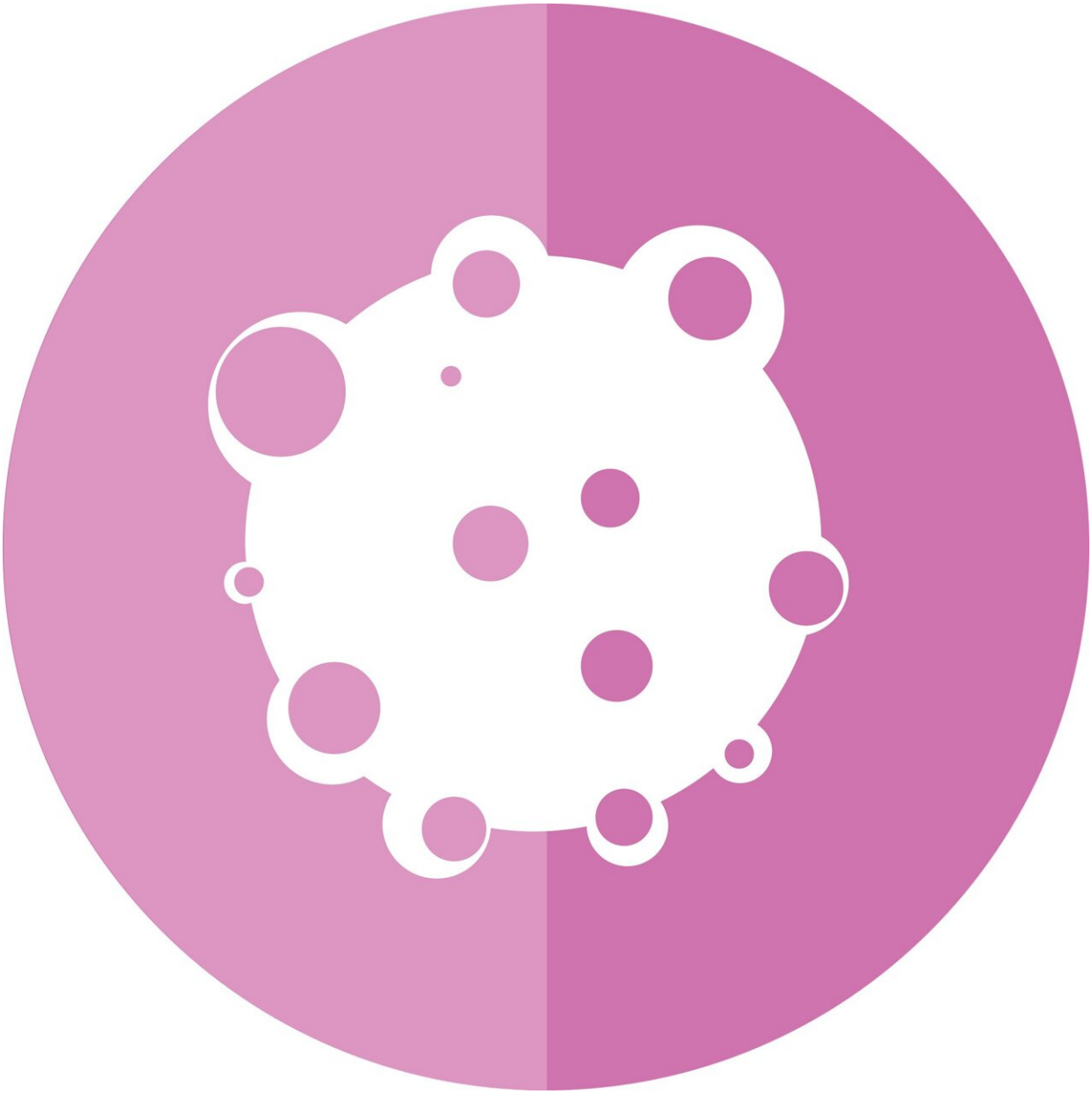
Study shows that genomic tumor profiling of pediatric tumors can enhance clinical care

June 23 2022



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Results of a study of molecular tumor profiling in young patients revealed a high rate of genetic alterations with potential for impacting clinical care, including clarifying diagnoses and treatment with matched, precision cancer drugs.

Reporting in *Nature Medicine*, researchers from Dana-Farber/Boston Children's Cancer and Blood Disorders Center said molecular profiling of solid tumors found clinically significant genetic variations in 298, or 6% of 345 pediatric patients. In 240 patients, the genetic "fingerprint" or pattern of cancer-related changes in the tumor's DNA could be used to choose a targeted, precision therapy matched to those alterations. Of these patients, 200 were eligible for matched drug therapy.

Targeted therapies were used to treat 29 patients, and 24% of the patients responded to the targeted drugs or experienced a durable clinical benefit. In addition, the molecular profiling—done by a process called next-generation sequencing—clarified the diagnostic classification in 17 patients.

"By providing a more accurate diagnosis or identifying a targeted therapy, molecular tumor profiling significantly impacts the care we provide. The result is cancer treatment that is more effective and, in some cases, has fewer side effects," said Katherine A. Janeway, MD, MMSc, Senior Physician, Dana-Farber / Boston Children's Cancer and Blood Disorders Center Director, Clinical Genomics, Dana-Farber Cancer Institute and Associate Professor of Pediatrics, Harvard Medical School.

The ongoing study, known as the GAIN/iCat2, is being carried out at 12

centers in the United States to evaluate the clinical impact of genomic sequencing of pediatric solid tumors, which is much less commonly performed than in adult patients with solid tumors. In adults, tumor profiling is recommended in national practice guidelines as an aid to diagnosis and treatment. But there are no such guidelines or insurance coverage decisions for using tumor profiling in pediatric solid malignancies and few clinical trials of tumor profiling include young people with cancer.

Pediatric solid tumors are much rarer than they are in adults, and large studies of genetic alterations are difficult to carry out. In fact, there were 59 different tumor types affecting the patients in this study and some of the cancers are so rare that they affected just one patient. Pediatric tumors also tend to have fewer gene mutations than those in adults, so there are fewer targets for drugs to attack—and fewer drugs available to target them. The net result is that most solid tumors in children are treated with standard chemotherapy or radiation rather than precision drug agents.

The current study is a prospective observational cohort study led by Janeway and Alanna J. Church, MD, associate director for Molecular Pediatric Pathology at Boston Children's Hospital and Katherine A. Janeway, MD, MMSc, director of Clinical Genomics at Dana-Farber and Boston Children's. Janeway has been working to bring personalized, molecularly targeted treatments to children with cancer. The results of Janeway's first study, called Individualized Cancer Therapy (iCat), were published in 2016 and showed that bringing clinical genomic sequencing to pediatric oncology practice is feasible. Janeway and colleagues are now conducting a follow-up study, the Genomic Assessment Improves Novel Therapy (GAIN) Consortium, iCat2 study.

The study participants were patients with relapsed/refractory or high-risk non-brain tumors at age 30 or younger; the mean age at diagnosis was 12

years. Researchers performed targeted DNA next-generation sequencing with OncoPanel testing on one or more tumor samples from each patient, with some samples subjected to RNA sequencing as well. Based on the analysis, a comprehensive report is created and sent to the referring physician. This allows the physician to develop a plan for the patient that takes into account the genetic changes detected in their tumors that are associated with matched drugs that have yielded success either in the laboratory or in the clinic in treating patients with such tumors. The study tracks each patient to determine the impact of the treatment plan on the patient's outcome. The primary goal of the study is to observe if the tumor profiling and matched targeted drug treatment affects overall survival.

Recommendations for molecularly targeted therapy (MTT) based on data from the previous iCat study were returned to 240 of the 345 patients whose tumors had at least one gene variant. Of these, 200 patients were eligible for assessment of receipt and response to MTT, being alive and having complete follow-up data. Ninety-six of the patients would not have been expected to consider targeted therapy because they were receiving frontline therapy, had no cancer-directed systemic therapy during the follow-up period, or no matched targeted drugs were available.

Seven patient who received matched targeted therapy had measurable significant responses to the therapy. In six of those tumors the therapies were matched to a gene fusion. Fusion genes are formed within a cell when a piece of one chromosome breaks off and attaches to another chromosome, causing broken DNA segments to fuse together to form an entirely new gene. Some of these genes produce fusion proteins that can cause cells to grow uncontrollably and form tumors.

"Gene fusions are very important in pediatric tumors," says Church. "It's an exciting time because there are so many new drugs that can target

these fusions and we have new tests that can reliably detect them."

Church and Janeway hope their work will help make genomic profiling standard of care for new or relapsed pediatric solid tumors, reimbursable by insurance—just as it is for adults.

"We know there are patients who aren't getting access to these tests because they are not being reimbursed consistently," says Church. "We want to broaden access to molecular profiling for every child with a solid tumor."This study was funded by: Wendy Precision For Kids Pan Mass Challenge Team; 4C's FundLamb Family Fund; C&S Wholesale Grocers and C&S Charities and Alexandra Simpson Pediatric Research Fund.

More information: Alanna Church, Molecular profiling identifies targeted therapy opportunities in pediatric solid cancer, *Nature Medicine* (2022). DOI: 10.1038/s41591-022-01856-6.
www.nature.com/articles/s41591-022-01856-6

Provided by Dana-Farber Cancer Institute