

**Advisory Committee on Heritable Disorders in
Newborns and Children**

**Summary of Fifth Meeting
May 9-10, 2016**

Please note: These minutes are pending formal approval by the Committee. Corrections or notations will be incorporated in the final minutes.

The Advisory Committee on Heritable Disorders in Newborns and Children (ACHDNC) was convened for its fifth meeting on Monday, May 9, 2016 and adjourned on Tuesday, May 10, 2016. In accordance with the provisions of Public Law 92-463, the meeting was open for public comment.

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I. Administrative Business: May 9, 2016

Joseph A. Bocchini, Jr. M.D.

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Professor and Chairman

Department of Pediatrics

Louisiana State University

Shreveport, LA

Debi Sarkar, M.P.H.

Designated Federal Official

Health Resources and Services Administration

Rockville, MD

A. Welcome and Roll Call

Dr. Joseph Bocchini welcomed Committee members and other participants to the fifth meeting of the Advisory Committee on Heritable Disorders in Newborns and Children (ACHDNC) and took roll. Voting members present were:

- Dr. Don Bailey
- Dr. Joseph Bocchini
- Dr. Jeffrey Botkin
- Dr. Fred Lorey
- Dr. Dietrich Matern
- Dr. Stephen McDonough
- Dr. Alexis Thompson

Ex Officio members present were:

- Agency for Healthcare Research and Quality: Dr. Kamila Mistry
- Centers for Disease Control and Prevention(CDC): Dr. Coleen A. Boyle
- Health Resources and Services Administration (HRSA): Dr. Michael Lu
- National Institutes of Health (NIH): Dr. Catherine Y. Spong
- U.S. Food and Drug Administration (FDA): Dr. Kellie B. Kelm

Organizational representatives present were:

- American Academy of Family Physicians (AAFP): Dr. Robert Ostrander
- American Academy of Pediatrics (AAP): Dr. Beth Tarini
- American College of Medical Genetics (ACMG): Dr. Michael Watson
- Association of Maternal and Child Health Programs (AMCHP): Dr. Kate Tullis
- Association of Public Health Laboratories (APHL): Dr. Susan Tanksley
- Association of State and Territorial Health Officials (ASTHO): Dr. Christopher Kus
- Department of Defense (DoD): Dr. Adam B. Kanis
- Genetic Alliance: Ms. Natasha Bonhomme
- National Society of Genetic Counselors (NSGC): Ms. Cate Walsh Vockley
- Society for Inherited Metabolic Disorders (SIMD): Dr. Carol Greene

B. Secretarial Correspondence

Dr. Bocchini reported on the Committee's correspondence submitted to the Secretary of Health and Human Services (HHS), Sylvia Mathews Burwell. He informed participants that both the MPS I and X-ALD recommendations were accepted by the Secretary, even though the proposals made for funding were not.

The RUSP has been expanded to include 34 conditions based on the Secretary's acceptance of the Committee's recommendations.

While funding recommendations were not accepted, the Secretary did encourage in her response that federal agencies continue to provide technical assistance and support to states with existing resources. As a result, HRSA has developed a new funding opportunity.

Ms. Sarkar informed participants that HRSA has issued a funding opportunity announcement called the *Newborn Screening Implementation Program Regarding Conditions Added to the RUSP*. The purpose of the program is to support states in increasing the number of newborns that are screened, identified, and referred for treatment for three conditions: Pompe disease, MPS I, and X-linked ALD. The funding amount is \$2 million per year, for a two-year project period. Applications are due on May 27, 2016. She asked participants to please feel free to contact her should they have any questions.

C. Approval of February Meeting Minutes

Committee members offered one recommended change to the meeting minutes for the February 2016 ACHDNC meeting: Dr. McDonough said he has retired and is no longer with Sanford Health. The Committee members present approved the amended minutes unanimously.

D. Other Business

Dr. Bocchini introduced Kate Tullis, PhD, who has a background in genetics, as the new representative of the Association of Maternal and Child Health Programs (AMCHP). He also informed participants that nominations are being accepted for the 2017 openings that will become available on the Committee. Nominations are due on May 16, 2016.

This year there will be a turnover of two Committee members. Also, two additional members need replacements as they have taken different positions within the government. The process is underway to complete the applications and acceptance of those four individuals. He encouraged everyone to consider nominating individuals who might be interested and qualified to be members of the Committee.

Ms. Sarkar reviewed the ethics and conflict of interest recusal requirements for voting members and outlined the process for participating in the webinar for Committee members, organizational representatives, and the public. She also reviewed the provision of interviews by Committee members and key portions of the Federal Advisory Committee Act that guides the operation of the Committee, including the role of public comment and participation by non-Committee members.

Dr. Bocchini informed participants that there are two additional meetings scheduled for this year:

- August 25-26, 2016 (Webcast and In-Person)
- November 3-4, 2016 (Webcast)

Dr. Bocchini also informed participants that the subcommittees will now be called "Workgroups" to fulfill specific requirements of the Federal Advisory Committee Act. He explained that while the names are being changed, the responsibilities of the groups remain the same.

Dr. Bocchini said the Pilot Study, Cost Analysis, and Timeliness Workgroups will provide recommendations or updates during this meeting. He informed participants that the Education and Training Workgroup is creating a companion piece to the ACT sheets that will provide primary care physicians with guidance and tips for discussing positive newborn screening results with parents. This Workgroup is also involved in an educational outreach project in collaboration with the Newborn Screening Clearinghouse/Babies First Test.

The Follow-Up and Treatment Workgroup is looking at promoting the role of clinical quality measures to promote long-term follow-up. This Workgroup is also examining state infrastructure for long-term follow-up.

The Laboratory Standards and Procedures Workgroup is working on a project to define and implement a mechanism for the periodic review and assessment of laboratory procedures utilized for effective and efficient testing of the conditions included in the uniform panel. The Workgroup is also working on another project to define and implement a mechanism for the periodic review and assessment of infrastructure and services needed for effective and efficient screening of the conditions included in the uniform panel.

Dr. Bocchini reviewed the agenda for the meeting and then turned the meeting over to the first presenter which discussed medical foods for patients with inborn errors of metabolism.

II. Medical Foods for Inborn Errors of Metabolism: Issues in Patient Access

Kathryn Camp, M.S., R.D., CSP(C)
Scientific Policy Analyst
Office of Dietary Supplements
National Institutes of Health
Bethesda, MD

Ms. Camp provided some background on the history of medical foods in the United States. Medical foods are the only recognized therapy for many inborn errors of metabolism (IEM) identified both clinically and through newborn screening. They have been used for nearly a century and have proven to reduce morbidity and mortality.

In 1958, the first medical food was marketed. It was called Lofenalac and was considered a drug. In 1973, such products were taken out of foods for special dietary use and put into their own category called “medical foods.” This had an unintended and unforeseen consequence. Medical foods lost all regulatory oversight because foods do not need to have premarket review to go into the marketplace.

In 1988, the Orphan Drug Amendments created a definition for a medical food which was “. . . a food which is formulated to be consumed or administered enterally under the supervision of a physician and which is intended for the specific dietary management of a disease or condition for which distinctive nutritional requirements, based on recognized scientific principles, are established by medical evaluation.”

This definition, however, did not provide the FDA with an evaluation mechanism to determine what fits into that category and what does not. The overall umbrella category for these products is still the food category which includes conventional foods, foods for special dietary use, medical foods, infant formulas, and dietary supplements.

Categorizing medical foods in the food category creates an inherent conflict because many foods cannot be used to diagnose, cure, mitigate, or treat disease, which are the terms that surround the use of a drug. However, medical foods are indeed used to treat a specific disease. When used early at birth (or near birth) and continued throughout life, medical foods can lead to normal or near normal health outcomes.

Medical foods are regulated under the Food, Drug and Cosmetic Act as well as the Fair Packaging and Labeling Act. They are exempt from nutritional labeling, health claims, and nutrient content claims requirements, because they do indeed have a health claim which is that they treat a medical condition.

They do not require a “nutrition facts label” or premarket review/approval by the FDA. However, manufacturers must be registered with the FDA and comply with current good manufacturing practices. Manufacturers also must be inspected every two years by the FDA.

Infant formulas are considered medical foods but regulated in their own “infant formula” category. They have strict labeling requirements and new products require a 90-day premarket notification to the FDA.

In 2013, the FDA released a draft guidance for industry that further clarified their thinking on medical foods. Although the final guidance has not yet been published, the draft guidance defines medical foods narrowly and constrains the types of products that fit within this category. More specifically, medical foods are defined as foods that are:

- Specially formulated and processed, as opposed to naturally occurring
- For partial or exclusive feeding orally or enteral feeding by tube
- For a patient with limited or impaired capacity to ingest, digest, absorb, or metabolize ordinary foods or certain nutrients whereby dietary management cannot be achieved by modification of the normal diet alone
- Used to manage unique nutrient needs resulting from a specific disease or condition determined by medical evaluation
- Intended for a patient receiving active, ongoing medical supervision

Medical foods can be costly and reach into the thousands of dollars per year. A survey by Dr. Susan Berry showed that 21 percent of parents paid greater than \$100 per month for formula, with some paying as high as \$500 a month. Almost half of all parents paid greater than \$100 a month for low-protein foods.

Patients can obtain medical foods in a variety of ways: by purchasing out of pocket; through state programs like Medicaid, CHIP, and WIC; via military health benefits; or through newborn screening programs or metabolic clinics. Many patients utilize multiple sources to obtain medical foods.

Prior to the Affordable Care Act, 38 states had passed mandates for state or private payer plan coverage of medical foods. In 10 states only formula is covered, while 28 states cover both formula and low-protein foods. Only six states have mandates to cover PKU while 16 states have mandates to cover select disorders. Also, 16 states have mandates to cover medical foods for all inborn errors for metabolism. The ACA does not specifically address coverage of medical foods for inborn errors, although newborn screening is a covered benefit without copay to families.

These and other challenges have been addressed through a variety of ways over the years including: Committee letters to the Secretary, legislative efforts, support by advocacy groups, work by professional organizations, position statements, conferences, and other efforts. Ms. Camp said that some of the same issues persist and meanwhile, nearly 500 babies are born each year with an IEM requiring medical foods as the primary management modality. She added that ultimately policy makers at the federal and state level must recognize the changes that need to be made. It will take leadership, commitment and persistence to navigate the complexities that lie ahead.

Committee Discussion

- Dr. Bailey asked if there were any published comparative cost-benefit analysis of the relative cost of not treating to society. He also asked why Congress hasn't moved forward. Is it because it's a state and not federal authority issue or are there big lobbying groups that are opposed?
- Ms. Camp said there has been no published information on the cost-benefit ratio of not treating versus treating because it's difficult to get that kind of information. She said that back in 2013 they tried to figure out a way to get it but couldn't. She explained that there are various issues with respect to legislation not being successful. Insurance companies are reluctant to allow foods to be covered, because that opens the door for foods for any kind of condition one can think of. Also, it's a small population of people, and even though it's a huge problem to the community, society as a whole might not view it as a big issue.
- Dr. McDonough thanked Ms. Camp for an outstanding presentation. He asked if WIC covers medical foods and low-protein foods for children with the 19 conditions identified in the RUSP.

- Ms. Camp replied that WIC covers metabolic formulas in all states, but they may have a formulary that only includes a specific formula. For example, for PKU there are a number of different products available, but WIC may only cover one of them, which may be a problem for a child that moves into a different state and they've been on a specific formula for years. Also, WIC only provides coverage up to five years of age. In addition, they do not cover low-protein foods.
- Dr. McDonough said that looking back at the history of the Guthrie test and PKU, one of the reasons it was marketed to states is that if a child was screened PKU they wouldn't have to pay for the cost of institutionalization, which was a benefit to state taxpayers. There was a partnership that came out of that, with a lot of states helping families with special formulas—a partnership that's now been lost. Right now the burden is placed on families. Dr. McDonough said he believed the previous Secretary made a poor decision. There was an opportunity to have medical foods and formulas be considered an essential health benefit. There is a new Secretary and she may think differently. He said he is hopeful that the Committee will revisit the issue and that the Follow-Up Treatment Workgroup will have an opportunity to work on this over the next year or so.
- Dr. Boyle suggested sharing state Medicaid best practices on the matter.
- Dr. Botkin said the economic argument could help convince a lot of key players. He added that it could be something the Committee could recommend to guide policymakers.
- Dr. Greene said that one does not talk about the cost-analysis for diabetics getting their insulin. There is no need to have a cost-benefit to have access to the formula for PKU, since it's the only treatment for the disorder. She suggested including in the analysis the cost of losing a life. In other words, what it would cost if a person is not treated as well as issues such as underemployment for those with PKU. She also informed the group that some old economic studies do exist.
- Dr. Tarini said that this is a public policy issue at its core. She added that it might be better to go "in" from a policy level at either the federal or state level. Going back to states and talking to Medicaid would be like going back to the beginning.
- Ms. Camp agreed with Dr. Tarini. She said it does need to be a federal effort because Medicaid coverage varies by state.
- Dr. Ostrander said he recommended that an AAFP policy be developed in the last report to the AAFP committee. He added that he would introduce a resolution at the American Congress of Delegates for the AAFP to seek draft legislation at the state level and policy at the national level to include medical foods in a narrowly defined manner. He suggested pursuing this as an essential care benefit under the ACA. He suggested approaching policy experts from organizations that have credibility to address this issue such as the AAFP, AAP, and ACOG.
- Dr. Bocchini agreed and said that the public policy components of AAFP, AAP, and the March of Dimes would make a powerful group.
- Dr. Matern said that in the Secretary's letter of February 15 regarding MPS I it states that the Affordable Care Act requires that most health plans cover the evidence-based preventive care and screening provided for in the comprehensive guidelines supported by HRSA. He asked if preventive care included treatment.
- Ms. Sarkar said it is only coverage for the newborn screening test.
- Michele Puryear, an audience member, said a cost-benefit analysis was done 30 years ago which was part of the justification for newborn screening for PKU. She said that Dr. Matern was likely referring to Bright Futures.
- Ms. Camp said that older studies are important, but a cost benefit analysis from 30 years ago might not take into consideration adults, older children, and under treatment.
- Ms. Sarkar said that in the letter the HRSA guidelines include the RUSP, so the Secretary might be referring to conditions that are added to the RUSP.
- Christine Brown, an audience member, said the Secretary's response indicated that she couldn't make a decision until the IOM report was completed. She said that the IOM report was finalized in October of 2011 and recommended that HHS further evaluate coverage for nutritional supplements and formulas for the treatment of inborn errors. However, that evaluation has not occurred. She added that with regard to the Department of Labor survey, she believes it included something general stating that most private insurance companies did not cover the cost of medical foods to treat inborn errors of metabolism, but that it depended on state mandate. She added that in

Wyoming the state mandates the coverage of medical foods and low-protein foods for conditions in newborn screening. Ms. Brown said she's received two examples of adults being denied coverage of medical foods in the health exchanges in California, even though the state has a mandate to cover them.

- Rani Singh, an audience member, said she's run a PKU camp for 25 years. She added that more than half of the women 18 and older lack access to medical foods. When they give birth the child is impacted by this. Also, many women are put on psychiatric drugs that are covered by insurance while medical foods are not covered.
- Dr. Kus said his understanding was that if a condition is in the RUSP it has been decided that those are conditions that are worth screening for and treating. He added that Bright Futures are guidelines for health promotion care but don't speak specifically to coverage, although the Academy does have a policy statement regarding health insurance coverage. It might be important for the Committee to review this policy.
- Dr. Bailey said the consequences of not doing this bear an enormous burden on the individual and society. He added that an updated and comprehensive analysis of the cost to society for not acting is very important.
- Ms. Camp said that a focus on maternal PKU syndrome would be helpful since it's a critical health policy issue.
- Dr. Bocchini said it would make sense for the Long Term Follow Up Workgroup to take a look at this issue to determine whether one should review the IOM and Department of Labor reports rather than writing a letter to the Secretary. The Workgroup should also examine the situation in states and determine if a policy statement from the Committee is needed to address the issue.
- Dr. McDonough said he was disappointed that medical foods weren't part of the charter. He said the Committee could send a new letter to the Secretary since the new Secretary might feel different [about the matter]. He added that the IOM report included recommendations about the modification of central based benefits over time. It also recommended the creation of committees, although Dr. McDonough said he believed none had yet been created.
- Dr. Bocchini said that he would like to bring it to the Workgroup for discussion so that it can then be presented to the Committee as a whole for discussion.
- Dr. Lu said there are two ways to do this: legislatively or administratively. With regards to the latter, it could be done through Medicaid or through preventive services under the ACA. He said there are four types of preventive services: Bright Futures, preventive services for women, newborn screening, and immunization. It could also be approached through the essential benefits which goes through the Office of Health Reform at HHS. Dr. Lu said he would be happy to follow-up to provide additional information on these mechanisms.

III. Pilot Study Workgroup – Report

Jeff Botkin, M.D., M.P.H.
Professor of Pediatrics and Medical Ethics
Associate Vice President for Research
University of Utah
Salt Lake City, Utah

Dr. Botkin said the Pilot Study Workgroup has completed its draft report, which has been distributed to Committee members. He said his presentation would only focus on the recommendations themselves.

He explained that the Workgroup's charge was to: 1) Recognize and support current efforts regarding pilot studies and evaluation; 2) Identify other resources that could support pilot studies and evaluation; and 3) Identify the information required by the Committee to move a nominated condition into the evidence review process (i.e., define the minimum pilot study data required for a condition to be accepted for evidence review).

Dr. Botkin said the question to be considered is "What data are the minimal necessary to move a nominated condition to the evidence review process?" and *not* "What evidence is necessary to approve a condition to

the RUSP?” For the purpose of the report he defined newborn screening pilot studies as “systematic investigations or public health activities that are designed to evaluate the efficacy and safety of incorporating a new test or condition on a population-based level into state newborn screening programs.

Dr. Botkin then presented the specific charges and their recommendations as per below:

Charge 1

Identify the information required by the Committee to move a nominated condition into the evidence review process (i.e., define the minimum pilot study data required for a condition to be accepted for evidence review).

Recommendation 1

Data should be available on the analytical validation of one or more screening modalities proposed for use in population based screening in newborns. Data should include information on precision, accuracy, the reportable range, detection limits, interference, reference intervals, and cost. Pilot studies for analytical validation should include use of dried bloodspots from a population of newborns, including known positive and negative specimens, in addition to laboratory prepared target specimens.

Recommendation 2

Data should be available on the net benefits of clinical interventions following early detection compared to clinical diagnosis. Early detection can be achieved through population screening pilot studies, through testing secondary to a family history of the condition, or through targeted screening of high-risk groups.

Recommendation 3

Data should be available from pilot studies involving population-based screening of identifiable newborns.

3a) The study should be sufficiently large to identify at least one true positive newborn for the condition under consideration

3b) The population included in the pilot study, and the screening protocol used, should be similar to the US population and to state NBS programs with respect to known prevalence of the condition, the timing and approach to screening, and the screening modality used.

Charge 2

To recognize and support current efforts regarding pilot studies and evaluation.

Recommendation 4

Sustained support should be provided by DHHS for the NIH initiatives that support pilot studies in newborn screening including the NBSTRN, NSIGHT, the Pilot Studies grants, Natural History grants, Innovative Therapies grants, and grants supported under the Parent Announcement.

Recommendation 5

Sustained support should be provided by DHHS to the CDC for its activities relevant to the support of pilot studies that address technical training and quality materials for state laboratories, assistance to state programs in obtaining laboratory equipment, the creation and distribution of “Validation Test Packages,” and the fostering of “Laboratories of Excellence.”

Charge 3

Identify other resources that could support pilot studies and evaluation.

Recommendation 6

DHHS should support the development of a network of “Centers of Excellence for Newborn Screening Pilot Studies.” This network should be comprised of state-based public health programs, laboratories, and research centers that would provide a stable, experienced, compliant,

efficient, and quality infrastructure for the conduct of population-based pilot studies for newborn screening.

After presenting the charges and recommendations below, Dr. Botkin opened the meeting for discussion.

Committee Discussion:

- Dr. Matern suggested considering modifying the language to reflect screening that doesn't use bloodspots to broaden the definition. For example, including physiological or pathology tests.
- Dr. Botkin agreed but also said it's important to deal with actual affected and unaffected babies, as opposed to artificially designed test systems.
- Dr. Green suggested adding something about the fact that a population might reflect the heterogeneity of the U.S. or state populations.
- Dr. Matern asked if it should be limited to newborns. Should it say "from a target population" in case one wants to do a pediatric screen or other screen later in life?
- Dr. Botkin agreed.
- Dr. Ostrander asked if the specimens would be obtained under real-world circumstances. He explained that specimens collected specifically for a pilot study may be collected with more attention than those in real-world circumstances.
- Dr. Cuthbert said the recommendation was targeted at the analytical validation, but clinical validation comes next. Analytical validation is the point at which the state (or program) has done developmental work and has come to a stable method and wants to show performance metrics that show the method is now ready to be taken into a new population. She agreed with Dr. Matern that one should consider what happens with point-of-care testing, but also advocated for dried bloodspot tests since CLIA requires it and so does the FDA. With respect to samples and populations, in many states they can actually use the last three months' worth of samples identified, or samples that reflect their own population, to determine the actual measurement values for a particular test. Many states collaborate with physicians to obtain permission to access dried bloodspots of affected individuals for testing. While clinical validation is something different, this is more of a retrospective analysis of bloodspots to determine parameters and determine that the test works and is stable.
- Dr. Kelm said that when the FDA reviews newborn screening assays most of the time—for example, for precision, detection limits, or interference—contrived samples are used, such as adult blood, because one can't obtain enough blood from a newborn, even through a dried bloodspot. She added that point-of-care samples, such as whole blood serum plasma, is a whole other "ball of wax."
- Dr. Botkin suggested modifying the text to read "pilot studies for analytical validation should include the use of biologic or other physiologic assessments from a population of newborns or other target population including known positive and negative specimens in addition to laboratory prepared target specimens."
- Ms. Wicklund asked how to address the incredibly small numbers and some of the data that doesn't clearly show a net benefit.
- Dr. Botkin said that, as a condition comes forward, if it's going to go move to evidence review there have to be some data on efficacy and safety, which can be obtained from different types of studies. However, whether or not the evidence review process and subsequently the Committee will find those data to be convincing is a separate question.
- Dr. Green suggested adding the word "and" between recommendations 3a and 3b.
- Dr. Puryear asked what was meant in recommendation 3b by the phrase "and the screening modality used."
- Dr. Botkin said he believed it was largely written in the context of bloodspot screening.
- Dr. Puryear asked if it would allow variability, such as point-of-care screening.
- Dr. Botkin said it would not. He said the data ought to be collected in a way that is interpretable in the U.S. context where the data would be applied for this purpose.

- Dr. Watson reminded the group that this was the case with Pompe disease outcomes where Taiwan had used the fluorescence assay and tandem mass spectrometry would be used in the United States, so the screening platform or testing modalities were different.
- Dr. Matern said he was concerned that it might prevent innovation such as using a completely different technology or approach to screening. He said it shouldn't be seen as a specific technology.
- Dr. Botkin explained that as a test comes forward and is proposed for inclusion on the RUSP that the proposal would include a certain test modality. If pilot studies were done using a very different test modality the mismatch might be problematic.
- Dr. Matern suggested stating that the test must be amenable to high throughput screening, but that the exact modality is irrelevant, as long as it can be done efficiently, effectively, and cheap.
- Dr. Urv said that different states test for SCID in different ways. It's only the outcome that needs to be similar. The outcome has to be the same because for some conditions there are a variety of competing tests.
- Dr. Watson said that a true positive should be a clinically affective infant, not late onset disease.
- Dr. Matern said that one true positive meant to him having a patient who, based on the diagnostic process, has the disease. Whether their phenotype is expressed at the time is a different story, but based on everything we know we would expect the patient to become symptomatic.
- Dr. Watson said the pilots are not only to find individuals with the disease. Their purpose is to find them, intervene, and show benefit. One needs those three conditions to be met to determine that it's a screening test that's good for newborn screening programs.
- Dr. Botkin agreed that those data elements are needed, but those data may not all come from the same study.
- Dr. Watson agreed.
- Dr. Bailey asked if the goal was more than just identifying one baby. Should the data show that one can scale up to do it in a broad way?
- Dr. Botkin said this was more about a threshold criterion to get the nomination up to the evidence review.
- Dr. Green said the term "true positive" is ambiguous because it might mean a laboratory true positive, but not necessarily a clinical true positive. For example, a SCID screen in a preterm infant would be a true positive, but not a clinically true positive.
- Dr. Botkin said the other complexity is the adult onset forms. Those cases would be true positives but not what the program is designed to identify for clinical intervention.
- Dr. Cuthbert agreed it would have to be a clinically verified case.
- Dr. Matern asked if "clinically verified" means that the patient must have symptoms.
- Dr. McDonough said he believed it was fine as written. It has a broad interpretation that gives the Committee guidance on what needs to be done.
- Dr. Urv said that, with respect to the fourth recommendation, she was concerned that it sounded like fiscal support. HHS does not provide money that is earmarked for this. Instead, the NIH itself earmarks the money for such activities. She suggested changing the wording to something that doesn't imply fiscal support, such as continued support.
- Dr. Spong said that having "support" twice in the beginning doesn't read well. She suggested removing the word "support" from recommendations four and five.
- Dr. Matern asked whether one should say only "laboratories" rather than state laboratories and state programs.
- Dr. Green asked if the CDC also does surveillance regarding newborn screening. She asked if that would be part of the sustained support.
- Dr. Boyle said that CDC does indeed carry out that type of surveillance.
- Dr. Botkin asked if surveillance could be an element of a pilot study.
- Dr. Boyle said it would be in terms of trying to understand the outcome and whether or not the program is effective—to be able to evaluate and identify both the effectiveness of the screen to identify children with the condition and then to follow up on the short term.
- Dr. Tanksley inquired about removing the word "state" from the recommendation.
- Dr. Cuthbert said the suggestion to remove the word "state" was to indicate that CDC would provide materials to any of the laboratories that would request them.

- Mr. Shone said that CDC does not provide those types of resources to non-state programs. Its charge is to assist states, not necessarily private laboratories and commercial programs. He said he was in favor of keeping the word "state" in the recommendation.
- Dr. Matern said that taking out the word "state" wouldn't mean that states would be out of the equation. It just would not be limited to state laboratories and state programs.
- Dr. Botkin said he was a bit nervous about de-highlighting the state connection.
- Dr. Cuthbert said there are some things that CDC provides exclusively for state programs, but there also are some things that CDC will generously give to other programs who request it. She added that validation packages are something new that CDC would be able to create specifically for states. But if anyone else requests it, they can also be made available. She suggested wordsmithing the recommendation to include the words "state" and "other."
- Dr. Bocchini said the Committee would accept the report of the Pilot Study Workgroup and its recommendations with the proviso that the recommendations would be wordsmithed and then sent to the Committee for further comments, if necessary.

IV. Public Comment

Laura Martin, Association for Creatine Deficiencies: Ms. Martin said she has a five-year-old son named Ryan who was diagnosed with GAMT deficiency just before his third birthday. Once he started receiving treatment his seizures stopped, his EEG normalized, and his coordination improved. He is a happy kid, affectionate, and playful.

He also has permanent brain damage that could have been prevented by newborn screening and currently attends a special school for multiple handicapped children where he gets speech therapy, music therapy, and physical therapy. He's still in diapers and scores at less than the first percentile in the standardized test. Ryan may never be able to live independently or care for a family of his own.

He has an older brother, a step sister, and a fraternal brother, none of whom have GAMT deficiencies. Ms. Martin said she sometimes feels guilty for the time and attention stolen from her other children, while she is focused on Ryan's care. She said she is also a genetic counselor but before Ryan's diagnosis she had never heard of GAMT deficiency. Ryan would have been a perfect candidate for newborn screening.

GAMT deficiency is a devastating disease when left untreated from birth. It has a treatment that is incredibly safe and not so expensive. Ms. Martin believes there are children and adults who are undiagnosed, wheelchair-bound, and unable to communicate. The first case of GAMT deficiency was diagnosed in 1994, more than 20 years ago. She asked the Committee to please vote today to move GAMT forward to condition review.

Missy Klor said her son was diagnosed at 13 months and is now eight years old. He was misdiagnosed with cerebral palsy and suffered 13 months of brain damage. He went through years of costly physical therapy, occupational, and speech therapy. In terms of the cost analysis, one could look at the continued care he would have needed versus how he is doing today. Today he can run and play. He takes two hours of gymnastics twice a week and also plays soccer.

At Duke, the doctors were knowledgeable about GAMT and screened him. He had to work hard to overcome his delays, but did so. He takes three supplements three times a day. Ms. Klor said she received approval from federal BlueCross and Blue Shield to have one of his foods covered, under preferred benefits, until he turns 22. This took four years of fighting. Currently, many children are undiagnosed or diagnosed at a later age. This causes seizures, difficulty speaking, and other challenges.

Ms. Klor asked the Committee to please consider voting for more futures like John. She said the Committee gets to vote on children that have a future that is not defined by GAMT, but instead a future they make for themselves. These children want to grow up and experience life to the fullest. Every parent wishes for a healthy child. She asked the Committee to please vote "yes" to add GAMT to newborn screening.

Kim Tuminello, Association for Creatine Deficiencies: Ms. Tuminello said she is the co-founder of the Association for Creatine Deficiencies and a mother of two children with GAMT. There is now a better understanding of this severe and devastating neurological disorder. GAMT is completely treatable if caught in the very beginning of life. Data from a pilot show there are no gaps in evidence and no false-positives. A Duke study also showed there are no false-negatives.

In terms of treatment, the children simply drink a cocktail of creatine and sodium benzoate three times a day along with a moderate protein diet. This saves them from having hundreds of seizures a day and being strapped to a wheelchair for the rest of their lives. Ms. Tuminello said her son was diagnosed when he was 10 years old and has gone through years of physical therapy, occupational therapy, and vision therapy. Today, he still continues to be in speech therapy in the school district.

Ms. Tuminello said her daughter has been treated since birth. She is 6 years old and never had a day of therapy or intervention in her life. The cost of treatment is close to nothing. Everything can be ordered off of Amazon.com. Today, there's technology to start testing for GAMT. The cost adds up to 49 cents per baby. This is cheaper when compared to the millions of dollars spent on lifetime treatment for special services, and eventually, being turned over to the state to receive life-long care. The longer we wait, more babies will go untreated. Ms. Tuminello said the Committee has an amazing opportunity to save these children and their families from unnecessary heart break.

Heidi Wallis is the mother of four children, two of whom live with GAMT. Children with GAMT are not instantly recognized at birth and the burden of diagnosis should not be on their primary care physician. Also, not every child develops alarming symptoms in the first few years of life. Ms. Wallis said her oldest daughter, Samantha, was slow to reach milestones. She began to walk at 18 months, which was considered barely "good enough." She did not have sloppiness or movement disorders, and until she turned five did not have seizures.

When she was three years old Samantha was diagnosed in the autism spectrum. Thankfully when she was five, the onset of seizures led to her getting an MRI, which is how her creatine deficiency was finally noticed. It was sheer luck which led her to a GAMT diagnosis and treatment.

Ms. Wallis said her son Louie was diagnosed at birth. Treatment has been miraculous for him. He is full of joy, intelligence, creativity, love, affection, and imagination. Louie scores in the typical range of cognitive testing. Four times a day he puts his playtime on pause to take a quick syringe of easily available and affordable powders mixed with water as treatment. Treatment has been simple for him, and very successful.

Samantha's IQ test scores are very low. Her speech is not always understandable. She can ride a bike, but not independently. She crosses lanes without looking. She's reckless and tries to take off on her bike alone and gets lost. She has improved with treatment, but will continue to suffer because of her late diagnosis for the rest of her life. She has a severe intellectual disability. The damage has been done. Ms. Wallis asked Committee members to please understand that there is not a second option for children with GAMT. They must be diagnosed at birth. She asked them to please recommend GAMT.

Jana Monaco said she is the mom Steven, an 18 year old who should be graduating from high school next month. That will not happen because he was diagnosed late at three-and-a-half years old, resulting in significant brain damage. This has taken away graduation and countless other dreams away from Steven. In contrast, his sister Caroline who is now 13, will have her graduation and many other dreams. The difference was early detection of her disorder and appropriate treatment with a diet plan, medical formula, and supplements. Formula and foods are identified as a critical component of treatment, but not everyone has access to them due to a lack of coverage. They are costly, but also essential.

The 2011 IOM report recommended further HHS evaluation of coverage of nutritional supplements and formulas needed for treatment. However, there has been no follow up and no further evaluation. Ms. Monaco asked the committee to please ask HHS to follow through.

In addition, NIH, FDA, CMS, and others organizations operate under various classifications and definitions. Ms. Monaco asked the Committee to ask the Secretary to end a disparity that has lingered for more than 10 years. She asked the Committee to invite the Secretary to initiate a joint meeting of these agencies and other key players mentioned this morning and convene and agree to a common definition and solutions to make life-long access to medical formulas and foods available and accessible to each and every child and adult who needs them.

If treatments are required for conditions in the RUSP, it is ethically wrong to allow them to be inaccessible to the very patients that need them. Ms. Monaco said the Committee has a moral responsibility to ensure that this component of life-long treatment be properly identified and available to the populations whose lives depend on them. She thanked the Committee for their continued work.

Christine Brown, National PKU Alliance: Ms. Brown said she is the executive director of the National PKU Alliance and also the mother of two children with PKU. She explained that in their last conference adults and parents were asked to free write their top-three concerns in dealing with PKU. Number three was the development of a home Phe monitor for better management of the condition. Number two was the development of new treatments. But the number one concern was access and coverage to medical foods to treat PKU.

She said we have all failed to accomplish support and access to treatment after the diagnosis is made on the newborn screening test. Ms. Brown said she believes the Committee has a moral obligation to her children and to the other 475 children born every year with a positive diagnosis that requires medical foods for treatment.

She asked the Committee to ask the Secretary to follow up, now that that Department of Labor Survey and IOM report has been out for more than five years. This issue of medical foods has been punted too many times. In the last 7 years, her patient organization has met with NIH, CMS, FDA, and the Office of Intergovernmental Affairs. They have also testified before HHS at the listening sessions on the essential health benefits. She said this has been going around and around for far too long.

Ms. Brown said one of her biggest dreams shouldn't be to have her children's medical foods covered. She said she wants to set her sights on something bigger and better for them and in order to do this she asked the Committee to be bold.

Carol Greene, Society for Inherited Metabolic Disorders: Ms. Greene said SIMD's updated statement on access to care would be a useful tool for those working to support the issue. She read the highlight of the Society's April 2016 statement on medical foods. "The SIMD strongly urges that all private and public systems for health care payment be mandated to cover specialized diets, including medical foods, for treatment of inborn errors of metabolism found through newborn screening or clinically diagnosed ... although medical foods are an essential medically necessary treatment for many inherited metabolic disorders, many health care payers deny coverage for medical foods and mandates are not consistent across states. The complex pattern of health care coverage in United States means that many individuals with inborn errors of metabolism are at significant risk of disability or death because of lack of access to the medical foods that are a critical part of their medical care. The lack of uniform and consistent coverage of medical foods throughout the United States threatens individuals and families. Because medical foods are essential treatments for many of the conditions detected by expanded newborn screening, failure to provide life-long access to these treatment modalities also threatens the success of public health policy." She said she hopes the Committee will be able to use this statement, which is offered as a tool in the fight to get medical foods covered.

Spencer Pearlman, Cure SMA: Mr. Pearlman said he is a board member of Cure SMA. Spinal muscular atrophy is an autosomal recessive genetic disorder that occurs in about 1 in 10,000 live births and is the leading genetic killer of children under the age of two. Mr. Pearlman urged the Committee to give serious consideration to the forthcoming nomination and evaluation of SMA for universal newborn screening. SMA families and clinicians feel that newborn screening is imperative for the treatment of this disorder.

In the last 10 years there have been significant advancements in the field. Of the 18 SMA drugs currently in development, 6 are in clinical trials and several are in phase 3. It is expected that one or more of these programs will undergo FDA review in 2017.

It's critical that SMA be added to the RUSP as soon as possible to ensure that patients can obtain access to treatment at the earliest possible moment. Both human natural history data and animal model data indicate there's only a very small opportunity after birth for effective intervention in the most common and severe form of SMA, type 1, which affects 60 to 70 percent of all individuals with SMA.

Preliminary data in mouse models also indicates that pre-symptomatic drug intervention is far more effective than post-symptomatic intervention. Additional studies show that proactive treatment of an infant with SMA in the first weeks or months of life prolongs survival and improves their quality of life. Furthermore, the technology for newborn screening for SMA has been successfully utilized in several ongoing pilot newborn screening programs, including those in New York state and Taiwan.

Mr. Pearlman said the SMA community strongly urges the Committee to take up consideration of the forthcoming SMA RUSP nomination, in particular because of the approaching availability of a treatment for SMA and the demonstrated benefits of early intervention.

Dean Suhr, RUSP Roundtable and California Model Legislation Involving the RUSP: Mr. Suhr said the next meeting of the RUSP Roundtable's will be held on August 24. He said he is involved in a project in California which is basically a study to address the issue of having 50 states with 50 policies relative to how a screen is implemented after it's approved and on the RUSP. In many cases this involves a legislative action of some kind. The legislation that will be proposed and introduced in California states that once a disease is on the RUSP, the legislative action is automatically taken care of. A law would be passed stating that if a condition is added to the RUSP through a thorough evidence review process, then that disease is acceptable to move forward with implementation.

The legislation would not request any specific timeline, nor include an appropriation that would allow the addition of that condition to be implemented. He said that in California appropriations that cover expenses relative to newborn screening are a matter of law already. The legislation would be a model legislation for all 50 states, or at least all states where legislators are involved in getting diseases onto the state panels.

Mr. Suhr added that some states seem to almost replicate the entire set of work that the Committee goes through in terms of evidence review. This is expected as every state's equipment and processes are a bit different, but it appears that there's a varying width of acceptance of the work the Committee is undertaking.

V. Guanidinoacetate Methyltransferase Deficiency (GAMT)–Update from the Nomination and Prioritization Workgroup

Dietrich Matern, M.D., Ph.D.
Chair, Division of Laboratory Genetics
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Dr. Matern said there are a total of 110 GAMT patients described in the literature. The phenotype is mild to severe intellectual disability and most patients have epilepsy that is difficult to control. In half of all patients, there is movement disorder and behavioral problems. AGAT, another creatine deficiency disorder, seems to be much more rare than GAMT but has a somewhat similar phenotype, with pronounced muscle weakness. There also is the X-linked transporter defect, which is the condition where most patients are identified.

Treatment is available and consists mostly of supplementation of creatine and ornithine, restriction of protein and/or arginine, and sodium benzoate. Parents can obtain creatine through various stores, as well as

Amazon.com, and is relatively cheap. He explained that the later one makes the diagnosis the more severe will be the phenotype. Therefore, initiation of treatment as early as possible is very important.

A study published in Germany a couple of years ago refers to a patient that was diagnosed in the first few months of life was doing very well. However, the parents decided to stop treatment. Unfortunately it didn't take long for the patient to have irreversible damage. Therefore, it is important that patients stay on treatment consistently throughout life.

A study from the University of Utah examined 10,000 newborn screening samples retrospectively and found a false positive rate of 0.08 percent by looking at the GAA to creatine ratio. However, they did not report any false positives because they had a second tier test to re-examine GAA and creatine, so the final false positive rate was 0 percent. The true positive rate, however, was also zero because they did not find an affected patient in the samples.

The Baylor Research Institute in Dallas carried out a study between 2008 and 2011 of nearly 20,000 babies, of which about 50 percent were from Mexico. They had a false positive rate of 0 percent, but they also did not identify a single patient in that study. In British Columbia a retrospective study examined 3,000 newborn screening samples. They had a false positive rate of 0.13 percent using GAA only, but could get rid of all false positives with the second-tier test. They also tested for two common mutations and happened to find two carriers of two novel mutations.

In Victoria, Australia, has been doing prospective newborn screening for GAMT deficiency since 2002. They have screened more than 1 million babies without finding a single true positive. The false positive rate with no second tier test is 0.02 percent. In terms of demographics, a Google search showed that 66 percent of Victorians self-identified as being of either Australian, Scottish, English, or Irish ancestry and less than 1 percent as aboriginal. Most immigrants are from the British Isles, China, Italy, Vietnam, Greece, and New Zealand.

A study in the Netherlands examined 500 newborn screening samples retrospectively. They did sequencing of the GAMT gene and measured GAA. Through sequencing they found two carriers, one with a known mutation and one with a novel mutation. Through measurement they found no false positives but also no true positives.

Based on these data, the presumed carrier frequency was estimated to be 1 in 250, which results in a calculated incidence of about 1 in 250,000 among the Dutch population. In the paper the Dutch population was described as consisting of individuals with Dutch, Turkish, Moroccan, Indonesian, German, Surinamese, Latin American, other European and Asian ethnic backgrounds.

In comparison, in Utah the calculated incidence was 1 in 114,000. Utah is currently actively screening for GAMT deficiency. They have screened 50,000 babies thus far and found a false positive that turned out to be a NICU baby, but no true positives.

In summary, GAMT deficiency is a serious medical condition. The natural history of GAMT deficiency seems well understood even though there are few patients known worldwide. Treatment is very similar to other conditions on the RUSP. Dried bloodspot based assays can be adopted for newborn screening quickly and at a very low cost. The sensitivity of the screening test is likely 100 percent with a nearly zero false positive rate. However, there is no agreed treatment strategy and no FDA-approved newborn screening or diagnostic assay. Also, no patients have ever been identified through prospective newborn screening.

Dr. Matern said the Workgroup recommended that the Committee not initiate an external evidence review because not a single case had been identified prospectively to date through newborn screening, which would make the evidence review very difficult. Also, the treatment guidelines appear to be in development but not finalized.

He suggested that the proponents work with other experts to formalize treatment guidelines. He also encouraged the continuation of newborn screening for GAMT deficiency in Utah and Australia and to

report back to the Workgroup as soon as a patient had been identified prospectively. He suggested that proponents resubmit a nomination when the above items were achieved.

Committee Discussion:

- Dr. Bailey said he didn't understand why the treatment guidelines were unclear. He asked Dr. Matern if he could provide some more information.
- Dr. Matern said the issue of the guidelines is a weak argument, since there are conditions that have been added to the RUSP which also had no clear guidelines, such as Pompe disease where there are questions in the literature about the right immune modulation. He said it would only take a short phone call with the proponents in Canada to fix that and write a paper that outlines more exactly what those guidelines should be.
- Dr. Bailey pointed out that the treatment is not dangerous.
- Dr. Matern agreed and said he believed it was not dangerous.
- Dr. Botkin said Dr. Matern mentioned that the clinical sensitivity of the testing was estimated to be 100 percent. He asked where that number came from in the absence of any real babies identified to date.
- Dr. Matern said it comes from one laboratory in Victoria, Australia. Australians feel that since they haven't diagnosed a patient with GAMT deficiency since 2002 through their clinical efforts, they believe there are no false negatives. Utah has been screening for more than a year and also hasn't made a clinical diagnosis yet.
- Dr. McDonough asked—knowing what is now known about how serious this condition is if children aren't picked up in time and the fact that there's an effective treatment—whether when the tandem mass was developed and the RUSP expanded if it was more likely than not that this condition would've been part of the panel back then.
- Dr. Matern said that at the time there was no screening test. He said that if the screening test would've been around it would likely be included.
- Dr. Spong asked why this wouldn't get moved forward to the condition review team. Is it because a case hasn't been identified? If so, how long would it take for that to happen? Also, what would be the harm in moving it forward while waiting for that one case to be identified?
- Dr. Matern said the harm is that a baby will be born in a state that could have been screening because the state is not and will not receive treatment.
- Dr. Spong said that would be the harm of not moving it forward. She asked if there would be any harm in moving forward.
- Dr. Matern said the harm is asking the evidence review to proceed and come up with the fact that there wasn't a single true positive. The data provided by the review would probably not add anything new that is not currently known.
- Dr. McDonough asked if there is more information about the condition, benefit of treatment, early detection, or perhaps [information on] some of the conditions that were added on the RUSP in that expansion.
- Dr. Matern believed it was a no-brainer. The condition is medically serious and there's a treatment that is cheap and can be done. Also, the screening test is not difficult to perform.
- Dr. McDonough said that the Committee should be careful of not getting too paralyzed by its own policies and miss an opportunity to help some kids.
- Dr. Greene said that, while she wasn't speaking for SIMD, at a personal level she thought it was a slam dunk. She added, however, that it's also important to follow the guidelines because they are meaningful. Also, the next person could come along and say "you didn't follow the guidelines for them, so why not do it for me as well?" Having said that, she added that the core of treatment is giving the child creatine. There is a treatment, but they are trying to make it better, just like we are trying to make the therapy for PKU better. But there is a treatment.
- Ms. Wicklund said that retrospectively they were able to take dried bloodspots and identify affected individuals. She asked if the limiting factor is identifying a true positive prospectively. She asked if this was related to the Committee's pilot recommendations about having to have one true positive.
- Dr. Matern agreed on the limiting factor.

- Dr. Botkin said that all the elements seem pretty solid to move forward, except for the failure of public health programs to yield affected kids. He said that everybody seems to believe it's a good test, but a million babies is a lot of babies without a single true positive. He asked if this was related to something about Australia. He said he didn't understand what the alternative explanations might be of that failure, but that all other elements seemed solid.
- Dr. Kelm asked if it would be simple to add this to the public health labs and current programs. She asked if anyone could weigh in on the public health impact.
- Dr. Matern said he thought it was easy. The CDC has the materials, so they have the test running in their own laboratory. They could also train others on the matter.
- Dr. Ostrander said the condition has a cheap and safe treatment, which has not been one of the Committee's previous criteria, but certainly gives one pause about whether one needs to be as strict about the criteria as opposed to ones where the treatments are dangerous and of unknown efficacy. Also, it can be proved that with the existing technology retrospective identified cases tested positive. He agreed with Dr. Greene about the treatment protocol. If one only has 110 cases worldwide, there are not going to be standardized treatment protocols that are going to be compared in a prospective way from no treatment or the standard treatment. It may be the case that for ultra-rare conditions, such as this one, that the thought process could be modified just a bit, taking into account and weighing in not only the criteria for true positives through screening and the treatment protocol, but also the safety and efficacy of the intervention.
- Dr. Bocchini asked Dr. Kemper what one positive case would mean to the evidence review.
- Dr. Kemper said the issue of finding one case originally came about when considering SCID. He said it goes beyond just finding one case. They can look at both the positive and the negative predictive values. Part of the evidence review is supposed to examine what would happen in the real world as state programs adopt screening. Dr. Kemper added that the Evidence Review Workgroup serves at the pleasure of the Committee and could certainly examine other aspects of GAMT such as natural history or what is presently known about treatment.
- Dr. McDonough asked Dr. Kemper to elaborate on his concern about the burden for programs.
- Dr. Kemper said one of their charges is to look at what it would take for state newborn screening programs to adopt screening for the condition in terms of cost, feasibility, and readiness. It's difficult to determine this with limited data from state health programs. It's not just about one positive case, but rather about the broader issues regarding implementation.
- Dr. Bocchini reminded the group that once the evidence review begins, there's a nine-month timeline within which it has to be completed, which can pose a challenge.
- Dr. Greene said that a good diagnostic test already exists. It's easy to collect urine on baby boys and easy to collect blood on both sexes. She asked what would be the statistical chances of finding no cases in one million, if the true frequency is 1 in 120,000 (or 1 in 250,000 in Australia). She believes it probably would be a reasonably high number, but was not sure because at least some of the frequency is based on DNA on what one presumes to be carriers and this assumes that everybody who is a carrier is symptomatic. She said she would be interested in obtaining such numbers.
- Dr. Tarini said she agreed with Dr. Kemper. She said that for MPS I there were two affected individuals. Historically, it seems ongoing conditions have been reviewed and cases identified from population-based screening that leaned strongly on past evidence of efficacy in studies that involved identification from family history, not on efficacy of treatment by what is found in the population. One of the children identified died after treatment, and this was not taken into consideration as affecting the assessment of efficacy of the treatment. She said the Committee had leaned more heavily on the historical studies done. If this was done that the past, one should consider whether to use the "one person" standard in this case.
- Dr. Kemper said that one of the challenges of hinging everything on one case is that the case identified through newborn screening might not develop clinical problems for years down the line, which is what happened with ALD.
- Dr. Botkin asked Dr. Kemper if there would be additional avenues of evidence to uncover that might help make a decision.
- Dr. Kemper explained that they haven't looked at what evidence is or is not out there. He said he couldn't comment on what else might be out there.

- Dr. Watson said there are patients from California and New York in the virtual repository and their spots could be pulled with consent to determine whether or not they would have been detectable on a newborn screen.
- Dr. Matern said that his colleagues in Utah, Canada, and Australia collected actual newborn screening samples from patients and ran them through their test. Those data are out there and it shows nicely how they have much higher GAA concentrations than those found in the normal population.
- Dr. Watson said that when it comes to ultra-rare conditions, part of the data one wants nominators to submit are data that are informative retrospectively. This happened in SCID. There were approximately 750,000 babies screened before the first one was found.
- Dr. McDonough said that if Utah is the only state testing it may take several years to get a true positive. In the meantime, if the statistics are reasonably accurate, there will be 20 to 40 children born every year in the U.S. who will be brain damaged if testing is not implemented. He said that his concern was there will be families and children who will be impacted because they won't be diagnosed. He added that the Committee has modified its criteria in the past.
- Dr. McDonough asked if it would be possible to conduct a bloodspot study during the nine-month evidence review period that would add information to the review process.
- Dr. Matern replied that they already took the original blood spots and ran them through the system. This was part of retrospective studies that showed higher GAA levels.
- Dr. Bocchini said this would not be the first time a nominated condition was close to being approved but missed some of the criteria and as a result went back to the nominating group for additional data to be obtained. This happened with Pompe disease and SCID, where a decision was delayed until a positive case was found.
- Ms. Wicklund questioned what additional level of evidence one true positive could provide compared to some of the evidence available from other sources. She said she struggled with the potential decision of reconsidering the nomination once a true positive is found. Perhaps looking at retrospective data in more detail could provide more information.
- Dr. Bocchini said it would depend on how that would influence the ability to prove that a newborn screening program in place could detect a positive in a newborn.
- Dr. Cuthbert said she understood the tension behind the issue, but supported the findings of the Nomination and Prioritization Committee.
- Dr. Matern said they are not adding the condition to the RUSP today, just considering whether it should move to the evidence review. The evidence review would then have to consider everything discussed today, including whether or not the test could be implemented in a public health laboratory.
- Dr. Bailey recommended moving it forward to the evidence review. He believed there is strong evidence regarding the benefit to babies. The cost of screening is also low, compared to some other conditions. He didn't believe the Committee would learn much more from the evidence review, but in the meantime it could request that the APHL provide a review of state capabilities. The advocates could also be asked to come together and develop consensus guidelines for treatment. Pilot studies are already ongoing, which could potentially yield more data, and in nine months the Committee decide whether to add it to the RUSP.
- Dr. Botkin said he wouldn't consider the lack of one prospectively identified baby to be a deal-breaker when there's other information available. One is the natural history. The other is the fact that there are many negatives with a million babies without false positives. He said there also have to be a lot of babies out there that never made it to the literature. He wondered if there's a way to collect information from clinicians, who are likely at the bottom of the referral pattern for these children, to get a better estimate on the population frequency for this condition. In addition, he said that Dr. Nicola Longo's publication provides additional information that might be reviewed in terms of the test performance as well as short-term and quick studies that could be done retrospectively with blood spots.
- Dr. Matern noted that in the paper there's also a mention of a registry that Dr. Stockler wanted to implement. He has emailed Dr. Stockler about this but has not yet heard back.
- Dr. Greene said she feels strongly that all clinicians would say there is a treatment for this condition. She also suggested the language for the criteria could be rewritten to state that the

sample size should be roughly twice the expected prevalence, to allow for a good chance to pick up at least one positive. This approach would also yield information about false positives. This change would allow the committee to stick to its guidelines and avoid losing credibility.

- Ms. Bonhomme suggested that the communication going back to the nominators and the public should clearly state why this condition did or did not move forward, and list next steps, because this is an issue that has come up with other conditions that have gone through the process. Parents and the public have become frustrated with this process because it can seem convoluted and unclear.
- Dr. Lu said the argument is that having a true positive helps establish prevalence and predictive value. But how valid is it to have one case as a numerator to help one establish that population's prevalence or predictive value? Also, how much more information on treatment efficacy will one case add compared to all the other information already available? He wondered whether the Committee is placing too much confidence in waiting for that one true positive case.
- Dr. Bocchini asked if individuals felt comfortable with approving a condition to be placed on the RUSP without having any babies identified by newborn screening. This was part of the reason why SCID wasn't recommended for the RUSP.
- Dr. McDonough said he would indeed feel comfortable. With cases that are so rare one may want to try it for a period of time, say three years, and if no cases have been picked up then stop doing it. He said he would rather err on the side of this approach, as long as it's not causing any harm. Looking at the preponderance of information now available the Committee should consider taking a leap forward and have faith that public health labs will do the testing appropriately. That's a better approach than not diagnosing children and as a result having them being damaged.
- Dr. Bailey said the discussion showed how complicated these decisions can be, especially for rare conditions. He said he was willing to take a chance and move forward with the evidence review.

Committee Vote:

- Dr. Botkin moved to accept the recommendation of the Nomination and Prioritization Committee and Dr. Kelm seconded.
- Dr. Bocchini explained that the motion being considered is not to carry out an external evidence review, but rather recommend that proponents work with other experts to formalize treatment guidelines and also encourage continuation of newborn screening prospective studies in Utah and Australia, and then report as soon as possible when a patient has been identified prospectively. The condition would then move forward to evidence review upon achievement of these milestones.
- The motion was accepted. Seven individuals voted for the motion: Drs. Bocchini, Botkin, Cuthbert, Kelm, Lorey, Mistry, and Thompson. Six individuals voted against: Drs. Bailey, Spong, Matern, McDonough, and Lu as well as Ms. Wicklund.
- Dr. Bocchini thanked everyone for their input and said it was an important but difficult and complicated decision to make. He said everyone feels this is a strong nomination and that the Committee would like to have the data necessary to move forward as soon as possible. He also thanked the families for attending.

VI. Committee Business: May 10, 2016

Joseph A. Bocchini, Jr. M.D.

Committee Chair

Professor and Chairman

Department of Pediatrics

Louisiana State University

Shreveport, LA

A. Welcome and Roll Call

Dr. Bocchini welcomed the Committee members, organizational representatives, and other participants to the second day of the meeting and took the roll. Voting members present were:

- Dr. Bailey
- Dr. Bocchini
- Dr. Botkin
- Dr. Lorey
- Dr. Matern
- Dr. McDonough
- Ms. Wicklund

Ex Officio members present were:

- Agency for Healthcare Research and Quality (AHRQ): Dr. Kamila Mistry
- Centers for Disease Control and Prevention (CDC): Dr. Coleen Boyle
- Food and Drug Administration (FDA): Dr. Kellie Kelm
- Health Resources and Services Administration (HRSA): Ms. Joan Scott (for Dr. Michael Lu)
- National Institutes of Health (NIH): Dr. Catherine Y. Spong

Organizational representatives present were:

- American Academy of Family Physicians (AAFP): Dr. Robert Ostrander
- American Academy of Pediatrics (AAP): Dr. Beth Tarini
- American College of Medical Genetics (ACMG): Dr. Michael Watson
- Association of Maternal and Child Health Programs (AMCHP): Dr. Kate Tullis
- Department of Defense (DoD): Dr. Adam B. Kanis
- Genetic Alliance: Ms. Natasha F. Bonhomme
- March of Dimes: Dr. Edward McCabe
- National Society of Genetic Counselors: Ms. Cate Walsh Vockley
- Society for Inherited Metabolic Disorders: Dr. Carol Greene

VII. Prenatal Education About Newborn Screening and Dried Bloodspots

Jeff Botkin, M.D., M.P.H.

Professor of Pediatrics and Medical Ethics

Associate Vice President for Research

University of Utah

Salt Lake City, Utah

Dr. Botkin's presentation focused on parent education about newborn screening and dried bloodspots. He explained that prenatal education has primarily been carried out through brochures provided in birthing facilities. This is not a particularly effective way to educate or inform parents about these issues and, for the most part, the brochures are not read. He explained that the perinatal period is not conducive to a thoughtful discussion about these issues and there has been relatively little incentive for health departments to do a

more energized job in that domain.

Women are pregnant for a long period of time, and parents are very interested in almost anything that is relevant to the baby. As a result, this would be an opportune time to address newborn screening and dried bloodspots rather than only during the perinatal period. However, surveys tend to show that prenatal care providers are not really plugged into newborn screening and are not addressing the issues on a consistent basis.

A 2006 study conducted by LSU, which was co-authored by Dr. Bocchini, provided an evidence base for the type of information they felt ought to be provided to parents. The study conducted a series of focus groups and determined seven things parents ought to know about newborn screening:

- All newborns are required by the state to get tested for some rare disorders before they leave the hospital
- Babies with these disorders may look healthy at birth
- Serious problems can be prevented if we find out about these problems right away
- To do the test, a nurse will take a few drops of blood from your baby's heel
- Your baby's health professional and hospital will get a copy of the test results. Ask about your baby's test results when you see your health professional
- Some babies need to be retested. If your baby needs to be retested, you will be notified. It is very important to get retested quickly
- Talk to your baby's health professional if you have questions

Dr. Botkin said they are currently conducting a literature review and have identified thus far 1,900 publications in the English language that report use of dried bloodspots from newborn screening sources. He explained that they will break those down on what types of research are being conducted, the states involved, and other important categories. He said they would have a report ready in the next six months or so. In addition,

Dr. Botkin and other colleagues have been conducting an NHGRI-supported study over the last couple of years, a four-year project. It is a collaboration between the University of Utah, Intermountain Healthcare, UCSF, and Albert Einstein in New York City.

These sites were initially selected because their approach to newborn screening and dried bloodspot management was similar. As a result, they wouldn't have to create separate informational resources for parents, since the policies surrounding the retention of bloodspots and parents opting out was consistent across states. While this has changed now in the aftermath of the Reauthorization Act, it was true while the study was being conducted.

The study had four specific aims:

- To determine what pregnant women, young mothers, and their partners want to know regarding the retention and use of residual bloodspot samples
- To create multimedia educational tools to be used in the prenatal care environment that will provide basic information about NBS and DBS
- To determine the impact of the prenatal education intervention on parental knowledge, attitudes, and decisions regarding NBS services and DBS
- To examine the normative/ethical implications of the results

The study identified seven things that parents want to know about residual bloodspots:

- Some states save leftover bloodspots after newborn screening is complete
- Leftover bloodspots can be used to improve the public's health in many ways
- No extra heel pricks are done to collect blood for other potential uses of the spots
- Safeguards are in place to protect the privacy of babies and families and to ensure the ethical

- conduct of research
- The baby's name or other identifiable information is not attached to the leftover bloodspots used in most research
- Because most research with leftover bloodspots is done anonymously, parents will usually not get results back from the research
- A parent may request that their baby's bloodspot not be used in research after newborn screening

Dr. Botkin explained the study also revealed two items they hadn't anticipated. The first was that it was a big deal for parents that no extra heel pricks would be done to collect the blood for potential uses. The study showed they would have been more concerned about the practice had there been an extra stick for the baby.

The other related to the safeguards in place to protect privacy and to ensure the ethical conduct of research. This was a revelation to most participants in focus groups. They general had no idea about the processes surrounding research, specifically the IRB process. He added that cloning came forward as the single most frequent concern that participants had. As a result, they decided to address this explicitly in the educational movie [Dr. Botkin proceeded to show the movies that were developed as part of the project].

Dr. Botkin provided the details of the project. They approached 1,247 individuals and 72 percent agreed to participate. They were assigned to one of three groups: 1) the control group for standard care, which is whatever parents normally get as part of their obstetric and neonatal service surrounding newborn screening and dried blood spots; 2) individuals who looked only at the newborn screening video; and 3) individuals who watched both movies.

There was a significant increase in knowledge about dried bloodspots for the individuals who watched the dried bloodspot movie. And individuals who watched both movies had higher knowledge scores than those who did not. Also, individuals who had a higher level of education had a higher increase in their knowledge. In addition, more individuals who watched one or two movies said they were "very supportive" about the newborn screening program when compared with controls.

Committee Discussion:

- Dr. Mistry asked about nonparticipants. She asked how nonparticipants could have affected the overall result.
- Dr. Botkin replied that there was no statistically significant difference in those who declined participation from those who did participate.
- Dr. Mistry asked if this was also with respect to those who refused the newborn screening.
- Dr. Botkin replied that only nine people refused newborn screening and clarified that they did not look at refusal for those who had declined to participate. They didn't have that information and didn't want to try to draw information from the state programs about peoples' decisions, so they only got their self-reports. For these reasons, they didn't have that information on folks who didn't participate.
- Dr. Spong asked if there would be any confusion from the mother's part about prenatal testing or screening during pregnancy versus newborn screening.
- Dr. Botkin explained that since the intervention was at around 38 weeks participants could minimize the confusion, but there is risk that there might be confusion. The other confusion that we were most concerned about was confusing newborn screening and dried bloodspots. He said they tried to provide a very different look and feel to the movie so that it clearly separated that these were different issues they had to be aware of.
- Dr. Kelm asked why there were two separate movies. In other words, why not just include, as part of that initial movie, what happens to the bloodspots afterwards?
- Dr. Botkin said that in their small implementation pilot they will be combining those two movies in a way that makes it a more seamless experience.
- Dr. Kelm said she was curious about the idea of using bloodspots for Zika. She said the Zika virus can only be detected for a very, very short period of time. And if looking for the IgM, it currently

cross reacts with Dengue.

- Dr. Botkin said he wasn't aware of anybody who was doing that, but it seemed conceptually feasible.
- Dr. Boyle said they looked into the matter a bit. She said that from a laboratory perspective it's very challenging to use, particularly the RNA.
- Dr. Cuthbert said they have not yet been approached but that the infectious disease team at CDC has this under control.
- Dr. Bailey gave Dr. Botkin kudos for the great videos. He asked if they were currently available to others, either for research or clinical purposes. He also asked how they would get people to actually look at them. He said that in this day and age a 12- minute of video seems like an eternity.
- Dr. Botkin said they are thinking about the matter. He said the dried bloodspot video has been revised to be consistent with the Reauthorization Act, so it's a bit different than what families saw in the study. Dr. Botkin said they would be happy to make them available. They are not posted yet in a downloadable form but are discussing the best way to approach the matter. He said they've also discussed the possibility of creating a commercial product, as it might be more attractive as a commercial product as opposed to just somebody posting it on the Web, but they are still thinking about all of those possibilities.
- Dr. McDonough said the video was very impressive and high quality. He suggested that in the first video, if results are positive, to get there sooner than the two weeks indicated in the video. He also said there's an opportunity to use the video in hospital prenatal classes and doctors' waiting rooms, since the latter sometimes show educational videos on a continuous loop. Also, in waiting rooms people often are waiting for more than six minutes to see their physician. He added that it could also be used prenatally. He believed there would be a be a good market for the videos, particularly if state public health labs get out to the hospitals and start promoting them. A lot of state public health labs visit hospitals on an annual basis and this is something they could show them during that visit.
- The experience could also be repeated in the hospital, where moms spend a day and a half having a baby. There's usually talk about the baby's exam, how the baby's doing, or they are watching a video on breast feeding, changing diapers, or another educational topic.
- Dr. Botkin said they need to better understand exactly how other video tools are being used in both the prenatal and postnatal environment. He said that some hospitals may have a health channel that includes content that is relevant to all patients, as opposed to this particular subclass of patients. He said they need to better understand the landscape to see where the videos might fit.
- Dr. Boyle asked if there was a lot of variation with the storage of bloodspots among the three sites.
- Dr. Botkin said there were no significant differences by site.
- Dr. Boyle said that one of the seven principles touched upon was that if a blood spot was used in research, the baby's name would not be attached to the bloodspot. However, this is not necessarily true if it's used in anonymized research.
- Dr. Botkin explained that there are bloodspots linked back to identifiers. But typically in those contexts, the investigator himself or herself does not have the identifying information. This is why, in most circumstances, it's not human subjects research even though somebody else might be able to track back that identity. Dr. Botkin said he believed that many spots are used that are completely anonymized. He said that one of the challenges was to articulate that type of protection in a way that was both accurate and understandable. He added that once they complete the study of 1,900 publications they'll have a better idea what level of the identification was exactly done. He said he was only aware of one study in which identifiable bloodspots were used.
- Ms. Scott said that about half of the participants had had a child before. She asked if there was any difference based on whether they were repeat parents or if this was their first pregnancy.
- Dr. Botkin said that was a good question. They didn't examine that particular question but could easily pull those data.
- Ms. Scott said it might be also interesting to ask if they have any family history of any issues, as that may also skew responses.
- Dr. Botkin agreed. He said they found a study that showed that parents of children with PKU and leukemia have distinctly different attitudes about dried bloodspot research than families in the general public.

- Dr. Watson said that ACOG was also doing education about newborn screening. He said that getting their support for getting this into offices would be key to getting the videos out there.
- Dr. Botkin said that Nancy Rose had a preliminary discussion with their educational office and they seem to be interested in the materials, but they haven't taken any particular steps at this point.
- Ms. Bonhomme said the Genetic Alliance has also been interested in that question. She added that in June they will carry out focus groups, in partnership with NewSTEPS 360, with the nurse leadership of AWHONN to determine where those decisions take place and how one could implement change. This focus group will focus on timeliness and include prenatal nurses as well as those in the nursery. She said they would be happy to share their findings.
- Dr. Greene said they were not able to publish a survey of neonatal nurses and nursery staff that showed extremely poor knowledge of newborn training. She thanked Dr. Botkin for the beautiful video and asked if there would be time for a revision for the next version. She said that a study that Genetic Alliance and University of Maryland published determined what questions families specifically have about newborn screening when they have received a positive newborn screening. She said the video leaves unanswered some of those key questions.
- Dr. Botkin said they are thinking about a revision and that Dr. Bailey's group is thinking about creative tools in that domain.
- Dr. Tarini said Dr. Botkin's presentation showed that the knowledge base between standard of care and newborn screening is pretty similar, but she also added that knowledge doesn't always translate into support of the program. So it's important to take a close look at what the objectives are in terms of education.
- Dr. Botkin said that was an excellent point. He said he would have loved to have seen a higher level of knowledge as a result. Their questions were very simple, which is why they had a baseline correct response rate that was high. If the questions are easy one might not see any increase in knowledge, because everybody gets them right at the beginning. So increased knowledge, particularly over that span of time, is a challenge. However, the fact that they saw substantial degrees of increased support was heartening. He said that both activities are worthwhile and should be supported.
- Ms. Bonhomme asked if there was a time difference in between the videos, for the group that saw both videos what was it.
- Dr. Botkin said they saw them one after the other.
- Ms. Bonhomme asked if people were asked how they wanted to get the information or where they would like to see the videos.
- Dr. Botkin said they did not. They just asked their assessment of what they saw.
- Ms. Bonhomme said it's something important to consider because people are finding information around pregnancy and early childhood in a range of different ways. She added that they also consistently see the confusion between prenatal screening and newborn screening. The clearinghouse constantly gets questions around prenatal screening in their contact form that have to be rerouted. She said they have developed a video with Children's National about congenital heart disease which is currently being shown in over 1,000 hospitals in English and Spanish three times a day. They work with the Newborn Channel but hospitals contract out with different agencies and then run whatever's on their platform. She said she would be happy to share that contact with Dr. Botkin.
- Dr. Botkin thanked Ms. Bonhomme for the offer. He said his staff was showing the videos to the patients on iPads and they would worry about them getting stolen and making sure they were clean between patients. He said each little thing has its own set of barriers to overcome in that regard.
- Dr. Tanksley replied about an earlier comment about whether research is anonymous versus identified. She said that's a distinction that needs to be made because specimens can be contributed for research in an identified manner, if the parents provide specific consent for that. She added that the law changed multiple times. At first it required disclosure that specimens could be used for quality assurance. Then it moved into a consent requirement for the parents to provide consent. Then it came time where they had to collect consent. Now they don't necessarily have to give consent, but they can refuse if they don't want the samples used specifically. She added that it is important for the integrity of the program, and to keep the program safe, to be able to show parents

- that their wishes will be respected.
- Dr. Botkin said that one of the goals is to help people be more informed. What they found in focus groups is that if the conversation starts by asking them what questions they have, they usually don't have any questions because typically they don't know much about it. But if the group is given 10-15 minutes worth of background, you can fill up the next hour with questions and conversation. Hopefully this is the sort of thing that can trigger some knowledge so that parents can then approach the doctor with questions and concerns.
 - Dr. Kus asked about Dr. Botkin's thinking on education relative to hearing screening and critical congenital heart disease.
 - Dr. Botkin said he didn't have a good answer for that. He said the resources ought to be out there and available, but there's a question as to how to integrate them in an effective fashion, as this can be challenging.
 - Ms. Vockley asked if he received any feedback from families about the language used, in terms of the complexity of words, and whether it had some impact on the knowledge gained.
 - Dr. Botkin said they didn't get anything specific. Participants provided feedback about the length of the movies, but for most part they were otherwise supportive.
 - Dr. Matern said there are one or two districts in Texas and Minnesota where they might want to try out the videos and get some feedback. He said it was impressive looking at 1,900 publications. For someone who is not aware of the issues, this may lead them to think there are a lot of problems with bloodspot testing, or that it should be a perfect test by now. He suggested dividing it into what actually led to improvements in newborn screening, because it seems that parents want to know that it did something good.
 - Dr. Botkin replied that they are planning on looking at whether the application was related to newborn screening or some other health problem.

VIII. Workgroup Updates

A. Cost Analysis Workgroup Update

*Alex Kemper, M.D., M.P.H., M.S.
Professor of Pediatrics
Duke University
Durham, North Carolina*

Dr. Kemper's presentation focused on cost assessment estimates. He said he contacted and received information from Missouri and Illinois. The study focused on estimating costs for two conditions: Pompe disease and MPS I. The estimates were for LSD single- or multiplex.

He explained that the single most common theme heard was that costs for newborn screening can vary greatly across many dimensions. These variations can be due to state size, birth rate, existing laboratory facilities and personnel, structure of the newborn screening costs, cost arrangements within and across states, and whether equipment is purchased or leased, among other factors.

Dr. Kemper explained that one of the challenges was to determine how to standardize highly variable state costs into a single point estimate and range. There seems to be no standard approach to estimating, and the estimates are usually specific to a state. Also, the cost components and categories can vary per state and some information may not be available in detail due to confidential or protected vendor pricing.

The cost estimate carried out by the Workgroup involved various parameters including equipment, consumables (e.g. disposable supplies and reagents), other lab expenses, labor, confirmatory testing referrals, and overhead or indirect costs.

The point estimate of cost per infant for one condition ranged from \$2.03 to \$2.08. The estimated total annual cost to screen 100,000 infants was \$202,500 and \$208,000 for the two states. He cautioned the

Committee that these estimates were based on various assumptions, such as economies of scale and other factors.

The next steps will include following up with states for pretest and interview vendors to obtain more specific information. The pretest information will be used to revise the cost assessment. There's also a need to identify secondary cost issues, such as treatment and long-term care, into the assessment. Dr. Kemper explained that they would present the final report and recommendations to the Committee during the August meeting. After feedback is received, they could then incorporate cost assessment into the current procedures and timelines of the condition review.

Committee Discussion:

- Dr. Matern said some of the numbers presented seemed to be on the low side. For MS/MS, based on what Perk & Elmer reported last year at the APHL/CDC meeting in Atlanta, the reagents per enzyme will cost \$1 dollar per enzyme, per test. If the cost is \$2 per condition, that would mean \$1 to measure the enzyme activity in one infant and \$1.08 for everything else: space, electricity, equipment, the person doing the test, the follow-up person, etc.
- Dr. Kemper said there's a big cost for the first test and then a marginal cost for each additional one.
- Dr. Lam added that the prices are from multiplexes. When states were asked about Pompe and MPS I, those particular states are doing multiplexes and are involved in reagent rental agreements. She said that they would follow up with Perk & Elmer.
- Dr. Kemper agreed that the amount might be underestimated.
- Dr. Matern said they currently do the testing now for three conditions in one state. He said he would love to give it to them for that price but can't because they already do it at no margin and the cost is more than what was presented.
- Dr. Lam said that for Pompe, MPS I, X-ALD, at rough glance, they are coming up with between \$1.50 all the way up to \$9 per infant and per test. Dr. Lam suggested taking these numbers "with a grain of salt."
- Dr. Matern asked if they had considered follow-up, false/positive, and implications of false/positive secondary tests.
- Dr. Kemper agreed those were add on additional tests.
- Dr. Tullis asked if they had looked at numbers for smaller states. She said she works in Delaware and their numbers never looked that good.
- Dr. Kemper said they had not.
- Dr. Urv said they might want to discuss the topic with some of their NIH contractors that are currently screening for Pompe, MPS I, and X-ALD. They have to detail their costs for NIH and it is part of their contract to provide those details. She said that she could put them in touch with those individuals, who could likely provide a more detailed outline of what to expect.
- Dr. Kemper said that would be very helpful.

B. Follow-Up and Treatment Workgroup Update

Stephen McDonough, M.D.
Retired Pediatrician
North Dakota

Dr. McDonough provided an update on the Follow-Up and Treatment Workgroup meeting which took place yesterday. There were 19 people present on site and 8 present by phone. The group agreed to focus on two priorities: 1) Clinical Quality Measures and 3) Medical Foods and Medical Formulas. Dr. Zuckerman briefed the group through a presentation on "Promoting the Role of Clinical Quality Measures to Promote LTFU of Newborn Screening."

There was discussion of potential roles of NewSTEPS in promoting clinical quality measures (CQM) for long-term follow-up (LTFU). They could include a list of CQMs for LTFU on their website along with

educational materials about CQM as part of their technical support mission. NewSTEPS would also support communication and assist in other areas.

Dr. McDonough also explained that the NBSTRN could have some potential roles in promoting CQMs for newborn screening. They have created the Longitudinal Pediatric Data Resource (LPDR) which is a database on newborn screening long term follow-up with common and disease-specific data elements. This database can provide a solid framework for CQM development and implementation.

All clinical quality measures for long-term follow-up of newborn screening should be based on fields already in this database, or they may need to be added. Data already stored in this database could support testing and demonstrating new CQMs. The database could also integrate CQMs and become a repository of CQM data.

Three proposed end products were identified for the workgroup:

- 1) A **case study** of successful use of CQMs for follow-up of newborn screening
- 2) A **report** to the full Committee highlighting the background, need, and opportunities to use CQMs in LTFU of newborn screening
- 3) A **how-to guide** for developing quality measures for newborn screening that could be distributed to newborn screening programs, regional genetics collaboratives, professional organizations, and disease specific organizations to help them begin the process of creating CQMs

Dr. McDonough explained that they will hopefully have more detailed information during the August Committee meeting. He added that another goal would be to possibly put together a letter that would be presented to this Committee to go to the Secretary regarding medical foods.

The Workgroup will also be working on a white paper that would be a source of information to decision makers about the importance of this issue. Dr. Sue Berry, from the University of Minnesota, who participated by phone, agreed to head up the Medical Foods subworkgroup. Dr. McDonough informed participants that the workgroup will hold a series of phone meetings between now and August when they will report back to the Committee as a whole.

C. Timeliness Workgroup Update

Kellie Kelm, Ph.D.

*Chief, Cardio-Renal Diagnostic Devices Branch
U.S. Food and Drug Administration
Silver Spring, MD*

Cathy Wicklund, M.S., C.G.C.

*Associate Professor in Obstetrics
and Gynecology-Clinical Genetics
Northwestern University
Chicago, IL*

Dr. Kelm informed the Committee that the Workgroup had held two calls since the February meeting. These calls focus on the Workgroup's first charge, which is to optimize successful strategies to address newborn screening specimen collection and transport and collect and disseminate timeliness specific practices from state newborn screening programs.

The Workgroup learned about improvements made by Missouri and Utah surrounding timeliness in newborn screening. They also held a brief call with Erin Dupree, the Chief Medical Officer and Vice President for Joint Commission Center for Transforming Healthcare, to inform her of what the Workgroup was doing. Since this was an introductory call, a follow-up call will be placed to determine any points where both groups can work together.

Utah examined the four different sub-processes that make up newborn screening: 1) sample collection and logistics; 2) sample receiving; 3) sample testing; and 4) reporting/follow-up coordination. Their goal was to determine the turnaround time in each of these subprocesses. They found bottlenecks in the first two subprocesses: sample collection and logistics and sample receiving.

One of the biggest challenges was transport time, so they developed a partnership with FedEx to provide courier service for hospitals that had a turnaround time of more than three days. The annual cost for implementing this strategy was \$19,000, and it did reduce the turnaround time to less than three days.

Utah also used both “carrots” and “sticks” to address underperforming hospitals. Carrots included establishing personal relationships with the hospitals, focusing on a real partner role and transparency, and conducting site visits, training, and process consulting. Sticks included a rule change that mandated sample collection between 24 and 48 hours of life. These strategies resulted in an overall reduction of transit time from 2013 to 2015.

To address the bottleneck in operations, Utah began an expanded newborn screening service in February 2015 to 7-day operations. Saturday operations included specimen accessioning, result reporting, and on-call follow up. Sunday operations included full day testing (of all tests) and on-call follow-up. This strategy resulted in a reduction of turnaround time for nearly all tests. In some cases the turnaround time was reduced by more than 20 percent.

Missouri found a variety of factors that impacted timeliness including:

- No weekend or holiday courier pickup
- Smaller birthing hospitals were not provided courier and had to use US mail
- The state laboratory did not work on weekends and some holidays
- Some hospitals displayed logistical issues that led to internal delays
- There was a lack of traceability for hospitals to promptly verify their samples were received by the state laboratory
- There was a lack of funding to remedy the above issues

Missouri approached some solutions and improvements that had no cost to the MSPHL, while others did have a cost. No cost solutions included working with hospitals that were not on the state courier system to self-transport their newborn screening samples to their nearest County Health Department. Other no-cost strategies included working one-on-one with hospitals displaying timeliness issues, providing customized monthly timeliness reports to laboratory and OB managers in those institution, and increased overall education on timeliness (e.g. during routine conversations with nurseries, laboratories, and primary care physicians).

Solutions requiring funding included implementing a holiday courier pickup starting on January 2014 (costing \$6,000 per year), Sunday courier pickups starting on July 2015 (\$36,000 per year), adding 8 more birthing hospitals to the current 46 routine hospital sites for the courier (\$44,000 per year), and implementing Saturday and Holiday testing starting on October 2015 (\$200,000 per year).

Missouri also developed a Saturday/Holiday work model. It was a 100 percent voluntary staffing process. It consisted of a skeleton crew of seven scientists to work each Saturday or Holiday to perform all screening tests (except for Thanksgiving, Christmas, and New Year’s Day). A manager was hired to run the Saturday/Holiday expansion and supervise adjunct staff, and two new newborn screening employees were hired agreeing to work Tuesday through Saturday. This resulted in significant changes. The percent of samples which had a transit time of three days or less increased from 67 to 87 percent.

Missouri also developed a newborn screening report access portal. This was a secure website for hospitals to verify that the state newborn screening laboratory had received their samples. This allowed hospitals to print and/or save their own NBS lab reports from this site and not have to wait for them to come through

the mail. It also reduced the number of calls to the state labs requesting reports.

D. Education and Training Workgroup Update

Cathy Wicklund, M.S., C.G.C.
*Associate Professor in Obstetrics
and Gynecology-Clinical Genetics
Northwestern University
Chicago, IL*

Beth Tarini, M.D., M.S., F.A.A.P.
*Associate Professor of Pediatrics
University of Michigan
Ann Arbor, MI*

Ms. Wicklund said that during their Workgroup meeting Ms. Bonhomme provided an update on the nomination education project. The purpose of this project is to provide educational guidance to groups that might be interested in preparing a nomination package. The project is almost concluded and will likely be completed by August, when it will be presented to the Workgroup for feedback.

The Workgroup is also involved in two other projects. The first focuses on creating a tool that provides primary care physicians with guidance and tips for discussing positive NBS results with parents, which could be used alongside the ACT sheets. This project focuses on the communication process itself and not necessarily on the medical information around a positive screen. ACMG has already developed the ACT sheets, so the idea is to add supplementary material.

Ms. Wicklund explained that Ms. Bonhomme and Dr. Greene have conducted focus groups with families that led to an article in *Genetics in Medicine* titled “The impact of false-positive newborn screening results on families: a qualitative study.” They have developed a one-page list of bulleted tips on communicating newborn screening results. The Workgroup also circulated the following specific questions for consideration when shaping the content for the tool:

- What are the key messages that should be provided to parents of children with positive initial NBS results?
- What pieces of information are missing from the ACT sheets?
- What communication processes/procedures should be utilized and which should be avoided?

The Workgroup is also considering different organizations that they could partner with to assist with this effort.

Dr. Tarini provided information on the second project, the Educational Outreach Project that seeks to map educational resources available on newborn screening and then disseminate them to target audiences to have them embedded within their resources. The goal would be to first compile a list of trusted sources. This would lead to the development of a descriptive web of what's available which would then allow one to describe the landscape and identify any gaps available in educational resources.

Next steps would include a Workgroup brainstorm to identify the audiences and goals of education. The Workgroup would also leverage any anticipated work of the NBS Clearinghouse Resource Repository in collating multiple educational resources.

E. Laboratory Procedures and Standards Workgroup Update

Kellie Kelm, Ph.D.

*Chief, Cardio-Renal Diagnostic Devices Branch
U.S. Food and Drug Administration
Silver Spring, MD*

Susan M. Tanksley, Ph.D.

*Manager, Laboratory Operations Unit
Texas Department of State Health Services
Austin, TX*

Dr. Kelm said the Workgroup heard presentations related to its two projects. The first project is on laboratory procedures and explores the role of next generation sequencing in newborn screening. The second project focuses on infrastructure and services, such as timeliness, the implications of earlier specimen collection, and the unforeseen consequences and costs of timeliness.

Two presentations focused on the role of next generation sequencing. Dr. Caggana provided an overview of the APHL Molecular Subcommittee and Dr. Baker discussed Next Generation Sequencing in a state newborn screening program. Two other presentations focused on timeliness. Dr. Feuchtbaum spoke about early specimen collection and Dr. Sontag about the unintended consequences and costs of timeliness.

During her presentation to the Workgroup, Dr. Caggana explained that there are a number of efforts they are currently undertaking including a molecular quality improvement program, NBS molecular workshops (an intensive, one-week training), a molecular assessment program, and a newborn screening molecular resources website that they host. They are also planning a meeting on next generation sequencing for the newborn screening community during the first quarter of 2017.

During her presentation to the Workgroup Dr. Baker discussed what Wisconsin is doing regarding next generation sequencing. They have identified 242 variants of CFTR2 and are working on a prospective study with two specific aims: 1) to further modify the established Illumina NGS method to expand the CFTR mutation panel up to 250 CF-causing mutations; and 2) to demonstrate that the IRT/NGS CF screening protocol can significantly reduce false positive results caused by identification of CF heterozygote carrier infants in a real-world NBS environment.

During her presentation to the Workgroup Dr. Feuchtbaum discussed the results of early collection efforts in California. They obtained population-level data to determine whether early specimens (collected from 12 to 23 hours) would be considered satisfactory based on screening performance. They analyzed for false-negative and false-positive rates in four disease categories: metabolic disorders, CAH, CH, and IRT for CF. The rates were compared between the early-collection group (12 to 23 hours) and the standard collection group (24 to 48 hours). No significant difference of false-negative rate was detected between the two collection-timing groups. Early specimens had a significantly higher false-positive rate for CH and IRT but a lower false-positive rate for MS/MS metabolic disorders. The results of the study were published in *Genetics in Medicine*.

During her presentation to the Workgroup Dr. Sontag reviewed state data provided by NY, MN, WI, and IA to determine the implications that earlier collection has on screening. Some of the concerns in terms of moving collection earlier include less time to consult with parents in the hospital prior to the screen, repeating testing due to more out-of-range/borderline results, asking for additional specimens due to more out-of-range/borderline results, an increase in missed cases (false negative), and an increase in presumptive positives (false positives). Dr. Sontag explained that additional data collection and further work is needed to reach definitive conclusions.

Committee Discussion:

- Dr. Matern informed the group that Dr. Rinaldo was currently meeting with colleagues from California, New York, Georgia, Norway, and Iceland discussing data and covariates for all of the newborn screening conditions which include birth weight, gestational age, and age at collection. He encouraged the Workgroup to invite someone from his meeting to give an update at the next meeting.
- Dr. Kelm thought that was a good idea.
- Dr. Boyle said there was a study supported by the Workgroup that took many years. Stuart Shapira and Harry Hannon worked on it and looked at some of the conditions that the California group examined in terms of early versus late collections.
- Dr. Kelm said that study was looking at one single screen versus two screen states. The problem was that there wasn't a clear conclusion about whether single screeners or two screens is actually more effective.
- Dr. Boyle agreed and said it was different for different conditions. She asked, with respect to California, if there were any takeaways from the results in terms of one having high and the other low false positives.
- Dr. Kelm said one of the conclusions was that the differences weren't large and also weren't as concerned clinically.
- Dr. Feuchtbaum agreed. She said they concluded that they really weren't big differences. She said the differences were in fact in the screen positive rates. As far as the screen negatives, which are basically the missed cases, they didn't see any differences in any of the disease categories that were looked at. With the screen positives there were higher rates of false positives for congenital hypothyroidism and for CF, but that was after the IRT test. With respect to CF, those cases don't get called out to families at that point. So there's no negative impact on the families because those cases go on for DNA panel testing and then sequencing. They reach out to the primary care provider and family only after that process is completed. For congenital hypothyroidism, the follow up does not entail the family going to a specialty follow-up clinic, such as a metabolic clinic. And it's the primary care provider that is asked to redraw the blood and perform the serum TSH and T4 test. She said the paper was published in *Genetics and Medicine*.
- Dr. Tarini said that, as a researcher, she always hesitates to rely on anecdotal data but explained that an MCAD positive is different from a congenital hypothyroid. She said her child had a false positive for congenital hypothyroidism and had to go through three subsequent draws because the thyroid didn't come down as quickly as it could have and it caused a bit of angst.
- Dr. Greene said that Maryland performs two screens. Their protocol is as follows: if the IRT is high on the screen when the baby is a day old (e.g. 250-300), it gets called out. However, if it is above the cut-off but not that high, nobody knows about it until the second screen comes in because it's not an emergency. And only if the second screen confirms the high IRT is it called out as a positive.
- Dr. Matern said that before they change the screening orders to a second routine screen across the country, which would significantly increase health care costs, he would suggest first looking at the data and how covariates could help.

IX. New Business

There was no new business to discuss.

X. Adjournment

Dr. Bocchini discussed some of the topics to be covered during the August meeting, including presentations from the NSIGHT grantees funded by NIH. He said they would continue to discuss long-term follow up and also hear from states and that have implemented testing for various LSDs. There will also be updates

from new steps on timeliness activities. Dr. Tarini will discuss the findings of her Robert Wood Johnson funded project.

Ms. Bonhomme suggested that the Committee consider discussing policies and policy around newborn screening. There have been a number of different new bills on Capitol Hill that could potentially affect newborn screening both at the state level and also have an impact on advocacy. She said that the website www.change.org lists a couple of petitions related to newborn screening conditions that might be of interest for the Committee.

Dr. Bocchini said they would also consider Dr. Matern's suggestion to discuss the data that are becoming available on covariance which might influence accuracy for newborn screening with respect to initial screens.

Dr. Bocchini recognized some of the Committee members for whom this would be their last meeting. He presented Andrea Williams with a certificate from HRSA to recognize her contributions and service to the Committee over the years. He also recognized Dr. Thompson, who was attending via phone, with a certificate. He added that with her background in hematology oncology, Dr. Thompson had made significant contributions to the Committee over the years.

He also thanked Dr. Botkin and said the Committee has enjoyed working with him. His background and efforts have led to multiple contributions for the Committee, as evidenced by the work he presented today as well as the work on the Workgroup that developed the recommendations for the pilot studies. Dr. Botkin was also presented with a certificate for his contributions.

Dr. Bocchini informed participants that they hoped they would have new Committee members installed by August. He reminded participants that they are still looking for additional individuals to replace next year's transitioning members of Committee.

Dr. Bocchini thanked all Committee members for their participation in the meeting as well as all Workgroup members for their work. He also thanked the organizational representatives and all attendees for their participation. In addition, he thanked Ms. Sarkar for all her efforts and contributions in organizing a successful meeting and developing the program.

With no additional business to address, Dr. Bocchini adjourned the meeting at 1:36 p.m.

Public Comments

April 24, 2016

Dear R.U.S.P. Members,

I was a junior in college when I began working at the local "Retardation Center". That is what it was called. It isn't called that anymore. My first encounter there was with a child diagnosed with PKU. Her mom was tired, she was aggressive and mom had no choice but to put her with us. "She bears watching, Melissa," they told me. Bears watching? She was just a little girl?! I was about to get an education in PKU and the devastating effects on her and her family. I was shocked to find out that PKU was a required newborn screening that she had not received. I was horrified to learn that one simple test could have prevented her life in an institution.

Fast forward and I'm 31. A friend has lost her 2 year old to MCAD. Had it been part of newborn screening, he'd be with her today. She started a movement that resulted in Ben's Law in Mississippi. It expanded newborn screening for our state. Why was this important to me? Because, I was sitting in a doctor's office with a child that was not meeting milestones. Nothing was adding up and she pushed me to be his advocate. It was not until he was 12 that I got some answers - Creatine Transporter Deficiency Syndrome. It was not until he was 17 that I found the Creatine Deficiency Community and learned that my life could be much more complicated. CTD is not treatable. I get it. I don't like it, but I get it. GAMT is treatable. I don't get that. Why can't we help those that can live life to the fullest if they have a simple test at birth that answers questions, and gives parents directions and gives families hope where often there is none?

Four letters on one list is all we are asking. We've brought it this far. Let us take it the rest of the way.

Sincerely,

Melissa Parker, Financial Director, Trustee
Association for Creatine Deficiencies

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Assistant Professor, Department
of Pediatrics-Medical Genetics
Duke University School of Medicine
North Carolina

Dr. Denise Morita, M.D.
Pediatric Neurologist
Granger Medical Clinic
Riverton, Utah

To: The U.S. Department of Health and Human Services
Advisory Committee on Heritable Disorders in Newborns and Children.

Re: Guanidinoacetate Methyltransferase Deficiency (GAMT) addition to the National
Recommended Universal Screening Panel (RUSP).

Dear Committee Members,

I am writing to you to tell you about what a devastating impact just a few months can make in a child's life when not diagnosed with GAMT. This Creatine Deficiency Syndrome looks different for everyone, and the chances of the doctors or parents finding out in time are not likely. GAMT is difficult to diagnose because it looks like so many of the other disorders out there, but this is an *easily treatable* disorder that is misdiagnosed, time after time. GAMT is a devastating neurological disease that causes seizures, developmental delays, movement disabilities and requires a lifetime of care if not caught early in life. You see, both of my children have been diagnosed with GAMT. My oldest son was not diagnosed until he was 10 months old, and as a 10 year old today, he still continues to suffer the consequences of not receiving the diagnosis and treatment until then.

Ty has endured years of physical therapy, occupational therapy, speech therapy and visual therapy. When Ty was born, his failure to thrive and global delays were heartbreaking, but as we watched him steadily decline day after day, we knew something had to be done, and quickly. The immediate difference once we started treating with creatine was nothing short of a miracle. I will never forget watching my son stand up, after only taking creatine for 7 days. It was just a few days before as a 10 month old baby, he could not even sit up without support.

Unfortunately, this story is told over and over again by families who have seen their children suffer unnecessarily. There is so much hope with the diagnosis of GAMT, but only if it is caught at the very beginning of life. The RUSP panel was designed for exactly this type of disease, and every future parent is counting on disorders like this being on the Newborn Screen.

Sincerely,

Kim Tuminello

President, Trustee

760-688-8032

Kim@creatineinfo.org

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Denise Morita, M.D.
Pediatric Neurologist
Granger Medical Clinic
Riverton, Utah

April 24, 2016

3338 Tucannon Cove, Bluffdale, Utah

To: the committee members

From: Ellie Wallis age 10

Dear committee members, I wish that every kid could be screened for G.A.M.T. at birth. My sister wasn't diagnosed until she was 5 and it has affected her a lot. If she was diagnosed at birth, my life could have been so much more different. We could have been able to go shopping together, braid each others hair, even sell lemonade in the summer together. But instead, she has seizures in the middle of the night, she has to go to special schools, and she can't express how she feels very well. Louis, on the other hand got diagnosed at birth and it is like he doesn't even have G.A.M.T. He is able to sing songs, play pretend, and do all the things an average 4 year old can do. Sometimes I wish that a magical fairy would come along and sprinkle fairy dust on Sam (my sister) and then Sam would be cured and be a normal sister. I'm not saying that I don't love her, because I love her with all my heart, I'm saying that I wish Sam could go to a regular school and be able to drive a car and go to college and be, well, normal. I would rather live on the moon for the rest of my life and eat dead flies than have any other kid go through what Sam had to.

From,

Ellie Wallis

April 20, 20156

Dear RUSP Review Committee,

Guanadinoacetate Methyltransferase Deficiency (GAMT) is a devastating disease. Children suffer brain damage; seizures, language and cognitive impairments; developmental delay and debilitating muscular issues as a result of toxicity from GAA build up in the brain. The onset of symptoms is immediate and the severity is progressive without treatment.

This disease impacts both patients and caregivers who will spend a lifetime fighting the long-lasting mental and physical effects of this genetic disorder. And while the disease itself is relentless, equally tragic is the knowledge that GAMT is **treatable**.

Today, GAMT patients needlessly suffer with life-long impairments. Parents search years for answers and by then, it's too late. Like PKU and other treatable disorders before them, GAMT is the perfect candidate for newborn screening. If the purpose of RUSP is to save those lives that can be saved, then I, along with the Association for Creatine Deficiencies and nearly 1,000 petitioners, implore you to consider adding GAMT to RUSP. These patients have treatment.

They need you to give them a chance at life.

Thank you for your consideration,

Whitnie Strauss

ACD Vice President, mother of a 6 year old with Creatine Transporter Deficiency
512.563.3188

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Pediatric Neurologist
Granger Medical Clinic
Riverton, Utah

Letters (04/25/2016 14:36)

(Status: Preliminary Signable)

WALLIS, SAMANTHA 07/28/2003

To whom it may concern,

Samantha is a patient of mine with a diagnosis of guanidinoacetate methyltransferase deficiency. Samantha was not diagnosed until she developed symptoms, and at that point, the damage is irreversible. The symptoms of GAMT are not easily differentiated from other common childhood disorders. Treatment for GAMT is successful if started as early a possible, prior to symptoms. Samantha's younger brother Louis was tested as a newborn and is currently asymptomatic. It is crucial to screen for GAMT as a part of the required newborn screening. Thank you for your cooperation in this matter.



Dr. Duffy
Southridge Pediatrics
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Authored By: JESSIE L DEE
Authored For: J. TIMOTHY DUFFY, MD



Southridge Pediatrics

Letters

EMPI: 547421796
MRN: 641-50-12
DOS: 04/25/2016

ROOM:

DOB: 07/28/2003

AGE: 12Y Age At Date Of Note

Name: WALLIS, SAMANTHA

Authored By: DEE, JESSIE L

Authored For: DUFFY, J. TIMOTHY

April 23, 2016

To the Advisory Committee on Heritable Disorders in Newborns and Children,

As geneticists involved in the diagnosis and care of patients with guanidinoacetate methyltransferase (GAMT) deficiency we are writing this letter in support of the nomination of GAMT deficiency to the RUSP.

The Medical Genetics group and Biochemical Genetics laboratory at Duke University have been involved in the diagnosis, management and research of creatine deficiency syndromes, including GAMT deficiency, since 2003. We care for several families with these disorders, including one family affected with GAMT deficiency. The focus of our research has been the development of diagnostic methods for creatine deficiency syndromes, and to investigate the feasibility of newborn screening for GAMT deficiency.

GAMT deficiency is a good candidate for newborn screening as:

- 1) early treatment prevents the serious neurological consequences of the disorder,
- 2) it can be detected in the newborn period,
- 3) the current tandem mass spectrometric methods used in newborn screening laboratories can be readily adapted for the detection of GAMT deficiency, and,
- 4) GAMT deficiency is an under recognized condition.

The benefits of detecting and treating GAMT deficiency before irreversible neurological damage occurs cannot be overstated. Patients with GAMT deficiency who have been treated from birth or from a very early age have had normal, or near-normal, development. The treatment is based on dietary modifications and is relatively straightforward. Working closely with metabolic physicians and dieticians, families have successfully implemented this special diet to the benefit of patients. If left untreated, patients develop intractable seizures, speech delay, intellectual disability, abnormal movements and behavioral issues. Treatment implemented after early development may prevent or reduce seizures and improve behaviors, but does not reverse the intellectual deficit or speech delay. Unfortunately, GAMT deficiency is a metabolic disorder that is under recognized leading to diagnostic delays. Therefore, there is a critical need for early detection by newborn screening.

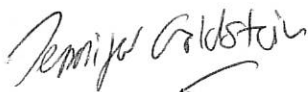
The infrastructure needed for newborn screening and follow-up of GAMT deficiency already exists. Patients with GAMT deficiency have an elevation of guanidinoacetate in blood in the newborn period, which is measurable in dried blood spots. The current tandem mass spectrometric methods for the measurement of acylcarnitines and amino acids used in newborn screening labs can be modified to also measure guanidinoacetate and creatine. Commercial stable isotope-labeled internal standards are available for both these compounds and they are detectable by non-derivatized or derivatized methods. Follow-up testing is available in several biochemical genetics laboratories in the US, and includes measurement of creatine and guanidinoacetate in blood and urine, and confirmation by gene sequencing.

To summarize, GAMT deficiency is a disorder that is similar to phenylketonuria, the prototype newborn screening disorder, in that it is detectable in the newborn period and early treatment by dietary modifications prevents severe neurologic impairment. Newborn screening for this disorder will benefit patients, their families, and their communities.

Yours sincerely,



Sarah P. Young, Ph.D. FACMG
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Dwight Koeberl, M.D. Ph.D., FACMG
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To: Advisory Committee on Heritable Disorders in Newborns and Children

Dear Committee Members:

As one of the leading rare disease patient advocacy organizations in the world, Global Genes collaborates with more than 500 patient advocacy and nonprofit organizations. We help these organizations grow and network, to improve their abilities to advocate for their communities, and to better develop their infrastructure to support the patients and families they represent.

The Association for Creatine Deficiencies (ACD) is a partner with Global Genes . The ACD has proven to be an excellent advocacy group for the creatine deficiency community. Our experience with them has been that they are extremely hands-on in staying up to date on current initiatives in the rare disease community, and in advocating on behalf of the patients and families they represent. They have remarkable resources and support for families such as Patient Strong™, a patient grant that helps families with the financial burdens of health care costs, social media platforms for support groups, and a quarterly newsletter, just to name a few. ACD has proven to be a model organization as they have been able to build a network of partnerships including an outstanding Scientific Medical Advisory Board. Members of their Medical Board include a pediatric neurologist and metabolic and mitochondrial biochemists from Utah, Rady's Children's U.C. San Diego, and Duke University. They are prepared to support creatine deficiency research, as they have built an impressive patient registry that is housed with the industry leader- PatientCrossroads.

We strongly believe the creatine deficiency community will benefit in significant and measurable ways from Newborn Screening. The research we have seen, and the patient success stories we have heard with early diagnosis, shows that **GAMT is an easily treatable disorder**. The most important take-away is that the severe debilitating symptoms of untreated **GAMT deficiency can be prevented**. Our sincere hope is that no other children will have to experience the inevitable decline in quality of life, before receiving the correct diagnosis of GAMT.

Sincerely,

Nicole Boice
Founder & CEO, Global Genes

They say that life is measured by the moments that take our breath away, but what about those moments when all hope seems lost and we can't catch our breath? Do those count too? Do we measure those? Those moments can change our lives, define who we are and alter life as we've known it. Typically when I share this story, I focus on all the happiness that it has brought into our lives and the miracle of what my son John has overcome. It's harder to share those moments when all hope seemed lost because the truth is they are heartbreaking and no one likes to hear a sad story. We all want the happily ever after that we think we deserve. However, sometimes in order to really appreciate what you have right in front of you, you have to remember where you've been.

Moment #1 – I can only describe this moment as watching a train wreck in slow motion, you can see it coming, but you don't know how bad it will be until it's over. My son John was only 6 months old and I knew he was not developing like other babies; something was wrong. It was time to take him to the doctors for his 6 month checkup. I can remember not wanting to go because I knew what was coming. It was all about to become real because once a doctor acknowledged that he was delayed there would be no turning back, no hiding my head in the sand. I would have to deal with the wreck that I knew was coming and hope that we both made it out on the other side. I was hopeful that maybe there would be pieces I could pick up and put back together, maybe even if there was something wrong, I could fix it. I am sitting in the waiting room filling out the 6 month milestone questionnaire and that's the moment I felt the impact from the train. My baby had failed the entire test. I couldn't honestly check yes to a single answer. I knew it was coming, but I didn't know it was going to be that bad. I hadn't even made it past the waiting room. The pediatrician called us back and it didn't take long for her to tell me that she was referring us to a pediatric neurologist. The ironic thing is that I can't even recall this exact moment and what she said because I wasn't listening to her. My mind was still stuck back in the waiting room with that damn test that my precious little baby had just failed. That was the first moment that made it hard for me to catch my breath and it changed everything.

Moment #2 - My next stop on this journey was to visit the pediatric neurologist that was 2 hours away from our home. She was certain John had cerebral palsy based on his symptoms and in her opinion there was little room for doubt that he had anything else. That was another one of those moments. I drove home, crying for the whole two hours, and yes, I drove, with my husband beside me and my mom in the backseat with my son. Why did I drive? Because when you're life is spinning out of control, you need to be able to control something, so I drove. I wasn't sobbing because I was trying to control that too... until I got home.

Moment #3 – I did my research on cerebral palsy and learned that there were varying degrees of severity. I spent numerous hours researching any possible treatments. At this point, John had been in physical therapy for a few months and it wasn't looking good. He wasn't making much progress. He was 10 months old and he couldn't sit up, couldn't hold his bottle, didn't babble and when you looked into his eyes he seemed lost in space. Then late one night, it all became just too much to take and I was at the lowest point I think I have ever felt in my life. I was at that moment that I now consider a very piece of the fabric that makes up my life, but it's also a moment that I have kept to myself, until now. Everyone in my house was asleep and I was having a break down. I was lying in bed and I couldn't catch my breath. It hurt. I hurt so much that I got down on my knees in the dark of my room and started

silently praying and crying. I begged. I told God that I would do whatever it took, that I would do whatever he wanted me to do, that I would follow whatever path he put before me, but to please help John walk; even if he walked with a walker, I would be happy with that. We could make a good life for him, but things would be just a little bit easier if he wasn't confined to a wheelchair the rest of his life and he could walk with support. Yes, I was trying to negotiate with God. Then, I crawled back into bed.

A few months later, I had come to terms with the fact that John had cerebral palsy and that life would be ok. We would manage. Life would be different and harder for him, but it could still be good. I would do everything I could to help him and give him the therapies he would need. I still had questions though and I still kept trying to solve the puzzle. I decided to go for a second opinion to see a developmental pediatrician. She too thought he had cerebral palsy, but she strongly recommended an MRI and blood work. Now, you may be thinking this is my Moment #4, when the 2nd doctor said it was cerebral palsy, but it wasn't. Don't forget, I had come to terms with a cerebral palsy diagnosis. It was an answer. Not the one I really wanted, but it was an answer. Even though some pieces of the puzzle didn't fit, I had two doctors that said they thought he had cerebral palsy, so it looked like that was going to be his diagnosis. We just needed the MRI to confirm it.

Moment #4 - I was pushing John in the stroller to the park near my house, when I got a phone call from the developmental pediatrician. The results from the MRI had come back. They were inconsistent with Cerebral Palsy. John did not have cerebral palsy. The MRI found that John had brain damage that was consistent with a Mitochondrial disorder, a Metabolic disorder or Carbon Monoxide poisoning. I cried. I didn't understand. He was supposed to have Cerebral Palsy. The MRI was supposed to confirm it. Now, what? Where do we start? What do we do next? The doctor said we needed to wait for the results from the blood work. We had to wait for an unknown future for my son. I didn't know if the next diagnosis would be better or worse or would there even be a diagnosis? The doctors were so certain it was cerebral palsy. I was devastated. I was back to no answers.

Eventually, I get the phone call with the results from the blood work. The doctor didn't want to tell me what they thought it was because while they had a suspicion they weren't sure. However, she finally said it looked like John had one of three Creatine Disorders and they wanted to know how soon I could get John to Duke Hospital for more blood work.

There are very few individuals that get a rare chance in life to truly make a difference and you are one of them. You get to vote to stop more moments like this from happening to moms and dads.

That is it for those tough moments. Yes, they have shaped my life and I will never forget them, but the rest of the moments are the ones that take your breath away in a good way. The moment they told me John had GAMT, was a great moment. I knew there was a treatment for it and things were looking better and brighter. We had a diagnosis and a treatment. Was it too late to fix all the brain damage that had been done? We didn't know for sure, but at least we had hope and hope is a great thing when you've been in the dark for a while. I'll never forget the first time I heard John laugh or when he took his first step or said his first word. My son was slowly coming back to life and I was along for the ride to watch it and enjoy every moment. We were given a miracle!

Do you remember moment #3, where I begged God to let John walk with a walker? Well, I remember it as I watch him run up and down the soccer field with his friends. And do you remember my promise to do whatever he wanted me to do? In 2011, I received a phone call from a doctor who had found my online blog and he encouraged me to start a nonprofit for children with this disorder. It was an idea that myself and another mother had tossed around before, but he gave me the name of a third mother that had prior experience with non-profits. All I could think was, "I hear you God." Today, the Association for Creatine Deficiencies has grown beyond what I could have ever dreamed and the mothers that are involved and on the board are incredible. Their time, dedication, skills and experience goes far beyond what I have ever been able to give. However, I made a strong promise that I would do whatever I could to get GAMT added to newborn screening, so that no parent ever had to go through what we did and so that every child could be given a future as bright as John's future, so here I stand before you today.

This is my story. These are the moments, good and bad, that have taken my breath away. It's not John's story. John is typical boy that can run and play. He has friends, he goes to gymnastics class, he plays soccer, he gets 100s on his spelling tests and he reads books. He has achieved more than I ever dreamed. He had to work hard to overcome his delays since he suffered 13 months of brain damage, but he did it and I couldn't be prouder. He has to take medicine and has a special diet, but so do a lot of kids these days. This diagnosis will not define John and his story. He may have his own ups and downs in life, but GAMT will not define John. John is the most loving and compassionate kid. He is full of hugs & kisses and I can't get enough of them. After all, at one point I didn't know if I would ever get them or hear the words "I love you" from him, but I have it all. I got it all.

Unfortunately, until GAMT is added to newborn screening, not every parent and child will be as lucky. John was diagnosed at 13 months old and has made a complete recovery. He has a normal life with no scars from the past. When children are diagnosed at a later age, they have brain damage that causes seizures, difficultly speaking, difficultly walking.... and the list of negative outcomes only gets longer. You get the opportunity to vote for more futures like John's. You get to vote for more children to have a future that is not defined by the 4 letters GAMT, but instead by what they want to make of the future for themselves. Those children will be able to grow up with a life relatively unaffected by GAMT and will be able to experience life to the fullest. And hopefully, just hopefully, life for them will be filled with all those good moments that take your breath away!

Missy Klor

Mom of GAMT child

April 25, 2016

Dear Advisory Committee on Heritable Disorders in Newborns and Children,

I have a son with GAMT deficiency, and I am writing today in hopes that you will vote to move GAMT forward toward ultimate inclusion on the RUSP. My son Ryan was diagnosed right before his third birthday. Prior to diagnosis he had global developmental delays and no speech. Around 2 ½ years of age, he started having seizures, which we learned were occurring as frequently as one per minute on EEG. He was diagnosed with Myoclonic Astatic Epilepsy, and tried two different seizure medications and the Ketogenic Diet with very little improvement. Around this time he started to fall frequently and his legs were covered in bruises. Ryan's neurologist was suspicious for a different genetic disorder, and she ordered a genetic epilepsy panel which sequenced 70 genes. This panel just happened to include GAMT, and to everyone's surprise he tested positive.

Even before I was a "GAMT mom," I was (and still am) a genetic counselor. As you can probably imagine, I've spent a lot of time thinking about how I could have missed this diagnosis in my own child. The thought certainly crossed my mind that Ryan could have "something genetic" causing his delays, but I reasoned with myself that a genetic diagnosis would be unlikely to change his medical management. I am embarrassed to admit it now, but I truly believed that all of the most treatable conditions were already included on the Newborn Screen, especially in a state like New York! So instead of genetic testing, I tested for lead. One day, it occurred to me that the painted tapestry over Ryan's crib might be a source of lead paint. It was a gift from a friend who had traveled to Africa. I was absolutely heartbroken thinking that my son might have lifelong disabilities due to a PREVENTABLE cause. I realized at that moment that I am completely okay with having a child with special needs; I love Ryan with all of my heart and I truly feel honored to be his mom. However, it was the *preventable* part that made me feel so sick.

Ryan is now almost 5. He remains far behind his fraternal twin brother in his abilities, and I know that he will continue to struggle due to brain damage sustained during his first three years of life. However, I am also well aware that he is one of the lucky ones. With creatine, ornithine and sodium benzoate treatment his seizures stopped within two weeks, and he is now talking in short sentences. He can communicate his wants and needs. Undoubtedly, there are a lot of other GAMT patients out there seizing, wheelchair bound and unable to speak due to lack of a proper diagnosis. The thought of this haunts me every day, and this is why I am writing to you.

I ask that you please vote to move GAMT forward for inclusion on the RUSP. It is a universally devastating disease, but development is normal when treated from birth. Treatment is extremely safe and inexpensive. It is a perfect candidate for Newborn Screening!

Sincerely,
Laura Martin

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Duke University School of Medicine
North Carolina

Dr. Denise Morita, M.D.
Pediatric Neurologist
Granger Medical Clinic
Riverton, Utah

April 20, 2016

To: The U.S. Department of Health and Human Services
Advisory Committee on Heritable Disorders in Newborns and Children.

Re: Guanidinoacetate Methyltransferase Deficiency (GAMT) addition to the National
Recommended Universal Screening Panel (RUSP).

Dear Committee Members,

Guanidinoacetate Methyltransferase Deficiency (GAMT) is a Creatine Deficiency Syndrome that is a **treatable** neurological disease. Unfortunately, babies and young children that have this disease do not get diagnosed early enough, or not at all. Without early treatment, they will suffer brain damage, which includes seizures, language impairments, developmental delays, and movement disabilities.

Without the proper diagnosis and available treatment, these children will grow to be adults needing life long care from others and will require government aid. These babies deserve a future life of independence and to be productive citizens.

It would be heartbreaking to not include GAMT in the national RUSP for early treatment.

I am a mother of an adult son with a creatine deficiency. I have spent 20 years advocating for children. I have no humility in this plea. **These babies need your recommendation, your vote for a healthy, productive, independent life.**

Again, they deserve nothing less.

Please vote to recommend and include GAMT on the National Newborn Screening Panel.

Thank you for your support.

Linda Cooper
ACD Founder, Trustee
Mother of a 21 year old diagnosed with Creatine Transporter Deficiency at age 9.

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Dr. Denise Morita, M.D.
Pediatric Neurologist
Granger Medical Clinic
Riverton, Utah

April 25, 2016

To: Advisory Committee on Heritable Disorders in Newborns and Children

Dear Committee Members:

I am writing to you as the mother of two children with GAMT. My daughter Samantha, who is now 12, was diagnosed at 5. My son Louis, who is now 4, was diagnosed at birth.

The first point I would like to make is that GAMT babies do not look different from any other children. There are no dysmorphic features or other tip-offs to immediately know that GAMT is present. Without a newborn screening there is no way to know that a child has GAMT and brain damage will begin immediately. Physicians and parents slowly begin to notice the symptoms of that brain damage increasing before the alarms start going off and most often it is too late at that point.



Sam- age 1.



Easter 2016, looking for eggs at noon after a morning seizure kept her in bed.

Secondly, the symptoms are very similar to other disorders. Every GAMT family I know has an initial misdiagnosis. For Samantha, the symptoms were slow to develop. She appeared so very “normal” for quite a long time. It wasn’t until she was around 2-½ that I started getting nervous at her lack of speech. At 3 she was diagnosed on the autism spectrum “by one point”. They explained that if she had scored one point lower on the autism test, she would simply be considered “developmentally delayed”. This was obviously no help to her. Every special ed preschool teacher, speech therapist, and occupational therapist Sam had would make comments like “She is really special. She is so bright. There is a light in her- I can tell she is going to really take off soon. Einstein didn’t talk till he was 3, 4, 5...” And that is how I felt for years. I held my breath, waited for the sudden improvement, but slowly her world grew darker.

At 5, Sam began having absence seizures. We went to a neurologist, did an EEG, and he said “Yup. Those are seizures! Let’s do an MRI just to make sure there isn’t a tumor or something

going on causing these.” According to the neurologist’s P.A., she suggested at the last minute to also run a spectroscopy. The absence of a creatine peak on that last-minute test is what finally led to a correct diagnosis of GAMT. Luck stepped in and helped change Sam’s course in life a bit. Without a newborn screening, the only way a GAMT child gets treatment is brain damage being done, and manifesting in ways that look like Autism, Cerebral Palsy, and Mitochondrial Disorder and then luck stepping in that a physician has heard of GAMT and thinks to run the additional testing for it.

When Sam was diagnosed, she was developmentally at about an 18 month old level. She could say maybe 10 words and sounded like a young toddler. “Mom” was “Muh”, “Duck” was “duh”, etc. With a LOT of work she was able to be potty trained just before she turned five. Nothing came about easily for her. With all of her challenges, it turns out she was actually ahead of many other GAMT kids at the same age who are so weak and have such extreme movement disorders that they must be strapped upright in wheelchairs so they can sit up.

Her pediatrician never suggested blood work or referred us out for specialist help except for autism testing, and then the neurologist when the seizures kicked in. I could choose to be bitter but honestly, I think she looked like so many other kids with autism that he was seeing. No symptoms stood out. Diagnosis for a GAMT kid is 100% luck right now. A full life or a life of misery is currently left to chance. I am certain that there are children living with an autism diagnosis who actually have GAMT deficiency.

After about 9 months of treatment, she could plug those final consonants on “Mom!”, “Duck!”, and could string together 3-4 words. “More juice Please”. Her “recovery” has slowly continued ever since. I have paid for costly home therapy programs- doing cognitive training, speech, math, and reading activities over and over. I have done everything I can think and afford to do to help her. For two years I kept her at home to homeschool her and push her forward, always hoping that because we had fixed her metabolic deficiency she could fully recover. Now at the age of 12 and finishing sixth grade she is in an all day special education classroom with the classification of “Intellectual Disability”. It took ten years, but she has learned to ride a bike. She reads and does math at an upper 1st grade- lower second grade level. She has intractable seizures. She has some pretty big mood swings and obsessive behaviors like picking at the same pimple till it bleeds for weeks and turns into a permanent scar. She shouts sometimes in public and melts down on the floor in the grocery store leaving us both in tears and going home to recover. She can’t wash her hair or brush her teeth well enough on her own to be healthy and clean so I help with both. She does not play with other children. At recess she walks around the playground and observes. She talks about friends, but doesn’t really understand how to have a friend. GAMT therapy has helped her improve. Her life could be worse. I am thankful for her diagnosis. But things could have been SO much better.

Knowing that we had GAMT in our DNA, we paused our family for a few years. Finally we decided to play the odds in 2011. Sam was 8 when Louis was born. I still had a lot of hope for extreme change for her and thought that with the 75% chance Louis wouldn’t have GAMT we were safe. I was wrong.

Days after his birth we received the bad news. I was wracked with guilt for having “done this to him.” Louis began taking his creatine, ornithine, and sodium benzoate four times a day. It tastes awful and it was a bit of a battle at first, but after a month or so he understood it was necessary to take before he could eat and he has been compliant ever since. That has been his treatment since birth. So simple. Some doctors debate on the need for a low protein diet, but he has only been restricted to a normal RDI of protein. In other words, no seconds of the main course at meals. No big deal! Our insurance covers his supplements under the Utah state guidelines of “medical foods” but even without insurance, at his current size his supplements would only cost \$0.55 per day (Sam is about \$1.95 and she is nearly full grown at 135 pounds!). Treatment is affordable and simple.

After years of working with Samantha, and raising a typical daughter and son in between Sam and Louis, I have some pretty keen eyes as to what is normal and what is not for children. Because of this, I have no doubt that treatment from birth for GAMT deficiency is 100% effective. Louis is imaginative. He is constantly initiating pretend play. He sings songs in tune with all the words pronounced correctly on his own. He learns ON HIS OWN. He picks up a crayon, sounds out the word “MOM” and writes it. He does not need therapists to explain how to use his legs, hands, and mouth. He has good muscle tone with no interventions. He makes jokes. He makes friends. He does not have seizures. He does not go to a special preschool. His preschool teachers report he is not only able to keep up and often surpass others academically, but he is the most liked child in the class. In a recent cognitive testing he received “typical” scores. I did not need this test to know that he is going to have a full and productive life.



I understand that this disorder is relatively new and so I can't be bitter for the loss of Samantha's chance at a full life. Everyone has done “their best” to help Sam. I understand that a new disorder takes time to understand, to develop therapies for, to develop technologies to detect, to educate the medical community about.

I firmly believe that GAMT is ready for newborn screening. It is now time to do “your best” for those families that trust in the system; that believe these types of treatable disorders have been ruled out when their child has had their screening done. If we fail to act now, parents will have the right to feel bitter.

The treatment works and is affordable and simple. The screening works. The consequences of not diagnosing are devastating. Newborn screening is the only solution. It is the only way to diagnose all of the children being born with GAMT early enough to save them. The population of GAMT patients exists. Even with the difficulty of differentiating GAMT from Autism and other disorders, our numbers continue to grow. There are GAMT patients in institutions carrying the wrong label, I have no doubt. Please help us end this. Please, please do not let another baby’s healthy brain begin to grow dark. Please help their families live normal lives where the parents can both work, the children can play and enjoy their siblings. Please do the right thing.

Please contact me with any questions you might have.

Regards,

Heidi Wallis

801-712-8826

heidi@creatineinfo.org

hwallis@gmail.com

3338 Tucannon Cove

Bluffdale, UT 84065

April 9, 2016

To whom it may concern:

The Association for Creatine Deficiencies will be putting together a cost analysis for children who are diagnosed with GAMT at birth, and those that are not. We are still putting these statistics together, and I will submit before the deadline at the end of this month.

If you have any questions, please don't hesitate to contact me.

Sincerely,

Kim Tuminello
President, Trustee
760-688-8032
Kim@creatineinfo.org
Association for Creatine Deficiencies Board of Trustees

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Duke University School of Medicine
North Carolina

Denise Morita, M.D.
Pediatric Neurologist
Granger Medical Clinic
Riverton, Utah

"I am a physician that works with children with GAMT and similar deficiencies. Picking up this disorder as early as possible and ensuring access to the appropriate treatment actually prevents progression and assists these children in being the healthiest they can be. I have seen that early detection and treatment stops very hard to control seizures, improves developmental and cognitive outcomes and prevents irreversible brain injury."

-Inna Hughes, Rochester, NY

"My son has Creatine Transporter Deficiency. It would have saved a lot of stress and heartache if we were to find out when he was a newborn as opposed to 4 years old. I fully support creatine deficiencies!"

-Kelly Shedd, BRIGGS DALE, CO

"So important to raise awareness and to get states to act. Read a March Forbes article on the role of RUSP to guide states' newborn screening programs. Glad to see this petition for GAMT."

-Lynn Amer, Austin, TX

"My son wasn't diagnosed with GAMT until he was 4 years old."

-Laura Eger, Grosse Pointe, MI

"I have a son with GAMT deficiency who was not diagnosed until right before his 3rd birthday. He has a history of medically intractable seizures, which stopped with proper treatment. However, he continues to struggle with global developmental delays due to brain damage sustained prior to diagnosis. I am signing because I want to ensure that future children with GAMT can benefit from early diagnosis and treatment!"

-Laura Martin, Penfield, NY

"I have a son with Aspergers/Autism. We had to fight for screening at age 8, any early intervention was lost. Please pass the law for early screening of GAMT, another family should not have to suffer or fight for a diagnosis or services when it is too late."

-Megan Churchill, Le Roy, NY

"I know a child with this disease. Can there at least be an option to choose testing for one's newborn?"

-Katie Strike, Cincinnati, OH

"My friend's children have GAMT."

-Sara Snow, Austin, TX

"Because I care and this is a solution"

-Sharon Reeder, Aliso Viejo, CA

"An ounce of prevention is worth a pound of cure - especially one that comes too late."

-Heather Harper, Mississauga, Canada

"Early detection is key. Let's do this!"

-Chris Anderson, Sandy, UT

"What a difference this will make in so many lives - and if you are not moved by the humanitarian value or that, think of the immeasurable cost savings throughout each child's lifetime!!!"

-Amanda Byron, Portland, OR

"I have a colleague whose children are effected and could have been treated if detected in time."

-Aubrey Cowan, Salt Lake City, UT

"Easily detectable and preventable! As stated, the cost is less than \$1 per child, but the reward is priceless."

-David Forsythe, Salt Lake City, UT

"I have a friend who's child's life would be easier if this were a GAMT screening at birth. DO IT!"

-Rich Rasmussen, Sandy, UT

"I have friends where this has been an impact / will be an impact"

-Tricia Spangler, San Diego, CA

"This could save families a lot of heart ache."

-Lorie Sousa, Encinitas, CA

"I know two great kids that have benefitted from this."

-Eric Hernandez, Carlsbad, CA

"It's ridiculous we're not already testing for this. What a simple thing to do to save a life."

-Kristin Cooper, Carlsbad, CA

"My friend, Kim Tuminello"

Heidi Murphy, Austin, TX

"I'm signing because I'm a mother who would do anything for her kids... And for kids everywhere."

-Sarah Linn, Atascadero, CA

"It needs to be done..early on"

-Barbara Phillips, Deweyville, TX

"A simple test that answers questions and possible saves lives"

-Danielle Caniglia, San Diego, CA

I'm signing because Ty and Paige Tuminello's prognosis would have been devastating if they hadn't been diagnosed and every child deserves the chance to receive an early and treatable diagnosis!!!

-Meredith Parra, Carlsbad, CA

"It is an important cause"

-Kevin Keene, Irvine, CA

"This screening is needed!!!! It will give so many kids the quality of life they deserve by a simple test!"

-Shanna Johnson, Encinitas, CA

"I'm signing as I believe in this cause. Thank you Kim."

-Mark Richardson, Mission Viejo, CA

Because early detection makes an amazing difference in the quality of life for those affected.

-Adam Tschop, Carlsbad, CA

"I am a medical geneticist who supports early diagnosis of treatable diseases."

-Emily Doherty, Daleville, VA

"I feel this is very important and can prevent our future from suffering."

-Rob Robinson, Saint Simons Island, GA

"In support of awareness and early detection."

-Tracy Miceli, Scottsville, NY

"There is nothing to lose, and so much possible gain to running this simple test! It would prevent so much pain and heartache, for all of these young babies!"

-Leisa Barlow, Noble, OK

"I'm signing because I know 2 precious children with this disorder and I believe that newborns should be tested!"

-Meredith Mitchell, Stuttgart, AR

"I'm concerned and excited that this test can help so many children"

-Donna Pigg, Austin, TX

"We have loved ones with Creatine Deficiency Disorder. Luckily the children were diagnosed as infants. They are leading normal lives. Those who haven't been diagnosed are unable to speak and will never care for themselves or enjoy all that life has to offer."

-Jennifer Doogan, Carlsbad, CA

“Newborn screening for diseases like GAMT impacts quality of life and reduces financial burdens to families and the general public.”

-Steve Strauss, Driftwood, TX

“My cousins son was diagnosed with this”

Jeff Turton, Durham, NC

“I am a nurse in genetics and metabolism”

-Cheryl CLow, Hudson, NY

“All children should have the right to be healthy and reach their fullest potential.”

-Stephanie Laniewski, Rochester, NY

“My sister's oldest child has GAMT and it went undiagnosed for quite some time. She has issues that she will never recover from and as a result will more than likely spend her adult life living with her parents. My sister's youngest however was tested at birth and GAMT was diagnosed, they were able to treat immediately and he has no problems.”

-Brent Kelley, Grand Junction, CO

“Children are our future. Be an example of who they need to be.”

-stu hoskins, Pella, IA

“My son has a creatine deficiency and early detection is crucial”

-Jessica Armour, Australia

“As a healthcare worker I often see too many times that corners are cut and that profit is the primary motive for healthcare.”

-Kirk Kingery, Salt Lake City, UT

“I know someone affected and therefore know the positive effects of early testing and intervention!”

-Danielle Donovan, Livonia, NY

“We shouldn't need a petition for this, the decision should be obvious!”

-Brandy Anderson, Meshoppen, PA

“My sister has two GAMT children, one who had late treatment, and one who had treatment after birth.”

-Benjamin Whiting, Telluride, CO

“My son has creatine transporter deficiency. He was not diagnosed till he was 4. And had about 5 epileptic seizures before we found out what was going on”

-tony mcreary, Swansboro, NC

"To show my support and advocate for this worthy cause."

-Rhonda Andrew, El Segundo, CA

"Newborns should be given the best chance possible of living a beautiful, whole life."

-Stephanie Sparkman, Midland, TX

"I have seen personally how this has affected the family."

-Laura Knox, Honeoye Falls, NY

"This relatively small step could spare children and families future despair."

-Kamal Amer, Austin, TX

"For a simple blood test that can be added to the already many bloodwork samples we do while pregnant, this seems irresponsible to not be included. The cost is less than \$1.00 and the cost to treat these misdiagnosed children must be much more than that."

-Jodi Chamberlain, Trabuco Canyon, CA

"Because I am an RN"

-Jamie Pair, Bakersfield, CA

"A friend's child was screened and diagnosed soon enough to make a difference. Would like to see this available to others."

-Vicki Pyle, San Marcos, CA

"Shouldn't have to ask why!!!"

-Hannah Kromka, pine knoll shores, NC

"The families affected by this condition need a proper diagnosis ASAP.... Delays in diagnosis and treatment result in unnecessary and preventable problems."

-Steve Logar, Elyria, OH

"I have a nephew with this and believe all children should be tested at birth."

-Kathi Snyder, Indian Land, U.S. Outlying Islands

"My grandson has this. He was diagnosed too late. One simple blood test would prevent the daily struggles that the child and family goes through."

-Pam Snyder, Briggsdale, CO

"This is a good cause."

-Mary Akerley, La Grange, IL

"Because it is save many heartaches"

-Rebecca Pobanz, Geneseo, IL

"I have 3 boys with CTD and if early testing helps find cures faster i am all for it."

-Michael Gardner, Kansas City, MO

"Why not sign if it saves our children"

-Cindy Wilkins, Arroyo Grande, CA

"It is important"

-Maria Trefogli, San Carlos, CA

"I am a cognitive neuroscientist and have become aware of this disorder through the association of creatine deficiencies. Through them, I have seen their studies and their tremendous progress in creating awareness for early detection. I agree with and support the necessity for getting this approved for newborn screening!"

-Stef Von Huben, Carlsbad, CA

"Someone I love was diagnosed"

-edward davis, Wilmington, DE

"This is so important!!!"

-Tiffany Rogers, Encinitas, CA

"This is an easy low cost solution to a disability that threatens families and the potential productivity of their children at an untold cost to society. It just makes sense to make this testing required."

-Katherine Doolittle, Nevada City, CA

"I'm a mommy and I would want to know and be able to give my hold the best he/she had!"

-Jill Geib, Buffalo, NY

"I'm signing because I want proper diagnosis for the illness so patients can receive the correct treatment."

-Patti Riggs, Austin, TX

"I'm signing because I believe this should be included in the testing of all newborn babys."

-Frances Billiot, Sulphur, LA

"Prevention is everything"

-Lorin Smith, Ridgecrest, CA

"My friend's grandson has this syndrome and realize the importance of early detection."

-Yvonne Wiggins, Scottsville, NY

"To raise awareness"

-Kara Collins, San Marcos, CA

"In support of a friend and her Family"

-Joel Shaw, Omaha, NE

"This needs to be recognized!"

-Jennifer Stone, San Marcos, CA

"This test needs to be done on every newborn!"

-Josette Choate, Bridge City, TX

"Good screening now means fewer problems later."

-Brenda Bradford, Palmyra, NY

"Because of the fact if there is a slight possibility of being detected early, it could clearly save a life."

-April Martinez, Vidor, TX

"Two of my grandchildren have a creatine disorder and I want to see more research and help for them all children born, undiagnosed and living with the effects of not receiving treatment for something that absolutely can be controlled."

-Linda Wallis, Cincinnati, OH

"My nephew Reid Strauss"

-Wade Worsham, Houston, TX

"this is a very important screening that will help many children"

-Pat McClelland, Little Rock, AR

"I'm signing because of my nephew."

-Nicole Klor, Republic, MO

"I am signing this because I understand the incredible value of this simple newborn screening in detecting GAMT deficiencies to allow early treatment. This is an obvious choice that this screening should be part of the RUSP."

-Stephanie Joo, Carlsbad, CA

"I am signing because I have 2 children with GAMT. Early diagnosis is the key to a healthy life!"

-Grant Tuminello, Carlsbad, CA

"It's the right thing to do!! Why wouldn't you do it if it could prevent children from having this issue."

-Cheryl Linscomb, Orange, TX

"I love my two baby cousins that were diagnosed with this! I hope that future parents will be able to know early and treat! I love you Ty and Paige!"

-Lauren Burns, Monticello, AR

"As a teacher of elementary children, the numbers of children being diagnosed with autism has increased exponentially in the past 16 years. As educators, we wonder what causes this and how we can best support children who are neural atypical. Hearing I'd this, though, makes me think that perhaps not all cases have been diagnosed correctly as Autism. Perhaps this type of early screening can eliminate the heartbreak and correctly diagnose our children!"

-Monica Mathers, Costa Mesa, CA

"My friend's grandson was born with this deficiency."

-Alexander Nancy, Granite Falls, NC

"My friend's grandson has this disorder. He is being treated and is living life symptom free."

-Laura Boldyrew, New Bern, NC

"I want this testing done on every child at birth."

-Cindy Beebe, Orange, TX

"My son is diagnosed CTD and could have been diagnosed much earlier in his life."

-Rodolfo Mier, Spring, TX

"It's a great thing for our children"

-Pam Vandenberg, Roy, UT

"I have kids & want them to have this option when they have kids!"

-Becki Pinckard, Chandler, AZ

"Getting the correct diagnosis EARLY is crucial for the lives of these children."

-Aimee Khan, Carlsbad, CA

"All children deserve a chance for a happy productive life."

-Colleen Horodnik, Bridgewater, NJ

"My grandson has this condition and early detection has helped getting him the services he needs to make great gains in all areas."

-Antoinette Abdo-Whelpton, Scottsville, NY

"if you can find something early to treat, then we should"

-suzanne hayles, carlsbad, CA

"I strongly believe that there should be newborn screening for GAMT."

-Kristen Heeres, Phoenix, AZ

"I know 2 children now leading a normal life due to early treatment. Happy!"

-Gail Carroll, Carlsbad, CA

"It is my understanding that an early screening blood test could prevent years of brain damage as children are worked through the process of eliminating other causes of their problems."

-Judy Rhodes Davis, Pelahatchie, MS

*****"My cousin's son has this...why would we not screen for something that is treatable and can change someone's life?"***

"Our nephew has this."

-Carol Potter, Montrose, PA

"When a simple blood test could diagnose this disease and prevent irreversible brain damage why in the world would anyone not make it available do all newborn children."

-Vickie Turner, Morehead City, NC

"I'm a pediatric neurologist and would love to see children with treatable conditions identified as early as possible so they can lead normal lives. I have seen children identified too late and by then the damage is irreversible."

-Guillermo Philipps, Estero, FL

"My nephew has GAMT and is now 7 living a normal boy childhood as he should- only thanks to the people who fought to diagnose him with this disorder versus Cerebral Palsy which I'm sure so many are diagnosed with on a daily basis!"

-Mad Furtner, Pine Knoll Shores, NC

"Someone I love has been impacted by this condition."

-Cassandra Maglin, Fort Rucker, AL

"I'm signing because I'm a witness to the difference early detection/diagnosis can make. Screening will make a huge difference in the lives of children and their families."

-Carolyn Johnston, San Marcos, CA

"Early detection is the key."

-Beth Wert, Mountain Top, PA

"We have a family member with Creatine Transport Disorder and would like to do our part to help bring awareness to these types of diseases."

-Jill Strauss, Corpus Christi, TX

"My daughter, 13 months, has one GAMT mutation. By the textbook you must have both genes mutated to have the disorder, but clinically she fits. She has seizures, developmental delay, and a movement disorder. Although anticonvulsants have stopped the seizures she is still only developing at half time and appears to have several movement disorders. We are hoping to start the creatine diet, but many obsticals have delayed the counsel we need to begin. I worry daily as I know the longer we wait the potential for a decrease in quality of life is high."

-Keszia Hale, Dunnellon, FL

"Family friends son has GMAT"

-Leanne Coppola, Wall, NJ

"This is a condition that if found early can make the difference in a child's life and their family. It is simply commen sense and necessary."

-Tara Perrotti, Manchester, NH

"I care. Every child should have a chance to be normal."

-Maureen Niescierenkoh, Rochester, NY

"My cousin got this"

-Asimah Ilyas, Oslo, Norway

*****Fordi min fetter har denne sykdomen og hindre at andre skal ikke få.**

-Rafia Yaqub, Oslo, Norway

"All children deserve our best efforts to assure their health. A tiny investment that will unimagivable dividends for the child, the family, the community and society At large."

-William LaCourse, Alfred, NY

"I care and support early detection"

-Susan Miller, Spencerport, NY

"We can prevent this disease from taking hold!"

-Stephanie Wallace, Carlsbad, CA

"Because I believe children deserve that chance to be healthy if there is anything we can about it."

-Sarah Smith, Brandeis, CA

"I have seen what a miracle early screening accomplishes."

-Kathy Furtner, Pine Knoll SHores, NC

"So more children can be diagnosed and treated."

-Sherry Worsham, Orange, TX

"It is important to find out early and get some treatment for it. It will help save lives.."

-colleen mahoney, Wilmington, DE

*****Vince Haygood, Belden, MS**

"I am a mom and this is something I believe in!"

-Michelle Wilton, Oceanside, CA

"My niece was diagnosed at the age of 13. So much pain and suffering could have been prevented if tested at birth."

-Lori Lundeen, East Peoria, IL

"I know a child who has this condition."

Donna Hunt, Forest, MS

"My 13 year old daughter was diagnosed last year at St. Louis Children's Hospital by our hero , Dr. Judith Weisenberg with GAMT..She was misdiagnosed for 10 years by various specialist and doctors. Her condition worsened to the point she went in self induced coma for 18 days after being airlifted with uncontrolled seizures. GAMT is definitely treatable as we have seen vast improvement in our daughter and she has not had one seizure since proper diagnosis and treatment. Unfortunately, since she was misdiagnosed with Autism for so many years, it is likely she will still have limited life skills. We pray this is passed so other parents have a better outcome . Such an easy and inexpensive test it is a "crime" not to be included. I could go on and on."

-Jennifer Lundeen, Bentonville, AR

"Early detection is simple and easy. Signing for John Klor, who was misdiagnosed but thankfully it was caught early enough he could receive treatment. Now he is a bright, healthy little boy."

-Jenny Glass, Wilmington, NC

"I'm signing because people I care about deal with gamt everyday."

-Christina Reilly, Bethlehem, GA

"All kids deserve a fair chance, and this simple test will help so many!"

-Pam Redela, Encinitas, CA

"GAMT deficiency is a treatable condition detectable by current NBS methods"

-Sarah Young, Durham, NC

"This is a simple test that can save a child from a misdiagnosis and treat them effectively!!"

-Heather Malloy, Chandler, AZ

"This is a major problem for this next generation."

-Jacque Baker, San Marcos, CA

"I have a great nephew who has been diagnosed....I care!"

-Lori Miller, Stanley, NY

"Committed to newborn screening"

-Sandra Baucom, Chesapeake, VA

"My 2nd cousin has this disease and I want to help save so many children!"

-Cindy Tillman, Rochester, NY

*"Sometimes G-d has a lot on his plate and needs help. Lets give him the help he needs.
SHARE"*

-Albert Luppo, Brentwood, NY

"A simple blood test can improve lives!"

-Catherine Kelley, New Albany, OH

"I believe in this cause!"

-Deanna Dolan, North Las Vegas, NV

"I have a child in my daycare who has this disease and would love to see more research on it"

-peggy zugie, Wilmington, DE

"Our children are important!"

-Lauren Queener, Clinton, TN

"This is so simple and could help so many."

-Carmen Polk, Pelahatchie, MS

"Because it can save children from being delayed and save lives!!"

-Meagan Foster, Newport, NC

"Let's help newborns and their families. For the Tuminello family"

-Renee Robison, Sherwood, AR

"Because this is so SIMPLE to add to newborn screening, it's a no brainer and will save so many lives! It must be done!"

-Mary Jo Finley, San Diego, CA

"I am a pediatric nurse practitioner who has seen this illness first hand through my cousin's son. We test for so many other uncommon but life threatening diseases through newborn screening, this one is equally important."

-Juli Granica, Hampton, VA

"Because it is the right thing to do!"
-Sheila Hogan, Santa Rosa Beach, FL

"On behalf of a grandchild with mitochondrial disease."
-Maggie White, Belden, MS

"For my nephew"
-Cindy Boyles, Greenville, MS

"My niece has this disorder"
-Sarah Cochrane, Wilmington, DE

"I believe in this."
-Rachel Malone, San Diego, CA

"Can save children from being untreated or treated too late"
-Susan Bishop, Newport, NC

"I have a grandson with GAMT"
-Nancy Williams, Saltillo, MS

"We need to protect the bases born with this disease and they deserve the right to a good life!!"
-Michelle Mora, Carlsbad, CA

"I'm signing because my son's best friend was diagnosed."
-Erica Reed, Woodstock, IL

"To help more children like our precious, Will Parker."
-Patty Till, Pelahatchie, MS

"My cousin is diagnosed"
-Rabeeah Aslam, Bolton, United Kingdom

"My Cousin's children will benefit from this as well as soooo many other children."
-PH Bean, Harrison, AR

"I wasn't even aware of this disease until a member of my family was diagnosed with this. So much precious time went by. Hopefully awareness will save others the heartache of not knowing what is wrong with their child"
-Kathryn Edwards, Clifton Springs, NY

"Although rare, diagnosis can be life changing and why not? It is a simple blood test!"
-Cynthia Roods, Webster, NY

"I'm signing this because of my two beautiful grandchildren who both GAMT. My grandson was the first diagnosed in the United States. The heartbreak we went through before GAMT was found could have been avoided with newborn screening."

-Sherry Tuminello, Stuttgart, AR

"We know Kim Tuminello and her children. We have followed her struggle to find out what was preventing her son Ty to thrive and develop normally during his first year of life! She NEVER gave up seeking help and praying. As a result, Ty is doing well and his sister was screened prior to birth. She, too, tested positive and received treatment early so thankfully is doing well now, too. These two children are doing well BECAUSE they were treated early and because they had a loving mother who was determined to seek an answer and find help for her children. How wonderful would it have been if a simple blood test at birth would have been available then! But now there is one!! For less than \$1.00 per child, this newborn screening test can save many children from the effects of GAMT!!"

-Patricia Stolk, Chesterfield, MO

"This is such a simple and necessary solution to saving quality of life for many children and families. As a mom, and educator, I fully support this cause and hope you will too."

-Cathrine Osthimer, Carlsbad, CA

"I am signing this because my Grand daughter was diagnosed with GAMT in March of 2008. She is now almost 9 years old."

-Adele Hornshaw, Fort St John, BC, Canada

"I'm signing because this screening would help so many families."

-LaLisa Lindemann, Vicksburg, MS

"This testing is so important, we all should get on board!"

-Nathan Vandenberg, Raeford, NC

"This is the right thing to do and all children deserve the best treatment and early diagnosis."

-Nancy Flad, Penfield, NY

"One simple test can dramatically change the life a child"

-Kathy Hales, Milford, OH

"For a friend who's son has a creatinine deficiency."

Blake Hill, Belden, MS

"My nephew's second child has this disorder."

-Caryne Prater, Pipe Creek, TX

“Both of my children have GAMT also. My son was not diagnosed until he was 10 months old and has had to endure years of several different kinds of therapy. My second child (my daughter) was diagnosed and treated immediately, and she has never been to a day of therapy in her life. This is exactly the type of disorder that should be put on Newborn Screening. It is literally saving lives!!”

-Kim Tuminello, Carlsbad, CA

“My son suffers from the nontreatable form of this Creatine Deficiency Syndrome. How can you not support this if it can be treated? In fact, how can you not support any testing that gives parents an idea of what they are up against? This is so very important for our community. Won't you please support this?”

-Melissa Parker, Morton, MS

“I lost a daughter to a mitochondrial disease.”

-Norma Gibson, Ukiah, CA

My Nephew has this illness..i want him cured..

-sajida Ashfaq, Bolton, United Kingdom

“I have 2 children with GAMT. One began treatment at 1 year old, the other at 6 years old. The one who was able to begin at 1 year old has a much different future than the one who began at 6 years old. Early treatment makes all the difference. Give all children the same opportunity by diagnosing and treating early.”

-Beth Robinson, Oswego, IL

“My daughter has GAMT, I think it would be so great to see this added to the newborn screening panel!”

-Shayla Hornshaw, Penticton, Canada

“This disorder is 100% treatable. My son has been treated since birth and scores as “typical” on cognitive testing. My daughter wasn't caught until 5 and she is diagnosed as in a special education classroom and will likely not be able to live independently and need care for the rest of her life. Treatment is affordable, easy and 100% effective. This will change many children's lives.”

-Heidi Wallis, Herriman, UT

“My stepdaughter was diagnosed with gamt at 8 and maybe if it had been sooner she could be living a normal life as a healthy child. She now has a feeding tube and can't speak and has several other issues caused by not being diagnosed and treated as an infant. We all love her the way she is but it is hard to imagine what she is feeling or thinking without her being able to

express herself. Hopefully this screening will let other children grow up without having the difficulties my daughters family has and continue to face.”

-Jenny Santana, Darlington, PA

“My son has a creatine deficiency.”

-Linda Cooper, Newport Beach, CA

“A friends daughter has this”

-Lisa Irwin, Wilmington, DE

“It is important to be able to help these babies, with this program in place!”

-Patti Goodell, Bountiful, UT

“My son has GAMT and went the first 18 months of life undiagnosed and untreated. He did not meet typical milestones and then started having seizures. This heartache is preventable. PLEASE help these kids have a good start and chance at life! Thank you!!”

-Laura Ward, Ogden, UT

“Our friends have grandchildren that suffer from this.”

-Scott Barrick, Draper, UT

“I know this is a good target for newborn screening because it is readily diagnosed with existing tandem mass spectrometry methodology, and most importantly, because early intervention can dramatically improve neurodevelopmental outcome.”

-Bruce Barshop, La Jolla, CA

“Everyone deserves the best possible shot at a happy healthy long life. I signed because it's a non invasive quick test that could help give a better quality of life to those diagnosed/affected with/by a GAMT deficiency.”

-vanessa perryman, Gilbert, AZ

“I care about this cause. It has touched lives very close to me”

-Dianne Bierman, Del Mar, CA

“My daughter has severe developmental delays, she sees a speech therapist, occupational therapist and will be going into a special education class next year instead of kindergarten.”

-Nicole Bahr, Toledo, OH

“It is immoral to do nothing to diagnose this in infants when an early diagnosis and treatment can have a 100% impact on the quality of life of the child.”

-Laurie Donlon, Morristown, NJ

“Someone in my family has a CD and I want to do what I can to help!”

-Katie Evans, Studio City, CA

"I am signing this petition because I know what a life changing difference it has made in these two young lives. My hope is that more and more parents will become educated and have the same Hope and change for their young children."

-Jennifer Pickard, Carlsbad, CA

"Ty and Paige Tuminello are my nephew and niece."

-Mary Fischer, Stuttgart, AR

"Why not? Lets save lives."

-Robin Sjostrom, Albuquerque, NM

"Someone daughter has this."

Lisa Cosbey, Rehoboth Beach, DE

Early treatment of GAMT Deficiency is effective and affordable



Benny was undiagnosed until 5 years of age. He attends a special education classroom where he requires 1:1 care. He battles seizures, Global Developmental Delays, is nonverbal, requires a communication device, and will need life-long care.

Late Diagnosis



Paige has been treated since birth. She is a 6 year old in the 1st grade, and has never required therapies. She has never needed interventions of any kind and attends a typical classroom. She has never had a seizure.

Newborn Diagnosis

Cost comparison: Newborn Screening and Treatment for GAMT vs. Lifelong Care

Lifelong Costs of Intellectually Disabled, Undiagnosed GAMT patient

GAMT is a Cerebral Creatine Deficiency Syndrome. If not treated at birth, this neurological disorder results in severe physical and cognitive disabilities. In 2003, RTI International and the CDC analyzed data from multiple surveys and reports to estimate the direct and indirect economic costs associated with Developmental Disabilities. On the basis of that analysis, the estimated **lifetime costs for a person with intellectual disabilities is \$1,312,314**. Additionally, a GAMT patient will require mobility and speech devices, and continuous physical, speech, and neurological care due to their condition.

Cost of GAMT Diagnosis through Newborn Screening

According to the Utah pilot study, the cost to check each blood spot, including labor, materials and the extremely rare second tier testing, averaged out to be \$0.49 per spot screened. The Utah pilot projects that the incidence of GAMT is approximately 1:120,000.




We can extrapolate from this that **the cost to identify a GAMT patient is only \$58,800**.

Cost to Treat GAMT when Detected at Birth

Based on current standards for GAMT treatment, a child diagnosed at birth will only require daily oral supplementation of creatine, ornithine, and sodium benzoate. As shown in Figure 1- the total daily cost ranges from less than \$0.93 in early childhood to around \$3.50 in adolescent years.

Total annual cost of treatment is \$339.45 to \$1,248.30.

Figure 1: *Daily cost of oral supplementation*

Cost of Oral Supplements	Daily Oral Supplements	Total daily cost to treat 40 pound child \$0.93 135 pound child \$3.42
<p><u>Creatine Monohydrate</u></p> <p>Available at GNC, Whole Foods, and Amazon</p> <p>\$25.00 for 1,000 grams</p>		<p>40 pound child \$0.23 per day</p> <p>135 pound child \$0.67 per day</p>
<p><u>L-Ornithine</u></p> <p>Available at JoMar Labs.com, nutrabio.com, and other sports supplement stores</p> <p>Appx \$45.00 for 500 grams</p>		<p>40 pound child \$0.59 per day</p> <p>135 pound child \$2.43 per day</p>
<p><u>Sodium Benzoate</u></p> <p>Available at compounding pharmacies and Amazon</p> <p>\$35.00 for 1,000 grams</p>		<p>40 pound child \$0.11 per day</p> <p>135 pound child \$0.32 per day</p>

April 24, 2016

Dear R.U.S.P. Members,

I was a junior in college when I began working at the local "Retardation Center". That is what it was called. It isn't called that anymore. My first encounter there was with a child diagnosed with PKU. Her mom was tired, she was aggressive and mom had no choice but to put her with us. "She bears watching, Melissa," they told me. Bears watching? She was just a little girl?! I was about to get an education in PKU and the devastating effects on her and her family. I was shocked to find out that PKU was a required newborn screening that she had not received. I was horrified to learn that one simple test could have prevented her life in an institution.

Fast forward and I'm 31. A friend has lost her 2 year old to MCAD. Had it been part of newborn screening, he'd be with her today. She started a movement that resulted in Ben's Law in Mississippi. It expanded newborn screening for our state. Why was this important to me? Because, I was sitting in a doctor's office with a child that was not meeting milestones. Nothing was adding up and she pushed me to be his advocate. It was not until he was 12 that I got some answers - Creatine Transporter Deficiency Syndrome. It was not until he was 17 that I found the Creatine Deficiency Community and learned that my life could be much more complicated. CTD is not treatable. I get it. I don't like it, but I get it. GAMT is treatable. I don't get that. Why can't we help those that can live life to the fullest if they have a simple test at birth that answers questions, and gives parents directions and gives families hope where often there is none?

Four letters on one list is all we are asking. We've brought it this far. Let us take it the rest of the way.

Sincerely,

Melissa Parker, Financial Director, Trustee
Association for Creatine Deficiencies

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Assistant Professor, Department
of Pediatrics-Medical Genetics
Duke University School of Medicine
North Carolina

Dr. Denise Morita, M.D.
Pediatric Neurologist
Granger Medical Clinic
Riverton, Utah

To: The U.S. Department of Health and Human Services
Advisory Committee on Heritable Disorders in Newborns and Children.

Re: Guanidinoacetate Methyltransferase Deficiency (GAMT) addition to the National
Recommended Universal Screening Panel (RUSP).

Dear Committee Members,

I am writing to you to tell you about what a devastating impact just a few months can make in a child's life when not diagnosed with GAMT. This Creatine Deficiency Syndrome looks different for everyone, and the chances of the doctors or parents finding out in time are not likely. GAMT is difficult to diagnose because it looks like so many of the other disorders out there, but this is an *easily treatable* disorder that is misdiagnosed, time after time. GAMT is a devastating neurological disease that causes seizures, developmental delays, movement disabilities and requires a lifetime of care if not caught early in life. You see, both of my children have been diagnosed with GAMT. My oldest son was not diagnosed until he was 10 months old, and as a 10 year old today, he still continues to suffer the consequences of not receiving the diagnosis and treatment until then.

Ty has endured years of physical therapy, occupational therapy, speech therapy and visual therapy. When Ty was born, his failure to thrive and global delays were heartbreaking, but as we watched him steadily decline day after day, we knew something had to be done, and quickly. The immediate difference once we started treating with creatine was nothing short of a miracle. I will never forget watching my son stand up, after only taking creatine for 7 days. It was just a few days before as a 10 month old baby, he could not even sit up without support.

Unfortunately, this story is told over and over again by families who have seen their children suffer unnecessarily. There is so much hope with the diagnosis of GAMT, but only if it is caught at the very beginning of life. The RUSP panel was designed for exactly this type of disease, and every future parent is counting on disorders like this being on the Newborn Screen.

Sincerely,

Kim Tuminello

President, Trustee

760-688-8032

Kim@creatineinfo.org

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Pediatric Neurologist
Granger Medical Clinic
Riverton, Utah

April 24, 2016

3338 Tucannon Cove, Bluffdale, Utah

To: the committee members

From: Ellie Wallis age 10

Dear committee members, I wish that every kid could be screened for G.A.M.T. at birth. My sister wasn't diagnosed until she was 5 and it has affected her a lot. If she was diagnosed at birth, my life could have been so much more different. We could have been able to go shopping together, braid each others hair, even sell lemonade in the summer together. But instead, she has seizures in the middle of the night, she has to go to special schools, and she can't express how she feels very well. Louis, on the other hand got diagnosed at birth and it is like he doesn't even have G.A.M.T. He is able to sing songs, play pretend, and do all the things an average 4 year old can do. Sometimes I wish that a magical fairy would come along and sprinkle fairy dust on Sam (my sister) and then Sam would be cured and be a normal sister. I'm not saying that I don't love her, because I love her with all my heart, I'm saying that I wish Sam could go to a regular school and be able to drive a car and go to college and be, well, normal. I would rather live on the moon for the rest of my life and eat dead flies than have any other kid go through what Sam had to.

From,

Ellie Wallis

April 20, 20156

Dear RUSP Review Committee,

Guanadinoacetate Methyltransferase Deficiency (GAMT) is a devastating disease. Children suffer brain damage; seizures, language and cognitive impairments; developmental delay and debilitating muscular issues as a result of toxicity from GAA build up in the brain. The onset of symptoms is immediate and the severity is progressive without treatment.

This disease impacts both patients and caregivers who will spend a lifetime fighting the long-lasting mental and physical effects of this genetic disorder. And while the disease itself is relentless, equally tragic is the knowledge that GAMT is **treatable**.

Today, GAMT patients needlessly suffer with life-long impairments. Parents search years for answers and by then, it's too late. Like PKU and other treatable disorders before them, GAMT is the perfect candidate for newborn screening. If the purpose of RUSP is to save those lives that can be saved, then I, along with the Association for Creatine Deficiencies and nearly 1,000 petitioners, implore you to consider adding GAMT to RUSP. These patients have treatment.

They need you to give them a chance at life.

Thank you for your consideration,

Whitnie Strauss

ACD Vice President, mother of a 6 year old with Creatine Transporter Deficiency
512.563.3188

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Pediatric Neurologist
Granger Medical Clinic
Riverton, Utah

Letters (04/25/2016 14:36)

(Status: Preliminary Signable)

WALLIS, SAMANTHA 07/28/2003

To whom it may concern.

Samantha is a patient of mine with a diagnosis of guanidinoacetate methyltransferase deficiency. Samantha was not diagnosed until she developed symptoms, and at that point, the damage is irreversible. The symptoms of GAMT are not easily differentiated from other common childhood disorders. Treatment for GAMT is successful if started as early a possible, prior to symptoms. Samantha's younger brother Louis was tested as a newborn and is currently asymptomatic. It is crucial to screen for GAMT as a part of the required newborn screening. Thank you for your cooperation in this matter.



Dr. Duffy
Southridge Pediatrics
3723 W 12600 South
Riverton, Ut 84065
801-285-4548/194732

Authored By: JESSIE L DEE
Authored For: J. TIMOTHY DUFFY, MD



Southridge Pediatrics

Letters

EMPI: 547421796
MRN: 641-50-12
DOS: 04/25/2016

ROOM:

DOB: 07/28/2003

AGE: 12Y Age At Date Of Note

Name: WALLIS, SAMANTHA

Authored By: DEE, JESSIE L

Authored For: DUFFY, J. TIMOTHY

April 23, 2016

To the Advisory Committee on Heritable Disorders in Newborns and Children,

As geneticists involved in the diagnosis and care of patients with guanidinoacetate methyltransferase (GAMT) deficiency we are writing this letter in support of the nomination of GAMT deficiency to the RUSP.

The Medical Genetics group and Biochemical Genetics laboratory at Duke University have been involved in the diagnosis, management and research of creatine deficiency syndromes, including GAMT deficiency, since 2003. We care for several families with these disorders, including one family affected with GAMT deficiency. The focus of our research has been the development of diagnostic methods for creatine deficiency syndromes, and to investigate the feasibility of newborn screening for GAMT deficiency.

GAMT deficiency is a good candidate for newborn screening as:

- 1) early treatment prevents the serious neurological consequences of the disorder,
- 2) it can be detected in the newborn period,
- 3) the current tandem mass spectrometric methods used in newborn screening laboratories can be readily adapted for the detection of GAMT deficiency, and,
- 4) GAMT deficiency is an under recognized condition.

The benefits of detecting and treating GAMT deficiency before irreversible neurological damage occurs cannot be overstated. Patients with GAMT deficiency who have been treated from birth or from a very early age have had normal, or near-normal, development. The treatment is based on dietary modifications and is relatively straightforward. Working closely with metabolic physicians and dieticians, families have successfully implemented this special diet to the benefit of patients. If left untreated, patients develop intractable seizures, speech delay, intellectual disability, abnormal movements and behavioral issues. Treatment implemented after early development may prevent or reduce seizures and improve behaviors, but does not reverse the intellectual deficit or speech delay. Unfortunately, GAMT deficiency is a metabolic disorder that is under recognized leading to diagnostic delays. Therefore, there is a critical need for early detection by newborn screening.

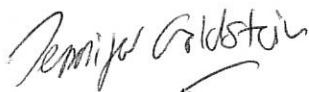
The infrastructure needed for newborn screening and follow-up of GAMT deficiency already exists. Patients with GAMT deficiency have an elevation of guanidinoacetate in blood in the newborn period, which is measurable in dried blood spots. The current tandem mass spectrometric methods for the measurement of acylcarnitines and amino acids used in newborn screening labs can be modified to also measure guanidinoacetate and creatine. Commercial stable isotope-labeled internal standards are available for both these compounds and they are detectable by non-derivatized or derivatized methods. Follow-up testing is available in several biochemical genetics laboratories in the US, and includes measurement of creatine and guanidinoacetate in blood and urine, and confirmation by gene sequencing.

To summarize, GAMT deficiency is a disorder that is similar to phenylketonuria, the prototype newborn screening disorder, in that it is detectable in the newborn period and early treatment by dietary modifications prevents severe neurologic impairment. Newborn screening for this disorder will benefit patients, their families, and their communities.

Yours sincerely,



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To: Advisory Committee on Heritable Disorders in Newborns and Children

Dear Committee Members:

As one of the leading rare disease patient advocacy organizations in the world, Global Genes collaborates with more than 500 patient advocacy and nonprofit organizations. We help these organizations grow and network, to improve their abilities to advocate for their communities, and to better develop their infrastructure to support the patients and families they represent.

The Association for Creatine Deficiencies (ACD) is a partner with Global Genes . The ACD has proven to be an excellent advocacy group for the creatine deficiency community. Our experience with them has been that they are extremely hands-on in staying up to date on current initiatives in the rare disease community, and in advocating on behalf of the patients and families they represent. They have remarkable resources and support for families such as Patient Strong™, a patient grant that helps families with the financial burdens of health care costs, social media platforms for support groups, and a quarterly newsletter, just to name a few. ACD has proven to be a model organization as they have been able to build a network of partnerships including an outstanding Scientific Medical Advisory Board. Members of their Medical Board include a pediatric neurologist and metabolic and mitochondrial biochemists from Utah, Rady's Children's U.C. San Diego, and Duke University. They are prepared to support creatine deficiency research, as they have built an impressive patient registry that is housed with the industry leader- PatientCrossroads.

We strongly believe the creatine deficiency community will benefit in significant and measurable ways from Newborn Screening. The research we have seen, and the patient success stories we have heard with early diagnosis, shows that **GAMT is an easily treatable disorder**. The most important take-away is that the severe debilitating symptoms of untreated **GAMT deficiency can be prevented**. Our sincere hope is that no other children will have to experience the inevitable decline in quality of life, before receiving the correct diagnosis of GAMT.

Sincerely,

Nicole Boice
Founder & CEO, Global Genes

They say that life is measured by the moments that take our breath away, but what about those moments when all hope seems lost and we can't catch our breath? Do those count too? Do we measure those? Those moments can change our lives, define who we are and alter life as we've known it. Typically when I share this story, I focus on all the happiness that it has brought into our lives and the miracle of what my son John has overcome. It's harder to share those moments when all hope seemed lost because the truth is they are heartbreaking and no one likes to hear a sad story. We all want the happily ever after that we think we deserve. However, sometimes in order to really appreciate what you have right in front of you, you have to remember where you've been.

Moment #1 – I can only describe this moment as watching a train wreck in slow motion, you can see it coming, but you don't know how bad it will be until it's over. My son John was only 6 months old and I knew he was not developing like other babies; something was wrong. It was time to take him to the doctors for his 6 month checkup. I can remember not wanting to go because I knew what was coming. It was all about to become real because once a doctor acknowledged that he was delayed there would be no turning back, no hiding my head in the sand. I would have to deal with the wreck that I knew was coming and hope that we both made it out on the other side. I was hopeful that maybe there would be pieces I could pick up and put back together, maybe even if there was something wrong, I could fix it. I am sitting in the waiting room filling out the 6 month milestone questionnaire and that's the moment I felt the impact from the train. My baby had failed the entire test. I couldn't honestly check yes to a single answer. I knew it was coming, but I didn't know it was going to be that bad. I hadn't even made it past the waiting room. The pediatrician called us back and it didn't take long for her to tell me that she was referring us to a pediatric neurologist. The ironic thing is that I can't even recall this exact moment and what she said because I wasn't listening to her. My mind was still stuck back in the waiting room with that damn test that my precious little baby had just failed. That was the first moment that made it hard for me to catch my breath and it changed everything.

Moment #2 - My next stop on this journey was to visit the pediatric neurologist that was 2 hours away from our home. She was certain John had cerebral palsy based on his symptoms and in her opinion there was little room for doubt that he had anything else. That was another one of those moments. I drove home, crying for the whole two hours, and yes, I drove, with my husband beside me and my mom in the backseat with my son. Why did I drive? Because when you're life is spinning out of control, you need to be able to control something, so I drove. I wasn't sobbing because I was trying to control that too... until I got home.

Moment #3 – I did my research on cerebral palsy and learned that there were varying degrees of severity. I spent numerous hours researching any possible treatments. At this point, John had been in physical therapy for a few months and it wasn't looking good. He wasn't making much progress. He was 10 months old and he couldn't sit up, couldn't hold his bottle, didn't babble and when you looked into his eyes he seemed lost in space. Then late one night, it all became just too much to take and I was at the lowest point I think I have ever felt in my life. I was at that moment that I now consider a very piece of the fabric that makes up my life, but it's also a moment that I have kept to myself, until now. Everyone in my house was asleep and I was having a break down. I was lying in bed and I couldn't catch my breath. It hurt. I hurt so much that I got down on my knees in the dark of my room and started

silently praying and crying. I begged. I told God that I would do whatever it took, that I would do whatever he wanted me to do, that I would follow whatever path he put before me, but to please help John walk; even if he walked with a walker, I would be happy with that. We could make a good life for him, but things would be just a little bit easier if he wasn't confined to a wheelchair the rest of his life and he could walk with support. Yes, I was trying to negotiate with God. Then, I crawled back into bed.

A few months later, I had come to terms with the fact that John had cerebral palsy and that life would be ok. We would manage. Life would be different and harder for him, but it could still be good. I would do everything I could to help him and give him the therapies he would need. I still had questions though and I still kept trying to solve the puzzle. I decided to go for a second opinion to see a developmental pediatrician. She too thought he had cerebral palsy, but she strongly recommended an MRI and blood work. Now, you may be thinking this is my Moment #4, when the 2nd doctor said it was cerebral palsy, but it wasn't. Don't forget, I had come to terms with a cerebral palsy diagnosis. It was an answer. Not the one I really wanted, but it was an answer. Even though some pieces of the puzzle didn't fit, I had two doctors that said they thought he had cerebral palsy, so it looked like that was going to be his diagnosis. We just needed the MRI to confirm it.

Moment #4 - I was pushing John in the stroller to the park near my house, when I got a phone call from the developmental pediatrician. The results from the MRI had come back. They were inconsistent with Cerebral Palsy. John did not have cerebral palsy. The MRI found that John had brain damage that was consistent with a Mitochondrial disorder, a Metabolic disorder or Carbon Monoxide poisoning. I cried. I didn't understand. He was supposed to have Cerebral Palsy. The MRI was supposed to confirm it. Now, what? Where do we start? What do we do next? The doctor said we needed to wait for the results from the blood work. We had to wait for an unknown future for my son. I didn't know if the next diagnosis would be better or worse or would there even be a diagnosis? The doctors were so certain it was cerebral palsy. I was devastated. I was back to no answers.

Eventually, I get the phone call with the results from the blood work. The doctor didn't want to tell me what they thought it was because while they had a suspicion they weren't sure. However, she finally said it looked like John had one of three Creatine Disorders and they wanted to know how soon I could get John to Duke Hospital for more blood work.

There are very few individuals that get a rare chance in life to truly make a difference and you are one of them. You get to vote to stop more moments like this from happening to moms and dads.

That is it for those tough moments. Yes, they have shaped my life and I will never forget them, but the rest of the moments are the ones that take your breath away in a good way. The moment they told me John had GAMT, was a great moment. I knew there was a treatment for it and things were looking better and brighter. We had a diagnosis and a treatment. Was it too late to fix all the brain damage that had been done? We didn't know for sure, but at least we had hope and hope is a great thing when you've been in the dark for a while. I'll never forget the first time I heard John laugh or when he took his first step or said his first word. My son was slowly coming back to life and I was along for the ride to watch it and enjoy every moment. We were given a miracle!

Do you remember moment #3, where I begged God to let John walk with a walker? Well, I remember it as I watch him run up and down the soccer field with his friends. And do you remember my promise to do whatever he wanted me to do? In 2011, I received a phone call from a doctor who had found my online blog and he encouraged me to start a nonprofit for children with this disorder. It was an idea that myself and another mother had tossed around before, but he gave me the name of a third mother that had prior experience with non-profits. All I could think was, "I hear you God." Today, the Association for Creatine Deficiencies has grown beyond what I could have ever dreamed and the mothers that are involved and on the board are incredible. Their time, dedication, skills and experience goes far beyond what I have ever been able to give. However, I made a strong promise that I would do whatever I could to get GAMT added to newborn screening, so that no parent ever had to go through what we did and so that every child could be given a future as bright as John's future, so here I stand before you today.

This is my story. These are the moments, good and bad, that have taken my breath away. It's not John's story. John is typical boy that can run and play. He has friends, he goes to gymnastics class, he plays soccer, he gets 100s on his spelling tests and he reads books. He has achieved more than I ever dreamed. He had to work hard to overcome his delays since he suffered 13 months of brain damage, but he did it and I couldn't be prouder. He has to take medicine and has a special diet, but so do a lot of kids these days. This diagnosis will not define John and his story. He may have his own ups and downs in life, but GAMT will not define John. John is the most loving and compassionate kid. He is full of hugs & kisses and I can't get enough of them. After all, at one point I didn't know if I would ever get them or hear the words "I love you" from him, but I have it all. I got it all.

Unfortunately, until GAMT is added to newborn screening, not every parent and child will be as lucky. John was diagnosed at 13 months old and has made a complete recovery. He has a normal life with no scars from the past. When children are diagnosed at a later age, they have brain damage that causes seizures, difficultly speaking, difficultly walking.... and the list of negative outcomes only gets longer. You get the opportunity to vote for more futures like John's. You get to vote for more children to have a future that is not defined by the 4 letters GAMT, but instead by what they want to make of the future for themselves. Those children will be able to grow up with a life relatively unaffected by GAMT and will be able to experience life to the fullest. And hopefully, just hopefully, life for them will be filled with all those good moments that take your breath away!

Missy Klor

Mom of GAMT child

April 25, 2016

Dear Advisory Committee on Heritable Disorders in Newborns and Children,

I have a son with GAMT deficiency, and I am writing today in hopes that you will vote to move GAMT forward toward ultimate inclusion on the RUSP. My son Ryan was diagnosed right before his third birthday. Prior to diagnosis he had global developmental delays and no speech. Around 2 ½ years of age, he started having seizures, which we learned were occurring as frequently as one per minute on EEG. He was diagnosed with Myoclonic Astatic Epilepsy, and tried two different seizure medications and the Ketogenic Diet with very little improvement. Around this time he started to fall frequently and his legs were covered in bruises. Ryan's neurologist was suspicious for a different genetic disorder, and she ordered a genetic epilepsy panel which sequenced 70 genes. This panel just happened to include GAMT, and to everyone's surprise he tested positive.

Even before I was a "GAMT mom," I was (and still am) a genetic counselor. As you can probably imagine, I've spent a lot of time thinking about how I could have missed this diagnosis in my own child. The thought certainly crossed my mind that Ryan could have "something genetic" causing his delays, but I reasoned with myself that a genetic diagnosis would be unlikely to change his medical management. I am embarrassed to admit it now, but I truly believed that all of the most treatable conditions were already included on the Newborn Screen, especially in a state like New York! So instead of genetic testing, I tested for lead. One day, it occurred to me that the painted tapestry over Ryan's crib might be a source of lead paint. It was a gift from a friend who had traveled to Africa. I was absolutely heartbroken thinking that my son might have lifelong disabilities due to a PREVENTABLE cause. I realized at that moment that I am completely okay with having a child with special needs; I love Ryan with all of my heart and I truly feel honored to be his mom. However, it was the *preventable* part that made me feel so sick.

Ryan is now almost 5. He remains far behind his fraternal twin brother in his abilities, and I know that he will continue to struggle due to brain damage sustained during his first three years of life. However, I am also well aware that he is one of the lucky ones. With creatine, ornithine and sodium benzoate treatment his seizures stopped within two weeks, and he is now talking in short sentences. He can communicate his wants and needs. Undoubtedly, there are a lot of other GAMT patients out there seizing, wheelchair bound and unable to speak due to lack of a proper diagnosis. The thought of this haunts me every day, and this is why I am writing to you.

I ask that you please vote to move GAMT forward for inclusion on the RUSP. It is a universally devastating disease, but development is normal when treated from birth. Treatment is extremely safe and inexpensive. It is a perfect candidate for Newborn Screening!

Sincerely,
Laura Martin

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Assistant Professor, Department
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Duke University School of Medicine
North Carolina

Dr. Denise Morita, M.D.
Pediatric Neurologist
Granger Medical Clinic
Riverton, Utah

April 20, 2016

To: The U.S. Department of Health and Human Services
Advisory Committee on Heritable Disorders in Newborns and Children.

Re: Guanidinoacetate Methyltransferase Deficiency (GAMT) addition to the National
Recommended Universal Screening Panel (RUSP).

Dear Committee Members,

Guanidinoacetate Methyltransferase Deficiency (GAMT) is a Creatine Deficiency Syndrome that is a **treatable** neurological disease. Unfortunately, babies and young children that have this disease do not get diagnosed early enough, or not at all. Without early treatment, they will suffer brain damage, which includes seizures, language impairments, developmental delays, and movement disabilities.

Without the proper diagnosis and available treatment, these children will grow to be adults needing life long care from others and will require government aid. These babies deserve a future life of independence and to be productive citizens.

It would be heartbreaking to not include GAMT in the national RUSP for early treatment.

I am a mother of an adult son with a creatine deficiency. I have spent 20 years advocating for children. I have no humility in this plea. **These babies need your recommendation, your vote for a healthy, productive, independent life.**

Again, they deserve nothing less.

Please vote to recommend and include GAMT on the National Newborn Screening Panel.

Thank you for your support.

Linda Cooper
ACD Founder, Trustee
Mother of a 21 year old diagnosed with Creatine Transporter Deficiency at age 9.

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Dr. Denise Morita, M.D.
Pediatric Neurologist
Granger Medical Clinic
Riverton, Utah

April 25, 2016

To: Advisory Committee on Heritable Disorders in Newborns and Children

Dear Committee Members:

I am writing to you as the mother of two children with GAMT. My daughter Samantha, who is now 12, was diagnosed at 5. My son Louis, who is now 4, was diagnosed at birth.

The first point I would like to make is that GAMT babies do not look different from any other children. There are no dysmorphic features or other tip-offs to immediately know that GAMT is present. Without a newborn screening there is no way to know that a child has GAMT and brain damage will begin immediately. Physicians and parents slowly begin to notice the symptoms of that brain damage increasing before the alarms start going off and most often it is too late at that point.



Sam- age 1.



Easter 2016, looking for eggs at noon after a morning seizure kept her in bed.

Secondly, the symptoms are very similar to other disorders. Every GAMT family I know has an initial misdiagnosis. For Samantha, the symptoms were slow to develop. She appeared so very “normal” for quite a long time. It wasn’t until she was around 2-½ that I started getting nervous at her lack of speech. At 3 she was diagnosed on the autism spectrum “by one point”. They explained that if she had scored one point lower on the autism test, she would simply be considered “developmentally delayed”. This was obviously no help to her. Every special ed preschool teacher, speech therapist, and occupational therapist Sam had would make comments like “She is really special. She is so bright. There is a light in her- I can tell she is going to really take off soon. Einstein didn’t talk till he was 3, 4, 5...” And that is how I felt for years. I held my breath, waited for the sudden improvement, but slowly her world grew darker.

At 5, Sam began having absence seizures. We went to a neurologist, did an EEG, and he said “Yup. Those are seizures! Let’s do an MRI just to make sure there isn’t a tumor or something

going on causing these.” According to the neurologist’s P.A., she suggested at the last minute to also run a spectroscopy. The absence of a creatine peak on that last-minute test is what finally led to a correct diagnosis of GAMT. Luck stepped in and helped change Sam’s course in life a bit. Without a newborn screening, the only way a GAMT child gets treatment is brain damage being done, and manifesting in ways that look like Autism, Cerebral Palsy, and Mitochondrial Disorder and then luck stepping in that a physician has heard of GAMT and thinks to run the additional testing for it.

When Sam was diagnosed, she was developmentally at about an 18 month old level. She could say maybe 10 words and sounded like a young toddler. “Mom” was “Muh”, “Duck” was “duh”, etc. With a LOT of work she was able to be potty trained just before she turned five. Nothing came about easily for her. With all of her challenges, it turns out she was actually ahead of many other GAMT kids at the same age who are so weak and have such extreme movement disorders that they must be strapped upright in wheelchairs so they can sit up.

Her pediatrician never suggested blood work or referred us out for specialist help except for autism testing, and then the neurologist when the seizures kicked in. I could choose to be bitter but honestly, I think she looked like so many other kids with autism that he was seeing. No symptoms stood out. Diagnosis for a GAMT kid is 100% luck right now. A full life or a life of misery is currently left to chance. I am certain that there are children living with an autism diagnosis who actually have GAMT deficiency.

After about 9 months of treatment, she could plug those final consonants on “Mom!”, “Duck!”, and could string together 3-4 words. “More juice Please”. Her “recovery” has slowly continued ever since. I have paid for costly home therapy programs- doing cognitive training, speech, math, and reading activities over and over. I have done everything I can think and afford to do to help her. For two years I kept her at home to homeschool her and push her forward, always hoping that because we had fixed her metabolic deficiency she could fully recover. Now at the age of 12 and finishing sixth grade she is in an all day special education classroom with the classification of “Intellectual Disability”. It took ten years, but she has learned to ride a bike. She reads and does math at an upper 1st grade- lower second grade level. She has intractable seizures. She has some pretty big mood swings and obsessive behaviors like picking at the same pimple till it bleeds for weeks and turns into a permanent scar. She shouts sometimes in public and melts down on the floor in the grocery store leaving us both in tears and going home to recover. She can’t wash her hair or brush her teeth well enough on her own to be healthy and clean so I help with both. She does not play with other children. At recess she walks around the playground and observes. She talks about friends, but doesn’t really understand how to have a friend. GAMT therapy has helped her improve. Her life could be worse. I am thankful for her diagnosis. But things could have been SO much better.

Knowing that we had GAMT in our DNA, we paused our family for a few years. Finally we decided to play the odds in 2011. Sam was 8 when Louis was born. I still had a lot of hope for extreme change for her and thought that with the 75% chance Louis wouldn’t have GAMT we were safe. I was wrong.

Days after his birth we received the bad news. I was wracked with guilt for having “done this to him.” Louis began taking his creatine, ornithine, and sodium benzoate four times a day. It tastes awful and it was a bit of a battle at first, but after a month or so he understood it was necessary to take before he could eat and he has been compliant ever since. That has been his treatment since birth. So simple. Some doctors debate on the need for a low protein diet, but he has only been restricted to a normal RDI of protein. In other words, no seconds of the main course at meals. No big deal! Our insurance covers his supplements under the Utah state guidelines of “medical foods” but even without insurance, at his current size his supplements would only cost \$0.55 per day (Sam is about \$1.95 and she is nearly full grown at 135 pounds!). Treatment is affordable and simple.

After years of working with Samantha, and raising a typical daughter and son in between Sam and Louis, I have some pretty keen eyes as to what is normal and what is not for children. Because of this, I have no doubt that treatment from birth for GAMT deficiency is 100% effective. Louis is imaginative. He is constantly initiating pretend play. He sings songs in tune with all the words pronounced correctly on his own. He learns ON HIS OWN. He picks up a crayon, sounds out the word “MOM” and writes it. He does not need therapists to explain how to use his legs, hands, and mouth. He has good muscle tone with no interventions. He makes jokes. He makes friends. He does not have seizures. He does not go to a special preschool. His preschool teachers report he is not only able to keep up and often surpass others academically, but he is the most liked child in the class. In a recent cognitive testing he received “typical” scores. I did not need this test to know that he is going to have a full and productive life.



I understand that this disorder is relatively new and so I can't be bitter for the loss of Samantha's chance at a full life. Everyone has done “their best” to help Sam. I understand that a new disorder takes time to understand, to develop therapies for, to develop technologies to detect, to educate the medical community about.

I firmly believe that GAMT is ready for newborn screening. It is now time to do “your best” for those families that trust in the system; that believe these types of treatable disorders have been ruled out when their child has had their screening done. If we fail to act now, parents will have the right to feel bitter.

The treatment works and is affordable and simple. The screening works. The consequences of not diagnosing are devastating. Newborn screening is the only solution. It is the only way to diagnose all of the children being born with GAMT early enough to save them. The population of GAMT patients exists. Even with the difficulty of differentiating GAMT from Autism and other disorders, our numbers continue to grow. There are GAMT patients in institutions carrying the wrong label, I have no doubt. Please help us end this. Please, please do not let another baby’s healthy brain begin to grow dark. Please help their families live normal lives where the parents can both work, the children can play and enjoy their siblings. Please do the right thing.

Please contact me with any questions you might have.

Regards,

Heidi Wallis

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heidi@creatineinfo.org

hwallis@gmail.com

3338 Tucannon Cove

Bluffdale, UT 84065

April 9, 2016

To whom it may concern:

The Association for Creatine Deficiencies will be putting together a cost analysis for children who are diagnosed with GAMT at birth, and those that are not. We are still putting these statistics together, and I will submit before the deadline at the end of this month.

If you have any questions, please don't hesitate to contact me.

Sincerely,

Kim Tuminello
President, Trustee
760-688-8032
Kim@creatineinfo.org
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Duke University School of Medicine
North Carolina

Denise Morita, M.D.
Pediatric Neurologist
Granger Medical Clinic
Riverton, Utah



Newborn Screening for Spinal Muscular Atrophy

Testimony of Cure SMA

Delivered by

Spencer Perlman, Board Member of Cure SMA

Meeting of the Advisory Committee on Heritable Disorders in Newborns and Children
May 9, 2016

Good afternoon. Dr. Bocchini and members of the Advisory Committee, thank you for the opportunity to testify today. My name is Spencer Perlman and I am a member of the Cure SMA Board of Directors. Cure SMA leads the way to a world without Spinal Muscular Atrophy, the number one genetic cause of death for infants. We support and direct comprehensive research that drives breakthroughs in treatment and care, and we provide families the support they need.

I'm testifying this afternoon as a representative of the entire SMA community regarding the committee's nomination and evaluation process for candidate conditions on the uniform newborn screening panel.

In the ten years since I last stood before this committee, there have been significant advancements toward the development and approval of a treatment for SMA. Through these advancements, we have also gained a much greater understanding of the disease and the importance of early intervention. We are at an exciting precipice, on the brink of seeing an approved treatment for SMA. Today, I urge the Advisory Committee to give serious consideration to the forthcoming nomination and evaluation of SMA for universal newborn screening.

As you know, SMA is an autosomal genetic disorder and the leading genetic killer of children under the age of 2. It occurs in about 1 of every 10,000 births, with 1 in about 50 people in the general population being carriers of the disease. Approximately 50 percent of affected children suffer from type 1 SMA, the most severe form. Historically, more than 95 percent of these children die in infancy or require extensive respiratory support by their second birthday.

Newborn screening is an issue that is of paramount importance within the SMA community. SMA families, as well as investigators and clinicians within the SMA community believe that newborn screening holds great promise for ensuring access to a treatment and helping to move toward a cure for this deadly disease.

Of the 18 drug development programs currently in the pipeline, six are in clinical trials, and several of those are in Phase 3 clinical trials, following positive trial results. We expect one or more of these drug development programs will result in a New Drug Application to the FDA in

2017. Therefore, it is of the utmost importance that SMA be added to the recommended uniform screening panel as soon as possible to ensure patients and families are made aware of the disease through newborn screening, told of the need for treatment, and can obtain treatment at the earliest possible moment.

Both human natural history data and animal model data suggest that early drug intervention is required for the greatest efficacy in SMA. Natural history data indicates that there's only a small opportunity for intervention in the most common and severe form of SMA - type 1. One study has shown that type 1 infants demonstrate normal motor neuron innervation during the pre-symptomatic phase of the disease, but suffer rapid and severe loss of motor units during the first three months of life. This can result in the loss of more than 90% of motor units within six months of age. A recent multi-center natural history study conducted by the NINDS NeuroNEXT clinical trial network reviewed infants under six months of age with genetically confirmed SMA. That study showed significant differences between infants with SMA and other infants at the baseline visit for motor function tests, suggesting very early motor neuronal deficits.

Preliminary data in mouse models also indicate that pre-symptomatic drug intervention is more effective than post-symptomatic, with the results being remarkably consistent. Tests have demonstrated the best results when drugs are given as early as possible. Little benefit has been observed with drug treatment after the first week of life in severe mouse models of SMA.

Studies have also shown that proactive treatment of an infant with SMA in the first few weeks-to-months of life prolongs survival and improves quality of life. For example, when infants with type 1 SMA receive proactive respiratory and nutritional support, these interventions can save lives. However, diagnostic delay is very common in SMA, and thus far, such interventions are typically only available in response to medical crises. These newborns should never have to wait to reach crisis. Newborn screening for SMA can change this.

The case for implementing universal newborn screening for SMA is made more convincing by the fact that the technology exists and has been successfully utilized in several ongoing pilot newborn screening programs, namely in New York State and in Taiwan. The CDC has also developed a multiplexed real-time PCR test to simultaneously screen for spinal muscular atrophy and severe combined immunodeficiency.

In conclusion, the SMA community strongly urges the Advisory Committee to take up consideration of the forthcoming SMA nomination with concerted focus on the availability of a treatment for SMA in the very near future, the success of the technology in screening for SMA, and the demonstrated benefits of early intervention. I thank the Committee for the opportunity to address you today.

Early treatment of GAMT Deficiency is effective and affordable



Benny was undiagnosed until 5 years of age. He attends a special education classroom where he requires 1:1 care. He battles seizures, Global Developmental Delays, is nonverbal, requires a communication device, and will need life-long care.

Late Diagnosis



Paige has been treated since birth. She is a 6 year old in the 1st grade, and has never required therapies. She has never needed interventions of any kind and attends a typical classroom. She has never had a seizure.

Newborn Diagnosis

Cost comparison: Newborn Screening and Treatment for GAMT vs. Lifelong Care

Lifelong Costs of Intellectually Disabled, Undiagnosed GAMT patient

GAMT is a Cerebral Creatine Deficiency Syndrome. If not treated at birth, this neurological disorder results in severe physical and cognitive disabilities. In 2003, RTI International and the CDC analyzed data from multiple surveys and reports to estimate the direct and indirect economic costs associated with Developmental Disabilities. On the basis of that analysis, the estimated **lifetime costs for a person with intellectual disabilities is \$1,312,314**. Additionally, a GAMT patient will require mobility and speech devices, and continuous physical, speech, and neurological care due to their condition.

Cost of GAMT Diagnosis through Newborn Screening

According to the Utah pilot study, the cost to check each blood spot, including labor, materials and the extremely rare second tier testing, averaged out to be \$0.49 per spot screened. The Utah pilot projects that the incidence of GAMT is approximately 1:120,000.




We can extrapolate from this that **the cost to identify a GAMT patient is only \$58,800**.

Cost to Treat GAMT when Detected at Birth

Based on current standards for GAMT treatment, a child diagnosed at birth will only require daily oral supplementation of creatine, ornithine, and sodium benzoate. As shown in Figure 1- the total daily cost ranges from less than \$0.93 in early childhood to around \$3.50 in adolescent years.

Total annual cost of treatment is \$339.45 to \$1,248.30.

Figure 1: *Daily cost of oral supplementation*

Cost of Oral Supplements	Daily Oral Supplements	Total daily cost to treat 40 pound child \$0.93 135 pound child \$3.42
<p><u>Creatine Monohydrate</u></p> <p>Available at GNC, Whole Foods, and Amazon</p> <p>\$25.00 for 1,000 grams</p>		<p>40 pound child \$0.23 per day</p> <p>135 pound child \$0.67 per day</p>
<p><u>L-Ornithine</u></p> <p>Available at JoMar Labs.com, nutrabio.com, and other sports supplement stores</p> <p>Appx \$45.00 for 500 grams</p>		<p>40 pound child \$0.59 per day</p> <p>135 pound child \$2.43 per day</p>
<p><u>Sodium Benzoate</u></p> <p>Available at compounding pharmacies and Amazon</p> <p>\$35.00 for 1,000 grams</p>		<p>40 pound child \$0.11 per day</p> <p>135 pound child \$0.32 per day</p>

"I am a physician that works with children with GAMT and similar deficiencies. Picking up this disorder as early as possible and ensuring access to the appropriate treatment actually prevents progression and assists these children in being the healthiest they can be. I have seen that early detection and treatment stops very hard to control seizures, improves developmental and cognitive outcomes and prevents irreversible brain injury."

-Inna Hughes, Rochester, NY

"My son has Creatine Transporter Deficiency. It would have saved a lot of stress and heartache if we were to find out when he was a newborn as opposed to 4 years old. I fully support creatine deficiencies!"

-Kelly Shedd, BRIGGS DALE, CO

"So important to raise awareness and to get states to act. Read a March Forbes article on the role of RUSP to guide states' newborn screening programs. Glad to see this petition for GAMT."

-Lynn Amer, Austin, TX

"My son wasn't diagnosed with GAMT until he was 4 years old."

-Laura Eger, Grosse Pointe, MI

"I have a son with GAMT deficiency who was not diagnosed until right before his 3rd birthday. He has a history of medically intractable seizures, which stopped with proper treatment. However, he continues to struggle with global developmental delays due to brain damage sustained prior to diagnosis. I am signing because I want to ensure that future children with GAMT can benefit from early diagnosis and treatment!"

-Laura Martin, Penfield, NY

"I have a son with Aspergers/Autism. We had to fight for screening at age 8, any early intervention was lost. Please pass the law for early screening of GAMT, another family should not have to suffer or fight for a diagnosis or services when it is too late."

-Megan Churchill, Le Roy, NY

"I know a child with this disease. Can there at least be an option to choose testing for one's newborn?"

-Katie Strike, Cincinnati, OH

"My friend's children have GAMT."

-Sara Snow, Austin, TX

"Because I care and this is a solution"

-Sharon Reeder, Aliso Viejo, CA

"An ounce of prevention is worth a pound of cure - especially one that comes too late."

-Heather Harper, Mississauga, Canada

"Early detection is key. Let's do this!"

-Chris Anderson, Sandy, UT

"What a difference this will make in so many lives - and if you are not moved by the humanitarian value or that, think of the immeasurable cost savings throughout each child's lifetime!!!"

-Amanda Byron, Portland, OR

"I have a colleague whose children are effected and could have been treated if detected in time."

-Aubrey Cowan, Salt Lake City, UT

"Easily detectable and preventable! As stated, the cost is less than \$1 per child, but the reward is priceless."

-David Forsythe, Salt Lake City, UT

"I have a friend who's child's life would be easier if this were a GAMT screening at birth. DO IT!"

-Rich Rasmussen, Sandy, UT

"I have friends where this has been an impact / will be an impact"

-Tricia Spangler, San Diego, CA

"This could save families a lot of heart ache."

-Lorie Sousa, Encinitas, CA

"I know two great kids that have benefitted from this."

-Eric Hernandez, Carlsbad, CA

"It's ridiculous we're not already testing for this. What a simple thing to do to save a life."

-Kristin Cooper, Carlsbad, CA

"My friend, Kim Tuminello"

Heidi Murphy, Austin, TX

"I'm signing because I'm a mother who would do anything for her kids... And for kids everywhere."

-Sarah Linn, Atascadero, CA

"It needs to be done..early on"

-Barbara Phillips, Deweyville, TX

"A simple test that answers questions and possible saves lives"

-Danielle Caniglia, San Diego, CA

I'm signing because Ty and Paige Tuminello's prognosis would have been devastating if they hadn't been diagnosed and every child deserves the chance to receive an early and treatable diagnosis!!!

-Meredith Parra, Carlsbad, CA

"It is an important cause"

-Kevin Keene, Irvine, CA

"This screening is needed!!!! It will give so many kids the quality of life they deserve by a simple test!"

-Shanna Johnson, Encinitas, CA

"I'm signing as I believe in this cause. Thank you Kim."

-Mark Richardson, Mission Viejo, CA

Because early detection makes an amazing difference in the quality of life for those affected.

-Adam Tschop, Carlsbad, CA

"I am a medical geneticist who supports early diagnosis of treatable diseases."

-Emily Doherty, Daleville, VA

"I feel this is very important and can prevent our future from suffering."

-Rob Robinson, Saint Simons Island, GA

"In support of awareness and early detection."

-Tracy Miceli, Scottsville, NY

"There is nothing to lose, and so much possible gain to running this simple test! It would prevent so much pain and heartache, for all of these young babies!"

-Leisa Barlow, Noble, OK

"I'm signing because I know 2 precious children with this disorder and I believe that newborns should be tested!"

-Meredith Mitchell, Stuttgart, AR

"I'm concerned and excited that this test can help so many children"

-Donna Pigg, Austin, TX

"We have loved ones with Creatine Deficiency Disorder. Luckily the children were diagnosed as infants. They are leading normal lives. Those who haven't been diagnosed are unable to speak and will never care for themselves or enjoy all that life has to offer."

-Jennifer Doogan, Carlsbad, CA

“Newborn screening for diseases like GAMT impacts quality of life and reduces financial burdens to families and the general public.”

-Steve Strauss, Driftwood, TX

“My cousins son was diagnosed with this”

Jeff Turton, Durham, NC

“I am a nurse in genetics and metabolism”

-Cheryl CLow, Hudson, NY

“All children should have the right to be healthy and reach their fullest potential.”

-Stephanie Laniewski, Rochester, NY

“My sister's oldest child has GAMT and it went undiagnosed for quite some time. She has issues that she will never recover from and as a result will more than likely spend her adult life living with her parents. My sister's youngest however was tested at birth and GAMT was diagnosed, they were able to treat immediately and he has no problems.”

-Brent Kelley, Grand Junction, CO

“Children are our future. Be an example of who they need to be.”

-stu hoskins, Pella, IA

“My son has a creatine deficiency and early detection is crucial”

-Jessica Armour, Australia

“As a healthcare worker I often see too many time that Corners are cut and that profit is the primary motive for healthcare.”

-Kirk Kingery, Salt Lake City, UT

“I know someone affected and therefore know the positive effects of early testing and intervention!”

-Danielle Donovan, Livonia, NY

“We shouldn't need a petition for this, the decision should be obvious!”

-Brandy Anderson, Meshoppen, PA

“My sister has two GAMT children, one who had late treatment, and one who had treatment after birth.”

-Benjamin Whiting, Telluride, CO

“My son has creatine transporter deficiency. He was not diagnosed till he was 4. And had about 5 epileptic seizures before we found out what was going on”

-tony mcreary, Swansboro, NC

"To show my support and advocate for this worthy cause."

-Rhonda Andrew, El Segundo, CA

"Newborns should be given the best chance possible of living a beautiful, whole life."

-Stephanie Sparkman, Midland, TX

"I have seen personally how this has affected the family."

-Laura Knox, Honeoye Falls, NY

"This relatively small step could spare children and families future despair."

-Kamal Amer, Austin, TX

"For a simple blood test that can be added to the already many bloodwork samples we do while pregnant, this seems irresponsible to not be included. The cost is less than \$1.00 and the cost to treat these misdiagnosed children must be much more than that."

-Jodi Chamberlain, Trabuco Canyon, CA

"Because I am an RN"

-Jamie Pair, Bakersfield, CA

"A friend's child was screened and diagnosed soon enough to make a difference. Would like to see this available to others."

-Vicki Pyle, San Marcos, CA

"Shouldn't have to ask why!!!"

-Hannah Kromka, pine knoll shores, NC

"The families affected by this condition need a proper diagnosis ASAP.... Delays in diagnosis and treatment result in unnecessary and preventable problems."

-Steve Logar, Elyria, OH

"I have a nephew with this and believe all children should be tested at birth."

-Kathi Snyder, Indian Land, U.S. Outlying Islands

"My grandson has this. He was diagnosed too late. One simple blood test would prevent the daily struggles that the child and family goes through."

-Pam Snyder, Briggsdale, CO

"This is a good cause."

-Mary Akerley, La Grange, IL

"Because it is save many heartaches"

-Rebecca Pobanz, Geneseo, IL

"I have 3 boys with CTD and if early testing helps find cures faster i am all for it."

-Michael Gardner, Kansas City, MO

"Why not sign if it saves our children"

-Cindy Wilkins, Arroyo Grande, CA

"It is important"

-Maria Trefogli, San Carlos, CA

"I am a cognitive neuroscientist and have become aware of this disorder through the association of creatine deficiencies. Through them, I have seen their studies and their tremendous progress in creating awareness for early detection. I agree with and support the necessity for getting this approved for newborn screening!"

-Stef Von Huben, Carlsbad, CA

"Someone I love was diagnosed"

-edward davis, Wilmington, DE

"This is so important!!!"

-Tiffany Rogers, Encinitas, CA

"This is an easy low cost solution to a disability that threatens families and the potential productivity of their children at an untold cost to society. It just makes sense to make this testing required."

-Katherine Doolittle, Nevada City, CA

"I'm a mommy and I would want to know and be able to give my hold the best he/she had!"

-Jill Geib, Buffalo, NY

"I'm signing because I want proper diagnosis for the illness so patients can receive the correct treatment."

-Patti Riggs, Austin, TX

"I'm signing because I believe this should be included in the testing of all newborn babys."

-Frances Billiot, Sulphur, LA

"Prevention is everything"

-Lorin Smith, Ridgecrest, CA

"My friend's grandson has this syndrome and realize the importance of early detection."

-Yvonne Wiggins, Scottsville, NY

"To raise awareness"

-Kara Collins, San Marcos, CA

"In support of a friend and her Family"

-Joel Shaw, Omaha, NE

"This needs to be recognized!"

-Jennifer Stone, San Marcos, CA

"This test needs to be done on every newborn!"

-Josette Choate, Bridge City, TX

"Good screening now means fewer problems later."

-Brenda Bradford, Palmyra, NY

"Because of the fact if there is a slight possibility of being detected early, it could clearly save a life."

-April Martinez, Vidor, TX

"Two of my grandchildren have a creatine disorder and I want to see more research and help for them all children born, undiagnosed and living with the effects of not receiving treatment for something that absolutely can be controlled."

-Linda Wallis, Cincinnati, OH

"My nephew Reid Strauss"

-Wade Worsham, Houston, TX

"this is a very important screening that will help many children"

-Pat McClelland, Little Rock, AR

"I'm signing because of my nephew."

-Nicole Klor, Republic, MO

"I am signing this because I understand the incredible value of this simple newborn screening in detecting GAMT deficiencies to allow early treatment. This is an obvious choice that this screening should be part of the RUSP."

-Stephanie Joo, Carlsbad, CA

"I am signing because I have 2 children with GAMT. Early diagnosis is the key to a healthy life!"

-Grant Tuminello, Carlsbad, CA

"It's the right thing to do!! Why wouldn't you do it if it could prevent children from having this issue."

-Cheryl Linscomb, Orange, TX

"I love my two baby cousins that were diagnosed with this! I hope that future parents will be able to know early and treat! I love you Ty and Paige!"

-Lauren Burns, Monticello, AR

"As a teacher of elementary children, the numbers of children being diagnosed with autism has increased exponentially in the past 16 years. As educators, we wonder what causes this and how we can best support children who are neural atypical. Hearing I'd this, though, makes me think that perhaps not all cases have been diagnosed correctly as Autism. Perhaps this type of early screening can eliminate the heartbreak and correctly diagnose our children!"

-Monica Mathers, Costa Mesa, CA

"My friend's grandson was born with this deficiency."

-Alexander Nancy, Granite Falls, NC

"My friend's grandson has this disorder. He is being treated and is living life symptom free."

-Laura Boldyrew, New Bern, NC

"I want this testing done on every child at birth."

-Cindy Beebe, Orange, TX

"My son is diagnosed CTD and could have been diagnosed much earlier in his life."

-Rodolfo Mier, Spring, TX

"It's a great thing for our children"

-Pam Vandenberg, Roy, UT

"I have kids & want them to have this option when they have kids!"

-Becki Pinckard, Chandler, AZ

"Getting the correct diagnosis EARLY is crucial for the lives of these children."

-Aimee Khan, Carlsbad, CA

"All children deserve a chance for a happy productive life."

-Colleen Horodnik, Bridgewater, NJ

"My grandson has this condition and early detection has helped getting him the services he needs to make great gains in all areas."

-Antoinette Abdo-Whelpton, Scottsville, NY

"if you can find something early to treat, then we should"

-suzanne hayles, carlsbad, CA

"I strongly believe that there should be newborn screening for GAMT."

-Kristen Heeres, Phoenix, AZ

"I know 2 children now leading a normal life due to early treatment. Happy!"

-Gail Carroll, Carlsbad, CA

"It is my understanding that an early screening blood test could prevent years of brain damage as children are worked through the process of eliminating other causes of their problems."

-Judy Rhodes Davis, Pelahatchie, MS

*****"My cousin's son has this...why would we not screen for something that is treatable and can change someone's life?"***

"Our nephew has this."

-Carol Potter, Montrose, PA

"When a simple blood test could diagnose this disease and prevent irreversible brain damage why in the world would anyone not make it available do all newborn children."

-Vickie Turner, Morehead City, NC

"I'm a pediatric neurologist and would love to see children with treatable conditions identified as early as possible so they can lead normal lives. I have seen children identified too late and by then the damage is irreversible."

-Guillermo Philipps, Estero, FL

"My nephew has GAMT and is now 7 living a normal boy childhood as he should- only thanks to the people who fought to diagnose him with this disorder versus Cerebral Palsy which I'm sure so many are diagnosed with on a daily basis!"

-Mad Furtner, Pine Knoll Shores, NC

"Someone I love has been impacted by this condition."

-Cassandra Maglin, Fort Rucker, AL

"I'm signing because I'm a witness to the difference early detection/diagnosis can make. Screening will make a huge difference in the lives of children and their families."

-Carolyn Johnston, San Marcos, CA

"Early detection is the key."

-Beth Wert, Mountain Top, PA

"We have a family member with Creatine Transport Disorder and would like to do our part to help bring awareness to these types of diseases."

-Jill Strauss, Corpus Christi, TX

"My daughter, 13 months, has one GAMT mutation. By the textbook you must have both genes mutated to have the disorder, but clinically she fits. She has seizures, developmental delay, and a movement disorder. Although anticonvulsants have stopped the seizures she is still only developing at half time and appears to have several movement disorders. We are hoping to start the creatine diet, but many obsticals have delayed the counsel we need to begin. I worry daily as I know the longer we wait the potential for a decrease in quality of life is high."

-Keszia Hale, Dunnellon, FL

"Family friends son has GMAT"

-Leanne Coppola, Wall, NJ

"This is a condition that if found early can make the difference in a child's life and their family. It is simply commen sense and necessary."

-Tara Perrotti, Manchester, NH

"I care. Every child should have a chance to be normal."

-Maureen Niescierenkoh, Rochester, NY

"My cousin got this"

-Asimah Ilyas, Oslo, Norway

******Fordi min fetter har denne sykdomen og hindre at andre skal ikke få.***

-Rafia Yaqub, Oslo, Norway

"All children deserve our best efforts to assure their health. A tiny investment that will unimagivable dividends for the child, the family, the community and society At large."

-William LaCourse, Alfred, NY

"I care and support early detection"

-Susan Miller, Spencerport, NY

"We can prevent this disease from taking hold!"

-Stephanie Wallace, Carlsbad, CA

"Because I believe children deserve that chance to be healthy if there is anything we can about it."

-Sarah Smith, Brandeis, CA

"I have seen what a miracle early screening accomplishes."

-Kathy Furtner, Pine Knoll SHores, NC

"So more children can be diagnosed and treated."

-Sherry Worsham, Orange, TX

"It is important to find out early and get some treatment for it. It will help save lives.."

-colleen mahoney, Wilmington, DE

*****Vince Haygood, Belden, MS**

"I am a mom and this is something I believe in!"

-Michelle Wilton, Oceanside, CA

"My niece was diagnosed at the age of 13. So much pain and suffering could have been prevented if tested at birth."

-Lori Lundeen, East Peoria, IL

"I know a child who has this condition."

Donna Hunt, Forest, MS

"My 13 year old daughter was diagnosed last year at St. Louis Children's Hospital by our hero , Dr. Judith Weisenberg with GAMT..She was misdiagnosed for 10 years by various specialist and doctors. Her condition worsened to the point she went in self induced coma for 18 days after being airlifted with uncontrolled seizures. GAMT is definitely treatable as we have seen vast improvement in our daughter and she has not had one seizure since proper diagnosis and treatment. Unfortunately, since she was misdiagnosed with Autism for so many years, it is likely she will still have limited life skills. We pray this is passed so other parents have a better outcome . Such an easy and inexpensive test it is a "crime" not to be included. I could go on and on."

-Jennifer Lundeen, Bentonville, AR

"Early detection is simple and easy. Signing for John Klor, who was misdiagnosed but thankfully it was caught early enough he could receive treatment. Now he is a bright, healthy little boy."

-Jenny Glass, Wilmington, NC

"I'm signing because people I care about deal with gamt everyday."

-Christina Reilly, Bethlehem, GA

"All kids deserve a fair chance, and this simple test will help so many!"

-Pam Redela, Encinitas, CA

"GAMT deficiency is a treatable condition detectable by current NBS methods"

-Sarah Young, Durham, NC

"This is a simple test that can save a child from a misdiagnosis and treat them effectively!!"

-Heather Malloy, Chandler, AZ

"This is a major problem for this next generation."

-Jacque Baker, San Marcos, CA

"I have a great nephew who has been diagnosed....I care!"

-Lori Miller, Stanley, NY

"Committed to newborn screening"

-Sandra Baucom, Chesapeake, VA

"My 2nd cousin has this disease and I want to help save so many children!"

-Cindy Tillman, Rochester, NY

*"Sometimes G-d has a lot on his plate and needs help. Lets give him the help he needs.
SHARE"*

-Albert Luppo, Brentwood, NY

"A simple blood test can improve lives!"

-Catherine Kelley, New Albany, OH

"I believe in this cause!"

-Deanna Dolan, North Las Vegas, NV

"I have a child in my daycare who has this disease and would love to see more research on it"

-peggy zugie, Wilmington, DE

"Our children are important!"

-Lauren Queener, Clinton, TN

"This is so simple and could help so many."

-Carmen Polk, Pelahatchie, MS

"Because it can save children from being delayed and save lives!!"

-Meagan Foster, Newport, NC

"Let's help newborns and their families. For the Tuminello family"

-Renee Robison, Sherwood, AR

"Because this is so SIMPLE to add to newborn screening, it's a no brainer and will save so many lives! It must be done!"

-Mary Jo Finley, San Diego, CA

"I am a pediatric nurse practitioner who has seen this illness first hand through my cousin's son. We test for so many other uncommon but life threatening diseases through newborn screening, this one is equally important."

-Juli Granica, Hampton, VA

"Because it is the right thing to do!"
-Sheila Hogan, Santa Rosa Beach, FL

"On behalf of a grandchild with mitochondrial disease."
-Maggie White, Belden, MS

"For my nephew"
-Cindy Boyles, Greenville, MS

"My niece has this disorder"
-Sarah Cochrane, Wilmington, DE

"I believe in this."
-Rachel Malone, San Diego, CA

"Can save children from being untreated or treated too late"
-Susan Bishop, Newport, NC

"I have a grandson with GAMT"
-Nancy Williams, Saltillo, MS

"We need to protect the bases born with this disease and they deserve the right to a good life!!"
-Michelle Mora, Carlsbad, CA

"I'm signing because my son's best friend was diagnosed."
-Erica Reed, Woodstock, IL

"To help more children like our precious, Will Parker."
-Patty Till, Pelahatchie, MS

"My cousin is diagnosed"
-Rabeeah Aslam, Bolton, United Kingdom

"My Cousin's children will benefit from this as well as soooo many other children."
-PH Bean, Harrison, AR

"I wasn't even aware of this disease until a member of my family was diagnosed with this. So much precious time went by. Hopefully awareness will save others the heartache of not knowing what is wrong with their child"
-Kathryn Edwards, Clifton Springs, NY

"Although rare, diagnosis can be life changing and why not? It is a simple blood test!"
-Cynthia Roods, Webster, NY

"I'm signing this because of my two beautiful grandchildren who both GAMT. My grandson was the first diagnosed in the United States. The heartbreak we went through before GAMT was found could have been avoided with newborn screening."

-Sherry Tuminello, Stuttgart, AR

"We know Kim Tuminello and her children. We have followed her struggle to find out what was preventing her son Ty to thrive and develop normally during his first year of life! She NEVER gave up seeking help and praying. As a result, Ty is doing well and his sister was screened prior to birth. She, too, tested positive and received treatment early so thankfully is doing well now, too. These two children are doing well BECAUSE they were treated early and because they had a loving mother who was determined to seek an answer and find help for her children. How wonderful would it have been if a simple blood test at birth would have been available then! But now there is one!! For less than \$1.00 per child, this newborn screening test can save many children from the effects of GAMT!!"

-Patricia Stolk, Chesterfield, MO

"This is such a simple and necessary solution to saving quality of life for many children and families. As a mom, and educator, I fully support this cause and hope you will too."

-Cathrine Osthimer, Carlsbad, CA

"I am signing this because my Grand daughter was diagnosed with GAMT in March of 2008. She is now almost 9 years old."

-Adele Hornshaw, Fort St John, BC, Canada

"I'm signing because this screening would help so many families."

-LaLisa Lindemann, Vicksburg, MS

"This testing is so important, we all should get on board!"

-Nathan Vandenberg, Raeford, NC

"This is the right thing to do and all children deserve the best treatment and early diagnosis."

-Nancy Flad, Penfield, NY

"One simple test can dramatically change the life a child"

-Kathy Hales, Milford, OH

"For a friend who's son has a creatinine deficiency."

Blake Hill, Belden, MS

"My nephew's second child has this disorder."

-Caryne Prater, Pipe Creek, TX

“Both of my children have GAMT also. My son was not diagnosed until he was 10 months old and has had to endure years of several different kinds of therapy. My second child (my daughter) was diagnosed and treated immediately, and she has never been to a day of therapy in her life. This is exactly the type of disorder that should be put on Newborn Screening. It is literally saving lives!!”

-Kim Tuminello, Carlsbad, CA

“My son suffers from the nontreatable form of this Creatine Deficiency Syndrome. How can you not support this if it can be treated? In fact, how can you not support any testing that gives parents an idea of what they are up against? This is so very important for our community. Won't you please support this?”

-Melissa Parker, Morton, MS

“I lost a daughter to a mitochondrial disease.”

-Norma Gibson, Ukiah, CA

My Nephew has this illness..i want him cured..

-sajida Ashfaq, Bolton, United Kingdom

“I have 2 children with GAMT. One began treatment at 1 year old, the other at 6 years old. The one who was able to begin at 1 year old has a much different future than the one who began at 6 years old. Early treatment makes all the difference. Give all children the same opportunity by diagnosing and treating early.”

-Beth Robinson, Oswego, IL

“My daughter has GAMT, I think it would be so great to see this added to the newborn screening panel!”

-Shayla Hornshaw, Penticton, Canada

“This disorder is 100% treatable. My son has been treated since birth and scores as “typical” on cognitive testing. My daughter wasn't caught until 5 and she is diagnosed as in a special education classroom and will likely not be able to live independently and need care for the rest of her life. Treatment is affordable, easy and 100% effective. This will change many children's lives.”

-Heidi Wallis, Herriman, UT

“My stepdaughter was diagnosed with gamt at 8 and maybe if it had been sooner she could be living a normal life as a healthy child. She now has a feeding tube and can't speak and has several other issues caused by not being diagnosed and treated as an infant. We all love her the way she is but it is hard to imagine what she is feeling or thinking without her being able to

express herself. Hopefully this screening will let other children grow up without having the difficulties my daughters family has and continue to face.”

-Jenny Santana, Darlington, PA

“My son has a creatine deficiency.”

-Linda Cooper, Newport Beach, CA

“A friends daughter has this”

-Lisa Irwin, Wilmington, DE

“It is important to be able to help these babies, with this program in place!”

-Patti Goodell, Bountiful, UT

“My son has GAMT and went the first 18 months of life undiagnosed and untreated. He did not meet typical milestones and then started having seizures. This heartache is preventable. PLEASE help these kids have a good start and chance at life! Thank you!!”

-Laura Ward, Ogden, UT

“Our friends have grandchildren that suffer from this.”

-Scott Barrick, Draper, UT

“I know this is a good target for newborn screening because it is readily diagnosed with existing tandem mass spectrometry methodology, and most importantly, because early intervention can dramatically improve neurodevelopmental outcome.”

-Bruce Barshop, La Jolla, CA

“Everyone deserves the best possible shot at a happy healthy long life. I signed because it's a non invasive quick test that could help give a better quality of life to those diagnosed/affected with/by a GAMT deficiency.”

-vanessa perryman, Gilbert, AZ

“I care about this cause. It has touched lives very close to me”

-Dianne Bierman, Del Mar, CA

“My daughter has severe developmental delays, she sees a speech therapist, occupational therapist and will be going into a special education class next year instead of kindergarten.”

-Nicole Bahr, Toledo, OH

“It is immoral to do nothing to diagnose this in infants when an early diagnosis and treatment can have a 100% impact on the quality of life of the child.”

-Laurie Donlon, Morristown, NJ

“Someone in my family has a CD and I want to do what I can to help!”

-Katie Evans, Studio City, CA

"I am signing this petition because I know what a life changing difference it has made in these two young lives. My hope is that more and more parents will become educated and have the same Hope and change for their young children."

-Jennifer Pickard, Carlsbad, CA

"Ty and Paige Tuminello are my nephew and niece."

-Mary Fischer, Stuttgart, AR

"Why not? Lets save lives."

-Robin Sjostrom, Albuquerque, NM

"Someone daughter has this."

Lisa Cosbey, Rehoboth Beach, DE

Public Comment to the Secretary's Advisory Committee on Heritable Disorders in Newborns and Children

5-9-2016

Michele Lloyd-Puryear, M.D., Ph.D.
Newborn Screening Consultant
Parent Project Muscular Dystrophy

On behalf of Parent Project Muscular Dystrophy [PPMD], I would like to thank the Committee for providing me with the opportunity to address you here today.

My name is Michele Puryear and I serve as a consultant to PPMD and I am here on behalf of the more than 8,000 individuals estimated to be living with Duchenne muscular dystrophy in the U.S. today. In addition, I am here on behalf of the thousands of babies that need to be screened for Duchenne muscular dystrophy. Ms. Annie Kennedy last spoke with you in February 2016 about our newborn screening work at PPMD.

Today, I will be providing an update on our activities since we last spoke with the Committee.

Duchenne muscular dystrophy (DMD) is one of the ten most severe and common pediatric genetic diseases and affects an estimated 1 in every 3,500-5000 male births. While DMD is a 100% fatal disease, in 2015 the therapeutic landscape changed and new treatments have been developed that target the different kinds of mutations causing DMD. Pending the launch of these new treatments, newborn screening of babies for DMD therefore becomes critical. The current treatments are based on the various genetic mutations causing DMD and include:

- Ataluren or Translarna™: It is estimated that a nonsense mutation is the cause of DMD in approximately 13% of patients, or about 2,000 patients in the USA/2,500 in the European Union [EU]. Ataluren received marketing authorization in the EU in August 2014 for the treatment of nonsense mutations for DMD in ambulatory patients aged five years and older, representing the first treatment approved for the underlying cause of the disease. Although the company developing ataluren received a "Refuse to File" letter from the FDA, the company has proceeded with clinical trials and actively is pursuing regulatory approvals for Translarna in DMD globally.
- Exon skipping therapy: There are two interventions in the regulatory pipeline that utilize exon skipping, Eteplirsen and Kyndrisa. Both benefit the same subset, or approximately 13% of the Duchenne population, whose disease may be modified through a skipping of the targeted exon 51.

Confirmatory trials for eteplirsen intervention are being led by Sarepta Therapeutics in the USA and an accelerated approval pathway for review commenced in 2015. After 3 years of eteplirsen treatment the six-minute walk distance was 151 meters better than natural history controls and fewer treated DMD patients had lost ambulation. Sarepta presented data to FDA last month and we are waiting for a final decision by FDA. Kyndrisa is being developed by Biomarin and is also under regulatory review.

In February 2016, we told you about our newborn screening initiative, which included the formation of a steering committee and six workgroups. The workgroups were set up to look at the existing data available for evidence review and gaps in the evidence that need to be addressed within a newborn screening pilot. In total more than 50 experts have been involved in this process. In addition, we are working in partnership with the NIH funded Newborn Screening Translational Research Network [NBSTRN] to address some of the issues and to facilitate the establishment of infrastructure needed for a pilot. The workgroups are: Outreach & Education for both health care professionals and families; Follow-up and Clinical Care considerations for pre-symptomatically identified infants with DMD; Laboratory Test Validation and Refinement; NBSTRN Integration: Clinical Integration Group and creation of a longitudinal pediatric data resource; ELSI; and finally, the Evidence Review Workgroup.

Highlights of our efforts over the past few months include the development of a paper by the DMD-ELSI workgroup to identify ELSI considerations that should be considered when conducting a newborn screening pilot. This project has become a collaborative effort with the NBSTRN-ELSI workgroup. The Follow-up and Clinical Care considerations workgroup has submitted a paper for publication. PPMD will be convening their Certified Duchenne Clinical Care directors and providers to develop treatment guidelines for the treatment of newborns; these will be piloted within a newborn screening pilot. This project will necessitate collaboration with AAP and ACMG, as we anticipate the creation of an ACTsheet for newborns. We also have begun working with NBSTRN to create an LPDR specific to DMD. This project is in collaboration with the Muscular Dystrophy Association and will utilize our registry and the registry developed by MDA.

Additionally, we anticipate the pilot to refine the screening test for creatine kinase that we reported on at your last meeting, will begin next month. PerkinElmer is leading this project, in partnership with the California Department of Health and will be using the residual newborn screening dried blood spots from the California Biobank. PPMD has been working with Certified Duchenne Care Centers based in California that have agreed to participate in the project. IRB approval from California State and at the local institutions has been obtained.

We acknowledge the extraordinary amount of work that still remains to be done in our path toward establishing newborn screening for Duchenne muscular dystrophy.

