Genetic sequencing can help guide treatment in children with solid tumors

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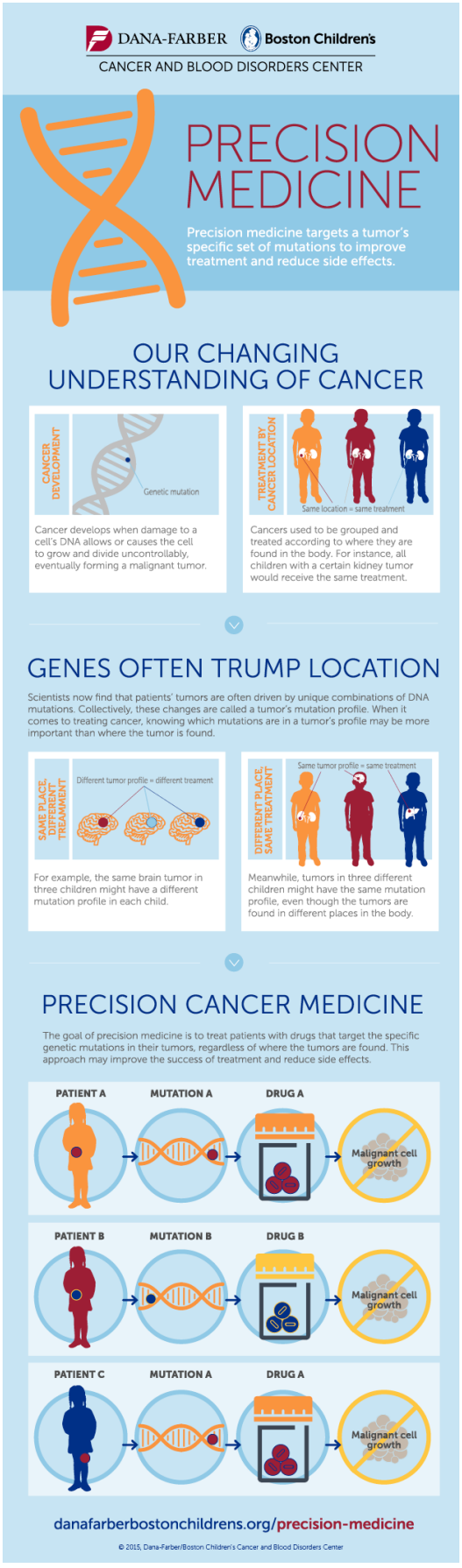
DANA-FARBER
Boston Children's
CANCER AND BLOOD DISORDERS CENTER
PRECISION MEDICINE
Precision medicine targets a tumor's specific set of mutations to improve treatment and reduce side effects.
OUR CHANGING UNDERSTANDING OF CANCER
CANCER DEVELOPMENT
Genetic mutation
Cancer develops when damage to a cell's DNA allows or causes the cell to grow and divide uncontrollably, eventually forming a malignant tumor.
TREATMENT BY CANCER LOCATION
Same location = same treatment
Cancers used to be grouped and treated according to where they are found in the body. For instance, all children with a certain kidney tumor would receive the same treatment.
GENES OFTEN TRUMP LOCATION
Scientists now find that patients' tumors are often driven by unique combinations of DNA mutations. Collectively, these changes are called a tumor's mutation profile. When it comes to treating cancer, knowing which mutations are in a tumor's profile may be more important than where the tumor is found.
SAME PLACE, DIFFERENT TREAMMENT
Different tumor profile = different treament
For example, the same brain tumor in three children might have a different mutation profile in each child.
DIFFERENT PLACE, SAME TREATMENT
Same tumor profile = same treatment
Meanwhile, tumors in three different children might have the same mutation profile, even though the tumors are found in different places in the body.
PRECISION CANCER MEDICINE
The goal of precision medicine is to treat patients with drugs that target the specific genetic mutations in their tumors, regardless of where the tumors are found. This approach may improve the success of treatment and reduce side effects.
PATIENT A
MUTATION A
DRUG A
Malignant cell growth
PATIENT B
MUTATION B
DRUG B
Malignant cell growth
PATIENT C
MUTATION A
DRUG A
Malignant cell growth
danafarberbostonchildrens.org/precision-medicine
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Infographic describing clinical genomic sequencing in pediatric oncology. Credit: DFCI

Clinical genomic sequencing is feasible in pediatric oncology and can be used to recommend therapy or pinpoint diagnosis in children with solid tumors, according to the multicenter Individualized CAncer Therapy (iCat) study led by investigators from Dana-Farber/Boston Children's Cancer and Blood Disorders Center. The study, published today in *JAMA Oncology*, is one of the first of its kind to be conducted in pediatric oncology. Its findings bolster the case for matching children to treatment based on a tumor's genetic characteristics and represent a significant step in making molecularly targeted, personalized therapy available to children with cancer.

While patients with adult cancers have benefitted greatly from a precision medicine approach founded in clinical genomic sequencing and targeted therapies, these gains are only beginning to reach pediatric patients. Because all childhood cancers are rare, there are relatively little data available on the mutations that drive pediatric tumors. Those tumors that have been sequenced tend to harbor few genetic mutations compared to adult cancers. In addition, because drug development efforts prioritize the needs of adult patients, relatively few targeted drugs are currently available for children. Even when a potentially useful targeted drug may already exist, it may lack dosing guidelines for children or may not be formulated in ways appropriate for young children, for instance, pill versus liquid form.

The iCat trial asked whether, given current genomic technologies and genetic knowledge, it is even feasible to sequence pediatric tumors in a

clinical context and return recommendations based on those results. The answer, researchers concluded, is yes.

"The story of precision medicine in pediatric cancer is just starting," said Katherine Janeway, MD, lead iCat investigator and clinical director of the Solid Tumor Center at Dana-Farber/Boston Children's. "Ours and other studies show that if we do this kind of sequencing we might find treatment opportunities for children. And they provide openings for expanding our knowledge of the childhood cancer genome and helping both clinicians and basic scientists understand which treatments work for a given tumor, which don't and why, all of which could fuel additional drug development for both pediatric and rare adult tumors."

As Janeway and her colleagues report, the iCat study collected tumor samples from 100 cancer patients seen at four centers across the United States between August 2012 and November 2013 for a variety of relapsed pediatric solid tumors. The investigators analyzed the samples using sequencing methods that would reveal the presence of known cancer-related alterations in 305 genes.

If the analysis revealed a clinically actionable genetic alteration—defined as an alteration for which a targeted therapy was available through a clinical trial or as an FDA-approved drug in an age-appropriate dose and formulation in the context of a clinical trial—the team made a treatment (or iCat) recommendation to the patient's oncologist. The team also forwarded any results supporting a change in diagnosis or suggesting that the patient may have a cancer predisposition syndrome. Enrolled patients were followed for a median of 6.8 months.

At the study's end, the team was able to make iCat recommendations for 31 out of the 100 enrolled patients. Three of those 31 patients underwent treatment based on the recommendation, though none responded. Among the 28 patients who did not receive their iCat-recommended

treatment, reasons included a) the patient was ineligible for or could not otherwise access a relevant clinical trial, b) the patient was responding well to current therapy, or c) the patient had died.

"We designed the study such that if we could make an iCat recommendation for 14 percent of participants, we could say that clinical sequencing was feasible," Janeway said. "We exceeded this benchmark."

In an additional 12 patients, the team identified genetic alterations suggesting a change in diagnosis and/or revealing that the patient may have a cancer predisposition syndrome.

The iCat study joins a recent and growing body of evidence supporting the feasibility and potential benefits of incorporating clinical genomics into pediatric cancer care. In the same issue of *JAMA Oncology*, a team led by investigators from Baylor College of Medicine report similarly successful efforts to generate genomic-based treatment recommendations for patients with pediatric solid or brain tumors. Researchers from the University of Michigan reported similar findings in JAMA in September 2015.

These and other studies are providing momentum for expanded efforts aimed at embedding clinical sequencing more deeply into pediatric oncology practice. Janeway and her colleagues have already launched a 12-center iCat follow-up study, the Genomic Assessment Informs Novel therapy (GAIN) consortium study. And in 2016, the National Cancer Institute plans to open a pediatric arm of its Molecular Analysis for Therapy Choice (MATCH) trial, which, according to the NCI website, "seeks to determine whether treating cancers according to their molecular abnormalities will show evidence of effectiveness."

"Pediatric oncology has lagged behind adult oncology when it comes to

incorporating targeted drugs and genomic testing or tumor profiling into treatment," Janeway said. "Together these studies indicate that we're starting to understand how to carry out clinical sequencing in pediatric oncology and which patients might benefit from it."

Provided by Dana-Farber Cancer Institute