New strategy for assessing natural history of leukodystrophies

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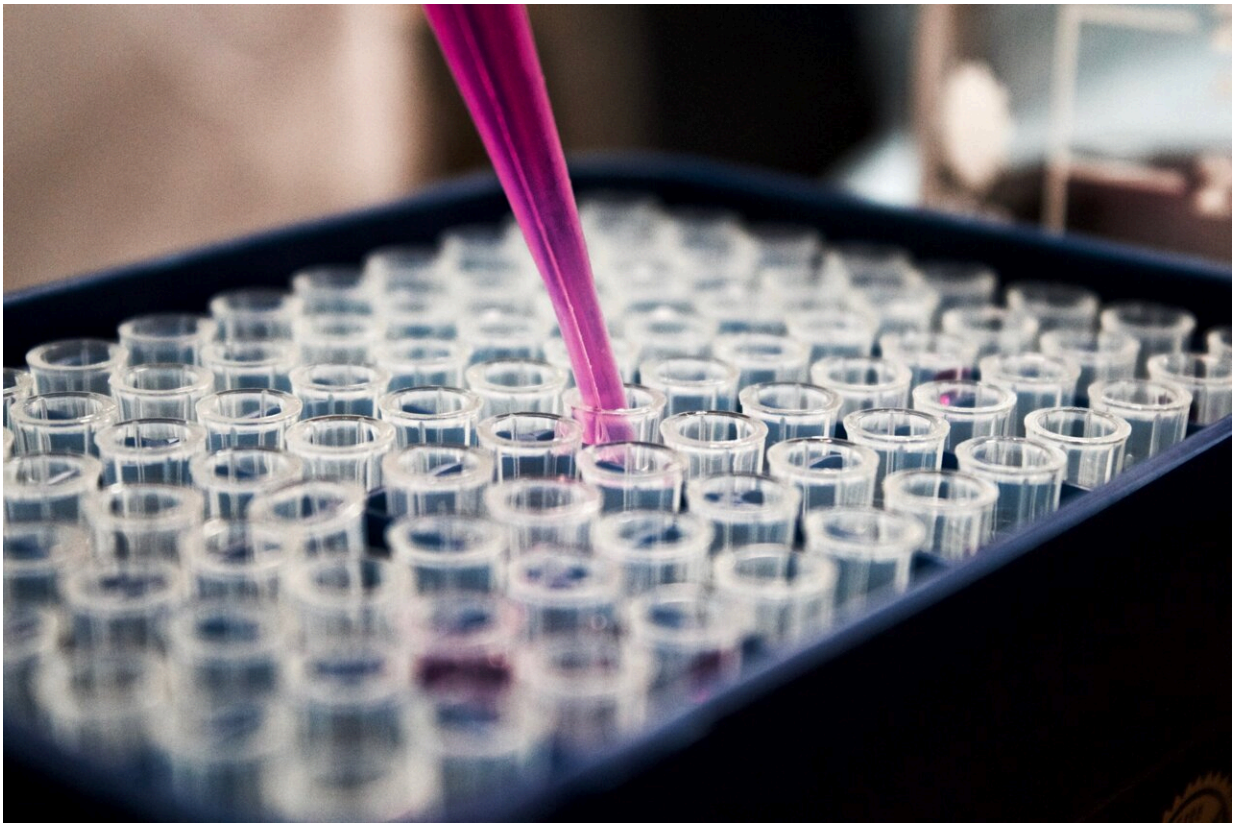

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Natural history studies serve as an important standard in medical research because they analyze demographic, genetic, environmental and other variables to better understand how a disease develops and its

clinical outcomes.

Because these studies are often prospective, identifying goals and following patients to learn about them, they are less ideal for very rare diseases where only a handful of patients with a particular illness have been properly identified.

In a new study, researchers from Children's Hospital of Philadelphia (CHOP) use various rare leukodystrophies to demonstrate how retrospective studies can integrate real world data to better capture the trajectory of illnesses and provide important information for forming future studies for patients with these rare diseases.

The findings were recently published in the journal *Molecular Genetics and Metabolism*.

Prospective studies are challenging for rare diseases—classified in the United States as a disease that affects fewer than 1 in 1,500 people—because many patients are not diagnosed with a rare disease right away, a journey often referred to as the "diagnostic odyssey," where families spend several years waiting for a proper diagnosis.

This delayed diagnosis can be further compounded when there are a smaller number of patients affected by these diseases, with both factors limiting the timely collection of natural history data. Without this important information, patients are often not diagnosed before symptoms begin, making it more challenging to chart the full history and potential course of their disease.

Leukodystrophies are a group of rare, genetic disorders that affect the white matter of the brain. Most leukodystrophies are neuro-degenerative, which can cause more destruction to the white matter and worsening symptoms, such as impairments in movement, speaking, vision, hearing

and mental and physical development. Given the challenges in studying the natural history of leukodystrophies, development of therapies to treat these diseases has been difficult.

The Global Leukodystrophy Initiative Clinical Trials Network (GLIA-CTN) is comprised of a network of research institutions across the U.S. working together to combat these challenges by mapping the clinical course of disease across different kinds of leukodystrophies. This gave researchers an important starting point to collaborate and find new ways of charting the natural history of rare diseases.

"By working together, we were able to look at the challenges facing natural history studies for these patients and develop standardized approaches that could better utilize the data that was already available in medical records," said lead study author Laura Adang, MD, Ph.D., an attending physician in the Division of Neurology at CHOP who specializes in the care of children with leukodystrophies.

"Using this approach allowed us to replicate many of the features of a clinical trial so that we could generate reproducible results to help guide us with trial design and expedite diagnosis for new patients."

In this study, researchers developed a series of standard operating procedures that delineated study processes and detailed a standardized approach to data extraction including diagnosis, clinical presentation and medical events that required specific interventions. Electronic case form reports and key variables were created so that analyzable data could be collected.

Simulating the "blinded" study approach often used in clinical trials, a blinded dual-rater approach was used to perform retrospective assessments, with a third rater reviewing discrepancies in how the first two scored the assessments.

The researchers found that this approach was successful at leveraging existing medical records to fill in key parts of natural history data for patients with leukodystrophies.

"Between mutated genes, medical events, and clinical presentation, leukodystrophies can vary wildly and often create complex puzzles for clinicians trying to make appropriate diagnoses and researchers attempting to develop new therapies," said senior study author Adeline Vanderver, MD, an attending physician in the Division of Neurology and program director of the Leukodystrophy Center at CHOP.

"The methodology explored in this study provides us with a viable alternative to randomized controlled trials and may help accelerate the design of future clinical trials for therapies for patients with rare diseases."

More information: Laura Ann Adang et al, Longitudinal natural history studies based on real-world data in rare diseases: Opportunity and a novel approach, *Molecular Genetics and Metabolism* (2024). DOI: 10.1016/j.ymgme.2024.108453

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