



Investigator: Daniel Shrey, MD **Grant Award Year:** 2021

Amount of PERF® Grant: \$200,000

Investigator Institution: Children's Hospital Orange County, Orange CA

Project Title: A Multimodal Biomarker-based Predictive Model for Infantile Spasms

Project Description: Infantile spasms is an often devastating form of epilepsy, characterized by chaotic brainwave patterns and clusters of brief seizures which typically begin in the first year of life. Without prompt and effective therapy, and too often despite our best treatments, these seizures and brainwave abnormalities impart severe developmental consequences. Patients with infantile spasms are at high risk for unrelenting seizures, cognitive disability, autism, and early death. Available therapies are simply inadequate. Initial response rates are modest, relapse rates are substantial, and the most effective therapies are risky and cannot safely be continued long-term. As a consequence, less than 20% of children with infantile spasms will go on to live normal lives. There are significant gaps in our understanding of infantile spasms. In particular, there is no established method to predict which treatments will work, and there is no effective strategy to monitor for impending relapse in those who respond to treatment. For this study, we will construct a robust cloud-based database to securely accommodate sharing of full-length brain wave recordings (long-term electroencephalography) and brain imaging (MRI) data. This type of data collection will allow us to curate a large amount of information for a rare disease, from twenty epilepsy centers nationwide, over a short period of time. This multimodal database will allow us to find a way to predict treatment response and relapse, and it will support future efforts that require robust data-sharing across centers. Once we are able to predict these outcomes for children with infantile spasms, we will be able to personalize the way their epilepsy is treated to more effectively control their seizures and ultimately improve their lives.

Project Goals/Objectives: 1. Implement a cloud-based data ecosystem for multimodal data. 2. Develop a biomarker to predict IS initial treatment response. 3. Develop a biomarker to predict IS relapse.

Outcome of Research: Thus far, we have obtained preliminary results from the study, as the final data cleaning and analysis is ongoing. These preliminary results described changes in the way infantile spasms was diagnosed and treated over the five years of

2016-2020, demonstrating an increased use of genetic panel testing in the diagnosis of infantile spasms, and increased use of prednisolone (with decreased use of ACTH) in 2019 and 2020, concurrent with the start of the COVID-19 pandemic. We also developed a training course for pediatric neurologists and trainees to teach them how to correctly interpret the EEGs of children with spasms and trained over 30 medical professionals. We assessed the effectiveness of this training and published the results, and we also made the training sessions broadly available to others via video recordings on the internet. Our preliminary analysis of the genetic testing data demonstrated that children with genetic diseases involving fetal brain cell migration were at higher risk for not responding to their spasms treatments, whereas children who had genetic conditions involving the mTOR pathway (like tuberous sclerosis, for instance), were more likely to respond to treatment. Lastly, we developed models of predicting whether a child with spasms would or would not respond to their first medication based on our preliminary data set. Our hope is that the finalization of the study data and its analysis once all data are cleaned and validated will allow us to reach our primary goals of developing robust ways to predict response to medications and also to predict which patients who respond to medications are at a high risk for disease relapse.

Subsequent Funding

Year: 2021

Funder: CHOC Neuroscience Institute

Amount: \$100,000

Project: Matching funds for this project to support expanding data collection for this project from 400 to 560 participants and to add four centers to the consortium for a total of 21 centers.

Potential Funding

An NIH R01 proposal (\$4.1 million budget) submitted in October 2025 proposing to leverage the dataset from the PERF® funded project to accomplish several key goals.

Subsequent Publications

Mytinger et al, A multicenter training and interrater reliability study of the BASED score for IESS.

Journal of Clinical Neurophysiology. *Jul 2024*. DOI: 10.1097/WNP.0000000000001101. PMID 38995949.

Subsequent Presentations

1. Mytinger JR, Albert DVF, Aylward SC, Beatty CW, Bhatta S, Bhatia S, Brock GN, Ciliberto MA, Choudhari PR, Clark DJ, Cohen JM, Czech TM, Fredwall MM, Gonzalez-Giraldo E, Harini C, Hunter SE, Sandoval Karamian AG, Katyayan A, Kistler I, Kulkarni N, Liu VB, McCabe C, Murray T, Neville K, Patel SH, Pavuluri S, Phillips DJ, Samanta D, Sirsi D, Spelbrink EM, Stafstrom CE, Steenari M, Takacs DS, Terrill T, Tran L,

Vidaurre J, Shrey DW. A multicenter training and interrater reliability study of the BASED score. Abstract & Poster. American Epilepsy Society, Annual Meeting. Dec 2023.

2. Sonal Bhatia, Shaun A. Hussain, Rani Singh, Sonam Bhalla, Peter Chang, Wei-Liang Chen, Michael A. Ciliberto, Jason Coryell, Chellamani Harini, Ann Hyslop, Cynthia Keator, Hollie Lai, Beth A. Lopour, Jennifer Madan Cohen, Venus Mostaghimi, John R. Mytinger, Sunil Naik, Kerri Neville, Adam Numis, Archana Pasupuleti, Debopam Samanta, Amanda G. Sandoval Karamian, Nilika Singhal, Deepa Sirsi, Emily M. Spelbrink, Carl E. Stafstrom, Danielle S. Takacs, Tyler Terrill, Linh Tran, Elissa Yozawit, Christopher J. Yuskaitis, Kelly G. Knupp, Renée A. Shellhaas, Zachary M. Grinspan, Daniel W. Shrey. Response to First Treatment for Infantile Epileptic Spasms Syndrome: Initial Analysis of the NIMBIS Study. Abstract & Poster. American Epilepsy Society, Annual Meeting. Dec 2023.

3. Daniel W. Shrey, Renée A. Shellhaas, Zachary M. Grinspan, Sonam Bhalla, Sonal Bhatia, Peter Chang, Wei-Liang Chen, Michael A. Ciliberto, Jason Coryell, Chellamani Harini, Ann Hyslop, Cynthia Keator, Hollie Lai, Beth A. Lopour, Jennifer Madan Cohen, Venus Mostaghimi, John R. Mytinger, Sunil Naik, Kerri Neville, Adam Numis, Archana Pasupuleti, Debopam Samanta, Amanda G. Sandoval Karamian, Rani Singh, Deepa Sirsi, Emily M. Spelbrink, Carl E. Stafstrom, Danielle S. Takacs, Tyler Terrill, Linh Tran, Elissa G. Yozawitz, Christopher J. Yuskaitis, Kelly G. Knupp, Shaun A. Hussain. Practice Trends in Infantile Epileptic Spasms Syndrome Diagnosis and Management Over a Five- Year Period (2016-2020): Initial Analysis of the NIMBIS Study. Abstract & Poster. American Epilepsy Society, Annual Meeting. Dec 2023.

4. Mongkol Chanvanichtrakool, Samanta Debopam, Rani Singh, Yuskaitis Christopher, Kelly Knupp, Archana Pasupuleti, Daniel Shrey, Jennifer Madan-Cohen, Cynthia Keator, Zachary Grinspan, Sonam Bhalla, Sonal Bhatia, John Mytinger, Sunil Naik, Adam Numis, Beth Lopour, Shaun Hussain, Michael Ciliberto, Kerri Neville, Ann Hyslop, Danielle Takacs, Deepa Sirsi, Wei-Liang Chen. Etiologies and Genetic Pathway Analysis Reveals Prognostic Insights in Infantile Epileptic Spasms Syndrome (IESS): A Multicenter Retrospective Study. Abstract & Poster. Child Neurology Society, Annual Meeting. Nov 2024.

Updated October 2025