Study signals new era of precision medicine for children with cancer

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A new study has shown the power of genetic testing to pick out the best drugs for children with cancer to extend and improve their lives—signaling a new era of precision medicine for young patients.

The pilot including more than 200 children found that half had gene mutations that are targetable by adult cancer drugs that are either available as standard treatment or via clinical trials.

Although few children on the study went on to receive adult drugs, those who did receive targeted therapies had significant benefits.

But the study also laid bare the regulatory and funding barriers to children receiving the newest drugs, as only 7 percent of those with targetable mutations were able to access the appropriate adult drug.

The study was led by the Institute of Cancer Research, London, and The Royal Marsden NHS Foundation Trust, and offered genetic testing of tumors to children as part of a clinical trial. Some 20 additional hospitals around the UK participated by sending children's biopsies in for testing.

The research is published in the *European Journal of Cancer* today (Thursday) and was primarily funded by the parent-led charity Christopher's Smile and the NIHR Biomedical Research Centre at The Royal Marsden NHS Foundation Trust and The Institute of Cancer Research (ICR).

Researchers used a gene panel test to read the DNA sequence of 91 genes that drive cancer's growth and spread from 223 children's tumor biopsies—looking for potentially 'targetable' mutations.

Solid tumors—such as those of the brain, central nervous system, bone and muscle—are rare but have much worse survival rates than children's blood cancers such as leukaemia. Surgery is often not possible and treatment is limited to 'blunt instrument' chemotherapies.

The researchers first validated the panel test, showing it to be than more than 99 percent sensitive at picking up the 91 mutations, even with just 50 nanograms of DNA—which is around 1,000 times less than the weight of a grain of table salt.

Using the test, they found 51 percent of tumor samples tested had mutations that could be targeted by adult cancer drugs.

The most common potentially treatable mutations were in the genes

ATRX, CDKN2A and CTNNB1 which were each found in 12 children's tumors. MYCN mutations were found in 11 tumors and PI3K3CA mutations in 10 tumors.

Three children had BRAF gene mutations—which are common in melanoma skin cancers and can be treated using a combination of the drugs dabrafenib and trametinib.

Using these melanoma drugs, one of the children had their brain tumor held in check for 13 months before developing resistance. Another was on the drug for nine months with no progression of disease. The third child couldn't tolerate the combination but had a response to dabrafenib for 15 months.

But there are still challenges to overcome, since the majority of children with targetable mutations didn't receive adult drugs—because there was no trial available for the drug in children, they were unable to access the drug on the NHS or they were too ill to receive an experimental treatment by the time they were tested.

For eight of the patients, there were samples available at diagnosis and after treatment—and in six of those, testing revealed that the cancer had acquired new mutations as it evolved in response to treatment. That highlights the need to take an additional biopsy at relapse to search for targetable mutations.

For 12 of the children, the researchers were also able to test for cancer gene mutations in DNA released from tumors into the bloodstream from a blood sample. They found blood tests picked up almost all of the mutations found in the tumor, and in some cases they also found extra mutations which were not detected in the tumor region biopsied.

In future work the researchers will use serial blood tests to monitor how

tumors evolve in response to therapies—which will be particularly useful in hard-to-biopsy tumors.

Additionally, for children with brain tumors, the researchers are now looking at using samples of cerebral-spinal fluid to find drug targets. Although lumbar punctures are invasive, they are less so than a brain biopsy.

Attempting to stay one step ahead of cancer by monitoring and predicting cancer evolution is one of the central strategies the ICR is pursuing as part of a pioneering research program to overcome the ability of cancers to adapt, evolve and become drug resistant.

The ICR—a charity and research institute—is raising the final £14 million of a £75 million investment in the new Centre for Cancer Drug Discovery to house a world-first program of 'anti-evolution' therapies.

Study author Dr. Sally George, Clinical Research Fellow at The Institute of Cancer Research, London, and Consultant Paediatric Oncologist at The Royal Marsden NHS Foundation Trust, said:

"Children deserve the very best cancer treatments, so they can live as long as possible and as well as possible. We desperately need better, more intelligently designed treatments which can give children longer with their families with fewer side effects.

"By testing tumors for specific gene mutations, we have shown it's possible to identify new smarter, kinder treatment options for children, which may potentially give these patients much longer with their families after conventional therapies have failed.

"But our study also exposes the desperately frustrating barriers that children still face in receiving new treatments—barriers which lie in the

regulations controlling how drugs for children are developed and approved."

Study leader Professor Louis Chesler, Professor of Paediatric Cancer Biology at The Institute of Cancer Research, London, and Consultant Paediatric Oncologist at The Royal Marsden NHS Foundation Trust, said:

"Our study has demonstrated that we have the scientific knowledge and technology to get children access to state-of-the-art testing and treatments. And because our testing currently only assesses a focused set of well-known and clinically meaningful mutations, it is more practical, faster and more cost-effective than looking at the whole genome.

"In future, I want to be able to treat more children whose tumors have these targetable mutations with better drugs, as currently not all children have access. But gathering the molecular data is the first practical step to making this possible. This data, and more that we are continuing to collect, will be good evidence to more clearly guide use of the most appropriate drug for each child.

"It is also very important that we extend very robust and detailed testing to children at time of diagnosis, so we can more accurately classify and treat these cancers in the first place. We will also be looking at the utility of the approaches for detecting cancer relapse, a very important area where we currently have few tools to anticipate what treatments may be required with adequate time to do so."

Dr. Mike Hubank, Head of Clinical Genomics at The Royal Marsden NHS Foundation Trust and Reader in Translational Genomics at The Institute of Cancer Research, London, said:

"The next steps for testing will be to look at using liquid biopsies to

detect targetable tumor mutations without having to rely on invasive biopsies to get the information.

"Our early results, presented here, show that we can detect more mutations in blood than we do in conventional biopsies. It is probably in the blood that we get a more complete picture of the whole tumor, and not just the small part of the tumor that was removed for testing. Blood-based testing will also allow us to monitor tumor response to treatment and may be able to detect relapses early, offering the possibility of finely tuned, personalized treatments in the future."

Karen Capel is the founder and trustee of UK children's cancer charity Christopher's Smile, who funded the development of the test. Karen and her husband Kevin have campaigned tirelessly to improve the treatment for children with cancer after their son Christopher died from medulloblastoma in 2008. Karen said:

"When our son died there was no biological information available to doctors about individual children's tumors. There is an urgent unmet need to provide new treatments for those children diagnosed with the most aggressive and hard-to-treat cancers.

"This test Professor Chesler and colleagues at the ICR developed is a first for children. We believe gene sequencing is the key foundation stone in enabling personalized medicine, and it will help to bring new treatments for children a step closer.

"Building on the foundations of the sequencing test, blood tests could provide critical information for any child from diagnosis throughout their treatment and into remission—opening the door for additional, continued or changed treatments. We are determined to fight for these liquid biopsies to become standard of care at the earliest opportunity."

More information: *European Journal of Cancer*, DOI: 10.1016/j.ejca.2019.07.027