U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

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HEALTH RESOURCES AND SERVICE ADMINISTRATION

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THE ADVISORY COMMITTEE ON HERITABLE DISORDERS IN NEWBORNS AND CHILDREN

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MEETING

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MONDAY,
MAY 9, 2016

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The Committee met in the Conference Room at NIH Events Management, 5635 Fishers Lane, Suite T500, Rockville, Maryland, at 9:31 a.m., Joseph A. Bocchini, Jr., Chair, presiding.

MEMBERS PRESENT:

JOSEPH A. BOCCHINI, JR., Chairperson
JEFFREY BOTKIN
CARLA CUTHBERT
KELLIE B. KELM
FRED LOREY*
MICHAEL LU
DIETRICH MATERN
STEPHEN McDONOUGH
KAMILA B. MISTRY
JOAN SCOTT
CATHERINE Y. SPONG
ALEXIS THOMPSON*
CATHERINE A. L. WICKLUND

DESIGNATED FEDERAL OFFICIAL:

DEBI SARKAR, Health Resources and Services Administration

ORGANIZATIONAL REPRESENTATIVES PRESENT:

JOSEPH R. BIGGIO, JR., M.D., American College of Obstetricians and Gynecologists*
NATASHA F. BONHOMME, Genetic Alliance
CHRISTOPHER KUS, Association of State & Territorial Health Officials*
CAROL GREENE, Society for Inherited Metabolic Disorders
ADAM KANIS, Department of Defense*
EDWARD R. B. McCABE, March of Dimes*
ROBERT OSTRANDER, American Academy of Family Physicians
SUSAN M. TANKSLEY, Association of Public Health Laboratories*
BETH TARINI, American Academy of Pediatrics
KATE TULLIS, Family Health and Systems Management Delaware Division of Health
CATE VOCKLEY, National Society of Genetic Counselors
MICHAEL S. WATSON, American College of Medical Genetics and Genomics

ALSO PRESENT:

CHRISTINE BROWN
KATHRYN CAMP
NANCY GREEN
ALEX KEMPER
MELISSA KLOR
LAURA MARTIN
JANA MONACO
SPENCER PERLMAN
MICHELE PURYEAR
SCOTT SHONE
RANI SINGH

DEAN SUHR*
KIM TUMINELLO
TIINA URV
HEIDI WALLACE

*** via telephone**

A-G-E-N-D-A

P-R-O-C-E-E-D-I-N-G-S

9:31 a.m.

CHAIR BOCCHINI: Good morning, everyone, and welcome to the May 2016 meeting of the Advisory Committee on Heritable Disorders in Newborns and Children.

Before we get started I'd like to introduce a new AMCHP representative, Dr. Kate Tullis. Dr. Tullis is currently the Title 5 Children and Youth with Special Health Care Needs director in the State of Delaware.

She has a background in genetics and with the state newborn screening program. So, Dr. Tullis, welcome to serve as a representative.

First I need to now do a roll call of the committee, members and organizational representatives. So, we'll start with Don Bailey.

MEMBER BAILEY: Here.

CHAIR BOCCHINI: I'm here. Jeff Botkin.

MEMBER BOTKIN: Here.

CHAIR BOCCHINI: Coleen Boyle.

MEMBER BOYLE: Here.

CHAIR BOCCHINI: Catherine Spong.

MEMBER SPONG: Here.

CHAIR BOCCHINI: Kellie Kelm.

MEMBER KELM: Here.

CHAIR BOCCHINI: Fred Lorey should be on the phone.

MEMBER LOREY: Yes, here.

CHAIR BOCCHINI: Thank you. Dieter Matern.

MEMBER MATERN: Here.

CHAIR BOCCHINI: Steve McDonough.

MEMBER MCDONOUGH: Here.

CHAIR BOCCHINI: Representing AHRQ, Kamila Mistry has not yet arrived. Michael Lu representing HRSA.

MEMBER LU: Here.

CHAIR BOCCHINI: Alexis Thompson by phone.

MEMBER THOMPSON: Here.

CHAIR BOCCHINI: Thank you, Alexis.

Cathy Wicklund has not yet arrived. And our DFO Debi Sarkar.

MS. SARKAR: Here.

CHAIR BOCCHINI: Now for the organizational representatives, representing the American Academy of Family Physicians, Robert Ostrander.

MR. OSTRANDER: Here.

CHAIR BOCCHINI: American Academy of Pediatrics, Beth Tarini.

MS. TARINI: Here.

CHAIR BOCCHINI: American College of Medical Genetics, Michael Watson.

MR. WATSON: Here.

CHAIR BOCCHINI: American College of Obstetricians and Gynecologists, Joseph Biggio by phone.

And then Association of Maternal and Child Health Programs, Kate Tullis.

MS. TULLIS: Here.

CHAIR BOCCHINI: Association of Public Health Laboratories, Susan Tanksley by phone.

And the Association of State and Territorial Health Officials, Chris Kus by phone.

MR. KUS: Here. And can I make a comment that I'm not able to get on the visual webinar. It just keeps spinning, so there's some technical difficulty.

CHAIR BOCCHINI: All right, thank you for making us aware of that. We'll look into it.

MR. KUS: Thanks.

CHAIR BOCCHINI: Department of Defense, Adam Kanis by phone.

MR. KANIS: Here.

CHAIR BOCCHINI: Genetic Alliance, Natasha Bonhomme.

MS. BONHOMME: Here.

CHAIR BOCCHINI: March of Dimes, Ed McCabe by phone.

National Society of Genetic Counselors, Cate Walsh Vockley.

MS. VOCKLEY: Here.

CHAIR BOCCHINI: And the Society of Inherited Metabolic Disorders, Carol Greene.

MS. GREENE: Here.

CHAIR BOCCHINI: Thank you all for being here and being a part of the meeting.

As you're aware, shortly after our last meeting we received the correspondence from the Secretary that she approved both our recommendation for MPS I and X-ALD, but she did not accept the proposals we made for funding recommendations.

So now the RUSP has been expanded to 34 conditions based on her acceptance of our recommendations.

Even though she didn't accept the funding recommendations, she did encourage in her response federal agencies to continue to provide technical assistance and support states with existing resources.

So, as a result HRSA has developed a funding opportunity, and I'm going to turn this to Debi to make you all aware of what HRSA is doing.

MS. SARKAR: Thanks, Dr. Bocchini.

So, HRSA issued a funding opportunity announcement called the Newborn Screening Implementation Program regarding conditions added to the Recommended Uniform Screening Panel.

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 for $2 million per year and it's a two-year project period. And due date for applications is May 27, 2016.

If you have any questions about it you can let me know after the meeting. Thanks.

CHAIR BOCCHINI: Thank you, Debi. I want to make everybody aware that nominations are open for the 2017 openings that will become available on the committee.

They are currently due within a short time, May 16.

We want to make everybody aware that this year there's a turnover of two members of

the committee. And in addition we are replacing two additional members who needed to leave the committee because they took different positions within the government.

The process is underway to complete the applications and acceptance of those four individuals, and we hope to have that information available shortly so that they can join the committee at our next meeting.

On the other hand, we now need additional people to fill the openings for 2017. So, I'd like to remind everybody to be thinking about individuals, those of you organizational representatives to think about individuals who might be interested and qualified to be members of the committee so that we could have again another robust group of potential nominees to consider.

So, here on the slide shows the individuals that we need, the background skills that individuals must have to be considered for the committee. And so we look forward to having

a large number of nominees from which to pick.

We now need to have a vote on acceptance of the minutes of the February meeting. Are there any additions or corrections to be made to the minutes that were distributed with the agenda book? Steve.

MEMBER MCDONOUGH: This is McDonough. I'm not with Sanford Health anymore. I'm retired. So that needs to be changed.

CHAIR BOCCHINI: Okay, we'll make that correction.

Hearing no others we will now vote to approve the February 2016 minutes with the one adjustment. Don Bailey?

MEMBER BAILEY: Approve.

CHAIR BOCCHINI: I approve. Jeff Botkin?

MEMBER BOTKIN: Approve.

CHAIR BOCCHINI: Coleen Boyle. Catherine Spong. Kellie Kelm.

MEMBER KELM: Approve.

CHAIR BOCCHINI: Fred Lorey.

MEMBER LOREY: Approve.

CHAIR BOCCHINI: Dieter Matern.

MEMBER MATERN: Approve.

CHAIR BOCCHINI: Steve McDonough.

MEMBER MCDONOUGH: Approve.

CHAIR BOCCHINI: And then Michael Lu.

MEMBER LU: Approve.

CHAIR BOCCHINI: And Alexis Thompson.

MEMBER THOMPSON: Approve.

CHAIR BOCCHINI: Okay, the minutes are approved from the prior meeting.

So, this slide shows the priorities that the committee set that are underway with three workgroups.

The Pilot Study Workgroup will present its report and recommendations today. The Cost Analysis Workgroup continues efforts and we'll receive an update from them today. And the Timeliness Workgroup which is a permanent workgroup will provide us with an update as well today. Well, during this meeting.

Now, I want to make everybody aware

that the standing subcommittees will now be termed "workgroups." And so we're just changing the name, we're not changing the responsibilities of each of those subcommittees.

We're changing the name to workgroups because this aligns appropriately with the requirements of the Federal Advisory Committee Act, the FACA Act.

And by terming them workgroups they allow them to continue their efforts in the way that they are. And so we will now just change the names, but again not change their responsibilities.

They will meet this afternoon as scheduled.

Just to remind you, the Education and Training Workgroups have prioritized with the approval of the full advisory committee creating a companion piece to the ACT sheets that will provided PCPs with guidance and tips for discussing positive newborn screening results with parents, and do an educational outreach

project in collaboration with Newborn Screening Clearinghouse Babies First test.

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

The Laboratory Standards and Procedures Workgroup is looking at defining and implementing a mechanism for periodic review, an assessment of lab procedures utilized for effective and efficient testing of the conditions included in the uniform panel, and defining and implementing a mechanism for periodic review and assessment of infrastructure and services needed for effective and efficient screening of the conditions included on the newborn screening uniform panel.

And just as a reminder our next two meetings, August 25 and 26, will be an in-person meeting and webcast. And then November 3 and 4 will be webinar.

So, during this meeting we will have a presentation on medical foods impact on patient access. That's to help continue our discussion on long-term follow-up in newborn screening.

We had a condition nominated, GAMT, for evaluation for inclusion on the RUSP. You will hear an update from the Nomination and Prioritization Workgroup on review of the packet of information that was presented to us, and discussion by the committee and a vote as to whether the condition is ready to be moved forward for evidence review.

We'll have discussion on prenatal education about newborn screening and dried blood spots, and then following this afternoon's discussions the workgroups will provide updates tomorrow on their activities.

So, I'm going to turn this over again to Debi to discuss ethics and conflicts of interest.

MS. SARKAR: Good morning, everyone. Thank you for joining us today. As usual I have

my standard reminders for the committee members.

First, the committee is advisory to the Secretary of Health and Human Services. Anyone associated with the committee or due to your membership on the committee if you receive inquiries about the committee or the committee's work please let Dr. Bocchini or I know prior to committing to an interview.

I must also remind committee members that you must recuse yourself from participation in all particular matters likely to affect the financial interests of any organization with which you serve as an officer, director, trustee, or general partner unless you are also an employee of the organization, or unless you have received a waiver from HHS authorizing you to participate.

And all of you have been doing this. I appreciate you letting me know prior to a vote if you think that there is a conflict.

So, the advisory committee's legislative authority is found in the Newborn

Screening Saves Lives Reauthorization Act of 2014.

This legislation established the committee and provides the duties and scope of work for the committee.

However, all committee activities are governed by the Federal Advisory Committee Act, otherwise known as FACA which sets the standards for the establishment, utilization and management of all federal advisory committees.

So, according to FACA all of our committee meetings are open to the public. If the public wish to participate in the discussion, the procedures for doing so are published in the Federal Register notice and we announce them at the opening of the meeting.

For this May meeting we put in the FRN, the Federal Register notice, that we would have a public comment period for today for 30 minutes.

Only with advance approval of the chair or DFO public participants may question

committee members or other presenters.

Public participants may submit written statements. And you'll find we have quite a few public comments. They were all included in the briefing book.

The written statements are part of the public record and any further public participation will be solely at the discretion of the chair or DFO.

And as always please remember to state your name and your organization first to ensure proper recording of our transcript and meeting minutes.

CHAIR BOCCHINI: Thank you, Debi. Now we're ready to begin the meeting with the first presentation on Medical Foods for Inborn Errors of Metabolism: Issues in Patient Access.

For that, I'm very pleased to introduce Kathryn Camp. Kathryn Camp joined the staff of the Office of Dietary Supplements in September of 2010.

After 25 years in clinical practice

caring for children with genetic and metabolic conditions she's working with ODS in the Office of Rare Diseases Research in the development of an evidence-based framework for nutrition interventions currently used to treat these rare disorders.

Prior to coming to ODS Ms. Camp provided staff support to the Secretary's Advisory Committee on Genetics Health and Society as a senior policy analyst in the Office of Biotechnology Activities at NIH.

She spent 13 years at Walter Reed Army Medical Center in the Department of Pediatrics providing clinical care to patients and continues to work with pediatric residents and fellows as a Red Cross volunteer.

So, Kathryn, it's good to have you here. We look forward to your presentation.

MS. CAMP: Thank you very much. And I do want to thank the organizers, particularly Joe, and Debi, and Joan for inviting me to present today to you.

And I'd also like to thank, on behalf of patients and clinical providers, the continued interest that the committee is taking in this very vexing issue.

I'm going to hopefully get through quite a lot of material in the time that I have so that there will be time for discussion.

So medical foods. Many of you know this, and if I go over information and data and such that you're already aware of just consider it to be a little bit of a reminder. There may be people listening who don't have all of the background that many of you have.

They are the only recognized therapy for many IEM identified on newborn screen and clinically. We can't forget those who are clinically diagnosed.

They do reduce morbidity and mortality. There's been a half a century history of use. So we always wonder then why aren't they accessible to all patients of all ages.

What I'm going to talk to you today

about, I'll give you a little bit of background on the history of medical food statutes in the United States.

I think it's important to know where things started in order to understand how we can move forward. Why and how they're used, what a medical food is and what it's not. There are a lot of products on the market that want to call themselves medical foods and they frankly don't meet the statutory definition.

I'll talk a little bit about barriers to access and reimbursement, some of the previous activities that have been undertaken to rectify the problem. And I'll provide a few thoughts on a plan moving forward but ultimately the plan moving forward has to come from the community.

And I do consult to the federal government so frankly I have no disclosures.

History of medical food statutes. So, back in 1958 which was when the first medical food came on the market. It was Lofenalac and it was manufactured by Mead Johnson it was

considered a drug. And up to 1972 this was the case when they were then put into the category of foods for special dietary use. Taken out of the drug category and put into a food category.

That was because their usefulness was widely accepted. They were limited in number at this point. There were probably only two products on the market and they were specifically for phenylketonuria.

It was considered that if they went into this category they would be less costly to develop. They wouldn't have to go through the rigorous evaluation that would be required if they were continued to be used as a drug.

In 1973 they were taken out of foods for special dietary use and put into their own category of medical foods. But this actually had unintended and unforeseen consequences because medical foods at this point lost all regulatory oversight because foods do not have premarket review to go into the marketplace.

In 1988 the Orphan Drug Amendments

created the definition for medical foods. And I'm sure most of you can recite this by heart. Maybe not most of you, but some of us.

And I'm just going to give you a second to read it because I don't want to actually read it out loud. But I would like to highlight a couple of important sections in this.

And that is that they are used under the supervision of a physician for specific dietary management of a disease or condition in which it is understood that there are distinct nutritional requirements based on recognized scientific principles. So you can't just go out there and put something on the market that somebody says well, this might work for neurocognitive development.

However, this particular definition did not provide FDA with an evaluation mechanism to determine what fits in that category and what does not fit. So the FDA has struggled with trying to determine this.

So the overall umbrella category for

these products is the food category. And under this category, and obviously there are conventional foods that are in here as well, foods for special dietary use, medical foods, infant formulas and dietary supplements.

And I'm not going to be talking about dietary supplements or these other products that are used in IEM because that's another hour and a half talk in and of itself. They are still important treatment modalities with their own issues.

Medical foods being in this food category, this is an inherent conflict because foods cannot be used to diagnose, cure, mitigate, or treat disease. Those are the terms that surround the use of a drug.

And I'm going to show you that in fact that's what we use medical foods for is to treat a specific disease.

So, medical foods for phenylalanine hydroxylase deficiency, and of course it's also previously and more commonly known as PKU, this

was then, drug looking.

This is medical foods for inborn errors of metabolism today.

And I'm showing you just a few examples of the many products that are available on the market for a variety of different disorders.

And you can see that they look a little nicer, they're not drug-like. Medical food manufacturers have spent inordinate amounts of time and money to produce products that looked a little bit more conventional, that had better nutritional composition and that were more palatable.

My industry colleagues tell me that as innovation goes up reimbursement goes down because as things start to look more and more like a food insurance companies are more and more likely to deny coverage.

This right here, this bar is actually a complete -- well, it's not complete, it doesn't have phenylalanine in it, but it is a product

that an insurance company looks at and says we're not paying for energy bars.

So the categories of medical foods, we need to understand these in order to understand why insurance coverage is so sort of sloppy.

The products with a full complement of nutrients except the offending nutrient, for example, in phenylalanine hydroxylase deficiency, these products would have all of the nutrition that would be required for growth and development for an infant, a child and an adult except with pH deficiency obviously it would exclude phenylalanine.

They come in a variety of forms, powder to be reconstituted, ready to drink, and bars.

Some state mandates will only cover the powder and not the ready to drink. Others won't cover this, that and the other.

And then there are modular products. And these are products that do not contain the full range of nutrients, such as amino acid

mixtures.

There are ready to drink low-volume low-calorie products that are more suitable for adults who have lower energy needs, tablets, sports drinks. This one over here, this Restore is actually glycomacropeptide. And it looks like a power drink. So, a school aged child would probably be okay putting that in their lunch box and taking it to school.

And then there is a category called foods modified to be low in protein, or also low-protein foods.

And these are baked goods, pasta, rice, et cetera. And they were developed to provide calories, provide extra nutrition in some cases, but primarily calories and variety in diets that are severely limited in protein.

And I consider them to fall into the medical food category. It sort of depends on how you actually define them. FDA is not sure whether they fit that category or not.

Again, what fits in the category

depends on what the intended use is.

So, medical foods are management modalities for inborn errors in metabolism that are identified on newborn screen and clinically.

But with respect to newborn screened conditions, 19 of the core conditions on the RUSP utilize medical foods and/or amino acids, vitamins, or cofactors. So we can't forget them, but we are again focusing on medical foods.

These conditions wouldn't be on the RUSP if it weren't for these treatments, right? I mean, the reason why conditions get to the RUSP is because there are treatments available.

And in the case of these 19 core conditions these are the treatments.

Medical foods are required for other IEM diagnosed clinically.

So this is obviously a table of the core RUSP conditions, and those that are in bold are treated with medical foods and/or single amino acids, amino acid mixtures, vitamins, or other cofactors.

And this equates to about slightly less than 500 infants born every year who require a medical food. It's over 600 for those who require -- if you add on those that require vitamins and cofactors such as biotinidase deficiency obviously utilizes Biotin.

So what happens if we don't treat these conditions?

It depends on the condition. Some conditions have less horrible outcomes, classic PKU, severe cognitive impairment, autistic-like features.

Maternal PKU syndrome is a very, very important and in my opinion neglected concern. Over 50 percent of adults are not being followed in a clinic and we must assume that half of them would be women.

If they're not being treated and they're of child-bearing age the risk of maternal PKU syndrome is obviously 100 percent.

And this is a condition where fetal exposure to elevated phenylalanine levels causes

microcephaly and poor outcome in the infant.

Homocystinuria, it varies. MSUD is one of the ones identified on newborn screen that if not treated will result in death. And that's true also for the organic acidemias MMA and PA and VLCADD has their own issues that one can't really ignore.

So I'm going to briefly go over the basic principles of dietary management. I'm going to use phenylalanine hydroxylase deficiency as an example.

And this is important because this helps us to understand how medical foods are able to be used to treat these conditions.

So, normal phenylalanine metabolism, food and metabolized tissue are where we get phenylalanine. It is an essential amino acid so our bodies do not make it, although in states of stress and illness our bodies will release phenylalanine out of the muscle.

So that's another important point is that we try to keep patients with these

conditions to not be catabolic.

So phenylalanine through the help and action of phenylalanine hydroxylase goes to tyrosine.

And then tyrosine goes on to make very important neurochemicals that go to the brain. Dopa, norepinephrine, epi, and melanin.

So what happens if there is no phenylalanine hydroxylase or little phenylalanine hydroxylase? We get -- obviously phenylalanine builds up in the blood and tyrosine becomes deficient.

So those neurochemicals are also going to become deficient. We get side pathways that also make metabolites that build up in the blood.

But another important aspect of this condition, of this problem is that phenylalanine is one of three aromatic amino acids and it will compete at the blood-brain barrier for uptake.

And so tryptophan and tyrosine get left out. And tyrosine, the little that's actually there, can't get in. And tryptophan is

of course an important precursor to serotonin.

And that is a serious condition when you lack sufficient serotonin. And that's probably, along with the dopa, norepinephrine, epi, et cetera, that cause some of the imbalances in the brain in patients with PKU.

So what do we do? How do we solve this? And this is what we can do with medical foods is we restrict the precursor, and that means we restrict the amount of whole natural protein that contains phenylalanine. And we try to prevent catabolism as I already mentioned.

And we supply the product and other essential nutrients.

And I'm going to show you a little bit about how we do this. Obviously it's done with medical foods.

They supply a source of protein for body growth and development that's devoid of the offending nutrient and it also contains essential nutrients, carbohydrate and fat.

And along with the very small amount

of natural protein in a carefully planned diet this is the primary intervention. And it will prevent or reduce adverse medical and developmental outcomes.

And when it is used early, at or near birth and continued throughout life it can lead to normal or near normal health outcomes.

And they work. This is a historical slide from Georgetown many, many years ago of a young man who was born prior to newborn screening.

He has the full phenotypic outcomes of PKU. And this is a little girl who was identified on newborn screening. Should she continue to follow a carefully planned diet throughout her lifetime we would expect her to have cognitive and developmental normalcy.

So, I want to just show you very quickly what a sample daily intake is for an 8-year-old boy with PKU. And Christine Brown's in the audience and I'm sure that she has great experience with these kinds of meal plans.

This is a very simple one because I wanted to be able to fit it on one screen. We do include other things that are a little bit more interesting.

Those items that are in black are medical foods, and those that are in red are natural foods. So, from the natural foods 6 grams of protein and 583 calories. A child that's 8 years old cannot live on that.

From the medical foods, 43 grams of protein and 825 calories. So what we get from that is a whole meal.

And please understand that 1 ounce of cheese or 1 ounce of chicken has this child's feed tolerance of 350 mgs of phenylalanine. And no one can live on 1 ounce of either one of those things.

So this slide is courtesy of Helen McCune, one of our metabolic superstars. This is dinner. And it represents one-third of the phenylalanine allotment for that child. And this wouldn't go very far.

This little tiny film of milk is all that this kid would get. If we add medical foods we actually have a meal.

And this is the gear needed to feed a child with maple syrup urine disease. This looks pretty medical, doesn't it? I mean, you don't buy these things at the Babies"R"Us.

So, we're going to switch gears now and talk a little bit about how statutes define medical foods.

They are distinguished from that category of foods for special dietary use. Remember we talked about that was where they were originally placed because they are intended for the specific dietary management of a disease or condition. Already mentioned that.

They meet distinct nutritional requirements and they must be used under medical supervision.

And specially formulated for the patient who is seriously ill or who requires the product as a major treatment modality.

And this is a very important point. FDA considers them to be used either orally or through tube feeding.

And it does not pertain to all foods fed to sick patients. So if you think about those of you who were in clinical care or have tried to boost up the calories and the nutritional intake for a patient who's ill you may use a product that I'm not going to name them, well maybe I am, like Ensure, Boost, PediaSure, et cetera. Those are not medical foods.

So the importance about medical food labeling. Medical food labeling is very specific and the requirements are, as I will show you, they are labeled for management of a specific medical disorder, disease, or condition.

And you can see there that this particular can of Phenex-2 has that information on it.

And labeled for use under medical supervision. You do not find these statements on

foods for special dietary use.

So how are they regulated? They're regulated under the Food, Drug and Cosmetic Act and the Fair Packaging and Labeling Act as are dietary supplement, by the way.

They are exempt from nutrition labeling, health claims and nutrient content claims requirements and you can understand why that is, because they do have a health claim which is that they treat a medical condition.

And they do not require a nutrition facts label because that would not be applicable or appropriate.

The ingredients must be approved food additives. Obviously they have to comply with general food regulations and certainly the GRAS regulations.

And they do not require premarket review or approval by FDA. And I'm going to probably say this a hundred times.

However, manufacturers must be registered with FDA and they must comply with

current good manufacturing practices. And they are inspected every two years by the FDA.

If the company also manufactures infant formulas they are inspected once a year.

And we were asked to find out from FDA the list of medical food products that were available and they don't have one. Because there's no premarket review there would be no reason for them to have a list.

However, if anyone's interested Genetic Metabolic Dietitians International does have a very nice list on their website.

Infant formulas. Again, this is a little bit of a different category. They are considered to be medical foods, but they are regulated as infant formulas. So they have a little bit more I should say oversight.

They are categorized as exempt infant formulas. And the exempt does not mean that they do not have a regulatory structure. It just means that they're exempt from the nutrition labeling because they are not required to contain

the offending nutrient.

They have strict labeling requirements again and new products do require a 90-day premarket notification to FDA. And this is different than medical foods for children and adults.

So in 2013 FDA came out with draft guidance for industry. And draft guidance is where we get a lot of information about what FDA is thinking about certain legislation, certain regulations that they're responsible for.

So, the definition of medical foods narrowly constrains the types of products that fit in this category. That is what they are thinking.

Medical foods are not this huge category of things that people can take for a number of different conditions.

And you can see some of these issues, specifically formulated and processed as opposed to naturally occurring. So, an orange or an apple, for example, would not be considered a

medical food.

For partial or exclusive feeding orally, or as enteral tube feeding, and for a patient with limited or impaired capacity whereby dietary management cannot be achieved by modification of the normal diet alone. And this is a very important point. And those italics, I put them in there because I view this as one of the keys to how we determine what a medical food is or isn't.

And it is used to manage unique nutrient needs resulting from a specific disease or condition, et cetera.

The final guidance has not been released. I'm hopeful that they will figure it out and get it out so that we actually can turn to this thinking as we consider how we move forward.

So, what a medical food is not. It is not a prescription drug. There's no premarket review or approval. They do not have NDC codes. They do not require a prescription.

But the regulation states that they are to be used under medical supervision and most medical food manufacturers require authorization from a healthcare provider before they will provide the product to a patient.

They are not products developed for pregnancy unless the pregnant woman has PKU because pregnancy is not a disease. Remember, in that thinking that FDA has these medical foods are for individuals with a specific disease.

And it's not for diabetes because diabetes can be modified with a normal diet.

What do medical foods cost? Well, they cost a lot compared to regular foods, but a whole lot less than Kuvan which is the first drug that was approved by FDA for phenylketonuria, $200,000 a year for an adult with pH deficiency.

They don't cost that much, but drugs get covered, and Kuvan gets covered, and medical foods in many cases do not.

So, this table came out of a paper that was published by Therrell, et al., in 2014.

And what we essentially did was we came up with a couple of categories in order to estimate what it cost above and beyond foods that would be purchased and consumed by an individual without a condition.

And committee members, you have this in your packet and the publication is readily available. I'd just like to focus on this final dark orange column.

You can see that for an infant it's over $2,000 a year. This is outside a typical expenditure. And it starts to march up. And when you get to an adult male or a pregnant woman it's close to $25,000.

And an adult male who does not have a good job, or does not have insurance is going to be hard-pressed to provide enough medical food for themselves at a cost of $25,000.

What do medical foods cost to families? Sue Berry published a paper that was a combined effort that came out of this committee that surveyed families asking questions about

their out-of-pocket expenses.

Twenty-one percent of parents paid greater than $100 a month for formula, and some as high as $500 a month. Forty-eight percent, so almost half of parents paid greater than $100 a month for low-protein foods.

So, how do patients get medical foods? From a bunch of different ways. This is such a hodgepodge it's just, it's frightening.

They purchase out-of-pocket from pharmacies, hospitals, health departments, medical supply companies, medical food companies. Sometimes they're reimbursed by private insurance and sometimes they're not.

They do get products through programs administered by states and these include Medicaid, CHIP and WIC. The military provides metabolic formula for dependents with inborn errors of metabolism, but they do not cover low-protein foods.

Newborn screening programs or metabolic clinics, some states actually tack an

additional charge onto the newborn screening and then those funds get put into sort of a warehouse in order to provide products for patients in that state.

Many patients utilize multiple sources. And this came out of Sue Berry's work. And that means that families are looking in multiple places to find things.

And any of you who have tried to advocate even for yourself or your family with respect to reimbursement can understand that this is a problem and most of you are probably not having to do that every single day.

Most medical food companies provide a small supply for newly diagnosed patients and they do cover some formula for pregnancy. But they're not in the business of providing free medical food for patients.

And while they are very, very good at filling in little gaps we cannot expect them to be a source for everyone all the time.

So, who pays? Depends on who you are,

how old you are, what your disorder is, depends on where you live, and it depends on what type of health benefits you have.

So prior to the Affordable Care Act 38 states had passed mandates for state or private payer plan coverage.

And we talk about state mandates a lot, and there's been another one added. But this is how it sort of breaks down on what gets covered and what doesn't.

In 10 states formula only was covered. In 28 states actually covered formula and low-protein foods, so a little bit over half of the states. PKU only in six states that had mandates, so that left all the rest of them out. Sixteen states had select disorders. So they didn't cover for everything, for all inborn errors. And 16 states covered all disorders.

So you can see that if you had condition A and you needed to move or you wanted to move you'd be having to find out whether your state had mandates, whether your insurance

company would cover it.

I think that Dr. Ostrander is going to say something in a little bit, but it's been difficult for people to even find out what their states do at this point.

So, since the Affordable Care Act? Well I don't know. I have not seen a formal national survey of state practices. I haven't seen one that has been undertaken in order to understand what's going on in every state.

The ACA does not specifically address coverage of medical foods for inborn errors, although newborn screening is a covered benefit without copay to families.

So the essential health benefit package included newborn screening, no copay, but was silent on the issue regarding treatment for these conditions.

So states with mandates may still have these mandates. They still may not apply to self-insured or federal programs. So state mandates do not apply to federal programs because

the feds cannot be -- well, if you understand history the feds cannot -- a state does not have to comply with a federal plan. Let me leave it at that.

So here's what metabolic dietitians report. And we had the NYMAC, the New York Mid-Atlantic regional collaborative did a small survey, very informal, of dietitians in the seven states that comprise that region. And we got a lot of very interesting information.

So, a patient with PKU lives in New Hampshire. New Hampshire has a mandate, but this patient has an Illinois insurance plan that does not have a mandate.

The patient's Illinois plan rejected coverage for metabolic formula. So it depends on where you live.

A patient living in Maryland which has a mandate has federal Blue Cross Blue Shield which doesn't cover medical foods for patients over age 22 unless it's tube fed or the sole source of nutrition. So, these adults are left

untreated.

There are very few adults with PKU. In fact I would probably say I could count them on one hand who have a gastrostomy tube for their feeding. Patients with PKU do not require gastrostomy tube feedings.

New Jersey has a comprehensive mandate, but Medicaid doesn't cover low-protein foods.

Patients in Pennsylvania which has a mandate for formula only are not able to get low-protein foods which affects their ability to fully comply with their diets.

So, we asked these dietitians how outcomes are affected by state policies. And these are just a couple of comments. I have pages more.

New York is losing uninsured adults to care. It's hard to keep a patient motivated to seek care when they do not have a good-paying job that has good insurance, and the copays and coinsurances can be prohibitive. They can be

$2,000 a year. And if you don't have a job $2,000 a year is a lot of money.

This lack of access to medical foods and subsequent need to have multiple jobs to pay out of pocket leads to inconsistent metabolic control.

And in Virginia state formula programs have become more restrictive since 2006 expanded newborn screening. And I don't think that that was the intention of the committee and of expanded newborn screening, to make it harder for patients to get their treatments. So, again, unintended consequences.

This is another big problem, Healthcare Common Procedure coding system. So this is how services and how products that are provided to patients are coded.

They're used by Medicare, monitored by CMS. And this is one of three HCPCS codes that are used for inborn errors. This is B4162. There are two more.

And the coding is for enteral formulas

for IEM administered through an enteral feeding tube with 100 calories equals one unit of reimbursement.

So, in this case CMS limits the definition of "enteral" to tube feeding. Reimbursement units are based on calories. This is a big problem because we calculate diets for inborn errors based on grams of protein.

Products for older children and adults are high in protein and lower in calories so reimbursement falls way short of needs.

Private insurance companies may or may not adopt these codes.

So what has been done in the past to fix this problem? I think we need to understand this so we can figure out what we need to do different moving forward.

You all wrote letters to the Secretary. You did a really good job back in the early days.

In May of 2009 the committee reiterated a 2007 recommendation to address gaps

in coverage and reimbursement.

And the request was that there be a more uniform approach to amend Medicaid for uniform coverage by state programs.

And five months later you got a response from the Secretary that enacting legislation is beyond the department's authority.

Okay, so that tells us something. We have to be careful what we ask because if it's beyond the department's authority then this kind of response will be sent back to you.

In 2010 the committee recommended that health reform, because this was when the Affordable Care Act was being put together, that healthcare reform ensure access to medical foods and foods modified to be low in protein -- so that was included in this request -- as essential healthcare services irrespective of the source of health coverage.

And by this time the Secretary had to turn around a response within 90 days so she did.

Her interim response was a response

will be forthcoming. I mean, this is a big issue and you have to give time to it so they worked on it for a total of five months.

And then the final response was I cannot adopt the committee's recommendations at this time.

The Secretary was awaiting a Department of Labor survey on the impact of this essential healthcare package and an IOM public workshop. And I think Christine Brown has a little bit of information about the outcome of this public workshop. There was a report that was released in October of this last year.

But I don't think the committee's heard from her regarding this issue. Is that correct? Yes.

So, legislative efforts. There have been a number of those.

The Medical Foods Equity Act of 2011 which was introduced into the Senate by John Kerry, it's often called the Kerry Act, would require federal health programs and private

insurance companies to cover medically necessary foods, formulas, pills, capsules and bars. So everything, all of these little possible items were included so that insurance companies couldn't say we don't cover bars.

It included foods modified to be low in protein and pharmacological doses of vitamins and amino acids as prescribed by a qualified medical provider.

One of the problems with this is that vitamins and amino acids are not drugs either so pharmacological is a little bit of a misused term. And they are not prescribed because they're not drugs. So it's a little bit of tweaking of the language that would have to be done as people move forward.

And it amended the Social Security Act definition of these products specifically for the treatment of conditions as recommended by this committee which left out who? Clinically diagnosed patients.

So, I'm just saying that there's some

things that have to be considered as one moves forward.

And then in 2013 the Medical Foods Equity Act was again introduced by John Delaney. But in 2013 the requirement for private insurance companies to cover these products was removed. The rest of the legislation was very similar. Neither one of these went anywhere.

American Health Security Act of 2011, '13 and '15 introduced by McDermott would have provided coverage for medical foods and reiterated the 1988 medical foods definition.

No committee action in any of the congresses for this particular piece of legislation.

There was a success story I would like to say, and I think on behalf of the National PKU Alliance, a Senate resolution designated December 3, 2015, as National PKU Awareness Day.

There were multiple mentions of medical foods in this resolution. But resolutions do not have any legislative power

behind them. So it's simply a statement and it's a yes, it's an important issue, but it doesn't actually make things happen in terms of insurance coverage.

Advocacy organizations have worked very, very hard in this arena. And I can tell you having been in this business for almost 30 years not just the advocacy organizations. And I'll talk a little bit about some of the other things.

The National PKU Alliance has advocated for coverage and reimbursement in a number of different ways, position statements. They have great educational information and resources on coverage under ACA on their website.

And they secure lead sponsors and lead advocacy in efforts for the Medical Foods Equity Act.

In 2011 the National Organization for Rare Diseases hosted a big, high-level conference on medical foods and came up with a number of things they were going to tackle.

We're still sitting here with the same issues. Time goes by, time goes by, and none of these things have changed, frankly.

Literature and professional organizations have worked for decades. There are a number of papers that have been published regarding this issue.

The Society for Inborn Errors of Metabolism and Genetic Metabolic Dietitians International have policy statements on medical foods.

The American Academy of Pediatrics also had policy statements on the use of foods for special dietary uses that included some mention of medical foods.

SIMD updated their policy statement in 2006.

I mentioned the Academy of Pediatrics and other organizations have worked on statements and are continuing to work on statements.

The PKU management guidelines that were published through ACMG made a very strong

statement - treatment for life mandates the need for medical insurance coverage for medications and medical foods regardless of age.

And GMDI nutrition management guidelines had a similar quote.

And then there's the National Institutes of Health for whom I work.

In 2000 the consensus statement on PKU -- I think there's some people in this audience who actually worked on that consensus statement -- was pretty strong. Reimbursement should be covered by third party providers.

By 2012 NIH was no longer in the business of making recommendations so this publication that was the proceedings for the scientific review conference sort of was a little bit wishy-washy because we really couldn't come out and say that we were going to demand coverage.

We did say that availability for medical foods is inconsistent due to this patchwork of state laws and state programs, and

that it impacts access.

So the players. Who are the players? There are a bunch of them.

Congress is responsible for making legislation. And if anything's going to happen we need Congress.

The FDA interprets and writes the regulations. And they also fund some research in this area.

CMS of course is responsible for Medicaid, Medicare, the CHIP programs. They review and refine and accept new HCPCS codes. HRSA which is obviously the mother of this committee provides health services.

NIH, we are the largest biomedical research funder in the world, $30 billion. So our role is more in understanding the science behind issues pertaining to medical foods as it relates to medical foods, that's NIH's role, and to inform policy. We don't make policy obviously.

USDA funds states to administer WIC

programs and WIC has formularies that are specific to each state.

And then obviously states. State legislation, the way that they provide health services, the way they administer WIC, et cetera.

And of most importance is this group down here, patients, families, advocacy organizations, professional societies and organizations, clinicians and researchers, and medical food and pharmaceutical companies.

So it's a big group of people and they all have to be involved. And frankly, if Congress is going to do any legislation or move forward with legislation all of these entities need to be considered and need to be at the table as discussions move forward on how to solve these dilemmas.

So, these are my thoughts on where we are now. Inborn errors are screened conditions because treatments are available but not for everyone.

Patients and families continue to be

saddled with high costs for medical foods. And when I say high costs for medical foods, it's a tiny amount of money in the broad scope of what society spends on treating diseases in people.

Clinicians spend significant time dealing with coverage and reimbursement which leaves less time for patient care and research. Clinicians spend up to 50 percent of their time advocating for their patients.

Families spend significant time dealing with coverage and reimbursement, leaving less time to play with their kids. If you're spending hours every week, or every month, or however, and Christine can probably attest to the amount of time that it takes trying to get the care that you need, not to mention the anxiety and the stress on whether you're going to get enough for this month, whether you're going to be able to navigate the system.

And if we're talking about families that have the wherewithal and the ability to navigate the system then if you're looking at

people who don't have that ability to navigate the system we have a larger problem.

Greater than 50 percent of adults with PKU are not being followed. Again I think this is a public health issue that really needs to be dealt with.

The effect of the Affordable Care Act on coverage and reimbursement nationally for medical foods is frankly not known at this time, at least it's not known to me. I'd love to hear from others whether we have some understanding of this national picture.

And bills introduced, but Congress has taken no action.

So, the future. Well hey, if we can't get medical foods covered, let's make new treatments. And patients want this. This is from the National PKU Alliance survey of patients - 91.4 percent of patients felt that it was very important to get new treatments.

But new treatments take decades and cost billions of dollars. So meanwhile, almost

500 babies are born each year with an IEM requiring medical foods as the primary management modality.

This is a small percentage of children, but for these patients and families it is 100 percent.

So, moving forward we need access for all. I think we need to understand the current status of state mandates. We need to understand efforts that are currently being undertaken.

But ultimately policymakers at the federal and state level must recognize the changes that need to be made. Everyone will need to gather together to chip away at the barriers and challenges.

And these are not mutually exclusive and there may be other approaches and other ways to work on this problem.

Regardless, it will take leadership, commitment and persistence to navigate the complexities that lie ahead. We have been attempting to navigate these complexities for the

last three decades.

And with that I'm going to close and thank you very much. And I can be reached at these contacts. So I hope I've given enough time for the committee to thoroughly discuss.

CHAIR BOCCHINI: I think you have. Kathryn, thank you for an excellent presentation and giving us a clear understanding of the state as it exists today.

So let's open this to the committee members first. Don?

MEMBER BAILEY: This is Don Bailey. Thank you very much for that informative and discouraging presentation.

I have to say when I saw the word "enteral" up there I thought it was "eternal" and that's actually true. You would need the treatment throughout their lives.

Two questions. One, you mentioned the cost analyses. And I'm wondering if anyone has published any kind of comparative cost-benefit analysis of what would be the relative cost of

not treating to society.

And then secondly, I know you probably can't fully answer this question, but is there anything you can say about why Congress hasn't moved forward when there have been so many positive directions?

Is there a lack of willingness to -- basically assuming this is a state authority and not a federal authority. Are there big lobbying groups that are somehow opposed to this? Are there identifiable reasons why Congress hasn't taken it?

MS. CAMP: So, let me answer your first question which is there has been no published information on the cost-benefit ratio of not treating versus treating because how do you get that information?

That's what I would really like to see. Because you can say what it costs to take care of a patient with methylmalonic aciduria in the ICU. There's certainly data about how frequently patients with some of these conditions

end up in hospital care.

But it doesn't mean necessarily that that is because of poor access to medical foods. And that's harder to get at. Are they just having a decompensation because they got sick? Did they get sick because they weren't adequately nourished?

We know that the lack of good nutrition can lead to problems with immune function. Kids get sicker, they get in the hospital. But that information is not available.

Back in 2013 we tried to figure out a way to get it and we just couldn't. So somebody certainly smarter than I can probably try for that effort.

MEMBER BAILEY: It does seem very important.

MS. CAMP: Yes, absolutely.

MEMBER BAILEY: And it seems like you could model it somehow even without actual data.

But again, cost-benefit analyses don't always carry the day. But on the other hand,

they can be powerful mechanisms for arguing if we don't do this then we have this kind of problem.

MS. CAMP: Right. But again, it's hard to know what patients are taking on a daily basis as well. So yes, that would be fantastic to get that information.

And I think that's what will ultimately drive the train if we can get it.

As far as why legislation has not been successful I think it's a host of different issues. But I know that 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.

And other than that I think it's just this is a small population of people even though it's a huge problem to us. And I don't think society views it as this enormous big issue like we do.

CHAIR BOCCHINI: Steve?

MEMBER MCDONOUGH: This is McDonough. I want to thank you for an outstanding

presentation and very helpful information.

I have one question and a couple of comments.

Does WIC cover medical foods and low-protein foods for children with conditions, those 19 conditions identified in the RUSP?

MS. CAMP: So, WIC covers metabolic formulas I believe in most states, in all states. But they may have a formulary that only includes a certain formula.

For example, for PKU there are a number of different products available, but WIC may only cover one. So if a child doesn't -- if a child moves into a state and they've been on a specific formula for years -- or it can't be that long. WIC only covers up to five years of age. So yes, it will take care of the first five years, but beyond that, no.

You may have to switch a formula. It's not always easy.

They do not cover low-protein foods as far as I know.

MEMBER MCDONOUGH: Thank you. If you go back and look at the history of the Guthrie test and PKU one of the reasons it was marketed to states is that if you screen children for PKU you won't have to pay for the cost of institutionalization. Kids who are severely developmentally disabled were in at that time institutions for lots of people who had developmental delays. So there was a real benefit to the state taxpayers, a cost saving in addition to helping families and people's lives.

And there was a partnership that came out of that where a lot of states helped families with their special formulas for kids with PKU. And that's basically been lost.

Right now the situation, yes, we're going to screen for all these conditions, but you're on your own in a lot of situations. And the burden is placed on the families, and the state taxpayers and federal taxpayers are still benefitting from these children not having substantial developmental delays.

And these families have to go through this ongoing struggle to help their kids.

I'm really happy that you presented the previous Secretary's recommendation and response. It's nice for the committee to get a chance to see that.

The previous Secretary I think made a very poor decision and it's really unfair that the families and kids will face the ongoing burden.

There was an opportunity to have medical foods and formulas be considered an essential health benefit.

And we have a new Secretary, and that Secretary may not be as willing to allow children to be treated as second-class citizens and be discriminated against, not getting the treatment.

So, I'm hopeful that the committee will re-look at this issue. I'm hopeful that the Follow-up and Treatment Workgroup will have an opportunity to work on this over the next year or so.

And this committee is advisory to the Department of Health and Human Services. And if I remember your slide up there, there are a whole lot of agencies who have a stake in this issue that are under the Health and Human Services.

And there's no reason that the Secretary cannot provide direction to these different federal agencies that these children and families need to be treated fairly. Thank you.

CHAIR BOCCHINI: Thank you, Steve. Coleen?

MEMBER BOYLE: Maybe just continuing on that, maybe a little bit different.

During the talk and remembering how much work we did in the follow-up committee on medical foods. And going back to your slide, whatever the slide number was where you were waiting for the response, or she was waiting for something from us, I believe.

MS. CAMP: No.

MEMBER BOYLE: The survey and the

public workshop.

MS. CAMP: She was waiting for the Department of Labor to complete their survey and for the IOM report.

MEMBER BOYLE: Right.

MS. CAMP: And actually the IOM report came out in October of this year.

MEMBER BOYLE: So maybe thinking a little bit more about what the -- so during your talk I was starting to think of what it is that we can do to be helpful in this. Because we did do a lot of work and it did come to a bit of a halt.

So, I don't know if you have any specific thoughts on that. It didn't come through at the end.

MS. CAMP: Well, because I can't frankly tell you guys what to do.

MEMBER BOYLE: Well, you can make suggestions.

MS. CAMP: Yes, indeed, but you are constrained by what you can do. And I think

looking at the past and seeing what hasn't worked may help to inform what might work in the future.

And I think it's not asking her -- well, I don't know. I mean, asking her to change Medicaid and to change some of these things is going to maybe end up with another "we can't do that."

So, I think it's going to take working with the department to understand what is possible.

MEMBER BAILEY: Maybe at the least we could have a formal follow-up from the committee saying that now that these surveys and reports are completed the committee would appreciate an update, a response from the Secretary. At least to get the ball moving again.

MEMBER BOYLE: So, in working with Medicaid in other areas it seems to work best if there are states that have best practices that can be shared. So that might be something very explicit that the committee can do.

MS. CAMP: So, we've done that, or

tried to do that in the past. And providing best practices to states may or may not --

MEMBER BOYLE: But through Medicaid. Not us, yes.

MS. CAMP: So again, that's a discussion with the department.

MEMBER BOYLE: Yes.

MS. CAMP: I mean, these are things that --

MEMBER BOYLE: Yes. Well, we can make that suggestion.

MS. CAMP: Absolutely. I agree totally with that.

MEMBER BOTKIN: I guess I would pick up on Don's recommendation. It seems to me that the economic argument is a pretty critical one here to convince a lot of the key players.

And to the extent that HHS funds a lot of research and analysis, a cost-benefit or cost effectiveness analysis of the provision of these foods seems to me to be something we could recommend. Not a short-term solution, but at

least it would provide quite a bit of information to help subsequent policymakers guide legislation.

MS. CAMP: There are a couple of hands raised behind you.

CHAIR BOCCHINI: If there are no additional questions from the committee then let's go around the table of the organization representatives.

There is a microphone that needs to be passed around, please. Identify yourself before you make your comment.

MS. GREENE: Carol Greene, SIMD. That was a fabulous presentation. Thank you.

It leads to some interesting things like what happens when states have mandates with limits that actually make things on average worse for everybody because now everybody can get it, but only part of it.

Or the issue of use of prescribed limited to drugs because I can prescribe physical therapy.

But I really want to speak to the issue of cost-benefit. I'm having a lot of trouble with cost analysis here.

We don't talk about cost analysis of can you get your insulin. We're talking about the only treatment that is available for these disorders. We don't need to prove that there's a cost-benefit to have access to the only treatment.

With that said, and you can probably hear the passion in my voice, I would also say that there's some very, very interesting problems to address when we look at cost-benefit.

One of them is there is a clean -- we do dollars -- there is a clean benefit to not treating the child with methylmalonic acidemia because it costs you nothing from healthcare.

You'd have to do the cost-benefit, the cost of a life lost. Because it will cost you less if you don't treat the child. You don't have to dialyze him, you don't have to readmit him, you don't have to take care of him, you

don't have to put in the G tube.

You also have to think about the cost-benefit of a young man or a young woman not treated with PKU. Your cost-benefit there is underemployment, losing your job, moodiness. Then you don't have health insurance. We know about people who are in jail. So lost taxes. The cost analysis of not treating PKU is tricky as Cathy said.

But it's also I think fundamentally wrong. It's the only treatment. I don't think we need to prove that there's a benefit.

And by the way, there is old literature that shows straight up the benefit of treating. It was at the time something like about $6 million to $8 million over a lifetime that we calculated in about nineteen eighties for the lifetime of a person from age 20 to age 60 living in an institution with PKU as opposed to at the time about $7,000 a year for the medical food.

So, there are old studies for the cost

analysis, but I think fundamentally it's wrong.

And I think another example is WIC I believe covers pregnant women for certain things, but not until you're pregnant. Your pregnancy test is positive. The organs have already formed. You've already got the malformations from the PKU.

So we've got some real fundamental limits to the only treatment available. I don't think we are asked to prove the cost-benefit of insulin for a diabetic. I don't think we have to prove the cost-benefit for the formula for PKU.

CHAIR BOCCHINI: Let's do Beth and then Bob.

MS. TARINI: Beth Tarini, AAP. So, on the heels of that comment which I agree with, Carol, to some extent it seems to me that this is a public policy issue at its core, and that there are elements of, sure, there might be data gaps here, data gaps there that you could shore up maybe and help strengthen the argument.

But at its core it seems to me that

this is a public policy challenge. And so I'm not clear that we necessarily in the committee have not exhausted our expertise in this area.

But at the same time that doesn't mean the committee doesn't have the authority to pull together those type of people.

Because you've gotten pretty close. You've gotten to the Hill. You've gotten bills in. And so the question is are there other ways in from a public policy standpoint either at the federal or at the state level. And do you want to just hit that hard.

I sort of feel like spinning back to the states, talking to Medicaid, it's just sort of going back to the beginning and trying to get back up the hill. Where you've gotten almost very close. We just need to get over it.

So, in short I think it's a public policy issue that needs policy experts. I don't dare say the word lobbyists, but in that type of arena to get through that last step.

MS. CAMP: So, I just want to comment

on that. I think you're absolutely right, and who the policy people will be ultimately I certainly don't know, frankly.

I think that it needs to be a federal effort. Because even if states, okay, X state mandates Medicaid but it only covers this much, it only covers this much. So you're still working with this patchwork, and you still have families having to make a decision on where they can move based on where they will have coverage.

MS. TARINI: It's possible if you get enough states as a critical mass you can move from the bottom up. You can create a disparity, for instance, and people can say well, 10 states Medicaid cover it, why don't these states.

So in other words, another policy angle or potential.

But I do agree with you, it seems if possible more efficient top down.

MS. CAMP: It's still years getting all of that up to go. And then you get these states that have very poor ability to finance

these kinds of things. They make decisions about what they're going to finance.

MR. OSTRANDER: Bob Ostrander, American Academy of Family Physicians.

I want to talk a minute about some organizations' roles. I've decided to make this a bit of a project of mine. In my last report to the academy committee that I answer to I recommended that they attend to this and make it AAFP policy.

And my intention is introduce a resolution at New York and then at the national congress of delegates for the American Academy of Family Physicians which I shared with some of the Follow-up and Treatment Subcommittee members, a policy to on the state level seek draft legislation, and on the national level seek policy to include medical foods narrowly defined -- I'll talk about in a second why I think that's important -- under the Affordable Care Act.

In preparation for all this I tried to sort out what's covered in New York and no one

seems to know.

You told me that you thought the dietitians knew. I contacted a couple of different channels from NYMAC and health department people at the Rural Health Council and they sent the question around.

And the best I could get was a policy statement about specifically formulas being covered by Medicaid. And I could get no other information. Nobody even knew what was supposed to be covered or not.

I think it's very important that we pursue this as an essential health benefit under the Affordable Care Act because the Affordable Care Act has not made care affordable.

We have a lot more people who are insured, but many, many of them as anybody in practice will tell you have these high deductible plans you talked about, especially the most vulnerable folks who have the non-professional jobs.

If it's not an essential healthcare

benefit, if it's mandated just to be covered, it's covered under that high deductible and copay.

I agree with Carol, this is a matter of justice and not finance. And I think that should be anybody who's working on this's primary focus.

However, on the finance side, forget the cost-benefit analysis. We're talking about 500 births per year out of a U.S. birth population of 4 million. This isn't going to move the needle on the total healthcare cost expenditures of this country an iota as long as it is just for medical foods.

I think we have to talk about the taxonomy of medical foods versus drugs. And this is a mess we've gotten ourselves into largely because of the Dietary Supplement Act of 1994 when the vitamin industry wanted all sorts of stuff defined as foods as long as they don't diagnose or treat conditions.

Hence this supplement enhances joint

health, this supplement is natural male enhancement. You don't say it treats arthritis or erectile dysfunction. You can still call it a food and not regulate it.

So, I think we have to understand what the pushback is going to be. I think it's going to be from the proponents of the Dietary Supplement Act's protections to not create another category of medical food.

But I think realistically that's what we're really saying. I mean, this is artificial to say something is a food not a drug.

These are foods that are used to treat conditions, and they're foods.

The other side of this is we're going to have to be aware of the bandwagon effect.

There's a lot of folks who really have celiac disease, and there's a whole lot of folks who have fad-based gluten intolerance, and they're all going to want their low-gluten modified foods.

And the argument will be hard to

counter that low-protein foods should be covered but gluten-free alternatives to things that we eat every day should not be. So I think we have to be aware of that.

I think the draft guidance that you presented, and I wasn't aware of that, is really tremendous.

I think the other thing that we need to be able to talk about to folks is that plants have carbohydrates.

I have a colleague who's a vegan who is a real proponent of that. He says the number one question he always gets is, well, where do you get your protein?

Well, plants are full of protein. Just because you're not eating animal products doesn't mean you're not getting protein. They have to be engineered foods if they're plant-based foods.

And that's maybe a minor point, but it's a big misconception when we're promoting this.

And I agree with Beth that this needs to be on the policy level. And if we can get some organizations that have some credibility that can use their policy experts like I hope the American Academy of Family Physicians can then I think we've got a shot here.

I certainly would love to see the American Academy of Pediatrics and ACOG do this in parallel with my efforts at the moment.

And if I can get it made official AAFP policy then join with us in a real push. Thanks.

CHAIR BOCCHINI: I think that's a great comment, Bob, and I think that public policy components of AAFP and the American Academy of Pediatrics, March of Dimes, could certainly form a powerful group to promote just what you said. So I think that would be certainly one direction towards federal legislation.

MEMBER MATERN: Dieter Matern. In the letter that the Secretary sent on February 16 regarding NPS 1 it states that the Affordable

Care Act requires that most health plans cover the evidence-based preventative care and screenings provided for in the comprehensive guidelines supported by HRSA.

Doesn't it mean preventative care include treatment?

MS. SARKAR: It's just coverage for the newborn screening test.

CHAIR BOCCHINI: Comments. Michele, were you interested in saying something?

MS. PURYEAR: Michele Puryear. There's already been a cost-benefit analysis. It was done 30 years ago. But that was part of the justification for screening for PKU.

There was a cost-benefit analysis for newborn screening in general. And they used specific cases or conditions to look at, hypothyroidism, PKU were two of them.

And I think Christine was probably going to say the other stuff I was going to say.

MS. CAMP: Can I just respond to that quickly?

A cost-benefit analysis from 30 years ago doesn't get to where we are now with adults and with older children, and really what the implications are for undertreatment. It's not just failure to treat, but undertreatment in these populations.

But I certainly appreciate those older studies. They're very important.

And I also agree with Carol. It's hard to wrap your arms around continuing to justify a treatment that we know works.

MS. PURYEAR: But it really points to the need, what Beth said. This is a policy issue.

MS. CAMP: Yes.

MS. PURYEAR: You're sort of skirting around the issue when you're talking about show that it works. We know that it works. We know that it's needed.

The other thing is I think, Debi, that what Dieter, Dr. Matern just quoted was talking about the HRSA guidelines and specifically Bright

Futures.

And I don't know whether the treatment guidelines, because that's part of the Affordable Care Act. And I don't know whether or not medical foods and formula are in Bright Futures. But that's one of the things that guides the Affordable Care Act or Bright Futures.

MS. SARKAR: This is Debi. So, what the Secretary is quoting in her letter, the HRSA guidelines actually includes the RUSP. And so she's just referring to conditions that are added to the RUSP that the screening test is covered by health insurance.

But it is a good question about Bright Futures. I don't know the answer to that.

MS. BROWN: Christine Brown with the National PKU Alliance. I just wanted to add some points of information.

The IOM report was finalized back in October of 2011. And so that was one of the things that the Secretary said that she couldn't make a decision on until that report was

finalized.

It was finalized almost five years ago and it actually recommended that the Department of Health and Human Services further evaluate coverage for nutritional supplements and formulas needed for the treatment of inborn errors.

So it did ask that the Secretary do that. I think to everybody's best knowledge that evaluation has not occurred.

The Department of Labor survey, I wasn't able to find anything last week, but I believe that there was something in there that was very general that said that most private insurance companies did not cover the cost of medical foods to treat inborn errors of metabolism, but that it really depended on state mandates.

And then the third thing is there was one state mandate that passed after the Affordable Care Act which was Wyoming. And that covers medical foods and low-protein foods for all conditions through newborn screening. So

that was in addition.

And I guess lastly, and I will be doing some public comment during the period after lunch, but I've now received in the last two weeks two examples in California where adults are trying to now get coverage under the exchanges and they're being denied coverage for medical foods even though the State of California has a mandate.

So I would say that the little that I know, the little data that I have is that even with people in the exchanges that supposedly those states have to follow state mandates, there are still routine denials.

MS. SINGH: Rani Singh. I wanted to highlight a little bit beyond the newborn screening the urgency not to drag our feet on this issue and the impact it's having on PKU women.

I've been doing a camp for 25 years and half of the girls who are 18 and older, they have had -- more than half the girls have had

lack of access to medical foods.

And when they are giving birth, and it could be more than one birth, the kid is impacted by it.

Also, these women are being put on a lot of psychiatric drugs which are covered by the insurance, but the medical foods are not.

So, I want to say we may negate the effect of newborn screening if we don't act now and help moving forward. So I just wanted to as a clinician bring that urgency and highlight that aspect.

CHAIR BOCCHINI: Thank you. Additional comments?

MR. KUS: This is Chris Kus. I'd like to make a comment if I get a chance.

CHAIR BOCCHINI: Yes, please, Chris. Go right ahead.

MR. KUS: Sure. I guess there's two points, one for me.

It was my impression by virtue of the fact that you are on the RUSP that we determined

these are conditions that are worth screening for and hence worth treating.

The second thing is somebody made comments about Bright Futures. And I may be wrong about this, but Bright Futures is really the guidelines for health promotion care and doesn't speak specifically to coverage, although the academy does have a policy statement with regard to health insurance coverage which I hadn't pulled up yet but we should look at.

CHAIR BOCCHINI: Thank you. Don.

MEMBER BAILEY: I appreciate the comments about your concerns about whether we really need a cost analysis. And I'm not a cost person.

But I do think that the consequences of not doing this bear enormous burden on the individuals and on society.

We've got old data showing that, but it's just with one or two conditions. And if we had -- numbers and costs are never going to drive policy, but having been in the early childhood

world for many years and trying to argue that it's the right thing to do as to what you were saying about medical foods, it's the right thing to do to provide early childhood education for children.

What got the attention was when you could show that there was a cost-benefit savings.

And so it's just a matter of building the case in a comprehensive way. The cost data are certainly not going to drive it, but I think it's just one piece of the puzzle that an update comprehensive cost to society of not acting would be important.

CHAIR BOCCHINI: Thank you, Don.

MS. CAMP: Can I just say really quickly that I think a focus on maternal PKU syndrome would maybe be helpful to have people sit up and listen. Because that is a critical health policy issue. And I think it's -- we don't really know.

CHAIR BOCCHINI: Kathryn, thank you very much.

MS. CAMP: Thank you very much for letting me present to you all.

CHAIR BOCCHINI: It's very clear that your presentation generated very significant, important discussion about this topic.

And what I think going forward is that it would make sense for the long-term follow-up committee to look at this issue to determine whether rather than a statement to the Secretary, maybe we need to consider going back over the IOM report, seeing if we can find a Department of Labor report, seeing what the current situation is in states which has clearly been outlined.

And maybe decide whether we need a policy statement from the committee that might address this issue, at least provide our input into that. So I'd like the long-term follow-up committee to consider looking at the data and maybe within some months kind of chew on this and see what we think might be beneficial going forward.

MEMBER MCDONOUGH: This is McDonough.

I can't speak for the full sub-workgroup or workgroup, but I would anticipate that there's going to be a lot of interest.

There was quite frankly a lot of disappointment in the subcommittee now workgroup that medical foods was not one of charges that came out of our last meeting.

I also don't see why we can't send another letter to the Secretary. I view the previous decision was a mistake. We have a new Secretary.

Every person in this room comes to these meetings with different life experiences. And we have different ways of looking at things. And just because one previous experience did not want to have this a part of an essential health benefit doesn't mean that the new Secretary would feel that way.

I think the Institute of Medicine report had recommendations to modify essential health benefits as time goes forward.

There was a mechanism in place and I

think there were some committees recommended to be created. And I don't think that they're doing that. I can't find them when I try to Google them.

But I think there's a lot of things we can do in this area if we were given the charge to do it.

But I will be advocating that the Secretary get another chance to re-look at this.

CHAIR BOCCHINI: Well, I think that may be the eventual conclusion of the work, but I'd like to bring it to the subcommittee, to the workgroup, and then let the workgroup kind of discuss, get the background data, and then consider going forward what can come back to the committee for full discussion and decisions.

Dr. Lu?

MEMBER LU: This is Michael Lu from HRSA.

The way I look at this in terms of moving forward, there are basically two ways to do this. One is to do this legislatively and the

other administratively.

I'm certainly not going to comment on the legislative mechanisms.

But I think as far as administrative mechanisms go that you can do this through Medicaid and that mostly has to do with state Medicaid policies.

You can do it through preventive services under the Affordable Care Act. And there are four different types of preventive services that are covered. And that's the preventive services for kids which is Bright Futures that we can certainly get more information in terms of what Bright Futures stipulates.

There's preventive services for women. There's the newborn screening which as Debi says does address specifically about the screening, but not necessarily the treatment. And then there's the immunization.

And then lastly there's -- you can do it through the essential benefits which really

kind of goes through our Office of Health Reform for HHS.

And so we'd certainly be happy to follow up with the long-term follow-up committee and provide some additional information about some of these mechanisms if that would be helpful.

CHAIR BOCCHINI: Great, thank you. All right. Thank you.

Let's move to the next item. Dr. Botkin has the Pilot Study Workgroup report or presentation. Jeff?

MEMBER BOTKIN: Thanks, Dr. Bocchini.

So, the Pilot Study Workgroup was created in May of 2014 so it's been two years. So about time that we came forward with our report. So it's been a wonderful opportunity to work with a great group of folks. And I'm pleased to see that many of these folks are here with us today in order to back me up when I make statements that perhaps somebody might want to expand upon.

So, it's been a good collaborative effort, and thanks so much to Debi and Elana too for their support for the committee.

You have in your briefing book these slides, but also the report itself. And there's been a flurry of activity over the last couple of months to pull this together. So I will not claim that this is a highly refined document.

But I think one of the questions I'll pose here in a second is how we want to address that report.

Hopefully many folks have had a chance to read the whole thing. What I'm going to do with this presentation is really just focus on the recommendations themselves.

Then I guess part of the strategy will be whether we want to as a committee either refine and come back at some later time the recommendations, whether we want to vote some of those through now, and then whether we want to vote the whole statement through.

And I think part of the challenge that

I need to better understand is that many of our colleagues who have provided substantial help with this statement are federal employees and have some difficulties with making recommendations themselves back to the federal government. So exactly how all of that will be woven together I'll be looking to Dr. Bocchini.

So, a very little background here before we dive into the specific recommendations. Obviously the evidence review process depended on quality data.

Pilot studies, a variety of different steps essentially yield evidence about several different aspects of the newborn screening system.

The Public Health Service Act recently passed as everybody knows. It very much shortened our timeline to come forward with recommendations.

So, that has compressed this set of issues for us. And so part of the purpose of the Pilot Study's recommendations is to try to make

sure that as recommendations come forward for formal evidence review that the data is present so that that review process can be as efficient as possible.

So, here's our charge. And I'll be touching back on each of these to categorize the recommendations.

But first, to recognize and support current efforts regarding pilot studies and evaluation. And there's really a lot of excellent work going on now that we intend to support.

Identify other resources that could support pilot studies and evaluation. That's a little bit more open-ended. We've tried to be creative with that domain.

And then identify the information required by the committee to move a nominated condition into the evidence review process. That is, define the minimum pilot study data required for a condition to be accepted for evidence review.

We've tried to be a little bit more specific here and we'll see how our thoughts fly with the group.

So, just to emphasize the question is what data are minimally necessary to move a nominated condition to the evidence review process. Not what evidence is necessary to actually approve a condition on the RUSP. So we're in that intermediate category with looking at the data from pilot studies.

So, here's what we decided to do with the definition. And I would say we did not really have a great opportunity to review this even among our writing group in great detail. And so we may want to welcome feedback on whether this is the correctly phrased definition. But I'll go ahead and read this.

For the purpose of this report and consistent with previous definitions newborn screening pilot studies are defined 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.

All right, so that's a mouthful. What this intends to say is that many of these, of course, will be categorized as research. But as we know in certain circumstances folks have been constrained by the requirements of a research agenda, and states have approved conditions on their recommended panels in a mode to collect data to evaluate the outcomes of those public health activities.

So I think for the purposes of this definition we also want to include those enterprises where data are being collected but perhaps under the public health rubric rather than under a separate research agenda. Hopefully that will make sense to folks.

And I think we're looking here at anything that's, again, directed at the public population-based evaluations.

So let me stop here for a second and

just see if anybody has any specific thoughts or concerns about this definition.

Okay. We certainly can come back to that as we delve in a little bit more detail about the recommendations themselves.

So again, here's our first charge, at least first charge I'll deal with in organizing these recommendations.

Identify the information required by the committee to move a nominating condition into the evidence review process.

So recommendation one. Apologies, I'll go ahead and read this.

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 blood spots from a population of newborns including known positive and negative specimens in addition to laboratory-prepared target specimens.

So again, that's a mouthful. It includes quite a bit of information to be sought on the laboratory phase of the newborn screening system.

So Dr. Bocchini, I think I'll probably stop with each of these recommendations. We could go through them all and then come back, but that might be too tough for folks to hear. So, thoughts on this. Dieter?

MEMBER MATERN: As part of the group I should have brought this up earlier, I guess.

You mentioned your use of dried blood spots. But as we know there's other screenings that don't use the blood spot. So we might have to broaden that definition to be whatever you have to test.

MEMBER BOTKIN: Very good. We should include use of dried blood or other biological

materials or some such thing? No?

MEMBER MATERN: We have the bedside test now, so I don't know, some physiological or pathology test.

MEMBER BOTKIN: Okay. Any specific recommendations anybody else has on that? I understand the points. The bedside test and to the extent that maybe we're going to go to saliva on some tests, or some other -- bilirubin we looked at that was a different modality. Nancy?

Okay. And I think the key point here is that you want to be dealing with actual affected and unaffected babies as opposed to artificially designed test systems.

MS. GREEN: This is Nancy Green from Columbia University. Thanks, Jeff. And I realize this is very hard so I appreciate the work of you and this committee.

The issue about the population of newborns. Do your recommendations go -- I don't know what's coming next, but there had previously been discussion about diverse populations,

sufficient numbers.

I mean, without actual specifics but something about the fact that a population might reflect the heterogeneity of the U.S. or state populations. Something to that effect.

MEMBER BOTKIN: Good, and I think you'll see that under recommendation three. So hopefully that will address that specific issue.

MEMBER MATERN: Dieter again. Actually, should we limit this to newborns, or should we just say from a target population in case we want to do some pediatric screen, or other screen later in life?

MEMBER BOTKIN: Okay.

MR. OSTRANDER: Is the point here when you said dried blood spots with Dieter's comments taken into account specimens that are obtained in real world circumstances?

Because obviously if they're collected specifically for a pilot study it may not be with the same degree of -- maybe with more attention than those that are collected in real world

circumstances. And I don't know if that was what you were implying, that they needed to use real world specimens or not.

MEMBER BOTKIN: Yes, and I'll look to Carla perhaps for some thoughts on that issue.

MEMBER CUTHBERT: Carla Cuthbert, CDC.

So, this particular recommendation really is targeted at the analytical validation. You'll find that the clinical validation comes next.

Analytical validation is really at the point at which the state or the program has done developmental work and has come to a stable method and wants to show performance metrics that actually show that this method is now ready to be taken into a new population.

So with respect to this that's why you've got a number of these parameters being identified.

And yes, Dieter's right, we should really consider what happens with point of care testing. But for the dried blood spot tests you

want to be able to do this. CLIA requires it. FDA in some form requires it as well. So, these are things that need to be done.

With respect to the samples and the populations you'll find that in many states they can actually use the last three months' worth of samples that they've identified, or that reflect their own population to see what the actual measurement values are for this particular test.

Many of the states will also collaborate with physicians who see these patients, get permission to be able to access the dried blood spots of affected and be able to go back and also test for that as well.

The clinical validation is something a little different. But this is more of a retrospective analysis of blood spots just so that they can determine these parameters, determine that the test works and that it's stable, and have this for a reference. I hope that's helpful.

MEMBER KELM: I can just speak to the

FDA. When we're reviewing newborn screening assays most of the time, for example, precision detection limits, interference, they actually use contrived samples, like take adults. Because you need a lot to do that. You can't take enough from a newborn, even dried blood spot.

And so they'll make dried blood spots. They'll just contrive them, for example, adult blood, make them so that you have enough samples. So it depends on the study.

And then obviously you want, yes, close to whatever sample type your test is going to use. So if it's going to start being point of care whole blood serum plasma then that's a whole 'nother ball of wax.

MEMBER BOTKIN: Okay, good. And I think that last phrase gets to the prepared specimens.

Okay, what I have then in terms of revision, and I won't claim that this is too precise yet.

So, pilot studies for analytical

validation should include 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. Sound good? Okay.

All right, recommendation two. 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.

So the intent here is to say that the pilot study itself need not be the vehicle that you're using to determine whether early detection and intervention is affected.

You can demonstrate efficacy of early intervention through other modalities. The population-based screening pilot may demonstrate the feasibility of the system in other ways, but

efficacy per se might be through the population-based pilot, but it might well be through other measures.

And again, I think the background material within the paper highlighted the SCID experience here as important, that folks had identified early intervention, bone marrow transplant as being effective with kids at an earlier age with SCID, and that the population-based pilot was not used to demonstrate that efficacy again. So, I think that's the central point with this recommendation.

MEMBER WICKLUND: Cathy Wicklund. And thanks again you guys for working on this.

This might be in the report, but I was wondering how to deal with though just the really incredibly small numbers and some of the data just doesn't clearly show the net benefit.

Are we just asking that we've tried to show the net benefit? I mean, this is where it seems like we're really having a hard time making the distinction between what to add to a RUSP or

not.

MEMBER BOTKIN: Yes, and I guess my response would be to say that as a condition comes forward if it's going to go to an evidence review there has to be some data.

Now, whether the evidence review process and subsequently the committee will find those data to be compelling or convincing is a separate level question.

But there needs to be some data on efficacy and safety, and that can come as stated here from a variety of different types of studies.

Okay, recommendation three. Data should be available from pilot studies involving population-based screening of identifiable newborns. So, not talking the identified blood spots.

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 U.S. population and to state newborn screening programs with respect to known prevalence of the condition, the timing and approach to screening, and the screening modality used.

So, 3A I think is something we've floated in discussions to the committee in the past. And this parallels again what we did with SCID so there's some precedent here.

But I think folks in our discussion raised the question about whether you even need one newborn. If you demonstrate feasibility of other aspects of the population-based program do you even need to identify an affected baby or not.

What we've decided is that one is a minimum number, but I think open to debate.

3B here is an indication of some of the challenges we've had in the past with studies done in other countries. And the question is is the nature of the condition different with

different populations, different perhaps ethnic/racial mixes. How do they do newborn screening in those countries. Are they using the same test modality that's being considered in this context, et cetera.

So you would want to study, if you're going to use it for this purpose, to be sufficiently similar -- what's the term here -- similar. And obviously that's a subjective word, but there it is.

All right, so let me stop talking and see what thoughts people have on this.

MS. GREEN: Just a quick question for the recommendations. Are they "and" or "or?"

MEMBER BOTKIN: They are "and." So maybe there needs to be an "and" between 3A and 3B.

Yes, yes, point well taken. That's right. These are all necessary as far as we've got. Michele?

MS. PURYEAR: Michele Puryear. I have a question on 3B. What do you mean by "and the

screening modality used?"

MEMBER BOTKIN: Yes, I'm not sure what we mean there. I guess we're really thinking about -- I mean it's largely written in the context of blood spot screening.

Perhaps this came forward -- maybe approach to screening would sufficiently capture the idea to the extent that maybe you're looking at different ways to do pulse oximetry or that type of thing.

MS. PURYEAR: So does that allow that kind of variability, point of care screening?

MEMBER BOTKIN: It would not. I mean, I think the point is 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.

MR. WATSON: Jeff, that came out of the Pompe disease outcomes where Taiwan had used the fluorescence assay and tandem aspect was going to be used in the United States. So the screening platform or testing modalities were

different.

MEMBER BOTKIN: Okay, good.

MS. PURYEAR: And that I understand, but would it include point of care testing. I mean, is there enough leeway there?

MEMBER BOTKIN: Well, I guess different types of point of care testing. Is that the question? If you had a different approach to pulse oximetry in one study versus others?

MS. PURYEAR: The condition that you were putting forth that used point of care testing instead of blood spots similar to hearing screening or screening for congenital heart disease.

MEMBER BOTKIN: Yes, that would.

MS. PURYEAR: It would include.

MEMBER BOTKIN: Yes, I think that's right. Dieter?

MEMBER MATERN: Dieter Matern. I'm really sorry, but it really helps to have these face-to-face meetings and see that on the screen.

So when it comes to the screening modality while I agree what Mike just said, I think -- or what I am concerned about is whether this would prevent innovation in using a completely different technology or approach to screening.

Because if we say it has to be tandem aspect, or it has to be whatever technology is already a part of screening then we might get stuck. So it must be a modality that is -- I mean, it has to be high throughput I think. But it shouldn't be seen as a specific technology.

MEMBER BOTKIN: Well, I guess I would say that as a test comes forward and being proposed for inclusion on the RUSP the proposal would include a certain test modality.

And if the pilot studies were done using a very different test modality then the question would be are those pilot studies sufficient evidence of what's being proposed. And I think you'd probably conclude that they were not.

Now, maybe you could make a case by case argument in that respect, but I think it's the mismatch between what's being proposed for inclusion and what the pilot studies collect data on that would be the mismatch that would be problematic here.

MS. GREENE: Carol Greene, SIMD. It took me just a moment to realize that apparently I heard what was just explained. Apparently people are reading this differently, reading what's on the screen to say that the modality used has to be one that's already in use in the state health department.

And I assumed this meant that the modality used in the pilot has to be the same one that you're proposing to be adopted. And apparently that language is not sufficiently clear and it should be made clear that it's not that you have to use tandem aspect that's already being used, but that there has to be a match.

MEMBER BOTKIN: Okay. All right, so point well taken. So the language here, I'm

going to think about how to -- there's not necessarily a really easy fix to this problem.

But I think -- Dieter.

MEMBER MATERN: Dieter again. I just wonder whether we should just state that it must be amenable to high throughput screening. And what the exact modality is is irrelevant. As long as you can do it efficiently and effectively and cheap.

MEMBER BOTKIN: Yes, and I think that was perhaps part of the intent of the earlier recommendations, although they do focus primarily on accuracy.

MS. URV: Because there's been a variety. Different states test in different ways for SCID. It's the outcome, or the outcome needs to be similar, and they need to meet the requirements of recommendation one.

MS. GREEN: You're saying comparable modality.

MS. URV: Yes, right. So, comparable modalities would be. And you want your outcome

to be the same because for some of the conditions we do have a variety of competing tests that are out there.

MR. WATSON: One true positive. One true positive isn't a whole lot of true positives. We sort of fell back to that with SCID because I think it was 600,000 babies or something. I think the committee was at the point where just give us one. Because it was supposed to be 1 in 100,000 with that definition.

So, I guess a true positive is a clinically effective infant, not somebody who had -- is confirmed to be a waiting, late onset disease or something like that?

It's getting increasingly sort of blurry, certainly across the LSDs that are coming into screening now with some of them at 90 percent late onset. That's a long wait to see really weather your intervention is going to lead to benefit or not.

MEMBER MATERN: Dieter again. I think one true positive in my mind means that you have

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.

MR. WATSON: It's not an analytical pilot that shows you can find people. It's a pilot to find them, intervene, show benefit.

And I think you have to get all of those together in order to say yes, it's a screening test that's good for newborn screening programs.

MEMBER BOTKIN: Well again, you have to have all of those data elements. But I think what this is saying is you don't have to have them all in the same study.

MR. WATSON: I'm good with not being all in the same study.

MEMBER BOTKIN: Don?

MEMBER BAILEY: We might want to go back as a group and rethink this particular recommendation because you can envision some

other odd scenarios.

Let's say you did a pilot study for some condition. You found a baby on the first day. Is that then -- so we're really talking about something more than just identifying one baby. We're talking about enough to show that you can scale up to do this system in a broad way.

And so maybe we need to go back and think about that statement in a little bit broader kind of perspective.

MEMBER BOTKIN: Well, that would certainly be fine.

I would say just to remind folks we're still talking about a threshold criterion to get it up to the evidence review.

So the evidence review in that circumstance might say well, okay, you passed our criteria by having an affected baby but you only screened 500 kids so this isn't going to fly.

Nancy, I think you had a comment again? Okay, should we try to go ahead?

MS. GREEN: Thank you. Nancy Green. So, recall that the concept or the term "true positive" is an ambiguous term because it might mean, as I think Mike is referring to, it might mean a laboratory true positive, but it doesn't necessarily mean a clinically true positive.

MEMBER BOTKIN: I'm sorry, say that a little bit louder for me.

MS. GREEN: That a true positive might be a laboratory true positive, confirmed by laboratory diagnosis, but not necessarily clinically true positive.

So while I understand that you wouldn't have to, you know, I think what the group is saying you wouldn't have to identify a child and then go to treatment and outcome. But that would be data collected from another source.

But I think you want to say that the true positive is clinically true positive to discern that from laboratory.

MEMBER BOTKIN: So is adding that term sufficient then, one true clinical positive

newborn?

MS. GREEN: You might want to ask a newborn screening person specifically about that.

You know, like a SCID screen, like a preterm infant would be a true positive, but it's not clinically true positive.

MEMBER BOTKIN: No, and I think the other complexity here is it may be one of the adult onset forms, say, that would be a true positive but it wouldn't be really what the program is designed to identify for clinical intervention.

MEMBER CUTHBERT: And Jeff, I think that the idea is that it would be a clinically identified patient. So you do want to go beyond the screened positive to be able to do the follow-up and verification with the early -- yes, sorry, you're correct, it is a clinically verified case.

MEMBER MATERN: But does clinically verified mean that the patient must have symptoms? Okay.

CHAIR BOCCHINI: So it would be a positive confirmatory test that the patient has the condition.

MEMBER MCDONOUGH: This is McDonough. I think what you've got there is just fine. I think there's enough broad interpretation there that gives the committee guidance on what we need to do.

I'm not sure if wordsmithing this and having it come back again and again is going to add that much. So I really like what you've done.

MEMBER BOTKIN: Okay, thank you. All right, so I do have one edit here that I think it's worth probably putting in that clinical true positive.

Now, whether we want to refine that further by saying a true positive for the actual babies that you want to treat, you're trying to find as opposed to other variants of positive I'm not sure yet.

I have some proposed language. I'm

not sure who this came from. I'm just jumping in on this.

Population included in the pilot study should be similar to the U.S. population including with respect to prevalence of the condition and the screening protocol used, be comparable to that proposed for screening in U.S. states with respect to the timing and approach to the screening and the screening modality used. So that could probably use some refinement as well but okay.

So, let me spend a little bit of time with -- about a revision and then we'll talk to Dr. Bocchini, see whether we can find a short period of time at some other point in the meeting to bring back a revision and see whether that would be acceptable to folks.

Other comments about this three? All right.

Second charge. Recognize and support current efforts regarding pilot studies and evaluation.

Recommendation four, 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.

So NIH has been doing a lot to support newborn screening in recent years and this is sort of a list of a variety of those activities that are described in more detail in the full paper.

And so this basically just says that these are important and valuable initiatives and HHS ought to continue to support these initiatives.

So, thoughts on this? Probably not much disagreement but are there additional things to add here perhaps, or other ideas? Tina?

MS. URV: I guess I would just be concerned that it sounds like fiscal support, and that it shouldn't -- HHS doesn't give us specific

money or earmarked money for this. The institute itself earmarks the money for these activities. So, just maybe wordsmith sustain, support to something that doesn't make it sound fiscal.

MEMBER BOTKIN: Okay. Recommendations?

MS. URV: I think it's fine to say continued -- sustain sounds like keep putting money into it. And I'm just always cautious of anything we send to HHS that kind of rings with money or dollars.

MEMBER BOTKIN: Yes. Continued support. Does that sound a little less fiscal?

MS. URV: Yes.

MEMBER BOTKIN: Okay. Make that revision. Other thoughts on this? Okay.

Recommendation five. Sustain or continued 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.

MEMBER SPONG: Just a wordsmithing I think for both this one and the last one. Having "support" twice in the beginning isn't -- doesn't read well.

I think that too the support of could come out of both four and five. So, for the activities relevant to pilot studies that address. And the same with the previous recommendation.

MEMBER BOTKIN: Okay, very good. All right, I'll make those changes. Other thoughts on this. Dieter?

MEMBER MATERN: Dieter. I'm just wondering whether it has to be state laboratories and state programs, or just laboratories.

MEMBER BOTKIN: Okay. So state or regional perhaps, or do you want to just eliminate the geographic aspect? Assistance to programs in obtaining laboratory equipment, et

cetera. Okay. Nancy?

MS. GREEN: Sorry for so many comments. I'm sorry, but does CDC also do surveillance regarding newborn screening? Would that be part of the sustain support aspect? Maybe it's a question for Coleen.

MEMBER BOYLE: Yes, we do. I mean, this is specific to laboratories so I think we'd have to create a different recommendation, or have a sub.

MEMBER BOTKIN: Yes, and this is mostly focused of course on pilot studies. So, would surveillance be an element of a pilot study?

MEMBER BOYLE: Sure, in terms of trying to understand the outcome, whether or not the program is effective. Be able to evaluate and identify both the effectiveness of the screen to identify children with the condition and then to follow them up short-term.

MEMBER BOTKIN: Could we just add a surveillance term in here, or is it sufficiently

different that we need -- could we say distribution and validation of test packages, population surveillance and the fostering of laboratories of excellence? Does that meet the need?

MEMBER BOYLE: Sure, I guess it could. I'd have to see it.

MEMBER BOTKIN: Okay.

MS. TANKSLEY: Hi, Jeff, this is Susan Tanksley. Can you hear me?

MEMBER BOTKIN: Yes.

MS. TANKSLEY: Hi. Just in regards to the comment about taking state away from this recommendation. Isn't the -- so is this for after the fact, or continued pilot studies, or is this for the pulling together the evidence prior to it being submitted for evidence review.

MEMBER BOTKIN: Yes, this is in the broad category of what can we do to recognize and support activities that are already ongoing with respect to relevance to pilot studies.

And so this is sort of recognizing

what's being done and supporting that that continue to be done.

MS. TANKSLEY: Okay. So it doesn't have to do with I guess promoting implementation moving forward after a recommendation.

MEMBER BOTKIN: Not primarily, no.

MS. TANKSLEY: Okay.

MEMBER BOTKIN: Carla, do you have any comment on that?

MEMBER CUTHBERT: Susan, removing of the term "state" was just to indicate that CDC would provide materials to any of the laboratories that would request.

MS. TANKSLEY: Okay.

MR. SHONE: I had basically the same comment and question that Susan had about state, especially around the line that says assistance to state programs in obtaining laboratory equipment.

So, CDC is not providing those types of resources to non-state programs. And I guess it gets back at the question of the charge to CDC

is to assist the states, not necessarily private laboratories and commercial programs.

So, I kind of am in favor of perhaps wordsmithing it to maintain "state" in there.

MEMBER BOTKIN: Could we say state and other laboratories or other programs?

MEMBER MATERN: That would be fine with me but I don't know why by taking it out it wouldn't include the state laboratories.

MEMBER BOTKIN: Okay. I'm sorry, Dieter, say that again?

MEMBER MATERN: By taking state out doesn't mean you take out the states out of the equation. It's just not limited to state laboratories and state programs.

MEMBER BOTKIN: Right. No, and I think -- but folks were a little nervous about I think de-highlighting the state connection there.

MR. SHONE: My question remains does CDC provide what is in here. I mean, the idea is continued support. So, if it's continuing support that exists is that support currently

provided outside of the programs.

MEMBER CUTHBERT: Thanks, Scott. This is Carla again.

So, there are some activities that CDC will provide exclusively for state programs. And you're absolutely right. And there are some things that we will generously give to other programs who request.

So, you're correct, we would help as states help with equipment and things like that. Validation packages again is something that's new that we would be able to create specifically for states. And again, if anyone else requests we can also make those available. Thank you for your clarification.

MS. URV: One example that might make sense to you is we might have investigators at the NIH who are developing new tests. And they're at a university or a small business.

And then they would go to the CDC because the NIH funding, we ask them to go to the CDC and work with them. So it's in the

developmental process.

MEMBER BOTKIN: So, does it still meet the need then to say state and other? Does that sort of get to both points here?

MEMBER CUTHBERT: We can do a little bit of wordsmithing and make sure that we include the word "state" and perhaps "other" as well. But we'll do some wordsmithing on that.

MEMBER BOTKIN: Okay. I'm going to move on then to charge three, identify other resources that could support pilot studies and evaluation. And this is our last recommendation.

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.

So this is a pie in the sky, but to

some extent how folks are already moving in some respects here. So let me just open it up for comments.

Okay, terrific. So perhaps we'll see if we can make some revisions and get these done in a way that will perhaps enable a vote during this meeting. Dr. Bocchini, is that?

CHAIR BOCCHINI: Well, it seems to me that the principles that you've elucidated have all been accepted by the committee. Or I don't see anybody who is opposed to the principles, but clearly we need a little wordsmithing for some of the things to make these recommendations more clear and to address all of the things that were raised.

So I would think that if we could -- well, I guess we would do two things. One, can we as a committee accept the report of the Pilot Study Workgroup and accept the recommendations with the proviso that these recommendations will be wordsmithed and then sent to the committee for further comments if necessary.

Is that fair? And then this way we don't have to bring it back for a vote. We could provide those if you can tomorrow, but I think we would then be able to address the recommendations.

If that's acceptable to the committee by a show of hands, approve? Then I think we can go forward. Okay. Does that sound fair?

MEMBER BOTKIN: Sounds great.

CHAIR BOCCHINI: Okay. Well Jeff, I want to thank you for your leadership in this and all the work that you've done.

And I want to thank all the committee members because this I think is a very important project and it's going to provide the recommendations and guidance for us to go forward in a very effective way as new conditions are nominated for inclusion on the RUSP. So I want to thank you all for the work you've done. Steve.

MEMBER MCDONOUGH: Jeff, this is your last meeting as a committee member I think. And

I just want to say that I have so much enjoyed all the work that you've done and the way you present yourself.

One of the cool things about coming out here is the chance -- you get to meet a lot of different people that I don't normally encounter in North Dakota.

I'm just so impressed by so many of you on what you've done. And I just want to thank you for your years of service to the committee. I know you'll be involved in ethics and newborn screening in the future. But it's been a real honor to get to know you, and again want to thank you for all you've done.

CHAIR BOCCHINI: Thank you for that comment. So, this concludes the morning session. We now have from now until 1 o'clock for lunch after which we will promptly start at 1 p.m. with the public comment section. Thank you.

(Whereupon, the above-entitled matter went off the record at 11:55 a.m. and resumed at 1:06 p.m.)

A-F-T-E-R-N-O-O-N S-E-S-S-I-O-N

(1:06 p.m.)

CHAIR BOCCHINI: Now, we're ready to start. I'd like to open the session with roll call. So, Don Bailey?

MEMBER BAILEY: Here.

CHAIR BOCCHINI: I'm here. Jeff Botkin?

MEMBER BOTKIN: Here.

CHAIR BOCCHINI: Carla Cuthbert for CDC?

MEMBER CUTHBERT: Here.

CHAIR BOCCHINI: Catherine Spong.

MEMBER SPONG: Here.

CHAIR BOCCHINI: Kellie Kelm.

MEMBER KELM: Here.

CHAIR BOCCHINI: Fred Lorey by phone. Dieter Matern.

MEMBER MATERN: Here.

CHAIR BOCCHINI: Steve McDonough.

MEMBER MCDONOUGH: Here.

CHAIR BOCCHINI: Kamila Mistry.

MEMBER MISTRY: Here.

CHAIR BOCCHINI: Michael Lu.

MEMBER LU: Here.

CHAIR BOCCHINI: Alexis Thompson by phone.

MEMBER THOMPSON: I'm here.

CHAIR BOCCHINI: Cathy Wicklund.

MEMBER WICKLUND: Here.

CHAIR BOCCHINI: And Debi Sarkar.

MS. SARKAR: Here.

CHAIR BOCCHINI: Now for organizational representatives. Bob Ostrander.

MR. OSTRANDER: Here.

CHAIR BOCCHINI: Beth Tarini.

MS. TARINI: Here.

CHAIR BOCCHINI: Michael Watson.

MR. WATSON: Here.

CHAIR BOCCHINI: Joseph Biggio. Kate Tullis.

MS. TULLIS: Here.

CHAIR BOCCHINI: Susan Tanksley by phone.

MS. TANKSLEY: I'm here.

CHAIR BOCCHINI: Chris Kus by phone.

MR. KUS: Here.

CHAIR BOCCHINI: Adam Kanis by phone.

MR. KANIS: Here.

CHAIR BOCCHINI: Natasha Bonhomme.

MS. BONHOMME: Here.

CHAIR BOCCHINI: Ed McCabe by phone.

MR. MCCABE: I'm here.

CHAIR BOCCHINI: Cate Walsh Vockley.

MS. VOCKLEY: Here.

CHAIR BOCCHINI: And Carol Greene.

MS. GREENE: Here.

CHAIR BOCCHINI: Thank you all. We're going to open this session with public comment. And there are a number of people who have signed up to make public comments.

We have a half an hour so I want to be careful about everybody please try and stick to the time allotted so that everyone gets a chance to make their comments.

So first we have four persons from the

Association for Creatine Deficiencies who will discuss newborn screening for GAMT deficiency.

They are Kim Tuminello, Laura Martin, Heidi Wallis and Melissa Klor. So if you'll all come to the microphone and then you can speak one after each other. Welcome.

MS. MARTIN: Hi. So my name's Laura Martin, and I'm here with the Association for Creatine Deficiencies today to tell you a little bit about my son.

This is Ryan. He'll be five years old in July. So Ryan was diagnosed with GAMT deficiency just before his third birthday on a genetic epilepsy panel.

He started treatment right away and within two weeks his seizures had completely stopped. His EEG normalized, his coordination improved, and, it took awhile, but he is talking now which is a huge relief to us.

He's got hundreds of words and he's able to put them together into short sentences. He can tell us things like hands cold, Mom, need

mittens.

He's a happy kid. He's affectionate. He's active and playful. We're very proud of him and excited for his future.

Since learning about Ryan's diagnosis I felt kind of torn between two different perspectives.

I try to live primarily in the first which is the one that I just told you about. I actually used to work at a home for adults with severe intellectual disabilities, mostly non-verbal, and I know what Ryan's future would have held had he not been diagnosed at such an early age.

But there's another side to this story that I wanted to share with you today, and that has to do with the fact that my son has permanent brain damage that could have been prevented by newborn screening.

So, Ryan currently attends a special school for multiply handicapped children where he gets speech therapy, physical therapy,

occupational therapy, music therapy, you name it.

He's still in diapers, and he scores at less than the first percentile on every standardized test he's ever had across domains.

He may never be able to live independently or care for a family of his own.

So, Ryan also has an older brother, a stepsister and a fraternal twin brother as well. And none of my other children have GAMT deficiency. But I want you to know that their lives have been impacted by the diagnosis as well.

I feel very guilty about all of the time and attention that's been stolen from my other kids while I focus so much of my energy on Ryan's care.

And coincidentally I happen to be a genetic counselor as well which adds to my guilt as you can imagine in so many ways. How could I work in this field and not know for so long that my own son has a treatable genetic disease.

The truth is that before Ryan's

diagnosis I had never heard of GAMT deficiency, but when he tested positive one of my very first thoughts was how could this not be on the newborn screening.

It's the perfect candidate for screening. It's a devastating disease when it's left untreated. Treated from birth kids are normal. It has a treatment that is just incredibly safe, and it also really couldn't be any less expensive. So Ryan just has creatinine and ornithine supplements.

So, ever since Ryan's diagnosis I feel like I've just been kind of carrying around this terrible secret because I know that there are other kids and adults out there with undiagnosed GAMT who are seizing and wheelchair-bound and unable to communicate.

And every year that goes by without putting this condition on the newborn screening that number is only going to grow.

The first case of GAMT deficiency was diagnosed in 1994 which is more than 20 years

ago. So I feel strongly that this has gone on for long enough and I ask that you please vote today to move GAMT forward toward the condition review team. Thank you.

CHAIR BOCCHINI: Thank you, Ms. Martin, for presenting your personal story. We appreciate it. Thank you.

MS. KLOR: Hi, my name is Missy Klor and I'm one of the cofounders of the Association for Creatine Deficiencies.

And my son was diagnosed at 13 months old with GAMT deficiency.

He's now eight years old. We went through a lot of tough moments on our journey to a diagnosis including being misdiagnosed with cerebral palsy.

None of it was easy and it was very scary at times, but we were lucky. John only suffered 13 months of brain damage.

John went through years of costly physical therapy, occupational therapy and speech therapy. But after eight years John only has

speech on a consultative basis and occupational therapy once a week. So in terms of a cost analysis you can look at the continued care that he would have received versus how he's doing today.

Today John is a typical boy that can run and play. He's eight years old and finishing the first grade. He loves to play with his friends. He takes two hours of gymnastics twice a week and is currently working on front and back hand springs.

That's kind of, you know, when he was two the physical therapist told me he no longer needs physical therapy. And as a mom I was hesitant to let that go with a kid with brain damage so I may have kind of overkilled taking on that expense myself, but the state, no one ever had to pay for any more continued physical therapy for him.

He plays soccer. He gets 100s and sometimes 110s on his spelling tests. He currently likes to read Goosebumps books.

Where was a time before John was diagnosed where the future did not look good for him. But we were lucky thanks to the doctors at Duke. They were knowledgeable about GAMT and screened him for it.

Today he has achieved more than I ever dreamed. He had to work hard to overcome his delays, but he did it and I couldn't be prouder.

John takes three supplements three times a day. Although the treatment can be relatively inexpensive I received approval from federal Blue Cross and Blue Shield to have one of his medical foods covered. I have a letter from them stating that we were granted an exception for it to be covered under our preferred benefits until John turns age 22.

And during the discussion about medical foods I actually looked at the letter that I received from them to see how many years it took me to get this letter. And John was diagnosed in 2009 and the letter is dated 2013. So it was four years of fighting.

John is also on a special diet, but so are a lot of kids these days so that really is no big deal at school or at home.

This diagnosis will not define John. Unfortunately until GAMT is added to newborn screening not every child and parent will be as lucky.

Currently many children are either undiagnosed or diagnosed at a later age. They have brain damage that causes seizures, difficulty speaking, difficulty walking, and the list of negative outcomes only gets longer.

I'm asking you to please consider voting for more futures like John's. You get to vote for more children to have a future that is not defined by the four letters GAMT, but instead by what they want to make for the future for themselves.

These children will be able to grow up with a life relatively unaffected by GAMT and will be able to experience life to the fullest.

They may not realize how lucky they

are to be diagnosed from birth, but that's okay. You and I and the other four mothers in the room that I stand here with today will know just how lucky they are.

I always tell John that I love him to the Moon and back. This year for Mother's Day he gave me a special gift. It was a list of all the things he loves about me, and at the very end it said I'd like to tell my mom that I love her from 10 galaxies and back.

Every parent should get that opportunity to hear those words from their children. But unfortunately with late diagnosis that's not always possible.

Every parent here has a different story to tell, but unfortunately the outcome of that story is ultimately defined by how quickly they were able to get the diagnosis of GAMT.

All every parent wishes for is a healthy child. Please vote yes to add GAMT to newborn screening.

MS. TUMINELLO: Hi, my name is Kim

Tuminello and I am a mother of two children with GAMT. I'm also the president and cofounder for the Association for Creatine Deficiencies and I'm here today to represent my family and the entire creatinine deficiency community.

I'm hoping that if you didn't know about this particular genetic disorder in the past that you now have a better understanding of this severe neurological disorder that is devastating in every way.

However, GAMT is completely treatable but only if it is caught in the very beginning of life.

It has been proven in studies that a newborn blood spot can detect the elevated guanidinoacetate level.

We know from Utah's pilot of newborn screening this past year that there are no gaps in evidence and no false positives.

We also know through a study at Duke that there are no false negatives and the rate of occurrence may be as high as 1 in 120,000 which

would be as many as 33 babies diagnosed each year just here in the U.S.

There is a safe and viable treatment that is a life-altering therapy. Our children simply drink a cocktail of creatinine, ornithine and sodium benzoate a few times a day along with a moderate low-protein diet.

This simple therapy saves them from a life of hundreds of seizures in a day, the inability to communicate and being strapped to a wheelchair for the rest of their lives.

My 10-year-old son Ty was not diagnosed until he was 10 months old. I guess we are considered one of the lucky ones because we got the earlier diagnosis than most.

But Ty has gone through years of physical therapy, occupational therapy, vision therapy and today he still continues to be in speech therapy through our school district in San Diego.

But because we knew to test for GAMT my daughter has been treated since birth and

Paige is now a typical 6-year-old in the first grade and has never had a day of therapy or intervention in her life.

Last year my daughter's kindergarten did a project in class for her school's open house and was asked to write about something that meant more to them than gold.

While most kids wrote about their puppy or new bike, Paige wrote, "My medicine means more to me than gold because without it I couldn't walk or talk." It's just that simple, isn't it?

While the value of diagnosing and treating GAMT deficiency from birth truly is far greater than gold, the actual cost of this life-saving treatment is practically nothing.

As a matter of fact, the cost is so inexpensive that even if a family didn't have insurance coverage of their own they could probably still afford to go to their local Whole Foods and supply their child with creatinine for about $20 a month.

Everything needed to treat this debilitating disorder could literally be ordered off of Amazon.

To think there is a family out there who believes they are just one of the statistics in the autism community, that their child has unexplained seizures and slowly or sometimes rapidly continue to watch their child slip away, and all they had to do was simply go to their local GNC and pick up something that literally would change the future of their child in every way imaginable.

Today labs across the country already have the tandem mass technology needed to start testing for GAMT. Even if second tier testing is needed it's estimated that the cost adds up to only be 49 cents a baby.

I'm sure every state will be happy to have this on newborn screening in comparison to the millions of dollars that would be spent over the lifetime of the child in school, special services, and eventually being turned over to the

state to receive lifelong care.

My fear today is the longer we wait more babies will go untreated. For them it would be too late. The damage will be done. And just with us four moms today we have six children.

Well, I have good news. GAMT is exactly the type of treatable disorder that RUSP is looking for. All of us here today have had many physicians who have said this should be a slam dunk. This should be a no brainer. And I certainly believe that to be true also.

But we know that you all have an awesome responsibility, but you also have an amazing opportunity to save these children and their families from the unnecessary heartbreak of GAMT.

The Association for Creatine Deficiencies has built a strong patient advocacy network.

We help families with resources and programs such as patient grants if they are not able to afford the treatment themselves.

And our community knows that they can depend on us to get the job done. Each of these mothers you see here today ironically left their families on Mother's Day to drive from the far northeast or fly across the country for this meeting today for just a few minutes to tell you about this rare but treatable disorder our children, and most importantly to save the countless other children in the future. Thank you for your consideration.

MS. WALLIS: Hi, my name is Heidi Wallis and I'm the mother of four children, two with GAMT and two without.

There are a few things I want to be sure you understand about children with GAMT.

First is that they do not look different. They are not instantly recognized at birth as having GAMT.

I tell you this because the burden of diagnosing these kids should not be on their primary care physician.

Also, not every GAMT child develops

symptoms that are alarming in the first few years of life.

My oldest daughter Samantha was slow to reach milestones, but for example, she did finally walk at 18 months. This was considered just barely good enough.

She did not have floppiness or movement disorders, and until she turned five she did not have seizures.

At three she was diagnosed barely on the autism spectrum and we were given a list of resources to go home and figure out how to live with this new diagnosis.

We as her parents knew something more was going on, but again it was not obvious or alarming enough for anyone to take our feelings seriously.

Thankfully at five the onset of seizures ended up getting her an MRI along with spectroscopy and that is how her creatinine deficiency was finally noticed.

Sheer luck led her to a GAMT diagnosis

and treatment, not unique symptoms or dysmorphic features.

Secondly, I would like you to know that treating a GAMT child from birth does not just help them. It does not just make their life a little better, or ease the symptoms. It absolutely saves their life.

My son Louis was diagnosed at birth. As I have watched him grow from a tiny baby to the 4 and a half year old preschooler that he is now treatment for him has been nothing short of miraculous.

He is full of joy, intelligence, creativity, love and affection, imagination and music. He scores in the typical range in cognitive testing.

He sticks to a regular RDI of protein every day so no over-indulging, and he has to put his playtime on pause four times a day to take a quick syringe full of easily available and affordable powders mixed with water.

Treatment has been simple for him and

very successful.

Treating a child with GAMT later in life can help them. Samantha went -- this is my daughter Samantha was diagnosed at five.

Samantha went from a 5-year-old that could only approximate a handful of words to having lots of actual speech. She can ride a bike.

But here's the problem. Her IQ tests very low. Her speech is not always understandable, not the pronunciation but the content. I don't know what she is trying to say to me. It is often meaningless, or quoting movies.

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 and I'm grateful that she's come as far as she has. But she will continue to suffer because of her late diagnosis for the rest of her life.

The damage has been done. She has a severe intellectual disability.

I ask you to please understand that there is not a second option for children with GAMT. They must be diagnosed at birth.

Treatment is successful. There is no question about it. Please recommend GAMT for the RUSP. Thank you.

CHAIR BOCCHINI: I want to thank all four of you for coming here today and presenting to the committee. We appreciate it. Thank you.

Next we have Christine Brown and Jana Monaco who would like to address the importance of access to quality care and treatment.

MS. MONACO: Good afternoon. My name is Jana Monaco and I am the parent of two children with isovaleric acidemia.

And I wanted to thank you to Kathy Camp for her great presentation this morning, although it was truly disheartening to me as a mom.

I'm also the advocacy liaison for the

Organic Acidemia Association.

Steven, now 18 as many of you know would be graduating from high school next month, but that's not going to happen. As you know, his late diagnosis due to lack of newborn screening paused his metabolic acidosis 15 years ago this month at age 3 and a half, resulting in his significant brain damage and taking away that and countless other dreams.

Caroline, now 13, will have that one and many other dreams. The difference is the early detection for her disorder and appropriate treatment with a detailed diet plan, medical formula and supplements. That's a cost-benefit if you really are looking for one.

In my 13 years of advocating for expanded newborn screening and follow-up and treatment medical formula and foods has been identified as a critical component of the treatment, though not everyone has access due to the lack of coverage for it.

They are costly, but they are

essential, and children like mine and Christine's depend on them to thrive.

In 2010 during my term on this very committee a letter was sent to the Secretary requesting that they be included as essential health benefits under the Affordable Care Act.

It didn't happen due to the Secretary's request for more information, particularly on insurance plans.

The IOM's report in October of 2011 recommended further evaluation of coverage by HHS of nutritional supplements and formulas needed for the treatment of inborn errors.

There has been no follow-up and no further evaluation, but we need you to ask HHS to follow through. Just as bureaucracy caused disparity in state newborn screening programs prior to the expanded recommendation from this committee resulting in kids like Steven so has its impact on medical formula and food coverage with NIH, FDA and CMS and others operating under various classifications and definitions, and

their own barriers.

We request that you ask the Secretary to end this disparity that has lingered for almost 10 years since we've expanded the newborn screening panel.

We ask that you invite her to initiate a joint meeting of these departments and other key players that Cathy mentioned this morning and convene and agree to a common definition and solutions to make lifelong access to medical formula and foods available and accessible to each and every child and adult who needs them.

If treatments are required for conditions to be included on the RUSP then it is ethically wrong to allow them to be inaccessible to the very patients that need them.

This committee has a moral responsibility to ensure that this component of lifelong treatment be properly identified and available to the population whose lives depend on them.

Please stop allowing this elephant in

the room to continue to remain while patients and families suffer the consequences. Thank you for your continued work.

CHAIR BOCCHINI: Thank you.

MS. BROWN: Hi, I'm Christine Brown. I have two children with PKU. I sit on the Long-Term Follow-up and Treatment Subcommittee and I'm also the executive director of the National PKU Alliance.

And many of you saw me present to the full committee a few months ago giving a patient perspective on long-term follow-up.

And you might remember that I put two pictures up of my two children with PKU. And many of you raised your hands when I asked you how many of you have similar pictures of when your children were born and that day.

And we all had some of those same questions when our children were born. What will they look like? What mark will they make on the world?

I had additional questions after the

diagnosis of PKU. Will they be able to go to school? Will they need an IEP? Will they need a 504 plan? Can they go to college? What are they going to eat on their prom date? Can they go on a business lunch?

But never in a million years that first week of asking those questions did I think to ask the question am I ever going to have to worry about their treatment being covered by an insurance company.

As a patient community the National PKU Alliance at our last conference asked adults and parents to free write what are their top three concerns in dealing with PKU.

Number three was the development of a home feed monitor for better management.

Number two was new treatments. And you saw from Cathy's presentation and my presentation a few months ago that 91 percent of our community said that new treatments are important.

But the number one concern that

trumped everything else was access and coverage to medical foods to treat PKU.

There is a failure here, and I think you all recognize that. We have all failed to accomplish support and access to treatment after the diagnosis is made on that newborn screening test.

As Jana said we believe you have a moral obligation. You have a moral obligation to my children, Connor and Kellen. You have a moral obligation to Jana's children Steven and Caroline, and to the other 475 children born every year with a positive diagnosis that requires medical foods for treatment.

I think we've already had some great discussion and some wonderful suggestions including asking the Secretary to follow up now that that Department of Labor survey has been out and the IOM report has been out for more than five years.

This issue of medical foods has been punted too many times. In the last seven years

we have been as a patient organization talking with the NIH. We met with CMS. They told us to meet with FDA. We talked to FDA. They said well, our definition of "enteral" is different than CMS.

We testified before HHS at the listening sessions on the essential health benefits. We were told to go to the Office of Intergovernmental and External Affairs, who told us to go the Office of the General Surgeon, who told us to go to the National Prevention Council, who told us to go back to HHS.

Then when we went to OPM and talked about the federal employee health benefit plans we were told they were going to lift the age limits on medical foods. That didn't happen and they referred us back to HHS and CMS.

It's been going around and around for far too long.

So again I ask you that same question I asked you two months ago. What hopes and dreams did you have for your children when they

were born?

One of my biggest dreams shouldn't have to be the dream of getting their medical foods covered.

I want to set my sights on something bigger and better for them, and in order to do this I ask you all to be bold. Thank you.

CHAIR BOCCHINI: Christine and Jana, thank you both very much.

And as you know from this morning's presentation and discussion we have asked the Long-Term Follow-up Committee to review the current information from those reports and to kind of come up with some plan to go forward to try and improve the situation. So thank you.

Next, Carol Greene is going to make us aware of the Society of Inherited Metabolic Disorders updated statement on access to care with focus on medical foods.

MS. GREENE: Thank you. So I am Carol Greene representing today the Society for Inherited Metabolic Disorders which is a

professional organization of those who work in the area of inborn errors, supports access to quality are including medical foods.

And we hope that our updated statement will be a useful tool to those who are working in support of this.

And in the interest of keeping to time even though it's only one page I'll just read highlights of our April 2016 statement on medical foods, and ask that the whole of the statement be included in the record.

So, the SIMD strongly urges that all private and public systems for healthcare payment be mandated to cover specialized diets including medical foods for treatment of inborn errors of metabolism found by newborn screening or clinically diagnosed.

Our statement describes what inborn errors of metabolism are and mentions the Orphan Drug Act definition of medical foods.

And we point out that although medical foods are an essential medically necessary

treatment for many inherited metabolic disorders many healthcare payers deny coverage for medical foods and mandates are not consistent across states.

The complex pattern of healthcare coverage in the 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 lifelong access to these treatment modalities also threatens the success of public health policy.

And that's for PKU, for isovaleric, that's the creatinine for GAMT, and we really hope that you will be able to use this statement

which we offer as a tool in the fight to get this covered.

CHAIR BOCCHINI: Thank you, Carol. Next, Spencer Perlman to talk about newborn screening for spinal muscular atrophy.

MR. PERLMAN: Good afternoon and thank you for the opportunity to testify today.

My name is Spencer Perlman. I am a member of the Cure SMA board of directors though I'm testifying today on behalf of the entire SMA community.

Being sensitive to time I will just briefly explain our purpose and our request, and ask that the remainder of my comments be submitted for the record.

As you all know SMA or spinal muscular atrophy is an autosomal recessive genetic disorder that occurs in about 1 in every 10,000 live births and is the leading genetic killer of children under the age of 2.

Today I urge the advisory committee to give serious consideration to the forthcoming

nomination and evaluation of SMA for universal newborn screening.

SMA families, investigators and clinicians all believe that newborn screening is imperative for ensuring access to effective treatment of this disorder.

In the 10 years since I last stood before this committee there have been significant advancements in the development of a treatment for SMA. And indeed this is a really exciting time as we are on the brink of seeing an approved therapy in the foreseeable future.

Of the 18 SMA drugs currently in development 6 are clinical trials including several in phase III. And we expect that one or more of these programs will undergo FDA NDA review in 2017.

Therefore it's critical that SMA be added to the recommended uniform screening panel 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 that there is 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 SMA individuals and frequently leads to death before the age of 2.

Preliminary data in mouse models also indicates that pre-symptomatic drug intervention is far more effective than post symptomatic.

And additional 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 the quality of life.

Furthermore, the technology for newborn screening for SMA has been successfully utilized in several ongoing pilot newborn screening programs including in New York State and in Taiwan.

So in conclusion the SMA community strongly urges the advisory 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.

I thank the committee for the opportunity to address you this afternoon.

CHAIR BOCCHINI: Thank you for your comments. We certainly look forward to receiving the nomination packet.

Now on the phone we have Mr. Dean Suhr to discuss the RUSP roundtable and California model legislation involving the RUSP. Mr. Suhr?

MR. SUHR: Yes, good afternoon. Thank you, Dr. Bocchini and I thank the committee for this time.

I wanted to touch on these two particular issues just briefly.

The RUSP roundtable is continuing. I spoke about that at the February meeting so I won't provide any more details on that except to say that our next meeting will be Wednesday, August 24, just prior to the next meeting in the

D.C. area.

On the state legislation I'm involved in a project in California, in basically a study to address the issue of the U.S. having 50 states with 50 policies relative to how a screen is implemented after it's approved and on the Recommended Uniform Screening Panel.

As you know, in many cases that involves a legislative action of some kind. And in fact, that legislative action is not necessarily tied to the RUSP. There are, I believe there are states that are mandated by legislative action without being on the RUSP.

However, what we're talking about here is what happens after the issue is put onto the RUSP.

The legislation that has been proposed and introduced in California is something that I'm participating in cooperation with the rare disease legislative advocate.

And it's a one and done we're calling it kind of in the global sense where once a

disease is on the RUSP a legislative action is automatically taken care of. So we would pass a law up front that says anything that is qualified on the RUSP by a thorough evidence review process that you all go through, that that disease is then acceptable to that state to go forward with implementation.

We're not requesting any specific timeline, nor are we able to include an appropriation that would allow that addition to be implemented.

I would highlight that in California that the appropriations that cover the expenses relative to newborn screening are actually a matter of law already. So that actually is not an issue in California.

We want to use this legislation as model legislation in all 50 states, or at least all states where the legislators are involved in getting these diseases onto the panels.

We recognize this will not work everywhere, but we're hoping that we can bring

the advocacy and the family groups together to do this kind of in a one and done sense.

We've run across an issue though that I want to just put in front of the committee. And I'm not sure how you would address this, or it might be just an undercurrent.

But there are a number of states that implement their screening, they almost replicate the entire set of work that the committee goes through in terms of evidence review.

And we expect some of that because every state's equipment is a little bit different, their processes are a little bit different.

But it appears that there's a varying width of acceptance of the work that the committee is doing.

And everybody recognizes that it's a baseline, but how much additional work is done on top of that is a question we're starting to run into across states. So that's something I'd like to throw back at you to maybe consider a little

different work effort in terms of how can we continue to build the credibility of the committee's work and continue to share the breadth and the depth of the work that you're doing.

So with that, I do thank you for all your work, and I thank you for the time.

CHAIR BOCCHINI: Thank you very much, Mr. Suhr. We appreciate your comments.

This will conclude the public comment session for this meeting. So we appreciate the input that we've received from the public comments. Thank you.

We're now going to go forward with the GAMT Nomination and Prioritization Workgroup report. Dr. Matern will present this information. And subsequent to the presentation there will be a discussion, decision, and a vote. Dieter?

MEMBER MATERN: Thank you. So I'll be talking on behalf of the Nomination and Prioritization Workgroup. And I don't have a

slide that actually mentions the members of that workgroup, but it includes Dr. Bocchini, and Dr. Cuthbert, and Dr. Scott, and Debi, and Fred Lorey, and probably I'm forgetting someone.

So, the nomination was submitted by Dr. Nicola Longo from the University of Utah and cosponsored by Dr. Marzia Pasquali also at the University of Utah and also running the biochem and genetics lab at ARUP Labs.

There was no advocacy group mentioned in their nomination but of course we have heard from the Association from Creatinine Deficiencies just before this presentation.

There are several questions that we had to answer reviewing the nomination package and then checking the literature with other experts that we realized are out there.

So, the first question of course is the nominated condition medically serious. Second, are there prospective pilot data either done in the U.S. or elsewhere from population-based assessment available for this disorder.

What about the case definition and the spectrum of this disorder. Is it well described? Is there a phenotypic range of children identified on a population-based screening?

What about the test's analytic validity? Do we know enough about the test to work analytically, but also has it clinical utility or other concerns with the test?

And then about treatment. Is there treatment? Are there medications that are FDA approved available or needed? So what about treatment.

First, I'd like to introduce you quickly to creatine deficiency syndromes. And I as a biochem geneticist, I have to show you a metabolic pathway, not so that you pass out, but just so you get an understanding.

I think it helps to figure out the approach that is taken to both the testing for the disorder and also the treatment.

So as you can see creatine is here located. It's also outside in the blood and

needs to get across cell membranes. But creatine first needs to be made unless you obtain it through food intake.

The pathway to synthesize creatine starts with arginine and glycine which is produced to guanidinoacetate which is then methylated to creatine. And then again it has to cross the cell membranes to get into the brain and muscle, and there's a creatine transporter.

So there are two enzymes involved, and the enzyme we're talking about is guanidinoacetate methyltransferase which is located here.

However, any of those enzymes, GAMT, AGAT, and then the transporter can be deficient and cause disease.

And this is taken from the gene reviews that was updated in December 2015 so it should be fairly up to date.

You can see there are 110 GAMT patients known in the literature. They present and that is what we heard earlier after a few

months of life to up to three years.

The phenotype is mild to severe intellectual disability. Most patients have epilepsy and the epilepsy is difficult to control. In half of the patients there is movement disorder and then their behavioral problems.

In AGAT the situation is that this is much more rare it appears than GAMT and again has a somewhat similar phenotype, muscle weakness being pronounced.

And then there is the X-linked transporter defect. This is the condition where most patients are identified. Again, onset is less than three years in those affected, boys, and similar phenotype to GAMT.

Treatment as we heard already from the parents is available and it's mostly supplementation of creatine and ornithine, and then restriction of protein and/or arginine and sodium benzoate. And the treatment is also established for the other conditions.

Here you see from Scriver's, the online metabolic textbook a picture taken from the chapter on GAMT deficiency.

And here you see one patient in A, B and C. And you can see the significant hypotonia here, dystonia here at 22 months, and then after being put on treatment you see that the patient seems to be doing better but is still having symptoms. And that is of course consistent with what we heard from the parents.

And this is an untreated patient at four years old.

So, important here of course is that the outcome is improved when you treat these patients as early as possible. And of course that is always good reason to think about newborn screening.

What about the biochemical genetic diagnosis? Guanidinoacetate, when you have a defect here is accumulating. And you can measure this in urine, CSF, plasma and now in dried blood spots and it is elevated.

If you look at the other conditions, AGAT deficiency and the transporter defect, GAA is low or up to normal. AGAT deficiency is normal in the other conditions, so GAA alone is not really helpful to identify the other creatine deficiency disorders.

However, you can also measure creatine and creatinine all at the same time as you do the GAA. You can do ratios and that kind of helps you a little bit better differentiating those different disorders.

There is a diagnostic algorithm again from the Gene Reviews article for patients that are presenting with symptoms that are suggestive or could be consistent with GAMT deficiency.

You do as a next step the measurement of GAA, creatine and creatinine in urine or in plasma. And then based on those results you can follow up using different studies including molecular genetic testing for the relevant genes. And if that results in a genotype of uncertain significance you might still have to do a

specific enzyme assay for each enzyme to arrive at a diagnosis.

But this is all doable because there are laboratories that offer this test. The only one that is a little bit tricky is the enzyme assay which I believe is only available in Amsterdam.

So, creatine, again I mentioned earlier the source of it is either the diet or biosynthesis. And the function is important as you can see here in the regeneration of ATP. And it is also a neurotransmitter in the CNS.

Because of the energy provision through creatine as we also heard from the parents you can obtain creatine in all kinds of stores, not only at Amazon but at Walmart. And since it is not yet reimbursed through health insurance it still is relatively cheap.

I always wonder if those costs would go up if health insurance actually would have to pay for it because those providers might think it's a good reason to jack up the price.

The pathophysiology of GAMT deficiency is basically, again, if you consider that you have this enzyme not working functionally you will have a deficiency of creatine and you will have accumulation of the precursor, guanidinoacetate which is a neurotoxic agent as far as we know.

So, the idea then is in treating these patients that you provide creatine at sufficient doses to overcome the blood-brain barrier and also maybe providing S-adenosyl L-methionine to potentially help any residual GAMT activity to be more effective.

And also to reduce guanidinoacetate which is accumulating. And you do this by providing ornithine, but also restricting arginine and maybe glycine by providing sodium benzoate.

So what are the outcomes of treatment? As we heard very effectively from the parents is that if you identify these patients basically at birth or shortly thereafter they can have a

normal life.

The later you make the diagnosis the more severe is the phenotype. So initiation of treatment as early as possible seems to be very important.

Also interesting is that in a paper that was published a couple of years ago there was a patient that was first reported in 2006 by a German group.

They found a patient who was diagnosed in the first few months of life and was doing very well, but apparently the parents then decided, well, this is kind of difficult and our child seems to be fine so they stopped treatment. And it didn't take long and then the patient had irreversible damage. So it is important that these patients stay on treatment consistently throughout life.

So back to our key questions. The nominated condition is medically serious. The answer I think is yes.

And I think we pretty well know what

the phenotypic spectrum looks like, at least based on these 110 patients.

What about treatment protocols? Are they defined? Are there FDA approved drugs, and are those all available?

So, in a paper by the Utah group they talk -- which is called Evidence-based Treatment of Guanidinoacetate Methyltransferase it indicates here very clearly that the recommendations for treatment of GAMT deficiency are evolving. So it might be that we don't have that nailed down completely.

In another paper a year later in 2014 a larger study of 48 patients where they review and provide recommendations for diagnosis, treatment and monitoring, one of the conclusions is that overall numerous questions regarding the evidence of the described treatment modalities still remain to be answered.

So, we might not have yet fully defined treatment protocols.

What about newborn screening? Are

there any pilot study data available and how good is the test?

So the proposed newborn screening test is to measure GAA but creatine has also been already mentioned as in use in Utah at least, and you could also measure creatinine along with the acylcarnitines and amino acid analysis.

So this is not a separate test. You don't have to buy new equipment. You don't have to add extra people to do the testing. All you have to do is add a few reagents and do a modification to your analysis in mostly the software. So it's really, as the parents indicated, fairly cheap.

Also, the CDC already is providing reference materials for GAA and creatine through their quality assurance program.

A second tier test is probably a good idea to have as also reported specifically from the proponents from Utah.

And what they basically do, they do the analysis for GAA and creatine again by liquid

chromatography tandem mass spectrometry which is not as common as the regular flow injection analysis in newborn screening laboratories, but really any mass spec you can do LC-MS/MS on.

So you may but also may not require extra equipment. But it also has many second tier tests. They could probably be regionalized.

And I think as there are a good number of second tier tests out there I would still propose to many screening laboratories to join forces and every screening lab should offer at least one second tier test and work with other neighboring states maybe to provide the test to their relevant populations.

There's also molecular genetic analysis of the GAMT gene available and has been proposed for newborn screening.

But what you find at the same time is that there are again variants of uncertain significance that are identified and therefore genotypes of uncertain significance. So it's really in my opinion not that helpful.

And it also is not yet typically used in a wide number of newborn screening programs.

So what is the status of newborn screening for GAMT deficiency?

Published data from the University of Utah looking at 10,000 newborn screening samples retrospectively, they found a false positive rate by just looking at GAA and the GAA to creatine ratio of 0.08 percent.

However, they didn't report any false positives, or any of those out because they have a second tier test to look at GAA and creatine again. And so the final false positive rate is zero percent.

And the true positive, however, is also zero. They didn't find an affected patient in those 10,000 samples.

The Baylor Research Institute in Dallas, Texas, did a study of nearly 20,000 babies of which about 50 percent were from Mexico. And they did this between 2008 and 2011.

They had a false positive rate of 0.5

percent just looking at GAA, but with the second tier test which basically means you take the original newborn screening sample, you do not tell anyone about this outside of the screening lab. You do the second tier test and if that is normal then you do not report it out.

So, in the end the false positive rate is zero which is extremely good. But they also didn't find a patient in that study.

In British Columbia they looked retrospectively at 3,000 newborn screening samples, had a false positive rate only using GAA of 0.13, 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. So coming back to what does this mean now. But those were only carriers so it really is supportive of the conclusion that there was no true positive in their cohort.

In Australia they've been actually doing prospective newborn screening for GAMT

deficiency since 2002 and have screened more than 1 million babies.

Their report in 2014 included only about 770,000 babies, but I communicated with Dr. Pitt in Australia and he confirmed that they're continuing screening. They have screened about a million babies and they didn't find a single true positive. And the false positive rate with apparently no second tier test is 0.02 percent.

Now, we always wonder if it's international does it reflect a very different population to what we would find in the U.S.

So I Googled the demographics of Victoria, Australia, and could find that 66 of Victorians identify as Australian, and then of Scottish, English, or Irish ancestry and less than 1 percent aboriginal. And most immigrants are from the British Isles, China, Italy, Vietnam, Greece and New Zealand. So, more or less like America maybe.

In the Netherlands a study that came out only this year, and for those of you who look

at what is in the briefing book this is basically two versions after what you have in front of you so this slide was not included.

They looked at 500 newborn screening samples retrospectively. They did sequencing of the GAMT gene and they measured GAA.

Through sequencing they found two carriers, one with a known mutation and one with a novel mutation. And based on expression studies they feel that it is a pathogenic mutation.

And through measurement they found no false positives, but also no true positive.

So based on this the presumed carrier frequency is 1 in 250 which would calculate an incidence of about 1 in 250,000 among the Dutch population.

And the Dutch population is described in that paper as consisting of individuals with Dutch, Turkish, Moroccan, Indonesian, German, Surinamese, Latin American, other European and Asian ethnic backgrounds. So, very diverse.

So, how frequent is GAMT deficiency? So, you can look at this based on calculation and based on prospective newborn screening.

So as I just mentioned, the Netherlands, they assume it to be 1 in 250,000.

In Utah they looked at the number of patients they had diagnosed over a 10-year period and then calculated it back to the live birth and came up with a calculated incidence of 1 in 114,000.

In Portugal in 2007 they had a report where they looked at 1,002 newborn screening samples that they tested for one mutation which appears to be common among patients with GAMT deficiency in Portugal and they found eight carriers.

So their calculated incidence is 1 in 63,000.

And based on prospective newborn screening in Australia as I mentioned less than 1 in 1 million, and in Utah less than 1 in 50,000.

So Utah is currently actually actively

screening for GAMT deficiency. And at this point they screened, as Dr. Pasquali mentioned to me earlier today, 50,000 so far. They had one false positive that turned out to be a NICU baby and at this point no true positive.

But if you look up here the estimated incidence is 1 in 114,000 so they should get there next year.

So in summary we believe that GAMT deficiency is a serious medical condition. The natural history of GAMT deficiency seems well understood even though there are only 110 patients known worldwide.

The treatment I think is very similar to many of the conditions on the RUSP. And I think that if you remember the discussion about PKU this morning I think there's a lot of overlap in how we would approach these patients. You need diet maybe, but certainly supplements and you need support.

The best outcomes is when treatment is started shortly after birth.

Dried blood spot based assays can be adopted for newborn screening quickly and at very low cost so that's new for us.

Prospective newborn screening is ongoing in Victoria and apparently in Utah. But again, at least in Australia very low incidence apparently. So, the sensitivity, however, of the screening test is also nicer than many of the conditions that we have added to the RUSP with a likely 100 percent sensitivity and near zero if not zero false positive rate.

So, should one add GAMT to newborn screening?

So, one could say well, we understand the natural history. Treatment is similar to many classic inborn errors of metabolism. The outcomes are best with early treatment. Newborn screening assay is cheap and easily implemented. And the newborn screening strategy has a high sensitivity and low false positive rate.

If you didn't want to do it you would say well, we only understand the natural history

on 110 patients. Is that enough?

There is no agreed upon treatment strategy. Metabolic control must be strict. No FDA approved newborn screening or diagnostic assay. And I don't believe that is really an issue because laboratory developed tests are just fine, so that shouldn't be an issue.

And, however, no patient has ever been identified through prospective newborn screening.

So, back to our key questions. Medically serious condition - yes. Prospective pilot study data - yes, not only Australia but also in Utah.

Case definition - yes, based on 110 patients. Analytic validity - yes. Clinical utility - well, the problem is no case identified prospectively yet.

And defined treatment protocols, you could argue well, they're not really that defined, so maybe not yet. But I think that is something that could be fixed.

So, what is the recommendation of the

workgroup to the advisory committee? At this point we would say we do not initiate external evidence review because not a single case has been identified prospectively through newborn screening which would really make the evidence review very difficult.

And then treatment guidelines appear to be in development but are not finalized.

What I think should also be recommended, or what we think should be recommended, that the proponents work with other experts to formalize the treatment guidelines and encourage the continuation of newborn screening for GAMT deficiency in Utah and Australia, and report ASAP back to us when a patient has been identified prospectively.

So, please we would say, proponents, resubmit a nomination immediately when above has been achieved. That's I think all I have.

CHAIR BOCCHINI: Dieter, thank you for that presentation. It was very clear and thorough. Appreciate it.

This is now open for discussion and questions from the committee and then from the organizational representatives. Don.

MEMBER BAILEY: Dieter, could you speak a little bit more about -- I don't understand why treatment guidelines are unclear. Maybe I just don't have the information, but can you give me a little bit more information?

MEMBER MATERN: I think what -- basically, and I would agree with do we really need this. Because if you look at conditions that we added only recently for Pompe disease there still in the literature you have questions about what is the right immune modulation, et cetera. So there are no clear guidelines there either.

So I would agree that this is a weak argument not to proceed because there is a lot of information out there. And it probably would be one short phone call among the proponents along with people and their colleagues in Canada to fix that and write a paper that outlines more exactly

what those guidelines are.

MEMBER BAILEY: Plus we're not talking about a dangerous treatment.

MEMBER MATERN: From what I understand it's not a dangerous treatment.

MEMBER BOTKIN: Dieter, thanks, it was very helpful.

You mentioned that the clinical sensitivity of the testing estimated to be 100 percent. Where does that number come from in the absence of any real babies identified yet?

MEMBER MATERN: So, that comes from the fact that specifically in Australia where you have this large area called Victoria which is served by one screening laboratory and one diagnostic laboratory.

And the Australians I think are very proud in their healthcare system and feel that since they haven't diagnosed a patient with GAMT deficiency since 2002 through their clinical efforts while they were screening that there are indeed no false negatives.

And in Utah I think at the same time they've been screening now probably for more than a year and didn't make a diagnosis clinically.

And again, the laboratory, there's only one biochem genetics lab. And even if another lab did the diagnosis the patient would be followed by Dr. Longo.

MEMBER MCDONOUGH: Knowing what we know now in 2016 about how serious this condition is, and there's effective treatment, and what happens when these children aren't picked up on time, if we knew that back when the tandem mass was developed and the RUSP was expanded is it more likely than not that this condition would have been part of that panel back then?

MEMBER MATERN: At the time there was no screening test so that is one thing. I think if the screening test would have been around I would believe that it would more likely be included than not.

MEMBER SPONG: So, I'm a little new to this, but is it -- I'm confused as to why this

wouldn't get moved forward just to the condition review team.

Is it just because we haven't identified one case using these prospectives? Is that the reason why? And how long could that take to happen? And what would be the harm in moving it forward while waiting for that one case?

MEMBER MATERN: Well, the harm of course is always that a baby will be born in a state that could have screened and will not receive the treatment.

MEMBER SPONG: That's the harm in not moving it forward, or in moving it forward? What's the harm in moving it forward?

MEMBER MATERN: Well, the problem I think for the evidence review, because we're just discussing here whether it should be moved forward to the evidence review. So we're not even talking about should it just be included.

I think the harm is that we're asking the evidence review to proceed and come up with

the fact that there was not a single true positive.

And so they don't really know what to -- well, they're not recommending us anything, but the data they will provide us will probably not add anything new that we don't know right now.

Yes, we had this discussion. Yes.

MEMBER MCDONOUGH: The point I was trying to raise with the question I asked is that there's probably -- I shouldn't say -- is there more information about this condition, the benefit of treatment, early detection, that perhaps some of the conditions that were added on the RUSP in that expansion? Do you have an opinion on that?

MEMBER MATERN: Well, to my counts this is a no brainer. Again, this is a condition that's medically serious. There's treatment that seems to be -- well, that is cheap, that can be done, and the screening test is not difficult. Does that answer your question?

Steve, do you have a question?

MEMBER MCDONOUGH: Well, we have to be careful we don't get too paralyzed by our policies and don't take an opportunity to help some kids.

MS. GREENE: Carol Greene, SIMD. Thanks for the excellent review.

And while personally I'm not speaking for the SIMD for me obviously it's a slam dunk. I identify the kids and I treat them.

I wanted to speak to two points. One is with respect to treatment. I think perhaps -- because if you don't follow your own guidelines then the next person coming along will of course say well, you've got your guidelines and you went ahead and did it, and why not for me as well. So, the guidelines are meaningful and there's reasons to follow them.

With that said I think perhaps we need a little bit more guidance on the interpretation of treatment is not set.

Because the treatment, core of

treatment is you give creatine. We're arguing around, you know, we're nibbling around the edges, can we make it better, what do we do with the diet. Do we give sodium benzoate which tastes nasty and nobody wants to drink it anyway. How much ornithine do we give.

But we've got a treatment, there's no doubt about it. I think we need to be a little careful about over-interpreting.

When somebody genuinely and honestly says we need to do better figuring out the best way to treat this that we don't lose sight of -- so I feel very strongly as a clinician, you know, I'm going to go talk to people. Do I give ornithine or not. But I'm giving creatine. That's no problem.

So, I think this one gets a yes when we have agreement about therapy. We're still trying to make the therapy for PKU better. I think this one gets a yes on therapy.

With respect to the question of has it met the criteria for pilot, I don't think the

SIMD -- I don't want to represent the SIMD of having an opinion, but I will say as the SIMD I think this one gets a yes on treatment. We're working to improve it, but we have a treatment.

MEMBER WICKLUND: Okay, so forgive me if you already said this, Dieter.

So, retrospectively they were able to take dried blood spots and identify affected individuals, right? So the limiting factor is identifying a true positive prospectively. Okay.

So, once that happens it still won't further delineate the natural history. Because if it's just till they identify a true positive, right, that's just the fact that they've identified a true positive.

And if they notify us immediately with that how does that add to our level of evidence? I guess I'm trying to tease out a little bit versus if we're trying to get more information about if they develop symptoms.

I guess I'm just trying to get my head wrapped around. Is this coming back to our pilot

recommendations about having to have one true positive? Anyway, I'm just a little muddled right now on that.

MEMBER MATERN: I think the answer is yes, but Jeff is getting ready to say something.

MEMBER BOTKIN: Well, it is rather ironic that this comes up immediately. But of course, that's the discussion we were having.

I think it just forces additional thought about what's the value of that one baby. That's not going to tell you anything additional.

I guess in my thinking it really demonstrates whether in fact you have a program that's effective in identifying affected kids or not.

Now, everybody seems to think this is a good test, but yet a million babies is a lot of babies without a single true positive.

And so what's the explanation there. Is it something about Australia? Is it something about these other programs that have yet to identify an affected baby? I don't understand

what the alternative explanations might be of that failure.

So, I have to agree, the rest of the elements seem pretty solid here to move forward, but I have to be disturbed by the failure of public health programs to yield affected kids.

MEMBER KELM: Well, you know, we obviously focused all of this information on the prospective.

But I guess one piece that would be great to have is how robust is the, you know, when they retrospectively just even look at their method and their cutoffs and have a retrospective sampling.

What kind of numbers are we talking about. How well did that look. That would probably be helpful for us to understand.

But there is one thing that I guess I also feel -- wanted to have a little bit more flavor from you is, I mean obviously you're saying this can be done, but what sort of insights from, I mean if Fred was on your group.

Is this really simple to add in the public health labs? I guess that was my question is that we have that public health impact assessment also. So how easy is this to add to a current program? I don't know if somebody can weigh in on that.

MEMBER MATERN: Yes. Personally I would think it is easy. And again, the CDC at least has the materials so they have the test running in their own laboratory. So they could train as they train anyone else on acylcarnitines and amino acids. Just make it part of their program. Or not.

CHAIR BOCCHINI: Fred, if you're on did you want to make a comment related to that question?

MEMBER LOREY: No, not at this time. Thanks.

CHAIR BOCCHINI: Okay, thanks.

MR. OSTRANDER: So, I think it's fortuitous actually this came right after Jeff's talk because I think it gives us food for thought

about the difference between rare conditions and ultra-rare conditions.

I mean, this is unique in that it has a cheap and safe treatment which has not been one of our previous criteria, but certainly gives one pause about whether we need to be as strict about the criteria in that setting as opposed to ones where the treatments are dangerous and of unknown efficacy.

So, even in your talk, Jeff, there was a comment about the value of having one true positive.

I mean, is one much different from zero? Yes, and maybe not. If you can prove that with the existing technology retrospective identified cases test positive I don't know that from a scientific standpoint it's all that different in a rare condition like this.

And I'm going to chime in with Carol's treatment protocol thing too. If you've only got 110 cases worldwide you're not going to have standardized treatment protocols that are going

to be compared in a prospective way from no treatment or the standard treatment.

So, it may be for ultra rare conditions that the thought process could be modified just a smidgeon, taking into account and weighing not only the criteria for true positives through screening and the treatment protocol on the one hand, but also on the other weighing the safety and efficacy of the intervention.

That might tip the scales and it sounds to me like in this case it might even be reasonable to consider it to have tipped the scales.

CHAIR BOCCHINI: So, I think, Alex, can you tell us what one positive case means to evidence review?

MR. KEMPER: And this is where I resolve all the mysteries.

So, before I branch out there I just wanted to thank Dieter for doing really an excellent presentation about GAMT deficiency in terms of digging up what evidence is out there.

So thank you very much for setting me up.

You know, this issue of finding one case we've oftentimes talked about as being really important and it's certainly where we came from with SCID.

It's a little bit difficult to articulate, but what I would say is in addition to finding the one case, we're able to look at all the cases that weren't GAMT deficient. So, we're able to look at both the positive predictive value and the negative predictive value.

And one of the things that we're supposed to do as part of our evidence review is also look at what would happen in the real world as state programs adopt screening. So, it really goes beyond just finding that one case.

Certainly we in the Evidence Review Workgroup, we serve at the pleasure of the advisory committee so we're happy to do whatever you ask us to do, including looking at things like natural history, or what's known presently

about treatment. Perhaps digging a little more than Dieter already did in his very nice presentation.

But the one part that we would really struggle with is in looking at the implementation side in terms of the burden on the newborn screening programs.

So, that to me is where the issue is. But again, we're happy to do anything you ask us to do. Anything.

MEMBER MCDONOUGH: Can you say a little bit more about your concern about the burden for programs?

MR. KEMPER: Yes. And I'm sensitive that the word "burden" as typically used in day to day language is burdensome.

So, one of the charges that we have is to look at what it would take for state newborn screening programs to adopt screening for the condition we're actually going to be talking at length about, issues of cost.

But also there are these sort of

broader issues of feasibility and readiness that are in our charge.

And so with limited data from state health programs it's difficult for us to do that. And so that's where the call for pilot studies came from.

And so to me it's not just the one positive case, but it's sort of the broader issues regarding implementation.

Again, we could do the other parts in terms of natural history and treatments and that kind of thing, but we would hit a wall when it comes to that one component.

And the degree to which that's important is up to you all again.

CHAIR BOCCHINI: Plus, once the evidence review begins there's really a timeline within which it now needs to be completed which also poses a problem.

MR. KEMPER: Right. Nine months. It's not just a good idea. It's the law.

MS. GREENE: Carol Greene again, SIMD.

Interesting discussion. Of course if you really want data from states about implementation then you're going to have to be holding everybody to have multiple pilots in multiple states because this one, you've actually got a pilot in a state.

What I wanted just to add is that there is, in terms of actually real life there is a very good diagnostic test and it's very easy to send. It's a little hard to collect urine on baby girls, but we do it all the time. And it's easy to collect urine on baby boys, and easy to collect blood on both sexes.

And so we've got a diagnostic test available. And we can offer a treatment.

What I am a little curious about is if anybody's got enough math to do the sock drawer problem. If the true frequency is really 1 in 120 or 1 in 250,000 in Australia what are the statistical chances of finding none in a million.

And I think that's a reasonably high number, but I don't know because at least some of

the frequency is based on DNA on what you presume to be carriers, and that assumes that everybody who's a carrier is symptomatic.

So, I'm really interested in the numbers and I think that maybe somebody's got that math.

MS. TARINI: This is Beth Tarini at the American Academy of Pediatrics.

I agree with Alex and the reason I agree is because if I remember correctly, others please correct me if I'm wrong, in either MPS I, I thought it was MPS I, there were two affected individuals, is that right? In Missouri. Or there were two affected I thought found in the population that underwent transplant. Am I correct?

At any rate, historically it seems ongoing conditions have been reviewed and cases have been identified from population-based screening that we have leveraged or leaned very strongly on past evidence of efficacy in studies that involve identification from family history,

not on efficacy of treatment by what is found in the population.

Because I believe of the minor number of children that were found, the small number, one of them died after the treatment. And that was not taken into consideration as affecting the assessment of efficacy of the treatment. We leaned much more heavily on what was the historical studies that were done.

That is to say if we have done that in the past when we've actually had cases identified and we've sort of not taken into consideration what the real life outcome was then I don't think it is consistent to use that one person standard here.

MR. KEMPER: And just to amplify on what you said too.

One of the problems with hinging everything on the case, not for this condition, but for a lot of other conditions is that the one case identified through newborn screening may not develop clinical problems for years down the

line. That was the problem with ALD.

But this is really certainly a different thing in that the one case identified, if they were going to develop symptoms you would expect it to happen earlier rather than later.

CHAIR BOCCHINI: Since this is under discussion we're trying to limit the comments to the committee and the organizational representatives.

MEMBER BOTKIN: Question back for Alex. And I think Dieter had suggested that if indeed there's an evidence review at this point it's unlikely to provide more information than what's been provided by the current review.

And I guess I wanted to see what your response was to that. Would there be additional avenues of evidence to uncover that might help make that decision?

Because basically the question would be would the committee be ready today to make a decision about the RUSP if in fact there's not any additional information that's going to be

forthcoming.

MR. KEMPER: I'm going to I guess plead the Fifth in that we haven't looked at what evidence is or is not out there.

I do know from conversations I've had with Dieter in the past that it sounds like he did a thorough job of looking out there, but I can't comment on what else may be out there.

MS. TARINI: This is Beth Tarini, AAP.

To Jeff's point which Kellie had raised the evidence review process is not just evidence review, am I correct? There's a public health impact analysis.

So while the evidence may be, and again we wouldn't know until you did it, may be not much more than this, there certainly would be this other component to the matrix that would have to be done.

MR. WATSON: -- things that run counter to what I said before which is when could I accept one case.

So if -- I was looking at the

testimony, the public comments. There was a lot of patients from California and New York, or families from California and New York all of whom are in our virtual repository and whose spots could be pulled with consent to see whether or not they would have been detectable on a newborn screen.

And that actually does get you a fair bit along the way. It doesn't get you past having a numerator of zero which makes statistics really hard, but I think there are things that can sort of make you feel a lot more comfortable with retrospective data that could get me to thinking about just one case justifying it.

When you think about the things that you're doing in the public health prospective pilot you really want to make sure that you can find them, get them into treatment, and intervene in time, and get the expected outcome.

You learn about penetrance which isn't a problem here because you've got a million babies screened with no screened positives let

alone true positives.

So when you start thinking about what are the things that you get out of the pilot you can really, I think a number of them can be dealt with and reduce the demands on a really ultra rare condition like this if you think about what it is you gain and lose by these different parameters.

MEMBER MATERN: So that is -- something that I haven't pointed out in my presentation is that actually of course our colleagues in Utah and in Canada and in Australia, they have added retrospective, collected actual newborn screening samples from patients and ran them through their test.

And that data is out there, and it shows nicely how they have much higher GAA concentrations than normal population.

MR. WATSON: Part of the data that you want people to submit is something that is really informative retrospectively when you've got these ultra rare situations.

I mean, this happened in SCID. It got really narrowly defined. We must have been around 750,000 babies into SCID when the first one was found. I mean, those are my vague recollections of five, six years ago.

MEMBER MCDONOUGH: If Utah is the only state that's going to be testing for this it may take several years to get a true positive.

In the meantime, if the statistics are reasonably accurate there are going to be 20 to 45, 40 children born in our country every year who are going to be brain damaged if we aren't doing the testing.

We've got these rare conditions. We've modified our criteria before. When we had this matrix together we actually approved a B3 and the Interagency Coordinating Committee approved it.

So I think we constantly have to look at what our criteria are, what we're presenting with and go from there.

I'm concerned if we drag this out

there are going to be families and kids who will be definitely impacted because they won't be diagnosed.

CHAIR BOCCHINI: Well, I think there's no question that based on Dieter's presentation it's pretty clear that the Nomination and Prioritization Committee felt very strongly that many of the criteria that are necessary to move this nomination forward haven't been met and recognize the seriousness of delay in treatment.

On the other hand, it's also recognized that we have a test that hasn't been proven to work in a newborn screening situation.

And as a result the decision was to accept basically the data that was submitted and ask that as soon as we meet that last criteria that we move forward to move this to evidence review as quickly as possible.

At the same time asking the nominators and the advocacy groups to get together to look at things that might also add additional data.

And as Mike suggested, that the

possibility of using other things to help make a stronger case could be done relatively quickly.

And all that is so that when we do get the data that we feel is necessary to move it to evidence review that we would ensure a greater likelihood of success because we would have met all of our criteria to go forward.

So that's the crux of what we've been discussing. And so I think that that's still I think a reasonable approach.

MEMBER MCDONOUGH: This is McDonough. Is it possible that it could be during the process of the evidence review that a study could be conducted during that nine-month period of the blood spots, working with the patients, the identified cases that we would have that information during that nine-month period?

MEMBER MATERN: So you mean that they take the original blood spots and run them through their system?

Yes, but they've done that already. So that was part of the retrospective studies

that they interspersed the true positive original newborn screening samples that were stored away and run them through the system and could show that their GAA levels are higher.

CHAIR BOCCHINI: And remember, this would not be the first time that a nominated condition was close to being approved but missed some of the criteria for which we went back to the nominating group and asked that that additional data be obtained, and that they only needed to submit the additional data, and then we moved it forward.

That happened with Pompe, SCID as you heard, it was -- the decision was delayed until a positive case was found and so on. So I don't think it's unprecedented that we would use the approach to meet our criteria.

MEMBER WICKLUND: So, I completely agree with that, but I guess I'm having a hard time with the -- we require the one true positive.

I think that if there's additional

data, retrospective data, or additional data that can be given to us that provides another level of evidence.

I'm just trying to figure out in my head what additional level of evidence does that one true positive really give us compared to some of the evidence that we have from other sources.

So, I -- so this is where I'm struggling by saying, you know, we'll consider it again after one true positive is found. Like that to me seems really narrow and that's the part I'm struggling with right now versus looking at retrospective data in more detail and getting more information that way.

CHAIR BOCCHINI: Well, I guess part of it depends on how that influences the ability to prove that a newborn screening program in place can detect a positive on a newborn.

So, I don't know whether people from the lab might be able to answer that better than or with more detail than I.

MEMBER CUTHBERT: So, I get the

tension. Dieter's talking about the perspective of being a biochemical geneticist and as one myself I understand that.

But putting on the public health hat which I have to be concerned about as well coming from CDC and so on it is not only just about the test.

While this condition does present itself in being one of the more positive ones. When it was nominated I breathed very heavily. I thought this was fantastic.

I think I would be a little bit more -- I do support what the Nomination and Prioritization Committee has said.

It is very important that, again, that we do this for consistency again of the guidelines that we've put forward.

My concern is whereas this might be a good one to sort of let slip through what does it say for every other one that will come next.

If we for every single condition look at our guidelines and say, well, this one meets

all of these but not this. We can let that pass. It just causes the committee to just not seem consistent.

And I think it was brought up that someone was saying that the state programs don't always consider the recommendations of the committee as strongly.

They go back and they review and they say well, we hear what the ACHDNC has said. We're going to do something a little different. We would like to have a little bit more evidence.

There is a bit of a disparity between what we say we will do and what we do do and there's the rub.

And again, as a biochemical geneticist this is fantastic. I really want to see this on.

But being a public health person and just recognizing that the committee has laid out guidance for itself it doesn't bode very well if we are not able to stick to our guidance.

And there's a lot more. In other conditions there's a lot more that you would

identify when you prospectively screen.

This might seem very simple because my goodness, you find them, you treat them, they're better. That seems very, very apparent.

But for other complicated diseases my concern is that it would not be so simple. And that's why there's a great tension with making this decision.

But again, I still support what the Nomination and Prioritization Committee says.

MEMBER MATERN: However, if we don't move it to the evidence review it will -- I mean, we're not adding it to the RUSP today. It's just a question whether we're moving it to the evidence review.

And the evidence review will have to look at everything we discussed today. They will have to look at whether the test as it would be implemented in a public health laboratory.

One of the things that I'm a little bit concerned about is what is happening in the screening labs right now when it comes to X-

adrenoleukodystrophy. You can identify X-ALD by using lysophosphatidylcholine with a separate assay, or along with the lysosomal storage disorders, or as has been proposed you can also add long chain acylcarnitines to the acylcarnitine panel and pick it up that way.

But I don't know how easy it will be to add GAA creatine and the long chain acylcarnitines if you use MRMs because at some point there's only so much you can do at a time even with a tandem mass spec.

So that is a thing that I don't know. I don't know if anyone from Perk & Elmer is here who can tell us what their plans are, those kind of questions.

MEMBER CUTHBERT: So, I can't speak for Perk & Elmer. This is Carla Cuthbert speaking again.

I can't speak for Perk & Elmer particularly, but I do know that Perk & Elmer is coming out with a modified neobased kit soon.

They did a presentation earlier this

year at the APHL newborn screening symposium. And they did indicate that they are including several new markers specifically to address X-ALD, SIMD ADA and GAMT is specifically not on that.

Now, perhaps they were not given a heads up about this so they had been working on what they knew had been added to the Recommended Uniform Screening Panel and that they recognized -- they're also looking to improve the detection of succinylacetone which has been a problem historically.

So, when we did ask them about GAMT they said that they were not planning on doing this again. They're listening to this presentation. Perhaps they will consider differently.

How that additional marker performs with their current expansion which they are working at to try to get to a sufficient level of acceptability before they roll that out is anybody's guess.

I don't know that, you know, we can ask them whether or not they can put this in, but that would be a hard request.

MEMBER LOREY: This is Fred. I spoke to them last week and it seemed they're not working on it.

MEMBER BAILEY: So I'm going to recommend we take a chance and move it forward to evidence review. I feel like we have a very strong evidence for benefit for these babies. The low cost of screening and relative to a lot of the other conditions we've got a pretty strong case already.

I actually don't think we'll learn much more from the evidence review, frankly, but in the meantime I think what we'll get is the APHL review of state capabilities.

We can ask the advocates to come together quickly and pull together some consensus guidelines for treatment.

These pilot studies are already ongoing. We'll potentially have more data. And

we'll know in nine months whether we can make a decision or not.

I mean, I realize we're going to pay Alex the big bucks to do the review, but I frankly think in -- okay, the small bucks -- I frankly think in this case that we've got a strong candidate here and that we should take a chance and move forward with the evidence review, recognizing that it may fail at the end, but I'm willing to take a chance on it myself.

MEMBER BOTKIN: Second.

MEMBER SPONG: So, Don has actually answered a couple of -- part of the question that I had. And again, some of it is education for me.

If I understand correctly the pilot criteria that we went through before lunch was the first time we kind of outlined what that was. So that isn't even really final yet, although one of those comments was that you needed to have a positive in order to move forward. But we haven't totally hammered those all out.

So, say this was the last meeting. What would be the harm in going ahead and moving this forward, getting that information?

I appreciate that you're not going to get a whole lot as Don just kind of reinforced to me, at least not from the evidence-based review.

But maybe while that process is going on and getting everything else that you would get in that nine-month period you would get other information that would be helpful rather than waiting for that one case and delaying the whole thing by not moving forward.

So, education is what I'm after here to understand and make an informed decision.

CHAIR BOCCHINI: Yes, the only difficulty is if we get out nine months out and we don't have the key data that's necessary a decision will have to be made to reject the packet.

MEMBER SPONG: So then could you not reconsider it at a later date if something positive did come up?

CHAIR BOCCHINI: Right, but that's the same thing as doing it -- by following our own criteria for including it.

But I understand your point. Cathy?

MEMBER WICKLUND: I was just going to say that I wonder if that would set us back even farther. Like if you move it forward through evidence review, you go through that process. I'm just trying to think about time-wise, but I don't know if we'd save time or not. Or if you would just almost set back the whole process even further. I don't know.

MEMBER BOTKIN: Jeff Botkin. A couple of thoughts.

And I think as the pilot group sort of thought about this identify one baby, I think that really was intended for a couple of things that may be worth unpacking here.

One was just to try to give some ball park for the sort of size of study we're talking about. As we talked a little bit earlier, it wouldn't be appropriate to say you have to have a

prospective population-based study, but you're done after the first thousand babies.

Or on the other hand it wouldn't be appropriate to say well, we kind of like 20 or 30 affected babies followed over 5 years because that would really give us some excellent data to make a decision. You have to find something in the middle.

So, I wouldn't necessarily personally consider that to be a hard and fast condition and be a deal-breaker in this situation when there's other information.

But the question I would have is whether there's other information that might be fostered by a recommendation to look for more data before formally going forward.

One's sort of the natural history. And I do think the fact that you've got lots of negatives with a million babies without false positives is very helpful.

If you had had 40 false positive babies in the first 100,000 kids that would be

very informative. So the fact that we've got zero, that too is informative in a good way.

I don't have a good feel for population prevalence at this point. You know, at 110 babies in the literature there's got to be lots of babies out there that never made it to the literature. Is there a way to collect information from clinicians who are likely at the bottom of the referral pattern for these kids to get a better estimate on what the population frequency is for this condition.

And then it sounds like with Nicole's other publication there's additional information that might be reviewed in terms of the test performance as well as potentially some short-term fairly quick studies that could be done retrospectively with blood spots.

So I guess my question is would an ask for more data decision by the committee at this point prompt that additional data to come together in a way that a going to evidence review decision wouldn't.

MEMBER MCDONOUGH: This is McDonough. Second Don's motion.

MEMBER MATERN: Just one comment.

MEMBER BAILEY: I didn't really make a formal motion, but I will eventually. When it's time I'll be glad to.

MEMBER MCDONOUGH: I thought I -- okay. That's my fault. When he does I'll second it.

MEMBER MATERN: While you find the microphone if I might just point out that in the paper here there is also a mention of this kind of registry that they wanted to implement.

Now, this was published in 2014 and if you click on this it will not get you anywhere.

I sent an email to Dr. Stuckler and asked her whether this is close to being live and I didn't get a response yet.

MS. GREENE: Carol Greene, SIMD. Two things. The quicker one first.

To contribute I hope to the committee's discussion about whether or not to

accept the recommendation of the review committee.

And that is the recommendation had two parts to it. One was based on the judgment that treatment was not yet. And I really do feel strongly that there needs to be some further guidance about what's meant by that because I really do think, and I think all the clinicians would say treatment is a yes on that one.

So that the recommendation wouldn't be based on something to do with the pilot and having guidance for treatment, but I would take off that for the treatment.

I think there is enough to go forward with treatment. That's just speaking as SIMD trying to offer that for the discussion of the committee.

The second thing is that perhaps what I'm hearing people trying to do with the studies should have at least one positive, but yes, of course if your positive is in the first thousand you can't stop there.

That maybe if the language of that was perhaps rewritten to say something like that the sample size should be sufficient, should be twice the expected prevalence or something so that you'd have a good chance of picking up at least one, and you'd know something about the false positives.

And I think what are the chances in the first million you don't pick out one of the four in that million that would be affected? I don't know the number, but it's a reasonable number.

So maybe if instead of sticking with the first positive you say that the pilot study size should be roughly twice your expected prevalence. And then you will have data, and you combine it with the historic and you'll have that data.

And the reason that I put that forward in this context is because I really want to support those who have said if you don't stick with your own guidelines you're going to lose the

credibility and the sense that you are -- I forget which group came and said that we're going to depend on you to do our evidence review.

If we don't stick to our own guidelines you lose that. And that's why states don't accept it. They want to do their own evidence review because we don't follow our own rules.

MS. TARINI: Beth Tarini, AAP. Quick question.

The previous examples where there were no children identified from prospective screening, was that vote for evidence review? Dieter brought this up I thought, but wanted clarification.

Were those votes for evidence review, or were those votes for nomination to the RUSP?

The reason I ask is because if it's the latter then this is not necessarily a deviation from procedure that we're voting to add to the RUSP when those votes said come back after you find a case.

MEMBER MATERN: I think it's all about determining whether we send it forward to the evidence review.

MS. TARINI: My point is the conversation here is about concern about deviation from protocol. And I'm trying to determine if this actually matches the protocol we think we're deviating from.

In the past when there was no case and we said no, come back when there's a case, were we saying no to evidence review, or were we saying no to addition to the RUSP?

MS. SARKAR: So, this is Debi. For X-ALD it was no to move it for evidence review.

MS. BONHOMME: Natasha Bonhomme, Genetic Alliance.

My comments kind of go to some of the things that have already been said. More so not whether this should be in, or whether this should move forward or not, but really the issue of communicating this out.

I think the fact that we've had about,

what, a 30-minute or so conversation about is this consistent or is it not is something that should be noted.

And that whatever the communication is that goes back to the nominators and back out to the public around this clearly lays out why this does or does not go, and clearly the next steps.

Because this is an issue that has come up with other conditions that have gone through the process. And to have the parents and the public become really frustrated with this process because it seems very convoluted and not clear when you have people who say this seems like a slam dunk, or this seems like a go, but it isn't.

I think we just need to be really careful about the communication that goes along with this because I think there could be an opportunity for clarity, but also clearly an opportunity for more confusion out to the public in terms of what is this process in terms of adding conditions to the RUSP.

And then also our having conversations

of why are advocates going straight to states to get these things. Shouldn't they go through the RUSP.

But clearly that's -- even for a condition that some would say is very obvious it's not clear.

And so I just really want whatever the communication is that goes back out to the world around this that there's just real attention to clarity in terms of why you choose what you choose to do, and the right next steps for families to follow up, or for the nominators to follow up.

MEMBER LU: I guess this will come down -- this decision to move it forward will come down to whether or not there is a case of true positive.

And I'm getting increasingly concerned whether that is misplaced.

I guess the argument I hear, one is that it helps -- having a true positive helps establish prevalence and predictive value. And

if you think about it, how valid is it to have one case as a numerator to help you establish that population prevalence, or predictive value.

And then the second is to establish that in terms of treatment efficacy and what Carol's saying. Again, I'm not sure how much information treatment efficacy from one case will tell you versus all the other information that we already have.

So again I think, I know that's the guidelines that we have around pilot studies, but I'm wondering whether we're placing too much confidence in waiting for that one case of true positive.

CHAIR BOCCHINI: So, I guess the important thing is would everybody be comfortable to approve something to be placed on the RUSP without having any baby identified by newborn screening?

I mean, to me that's the crux of the argument. And I think that was part of the argument for SCID as to why it wasn't recommended

for the RUSP until that positive occurred.

I think that's the one question we need to feel comfortable with if you're going forward and then don't have that.

MEMBER MCDONOUGH: This is McDonough. Yes, I would be. And if we have to eventually get to the point with such conditions that are so rare to say, okay, we think the evidence looks good. We're going to try this. We're going to give it three years. And if we haven't picked up any cases then we'll stop doing it.

I would rather that this committee work on identifying cases to help these kids and families out, and err maybe on the side of, well, maybe we shouldn't have done this. As long as it's not causing harm.

Again, if California was doing the pilot study, was doing their state we would probably have evidence pretty quickly where there are a large number of births. But if it's just going to be Utah it's going to take a long time.

So, I would answer yes to that.

Looking at the preponderance of information that we have with these rare conditions that we need to take that leap forward, that we have faith in our public health labs that they can do the testing appropriately.

And if we did it wrong and we didn't pick up cases that we can back off from that. But that's better than letting these kids not be diagnosed and being damaged because that's the thing we don't -- the longer we wait, we don't have these families coming back.

And you're taking a look at the kids and saying okay, we didn't do this and this is what happened. We don't see that.

MEMBER BAILEY: So, just to follow up on that a little bit.

And this shows how complicated these decisions are for us really, and especially again for rare conditions.

If you think about some of the other conditions we've reviewed. So if this disorder had a very expensive laboratory test, if it made

a lot of errors in the test, if the treatment had to be a stem cell transplant or some other particularly dangerous treatment, or if it identified children with many different severity types that we didn't know whether to treat a child or not treat a child, having to make all those complicated decisions, then I would say yes, we need more -- I would feel less confident about screening for a condition, adding a condition that we never had.

But we're not talking about that here. So I would feel, and I'm not voting to put it on the RUSP yet, because I think we still need to go through this process and get a little bit more data.

But I still feel what I said earlier that I'm willing to take that chance and move forward for the evidence review.

CHAIR BOCCHINI: Well, I think if we've completed the discussion then we are open to take a -- if someone wants to make a motion.

MEMBER BAILEY: Well, does the

recommendation of the nominating committee not constitute a motion?

CHAIR BOCCHINI: It does not. It opens the opportunity for discussion. The nomination needs to come from the committee. I'm sorry, the motion needs to come from the committee.

MEMBER BOTKIN: Yes, Jeff Botkin. I just recognized how very difficult this is for everybody. I'm going to move to support the recommendation of the Nomination Committee.

MEMBER KELM: Second.

CHAIR BOCCHINI: Moved and seconded that the recommendations of the Nomination and Prioritization Committee be accepted.

We'll now do a -- no, no, there is time for discussion before vote.

MEMBER WICKLUND: Is this implying also that there has to be an identified case? I mean, what I'm saying is that in order to move it forward is this recommending that there has to be an identified case before they can bring it back

to us?

CHAIR BOCCHINI: It does. But in addition, I think based on the discussion we certainly can add that additional information can be brought forward. If there is a repository that has blood spots that can be looked at retrospectively and other things that were mentioned, that that can come forward as well. Dieter?

MEMBER MATERN: Well, I think we know already now that there is a repository, so what are they supposed to tell us? As you've just heard already at the meeting there is a repository.

CHAIR BOCCHINI: So, the recommendation does certainly continue to include the finding of a case.

MEMBER BAILEY: Call the question.

CHAIR BOCCHINI: So, the motion is to accept the recommendation of the Nomination and Prioritization Committee that we do not initiate external evidence review, but that we recommend

that the proponents work with other experts to formalize treatment guidelines. And that certainly doesn't mean that treatment guidelines -- I mean, it would certainly just improve the consensus, but it doesn't mean that treatment is not appropriate. But we can discuss that.

And 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. And that the plan would be to move, if that's accepted, then move that forward to evidence review upon achievement of that milestone.

MEMBER MATERN: One more. So, if you were against it does it mean automatically if there was a majority to vote against this motion that it would motion towards the evidence review?

CHAIR BOCCHINI: No, it would mean there would need to be a second motion for that. So, Don Bailey.

MEMBER BAILEY: No.

CHAIR BOCCHINI: So, I'm going to vote

yes. Dr. Botkin?

MEMBER BOTKIN: Yes.

CHAIR BOCCHINI: Carla Cuthbert.

MEMBER CUTHBERT: Yes.

CHAIR BOCCHINI: Catherine Spong.

MEMBER SPONG: No.

CHAIR BOCCHINI: Kellie Kelm.

MEMBER KELM: Yes.

CHAIR BOCCHINI: Fred Lorey.

MEMBER LOREY: Yes.

CHAIR BOCCHINI: Dieter Matern.

MEMBER MATERN: No.

CHAIR BOCCHINI: Steve McDonough.

MEMBER MCDONOUGH: No.

CHAIR BOCCHINI: Kamila Mistry.

MEMBER MISTRY: Yes.

CHAIR BOCCHINI: Michael Lu.

MEMBER LU: No.

CHAIR BOCCHINI: Alexis Thompson.

MEMBER THOMPSON: Yes.

CHAIR BOCCHINI: And Cathy Wicklund.

MEMBER WICKLUND: I'm going to say no.

CHAIR BOCCHINI: Okay. Well, thank you all very much. I know that was a very important but very difficult and complicated decision to make.

I have seven yes and five no so the outcome is that -- six, I'm sorry. All right, just to be sure, seven yes. Okay.

So, I think the important thing is that we all feel this is a strong nomination and that we would like to have the data necessary to move forward as soon as possible. So thank you all very much for that.

And we want to thank the families for being here to make the case of how important this is for us.

So with that that will conclude this session. We do have the workgroups meeting. And Debi, do you want to go through where the location is of each of the meetings for the workgroup?

MS. SARKAR: Just before, do you want to just clarify what the final vote is?

CHAIR BOCCHINI: Okay, so the final vote was in favor of the recommendation of the Nomination and Prioritization Committee to -- not to initiate external evidence review at this time.

MS. SARKAR: And we will follow up with the nominators with next steps.

CHAIR BOCCHINI: Right.

MS. SARKAR: So, we will have our three standing workgroups meeting this afternoon until 5 p.m.

The Education and Training Workgroup will be meeting here in this building. The Follow-up and Training Workgroup and the Laboratory Standards and Procedures Workgroup, if we could all meet upstairs by the café within the next 10 minutes we need to walk across the street to 5600 Fishers Lane.

You'll need your driver's license, a picture ID. You'll have to sign in, go through security. We will have HRSA staff there to escort you to the meeting rooms.

So, Laboratory Workgroup and Follow-up and Training Workgroup members, please meet us upstairs in 10 minutes. Thank you.

(Whereupon, the above-entitled matter went off the record at 3:09 p.m.)

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C E R T I F I C A T E

This is to certify that the foregoing transcript

In the matter of: The Advisory Committee on Heritable Disorders in Newborns and Children

Before: HHS Health Resources & Service Administration

Date: 05-09-16

Place: Rockville, Maryland

was duly recorded and accurately transcribed under my direction; further, that said transcript is a true and accurate record of the proceedings.

Neal R Gross

Court Reporter