Study Shows DNA Sequencing Brings Greater Precision to Childhood Cancer

directorsblog.nih.gov/2016/02/09/study-shows-dna-sequencing-brings-greater-precision-to-childhood-cancer/

by Dr. Francis Collins

Caption: Baylor's Sharon Plon consults with a family at the Texas Children's Cancer Center in Houston.
Credit: Paul V. Kuntz/Texas Children's Hospital

An impressive number of fundamental advances in our understanding of cancer have occurred over the past several decades. One of the most profound is the realization that cancer is a disease of the genome, driven by a wide array of changes in DNA—some in the germline and affecting all cells of the body, but most occurring in individual cells during life (so-called "somatic mutations"). As the technology for sequencing cancer genomes has advanced, we are learning that virtually all cancers carry a unique set of mutations. Most are DNA copying errors of no significance (we call those "passengers"), but a few of them occur in genes that regulate cell growth and contribute causatively to the cancer (we call those "drivers"). We are now learning that it may be far more important for treating cancer to figure out what driver mutations are present in a patient's tumor than to identify in which organ it arose. And, as a new study shows, this approach even appears to have potential to help cancer's littlest victims.

Using genomic technology to analyze both tumor and blood samples from a large number of children who'd been newly diagnosed with cancer, an NIH-funded research team uncovered genetic clues with the potential to refine diagnosis, identify inherited cancer susceptibility, or guide treatment for nearly 40 percent of the children [1]. The potential driver mutations spanned a broad spectrum of genes previously implicated not only in pediatric cancers, but also in adult cancers. While much more work remains to determine how genomic analyses can be used to devise precise, new strategies for treating kids with cancer, the study provides an excellent example of the kind of research that NIH hopes to accelerate under the nation's new cancer "moonshot," a research initiative recently announced by the President and being led by the Vice President.

The latest findings come from the Baylor College of Medicine Advancing Sequencing in Childhood Cancer Care (BASIC3) study, led by Will Parsons and Sharon Plon, who are affiliated with Baylor and the Texas Children's Cancer Center, Houston. BASIC3 enrolled 150 previously untreated children with cancer. The kids, whose average age was 7, were ethnically diverse and almost equally divided between boys and girls. All had solid tumors, with about a third diagnosed with cancers of the brain or spinal cord.

Of the 150 kids, 121 had frozen tumor samples that were adequate for genomic analysis to look for mutations. The analysis consisted of deep sequencing the exomes—the 1.5 percent of the genome that encodes proteins—of both the cancerous tumor and, as a point of comparison and additional information, healthy blood cells. Once the data were analyzed, the families and doctors received a tumor report and a "germline" report assembled

from the healthy blood cells.

The tumor reports showed, in sum, more than a quarter of the tumors had germline or somatic mutations with established or potential clinical relevance. While those changes popped up in several genes known for driving cancer, many weren't known to be associated with childhood cancers and more targeted genetic testing likely would not have caught them.

The germline reports showed 15 children—10 percent—carried gene variants in all the cells of their bodies that made them more susceptible to cancer. Some of those genes had known links to childhood cancers, while others, such as BRCA1, have previously been associated with adult cancers. Another eight patients carried mutations in other genes with medical implications unrelated to their cancer diagnosis. All told, in nearly 40 percent of cases, the DNA data produced a genetic finding that doctors and family members might want to consider when making decisions about medical testing or treatment.

Indeed, the BASIC3 researchers report the genetic information has already made a difference for some families. Independent of the study, the siblings of kids found to carry gene variants associated with childhood cancer susceptibility have undergone genetic testing to learn if they are also more vulnerable. In one of those siblings, the test results led to the early diagnosis of a previously undetected cancer.

Because most childhood cancer patients are treated according to established clinical treatment protocols, it remains to be seen to what extent the inclusion of genetic information in the children's medical records will influence the delivery of care. That question was addressed in a second study in the same issue of *JAMA Oncology*, which explored the utility of molecular tumor profiles for 100 children with more advanced or recurrent cancers. The researchers, led by Katherine Janeway at the Dana-Farber Cancer Institute, Boston, reported that the genetic findings produced a treatment recommendation for these kids 31 percent of the time [2].

The BASIC3 study, which is ongoing and nearing its target enrollment of 280 patients, will further explore this emerging issue. The researchers want to learn how to incorporate genomic sequencing technologies into the pediatric cancer clinic. That includes making headway with issues ranging from explaining exome sequencing to patients and families, to collecting and sequencing samples in the clinical lab, to delivering the results to doctors and patients in a reasonable period of time and in a way everyone can understand. What they and other research groups learn in the years ahead will be critical to help improve care for the roughly 15,000 American children and adolescents diagnosed with cancer each year, as well as the many thousands more worldwide [3].

References:

[1] Diagnostic Yield of Clinical Tumor and Germline Whole-Exome Sequencing for Children With Solid Tumors. Parsons DW, Roy A, Yang Y, Wang T, Scollon S, Bergstrom K, Kerstein RA, Gutierrez S, Petersen AK, Bavle A, Lin FY, López-Terrada DH, Monzon FA, Hicks MJ, Eldin KW, Quintanilla NM, Adesina AM, Mohila CA, Whitehead W, Jea A, Vasudevan SA, Nuchtern JG, Ramamurthy U, McGuire AL, Hilsenbeck SG, Reid JG, Muzny DM, Wheeler DA, Berg SL, Chintagumpala MM, Eng CM, Gibbs RA, Plon SE. JAMA Oncol. 2016 Jan 28. [Epub ahead of print]

[2] Multicenter Feasibility Study of Tumor Molecular Profiling to Inform Therapeutic Decisions in Advanced Pediatric Solid Tumors: The Individualized Cancer Therapy (iCat) Study. Harris MH, DuBois SG, Glade Bender JL, Kim A, Crompton BD, Parker E, Dumont IP, Hong AL, Guo D, Church A, Stegmaier K, Roberts CW, Shusterman S, London WB, MacConaill LE, Lindeman NI, Diller L, Rodriguez-Galindo C, Janeway KA. JAMA Oncol. 2016 Jan 28. [Epub ahead of print]

[3] Childhood and adolescent cancer statistics, 2014. Ward E, DeSantis C, Robbins A, Kohler B, Jemal A. CA Cancer J Clin 2014 Mar-Apr;64(2):83-103.

Links:

Childhood Cancers (National Cancer Institute/NIH)

Donald Williams Parsons (Baylor College of Medicine, Houston)

Sharon Plon (Baylor College of Medicine, Houston)

BASIC3 Study (Clinical Sequencing Exploratory Research Consortium)

NIH Support: National Human Genome Research Institute; National Cancer Institute