COMPASS

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Cure SMA Funding Network of Prominent SMA Clinical Research and Treatment Centers in the U.S.

In the midst of the ongoing Coronavirus (COVID-19) global pandemic, Cure SMA announced this spring its new funding for the Pediatric Neuromuscular Clinical Research Network (PNCRN). In 2020, Cure SMA will provide $1.2 million to this Network of highly skilled clinical trial investigators, clinical evaluators, clinical coordinators, statisticians, and data management personnel.

In recent years, there have been many important medical breakthroughs, offering new and effective SMA treatment options. The PNCRN has been involved in the seminal clinical trials that have led to the U.S. Food and Drug Administration (FDA) approvals of anti-sense oligonucleotides, gene transfer strategies, and other breakthrough treatments that have changed forever the natural course of the disease. Their work continues to develop and refine more sensitive outcome measures, conduct ongoing clinical trials, accelerate newborn screening programs, and identify promising new treatment approaches.

"In these unprecedented times, we see the investment in the PNCRN as critical in our mission to advance treatment and care," says Kenneth Hobby, President of Cure SMA. "We are eager to build on the past accomplishments of the Network, made possible by the generous and continuous sponsorship from the SMA Foundation."

Originally funded by the SMA Foundation in 2004, the PNCRN established a team of SMA clinical trial experts that have integrated clinical research, education, and care to achieve the best possible clinical trial outcomes. Cure SMA has collaborated with the SMA Foundation as co-sponsor of the PNCRN since 2018.

"The SMA Foundation has built and supported this Network for the past 15 years to establish a group of multidisciplinary SMA expert centers that support clinical trials," said Loren A. Eng, President, SMA Foundation.

"Through the PNCRN, the Foundation has supported key clinical research studies, such as the SMA Natural History Study and the development of key SMA outcome measures that currently are accepted and used globally. The Natural History of SMA in the modern era was clearly defined by the Network and has been used as a key benchmark to assess safety and effectiveness of potential therapies, and ultimately to obtain recent treatment approvals."

To date, Cure SMA has provided $2.2M in funding for the Pediatric Neuromuscular Clinical Research Network to help advance clinical research and care

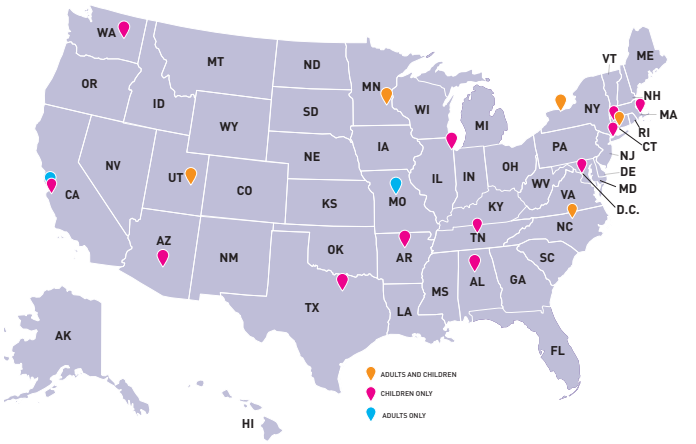
Six sites comprise the PNCRN for SMA, including Columbia University Medical Center, Boston Children's Hospital (BCH), Children's Hospital of Philadelphia (CHOP), Stanford Health Care, Nemours Children's Health System, and a data coordinating center at the University of Rochester.

"Since the advent of effective SMA treatments, the recognition and description of new SMA phenotypes in treated patients and the durability of the approved treatments have emerged as critical issues, making the continuing work to understand the disease mechanisms and phenotype-genotype correlations that much more important," says Darryl De Vivo, M.D., Director of the PNCRN and Professor of Neurology and Pediatrics, Columbia University Irving Medical Center, New York City. "Cure SMA's leadership in SMA research, and its new support of the PNCRN, will allow us to sustain this ground-breaking collaboration in SMA research and clinical care, especially as we expand the number of effective treatments for SMA and pursue the ultimate vision of a cure."

cure SMA Make today a breakthrough.

These clinical research and treatment sites have also now been integrated into the established Cure SMA Care Center Network, which will lead to real-world evidence that increases access to approved treatments and improves care for individuals and families with SMA.

19 Sites in the Cure SMA Care Center Network



We spoke with three members of the PNCRN to get their perspectives on the new funding and leadership role Cure SMA will play. Here is what they have to say about the accomplishments and future of the PNCRN.

Darryl De Vivo, M.D.
Founding Director, PNCRN for SMA Clinical Trials and Professor of Neurology and Pediatrics, Columbia University Irving Medical Center

Basil T. Darras, M.D.
Chief, Division of Clinical Neurology and Director, Neuromuscular Center and SMA Program, Boston Children's Hospital; Joseph J. Volpe Chair in Neurology, Harvard Medical School

John W. Day, M.D., Ph.D.
Professor of Neurology and Pediatrics and Director, Division of Neuromuscular Medicine, Stanford University

What has been the value of forming the PNCRN?

DE VIVO: The SMA Foundation under the direction of Loren Eng and Dinakar Singh put their trust in us at Columbia University Medical Center to create a clinical program that would focus entirely on SMA and ultimately lead to the development of an effective treatment for this genetically determined disease. The PNCRN has made seminal contributions to our understanding of SMA since its creation in 2004.

The first goal was to establish a uniform standard of care for patients at the clinical sites to minimize any "background noise" as it relates to the assessment of patients and the measurement of outcomes. Secondly, we found it essential to develop a mechanism that would allow all members of the team to "speak with one voice." This goal was accomplished by monthly conference calls and annual meetings, and subsequently by preparing and publishing important manuscripts that focused on the natural history of the disease, the value of important outcome measures like the expanded version of the Hammersmith Motor Scale, the defining of the natural history of the disease, and the formation of an effective series of clinical trials. This attention to uniformity and reliability as it relates to standard of care and outcome measures allowed the Network to generate reliable longitudinal data as we positioned ourselves to conduct pivotal clinical trials.

DARRAS: The formation of the PNCRN highlights the value of cooperation and coordination in the pursuit of scientific advances. On their own, the centers that came together in the Network would not have been able to accomplish the goal of finding an effective treatment for SMA within a decade. The Network allowed each center to focus on its strengths and combine those strengths into a multi-site team of dedicated and resourceful professionals. The public face of the Network is the successful achievement of its aims, but behind the scenes of these successes were innumerable meetings of team members to carve out hypotheses and to establish the scientifically laborious pathway toward evidence. In short, the Network illustrates the value of scientific collaboration and can serve as an example for physician-scientists who are similarly searching for treatments for other diseases.

DAY: The PNCRN has played a unique role in SMA care and research, establishing a large cohort of patients with SMA, and monitoring their course. With this well-defined population, the PNCRN was able to develop and validate functional measures, and to collect specimen repositories that played an essential role in establishing standards of care, determining the natural history of untreated SMA, developing outcome measures to monitor the time course objectively and quantitatively, and establishing a clinical trial network that facilitated treatment development and verification.

What do you see as the greatest accomplishments to date for the PNCRN?

DE VIVO: The single most important accomplishment of the PNCRN is to establish a highly organized network made up of academic centers of excellence, all working closely together with clearly defined common goals. As a result, the Network has developed a number of studies that are now frequently cited and utilized by other groups globally, such as our natural history studies and our newly created and revised outcome measures, including the Hammersmith expanded, the CHOP INTEND, the 6-Minute Walk Test, and the PEDI-CAT measures. The PNCRN has also advised other developing organizations and companies and has

generously shared its outcome measures, clinical trials experience, and aggregate data to facilitate work being done in other settings. Finally, the SMA biorepository has provided tissue samples and reagents to other collaborating investigators to facilitate their independent research programs.

DARRAS: The most visible accomplishments of the PNCRN are its major contributions towards the investigations of the first two approved treatments for SMA: the antisense oligonucleotide nusinersen, and the gene replacement therapy AVXS-101. The nusinersen and AVXS-101 clinical trials would not have been possible without the PNCRN's preceding natural history studies and investigations that developed and validated outcome measures for SMA. When regulatory approvals were granted, largely based on data from PNCRN studies and clinical trials, SMA became a treatable disease for the first time in history.

DAY: The PNCRN established a network of sites providing comprehensive care for a large population of SMA patients. The experienced physical therapists at each site developed and validated different measures of motor function for patients with SMA at various degrees of severity that were essential to subsequent clinical research. These measures allowed the PNCRN to define the natural history of SMA in both infants and children, which has been an invaluable contribution to the monitoring of patients and optimization of their care. Furthermore, having established SMA natural history and having validated outcome measures for different levels of severity, the PNCRN helped refine clinical trial design and then participated in groundbreaking studies that verified efficacy of novel SMA treatments.

The PNCRN PIs have been involved in the drug trials for all approved SMA drugs, including the one under NDA review with the FDA, with leadership roles in trial design and selection of trial endpoints.

With Cure SMA's expanded involvement, what are the future goals for the PNCRN?

DE VIVO: Newer treatments, higher doses of existing treatments, combination therapies, and better understanding of the pathophysiology of the disease process are some of the avenues that need to be explored to answer many of the existing questions with SMA. In order to do this, we welcome the opportunity to partner with Cure SMA as we continue to explore this genetic disease, hoping on the one hand to prevent this autosomal recessive condition from occurring, while on the other hand exploring effective treatments to fully rescue the symptomatic patients with SMA. Our current study results indicate that early treatment of the pre-symptomatic infant using available therapies is both necessary and sufficient to allow normal growth and development, but later treatment of the symptomatic child appears to be insufficient, although likely necessary as part of the treatment program.

DARRAS: The future goals of the PNCRN align with Cure SMA's vision of a world without SMA. To this end, the Network plans to disseminate widely its expertise in clinical research collaboration and its collection of biorepository materials with investigators throughout the U.S. who wish to contribute toward that vision. Further, the Network plans to extend its reach in two crucial directions: (1) to include adults with SMA in order to develop additional treatment options, and (2) to improve newborn screening efforts in order to provide the earliest possible treatment of affected newborns. Finally, the Network seeks to diminish the incidence of the disease by educating the public and medical community about preconception carrier screening and the use of reproductive technologies.

PEDIATRIC NEUROMUSCULAR CLINICAL RESEARCH NETWORK

Columbia | Columbia University Irving Medical Center
Stanford University
Boston Children's Hospital — Until every child is well™
Nemours Children's Health System
Children's Hospital of Philadelphia
University of Rochester

DAY: Being integrated into the Cure SMA Care Center Network, the PNCRN is now poised to characterize the new course of SMA that is coming to light as more patients are treated with definitive forms of treatment. This is requiring development of novel forms of evaluation that can accurately and objectively measure continued mobility issues and unmet needs in patients after genetic correction. These measures will help optimize treatment in patients of all ages and will define the residual functional challenges. Having defined and quantified patients' unmet needs, the PNCRN is also now able to work with Cure SMA to assure that we are developing and deploying complementary treatments that will continue to improve function in individuals of all ages affected by SMA.

What do you hope the PNCRN will do for people affected by SMA?

DE VIVO: The PNCRN is dedicated to the conduct of clinical trials for as long as there are symptomatic patients with SMA who cannot be completely rescued living in the U.S. The partnership with Cure SMA will allow us to expand several initiatives to achieve this national goal. However, we also want to assist patients living elsewhere in the world by collaborating with colleagues in Europe and the U.S. as part of the international SMA Consortium (iSMAC). The PNCRN, at the same time, has partnered with the Cure SMA registry and we ultimately hope to harmonize the several registries that have emerged in recent years so that the "whole will be more than the sum of its parts." Each registry clearly has been created to address specific needs, but it will be important to advocate for common methodologies, whenever possible, to permit efficient data sharing. A central registry with private spaces for the several stakeholders would be collaborative and financially efficient.

DARRAS: The PNCRN will without doubt advance SMA research with two main purposes in mind: to make treatments for symptomatic patients more effective, and to prevent SMA through treatment very early in life and possibly *in utero*. As part of this endeavor, the PNCRN will develop better, more sensitive outcome measures that will facilitate the investigation of new drugs and reliably investigate and reveal which treatments are appropriate for which patients. The PNCRN will also be a driving force to advance research on rehabilitative technologies for patients who may not benefit from the new treatments.

DAY: The PNCRN and Cure SMA are positioned to work with patients and families in the SMA community to define the evolving features of SMA after genetic correction, and to then establish evidence-based standards of care that establish optimal nutrition, sleep and exercise. The PNCRN and Cure SMA Care Centers will also define unmet functional needs and help identify novel treatments that will continue to improve function. The overall goal of the PNCRN, working with Cure SMA and the Cure SMA Care Center Network, is to combat and ultimately conquer SMA by helping generate, validate, and utilize the next generation of treatments that can improve function in individuals of all ages who are affected by this condition.

OUR GOAL IS TO CURE SMA.

Funding the PNCRN helps bring us closer to achieving this goal by aligning the unmet needs of the larger SMA community with the research goals of premier clinical research sites for SMA. This investment is only possible because of the generous and dedicated support of our donors.

To learn more about this project or to make a gift, please contact Erin Kelly, Vice President of Development, at erin@curesma.org.

To learn more about SMA, clinical research, and care approaches for those affected by SMA, visit www.curesma.org.

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