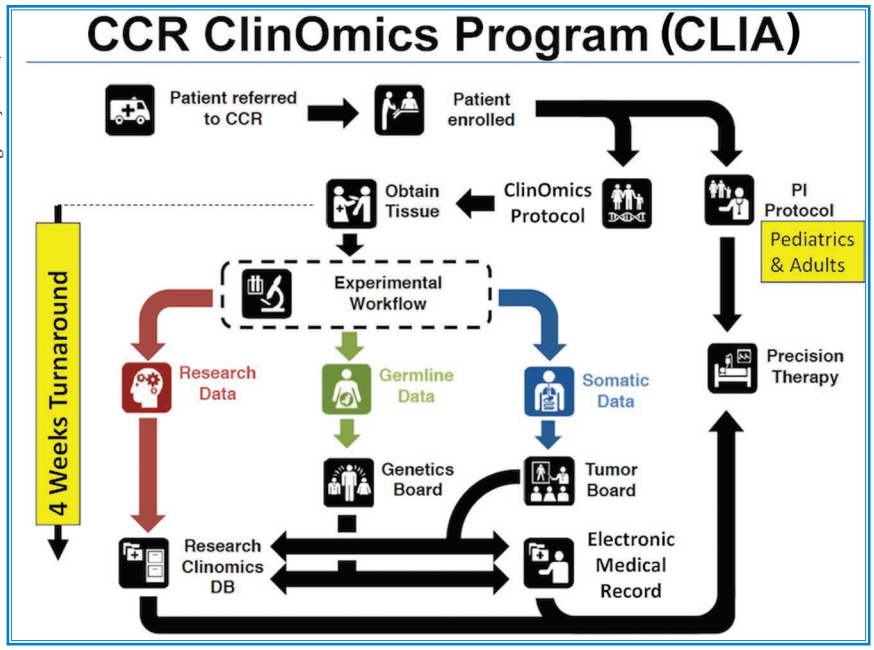
Precision Pediatric Oncology

A new study paves the way for precision therapy trials at NCI.

(Figure: J. Khan, CCR)



Schema for CCR's planned genomics-guided CLIA sequencing program (ClinOmics)

Current excitement around tailoring treatments to abnormalities in tumor tissues is predominantly focused on adults. Pediatric tumors, so the literature argues, do not have the same range of somatic mutations as seen in adults, and so the value of an individualized, comprehensive genomic analysis may not be as obvious.

Javed Khan, M.D., Deputy Chief of CCR's Genetics Branch, and his colleagues decided to test the insights to be gained from a genomics approach to pediatric cancers. For 59 patients referred to the NIH Clinical Center between 2010 and 2014, with a range of 20 solid tumor types, they analyzed the sequences of all protein-coding genes in both tumor and nontumor cells through whole exome sequencing (WES). They also studied the mRNA profile through whole transcriptome sequencing (WTS), and copy number alterations in the tumor genome through single nucleotide polymorphisms (SNP) arrays. Their results were recently published in *Clinical Cancer Research.*

The majority of patients (73 percent) had recurrent/resistant cancers, which probably accounted for the higher number of observed tumor mutations than has previously been reported in pediatric tumors. About two-thirds of the mutations were identified through a combination of WES and WTS, but SNP arrays also accounted for a sizeable fraction. Approximately 50 percent had clinically actionable mutations in the tumor—that is, genetic alterations in the person's tumor that changed their diagnosis or that could be targeted with FDA-approved drugs or agents being tested in existing clinical trials—and 12 percent had a significant germline mutation that may be important in the management of the patient and their family.

The team described two cases in which their analyses could have informed the course of therapy. In the first, a patient diagnosed with epithelioid inflammatory myofibroblastic sarcoma, driven by a RANBP2-ALK fusion gene, was treated with the ALK inhibitor, crizotinib. When the patient relapsed eight months later, WTS and WES showed that the relapsed tumors acquired a secondary mutation in the ALK coding region previously linked to crizotinib resistance.

In the second case, a patient's initial diagnosis of melanocytic neuroectodermal tumor was later changed to melanoma, based on histology undertaken after the disease progressed despite chemotherapy. A mutation known as a common driver of uveal melanoma was revealed with WES and WTS of the metastatic tumor.

Based on the potential of this approach, CCR established the ClinOmics program to enable precision therapy trials in children and adults with cancer enrolled on NCI trials. However, other challenges remain for precision pediatric oncology. Only 24 patients in this study had a mutation with a corresponding drug, either approved or in clinical trials. "There are still many mutations that can be documented with a high degree of confidence, but whose significance is unknown and undruggable," said Khan. "Resistance can develop very quickly, even to targetable mutations. Therefore, future clinical trials should utilize immune-based or combination therapies—even for patients whose tumors harbor a genetic alteration for which a targeted therapy already exists."

To learn more about Dr. Khan's research, please visit his CCR website at https://ccr.cancer.gov/Genetics-Branch/javed-khan.