

# Research Compass



*a Families of Spinal Muscular Atrophy publication dedicated to Research News*

## The Critical Role: Newborn screening for early detection and treatment of SMA

*At the end of September, Families of SMA sponsored a Congressional Breakfast to educate legislators and their staff about Spinal Muscular Atrophy and the importance of newborn screening. Jill Jarecki, FSMA Research Director; Dr. Thomas Crawford; Dr. Thomas Prior; and Dr. Rodney Howell gave an informative and compelling presentation which was well received by all those who attended. This article, by Dr. Howell, emphasizes the current status of newborn screening for SMA.*

Newborn screening for genetic disease has been in place for over 40 years in the United States. The program started when it was discovered that the profound mental retardation seen in untreated phenylketonuria (PKU), an abnormality of amino acid metabolism, could be wholly prevented by a special diet, but only if the disease was detected in infancy, and treatment immediately begun. Hence, a special newborn screening test was developed, using dried blood spots from the baby, and soon became universal in the United States. Over the years, additional treatable disorders have been added to the newborn screening panel. There has been a great variation in these additions since newborn screening is a state public health function. Newborn screening is clearly one of the most important, and successful programs we have for preventing severe disability, and indeed at times saving lives. Virtually all of the conditions which are on the newborn screening panels are uncommon, and many are classified as "rare diseases", a term applied to diseases which affect fewer than

200,000 people in the United States.

At the current time there is a nationwide effort to expand newborn screening, and importantly provide a consistent panel of newborn screening tests to all of the more than 4 million babies born each year within the United States. Since newborn screening is in all instances organized along state lines, there is enormous variability in the number of conditions which are screened for in the newborn period, ranging from just a few up to more than 40 conditions. A major recent report has been prepared by the American College of Medical Genetics (ACMG) under a contract with the Health Resources and Services Administration (HRSA) which has recommended that the "core" panel of conditions include screening for 29 conditions. This very lengthy complete report is posted on the HRSA website (<http://mchb.hrsa.gov/screening>). It has been reviewed over the past year and a half by the HHS Secretary's Advisory Committee on Heritable Disorders and Genetic Diseases in Newborns and Children, which is charged with advising the Secretary of Health and Human Services on newborn screening. This Committee has supported and recommended the ACMG report to the Secretary of HHS. The minutes and deliberations of this national body are also posted on the internet (<http://mchb.hrsa.gov/programs/genetics/committee>). The rationale for including conditions on the panel is outlined in the ACMG report, but includes at a minimum that the condition have a recognized treatment and that there be a screening test that can be reliably and accurately applied to

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the entire newborn population. The important value to the family, and patient, of having information and a diagnosis, even before a treatment is available, was clearly recognized.

There are a group of conditions in the ACMG report which were not included because a treatment and/or a proven screening test was not available. SMA would fall in this category at the time the report was prepared. It is planned that this recommended list will be a changing one, and that many more conditions will be added as new treatments and new tests become available.

Exciting things are happening with SMA at the current time. There are novel treatments in trials which will hopefully be beneficial for SMA. There are other exciting and logical treatments that are yet to be taken to clinical trials, but which could be most promising.

For any of the treatments under consideration to be maximally effective, newborn screening must be in place. This is a tall order. Newborn screening is not simply a test as some might think, but indeed it requires a very complex system. Firstly, one must have a highly accurate diagnostic test that will detect all affected infants with SMA, and at the same time have a minimal number of

**Continued inside**

## Project Cure Update

Dr. Sandra Reyna, Clinical Trials Manager Project Cure SMA

We are happy to report positive news from Project Cure SMA. The phase II multi-center clinical trial that we have been reporting on in the past is up and running! SMA CARNI-VAL is for children with SMA Types II and III.

The six centers working on this project have (or will) each enlist 15 patients. Because of the policies at each of the Universities involved the sites are at slightly different stages – but all should be up and running and fully enrolled by the end of the year. The study will last 12 months, so we should have results to report in early 2007.

The University of Utah enrolled their first study patient on September 20, 2005 for a total of 11 study patients to date. Detroit is scheduled to enroll their first patient on October 26, 2005. Baltimore, MD and Columbus, Ohio have obtained Institutional Review Board approval and will be enrolling their first patients in the upcoming weeks. The other two sites, Canada and Wisconsin, have submitted their Institutional Review Board applications and are currently under review with an anticipated start date between November and December 2005. If you attempted to participate in this Project Cure Clinical Trial and were not accepted because of space limitations, or other reasons, please do not be discouraged. While we are hopeful that this trial will lead to a potential treatment for SMA, this is not the only clinical study planned. We encourage patients and families who are interested in clinical studies to contact

the International Patient Registry at Indiana University to ensure that your records are on file and that you will receive information about any potentially appropriate studies.

Phase I clinical trials which have been carried out in Salt Lake City, Utah are coming to the end. We are anticipating data analysis for Phase I trials to be completed by June 2006, watch the FSMA web site for an update – or hear from us in person at the Families of SMA conference in San Diego next summer.

Additionally, we cannot caution families strongly enough that while preliminary data on the clinical trials is promising -- it is only preliminary. There are serious side effects possible from the medications and we strongly discourage any families from arranging to receive these medications outside of a clinical study setting. This is for the health and safety of your

children.

Finally, Project Cure SMA is proud to announce that SMA CARNI-VAL Trial has been registered with ClinicalTrials.gov as a participant of the Clinical Trials Data Bank. The Clinical Trials Data Bank was initiated by the federal government this summer as part of a policy to encourage all clinical trials to be part of a centralized resource for providing current information on clinical trials to individuals with serious or life threatening diseases or conditions, to other members of the public, and to the health care providers and researchers. The web link is to the Data Bank is: <http://clinicaltrials.gov/>.



# FSMA

was founded in 1984 for the purpose of raising funds to promote research to find a cure for Spinal Muscular Atrophy, and to support families affected by SMA. FSMA is the largest private funder of SMA research and is leading the way to find a cure.

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## Research Director's Update

Dear Families,

When I last updated you about the research activities at FSMA, we were preparing for the 9th Annual International Spinal Muscular Atrophy Research Group Meeting held in Philadelphia June 23<sup>rd</sup> through 25<sup>th</sup>. I am excited to report that the meeting was a big success and was the largest research meeting to date. A tremendous amount of interest was shown by the research community this year with over 150 researchers attending and greater than a 50% increase in the number of research presentations. I believe that the increasing size of our meeting is indicative of the progress and excitement that is ongoing in the SMA research community. I can safely say

the fact that we are beginning to see basic research discoveries moving into clinical testing in SMA patients (for example, the CARNI-VAL Phase II clinical trial being conducted by Project Cure) is very satisfying to the SMA research community and is driving interest in the SMA field. With continued support from FSMA this positive energy will only increase, and many exciting new research discoveries will be made in the next year and reported on at the conference next year.

Of course, one extremely important way that FSMA supports SMA research is through our grant application program, which funds basic research discoveries in SMA biology. This is an essential component of our



**Jill Jarecki, Ph.D.**

multi-pronged approach to finding a treatment and ultimately a cure for SMA, as basic research activities feed the drug development projects, which then in turn lead to clinical testing of new drugs. As we do each year, this summer FSMA issued a call for grant applications for the upcoming year. This year our call for applications focused on a number of research areas, including projects to test whether motor neuron death in SMA is due to nuclear or axonal SMN functions and projects to identify new "druggable" molecular targets for SMA therapeutic intervention, which could lead to new and more focused drug development projects in the future. Grants were due on September 15<sup>th</sup>, and we received a tremendous response with a 50% increase the number of grants received this year over last, which again shows an increasing level of excitement in conducting SMA research. I am very excited about the potential of these projects, and I look forward to hearing the reviews from our scientific advisory board (SAB), which assesses each grant and ranks them in order of importance. Grant awards will be announced in December.

Thank you very much for your continued support. Together we can find a cure.

Sincerely,  
Jill Jarecki, Ph.D.

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## Newborn screening continued from front

false positives (since one is screening millions of babies, a significant number of false positives can paralyze the system). The technology must also be priced reasonably in order that it can be available to the entire population. Then one must have people and technology available to confirm, to provide expert genetic counseling, and then have access to appropriate treatment and follow-up. Every child who is screened positive must have long term follow up and monitoring. This is essential as we will be following children with a new treatment, and their detailed outcomes must be studied and known.

Recently, the National Institute of Child Health and Human Development has funded a key scientist to further develop newborn screening tests for SMA, which will have all the needed requirements for public health laboratory use. This is a huge undertaking, and it is essential that we work very hard to support this critical newborn

screening test development, and the systems to follow-up these tests with proper confirmation, counseling and hopefully effective treatment. It is critical that everybody understand the importance, and complexity, of newborn screening.

Without effective newborn screening, the long sought after treatments for SMA will not achieve the results we all hope to see. Newborn screening must be ready to begin, after proper trials and systems are in place, the minute an effective treatment is available.

R. Rodney Howell, M. D.\*  
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Miller School of Medicine  
University of Miami  
Miami, Florida

\*Dr. Howell Chairs the Advisory Committee on Heritable Disorders and Genetic Diseases in Newborns and Children.

## Why should we consider **newborn screening for SMA?**

By Dr. Thomas Prior, Ohio State University

While there is a blood test for SMA, most newborns are not tested for SMA unless symptoms are present. Although for the majority of tests on a newborn screen the diseases are treatable, there are still strong reasons to consider placing SMA for inclusion in newborn screening.

First there are benefits to the family. It means an immediate diagnosis, thus allowing families to make early and informed decisions. Most importantly as a result of an early diagnosis a child may be enrolled in a therapeutic

trial at a time period when there are still a number of motor neurons present. From Dr. Kathy Swoboda's studies, through Project CURE SMA, it has been shown that significant disease progression occurs in the postnatal period. If a therapeutic compound is identified that either rescues motor neurons or prevents motor neuron denervation, then newborn screening would be indicated.

The actual newborn test for SMA would differ than current testing which measure abnormal metabolites. The SMA screen would be a DNA test for the detection of the deletion of the SMN1 gene. Rather than having

to test for many different types of gene mutations, as is the case with cystic fibrosis, the test would simply determine if both copies of the SMN1 exon 7 are absent (consistent with the diagnosis of SMA). It is technologically feasible to perform the test on the heel stick blood spots that are being used for all newborn screening. However the test must be done with the same robustness and cost efficiency as the current blood spot test are. I feel with the advances in the DNA technology this can be accomplished!

If you have a question, please email it to: [info@fsma.org](mailto:info@fsma.org).



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