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Study points to expanded genomic testing that aims to benefit children and young adults with cancer

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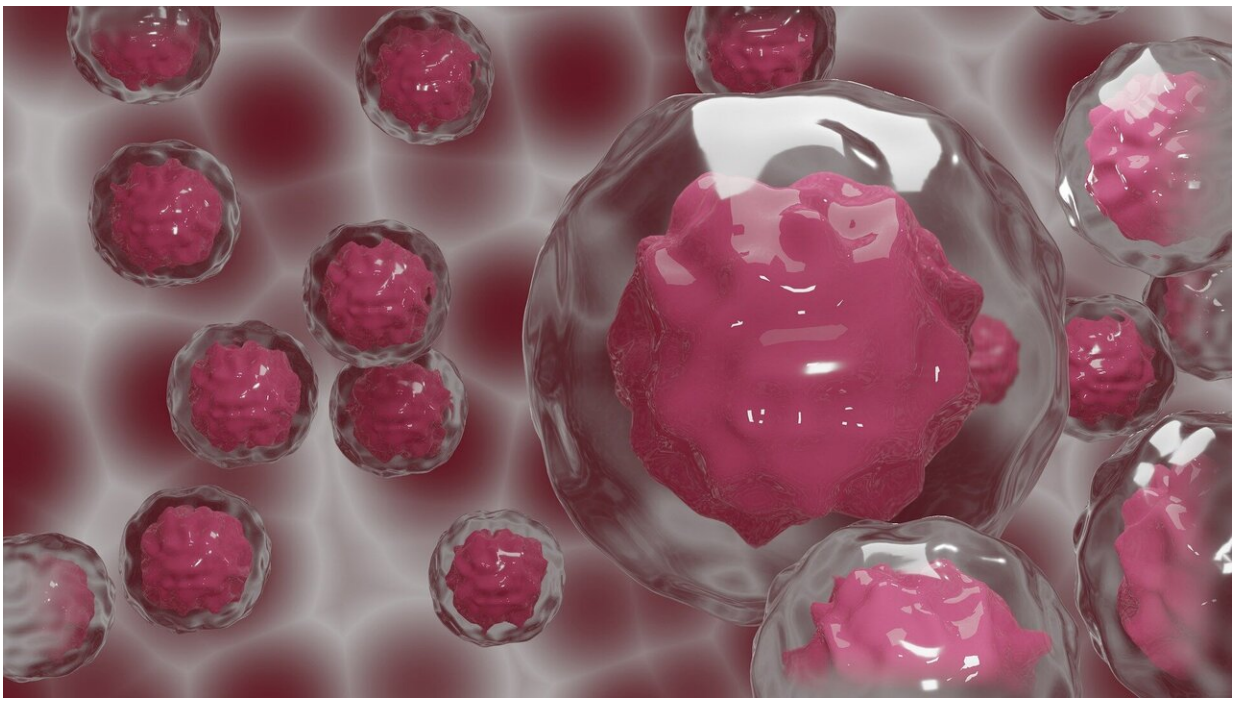

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New findings from researchers at Memorial Sloan Kettering Cancer Center (MSK) and published today in the journal *Nature Communications* report the results of using a comprehensive sequencing approach on 114 pediatric, adolescent, and young adult patients with

solid tumors. The researchers found that their approach identified at least one additional cancer-associated oncogenic variant in 54% of patients (62 out of 114), compared with the current standard genetic sequencing test MSK-IMPACT. Of these, 33 patients had one or more findings that were of direct clinical or potentially actionable relevance.

DNA sequencing tests that look for mutations in cancer-associated genes have become a standard of care at leading centers, including at MSK. The MSK test, called MSK-IMPACT, can detect mutations in 500-plus cancer-related genes. From this information, doctors can then determine if an available drug might benefit a particular patient, based on the tumor's genetic profile.

This cancer-gene-panel approach works very well for adults with common types of cancer, like breast, colorectal, lung, and prostate cancer. But for rare cancers in children and young adults, these panel tests have not been as useful for matching patients to appropriate therapies. That is because, as researchers are coming to realize, the types of mutations that drive tumors in young patients tend to be different than those in adult patients.

"Adult cancers are usually caused by a lifelong accumulation of mutations from exposure to things like sunlight, cigarette smoke, and carcinogens in the diet," explains physician-scientist Andrew Kung, who is Chair of the Department of Pediatrics at MSK and who researches the molecular causes of childhood cancers. "Those mutations are usually what are called point mutations—where a single letter of DNA is changed in a gene."

"With pediatric cancers," he continues, "the driving mutations tend to be structural changes affecting whole sections of chromosomes. These are often located outside of the boundaries of known cancer genes, where they go undetected by existing tests."

To better visualize these structural variants, researchers need a way of reading not only the changes to the spellings of particular "words," or cancer genes, but also the organization of those words in the context of paragraphs and chapters. That's what a technique called whole genome DNA and RNA sequencing provides, and Dr. Kung and his colleagues believe it may make an important difference in the care of children with cancer.

"Everyone agrees that whole genome sequencing will eventually become the go-to diagnostic test to profile tumors," says MSK computational oncologist Elli Papaemmanuil. "But there have been several obstacles standing in the way."

The biggest one, she says, is being able to make sense of the vast amount of data that comes from sequencing the billions of DNA letters making up an entire genome—pinpointing and, relatedly, conveying the clinically relevant information to doctors in a timeframe that could help with care decisions. In the published research, the researchers have refined the analysis of such data to be accomplished in a few days, compared with standard approaches that require weeks or months.

Not yet a replacement for other tests

The researchers emphasize that the new platform is not currently a replacement for panel-based tests, such as MSK-IMPACT, which work well for capturing relevant mutations in adult patients with common tumors—and have made a difference in their outcomes.

"What we are trying to do is to bring a more comprehensive approach to pediatric patients and others with rare cancers, a minority of whom benefit from panel-based testing," says Dr. Kung. "We want to make precision medicine more inclusive and a possibility for every cancer patient."

The study authors say the benefits for pediatric patients are so compelling that this type of testing is now being made available to every pediatric patient at MSK through philanthropic funding.

More information: "Feasibility of whole genome and transcriptome profiling in pediatric and young adult cancers", *Nature Communications* (2022). DOI: 10.1038/s41467-022-30233-7

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