BOSTON CHILDREN'S HOSPITAL HARVARD MEDICAL SCHOOL

ROBERT'S PROGRAM ON SUDDEN UNEXPECTED DEATH IN PEDIATRICS

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Robert's Program 2024 Annual Newsletter

Each year, we provide an update on where things stand with Robert's Program to the families we are so privileged to try to help, and the families and friends whose generosity makes our efforts possible. We like to think that we all have a stake in our progress. We hope you agree. This is our latest report, covering 2024.

Our Team

We are proud to have seen our program evolve and grow over the past year. Rick Goldstein remains the Director of Robert's Program, supported by Ingrid Holm, Associate Director, and Monica Wojcik, Assistant Director. Ann Poduri, who has been our marvelous Director of Research, recently began in her new position as the Deputy Director of the National Institutes of Health (NIH) National Institute of Neurological Disorders and Stroke. Ann will remain involved as an active collaborator with Robert's Program, participating in case assessments and continuing the zebrafish research from our program.

We are excited to share some new additions. Sarah McCarthy has joined our team as the Director of Psychology. Sarah comes to us from the Mayo Clinic, though we knew her during her training and as a junior faculty member at the Dana-Farber Cancer Institute. Sarah is a psychologist who focuses on the psychology of loss and is deeply committed to supporting Robert's Program families. She is looking forward to sharing her expertise in pediatric and adult bereavement, and will bring new availability and responsiveness to Robert's Program. Speaking personally, Sarah's addition makes me very hopeful about improving our efforts at understanding and supporting family coping after loss. We are grateful to the philanthropy from Cameron's Fund that makes this possible.

In another major development, we are thrilled to welcome Kathleen Garvey as our new program coordinator and genetic counselor. Kathleen replaces Bree Martin, and has adapted quickly and

spectacularly to her position. Kathleen brings advanced genetic analysis skills along with her superb interpersonal skills, and I hope you all will join me in welcoming her! In yet another improvement, Mara Jendro has joined Robert's Program as our research assistant. Mara will work closely with Kathleen while also working on research efforts. Related to these new additions, we also said goodbye to Bree Martin and Rebecca Chicoye, with thanks for all they did for Robert's Program.

Our team is growing, and we are all looking forward to continuing our important work and mission.

Our Work with Families

Robert's Program continues to enroll families from across the United States and Canada in our program of comprehensive clinical care for sudden unexpected death in pediatrics (SUDP), including SIDS and SUDC. Our research cohort continues to grow, and we are nearing 650 enrolled cases. We are committed to providing unparalleled interdisciplinary assessments of medical, familial, pathologic and genetic details to our families, and doing so in the most sensitive way for affected families. We increasingly learn of efforts to replicate our approach elsewhere.

The mission of Robert's Program extends beyond our clinical services and basic science research. We also hope to provide support and resources to those experiencing such tragic loss. From the beginning of Robert's Program, we have integrated attention to grief and bereavement. We have benefitted enormously from Sue Morris' exceptional leadership and innovation, notably through her groups offering bereavement support to Massachusetts families and families whose children were patients at Boston Children's Hospital. We intend to build on and expand those efforts with the addition of Dr. McCarthy. It is our goal that families feel heard and supported not only during the evaluation but that our commitment to be of assistance is unending. There will be more details to come on the structure and timeline for these groups and other initiatives, but please contact us if this opportunity would be of interest to your family, if you have ideas about services that your family would find helpful, and/or if you have additional questions.

Expanding Our Reach

Last year, our program was formally accepted into the Children's Rare Disease Cohort (CRDC) which supports genomic research focused on rare diseases, aimed to expedite pediatric precision medicine. This teamwork with the CRDC has allowed expansion to genome testing, faster genetic testing turnaround times, facilitated collaboration with other genetic researchers at BCH, and improved our genetic analysis tools. Many families have already benefited from this expansion, and we look forward to learning more about our cohort with the use of genomic sequencing and analysis.

Robert's Program New Publications

We continue to make academic contributions that change the way the problem of sudden unexplained deaths in infants and children is seen. Here is a summary of just a few published over the past year.

Bree Martin was the first author of a case report this year entitled *Sudden Death in a Child With Ocular Lesions.* The publication highlights a case where a Robert's Program review led to a post-mortem diagnosis of Carney Complex, and an explanation for the child's sudden death. This case report is an example of a diagnosis that became apparent through a family's involvement with Robert's Program, when otherwise they would have not been provided with an explanation for their child's death.

> Martin, B. E., Vargas, S. O., Hindman, H. B., Rothstein, A., Folberg, R., & Goldstein, R. D. (2024). *Sudden Death in a Child With Ocular Lesions*. JAMA ophthalmology, 142(4), 388–389.

Robin Haynes led an effort to understand the role of neuroinflammation in certain cases of sudden unexplained infant death. In a multicenter collaboration, she was able to identify a subset of infants with evidence of elevated neuroinflammation and, in one case, identify the actual virus. This is another example of a diagnosis that otherwise would have not been provided becoming apparent through our research.

> Ramachandran, P. S., Okaty, B. W., Riehs, M., Wapniarski, A., Hershey, D., Harb, H., Zia, M., Haas, E. A., Alexandrescu, S., Sleeper, L. A., Vargas, S. O., Gorman, M. P., Campman, S., Mena, O. J., Levert, K., Hyland, K., Goldstein, R. D., Wilson, M. R., & Haynes, R. L. (2024). *Multiomic Analysis of Neuroinflammation and Occult Infection in Sudden Infant Death Syndrome.* JAMA neurology, 81(3), 240–247.

As Robert's Program's advances become better known, we are pleased to see interest from clinicians who are among the first responders. In this review, we present the body of research on the disease basis of SUDC in the leading journal in pediatric emergency medicine.

> Wojcik, M. H., Krous, H. F., & Goldstein, R. D. (2023). *Sudden Unexplained Death in Childhood: Current Understanding.* Pediatric emergency care, 39(12), 979–983.

The research focus on the role of serotonin in sudden infant death that began with Hannah Kinney continues in the excellent work from Robin Haynes, elucidating further details and an increasingly sophisticated model.

> Cummings, K. J., Leiter, J. C., Trachtenberg, F. L., Okaty, B. W., Darnall, R. A., Haas, E. A., Harper, R. M., Nattie, E. E., Krous, H. F., Mena, O. J., Richerson, G. B., Dymecki, S. M., Kinney, H. C., & Haynes, R. L. (2024). *Altered 5-HT2A/C receptor binding in the medulla oblongata in the sudden infant death syndrome (SIDS): Part II. Age-associated alterations in serotonin receptor binding profiles within medullary nuclei supporting cardiorespiratory homeostasis.* Journal of neuropathology and experimental neurology, *83*(3), 144–160.

Other Relevant Publications Involving Robert's Program Clinicians and Researchers

Frelinger, 3rd AL, Haynes RL, Goldstein RD, Berny-Lang MA, Gerrits AJ, Riehs M, Haas EA, Paunovic B, Mena OJ, Campman SC, Milne GL, Sleeper LA, Kinney HC, Michelson A. *Dysregulation of platelet serotonin, 14-3-3, and GPIX in sudden infant death syndrome.* Scientific reports. 2024 May 15; 14(1): 11092.

Goldstein RD, Poduri A. *Seizures and Sudden Death Beyond SUDEP*. Neurology. 2024 Feb 13; 102(3): e208119.

Holm IA, Green RC. *The BabySeq Project: A clinical trial of genome sequencing in a diverse cohort of infants.* Am J Hum Genet. 2024 Sep 10:S0002-9297(24)00297-0.

Kristensen P, Dyregrov A, Rognum TO, Goldstein RD. *Bereaved parents' perceptions of the doll reenactment after sudden unexpected infant deaths.* Pediatrics. Forthcoming.

Saxton, S., Dickinson, G., Wang, D., Zhou, B., Um, S. Y., Lin, Y., Rojas, L., Sampson, B. A., Graham, J. K., & Tang, Y. (2023). *Molecular genetic characterization of sudden deaths due to thoracic aortic dissection or rupture.* Cardiovascular pathology: the official journal of the Society for Cardiovascular Pathology, *65*, 107540.

Saxton, S., Kontorovich, A. R., Wang, D., Zhou, B., Um, S. Y., Lin, Y., Rojas, L., Tyll, E., Dickinson, G., Stram, M., Harris, C. K., Gelb, B. D., Sampson, B. A., Graham, J. K., & Tang, Y. (2024). *Cardiac genetic test yields and genotype-phenotype correlations from large cohort investigated by medical examiner's office.* Cardiovascular pathology: the official journal of the Society for Cardiovascular Pathology, 72, 107654.

Wojcik MH, Lemire G, Berger E, Zaki MS, Wissmann M, Win W, White SM, Weisburd B, Wieczorek D, Waddell LB, Verboon JM, VanNoy GE, Töpf A, Tan TY, Syrbe S, Strehlow V, Straub V, Stenton SL, Snow H, Singer-Berk M, Silver J, Shril S, Seaby EG, Schneider R, Sankaran VG, Sanchis-Juan A, Russell KA, Reinson K, Ravenscroft G, Radtke M, Popp D, Polster T, Platzer K, Pierce EA, Place EM, Pajusalu S, Pais L, Õunap K, Osei-Owusu I, Opperman H, Okur V, Oja KT, O'Leary M, O'Heir E, Morel CF, Merkenschlager A, Marchant RG, Mangilog BE, Madden JA, MacArthur D, Lovgren A, Lerner-Ellis JP, Lin J, Laing N, Hildebrandt F, Hentschel J, Groopman E, Goodrich J, Gleeson JG, Ghaoui R, Genetti CA, Gburek-Augustat J, Gazda HT, Ganesh VS, Ganapathi M, Gallacher L, Fu JM, Evangelista E, England E, Donkervoort S, DiTroia S, Cooper ST, Chung WK, Christodoulou J, Chao KR, Cato LD, Bujakowska KM, Bryen SJ, Brand H, Bönnemann CG, Beggs AH, Baxter SM, Bartolomaeus T, Agrawal PB, Talkowski M, Austin-Tse C, Abou Jamra R, Rehm HL, O'Donnell-Luria A. *Genome Sequencing for Diagnosing Rare Diseases.* N Engl J Med. 2024 Jun 6;390(21):1985-1997.

Wojcik MH, Del Rosario MC, Feldman HA, Smith HS, Holm IA. *Multidimensional and Longitudinal Impact of a Genetic Diagnosis for Critically Ill Infants.* medRxiv [Preprint]. 2024 Jul 1:2024.06.29.24309646.

International Nomenclature for the Diagnosis of Sudden Unexplained Deaths in Infants and Children

In 2017, we began an effort to improve diagnostic practices around the world for sudden infants and child deaths by convening an international group to discuss the issues and make recommendations to the World Health Organization. These efforts are now nearing approval and are on their way to being incorporated into the International Classification of Diseases (ICD-11). The changes include the formal recognition of SUDC as a valid cause of death, and a more

inclusive definition of sudden infant death to better capture the extent of the problem and make international comparisons easier. The proposals will likely be implemented in ICD-11 either in the next year's release or possibly 2027.

National Academies of Sciences

Last November, the Committee on Science, Technology, and Law of The National Academies of Sciences, Engineering, and Medicine asked Robert's Program to be a leading voice in a review of the interface between law enforcement and bereaved families after sudden death in infants and children. The committee has recommended a consensus study on sudden unexplained death in infants, and we expect to play a major role in the initiative.

ISPID Bereavement Peer Support Training

Dr. Goldstein led efforts to develop an international certification tailored towards the people who provide peer support for SIDS and SUDC parent organizations. The course was a successfully delivered at the meetings of the International Society for the Study and Prevention of Infant and Perinatal Deaths (ISPID) in October 2023. The course is being evaluated and revised, and it will be offered again at the next ISPID international meeting in October 2025 in San Diego.

Conferences and Presentations

Physicians from Robert's Program have been invited to speak at every major venue attracting investigators into the problem of sudden unexpected deaths in pediatrics, including the International Society for the Study and Prevention of Infant and Perinatal Deaths (ISPID), the American Academy of SIDS Prevention Physicians, Microsoft SIDS Summit, the Soria Moria meeting in Oslo, Norway, The California SIDS Conference, and the National Association of Medical Examiners. Our work has been highlighted by Le Monde, The Washington Post, New York Times, Bloomberg News, the BBC, and others.

This year's CJ/Kinney Grand Rounds

It gives us tremendous pleasure to announce that our speaker for this year's C.J./Kinney Grand Rounds on Sudden Unexpected Death in Pediatrics will be our own Robin Haynes, PhD, Assistant Professor of Pathology at Boston Children's Hospital and Harvard Medical School, and the Director of the CJ Murphy Laboratory for SIDS Research at Boston Children's, also known as the Haynes lab. Robin is a distinguished and beloved member of our community, dedicated to addressing sudden unexplained infant deaths. She was selected for her unique combination of independent research accomplishments, international respect for her work, and her ongoing commitment to advancing Hannah's foundational contributions to science. The rounds are scheduled for March 26th, 2025. Parents are invited and the events will include a parent luncheon after the rounds.

Ongoing Research, Projects, and Grants

We are immensely grateful for the support of the organizations, foundations, researchers, and families who have donated their time and resources to supporting Robert's Program.

Ongoing NIH support for work by members of our group includes:

"Multiomic Investigation of Sudden Unexplained Pediatric Deaths," (Goldstein, Holm, Wojcik, Co-PIs), under review NINDS.

"Brainstem Arousal Network in Human Consciousness: Healthy development vs SIDS," (Zollei PI), Sponsored by NIH.

"The Burden of Genetic Disorders in Infant Mortality," (Wokcik PI), Sponsored by NIH.

"Inflammatory stressors in serotonergic brainstem dysfunction and SIDS," (Haynes PI), Sponsored by NIH.

"Does neurotransmitter plasticity of para-serotonergic neurons augment autoresuscitation following perinatal stress and buffer SIDS risk?," (Dymecki, Haynes, and Leiter, Co-PIs), Sponsored by NIH.

"Dried blood spot proteomics analysis of newborn screening cards to identify prognostic markers of SIDS risk," (Haynes, Steen, Co-PIs), Sponsored by NIH.

"Brainstem microRNA dysregulation in the pathogenesis of sudden infant death syndrome (SIDS)," (Haynes PI), Sponsored by NIH.

Additional grants supporting our work by various key foundations:

"Genomic Autopsy for Unexplained Infant Death," (Wojcik PI), Sponsored by American SIDS Institute.

"MicroRNA analysis in SIDS," (Haynes PI), Sponsored by American SIDS Institute.

"Modelling genetic findings in sudden unexpected death in pediatrics in zebrafish Phase 2—Focus on DEPDC5," (Goldstein, R. PI, Poduri, A. Co-PIs), Sponsored by Cooper Trewin Foundation.

"International Certification for Peer Support Offered to Parents Following the Sudden Unexplained Death of Their Infants," (Goldstein PI), Sponsored by the C.J. Foundation for SIDS.

"The impact of infant medical history on parental grief," (McCullough, Goldstein, Co-PIs), Harvard Combined Program in Neonatal-Perinatal Medicine.

A Message from Rick Goldstein

Dear Robert's Program community,

It is an extraordinary privilege to play a part in this remarkable program. When Hannah Kinney and I first questioned whether the field was ready for change, we had no idea of the scale of transformation or the serious efforts that would follow. We did not fully appreciate the dedication of the doctors and researchers in Robert's Program to tackling this challenge, nor their humbling loyalty to our mission. And we couldn't have anticipated the powerful community of parents who would emerge around us. I am deeply grateful to each of you.

One thing that has not changed from the beginning is our desire to help. We continue to try to learn and grow. We know our efforts may sometimes come up short, but we are unwavering in our motivation to improve the lives of families reeling from this terrible loss. Please take a moment to watch this moving video about Robert's Program, featuring a Robert's Program parent, Maile Carter Madigan, here. Maile's message means so much to all of us and gives us hope that we are getting somewhere.

At the core of our work is bringing the most up-to-date methods to understanding the catastrophic loss of SUDP and providing support to families who find themselves needing it. We are honored that throughout our program's history, our efforts have been underwritten by donations from families who respond to their personal pain by trying to help others. Our families are the foundation of this program. Without you, we would not be where we are today. Because of you, we will continue to fight for understanding and prevention of sudden death in infants and children, and greater compassion for those who are affected.

Thank you. Thank you. Thank you.