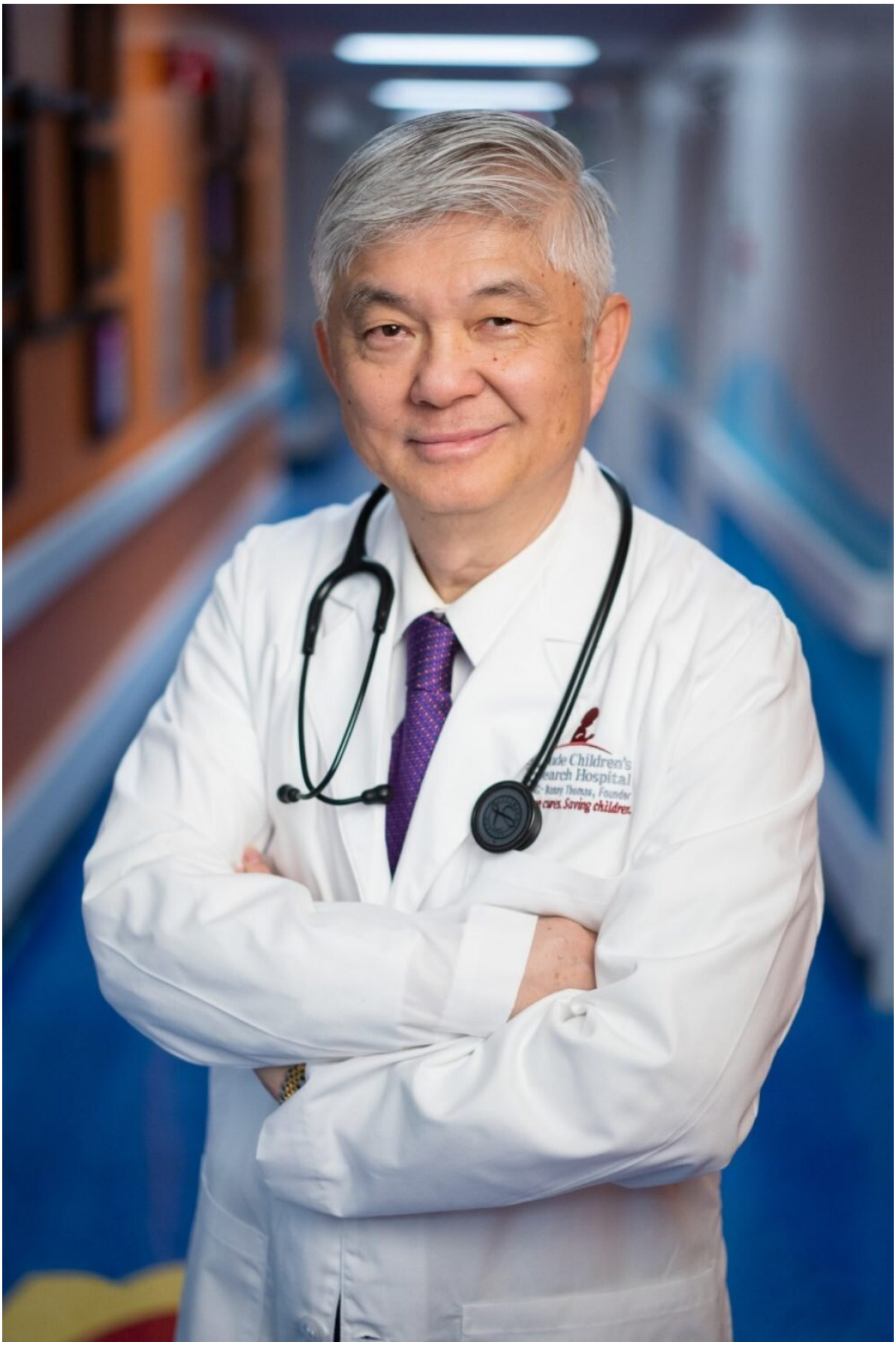
# Risk-directed childhood leukemia treatment takes a step forward

April 12 2021



Corresponding author Ching-Hon Pui, M.D., St. Jude Oncology Department chair, helped discover how genomic analysis can improve outcomes for children with acute lymphoblastic leukemia. Credit: St. Jude Children's Research Hospital

Comprehensive genomic analyses have helped researchers identify more than 20 subtypes of acute lymphoblastic leukemia (ALL) based on the genetic mutations that drive the disease. Research led by St. Jude Children's Research Hospital scientists showed that combining these data with leukemia response measurements improves prediction of relapse risk.

Currently, patients' response to treatment influences the type of therapy administered for ALL. This risk-directed approach involves assessing minimal residual disease, the level of leukemic cells in the blood or bone marrow of patients at defined points during treatment

A study that appears today in the journal *Blood Cancer Discovery* demonstrates that integrated use of genomic subtyping and minimal residual disease measurement improves risk stratification and relapse prediction in ALL. "Both factors, genomic analysis and minimal residual disease assessment, are required to accurately gauge patients' risk and tailor their therapy," said Ching-Hon Pui, M.D., St. Jude Oncology Department chair.

Pui and Charles Mullighan, M.B.B.S., M.D., of the St. Jude Department of Pathology, are co-corresponding authors of the study.

## More long-term survivors with a better quality of life

ALL is the most common childhood cancer diagnosis. The five-year survival rate of 94% is among the highest of childhood cancers. But the prognosis remains poor for patients who relapse. The late effects of treatment also leave adult survivors of childhood cancer at risk for chronic health problems.

Risk-directed therapy based on minimal residual disease is now standard for treatment of pediatric ALL. The approach helps to identify patients who need more intensive therapy to reduce their risk of relapse as well as low-risk patients who are candidates for reduced treatment.

This analysis involved 598 children and adolescents with ALL who enrolled in the St. Jude Total Therapy 16 clinical trial. Patients joined the study from October 2007 to March 2017.

Total Therapy 16 measured levels of minimal residual disease at days 8, 15 and 42 to guide patients' therapy. Patients with fewer than one leukemic cell in 10,000 blood cells were considered minimal residual disease negative.

## Subtype as a risk predictor

"We showed in the context of a minimal-residual-disease-based, risk-adapted study of childhood ALL that many of the recently described subtypes of ALL are associated with prognosis," Mullighan said. "The data indicated that patients with certain genetic ALL subtypes are almost always curable with conventional chemotherapy guided by early minimal-residual disease assessment."

Those subtypes included ETV6-RUNX1-positive and high-hyperdiploid ALL. None of the 95 low-risk patients with those subtypes and no minimal residual disease at day eight relapsed. In the current St. Jude

clinical trial, called Total Therapy 17, treatment has been reduced for patients who fit this profile.

"If effective, the strategy may ultimately help reduce treatment abandonment and treatment-related deaths for similar patients in low- and middle-income countries," said co-first author Sima Jeha, M.D., of the departments of Oncology and Global Pediatric Medicine.

Genomic analysis also demonstrated the current limitations of minimal residual disease as a risk predictor. Researchers identified patients with nine subtypes who relapsed despite being minimal residual disease negative at day 42 of treatment. The subtypes were T-cell ALL, TCF3-PBX1, PAX5alt, iAMP21, BCR-ABL1, BCR-ABL1-like, ETV6-RUNX1-like, KMT2A-rearranged and MEF2D-rearranged.

"The findings emphasize the need for novel therapies and immunotherapy for patients with ALL subtypes that are resistant to current intensive chemotherapy," Pui said. "We are testing this approach in our current clinical trial."

**More information:** Sima Jeha et al. Clinical significance of novel subtypes of acute lymphoblastic leukemia in the context of minimal residual disease-directed therapy, *Blood Cancer Discovery* (2021). DOI: 10.1158/2643-3230.BCD-20-0229

Provided by St. Jude Children's Research Hospital