On Cancer

MSK's Expanded Genomics Program Takes a Deep Dive into the Causes of Childhood Cancer

By Julie Grisham, **Monday, September 30, 2019**

Molecular geneticist and data scientist Elli Papaemmanuil is leading MSK's Expanded Genomics Program.

Summary

> About half of pediatric tumors have a significant mutation that can be identified with standard clinical tests. MSK researchers are looking for a better way to detect mutations in the rest.

MSK-IMPACT™ detects changes in more than 400 cancer-associated genes. The test has made a meaningful difference for many adults treated at Memorial Sloan Kettering. By identifying the mutations driving a tumor's growth, test results may indicate which targeted therapy or immunotherapy is likely to work against a tumor. Results can also be used to find an appropriate clinical trial.

But the picture is quite different for children with cancer. About half of their tumors do not have a significant mutation that can be identified with MSK-IMPACT or any other standard clinical test. For these kids, developing new forms of molecular diagnosis is essential.

"As a whole, pediatric cancers are a collection of very diverse and very rare tumor types," says MSK molecular geneticist and data scientist **Elli Papaemmanuil**. "Their genomes are very different from the genomes of most cancers seen in adults. We still have so much to learn about them."

This is the motivation behind the establishment of MSK's Expanded Genomics Program. The program, led by Dr. Papaemmanuil, was launched in September 2018 to develop a way to comprehensively map the unique changes driving each individual tumor. The ultimate goal is to understand and eventually identify personalized treatment approaches for every child treated for cancer at **MSK Kids**.

For Child & Teen Patients

MSK Kids is dedicated to caring for children, teens, and young adults with cancer, immune deficiencies, and benign blood disorders.

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Going Beyond the Standard Approach

In the lab, the Expanded Genomics team has already performed an in-depth examination of tumors from more than 120 children treated at MSK. This analysis includes looking at the gene mutations detected by MSK-IMPACT, sequencing the rest of the tumor genome, and measuring levels of RNA. Changes in RNA can help indicate which genes are affected.

“We hope to be in a position where we can identify the novel genetic events that define each tumor and explain what’s driving the cancer,” Dr. Papaemmanuil says. “By learning more about these disease-defining changes, we aim not only to pinpoint which drugs are likely to be effective but also to develop diagnostic and prognostic markers.” These markers would help doctors determine which cancers may be more aggressive and require more treatment, and which tumors can successfully be cured with less-aggressive therapies, enabling patients to avoid side effects.

Finding New Clues about Cancer’s Origins

Another important aspect of genomic research in pediatric cancer is that it can identify which tumors may be caused by inherited mutations. Current literature, as well as work by MSK geneticist and pediatric oncologist **Michael Walsh**, suggests that about 10 to 15% of children with cancer have germline (hereditary) mutations.

Knowing when a cancer is caused by a hereditary mutation can benefit whole families because relatives can get tested for the same mutation. If they have it, they may be able to enroll in screening programs to catch cancer at an earlier stage or have preventive care.

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A large proportion of cancer susceptibility genes affect repairing DNA damage under normal conditions. Expanded genomic analysis can readily pinpoint the evidence of damaged DNA in people with impaired DNA repair genes. This provides another way to identify people with inherited gene mutations.

Additionally, the presence of these mutations can suggest who may benefit from treatment with immunotherapy drugs, such as checkpoint inhibitors. These drugs work better against tumors that have a lot of mutations. Traditionally, they have not been used to treat pediatric cancers because tumors in younger people tend to have fewer mutations.

Taking Lab Findings into the Clinic

As promising as this research is, more work needs to be done before these types of analyses can be used to make decisions about patient care. "One of our big aims right now is to evaluate whether these comprehensive sequencing approaches are informative enough to be clinically helpful," Dr. Papaemmanuil says. "We are still in the early stages of this research. Yet in our early findings, we showcase that with comprehensive sequencing techniques, we can identify diagnostic-, prognostic-, and therapy-informing markers that would have not been picked up by standard clinical sequencing tests."

Her team is working with pediatric oncologists to validate their laboratory findings. They want to determine the best way to match each genetic signature to existing or investigational drugs. As an integral part of the MSK Kids **Pediatric Translational**

Medicine Program, the Expanded Genomics team collaborates with doctors who can use the results from this wide-ranging genomic testing to find targeted therapies for childhood cancers.

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