

Indications™

Newsletter of The Lysosomal Disease Network™

May 2015

All past issues can be downloaded from the upper-right area of the LDN homepage at: www.LysosomalDiseaseNetwork.org

Vol. 2, No. 4

Lysosomal Disease Network Urges Patients to Join the Rare Diseases Clinical Research Network Contact Registry

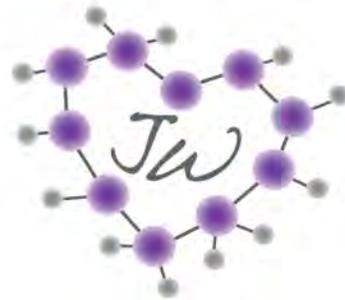
The NIH's Rare Diseases Clinical Research Network (RDCRN) **Contact Registry** exists to inform patients and/or parents of patients about clinical research studies. Joining the contact registry will help researchers identify and recruit patients who are eligible for participation in future research studies. This is critically important in rare disease research, because it is often very difficult for researchers to find enough patients who have any given rare disease, in order to reach statistical significance in their data analysis. If the level of statistical significance cannot be attained due to lack of sufficient numbers of subjects, then researchers assume that any beneficial results they recorded during their study could have been due to chance, not to their study's intervention(s).

Patients who participate in research make it possible for researchers to find new treatments, create new studies, and work for the improvement of quality of life of those affected by rare diseases. Those who have joined the RDCRN Contact Registry can choose to be available to be contacted in the future about clinical research opportunities and updates on the

(Continued on Page 5)

Meet Our Patient Advocacy Groups

The LDN considers itself lucky to have dedicated patient advocacy groups as members of the Network. This issue, we present with gratitude . . .



Jonah's Just Begun
jonahsjustbegun.org

By Evelyn Redtree, M.S., Jill Wood, and Dr. Sean Ekins

Jonah's Just Begun – Foundation to Cure Sanfilippo Inc. (JJB) is a 501(c)3 charitable foundation that raises funds and then distributes them to academic researchers focused on Sanfilippo syndrome types C & D. Jonah's Just Begun has two goals: first, to help fund the scientific research that will ultimately lead to a cure for Sanfilippo syndrome types C & D; and second, to raise awareness for all rare diseases. Jonah's Just

(Continued on Page 2)

In This Issue . . .

Title or Subject	Page
Meet Our Patient Advocacy Groups	1
RDCRN Contact Registry Needs Patients	1
LDN Research Matters: Pilot Project 3	4
Meet the Principal Investigators	5
Check Your Knowledge: MPS III	6
Newborn Screening Recent Developments	11
PCORI Offers Research Funding	11
Calendar of Upcoming Events	14
Keys to Understanding the LDN	15

The Lysosomal Disease Network (U54NS065768) is a part of the NCATS Rare Diseases Clinical Research Network (RDCRN). RDCRN is an initiative of the Office of Rare Diseases Research (ORDR), NCATS, funded through a collaboration between NCATS and the National Institute of Neurological Disorders and Stroke (NINDS), and the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Meet Our Patient Advocacy Groups

Jonah's Just Begun

(Continued from Page 1)

Begun also works to empower and encourage others affected by rare diseases to advocate for cures. As a fundraising and legislative advocacy organization, rather than a patient and family services organization, Jonah's Just Begun is similar to The Ryan Foundation, which was profiled in the December 2014 issue of "Indications."



Jeremy Weishaar (left), Jonah Weishaar, Jill Wood

Jonah's Just Begun was founded in 2010 by Jill Wood and Jeremy Weishaar, whose son Jonah was diagnosed with Sanfilippo syndrome type C (MPS IIIC) during his first year of life. From Jonah's second to third birthdays they traveled the world, connecting with other parents of children with MPS IIIC, building a patient population, and establishing a team of investigators eager to work with Jonah's Just Begun. An international board of directors was established (<http://jonahsjustbegun.org/board-of-directors/>), along with a scientific advisory board (<http://jonahsjustbegun.org/scientific-advisory-board/>).

Jonah's Just Begun is also a co-founder of HANDS (Helping Advance Neurodegenerative Disease Science), a consortium of patient groups, scientists and clinicians that work together to drive the science for treatment and cure for Sanfilippo syndrome type C. The other patient advocacy groups that con-

stitute HANDS are JLK-Sanfilippo Research Foundation in Massachusetts (<http://www.jlksanfilippofoundation.com/>), Levi's Life, Love & Laughter in Wisconsin (<http://www.levislifelovelaughter.org/>), Le combat de Haitem-contre-Sanfilippo in France (<http://lecombatdehaitemcontresanfilippo.org>), Sanfilippo Sud in France (<http://sanfilipposud.org/>), Sanfilippo Portugal (<http://jonahsjustbegun.org/sanfilippo-portugal/>), and Sanfilippo Barcelona (<http://www.sanfilippobcn.org/>).

HANDS primary investigators are: Alexey Pshezhetsky, Department of Pediatrics, University of Montreal; Brian Bigger, Senior Research Fellow at University of Manchester; Patricia Dickson, M.D., at Los Angeles Biomedical Research Institute at Harbor UCLA Medical Center; and Alessandro Fraldi, Assistant Investigator at the Telithon Institute of Genetics and Medicine (TIGEM). (For more information about TIGEM, visit: <http://www.tigem.it/>.)

Jill remarked, "Everyone in the consortium plays an important role in creating treatments for ultra-rare diseases. The patient groups fund the science. The scientists conduct the research. The clinicians provide advice and support to the patient groups. Together, these are the people that will find a treatment and a cure. Together, these are helping HANDS." So far, collectively HANDS has raised approximately \$1.5 million for Sanfilippo syndrome research.

Jill also worked to start a new biotech company in 2012 called Phoenix Nest, Inc. (<http://www.phoenixnestbiotech.com/>). She co-founded it with Sean Ekins, M.Sc., Ph.D., D.Sc, clinical pharmacologist, who serves as President and Chief Executive Officer of Phoenix Nest. Jill serves as Chief Financial Officer. Phoenix Nest was created to help take the Sanfilippo syndrome research that has been funded by Jonah's Just Begun/HANDS (and others) and translate it to clinical trials. As a startup, Phoenix Nest can also apply for the NIH's STTR/SBIR grants. Phoenix Nest has been successful in winning one STTR to date from the National Institute of Neurological Disorders and Stroke (NINDS) (grant # 1R41NS089061), which currently funds research performed in collaboration with Dr. Patricia Dickson (working at Los Angeles Biomedical Research Institute at Harbor UCLA Medical Center) on Sanfilippo syndrome type D. Readers may recall the crucial role of



(Continued on Page 3)

Meet Our Patient Advocacy Groups

Jonah's Just Begun

(Continued from Page 2)

Patricia Dickson in MPS treatment research, as mentioned in our December 2014 article about The Ryan Foundation. (See pages 3 and 6 in that issue.) Links for all past issues: www.LysosomalDiseaseNetwork.org. Phoenix Nest, Inc. will be applying for a phase II grant later this year.

Phoenix Nest's goal is to commercialize a treatment for children affected by MPS IIIC and IIID. Jill said, "We are actively looking for other researchers that might have research projects that could lead to different therapeutic options for Sanfilippo syndrome, and who would be amenable to collaboration. Although the patient population for this disease is tiny compared to other diseases, we have the opportunity to move fast, develop treatments and capture the market. Our goal is to reinvest back into more research that can help our disease community."

Jonah's Just Begun fundraising efforts rely heavily on crowdsourcing and online non-profit programs like: eBay's "Giving Works" (<http://jonahsjustbegun.org/eBay/>); Amazon.com's "AmazonSmile" (<http://jonahsjustbegun.org/amazon-store/>); and CrowdRise (<http://jonahsjustbegun.org/crowdrise/>). Jonah's Just Begun's "Holiday Remit" fundraiser is its most profitable in-house fundraiser.

Jonah's Just Begun's fundraisers include ordinary people as well as celebrities. For example, visit: <https://www.crowdrise.com/fundraise-and-volunteer/donations/jonnyleemiller50miler/jonnyleemiller>. Jill remarked, "Physical fundraising is a very difficult thing for a parent to do when taking care of a sick child, running a 501(c)3 charitable organization, and managing a biotech company. Jonah's Just Begun therefore is fortunate to depend on a network of friends, family and supporters to host fundraisers." So far, Jonah's Just Begun has raised a total of \$750,000 for research into treatment and cure of Sanfilippo syndrome type C.

Jill said, "When we received Jonah's diagnosis our geneticist told us to have hope, that treatments that



Lobbying at the Capitol in Washington, D.C. From Left: Jennifer Bernstein, Vice President, Horizon Government Affairs; Julia Jenkins, Executive Director of EveryLife Foundation for Rare Diseases; actor Jonny Lee Miller; Jill Wood

were unimaginable just 10 years ago are a reality today. Now I realize how fortunate we were to receive this advice. Not many parents receive this kind of hope, many are told to take their children home and make them comfortable."

She continued, "Parents in a similar situation ask me continually how we did it. We still have a long way to go. But I am very fortunate to live just outside of NYC; we are surrounded by the nation's top hospitals. Geneticists and clinicians from our neighboring hospitals gave us our marching orders: build your patient population, find the scientists interested in Sanfilippo syndrome, initiate a natural history study and start fundraising. Our advisors believed in us, they made connections for us and are always readily available to act as a sounding board and to offer advice. Our scientists have supported our efforts at JJB and Phoenix Nest beyond our wildest expectations. They have enabled us to create slides and posters and to write grants. They have also put in countless hours of work beyond what they have to, in order to help us move research forward. The Every Life Foundation for Rare Diseases (<http://everylifefoundation.org/>) and the RDLA (Rare Disease Legislative Advocates, at <http://rareadvocates.org/>) have given us tremendous support and the tools to help us by expanding legislation for rare diseases.

"I hope to encourage other parents to set out to drive the science for a treatment for their child's disease. Yes, it takes a lot of hard work but it can be done. Working together with other like-minded families allows

(Continued on Page 10)



LDN Research Matters



Pilot Project 3: Natural History Study for MPS IIIC and MPS IIID

By Evelyn S. Redtree, M.S. and Paul Levy, M.D.

LDN Pilot Project 3, “Natural History Study for MPS IIIC and MPS IIID” is led by Paul Levy, M.D. (see page 5). The study site is Montefiore Medical Center in New York City. Pilot Project 3 is a two-year prospective natural history study that employs techniques developed in a previous LDN pilot study, LDN Protocol 6707, entitled “Characterizing the neurobehavioral phenotype(s) in MPS III.” Paul Levy will be studying the rarest forms of Sanfilippo syndrome, types C and D, using well-validated protocols developed at the University of Minnesota with the support of industry (Shire). He will be using the Sanfilippo Behavior Rating Scale, previously developed by Michael Potegal, Ph.D. for LDN Protocol 6707. In addition, Dr. Levy will be using the resources of the LDN cores for MRI and neurocognitive assessments.

Dr. Levy has partnered with Jonah’s Just Begun (see page 1) to identify the study population of 15 patients with MPS IIIC and 2 patients with MPS IIID, ranging in age from babyhood to adulthood. Dr. Levy hypothesizes that disease progression will be manifested by neurocognitive decline, and will correlate with genotype and/or residual enzyme activity, as well as with an increase in glycosaminoglycans levels in subjects’ urine. Most evaluations will be scheduled on a yearly basis, unless there is significant change that warrants an intervening evaluation, in which case visits will be scheduled more frequently. Brain imaging by MRI will be done every other year, unless clinical changes warrant an MRI sooner.

This study has three aims. Firstly, this study aims to document the clinical course of disease. Clinical evaluation and follow up of issues related to Sanfilippo syndrome, including developmental arrest, regression, behavioral problems, sleep disturbance, orthopedic issues (hips, joint contractures), diarrhea, and frequent ear and sinus infections will be done by



questionnaire and interview at each yearly follow-up visit. Standard neuropsychological testing will be administered to document the cognitive status of patients and correlate this with their disease status. Cognitive regression over time will be documented by following longitudinal changes revealed by the neuropsychological testing.

MRI examinations will be used to observe and document brain structure, myelination, ventricular size and cortical atrophy changes over time, as have been reported in previous studies. Measurement of brain volumetrics and diffusion tensor imaging are tools that will be used to document these longitudinal changes in patients with Sanfilippo syndrome types C and D.

Determining the long-term developmental and functional outcomes of children with inherited metabolic diseases who have been identified by newborn screening should be an essential component of all newborn screening programs. Unfortunately, in New York State and elsewhere, long-term outcomes are not being assessed due to the high cost of neurologic and medical follow-up, and the barriers that prevent sharing of privileged medical information.

Secondly, this study aims to evaluate biomarkers as correlates to disease status. Residual enzyme activity (in blood leukocytes or fibroblasts) will be measured; attempt will be made to correlate the findings with genotype and disease progression with time. Urinary glycosaminoglycans will also be measured; attempt will be made to correlate any changes with disease progression. Because increased cerebrospinal fluid (CSF) pressure has been suggested as a cause for some of the severe behavior problems seen in Sanfilippo syndrome, CSF pressure measurements will be performed during spinal tap.

Thirdly, this study aims to compare its data with other studies of Sanfilippo patients to help better delineate the phenotypes and differences between MPS types IIIC and IIID, with MPS IIIA and IIIB.



MPS Society (UK) Presents Enlightening Video about Their Role in the UK

This video highlights the role of the patient advocacy group in the lives of patients and their families. The video can be viewed at: <https://vimeo.com/85514654>.

Meet the Principal Investigators



Paul Levy, M.D.

Principal Investigator of LDN Pilot Project 3, Paul Levy, M.D. is Assistant Professor of Pediatrics and Pathology; Director, Center for Inherited Metabolic Disorders; Director, Biochemical Genetics Laboratory; and Site Director, NY State Newborn Screening Referral Site for Inherited Metabolic Diseases, all at Albert Einstein College of Medicine, Children's Hospital at Montefiore, Bronx, NY.



Paul Levy, M.D.

As a pediatric geneticist, Dr. Levy is a care provider for both general genetics patients and those with inherited metabolic disorders, including lysosomal diseases. In the more than 20 years that he has served at Albert Einstein College of Medicine, Children's Hospital at Montefiore, he has provided care to

numerous lysosomal disease patients, including those having Fabry disease, Gaucher disease, Hunter syndrome, Sanfilippo syndrome, Morquio syndrome or Maroteaux-Lamy syndrome.

He is also interested in organic acidurias, amino acid disorders, and disorders that result in hypoglycemia among others. He also has an interest in PKU and how tetrahydrobiopterin affects patients' treatment. Dr. Levy runs the Biochemical Genetics Laboratory for the Department of Pathology at Montefiore.



When he is not tinkering in the lab, he is an amateur carpenter and builds furniture in his spare time.

Selected Paul Levy, M.D. Publications:

P.A. Levy, An overview of newborn screening. *J Dev Behav Pediatr* 31(7) (2010) 622-631. PMID: 20814260.

P.K. Duffner, M. Caggana, J.J. Orsini, D.A. Wenger, M.C. Patterson, C.J. Crosley, J. Kurtzberg, G.L. Arnold, M.L. Escolar, D.J. Adams, M.R. Andriola, A.M. Aron, E. Cialfaloni, A. Djukic, R.W. Erbe, P. Galvin-Parton, L.E. Helton, E.H. Kolodny, B.E. Kosofsky, D.F. Kronn, J.M. Kwon, P.A. Levy, J. Miller-Horn, T.P. Naidich, J.E. Pellegrino, J.M. Provenzale, S.J. Rothman, M.P. Wasserstein, Newborn screening for Krabbe disease: the New York State model. *Pediatr Neurol* 40(4) (2009) 245-252; discussion 253-255. PMID: 19302934.

P.A. Levy, Inborn errors of metabolism: Part 1 - Overview. *Pediatr Rev* 30(4) (2009) 131-137; quiz 137-138. PMID: 19339386.

P.A. Levy, Inborn errors of metabolism: Part 2 - Specific disorders. *Pediatr Rev* 30(4) (2009) e22-28. PMID: 19339383.

P.A. Levy, J.B. Miller, E. Shapira, The advantage of phenylalanine to tyrosine ratio for the early detection of phenylketonuria. *Clin Chim Acta* 270(2) (1998) 177-181. PMID: 9544454.



Join the RDCRN Contact Registry

(Continued from Page 1)

progress of the research projects. The RDCRN contact registry is free of charge.

After you have joined and submitted information online, the data is stored in a secure database. No personal identifying information (such as your name, address, telephone number) will be given to **anyone** without your **explicit** approval. For details: <http://www.rare-diseasesnetwork.org/registry/index.htm>



Check Your Knowledge of Lysosomal Diseases

How well do you know Sanfilippo syndrome?



By Evelyn S. Redtree, M.S. and Brenda Diethelm-Okita, M.P.A.

Introduction to an Understanding of Sanfilippo Syndrome

The December 2013 issue of “**Indications**” presents information about the mucopolysaccharidosis (MPS) diseases, beginning on page 5. On page 9 we pay tribute to Dr. Sylvester Sanfilippo, who first characterized the disease that carries his name. (All past issues of “**Indications**” can be downloaded using links in the upper-right area of the Lysosomal Disease Network’s homepage at: www.LysosomalDiseaseNetwork.org.)

Mucopolysaccharidosis type III, a.k.a. Sanfilippo syndrome, results from any of four different altered genes, each responsible for production of a different lysosomal enzyme needed to completely break down the heparan sulfate sugar chain. Based upon the altered gene, types are identified as A, B, C or D. The deficient enzyme for each type is as follows. Type A: heparan N-sulfatase; type B: alpha-N-acetylglucosaminidase; type C: acetyl CoA:alpha-glucosaminide acetyltransferase; type D: N-acetylglucosamine 6-sulfatase. Like other lysosomal diseases, expression of phenotypes is found along a continuum that is determined by level of residual enzyme activity; this should be kept in mind when learning about clinical presentation. Because of the continuum of phenotypes, generalizations about Sanfilippo syndrome presentation should be used with caution. For every generalization, exceptions are easily found in the literature, as well as in the clinic.

Keeping that in mind, generally for all four types of Sanfilippo syndrome, after an initial symptom-free interval than can last more than two years, patients initially present with a slowing of their rate of development and sleep disturbances; followed by cessation of further development, and behavioral prob-

lems. Developmental regression follows; characterized by progressive cognitive impairment and neurodegeneration including gradual loss of language, with eventual dementia. In the middle stages, there can be progressive severe behavioral problems (including increasing loss of normal fear, autistic-like symptoms of lack of social reciprocity, and hyperactivity),¹ and sleep disturbances that are concurrent with normal strength and physical mobility; these present a great challenge for care-givers. In the later stages, patients demonstrate progressive motor disease, including loss of mobility and continence. Other symptoms may include hearing impairment, recurrent upper airway and ear infections, diarrhea, and epilepsy.² In the late phase of the illness, patients become increasingly immobile and unresponsive, with dysphagia, drooling and seizures. The phenotypes of these diseases may include visceromegaly, little or no corneal clouding, and little or no vertebral changes.

Genetic Bases of Sanfilippo Syndrome

Sanfilippo syndrome is inherited in an autosomal recessive manner. Numerous different mutations, some inherited and some de novo, affecting each of the four genes have been identified in the scientific literature. The four genes carrying the defects are:

Sanfilippo syndrome type:	Altered Gene:	Cytogenic Location:
MPS IIIA	SGSH	17q25.3
MPS IIIB	NAGLU	17q21
MPS IIIC	HGSNAT	8p11.21
MPS IIID	GNS	12q14

Incidence of Sanfilippo Syndrome

Sanfilippo syndrome is a global disease occurring in all races and locations. There is great variation in incidence rates that have been reported from different locations. Over the years, various studies have revealed: in British Columbia, MPS IIIA had an incidence of 1:324,617 live births;³ in western Australia, all four types combined had an incidence of 1:58,000;⁴ in the Netherlands 1.16:100,000 to 0.88:100,000;⁵ in France 0.68:100,000;⁶ in the United Kingdom 1.21:100,000;⁶ and in Northern Ireland 1:280,000.⁷ From these data it is clear that it would be inaccurate to postulate a general, global incidence rate for Sanfilippo syndrome, although such a generalization is often found in online



(Continued on Page 7)

Check Your Knowledge of Lysosomal Diseases

How well do you know Sanfilippo syndrome?



(Continued from Page 6)

articles about MPS III. The National MPS Society quotes an incidence of 1:70,000 births for MPS III, and overall incidence of *all* MPS diseases of 1:25,000.

Details of Sanfilippo Syndrome Presentation

Sanfilippo syndrome type A has been reported to be the most severe, with earlier onset and more rapid progression of symptoms, with shorter survival.⁸ Among those with type A there is wide phenotypic variability, yet patients can be categorized into 3 main groups: a severe, intermediate, and attenuated phenotype.¹ The life-span of an MPS IIIA affected child does not usually extend beyond late teens to early twenties, with some exceptions. Those patients having the intermediate phenotype of type A may have a slower regression of abilities and may live into adulthood.¹

The Lysosomal Disease Network funded a pilot study (LDN Protocol number 6707) at the University of Minnesota that sought to characterize the neurobehavioral phenotype(s) in MPS III types A and B.⁹ Researchers concluded that an increased incidence of autistic-like social behaviors occurred between ages 3 and 4 in children with early-onset MPS IIIA.¹⁰ Although more frequent in the severely impaired, autism spectrum disorder behaviors were observed across the entire range of cognitive impairment.¹⁰ Children with MPS IIIA reportedly mouth things (their hands, their clothes or anything they can get hold of), explore novel environments almost continuously, disregard danger, empathize/socialize less, and comply less with their parents.⁹ Using parental responses to questionnaire, researchers quantified these children's abnormal oral behaviors.⁹ Their study also quantified a deficit in fear-learning in these children, that may contribute to the heedlessness of danger that these children routinely show.⁹ Brain magnetic resonance imaging (MRI) of a subset

of the children with MPS IIIA showed volume loss that was greater in the amygdala than in the hippocampus; only amygdala loss correlated with reduced fearfulness.⁹

Sanfilippo syndrome type B: The clinical presentation of type B is generally the same as for type A, but may possibly have symptom onset somewhat later, and disease progression possibly slower. The clinical severity of type B ranges from mild to severe.¹¹

Sanfilippo syndrome type C: The clinical presentation of type C is generally the same as for type A, with later onset and slower disease progression. Again, type C demonstrates variable severity. Intellectual regression and loss of speech may precede the onset of motor impairment by more than 10 years.¹² One study found that mean age of patient death was 34 years.¹²

Sanfilippo syndrome type D: Research has suggested that MPS IIID cannot be distinguished clinically from Sanfilippo syndrome type A, but with later onset and slower disease progression.¹³ As with the other types, clinical severity of type D can range from mild to severe. Type D is the rarest form.

Treatment of Sanfilippo Syndrome

Traditionally, there have not been treatment options for those with Sanfilippo syndrome. And, since the effectiveness of enzyme replacement therapy is known to be hampered by the blood-brain barrier, any effective treatment for Sanfilippo would need to overcome the hurdle presented by the blood-brain barrier in order to produce any neurological benefits for these patients.

Reported research in the use of umbilical cord blood-derived hematopoietic stem cells in two MPS III patients who were transplanted prior to onset of any symptoms concluded that there was no beneficial effect of such transplant in these patients.¹⁴ The researchers followed these transplanted patients for five years following successful donor-cell engraftment.¹⁴ In these patients they found comparable natural history of progressive neurological deterioration with regression of cognitive skills and behavioral disturbances as in non-transplanted MPS III patients who had the same combination of mutations.¹⁴



(Continued on Page 8)

Check Your Knowledge of Lysosomal Diseases

How well do you know Sanfilippo syndrome?



(Continued from Page 7)

In recent years several clinical trials for MPS III A and IIIB have been initiated by pharmaceutical companies in both Europe and the US. These trials are described, in brief, below.

Readers wishing to learn about some additional recent and current studies should search for “Sanfilippo syndrome” on ClinicalTrials.gov at: <https://clinicaltrials.gov/ct2/search/index>.

Lysogene

In 2013 the Paris, France-based company Lysogene (<http://www.lysogene.com/>) successfully completed an open-label, single arm Phase I/II clinical trial of its gene therapy product called SAF-301 for treatment of Sanfilippo syndrome type A. Four children affected by MPS IIIA were administered SAF-301 directly into their brain. The one-time neurosurgical procedure involved intracerebral administration of adeno-associated viral vector (specifically using AAVrh10 vector) carrying a healthy, recombinant copy of the human SGSH gene. SAF-301 was administered to both sides of the brain through 6 image-guided tracks, with 2 deposits of SAF-301 per track. The study subjects were three patients around 6 years of age, and one patient nearly 3 at the time of treatment, all of whom demonstrated that the gene therapy and neurosurgical procedure is safe and well tolerated.¹⁵ Researchers reported that these subjects' efficacy profiles are encouraging.¹⁵ For more information about this clinical trial, search for NCT01-474343 on ClinicalTrials.gov.

Lysogene is conducting an extension study of these same subjects, in order to observe and document the long-term effects of this treatment, and to investigate potential biomarkers of interest. The expected study completion date is June 2017. For more information, search for NCT02053064 on ClinicalTrials.gov.



Lysogene has obtained orphan drug designation for SAF-301 from the FDA and from its counterpart in Europe, the European Medical Agency (EMA). The company is currently in the planning stage of this clinical trial's Phase III. It will be a multi-site, non-randomized, uncontrolled study and will enroll up to 20 patients with MPS IIIA in Europe and the U.S., in order to investigate the efficacy, safety and tolerability of SAF-301. Phase III will likely begin in 2016, if not sooner. For more details visit: <http://www.lysogene.com/pioneering-science/pipeline/>.

Institut Pasteur

At the Institut Pasteur in Paris, a clinical trial of gene therapy for Sanfilippo syndrome type B was carried out beginning in 2013, coordinated by the Institut Pasteur (the trial's sponsor), French Institute of Health and Medical Research (Inserm), AFM-Téléthon, and Vaincre les Maladies Lysosomales (VML). The trial was conducted at Bicêtre Hospital in Paris. This clinical trial was the result of 10 years of collaborative research carried out by Professor Jean-Michel Heard and his team at the Institut Pasteur, in partnership with the fundraiser AFM-Téléthon. This gene therapy trial also involved intracerebral administration of an adeno-associated viral vector, this time carrying a healthy, recombinant copy of the human NAGLU gene.

ESTEVE

ESTEVE is a Spanish biotechnology company that is in the pre-clinical stage of development of a gene therapy product for Sanfilippo syndrome type A. The administration route will involve one single intracranial procedure with administration into the cerebrospinal fluid. The new product has received orphan drug designation by both the FDA and the EMA. ESTEVE plans a Phase I/II clinical trial that is scheduled for the third quarter of 2015. This project for development of gene therapies for the treatment of mucopolysaccharidoses is part of a public-private partnership between ESTEVE; the Universitat Autònoma de Barcelona; the Spanish Ministry of Health, Social Policy and Equality; and the Spanish Ministry of Economy and Competitiveness. Currently, safety pre-clinical development and a retrospective natural history study of Spanish subjects affected by Sanfilippo syndrome type A are ongoing.

(Continued on Page 9)

Check Your Knowledge of Lysosomal Diseases

How well do you know Sanfilippo syndrome?



(Continued from Page 8)

For details, visit: <http://www.esteve.es/EsteveFront/PressRoom.do?op=GR&con=3494&div=idi&con=3494&lng=en>.

University of Manchester, in the United Kingdom

Dr. Brian Bigger at the University of Manchester has used lentiviral-HSC stem cell gene therapy to treat Sanfilippo syndrome type A in mouse models of the disease. The research was funded by the UK's MPS Society and the Sanfilippo Children's Research Foundation (based in Canada). Dr. Bigger and his team are hoping to bring a treatment to trial in patients soon. They have been working on manufacturing a vector for use in humans, and hope to use this in a clinical trial with patients at Central Manchester University Hospital NHS Foundation Trust, possibly in 2015. To freely download the 2013 peer-reviewed article describing this work in the mouse models, visit: <http://www.nature.com/mt/journal/vaop/ncurrent/pdf/mt2013141a.pdf>.



The University of Manchester is also currently conducting a Phase III double-blinded, placebo-controlled clinical trial of substrate-reduction therapy for MPS IIIA using high-dose oral genistein aglycone, a tyrosine kinase inhibitor. Previous research done by Dr. Wegrzyn in Poland had concluded that genistein aglycone had a potential efficacy for Sanfilippo patients at high dosage. It has already been found to reduce the amount of complex sugars stored in the brains of mice with Sanfilippo syndrome, and to improve their brain function.¹⁶ This human trial seeks to determine the correct and safe dose, the effect of the drug on delaying the progression of the disease, and whether and how it improves symptoms. Dr. Brian Bigger reports that more than half of the planned enrollment has been achieved, and the study is proceeding very well.¹⁷



Shire

Shire funded a longitudinal, prospective, observational natural history study of patients with Sanfilippo syndrome type A. Although peer-reviewed papers based on Shire's natural history study of patients with Sanfilippo syndrome type A haven't yet been published, abstracts were presented at the 2012, 2014 and 2015 WORLD Symposia. These abstracts are available in the 2012, 2014 and 2015 February issues of *Molecular Genetics and Metabolism*.^{18,19,20}

Shire has developed an enzyme replacement therapy for the treatment of MPS IIIA using recombinant human sulfamidase (rhHNS). As the enzyme is not able to cross the blood-brain barrier, the rhHNS is administered into the patient's cerebral spinal fluid (CSF) via a surgically implanted intrathecal drug delivery device.

Shire completed a multi-site, international Phase I/II non-randomized, uncontrolled, open-label, safety/efficacy study of rhHNS with patients in the UK (St. Mary's Hospital, Manchester) and the Netherlands (Emma Children's Hospital, Academic Medical Center, Amsterdam). Shire is now conducting an extension of that study, with the same subjects. The anticipated completion date of their extension study is December 2016. For more information about this clinical trial, search for NCT01299727 on ClinicalTrials.gov.

Shire also has a multi-site, international, randomized, controlled, open-label Phase IIb safety and efficacy study currently underway for rhHNS. The expected completion date of this clinical trial is March 2016. For more information about this clinical trial, search for NCT02060526 on ClinicalTrials.gov.

In Barcelona, Spain, Shire also has an ongoing open-label extension of their previous study HGT-SAN-093, that is evaluating the safety and efficacy of their product HGT-1410 (recombinant human heparan N sulfatase) for Sanfilippo syndrome type A, with administration via an intrathecal drug delivery device. For more information about this clinical trial, search for NCT-02350816 on ClinicalTrials.gov.

BioMarin Pharmaceutical Inc.

BioMarin Pharmaceutical Inc. announced last December that the FDA has granted orphan drug designation

(Continued on Page 12)

Meet Our Patient Advocacy Groups

Jonah's Just Begun

(Continued from Page 3)

you to share the burden. I hear all the time that it takes decades and hundreds of millions to a billion dollars, to create a treatment. This may be true for a major disease, but not for a rare disease. In less than 5 years HANDS has taken a disease with no treatment option and almost zilch in the way of research, to the brink of clinical trial. We have four thriving research



Jill Wood and son Jonah enjoy meeting with eminent lysosomal disease scientists last winter in New York City. Behind Jill, from left: Drs. Andrea Ballabio and Graciana Diez-Roux of TIGEM; Dr. Alexey Pshezhetsky of the University of Montreal; Dr. Steven Walkley of Albert Einstein College of Medicine of Yeshiva University; Dr. Fred Maxfield of Weill Cornell Medical College, Cornell University.

programs in the works. When we started we didn't even have a mouse model, now we have mouse models for type C and D (the latter due to the generosity of Taconic (<http://www.taconic.com/>)). I have no doubt that we will be in a clinical trial for either type C or D within two–three years. We will have done all of this in much less than the 10 years and ten million dollars. Once you get the science started, others will take notice. It is important that as the science moves forward papers are published, data are presented at conferences, and this then lays the foundation for proposing and hopefully winning large institutional grants for our researchers.”



The faces of attendees at a conference held in Switzerland reveal intense learning taking place. Teaching with the aid of a laptop computer was Kim Helmsley, Head, CNS Therapeutics Group, Lysosomal Diseases Research Unit, SAHMRI, of Adelaide, Australia. Beginning with Jill Wood on the left, those sitting on the floor were Christina Sanchez, co-founder of Stop Sanfilippo-Madrid; Raquel Marques of Sanfilippo Portugal; and Tomasz Slabolepszy and Arleta Feldman of Mały Maciek i Wielcy Czarodzieje. Sitting behind Christina Sanchez was her husband Emilio López Álvarez, co-founder of Stop Sanfilippo-Madrid.

Jill concluded, “While we push forward the science to bring it to a clinical trial, HANDS has turned its attention to finding the other patients out there. We have created a Sanfilippo patient registry (<https://connect.patientcrossroads.org/>), and with the help of the Lysosomal Disease Network, our natural history study for MPS IIIC and IIID will start recruiting this summer.”



Learn More . . .

2014 Rare Disease Congressional Caucus:
<https://www.youtube.com/watch?v=NXRg-qmBY1k>

The National MPS Society's page about Sanfilippo syndrome: <http://mpssociety.org/mps/mps-iii/>

(Continued on Page 11)

Meet Our Patient Advocacy Groups

Jonah's Just Begun

(Continued from Page 10)



Learn More . . .

Alliance Sanfilippo, co-founded by Karen Aiach, also co-founder of Lysogene (see page 8 in this issue of "Indications," about Lysogene): <http://www.eurordis.org/content/member-profile-alliance-sanfilippo>

Medical biochemistry details about MPS III, all four types: <http://themedicalbiochemistrypage.org/sanfilipposyndromes.php>

The MPS Society (UK) has a link to a downloadable 8-page .pdf MPS III summary and care-guide here: <http://www.mppsociety.org.uk/conditions/mps-diseases/mps-iii/>

Kentucky Becomes the 7th State to Mandate Krabbe Disease Newborn Screening

On April 1, 2015, Kentucky Governor Steve Beshear signed Anna's Law, that mandated Krabbe disease newborn screening in Kentucky. Anna Taylor, for whom this law was named, traveled to the bill signing with her parents, Nathan and Sarai. They stood by, watching the strokes of the Governor's pen. Because of Anna's Law, future babies born in Kentucky will have the chance to be diagnosed in time for lifesaving Krabbe disease treatment – an opportunity Anna should have had, but didn't. She died of Krabbe disease the next day.

What diseases are included in newborn screening where you live?



Newborn Screening for MPS I: Recommendation Has Been Made to the Secretary of Health and Human Services

On February 13, 2015, the Discretionary Advisory Committee on Heritable Disorders in Newborns and Children voted "YES" to recommend to the Secretary of Health & Human Services that mucopolysaccharidosis I (MPS I) be added to the "Recommended Uniform Newborn Screening Panel." The Committee recommends that each state's newborn screening program include a "Uniform Screening Panel" which includes the disorders selected based on "Newborn Screening: Towards a Uniform Screening Panel and System" (<http://mchb.hrsa.gov/programs/newbornscreening/screeningreport.html>).

National MPS Society Executive Director, Barbara Wedehase, submitted comments on behalf of the National MPS Society, including: "The mission of the Society is to ensure that treatments are available to all children with MPS and related diseases. We are fortunate that there are currently treatments for MPS I (with even more on the way), and our next step is to ensure all families have access to these treatments as early as possible. The diagnosis in the newborn period allows for early treatment options that will optimize the future of children with MPS I. By removing the diagnostic odyssey faced by most parents of a child with MPS I, we will reduce the personal anguish parents experience--realizing there are problems, but unable to obtain a diagnosis. In addition, the costs of evaluations and testing will be reduced, not to mention time-to-diagnosis."

The National MPS Society will submit applications for other MPS diseases, once newborn screening pilot data is available. This is a requirement of the application. For more information, visit: <http://mppsociety.org/posts/news/mps-i-approved-for-newborn-screening/>.

PCORI Offers Research Funding for Patient-Centered Outcomes Research

PCORI's *Pipeline to Proposal Awards* aim to build a national community of patients, stakeholders, and researchers who have the expertise and passion to participate in **patient-centered outcomes research**, creating partnerships within that community leading to high-quality research proposals. Applications for another round of **Tier I support** are expected to open in fall 2015. Visit: <http://www.pcori.org/funding-opportunities/programmatic-funding/pipeline-proposal-awards>.

Check Your Knowledge of Lysosomal Diseases

How well do you know Sanfilippo syndrome?



(Continued from Page 9)

for BMN 250, an enzyme replacement therapy for Sanfilippo syndrome type B that uses recombinant human NAGLU with an IGF2, or glycosylation independent lysosomal targeting (GILT) tag. BMN 250 is a novel fusion of α -N-acetylglucosaminidase (NAGLU) with a peptide derived from insulin-like growth factor 2 (IGF2). BMN 250 will be delivered directly to the brain using BioMarin's patented technology. BioMarin expects to initiate clinical studies with BMN 250 in mid-2015. More information can be found at: https://www.bmrn.com/pipeline/clinical-trials/GILT_rhNAGLU.php

Abeona Therapeutics, Inc.

Abeona Therapeutics, Inc. is developing gene therapy products for Sanfilippo syndrome type A and type B. Abeona has partnered with researchers at Nationwide Children's Hospital in Columbus, Ohio, who have initiated a prospective natural history study and registry of patients affected by Sanfilippo syndrome type A and B. This is in preparation for Phase I/II clinical trials. Researchers at Nationwide Children's Hospital working on this project include Kevin M. Flanigan, M.D.; Haiyan Fu, Ph.D.; and Douglas M. McCarty, Ph.D. The expected completion date of this natural history study is October 2015. For more information about it, search for NCT02037880 on ClinicalTrials.gov. An international coalition of patient advocacy groups have provided significant funding for this project; learn more about this coalition of groups at <http://abeonatherapeutics.com/patient-group-supporters/>.

Synageva BioPharma Corp.

Currently ongoing is a multi-site, international clinical trial of enzyme replacement therapy for patients with Sanfilippo syndrome type B. Synageva BioPharma Corp. is assessing their investigational agent called SBC-103 as part of this open-label Phase I/II

study. SBC-103 was granted orphan designation by the FDA in April 2013 and the EMA in June 2013, and received Fast Track designation by the FDA in January 2015. The principal investigator of one of the U.S. sites for this clinical trial is Chester B. Whitley, Ph.D., M.D., Professor, Advanced Therapies Program, Departments of Pediatrics and of Experimental and Clinical Pharmacology at the University of Minnesota, and principal investigator of the Lysosomal Disease Network. Dr. Whitley said, "The potential impact for these children cannot be overestimated. Sanfilippo syndrome was discovered at the University of Minnesota, and our team is uniquely prepared and excited to help assess treatment for these patients." For more information about this clinical trial, search for NCT02324049 at ClinicalTrials.gov.

Synageva BioPharma Corp. is also conducting retrospective and prospective natural history studies in MPS IIIB. These include a retrospective natural history study of deceased MPS IIIB patients that began in July 2013, and a prospective, longitudinal natural history study in living MPS IIIB patients that began in September 2014. For more information, search for NCT0229-3408, and NCT02293382, on ClinicalTrials.gov.

It is clear this is an intensely productive time in research for effective treatments for Sanfilippo syndrome type A and type B. Our hope is that type C and type D will also be addressed with effective new treatments as soon as possible, even though the patient populations are smaller for these types. Coalitions of patient advocacy groups continue their herculean efforts to make such treatments a reality.

References Cited:

¹Personal e-mail communication with Dr. Elsa Shapiro dated 5-8-2015.

²M.J. Valstar, S. Neijs, H.T. Bruggenwirth, R. Olmer, G.J. Ruijter, R.A. Wevers, O.P. van Diggelen, B.J. Poorthuis, D.J. Halley, F.A. Wijburg, Mucopolysaccharidosis type IIIA: clinical spectrum and genotype-phenotype correlations. *Ann Neurol* 68(6) (2010) 876-887. PMID: 2106-1399.

³R.B. Lowry, D.A. Applegarth, J.R. Toone, E. MacDonald, N.Y. Thunem, An update on the frequency of mucopol-



(Continued on Page 13)

Check Your Knowledge of Lysosomal Diseases

How well do you know Sanfilippo syndrome?



(Continued from Page 12)

ysaccharide syndromes in British Columbia. *Hum Genet* 85(3) (1990) 389-390. PMID: 2118475.

⁴J. Nelson, J. Crowhurst, B. Carey, L. Greed, Incidence of the mucopolysaccharidoses in Western Australia. *Am J Med Genet A* 123A(3) (2003) 310-313. PMID: 14608657.

⁵B.J. Poorthuis, R.A. Wevers, W.J. Kleijer, J.E. Groener, J.G. de Jong, S. van Weely, K.E. Niezen-Koning, O.P. van Diggelen, The frequency of lysosomal storage diseases in The Netherlands. *Mol Genet Metab* 105(1-2) (1999) 151-156. PMID: 10480370.

⁶B. Héron, Y. Mikaeloff, R. Froissart, G. Caridade, I. Maire, C. Caillaud, T. Levade, B. Chabrol, F. Feillet, H. Ogier, V. Valayannopoulos, H. Michelakakis, D. Zafeiriou, L. Lavery, E. Wraith, O. Danos, J-M Heard, M. Tardieu, Incidence and natural history of mucopolysaccharidosis type III in France and comparison with United Kingdom and Greece. *Am J Med Genet A* 155A(1) (2011) 58-68. PMID: 21204211.

⁷J. Nelson, Incidence of the mucopolysaccharidoses in Northern Ireland. *Hum Genet* 101(3) (1997) 355-358. PMID: 9439667.

⁸J.J.P. van de Kamp, M.F. Niermeijer, K. von Figura, M.A.H. Giesberts, Genetic heterogeneity and clinical variability in the Sanfilippo syndrome (types A, B, and C). *Clin Genet* 20(2) (1981) 152-160. PMID: 6796-310.

⁹M. Potegal, B. Yund, K. Rudser, A. Ahmed, K. Delaney, I. Nestrail, C.B. Whitley, E.G. Shapiro, Mucopolysaccharidosis Type IIIA presents as a variant of Klüver-Bucy syndrome. *J Clin Exp Neuropsychol* 35(6) (2013) 608-616. PMID: PMC3931576. Article freely available online: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3931576/>.

¹⁰R.K. Rumsey, K. Rudser, K. Delaney, M. Potegal, C.B. Whitley, E.G. Shapiro, Acquired autistic behaviors in children with mucopolysaccharidosis type IIIA. *J Pediatr* 164(5) (2014) 1147-1151.e1. PMID: PMC4041612. Article freely available online: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4041612/>.

¹¹Y. Chinen, T. Tohma, Y. Izumikawa, H. Uehara, T. Ohta, Sanfilippo type B syndrome: five patients with an R565P homozygous mutation in the alpha-N-acetylglucosaminidase gene from the Okinawa islands in Japan. *J Hum Genet* 50(7) (2005) 357-359. PMID: 1593-3803.

¹²G.J. Ruijter, M.J. Valstar, J.M. van de Kamp, R.M. van der Helm, S. Durand, O.P. van Diggelen, R.A. Wevers, B.J. Poorthuis, A.V. Pshezhetsky, F.A. Wijburg, Clinical and genetic spectrum of Sanfilippo type C (MPS IIIC) disease in the Netherlands. *Mol Genet Metab* 93(2) (2008) 104-111. PMID: 18024218.

¹³R. Gatti, C. Borrone, P. Durand, S. De Virgillis, G. Sanna, A. Cao, K. von Figura, H. Kresse, E. Paschke, Sanfilippo type D disease: clinical findings in two patients with a new variant of mucopolysaccharidosis III. *Eur J Pediatr* 138(2) (1982) 168-171. PMID: 6807676.

¹⁴L. Welling, J.P. Marchal, P. van Hasselt, A.T. van der Ploeg, F.A. Wijburg, J.J. Boelens, Early umbilical cord blood-derived stem cell transplantation does not prevent neurological deterioration in mucopolysaccharidosis type III. *JIMD Rep* 18 (2015) 63-68. PMID: PMC4361923. Article freely available online: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4361923/>.

¹⁵M. Tardieu, M. Zérah, B. Husson, S. de Bournonville, K. Deiva, C. Adamsbaum, F. Vincent, M. Hocquemiller, C. Broissand, V. Furlan, A. Ballabio, A. Fraldi, R.G. Crystal, T. Bagnon, T. Roujeau, J.M. Heard, O. Danos, Intracerebral administration of adeno-associated viral vector serotype rh.10 carrying human SGSH and SUMF1 cDNAs in children with mucopolysaccharidosis type IIIA disease: results of a phase I/II trial. *Hum Gene Ther* 25(6) (2014) 506-516. PMID: 24524415.

¹⁶M. Malinowska, F.L. Wilkinson, K.J. Langford-Smith, A. Langford-Smith, J.R. Brown, B.E. Crawford, M.T. Vanier, G. Gryniewicz, R.F. Wynn, J.E. Wraith, G. Wegrzyn, B.W. Bigger, Genistein improves neuropathology and cor-



(Continued on Page 14)

Calendar of Upcoming Events



The annual "Michael, Marcia & Christa Parseghian Scientific Conference" for Niemann-Pick type C disease research will be held June 11 -13, 2015 at the University of Notre Dame. Researchers will gather for three days to discuss the advances in NP-C research. This yearly meeting helps to form collaborations and determine the future direction of NP-C research. Visit: <http://www.parseghian.org/events.html>, or call: (520) 577-5106.

Canadian Association of Pompe's 2015 "CAP Conference and AGM" will be held in Montreal, Quebec, Canada, June 20 - 21, 2015. For further information, visit: <http://www.pompecanada.com/events/109-2015-cap-conference-and-agm-save-the-date>

Hunter's Hope Foundation 2015 annual Family & Medical Symposium: the medical symposium is July 6 - 9 and family symposium is July 8 - 12. **Family Registration Deadline: May 25, 2015.** For more information, visit: http://www.huntershope.org/site/PageServer?pagename=familyprograms_symposium

Batten Disease Support and Research Association Family Conference 2015, July 9 - 12, 2015 at The Eaglewood Resort and Spa, 1401 Nordic Road, Itasca, Illinois, USA. Details: <http://bdsra.org/> and www.eaglewoodresort.com

United Leukodystrophy Foundation's 2015 Annual Scientific Meeting and Family Conference, July 15 - 18, 2015 at Embassy Suites Downtown Old Market in Omaha, Nebraska, USA. Visit: <http://ulf.org/conferences>

Cystinosis Research Network 2015 Family Conference, July 16 - 18, 2015 at Doubletree by Hilton Chicago Magnificent Mile, Chicago, Illinois, USA. Visit: <https://cystinosis.org/news/announcements/188-2015-family-conference-announced>

Glycoproteinoses: Fourth International Conference on Advances in Pathogenesis and Therapy (a combined scientific and family conference), July 23 - 26th, 2015, in St. Louis, Missouri, USA. Visit: www.ISMRD.org

National Niemann-Pick Disease Foundation 23rd Annual Family Support and Medical Conference, August 6 - 9, 2015 in Rosemont, Illinois, USA at Loews Chicago O'Hare Hotel. Details: http://www.nnpdf.org/familyservices_03.html

The Association for Glycogen Storage Disease 2015 Family/Professional Conference, September 18 - 19, 2015 in Oklahoma City, Oklahoma, USA. For updates, visit: <http://www.agsdus.org/>

Acid Maltase Deficiency Association (AMDA) International Patient and Scientific Conference, Oct. 30 - Nov. 1, 2015 in San Antonio, Texas, USA, at the Holiday Inn Riverwalk. An online registration page will soon appear on the AMDA website, but in the meantime everyone is encouraged to begin making hotel reservations. Details: <http://www.amda-pompe.org/index.php/main/>

Check Your Knowledge of Lysosomal Diseases



How well do you know Sanfilippo syndrome?

(Continued from Page 13)

rects behaviour in a mouse model of neurodegenerative metabolic disease. PLoS One 5(12) (2010) e14192. PMID: PMC2995736. Article freely available online: <http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0014192>.

¹⁷Personal e-mail communication with Dr. Brian Bigger dated 5-8-2015.

¹⁸I. Nestrasil, A. Ahmed, K. Rudser, K. Delaney, P. Haslett, C. Richard, E.G. Shapiro, C.B. Whitley, Brain volumes and cognitive function in MPS IIIA (Sanfilippo syndrome type A): cross-sectional study. Mol Genet Metab 105(2) (2012) S48-S49 (Abstract).

¹⁹K. Delaney, C.B. Whitley, M. Cleary, H. Bullock, L. Arash, E. Mengel, M. Hartmann, P. Harmatz, N. Napier-Ionascu, N. Nair, P. Haslett, E.G. Shapiro, MPS IIIA and MPS IIIB: a preliminary comparison of disease trajectory using baseline data from two independent natural history studies. Mol Genet Metab 111(2) (2014) S35-S36 (Abstract).

²⁰I. Nestrasil, A. Ahmed, V. Kovac, K.D. Rudser, K. Delaney, A. Barbier, C.B. Whitley, E.G. Shapiro, Brain volumes and cognitive function in MPS IIIB (Sanfilippo syndrome type B). Mol Genet Metab 114(2) (2015) S87 (Abstract).

Of Related Interest . . .

Online report (with downloadable .pdf file) of a 2013 high-dose genistein clinical trial in MPS patients, conducted in the U.S.: <http://www.sciencedirect.com/science/article/pii/S109671921300214X>.

Indications™

©2015 The Lysosomal Disease Network™

Content development, writing, editing,
design and layout: Evelyn Redtree, M.S.
LDNed@umn.edu

*Keys to Understanding
the Lysosomal Disease Network*

Lysosomal Disease Network

