HARMONY ALLIANCE

Data-driven research in Pediatric HM

Researchers validate novel risk profile for childhood ALL using real-world data.

Childhood acute lymphoblastic leukemia (ALL) has a good prognosis. However, detecting children with a risk of relapse due to minimal residual disease remains a challenge. That could change thanks to a novel risk profile validated with HARMONY real-world data. The enhanced risk profile will enable oncologists to detect more young patients at risk.

High hyperdiploidy (HeH) is the most common form of childhood ALL and accounts for about one-quarter of all relapse cases. Although many risk profiles for HeH have been published, these have failed to provide a consensus. That is because many variants of HeH exist, making it hard to determine which variants accurately predict a favorable outcome.

Newcastle University

Amir Enshaei, HARMONY Alliance Partner, Newcastle University:
"The HARMONY Big Data platform provides a unique resource of accessible high-quality data to undertake biomarker studies. Having access to a large number of patients (one to 80 years old) who are treated on different treatment protocols across the world, makes it possible to discover previously unseen patterns in treatment response and survival. The big data platform enables us to create and validate more accurate and robust outcome prediction models".

Enshaei and the project research team set out to resolve this issue. They analyzed two previously published UK pediatric trials to determine which variants of HeH best predicted a favorable outcome. The trisomic status of four chromosomes, namely 5, 17, 18 and 20, was found to provide the best risk profile, which defined a low-risk group (relapse risk less than 5%) and a poor-risk group (relapse risk of about 15%).

This novel UKALL HeH risk profile outperformed all other profiles and was easy to measure and implement. However, it could not be applied to a wide range of

clinical settings and treatment pathways because it was only based on UK data. Further validation of the protocol to make it more generalizable required a larger and more diverse set of real-world data. With this in mind, the research team turned to the HARMONY data platform.

The research team extracted a cohort of 10,042 patients from the platform who all had a confirmed diagnosis of ALL. From these patients, a total of 1,169 cases were obtained for the final analysis compared to 456 in the UK cohort. The dataset was highly heterogeneous, comprising patients treated in pediatric and adult trials from multiple countries over a period spanning 26 years. This heterogeneity increased the robustness of the analyses, which confirmed that the risk profile was valid for all patient subgroups and treatment pathways. The profile proved to be valid not just for children but also for adults.

Furthermore, the large real-world dataset enabled the team to increase the accuracy of the risk estimates, raise the risk profile's predictive power from 0.58 to 0.64, and reduce its predictive errors. This thorough evaluation of the UKALL HeH risk profile and confirmation of its robustness means that oncologists can confidently use it to detect ALL patients at risk of developing a relapse.

Enshaei: "We propose that the novel and validated high hyperdiploid good risk profile is superior in defining good risk high hyperdiploidy and future clinical trials and treatment protocols using high hyperdiploidy as a risk stratification factor should consider modifying the definition and incorporate this novel UKALL high hyperdiploid profile. The proposed profile identified low-risk patients who have an excellent chance of a potential cure and should be considered for treatment de-intensification to avoid potential over-treatment and harmful side effects".

Results published by researchers of the HARMONY Alliance in **Nature Leukemia**

The HARMONY Alliance is a public-private partnership for Big Data in Hematology. Our mission is to unlock and spread valuable knowledge on blood cancer to speed up the development of improved treatments for patients and more effective treatment strategies. The EU grant phase (European Commission's Innovative Health Initiative, IHI) that made this possible has ended per March 2024. Thanks to the strong commitment and drive of our Partners and Associated Members, we have the unique opportunity to continue our work as a non-profit, collaborative research foundation. The HARMONY Alliance Foundation will build upon the achievements of the HARMONY Alliance (HARMONY and HARMONY PLUS).