Children's Foundation Research Institute

Research Matters

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NICUSeq Study: Swift, affordable access to whole-genome sequencing could enable greater diagnostic equity

Le Bonheur was one of five children's hospitals to participate in a randomized clinical trial, coordinated by Illumina, Inc. scientists, to determine the effect of clinical whole-genome sequencing (cWGS) on clinical management of critically-ill newborns in the U.S. Le Bonheur Genetics Chief Chester W. Brown, MD, PhD, led the hospital's investigation efforts and co-authored a study with Illumina and fellow Le Bonheur and University of Tennessee Health Science Center (UTHSC) investigators. Findings show that using cWGS outperforms the current standard of care twofold for critically-ill newborns suspected of having a genetic condition, both in terms of diagnostic efficacy and change of clinical management. Findings from the "NICUSeq Randomized Time-Delayed Trial" were recently published in *JAMA Pediatrics* and include data supporting the widespread adoption and implementation of cWGS for critically-ill newborns.

"The NICUSeq study shows us the importance of large-scale genetic testing in newborns, leading to early diagnosis of genetic conditions and informing decision making for physicians and families," said Brown, who also holds the St. Jude Chair of Excellence in Genetics at UTHSC.

Genetics Chief Chester W. Brown, MD, PhD

A total patient population of 354 critically-ill newborns of diverse ethnicities were enrolled in the study, which took place at four sites in addition to Le Bonheur — Children's Hospital of Philadelphia, Children's Hospital & Medical Center in Omaha/University of Nebraska Medical Center, Children's Hospital of Orange County/ Rady Children's Institute for Genomic Medicine and St. Louis Children's Hospital/Washington University. The newborns were randomized to receive cWGS results within either 15 or 60 days of evaluation for a suspected genetic condition, with a total observation period of 90 days. In both the early (15 days) and delayed (60 days) arms of the study, access to cWGS doubled the number of patients who received a precision diagnosis and corresponding change in clinical management.

Study findings complement a growing body of literature demonstrating that cWGS leads to more focused, and therefore improved, patient care and should be considered a primary tool when assessing critically-ill newborns with a suspected genetic condition. Results also suggest that swift, affordable access to cWGS may help reduce health care disparities by enabling greater diagnostic equity, as the study mirrored the real-world variables affecting patient care. The NICUSeq findings support the widespread adoption and implementation of cWGS as a first-line genetic test for critically-ill newborns, increasing the probability of greater diagnostic accuracy and potentially life-saving care changes.

The next step is to determine how to implement the findings from the study into clinical standards of care, which poses some challenges, says Brown. He is currently part of a state-wide initiative to make medical genetic services, including cWGS and other genetic testing, readily accessible to all Tennesseans with rare genetic disorders.

"Having this type of genetic information provides immediate and sustainable benefits with lifelong value, providing a genetic 'report card' that can be used to direct medical care throughout life," said Brown. "We are proud that Le Bonheur and UTHSC contributed to this important effort to improve medical care for babies of the greater Memphis community."

THE UNIVERSITY OF TENNESSEE HEALTH SCIENCE CENTER

Le Bonheur Children's Hospital

Study: Trigeminal autonomic cephalalgias can begin early in life and exhibit similar symptoms as adults

Director of the Neuroscience Institute's Comprehensive Headache Center Ankita Ghosh, MD, examines a patient in headache clinic.

All five headache disorders comprising trigeminal autonomic cephalalgias (TAC) can begin early in life and exhibit many of the same symptoms as TACs in adults, according to a study published in *Cephalalgia* by Director of Le Bonheur's Comprehensive Headache Center Ankita Ghosh, MD. Literature on TACs in pediatric populations has been very limited and little is known about these headaches in children.

TACs include cluster headache, paroxysmal hemicrania, short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT), short-lasting unilateral neuralgiform headache attacks with cranial autonomic symptoms (SUNA) and hemicrania continua. Lack of study into these headache disorders in children means that many can experience a delay in diagnosis or a misdiagnosis of their headache disorder.

"Cluster headache, the most common TAC, typically has a delay in diagnosis of several years because of atypical headache features and lack of awareness of cluster headache in younger patients," said Ghosh. "The objectives of our review and meta-analysis were to report on the full age ranges of pediatric TACs and determine if kids and adults with TACs display similar symptoms."

In the meta-analysis, Ghosh and colleagues identified 86 studies for systematic review with patients from 24 countries and five continents. Results showed that every type of TAC can begin early in life. The youngest age of diagnosis for each TAC in this review was 1 year old for cluster headache and SUNA, 2 years old for paroxysmal hemicrania and SUNCT and 6 years old for hemicrania continua.

In this review, cluster headache was the pediatric TAC with the most available data. Cluster headaches were shown to be present in every pediatric age (1-18 years) and met the full criteria for cluster headaches established for adults in the ICHD-3 (International Classification of Headache Disorders). The most common differences between adult and pediatric symptoms were frequency and location of attacks. Cluster headache diagnosis was delayed or misdiagnosed as migraine in pediatric patients because children had fewer cranial autonomic features and instances of restlessness but similar rates of migraine symptoms.

The other types of TACs reviewed in this meta-analysis met most but not all ICHD-3 criteria, and very few studies examined these headache disorders in children. Further study is needed to understand the differences between adult and pediatric onset for these headache disorders.

Creating Value

Many roles of a centralized pediatric fellowship office

To determine an overview of the landscape of fellowship offices in the U.S., Pediatric Fellowship Office Director and Le Bonheur Cardiologist Michael Rebolledo, MD, MBA, MPH, and Pediatric Fellowship Office Administrative Coordinator Jayme McGrail published the article "Creating Value: Many Roles of a Centralized Pediatric Fellowship Office" in *Academic Pediatrics*. The article intended to determine how frequently a centralized administrative model is used for fellowship programs and to better understand some of the barriers to implementation at other institutions.

"Not much has been published on fellowship office administrative models, and we wanted to build on the limited literature available," said Rebolledo. "Through this paper, we're also able to share the lessons we learned during the development of our own centralized fellowship office."

Le Bonheur Hospital Medicine Fellow Mary Katherine Hood, MD, examines a patient.

McGrail and Rebolledo conducted a survey of designated institutional officials (DIOs) from children's hospitals that ranked among the "Best Children's Hospitals" in *U.S. News & World Report* for 2019-20. The six-question survey asked which fellowship programs were offered at their institution and if they used a centralized pediatric fellowship office model. The paper also shared Le Bonheur and UTHSC's framework for a centralized office and the benefits of this model.

Outcomes included:

- 54% used a centralized fellowship office; 40% did not use a centralized fellowship office; 6% selected other
- Among those without a centralized fellowship office, 78% had considered developing a centralized fellowship office, while 22% had not
- Among those with a centralized fellowship office, the governance structure was most commonly the Department of Pediatrics (66.7%) and Graduate Medical Education (GME) (51.9%) followed by hospital administration (11.1%) and other (8.4%)
- Funding source was most commonly the Department of Pediatrics (66.7%) and hospital administration (40.7%) followed by GME (33.3%) and other (11.1%)
- The greatest barriers to this model were satisfaction with the current structure and difficulty achieving buy-in from stakeholders.

"Among our survey sample, a centralized pediatric fellowship administrative model is not only feasible but commonly utilized," said Rebolledo. "A centralized office can reduce overlap and streamline shared processes eliminating inefficiencies."

Intervening for IBD

Research shows potential of psychological intervention to improve quality of life for at-risk adolescents with inflammatory bowel disease (IBD)

Psychological interventions for adolescents with inflammatory bowel disease (IBD) may help to improve adherence to treatments and health-related quality of life (HRQoL) says research published in *Behavioral Medicine* by Le Bonheur Gastroenterologists Mark R. Corkins, MD, and John R. Whitworth, MD. The research was conducted in conjunction with Psychologist Kimberly L. Klages and colleagues from the department of Psychology at the University of Memphis. Their study of adolescents with IBD showed that psychosocial problems, disease severity and identifying as Black led to lower HRQoL scores.

Le Bonheur Chief of Pediatric Gastroenterology Mark R. Corkins, MD, (above left) and Gastroenterologist John R. Whitworth, MD, conducted a study about the impact of inflammatory bowel disease on health-related quality of life.

"Youth with IBD typically experience disruptions to their health-related quality of life," said Whitworth. "The findings of our study show that a psychological approach to coping with psychosocial problems and IBD symptoms may influence patients better adhering to their treatment plan and improving their quality of life."

HRQoL of youth is influenced by three interacting factors — sociodemographic and disease characteristics, psychosocial problems and health-related behaviors. This is the first time that research has looked at the impact of these factors on HRQoL of adolescents with IBD, with the study aiming to better understand the relationship among these factors and their influence on HRQoL.

Data was collected from 107 adolescent-caregiver pairs in Le Bonheur's outpatient gastroenterology clinic. Patients were between 12 and 20 years old with a diagnosis of ulcerative colitis or Crohn's disease. The patient and caregiver each independently completed the following questionnaires and measurements:

- The Medication Adherence Questionnaire (MAM)
- Self-Care Inventory-Revised (SCI-R-IBD)
- A visual analog scale to measure medication adherence
- The Pediatric Symptom Checklist-17 (PSC-17)
- PedsQL™ Gastrointestinal Symptoms Scales

The results of the study showed:

- Psychosocial problems were associated with worse HRQoL and adherence behaviors.
- HRQoL scores were lower for youth who were Black, had more severe disease or had greater psychosocial problems.
- Those with more severe disease had better adherence behaviors.
- Those with nonpublic insurance were associated with greater adherence behaviors and lower psychosocial problems.
- Age, disease duration, disease activity and gender did not predict psychosocial problems, adherence behaviors or HRQoL.

"Out of all of our study findings, we found the effect of psychosocial problems on HRQoL and adherence to be quite large," said Corkins. "Our findings indicate factors by which youth with IBD can be quickly and cost-effectively screened to identify those at risk for lower HRQoL."

The results of the study have clinical and economic significance for patients and clinicians treating IBD. By screening patients for risk factors such as insurance status, disease severity, psychosocial problems, race and adherence behaviors interventions can take place quickly to prevent decline in quality of life. Implementing psychological interventions focused on psychosocial problems, symptom coping and medication adherence may help enhance adherence behaviors and HRQoL while also preventing the treatment cost for long-term medical and psychological complications that can occur among adolescents with IBD. Le Bonheur gastroenterologists plan to use the data to demonstrate the need for psychologists in the care of pediatric patients with IBD.

CFRI published 317 articles in 2021

In 2021, CFRI researchers continued the upward trend in articles published with a total of 317 publications. This is the fifth year in a row that CFRI investigators have published more than 200 manuscripts. Thanks to the work of these investigators, the CFRI continues to search for answers for children who depend on cutting-edge research and clinical trials.

Le Bonheur, UTHSC join Genomic Information Commons

Le Bonheur and UTHSC recently joined the Genomic Information Commons (GIC), a continuously updated and searchable genomic data commons. As part of this partnership, Le Bonheur and UTHSC will provide deidentified genomics and clinical data to the collaborative members and will be able to query other partner institutions for data and sample contributions. The GIC was founded by leaders at Boston Children's Hospital, Harvard Medical School, Cincinnati Children's Hospital Medical Center, the Children's Hospital of Philadelphia, St. Louis Children's Hospital/Washington University at St. Louis and the University of Pittsburgh Medical Center.

Speaking Up for Children with TSC

Research shows infants with tuberous sclerosis complex (TSC) have delayed precursors of speech development

Le Bonheur Pediatric Neurologist and Neurodevelopmental Disabilities Specialist Tanjala Gipson, MD, meets with a patient during tuberous sclerosis complex (TSC) clinic. Gipson's research into TSC found that precursors of speech development are delayed in infants with TSC and may signal poor language and development outcomes.

In the first published research of its kind, Le Bonheur Pediatric Neurologist and Neurodevelopmental Disabilities Specialist Tanjala Gipson, MD, and her colleague Psycholinguist Kimbrough Oller, PhD, and his team at the University of Memphis, have found that precursors of speech development are delayed in infants with tuberous sclerosis complex (TSC).

These findings may signal poor language and developmental outcomes, according to the study published by Gipson, who is director of the TSC-Associated Neuropsychiatric Disorders (TAND) Clinic, and colleagues, in *Pediatric Neurology*. Delays in early vocalizations were seen across all parameters in the study. Children and infants with TSC can experience associated neurodevelopmental issues that are known as TSC-associated neuropsychiatric disorders (TAND), including significant problems in communication and language. Only 28% of people with TSC have typical lingual function and up to 50% of those with TSC have autism spectrum disorder, which also impacts communication and language.

"The earlier we can detect delays, the earlier we can provide intervention," said Gipson. "Currently children with TSC are diagnosed with autism at 7 years old on average. This research may allow us to detect autism as early as 6 to 9 months old."

The study analyzed 74 audio-video recordings from the TSC Autism Center of Excellence Research Network of 40 randomly-selected infants with TSC. Researchers reviewed samples and determined the number of canonical (well-formed syllable structure typified by consonant-vowel combinations) and non-canonical syllables produced by the infants. Results were compared with two groups of typically-developing (TD) infants — 41 infants recorded in a laboratory setting and 39 infants recorded all day in the home through Language Environment Analysis (LENA). All recordings analyzed were taken at 12 months old.

Researchers determined volubility (total number of protophone syllables per minute), canonical babbling (number of consonant-vowel combinations) and the canonical babbling ratio (canonical syllables/total syllables) and compared results between TD infants and infants with TSC.

Volubility for infants with TSC was less than half that of TD infants from laboratory recordings. TD infants had a mean of 9.82 syllables per minute compared to 3.99 for those with TSC. When compared with LENA recordings, the rate of vocalization was more than three times higher in TD infants compared to infants with TSC, with a mean of 14.65 syllables per minute. The canonical babbling ratio (CBR) of infants with TSC was a mean of .117 compared to .346 in the laboratory recordings and .173 in the LENA recordings.

"Our results showed delays across all study parameters — canonical babbling, volubility and CBR," said Gipson. "This data suggest that at 12 months many, perhaps most, infants with TSC show signs of delay in the vocal foundations for speech and language. The current results provide a benchmark suggesting that vocal development may be substantially delayed in TSC."

Gipson's long-term goal is to develop a body of knowledge in TSC about a variety of precursors to speech and language to help illuminate the development of language difficulties and other neurodevelopmental disorders in infants with TSC. Gipson and her team intend to conduct additional research to standardize methodology, increase sample size and further assess the correlation between early vocalizations and language outcomes in infants with TSC. Their next step is assessing vocal precursors to language in all 130 infants in the TSC Autism Center of Excellence Research Network and relating them to the infant's language outcomes at 36 months.

CFRI first to enroll patient in four studies

In four unique industry-sponsored clinical trials, the CFRI Clinical Research Team was the first to randomize a patient in the United States for each study. This significant accomplishment is the result of the hard work of the entire CFRI team including principal investigators and research coordinators.

In early 2021, CFRI Senior Director Marie Jackson, PhD, MBA, and CFRI Scientific Director Dennis Black, MD, challenged the team to focus on identifying and addressing barriers to rapid study startup. CFRI began participating in the Pediatric Improvement Collaborative for Clinical Trials & Research (PICTR) quality improvement program led by I-ACT for Children. The PICT-R team reviewed study feasibility as well as budgeting, contracting and regulatory processes to identify and mitigate pinch points. As a result of the team's focus on startup, CFRI has been able to quickly launch studies and bring clinical trials to Le Bonheur patients and families.