

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

+ + + + +

MEETING

+ + + + +

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

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## 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.

1 CHAIR BOCCHINI: Coleen Boyle.

2 MEMBER BOYLE: Here.

3 CHAIR BOCCHINI: Catherine Spong.

4 MEMBER SPONG: Here.

5 CHAIR BOCCHINI: Kellie Kelm.

6 MEMBER KELM: Here.

7 CHAIR BOCCHINI: Fred Lorey should be  
8 on the phone.

9 MEMBER LOREY: Yes, here.

10 CHAIR BOCCHINI: Thank you. Dieter  
11 Matern.

12 MEMBER MATERN: Here.

13 CHAIR BOCCHINI: Steve McDonough.

14 MEMBER MCDONOUGH: Here.

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

18 MEMBER LU: Here.

19 CHAIR BOCCHINI: Alexis Thompson by  
20 phone.

21 MEMBER THOMPSON: Here.

22 CHAIR BOCCHINI: Thank you, Alexis.

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

3 MS. SARKAR: Here.

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

8 MR. OSTRANDER: Here.

9 CHAIR BOCCHINI: American Academy of  
10 Pediatrics, Beth Tarini.

11 MS. TARINI: Here.

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

14 MR. WATSON: Here.

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

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

20 MS. TULLIS: Here.

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

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

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

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

9                   MR. KUS: Thanks.

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

12                  MR. KANIS: Here.

13                  CHAIR BOCCHINI: Genetic Alliance,  
14 Natasha Bonhomme.

15                  MS. BONHOMME: Here.

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

18                  National Society of Genetic  
19 Counselors, Cate Walsh Vockley.

20                  MS. VOCKLEY: Here.

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



1 MS. GREENE: Here.

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

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

10 So now the RUSP has been expanded to  
11 34 conditions based on her acceptance of our  
12 recommendations.

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

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

22 MS. SARKAR: Thanks, Dr. Bocchini.

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

5 The purpose of the program is to  
6 support states in increasing the number of  
7 newborns that are screened, identified and  
8 referred for treatment for three conditions -  
9 Pompe disease, MPS I and X-linked ALD.

10 The funding amount is for \$2 million  
11 per year and it's a two-year project period. And  
12 due date for applications is May 27, 2016.

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

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

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

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

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

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

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

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

1 a large number of nominees from which to pick.

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

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

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

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

15 MEMBER BAILEY: Approve.

16 CHAIR BOCCHINI: I approve. Jeff  
17 Botkin?

18 MEMBER BOTKIN: Approve.

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

21 MEMBER KELM: Approve.

22 CHAIR BOCCHINI: Fred Lorey.

1 MEMBER LOREY: Approve.

2 CHAIR BOCCHINI: Dieter Matern.

3 MEMBER MATERN: Approve.

4 CHAIR BOCCHINI: Steve McDonough.

5 MEMBER MCDONOUGH: Approve.

6 CHAIR BOCCHINI: And then Michael Lu.

7 MEMBER LU: Approve.

8 CHAIR BOCCHINI: And Alexis Thompson.

9 MEMBER THOMPSON: Approve.

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

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

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

22 Now, I want to make everybody aware

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

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

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

14 They will meet this afternoon as  
15 scheduled.

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

1 project in collaboration with Newborn Screening  
2 Clearinghouse Babies First test.

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

8 The Laboratory Standards and  
9 Procedures Workgroup is looking at defining and  
10 implementing a mechanism for periodic review, an  
11 assessment of lab procedures utilized for  
12 effective and efficient testing of the conditions  
13 included in the uniform panel, and defining and  
14 implementing a mechanism for periodic review and  
15 assessment of infrastructure and services needed  
16 for effective and efficient screening of the  
17 conditions included on the newborn screening  
18 uniform panel.

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

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

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

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

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

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



1 my standard reminders for the committee members.

2 First, the committee is advisory to  
3 the Secretary of Health and Human Services.

4 Anyone associated with the committee or due to  
5 your membership on the committee if you receive  
6 inquiries about the committee or the committee's  
7 work please let Dr. Bocchini or I know prior to  
8 committing to an interview.

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

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

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

1 Screening Saves Lives Reauthorization Act of  
2 2014.

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

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

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

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

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

1 committee members or other presenters.

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

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

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

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

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

22 After 25 years in clinical practice

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

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

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

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

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

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

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

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

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

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

22           What I'm going to talk to you today

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

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

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

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

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

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

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

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

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

22 In 1988 the Orphan Drug Amendments

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

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

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

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

22 So the overall umbrella category for



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

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

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

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

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

1 was then, drug looking.

2 This is medical foods for inborn  
3 errors of metabolism today.

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

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

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

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

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

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

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

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

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

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

1 mixtures.

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

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

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

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

22           Again, what fits in the category

1 depends on what the intended use is.

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

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

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

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

16 Medical foods are required for other  
17 IEM diagnosed clinically.

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

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

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

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

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

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

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

1 microcephaly and poor outcome in the infant.

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

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

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

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

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

1 conditions to not be catabolic.

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

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

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

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

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

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



1 of course an important precursor to serotonin.

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

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

13 And we supply the product and other  
14 essential nutrients.

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

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

22 And along with the very small amount

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

1 foods for special dietary use.

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

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

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

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

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

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

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

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

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

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

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

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

1 the offending nutrient.

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

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

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

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

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



1 medical food.

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

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

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

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

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

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

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

13          What do medical foods cost? Well,  
14          they cost a lot compared to regular foods, but a  
15          whole lot less than Kuvan which is the first drug  
16          that was approved by FDA for phenylketonuria,  
17          \$200,000 a year for an adult with pH deficiency.

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

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

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

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

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

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

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

1 their out-of-pocket expenses.

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

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

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

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

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

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

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

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

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

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

22 So, who pays? Depends on who you are,

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

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

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

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

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

1 company would cover it.

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

6 So, since the Affordable Care Act?

7 Well I don't know. I have not seen a formal  
8 national survey of state practices. I haven't  
9 seen one that has been undertaken in order to  
10 understand what's going on in every state.

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

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

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

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

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

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

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

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



1 untreated.

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

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

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

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

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

1       \$2,000 a year. And if you don't have a job  
2       \$2,000 a year is a lot of money.

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

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

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

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

22              And the coding is for enteral formulas

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

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

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

12 Private insurance companies may or may  
13 not adopt these codes.

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

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

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

1 in coverage and reimbursement.

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

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

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

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

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

22 Her interim response was a response

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

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

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

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

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

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

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

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

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

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

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

1 things that have to be considered as one moves  
2 forward.

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

9 American Health Security Act of 2011,  
10 '13 and '15 introduced by McDermott would have  
11 provided coverage for medical foods and  
12 reiterated the 1988 medical foods definition.

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

16 There was a success story I would like  
17 to say, and I think on behalf of the National PKU  
18 Alliance, a Senate resolution designated December  
19 3, 2015, as National PKU Awareness Day.

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

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

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

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

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

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



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

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

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

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

16           SIMD updated their policy statement in  
17 2006.

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

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

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

4 And GMDI nutrition management  
5 guidelines had a similar quote.

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

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

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

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

1 that it impacts access.

2 So the players. Who are the players?

3 There are a bunch of them.

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

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

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

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

22 USDA funds states to administer WIC

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

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

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

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

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

22 Patients and families continue to be

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

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

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

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

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

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

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

13 And bills introduced, but Congress has  
14 taken no action.

15 So, the future. Well hey, if we can't  
16 get medical foods covered, let's make new  
17 treatments. And patients want this. This is  
18 from the National PKU Alliance survey of patients  
19 - 91.4 percent of patients felt that it was very  
20 important to get new treatments.

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

1 500 babies are born each year with an IEM  
2 requiring medical foods as the primary management  
3 modality.

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

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

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

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

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

1 last three decades.

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

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

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

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

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

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



1 not treating to society.

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

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

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

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

1 end up in hospital care.

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

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

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

16 MEMBER BAILEY: It does seem very  
17 important.

18 MS. CAMP: Yes, absolutely.

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

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

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

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

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

9 As far as why legislation has not been  
10 successful I think it's a host of different  
11 issues. But I know that insurance companies are  
12 reluctant to allow foods to be covered because  
13 that opens the door for foods for any kind of  
14 condition one can think of.

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

20 CHAIR BOCCHINI: Steve?

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

1 presentation and very helpful information.

2 I have one question and a couple of  
3 comments.

4 Does WIC cover medical foods and low-  
5 protein foods for children with conditions, those  
6 19 conditions identified in the RUSP?

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

11           CHAIR BOCCHINI: Thank you, Steve.  
12 Coleen?

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

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

21           MS. CAMP: No.

22           MEMBER BOYLE: The survey and the

1 public workshop.

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

5 MEMBER BOYLE: Right.

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

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

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

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

19 MEMBER BOYLE: Well, you can make  
20 suggestions.

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



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

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

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

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

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

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

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

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

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

7               MEMBER BOYLE: Yes.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

1 don't have to put in the G tube.

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

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

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

22 So, there are old studies for the cost

1 analysis, but I think fundamentally it's wrong.

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

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

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

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

22 But at its core it seems to me that

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

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

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

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

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

22 MS. CAMP: So, I just want to comment

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

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

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

16 So in other words, another policy  
17 angle or potential.

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

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



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

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

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

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

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

1       seems to know.

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

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

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

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

22                   If it's not an essential healthcare

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

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

8 However, on the finance side, forget  
9 the cost-benefit analysis. We're talking about  
10 500 births per year out of a U.S. birth  
11 population of 4 million. This isn't going to  
12 move the needle on the total healthcare cost  
13 expenditures of this country an iota as long as  
14 it is just for medical foods.

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

22 Hence this supplement enhances joint

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

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

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

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

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

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

22 And the argument will be hard to

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

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

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

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

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

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

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

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

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

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

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

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

5 Doesn't it mean preventative care  
6 include treatment?

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

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

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

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

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

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

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

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

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

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

15           MS. CAMP: Yes.

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

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



1 Futures.

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

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

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

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

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

1 finalized.

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

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

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

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

1 that was in addition.

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

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

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

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

1 lack of access to medical foods.

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

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

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

13 CHAIR BOCCHINI: Thank you.  
14 Additional comments?

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

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

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

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

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

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

11 CHAIR BOCCHINI: Thank you. Don.

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

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

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

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

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

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

14 CHAIR BOCCHINI: Thank you, Don.

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

21 CHAIR BOCCHINI: Kathryn, thank you  
22 very much.

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

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

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

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

22 MEMBER MCDONOUGH: This is McDonough.

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

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

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

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

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

22 There was a mechanism in place and I



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

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

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

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

17 Dr. Lu?

18 MEMBER LU: This is Michael Lu from  
19 HRSA.

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

1 other administratively.

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

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

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

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

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

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

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

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

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

13 MEMBER BOTKIN: Thanks, Dr. Bocchini.

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

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

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

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

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

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

22           And I think part of the challenge that

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

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

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

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

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

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

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

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

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

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

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

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

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

18           For the purpose of this report and  
19 consistent with previous definitions newborn  
20 screening pilot studies are defined as systematic  
21 investigations or public health activities that  
22 are designed to evaluate the efficacy and safety

1 of incorporating a new test or condition on a  
2 population-based level into state newborn  
3 screening programs.

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

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

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

22 So let me stop here for a second and



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

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

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

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

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

14 Data should be available on the  
15 analytical validation of one or more screening  
16 modalities proposed for use in population-based  
17 screening in newborns.

18 Data should include information on  
19 precision, accuracy, the reportable range,  
20 detection limits, interference, reference  
21 intervals and cost.

22 Pilot studies for analytical

1 validation should include use of dried blood  
2 spots from a population of newborns including  
3 known positive and negative specimens in addition  
4 to laboratory-prepared target specimens.

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

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

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

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

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

1 materials or some such thing? No?

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

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

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

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

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

1 sufficient numbers.

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

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

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

14 MEMBER BOTKIN: Okay.

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

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

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

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

6 MEMBER CUTHBERT: Carla Cuthbert, CDC.  
7 So, this particular recommendation  
8 really is targeted at the analytical validation.  
9 You'll find that the clinical validation comes  
10 next.

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

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

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

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

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

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

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

22 MEMBER KELM: I can just speak to the

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

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

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

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

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

22 So, pilot studies for analytical

1 validation should include use of biologic or  
2 other physiologic assessments from a population  
3 of newborns or other target population including  
4 known positive and negative specimens in addition  
5 to laboratory prepared target specimens. Sound  
6 good? Okay.

7 All right, recommendation two. Data  
8 should be available on the net benefits of  
9 clinical interventions following early detection  
10 compared to clinical diagnosis. Early detection  
11 can be achieved through population screening  
12 pilot studies, through testing secondary to a  
13 family history of the condition, or through  
14 targeted screening of high-risk groups.

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

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



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

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

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

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

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

1 not.

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

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

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

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

19 3A, the study should be sufficiently  
20 large to identify at least one true positive  
21 newborn for the condition under consideration.

22 3B, the population included in the

1 pilot study and the screening protocol used  
2 should be similar to the U.S. population and to  
3 state newborn screening programs with respect to  
4 known prevalence of the condition, the timing and  
5 approach to screening, and the screening modality  
6 used.

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

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

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

19 3B here is an indication of some of  
20 the challenges we've had in the past with studies  
21 done in other countries. And the question is is  
22 the nature of the condition different with

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

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

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

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

15 MEMBER BOTKIN: They are "and." So  
16 maybe there needs to be an "and" between 3A and  
17 3B.

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

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

1 screening modality used?"

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

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

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

13 MEMBER BOTKIN: It would not. I mean,  
14 I think the point is the data ought to be  
15 collected in a way that is interpretable in the  
16 U.S. context where the data would be applied for  
17 this purpose.

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

1 different.

2 MEMBER BOTKIN: Okay, good.

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

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

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

16 MEMBER BOTKIN: Yes, that would.

17 MS. PURYEAR: It would include.

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

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

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

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

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

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

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

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

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

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



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

3 But I think -- Dieter.

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

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

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

19 MS. GREEN: You're saying comparable  
20 modality.

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

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

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

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

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

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

1 a patient who based on the diagnostic process has  
2 the disease. Whether their phenotype is  
3 expressed at the time is a different story, but  
4 based on everything we know we would expect the  
5 patient to become symptomatic.

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

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

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

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

19 MEMBER BOTKIN: Don?

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

1 other odd scenarios.

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

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

12 MEMBER BOTKIN: Well, that would  
13 certainly be fine.

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

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

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

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

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

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

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

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

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

1 newborn?

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

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

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

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

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

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

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

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

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

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

22                   I have some proposed language. I'm

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

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

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

18 Other comments about this three? All  
19 right.

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



1           Recommendation four, sustained support  
2           should be provided by DHHS for the NIH  
3           initiatives that support pilot studies in newborn  
4           screening including the NBSTRN, NSIGHT, the pilot  
5           studies grants, natural history grants,  
6           innovative therapies grants, and grants supported  
7           under the parent announcement.

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

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

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

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

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

5 MEMBER BOTKIN: Okay.

6 Recommendations?

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

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

14 MS. URV: Yes.

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

17 Recommendation five. Sustain or  
18 continued support should be provided by DHHS to  
19 the CDC for its activities relevant to the  
20 support of pilot studies that address technical  
21 training and quality materials for state  
22 laboratories, assistance to state programs in

1 obtaining laboratory equipment, the creation and  
2 distribution of validation test packages, and the  
3 fostering of laboratories of excellence.

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

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

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

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

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

1 cetera. Okay. Nancy?

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

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

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

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

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

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

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

8 MEMBER BOTKIN: Okay.

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

11 MEMBER BOTKIN: Yes.

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

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

22 And so this is sort of recognizing

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

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

6 MEMBER BOTKIN: Not primarily, no.

7 MS. TANKSLEY: Okay.

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

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

14 MS. TANKSLEY: Okay.

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

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

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

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

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

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

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

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

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

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

1 provided outside of the programs.

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

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

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

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

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



1 developmental process.

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

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

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

13 DHHS should support the development of  
14 a network of centers of excellence for newborn  
15 screening pilot studies.

16 This network should be comprised of  
17 state-based public health programs, laboratories  
18 and research centers that would provide a stable,  
19 experienced, compliant, efficient and quality  
20 infrastructure for the conduct of population-  
21 based pilot studies for newborn screening.

22 So this is a pie in the sky, but to

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

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

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

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

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

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

9           MEMBER BOTKIN: Sounds great.

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

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

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

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

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

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

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

20 (Whereupon, the above-entitled matter  
21 went off the record at 11:55 a.m. and resumed at  
22 1:06 p.m.)

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

2 (1:06 p.m.)

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

6 MEMBER BAILEY: Here.

7 CHAIR BOCCHINI: I'm here. Jeff  
8 Botkin?

9 MEMBER BOTKIN: Here.

10 CHAIR BOCCHINI: Carla Cuthbert for  
11 CDC?

12 MEMBER CUTHBERT: Here.

13 CHAIR BOCCHINI: Catherine Spong.

14 MEMBER SPONG: Here.

15 CHAIR BOCCHINI: Kellie Kelm.

16 MEMBER KELM: Here.

17 CHAIR BOCCHINI: Fred Lorey by phone.  
18 Dieter Matern.

19 MEMBER MATERN: Here.

20 CHAIR BOCCHINI: Steve McDonough.

21 MEMBER MCDONOUGH: Here.

22 CHAIR BOCCHINI: Kamila Mistry.

1 MEMBER MISTRY: Here.

2 CHAIR BOCCHINI: Michael Lu.

3 MEMBER LU: Here.

4 CHAIR BOCCHINI: Alexis Thompson by  
5 phone.

6 MEMBER THOMPSON: I'm here.

7 CHAIR BOCCHINI: Cathy Wicklund.

8 MEMBER WICKLUND: Here.

9 CHAIR BOCCHINI: And Debi Sarkar.

10 MS. SARKAR: Here.

11 CHAIR BOCCHINI: Now for  
12 organizational representatives. Bob Ostrander.

13 MR. OSTRANDER: Here.

14 CHAIR BOCCHINI: Beth Tarini.

15 MS. TARINI: Here.

16 CHAIR BOCCHINI: Michael Watson.

17 MR. WATSON: Here.

18 CHAIR BOCCHINI: Joseph Biggio. Kate  
19 Tullis.

20 MS. TULLIS: Here.

21 CHAIR BOCCHINI: Susan Tanksley by  
22 phone.

1 MS. TANKSLEY: I'm here.

2 CHAIR BOCCHINI: Chris Kus by phone.

3 MR. KUS: Here.

4 CHAIR BOCCHINI: Adam Kanis by phone.

5 MR. KANIS: Here.

6 CHAIR BOCCHINI: Natasha Bonhomme.

7 MS. BONHOMME: Here.

8 CHAIR BOCCHINI: Ed McCabe by phone.

9 MR. MCCABE: I'm here.

10 CHAIR BOCCHINI: Cate Walsh Vockley.

11 MS. VOCKLEY: Here.

12 CHAIR BOCCHINI: And Carol Greene.

13 MS. GREENE: Here.

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

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

22 So first we have four persons from the

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

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

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

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

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

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



1 mittens.

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

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

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

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

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

1 occupational therapy, music therapy, you name it.

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

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

7 So, Ryan also has an older brother, a  
8 stepsister and a fraternal twin brother as well.

9 And none of my other children have GAMT  
10 deficiency. But I want you to know that their  
11 lives have been impacted by the diagnosis as  
12 well.

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

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

22 The truth is that before Ryan's

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

22           They may not realize how lucky they

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

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

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

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

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

22 MS. TUMINELLO: Hi, my name is Kim



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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

1 state to receive lifelong care.

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

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

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

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

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

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

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

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

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

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

22           Also, not every GAMT child develops

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

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

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

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

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

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

22 Sheer luck led her to a GAMT diagnosis

1 and treatment, not unique symptoms or dysmorphic  
2 features.

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

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

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

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

22 Treatment has been simple for him and



1 very successful.

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

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

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

15 She can ride a bike, but not  
16 independently. She crosses lanes without  
17 looking. She's reckless and tries to take off on  
18 her bike alone and gets lost.

19 She has improved with treatment and  
20 I'm grateful that she's come as far as she has.  
21 But she will continue to suffer because of her  
22 late diagnosis for the rest of her life.

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

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

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

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

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

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

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

22           I'm also the advocacy liaison for the

1 Organic Acidemia Association.

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

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

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

22 They are costly, but they are

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

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

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

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

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

1 their own barriers.

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

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

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

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

22 Please stop allowing this elephant in

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

4 CHAIR BOCCHINI: Thank you.

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

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

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

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

22 I had additional questions after the

1 diagnosis of PKU. Will they be able to go to  
2 school? Will they need an IEP? Will they need a  
3 504 plan? Can they go to college? What are they  
4 going to eat on their prom date? Can they go on  
5 a business lunch?

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

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

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

17 Number two was new treatments. And  
18 you saw from Cathy's presentation and my  
19 presentation a few months ago that 91 percent of  
20 our community said that new treatments are  
21 important.

22 But the number one concern that

1 trumped everything else was access and coverage  
2 to medical foods to treat PKU.

3 There is a failure here, and I think  
4 you all recognize that. We have all failed to  
5 accomplish support and access to treatment after  
6 the diagnosis is made on that newborn screening  
7 test.

8 As Jana said we believe you have a  
9 moral obligation. You have a moral obligation to  
10 my children, Connor and Kellen. You have a moral  
11 obligation to Jana's children Steven and  
12 Caroline, and to the other 475 children born  
13 every year with a positive diagnosis that  
14 requires medical foods for treatment.

15 I think we've already had some great  
16 discussion and some wonderful suggestions  
17 including asking the Secretary to follow up now  
18 that that Department of Labor survey has been out  
19 and the IOM report has been out for more than  
20 five years.

21 This issue of medical foods has been  
22 punted too many times. In the last seven years



1 we have been as a patient organization talking  
2 with the NIH. We met with CMS. They told us to  
3 meet with FDA. We talked to FDA. They said  
4 well, our definition of "enteral" is different  
5 than CMS.

6 We testified before HHS at the  
7 listening sessions on the essential health  
8 benefits. We were told to go to the Office of  
9 Intergovernmental and External Affairs, who told  
10 us to go to the Office of the General Surgeon, who  
11 told us to go to the National Prevention Council,  
12 who told us to go back to HHS.

13 Then when we went to OPM and talked  
14 about the federal employee health benefit plans  
15 we were told they were going to lift the age  
16 limits on medical foods. That didn't happen and  
17 they referred us back to HHS and CMS.

18 It's been going around and around for  
19 far too long.

20 So again I ask you that same question  
21 I asked you two months ago. What hopes and  
22 dreams did you have for your children when they

1 were born?

2 One of my biggest dreams shouldn't  
3 have to be the dream of getting their medical  
4 foods covered.

5 I want to set my sights on something  
6 bigger and better for them, and in order to do  
7 this I ask you all to be bold. Thank you.

8 CHAIR BOCCHINI: Christine and Jana,  
9 thank you both very much.

10 And as you know from this morning's  
11 presentation and discussion we have asked the  
12 Long-Term Follow-up Committee to review the  
13 current information from those reports and to  
14 kind of come up with some plan to go forward to  
15 try and improve the situation. So thank you.

16 Next, Carol Greene is going to make us  
17 aware of the Society of Inherited Metabolic  
18 Disorders updated statement on access to care  
19 with focus on medical foods.

20 MS. GREENE: Thank you. So I am Carol  
21 Greene representing today the Society for  
22 Inherited Metabolic Disorders which is a

1 professional organization of those who work in  
2 the area of inborn errors, supports access to  
3 quality are including medical foods.

4 And we hope that our updated statement  
5 will be a useful tool to those who are working in  
6 support of this.

7 And in the interest of keeping to time  
8 even though it's only one page I'll just read  
9 highlights of our April 2016 statement on medical  
10 foods, and ask that the whole of the statement be  
11 included in the record.

12 So, the SIMD strongly urges that all  
13 private and public systems for healthcare payment  
14 be mandated to cover specialized diets including  
15 medical foods for treatment of inborn errors of  
16 metabolism found by newborn screening or  
17 clinically diagnosed.

18 Our statement describes what inborn  
19 errors of metabolism are and mentions the Orphan  
20 Drug Act definition of medical foods.

21 And we point out that although medical  
22 foods are an essential medically necessary

1 treatment for many inherited metabolic disorders  
2 many healthcare payers deny coverage for medical  
3 foods and mandates are not consistent across  
4 states.

5 The complex pattern of healthcare  
6 coverage in the United States means that many  
7 individuals with inborn errors of metabolism are  
8 at significant risk of disability or death  
9 because of lack of access to the medical foods  
10 that are a critical part of their medical care.

11 The lack of uniform and consistent  
12 coverage of medical foods throughout the United  
13 States threatens individuals and families.

14 Because medical foods are essential  
15 treatments for many of the conditions detected by  
16 expanded newborn screening failure to provide  
17 lifelong access to these treatment modalities  
18 also threatens the success of public health  
19 policy.

20 And that's for PKU, for isovaleric,  
21 that's the creatinine for GAMT, and we really  
22 hope that you will be able to use this statement

1 which we offer as a tool in the fight to get this  
2 covered.

3 CHAIR BOCCHINI: Thank you, Carol.

4 Next, Spencer Perlman to talk about newborn  
5 screening for spinal muscular atrophy.

6 MR. PERLMAN: Good afternoon and thank  
7 you for the opportunity to testify today.

8 My name is Spencer Perlman. I am a  
9 member of the Cure SMA board of directors though  
10 I'm testifying today on behalf of the entire SMA  
11 community.

12 Being sensitive to time I will just  
13 briefly explain our purpose and our request, and  
14 ask that the remainder of my comments be  
15 submitted for the record.

16 As you all know SMA or spinal muscular  
17 atrophy is an autosomal recessive genetic  
18 disorder that occurs in about 1 in every 10,000  
19 live births and is the leading genetic killer of  
20 children under the age of 2.

21 Today I urge the advisory committee to  
22 give serious consideration to the forthcoming

1 nomination and evaluation of SMA for universal  
2 newborn screening.

3 SMA families, investigators and  
4 clinicians all believe that newborn screening is  
5 imperative for ensuring access to effective  
6 treatment of this disorder.

7 In the 10 years since I last stood  
8 before this committee there have been significant  
9 advancements in the development of a treatment  
10 for SMA. And indeed this is a really exciting  
11 time as we are on the brink of seeing an approved  
12 therapy in the foreseeable future.

13 Of the 18 SMA drugs currently in  
14 development 6 are clinical trials including  
15 several in phase III. And we expect that one or  
16 more of these programs will undergo FDA NDA  
17 review in 2017.

18 Therefore it's critical that SMA be  
19 added to the recommended uniform screening panel  
20 as soon as possible to ensure that patients can  
21 obtain access to treatment at the earliest  
22 possible moment.

1           Both human natural history data and  
2 animal model data indicate that there is only a  
3 very small opportunity after birth for effective  
4 intervention in the most common and severe form  
5 of SMA type 1 which affects 60 to 70 percent of  
6 all SMA individuals and frequently leads to death  
7 before the age of 2.

8           Preliminary data in mouse models also  
9 indicates that pre-symptomatic drug intervention  
10 is far more effective than post symptomatic.

11           And additional studies have also shown  
12 that proactive treatment of an infant with SMA in  
13 the first few weeks to months of life prolongs  
14 survival and improves the quality of life.

15           Furthermore, the technology for  
16 newborn screening for SMA has been successfully  
17 utilized in several ongoing pilot newborn  
18 screening programs including in New York State  
19 and in Taiwan.

20           So in conclusion the SMA community  
21 strongly urges the advisory committee to take up  
22 consideration of the forthcoming SMA RUSP

1 nomination, in particular because of the  
2 approaching availability of a treatment for SMA  
3 and the demonstrated benefits of early  
4 intervention.

5 I thank the committee for the  
6 opportunity to address you this afternoon.

7 CHAIR BOCCHINI: Thank you for your  
8 comments. We certainly look forward to receiving  
9 the nomination packet.

10 Now on the phone we have Mr. Dean Suhr  
11 to discuss the RUSP roundtable and California  
12 model legislation involving the RUSP. Mr. Suhr?

13 MR. SUHR: Yes, good afternoon. Thank  
14 you, Dr. Bocchini and I thank the committee for  
15 this time.

16 I wanted to touch on these two  
17 particular issues just briefly.

18 The RUSP roundtable is continuing. I  
19 spoke about that at the February meeting so I  
20 won't provide any more details on that except to  
21 say that our next meeting will be Wednesday,  
22 August 24, just prior to the next meeting in the



1 D.C. area.

2 On the state legislation I'm involved  
3 in a project in California, in basically a study  
4 to address the issue of the U.S. having 50 states  
5 with 50 policies relative to how a screen is  
6 implemented after it's approved and on the  
7 Recommended Uniform Screening Panel.

8 As you know, in many cases that  
9 involves a legislative action of some kind. And  
10 in fact, that legislative action is not  
11 necessarily tied to the RUSP. There are, I  
12 believe there are states that are mandated by  
13 legislative action without being on the RUSP.

14 However, what we're talking about here  
15 is what happens after the issue is put onto the  
16 RUSP.

17 The legislation that has been proposed  
18 and introduced in California is something that  
19 I'm participating in cooperation with the rare  
20 disease legislative advocate.

21 And it's a one and done we're calling  
22 it kind of in the global sense where once a

1 disease is on the RUSP a legislative action is  
2 automatically taken care of. So we would pass a  
3 law up front that says anything that is qualified  
4 on the RUSP by a thorough evidence review process  
5 that you all go through, that that disease is  
6 then acceptable to that state to go forward with  
7 implementation.

8 We're not requesting any specific  
9 timeline, nor are we able to include an  
10 appropriation that would allow that addition to  
11 be implemented.

12 I would highlight that in California  
13 that the appropriations that cover the expenses  
14 relative to newborn screening are actually a  
15 matter of law already. So that actually is not  
16 an issue in California.

17 We want to use this legislation as  
18 model legislation in all 50 states, or at least  
19 all states where the legislators are involved in  
20 getting these diseases onto the panels.

21 We recognize this will not work  
22 everywhere, but we're hoping that we can bring

1 the advocacy and the family groups together to do  
2 this kind of in a one and done sense.

3 We've run across an issue though that  
4 I want to just put in front of the committee.  
5 And I'm not sure how you would address this, or  
6 it might be just an undercurrent.

7 But there are a number of states that  
8 implement their screening, they almost replicate  
9 the entire set of work that the committee goes  
10 through in terms of evidence review.

11 And we expect some of that because  
12 every state's equipment is a little bit  
13 different, their processes are a little bit  
14 different.

15 But it appears that there's a varying  
16 width of acceptance of the work that the  
17 committee is doing.

18 And everybody recognizes that it's a  
19 baseline, but how much additional work is done on  
20 top of that is a question we're starting to run  
21 into across states. So that's something I'd like  
22 to throw back at you to maybe consider a little

1 different work effort in terms of how can we  
2 continue to build the credibility of the  
3 committee's work and continue to share the  
4 breadth and the depth of the work that you're  
5 doing.

6 So with that, I do thank you for all  
7 your work, and I thank you for the time.

8 CHAIR BOCCHINI: Thank you very much,  
9 Mr. Suhr. We appreciate your comments.

10 This will conclude the public comment  
11 session for this meeting. So we appreciate the  
12 input that we've received from the public  
13 comments. Thank you.

14 We're now going to go forward with the  
15 GAMT Nomination and Prioritization Workgroup  
16 report. Dr. Matern will present this  
17 information. And subsequent to the presentation  
18 there will be a discussion, decision, and a vote.  
19 Dieter?

20 MEMBER MATERN: Thank you. So I'll be  
21 talking on behalf of the Nomination and  
22 Prioritization Workgroup. And I don't have a

1 slide that actually mentions the members of that  
2 workgroup, but it includes Dr. Bocchini, and Dr.  
3 Cuthbert, and Dr. Scott, and Debi, and Fred  
4 Lorey, and probably I'm forgetting someone.

5 So, the nomination was submitted by  
6 Dr. Nicola Longo from the University of Utah and  
7 cosponsored by Dr. Marzia Pasquali also at the  
8 University of Utah and also running the biochem  
9 and genetics lab at ARUP Labs.

10 There was no advocacy group mentioned  
11 in their nomination but of course we have heard  
12 from the Association from Creatinine Deficiencies  
13 just before this presentation.

14 There are several questions that we  
15 had to answer reviewing the nomination package  
16 and then checking the literature with other  
17 experts that we realized are out there.

18 So, the first question of course is  
19 the nominated condition medically serious.  
20 Second, are there prospective pilot data either  
21 done in the U.S. or elsewhere from population-  
22 based assessment available for this disorder.

1           What about the case definition and the  
2 spectrum of this disorder. Is it well described?

3 Is there a phenotypic range of children  
4 identified on a population-based screening?

5           What about the test's analytic  
6 validity? Do we know enough about the test to  
7 work analytically, but also has it clinical  
8 utility or other concerns with the test?

9           And then about treatment. Is there  
10 treatment? Are there medications that are FDA  
11 approved available or needed? So what about  
12 treatment.

13           First, I'd like to introduce you  
14 quickly to creatine deficiency syndromes. And I  
15 as a biochem geneticist, I have to show you a  
16 metabolic pathway, not so that you pass out, but  
17 just so you get an understanding.

18           I think it helps to figure out the  
19 approach that is taken to both the testing for  
20 the disorder and also the treatment.

21           So as you can see creatine is here  
22 located. It's also outside in the blood and

1 needs to get across cell membranes. But creatine  
2 first needs to be made unless you obtain it  
3 through food intake.

4 The pathway to synthesize creatine  
5 starts with arginine and glycine which is  
6 produced to guanidinoacetate which is then  
7 methylated to creatine. And then again it has to  
8 cross the cell membranes to get into the brain  
9 and muscle, and there's a creatine transporter.

10 So there are two enzymes involved, and  
11 the enzyme we're talking about is  
12 guanidinoacetate methyltransferase which is  
13 located here.

14 However, any of those enzymes, GAMT,  
15 AGAT, and then the transporter can be deficient  
16 and cause disease.

17 And this is taken from the gene  
18 reviews that was updated in December 2015 so it  
19 should be fairly up to date.

20 You can see there are 110 GAMT  
21 patients known in the literature. They present  
22 and that is what we heard earlier after a few

1 months of life to up to three years.

2 The phenotype is mild to severe  
3 intellectual disability. Most patients have  
4 epilepsy and the epilepsy is difficult to  
5 control. In half of the patients there is  
6 movement disorder and then their behavioral  
7 problems.

8 In AGAT the situation is that this is  
9 much more rare it appears than GAMT and again has  
10 a somewhat similar phenotype, muscle weakness  
11 being pronounced.

12 And then there is the X-linked  
13 transporter defect. This is the condition where  
14 most patients are identified. Again, onset is  
15 less than three years in those affected, boys,  
16 and similar phenotype to GAMT.

17 Treatment as we heard already from the  
18 parents is available and it's mostly  
19 supplementation of creatine and ornithine, and  
20 then restriction of protein and/or arginine and  
21 sodium benzoate. And the treatment is also  
22 established for the other conditions.



1                   Here you see from Scriver's, the  
2 online metabolic textbook a picture taken from  
3 the chapter on GAMT deficiency.

4                   And here you see one patient in A, B  
5 and C. And you can see the significant hypotonia  
6 here, dystonia here at 22 months, and then after  
7 being put on treatment you see that the patient  
8 seems to be doing better but is still having  
9 symptoms. And that is of course consistent with  
10 what we heard from the parents.

11                   And this is an untreated patient at  
12 four years old.

13                   So, important here of course is that  
14 the outcome is improved when you treat these  
15 patients as early as possible. And of course  
16 that is always good reason to think about newborn  
17 screening.

18                   What about the biochemical genetic  
19 diagnosis? Guanidinoacetate, when you have a  
20 defect here is accumulating. And you can measure  
21 this in urine, CSF, plasma and now in dried blood  
22 spots and it is elevated.

1           If you look at the other conditions,  
2           AGAT deficiency and the transporter defect, GAA  
3           is low or up to normal. AGAT deficiency is  
4           normal in the other conditions, so GAA alone is  
5           not really helpful to identify the other creatine  
6           deficiency disorders.

7           However, you can also measure creatine  
8           and creatinine all at the same time as you do the  
9           GAA. You can do ratios and that kind of helps  
10          you a little bit better differentiating those  
11          different disorders.

12          There is a diagnostic algorithm again  
13          from the Gene Reviews article for patients that  
14          are presenting with symptoms that are suggestive  
15          or could be consistent with GAA deficiency.

16          You do as a next step the measurement  
17          of GAA, creatine and creatinine in urine or in  
18          plasma. And then based on those results you can  
19          follow up using different studies including  
20          molecular genetic testing for the relevant genes.  
21          And if that results in a genotype of uncertain  
22          significance you might still have to do a

1 specific enzyme assay for each enzyme to arrive  
2 at a diagnosis.

3 But this is all doable because there  
4 are laboratories that offer this test. The only  
5 one that is a little bit tricky is the enzyme  
6 assay which I believe is only available in  
7 Amsterdam.

8 So, creatine, again I mentioned  
9 earlier the source of it is either the diet or  
10 biosynthesis. And the function is important as  
11 you can see here in the regeneration of ATP. And  
12 it is also a neurotransmitter in the CNS.

13 Because of the energy provision  
14 through creatine as we also heard from the  
15 parents you can obtain creatine in all kinds of  
16 stores, not only at Amazon but at Walmart. And  
17 since it is not yet reimbursed through health  
18 insurance it still is relatively cheap.

19 I always wonder if those costs would  
20 go up if health insurance actually would have to  
21 pay for it because those providers might think  
22 it's a good reason to jack up the price.

1           The pathophysiology of GAMT deficiency  
2           is basically, again, if you consider that you  
3           have this enzyme not working functionally you  
4           will have a deficiency of creatine and you will  
5           have accumulation of the precursor,  
6           guanidinoacetate which is a neurotoxic agent as  
7           far as we know.

8           So, the idea then is in treating these  
9           patients that you provide creatine at sufficient  
10          doses to overcome the blood-brain barrier and  
11          also maybe providing S-adenosyl L-methionine to  
12          potentially help any residual GAMT activity to be  
13          more effective.

14          And also to reduce guanidinoacetate  
15          which is accumulating. And you do this by  
16          providing ornithine, but also restricting  
17          arginine and maybe glycine by providing sodium  
18          benzoate.

19          So what are the outcomes of treatment?  
20          As we heard very effectively from the parents is  
21          that if you identify these patients basically at  
22          birth or shortly thereafter they can have a

1 normal life.

2 The later you make the diagnosis the  
3 more severe is the phenotype. So initiation of  
4 treatment as early as possible seems to be very  
5 important.

6 Also interesting is that in a paper  
7 that was published a couple of years ago there  
8 was a patient that was first reported in 2006 by  
9 a German group.

10 They found a patient who was diagnosed  
11 in the first few months of life and was doing  
12 very well, but apparently the parents then  
13 decided, well, this is kind of difficult and our  
14 child seems to be fine so they stopped treatment.  
15 And it didn't take long and then the patient had  
16 irreversible damage. So it is important that  
17 these patients stay on treatment consistently  
18 throughout life.

19 So back to our key questions. The  
20 nominated condition is medically serious. The  
21 answer I think is yes.

22 And I think we pretty well know what

1 the phenotypic spectrum looks like, at least  
2 based on these 110 patients.

3 What about treatment protocols? Are  
4 they defined? Are there FDA approved drugs, and  
5 are those all available?

6 So, in a paper by the Utah group they  
7 talk -- which is called Evidence-based Treatment  
8 of Guanidinoacetate Methyltransferase it  
9 indicates here very clearly that the  
10 recommendations for treatment of GAMT deficiency  
11 are evolving. So it might be that we don't have  
12 that nailed down completely.

13 In another paper a year later in 2014  
14 a larger study of 48 patients where they review  
15 and provide recommendations for diagnosis,  
16 treatment and monitoring, one of the conclusions  
17 is that overall numerous questions regarding the  
18 evidence of the described treatment modalities  
19 still remain to be answered.

20 So, we might not have yet fully  
21 defined treatment protocols.

22 What about newborn screening? Are

1       there any pilot study data available and how good  
2       is the test?

3               So the proposed newborn screening test  
4       is to measure GAA but creatine has also been  
5       already mentioned as in use in Utah at least, and  
6       you could also measure creatinine along with the  
7       acylcarnitines and amino acid analysis.

8               So this is not a separate test. You  
9       don't have to buy new equipment. You don't have  
10      to add extra people to do the testing. All you  
11      have to do is add a few reagents and do a  
12      modification to your analysis in mostly the  
13      software. So it's really, as the parents  
14      indicated, fairly cheap.

15              Also, the CDC already is providing  
16      reference materials for GAA and creatine through  
17      their quality assurance program.

18              A second tier test is probably a good  
19      idea to have as also reported specifically from  
20      the proponents from Utah.

21              And what they basically do, they do  
22      the analysis for GAA and creatine again by liquid

1 chromatography tandem mass spectrometry which is  
2 not as common as the regular flow injection  
3 analysis in newborn screening laboratories, but  
4 really any mass spec you can do LC-MS/MS on.

5 So you may but also may not require  
6 extra equipment. But it also has many second  
7 tier tests. They could probably be regionalized.

8 And I think as there are a good number  
9 of second tier tests out there I would still  
10 propose to many screening laboratories to join  
11 forces and every screening lab should offer at  
12 least one second tier test and work with other  
13 neighboring states maybe to provide the test to  
14 their relevant populations.

15 There's also molecular genetic  
16 analysis of the GALT gene available and has been  
17 proposed for newborn screening.

18 But what you find at the same time is  
19 that there are again variants of uncertain  
20 significance that are identified and therefore  
21 genotypes of uncertain significance. So it's  
22 really in my opinion not that helpful.



1           And it also is not yet typically used  
2 in a wide number of newborn screening programs.

3           So what is the status of newborn  
4 screening for GALT deficiency?

5           Published data from the University of  
6 Utah looking at 10,000 newborn screening samples  
7 retrospectively, they found a false positive rate  
8 by just looking at GAA and the GAA to creatine  
9 ratio of 0.08 percent.

10           However, they didn't report any false  
11 positives, or any of those out because they have  
12 a second tier test to look at GAA and creatine  
13 again. And so the final false positive rate is  
14 zero percent.

15           And the true positive, however, is  
16 also zero. They didn't find an affected patient  
17 in those 10,000 samples.

18           The Baylor Research Institute in  
19 Dallas, Texas, did a study of nearly 20,000  
20 babies of which about 50 percent were from  
21 Mexico. And they did this between 2008 and 2011.

22           They had a false positive rate of 0.5

1 percent just looking at GAA, but with the second  
2 tier test which basically means you take the  
3 original newborn screening sample, you do not  
4 tell anyone about this outside of the screening  
5 lab. You do the second tier test and if that is  
6 normal then you do not report it out.

7 So, in the end the false positive rate  
8 is zero which is extremely good. But they also  
9 didn't find a patient in that study.

10 In British Columbia they looked  
11 retrospectively at 3,000 newborn screening  
12 samples, had a false positive rate only using GAA  
13 of 0.13, but could get rid of all false positives  
14 with the second tier test.

15 They also tested for two common  
16 mutations and happened to find two carriers of  
17 two novel mutations. So coming back to what does  
18 this mean now. But those were only carriers so  
19 it really is supportive of the conclusion that  
20 there was no true positive in their cohort.

21 In Australia they've been actually  
22 doing prospective newborn screening for GAMT

1 deficiency since 2002 and have screened more than  
2 1 million babies.

3 Their report in 2014 included only  
4 about 770,000 babies, but I communicated with Dr.  
5 Pitt in Australia and he confirmed that they're  
6 continuing screening. They have screened about a  
7 million babies and they didn't find a single true  
8 positive. And the false positive rate with  
9 apparently no second tier test is 0.02 percent.

10 Now, we always wonder if it's  
11 international does it reflect a very different  
12 population to what we would find in the U.S.

13 So I Googled the demographics of  
14 Victoria, Australia, and could find that 66 of  
15 Victorians identify as Australian, and then of  
16 Scottish, English, or Irish ancestry and less  
17 than 1 percent aboriginal. And most immigrants  
18 are from the British Isles, China, Italy,  
19 Vietnam, Greece and New Zealand. So, more or  
20 less like America maybe.

21 In the Netherlands a study that came  
22 out only this year, and for those of you who look

1 at what is in the briefing book this is basically  
2 two versions after what you have in front of you  
3 so this slide was not included.

4 They looked at 500 newborn screening  
5 samples retrospectively. They did sequencing of  
6 the GAMT gene and they measured GAA.

7 Through sequencing they found two  
8 carriers, one with a known mutation and one with  
9 a novel mutation. And based on expression  
10 studies they feel that it is a pathogenic  
11 mutation.

12 And through measurement they found no  
13 false positives, but also no true positive.

14 So based on this the presumed carrier  
15 frequency is 1 in 250 which would calculate an  
16 incidence of about 1 in 250,000 among the Dutch  
17 population.

18 And the Dutch population is described  
19 in that paper as consisting of individuals with  
20 Dutch, Turkish, Moroccan, Indonesian, German,  
21 Surinamese, Latin American, other European and  
22 Asian ethnic backgrounds. So, very diverse.

1           So, how frequent is GAMT deficiency?  
2           So, you can look at this based on calculation and  
3           based on prospective newborn screening.

4           So as I just mentioned, the  
5           Netherlands, they assume it to be 1 in 250,000.

6           In Utah they looked at the number of  
7           patients they had diagnosed over a 10-year period  
8           and then calculated it back to the live birth and  
9           came up with a calculated incidence of 1 in  
10          114,000.

11          In Portugal in 2007 they had a report  
12          where they looked at 1,002 newborn screening  
13          samples that they tested for one mutation which  
14          appears to be common among patients with GAMT  
15          deficiency in Portugal and they found eight  
16          carriers.

17          So their calculated incidence is 1 in  
18          63,000.

19          And based on prospective newborn  
20          screening in Australia as I mentioned less than 1  
21          in 1 million, and in Utah less than 1 in 50,000.

22          So Utah is currently actually actively

1 screening for GAMT deficiency. And at this point  
2 they screened, as Dr. Pasquali mentioned to me  
3 earlier today, 50,000 so far. They had one false  
4 positive that turned out to be a NICU baby and at  
5 this point no true positive.

6 But if you look up here the estimated  
7 incidence is 1 in 114,000 so they should get  
8 there next year.

9 So in summary we believe that GAMT  
10 deficiency is a serious medical condition. The  
11 natural history of GAMT deficiency seems well  
12 understood even though there are only 110  
13 patients known worldwide.

14 The treatment I think is very similar  
15 to many of the conditions on the RUSP. And I  
16 think that if you remember the discussion about  
17 PKU this morning I think there's a lot of overlap  
18 in how we would approach these patients. You  
19 need diet maybe, but certainly supplements and  
20 you need support.

21 The best outcomes is when treatment is  
22 started shortly after birth.

1           Dried blood spot based assays can be  
2 adopted for newborn screening quickly and at very  
3 low cost so that's new for us.

4           Prospective newborn screening is  
5 ongoing in Victoria and apparently in Utah. But  
6 again, at least in Australia very low incidence  
7 apparently. So, the sensitivity, however, of the  
8 screening test is also nicer than many of the  
9 conditions that we have added to the RUSP with a  
10 likely 100 percent sensitivity and near zero if  
11 not zero false positive rate.

12           So, should one add GAMT to newborn  
13 screening?

14           So, one could say well, we understand  
15 the natural history. Treatment is similar to  
16 many classic inborn errors of metabolism. The  
17 outcomes are best with early treatment. Newborn  
18 screening assay is cheap and easily implemented.  
19 And the newborn screening strategy has a high  
20 sensitivity and low false positive rate.

21           If you didn't want to do it you would  
22 say well, we only understand the natural history

1 on 110 patients. Is that enough?

2 There is no agreed upon treatment  
3 strategy. Metabolic control must be strict. No  
4 FDA approved newborn screening or diagnostic  
5 assay. And I don't believe that is really an  
6 issue because laboratory developed tests are just  
7 fine, so that shouldn't be an issue.

8 And, however, no patient has ever been  
9 identified through prospective newborn screening.

10 So, back to our key questions.  
11 Medically serious condition - yes. Prospective  
12 pilot study data - yes, not only Australia but  
13 also in Utah.

14 Case definition - yes, based on 110  
15 patients. Analytic validity - yes. Clinical  
16 utility - well, the problem is no case identified  
17 prospectively yet.

18 And defined treatment protocols, you  
19 could argue well, they're not really that  
20 defined, so maybe not yet. But I think that is  
21 something that could be fixed.

22 So, what is the recommendation of the



1 workgroup to the advisory committee? At this  
2 point we would say we do not initiate external  
3 evidence review because not a single case has  
4 been identified prospectively through newborn  
5 screening which would really make the evidence  
6 review very difficult.

7 And then treatment guidelines appear  
8 to be in development but are not finalized.

9 What I think should also be  
10 recommended, or what we think should be  
11 recommended, that the proponents work with other  
12 experts to formalize the treatment guidelines and  
13 encourage the continuation of newborn screening  
14 for GAMT deficiency in Utah and Australia, and  
15 report ASAP back to us when a patient has been  
16 identified prospectively.

17 So, please we would say, proponents,  
18 resubmit a nomination immediately when above has  
19 been achieved. That's I think all I have.

20 CHAIR BOCCHINI: Dieter, thank you for  
21 that presentation. It was very clear and  
22 thorough. Appreciate it.

1           This is now open for discussion and  
2           questions from the committee and then from the  
3           organizational representatives. Don.

4           MEMBER BAILEY: Dieter, could you  
5           speak a little bit more about -- I don't  
6           understand why treatment guidelines are unclear.  
7           Maybe I just don't have the information, but can  
8           you give me a little bit more information?

9           MEMBER MATERN: I think what --  
10          basically, and I would agree with do we really  
11          need this. Because if you look at conditions  
12          that we added only recently for Pompe disease  
13          there still in the literature you have questions  
14          about what is the right immune modulation, et  
15          cetera. So there are no clear guidelines there  
16          either.

17          So I would agree that this is a weak  
18          argument not to proceed because there is a lot of  
19          information out there. And it probably would be  
20          one short phone call among the proponents along  
21          with people and their colleagues in Canada to fix  
22          that and write a paper that outlines more exactly

1 what those guidelines are.

2 MEMBER BAILEY: Plus we're not talking  
3 about a dangerous treatment.

4 MEMBER MATERN: From what I understand  
5 it's not a dangerous treatment.

6 MEMBER BOTKIN: Dieter, thanks, it was  
7 very helpful.

8 You mentioned that the clinical  
9 sensitivity of the testing estimated to be 100  
10 percent. Where does that number come from in the  
11 absence of any real babies identified yet?

12 MEMBER MATERN: So, that comes from  
13 the fact that specifically in Australia where you  
14 have this large area called Victoria which is  
15 served by one screening laboratory and one  
16 diagnostic laboratory.

17 And the Australians I think are very  
18 proud in their healthcare system and feel that  
19 since they haven't diagnosed a patient with GAMT  
20 deficiency since 2002 through their clinical  
21 efforts while they were screening that there are  
22 indeed no false negatives.

1           And in Utah I think at the same time  
2 they've been screening now probably for more than  
3 a year and didn't make a diagnosis clinically.

4           And again, the laboratory, there's  
5 only one biochem genetics lab. And even if  
6 another lab did the diagnosis the patient would  
7 be followed by Dr. Longo.

8           MEMBER MCDONOUGH: Knowing what we  
9 know now in 2016 about how serious this condition  
10 is, and there's effective treatment, and what  
11 happens when these children aren't picked up on  
12 time, if we knew that back when the tandem mass  
13 was developed and the RUSP was expanded is it  
14 more likely than not that this condition would  
15 have been part of that panel back then?

16           MEMBER MATERN: At the time there was  
17 no screening test so that is one thing. I think  
18 if the screening test would have been around I  
19 would believe that it would more likely be  
20 included than not.

21           MEMBER SPONG: So, I'm a little new to  
22 this, but is it -- I'm confused as to why this

1 wouldn't get moved forward just to the condition  
2 review team.

3 Is it just because we haven't  
4 identified one case using these prospectives? Is  
5 that the reason why? And how long could that  
6 take to happen? And what would be the harm in  
7 moving it forward while waiting for that one  
8 case?

9 MEMBER MATERN: Well, the harm of  
10 course is always that a baby will be born in a  
11 state that could have screened and will not  
12 receive the treatment.

13 MEMBER SPONG: That's the harm in not  
14 moving it forward, or in moving it forward?  
15 What's the harm in moving it forward?

16 MEMBER MATERN: Well, the problem I  
17 think for the evidence review, because we're just  
18 discussing here whether it should be moved  
19 forward to the evidence review. So we're not  
20 even talking about should it just be included.

21 I think the harm is that we're asking  
22 the evidence review to proceed and come up with

1 the fact that there was not a single true  
2 positive.

3 And so they don't really know what to  
4 -- well, they're not recommending us anything,  
5 but the data they will provide us will probably  
6 not add anything new that we don't know right  
7 now.

8 Yes, we had this discussion. Yes.

9 MEMBER MCDONOUGH: The point I was  
10 trying to raise with the question I asked is that  
11 there's probably -- I shouldn't say -- is there  
12 more information about this condition, the  
13 benefit of treatment, early detection, that  
14 perhaps some of the conditions that were added on  
15 the RUSP in that expansion? Do you have an  
16 opinion on that?

17 MEMBER MATERN: Well, to my counts  
18 this is a no brainer. Again, this is a condition  
19 that's medically serious. There's treatment that  
20 seems to be -- well, that is cheap, that can be  
21 done, and the screening test is not difficult.  
22 Does that answer your question?

1 Steve, do you have a question?

2 MEMBER MCDONOUGH: Well, we have to be  
3 careful we don't get too paralyzed by our  
4 policies and don't take an opportunity to help  
5 some kids.

6 MS. GREENE: Carol Greene, SIMD.  
7 Thanks for the excellent review.

8 And while personally I'm not speaking  
9 for the SIMD for me obviously it's a slam dunk.  
10 I identify the kids and I treat them.

11 I wanted to speak to two points. One  
12 is with respect to treatment. I think perhaps --  
13 because if you don't follow your own guidelines  
14 then the next person coming along will of course  
15 say well, you've got your guidelines and you went  
16 ahead and did it, and why not for me as well.  
17 So, the guidelines are meaningful and there's  
18 reasons to follow them.

19 With that said I think perhaps we need  
20 a little bit more guidance on the interpretation  
21 of treatment is not set.

22 Because the treatment, core of

1 treatment is you give creatine. We're arguing  
2 around, you know, we're nibbling around the  
3 edges, can we make it better, what do we do with  
4 the diet. Do we give sodium benzoate which  
5 tastes nasty and nobody wants to drink it anyway.  
6 How much ornithine do we give.

7 But we've got a treatment, there's no  
8 doubt about it. I think we need to be a little  
9 careful about over-interpreting.

10 When somebody genuinely and honestly  
11 says we need to do better figuring out the best  
12 way to treat this that we don't lose sight of --  
13 so I feel very strongly as a clinician, you know,  
14 I'm going to go talk to people. Do I give  
15 ornithine or not. But I'm giving creatine.  
16 That's no problem.

17 So, I think this one gets a yes when  
18 we have agreement about therapy. We're still  
19 trying to make the therapy for PKU better. I  
20 think this one gets a yes on therapy.

21 With respect to the question of has it  
22 met the criteria for pilot, I don't think the



1       SIMD -- I don't want to represent the SIMD of  
2       having an opinion, but I will say as the SIMD I  
3       think this one gets a yes on treatment. We're  
4       working to improve it, but we have a treatment.

5                   MEMBER WICKLUND: Okay, so forgive me  
6       if you already said this, Dieter.

7                   So, retrospectively they were able to  
8       take dried blood spots and identify affected  
9       individuals, right? So the limiting factor is  
10      identifying a true positive prospectively. Okay.

11                  So, once that happens it still won't  
12      further delineate the natural history. Because  
13      if it's just till they identify a true positive,  
14      right, that's just the fact that they've  
15      identified a true positive.

16                  And if they notify us immediately with  
17      that how does that add to our level of evidence?  
18      I guess I'm trying to tease out a little bit  
19      versus if we're trying to get more information  
20      about if they develop symptoms.

21                  I guess I'm just trying to get my head  
22      wrapped around. Is this coming back to our pilot

1 recommendations about having to have one true  
2 positive? Anyway, I'm just a little muddled  
3 right now on that.

4 MEMBER MATERN: I think the answer is  
5 yes, but Jeff is getting ready to say something.

6 MEMBER BOTKIN: Well, it is rather  
7 ironic that this comes up immediately. But of  
8 course, that's the discussion we were having.

9 I think it just forces additional  
10 thought about what's the value of that one baby.  
11 That's not going to tell you anything additional.

12 I guess in my thinking it really  
13 demonstrates whether in fact you have a program  
14 that's effective in identifying affected kids or  
15 not.

16 Now, everybody seems to think this is  
17 a good test, but yet a million babies is a lot of  
18 babies without a single true positive.

19 And so what's the explanation there.  
20 Is it something about Australia? Is it something  
21 about these other programs that have yet to  
22 identify an affected baby? I don't understand

1 what the alternative explanations might be of  
2 that failure.

3 So, I have to agree, the rest of the  
4 elements seem pretty solid here to move forward,  
5 but I have to be disturbed by the failure of  
6 public health programs to yield affected kids.

7 MEMBER KELM: Well, you know, we  
8 obviously focused all of this information on the  
9 prospective.

10 But I guess one piece that would be  
11 great to have is how robust is the, you know,  
12 when they retrospectively just even look at their  
13 method and their cutoffs and have a retrospective  
14 sampling.

15 What kind of numbers are we talking  
16 about. How well did that look. That would  
17 probably be helpful for us to understand.

18 But there is one thing that I guess I  
19 also feel -- wanted to have a little bit more  
20 flavor from you is, I mean obviously you're  
21 saying this can be done, but what sort of  
22 insights from, I mean if Fred was on your group.

1           Is this really simple to add in the  
2 public health labs? I guess that was my question  
3 is that we have that public health impact  
4 assessment also. So how easy is this to add to a  
5 current program? I don't know if somebody can  
6 weigh in on that.

7           MEMBER MATERN: Yes. Personally I  
8 would think it is easy. And again, the CDC at  
9 least has the materials so they have the test  
10 running in their own laboratory. So they could  
11 train as they train anyone else on acylcarnitines  
12 and amino acids. Just make it part of their  
13 program. Or not.

14          CHAIR BOCCHINI: Fred, if you're on  
15 did you want to make a comment related to that  
16 question?

17          MEMBER LOREY: No, not at this time.  
18 Thanks.

19          CHAIR BOCCHINI: Okay, thanks.

20          MR. OSTRANDER: So, I think it's  
21 fortuitous actually this came right after Jeff's  
22 talk because I think it gives us food for thought

1 about the difference between rare conditions and  
2 ultra-rare conditions.

3 I mean, this is unique in that it has  
4 a cheap and safe treatment which has not been one  
5 of our previous criteria, but certainly gives one  
6 pause about whether we need to be as strict about  
7 the criteria in that setting as opposed to ones  
8 where the treatments are dangerous and of unknown  
9 efficacy.

10 So, even in your talk, Jeff, there was  
11 a comment about the value of having one true  
12 positive.

13 I mean, is one much different from  
14 zero? Yes, and maybe not. If you can prove that  
15 with the existing technology retrospective  
16 identified cases test positive I don't know that  
17 from a scientific standpoint it's all that  
18 different in a rare condition like this.

19 And I'm going to chime in with Carol's  
20 treatment protocol thing too. If you've only got  
21 110 cases worldwide you're not going to have  
22 standardized treatment protocols that are going

1 to be compared in a prospective way from no  
2 treatment or the standard treatment.

3 So, it may be for ultra rare  
4 conditions that the thought process could be  
5 modified just a smidgeon, taking into account and  
6 weighing not only the criteria for true positives  
7 through screening and the treatment protocol on  
8 the one hand, but also on the other weighing the  
9 safety and efficacy of the intervention.

10 That might tip the scales and it  
11 sounds to me like in this case it might even be  
12 reasonable to consider it to have tipped the  
13 scales.

14 CHAIR BOCCHINI: So, I think, Alex,  
15 can you tell us what one positive case means to  
16 evidence review?

17 MR. KEMPER: And this is where I  
18 resolve all the mysteries.

19 So, before I branch out there I just  
20 wanted to thank Dieter for doing really an  
21 excellent presentation about GAMT deficiency in  
22 terms of digging up what evidence is out there.

1 So thank you very much for setting me up.

2 You know, this issue of finding one  
3 case we've oftentimes talked about as being  
4 really important and it's certainly where we came  
5 from with SCID.

6 It's a little bit difficult to  
7 articulate, but what I would say is in addition  
8 to finding the one case, we're able to look at  
9 all the cases that weren't GAMT deficient. So,  
10 we're able to look at both the positive  
11 predictive value and the negative predictive  
12 value.

13 And one of the things that we're  
14 supposed to do as part of our evidence review is  
15 also look at what would happen in the real world  
16 as state programs adopt screening. So, it really  
17 goes beyond just finding that one case.

18 Certainly we in the Evidence Review  
19 Workgroup, we serve at the pleasure of the  
20 advisory committee so we're happy to do whatever  
21 you ask us to do, including looking at things  
22 like natural history, or what's known presently

1 about treatment. Perhaps digging a little more  
2 than Dieter already did in his very nice  
3 presentation.

4 But the one part that we would really  
5 struggle with is in looking at the implementation  
6 side in terms of the burden on the newborn  
7 screening programs.

8 So, that to me is where the issue is.  
9 But again, we're happy to do anything you ask us  
10 to do. Anything.

11 MEMBER MCDONOUGH: Can you say a  
12 little bit more about your concern about the  
13 burden for programs?

14 MR. KEMPER: Yes. And I'm sensitive  
15 that the word "burden" as typically used in day  
16 to day language is burdensome.

17 So, one of the charges that we have is  
18 to look at what it would take for state newborn  
19 screening programs to adopt screening for the  
20 condition we're actually going to be talking at  
21 length about, issues of cost.

22 But also there are these sort of



1 broader issues of feasibility and readiness that  
2 are in our charge.

3 And so with limited data from state  
4 health programs it's difficult for us to do that.  
5 And so that's where the call for pilot studies  
6 came from.

7 And so to me it's not just the one  
8 positive case, but it's sort of the broader  
9 issues regarding implementation.

10 Again, we could do the other parts in  
11 terms of natural history and treatments and that  
12 kind of thing, but we would hit a wall when it  
13 comes to that one component.

14 And the degree to which that's  
15 important is up to you all again.

16 CHAIR BOCCHINI: Plus, once the  
17 evidence review begins there's really a timeline  
18 within which it now needs to be completed which  
19 also poses a problem.

20 MR. KEMPER: Right. Nine months.  
21 It's not just a good idea. It's the law.

22 MS. GREENE: Carol Greene again, SIMD.

1           Interesting discussion. Of course if  
2 you really want data from states about  
3 implementation then you're going to have to be  
4 holding everybody to have multiple pilots in  
5 multiple states because this one, you've actually  
6 got a pilot in a state.

7           What I wanted just to add is that  
8 there is, in terms of actually real life there is  
9 a very good diagnostic test and it's very easy to  
10 send. It's a little hard to collect urine on  
11 baby girls, but we do it all the time. And it's  
12 easy to collect urine on baby boys, and easy to  
13 collect blood on both sexes.

14           And so we've got a diagnostic test  
15 available. And we can offer a treatment.

16           What I am a little curious about is if  
17 anybody's got enough math to do the sock drawer  
18 problem. If the true frequency is really 1 in  
19 120 or 1 in 250,000 in Australia what are the  
20 statistical chances of finding none in a million.

21           And I think that's a reasonably high  
22 number, but I don't know because at least some of

1 the frequency is based on DNA on what you presume  
2 to be carriers, and that assumes that everybody  
3 who's a carrier is symptomatic.

4 So, I'm really interested in the  
5 numbers and I think that maybe somebody's got  
6 that math.

7 MS. TARINI: This is Beth Tarini at  
8 the American Academy of Pediatrics.

9 I agree with Alex and the reason I  
10 agree is because if I remember correctly, others  
11 please correct me if I'm wrong, in either MPS I,  
12 I thought it was MPS I, there were two affected  
13 individuals, is that right? In Missouri. Or  
14 there were two affected I thought found in the  
15 population that underwent transplant. Am I  
16 correct?

17 At any rate, historically it seems  
18 ongoing conditions have been reviewed and cases  
19 have been identified from population-based  
20 screening that we have leveraged or leaned very  
21 strongly on past evidence of efficacy in studies  
22 that involve identification from family history,

1 not on efficacy of treatment by what is found in  
2 the population.

3 Because I believe of the minor number  
4 of children that were found, the small number,  
5 one of them died after the treatment. And that  
6 was not taken into consideration as affecting the  
7 assessment of efficacy of the treatment. We  
8 leaned much more heavily on what was the  
9 historical studies that were done.

10 That is to say if we have done that in  
11 the past when we've actually had cases identified  
12 and we've sort of not taken into consideration  
13 what the real life outcome was then I don't think  
14 it is consistent to use that one person standard  
15 here.

16 MR. KEMPER: And just to amplify on  
17 what you said too.

18 One of the problems with hinging  
19 everything on the case, not for this condition,  
20 but for a lot of other conditions is that the one  
21 case identified through newborn screening may not  
22 develop clinical problems for years down the

1 line. That was the problem with ALD.

2 But this is really certainly a  
3 different thing in that the one case identified,  
4 if they were going to develop symptoms you would  
5 expect it to happen earlier rather than later.

6 CHAIR BOCCHINI: Since this is under  
7 discussion we're trying to limit the comments to  
8 the committee and the organizational  
9 representatives.

10 MEMBER BOTKIN: Question back for  
11 Alex. And I think Dieter had suggested that if  
12 indeed there's an evidence review at this point  
13 it's unlikely to provide more information than  
14 what's been provided by the current review.

15 And I guess I wanted to see what your  
16 response was to that. Would there be additional  
17 avenues of evidence to uncover that might help  
18 make that decision?

19 Because basically the question would  
20 be would the committee be ready today to make a  
21 decision about the RUSP if in fact there's not  
22 any additional information that's going to be

1       forthcoming.

2                   MR. KEMPER:   I'm going to I guess  
3       plead the Fifth in that we haven't looked at what  
4       evidence is or is not out there.

5                   I do know from conversations I've had  
6       with Dieter in the past that it sounds like he  
7       did a thorough job of looking out there, but I  
8       can't comment on what else may be out there.

9                   MS. TARINI:   This is Beth Tarini, AAP.

10                   To Jeff's point which Kellie had  
11       raised the evidence review process is not just  
12       evidence review, am I correct?  There's a public  
13       health impact analysis.

14                   So while the evidence may be, and  
15       again we wouldn't know until you did it, may be  
16       not much more than this, there certainly would be  
17       this other component to the matrix that would  
18       have to be done.

19                   MR. WATSON:   -- things that run  
20       counter to what I said before which is when could  
21       I accept one case.

22                   So if -- I was looking at the

1 testimony, the public comments. There was a lot  
2 of patients from California and New York, or  
3 families from California and New York all of whom  
4 are in our virtual repository and whose spots  
5 could be pulled with consent to see whether or  
6 not they would have been detectable on a newborn  
7 screen.

8 And that actually does get you a fair  
9 bit along the way. It doesn't get you past  
10 having a numerator of zero which makes statistics  
11 really hard, but I think there are things that  
12 can sort of make you feel a lot more comfortable  
13 with retrospective data that could get me to  
14 thinking about just one case justifying it.

15 When you think about the things that  
16 you're doing in the public health prospective  
17 pilot you really want to make sure that you can  
18 find them, get them into treatment, and intervene  
19 in time, and get the expected outcome.

20 You learn about penetrance which isn't  
21 a problem here because you've got a million  
22 babies screened with no screened positives let

1 alone true positives.

2 So when you start thinking about what  
3 are the things that you get out of the pilot you  
4 can really, I think a number of them can be dealt  
5 with and reduce the demands on a really ultra  
6 rare condition like this if you think about what  
7 it is you gain and lose by these different  
8 parameters.

9 MEMBER MATERN: So that is --  
10 something that I haven't pointed out in my  
11 presentation is that actually of course our  
12 colleagues in Utah and in Canada and in  
13 Australia, they have added retrospective,  
14 collected actual newborn screening samples from  
15 patients and ran them through their test.

16 And that data is out there, and it  
17 shows nicely how they have much higher GAA  
18 concentrations than normal population.

19 MR. WATSON: Part of the data that you  
20 want people to submit is something that is really  
21 informative retrospectively when you've got these  
22 ultra rare situations.



1 I mean, this happened in SCID. It got  
2 really narrowly defined. We must have been  
3 around 750,000 babies into SCID when the first  
4 one was found. I mean, those are my vague  
5 recollections of five, six years ago.

6 MEMBER MCDONOUGH: If Utah is the only  
7 state that's going to be testing for this it may  
8 take several years to get a true positive.

9 In the meantime, if the statistics are  
10 reasonably accurate there are going to be 20 to  
11 45, 40 children born in our country every year  
12 who are going to be brain damaged if we aren't  
13 doing the testing.

14 We've got these rare conditions.  
15 We've modified our criteria before. When we had  
16 this matrix together we actually approved a B3  
17 and the Interagency Coordinating Committee  
18 approved it.

19 So I think we constantly have to look  
20 at what our criteria are, what we're presenting  
21 with and go from there.

22 I'm concerned if we drag this out

1 there are going to be families and kids who will  
2 be definitely impacted because they won't be  
3 diagnosed.

4 CHAIR BOCCHINI: Well, I think there's  
5 no question that based on Dieter's presentation  
6 it's pretty clear that the Nomination and  
7 Prioritization Committee felt very strongly that  
8 many of the criteria that are necessary to move  
9 this nomination forward haven't been met and  
10 recognize the seriousness of delay in treatment.

11 On the other hand, it's also  
12 recognized that we have a test that hasn't been  
13 proven to work in a newborn screening situation.

14 And as a result the decision was to  
15 accept basically the data that was submitted and  
16 ask that as soon as we meet that last criteria  
17 that we move forward to move this to evidence  
18 review as quickly as possible.

19 At the same time asking the nominators  
20 and the advocacy groups to get together to look  
21 at things that might also add additional data.

22 And as Mike suggested, that the

1 possibility of using other things to help make a  
2 stronger case could be done relatively quickly.

3 And all that is so that when we do get  
4 the data that we feel is necessary to move it to  
5 evidence review that we would ensure a greater  
6 likelihood of success because we would have met  
7 all of our criteria to go forward.

8 So that's the crux of what we've been  
9 discussing. And so I think that that's still I  
10 think a reasonable approach.

11 MEMBER MCDONOUGH: This is McDonough.  
12 Is it possible that it could be during the  
13 process of the evidence review that a study could  
14 be conducted during that nine-month period of the  
15 blood spots, working with the patients, the  
16 identified cases that we would have that  
17 information during that nine-month period?

18 MEMBER MATERN: So you mean that they  
19 take the original blood spots and run them  
20 through their system?

21 Yes, but they've done that already.  
22 So that was part of the retrospective studies

1 that they interspersed the true positive original  
2 newborn screening samples that were stored away  
3 and run them through the system and could show  
4 that their GAA levels are higher.

5 CHAIR BOCCHINI: And remember, this  
6 would not be the first time that a nominated  
7 condition was close to being approved but missed  
8 some of the criteria for which we went back to  
9 the nominating group and asked that that  
10 additional data be obtained, and that they only  
11 needed to submit the additional data, and then we  
12 moved it forward.

13 That happened with Pompe, SCID as you  
14 heard, it was -- the decision was delayed until a  
15 positive case was found and so on. So I don't  
16 think it's unprecedented that we would use the  
17 approach to meet our criteria.

18 MEMBER WICKLUND: So, I completely  
19 agree with that, but I guess I'm having a hard  
20 time with the -- we require the one true  
21 positive.

22 I think that if there's additional

1 data, retrospective data, or additional data that  
2 can be given to us that provides another level of  
3 evidence.

4 I'm just trying to figure out in my  
5 head what additional level of evidence does that  
6 one true positive really give us compared to some  
7 of the evidence that we have from other sources.

8 So, I -- so this is where I'm  
9 struggling by saying, you know, we'll consider it  
10 again after one true positive is found. Like  
11 that to me seems really narrow and that's the  
12 part I'm struggling with right now versus looking  
13 at retrospective data in more detail and getting  
14 more information that way.

15 CHAIR BOCCHINI: Well, I guess part of  
16 it depends on how that influences the ability to  
17 prove that a newborn screening program in place  
18 can detect a positive on a newborn.

19 So, I don't know whether people from  
20 the lab might be able to answer that better than  
21 or with more detail than I.

22 MEMBER CUTHBERT: So, I get the

1       tension. Dieter's talking about the perspective  
2       of being a biochemical geneticist and as one  
3       myself I understand that.

4                But putting on the public health hat  
5       which I have to be concerned about as well coming  
6       from CDC and so on it is not only just about the  
7       test.

8                While this condition does present  
9       itself in being one of the more positive ones.  
10       When it was nominated I breathed very heavily. I  
11       thought this was fantastic.

12               I think I would be a little bit more  
13       -- I do support what the Nomination and  
14       Prioritization Committee has said.

15               It is very important that, again, that  
16       we do this for consistency again of the  
17       guidelines that we've put forward.

18               My concern is whereas this might be a  
19       good one to sort of let slip through what does it  
20       say for every other one that will come next.

21               If we for every single condition look  
22       at our guidelines and say, well, this one meets

1 all of these but not this. We can let that pass.  
2 It just causes the committee to just not seem  
3 consistent.

4 And I think it was brought up that  
5 someone was saying that the state programs don't  
6 always consider the recommendations of the  
7 committee as strongly.

8 They go back and they review and they  
9 say well, we hear what the ACHDNC has said.  
10 We're going to do something a little different.  
11 We would like to have a little bit more evidence.

12 There is a bit of a disparity between  
13 what we say we will do and what we do do and  
14 there's the rub.

15 And again, as a biochemical geneticist  
16 this is fantastic. I really want to see this on.

17 But being a public health person and  
18 just recognizing that the committee has laid out  
19 guidance for itself it doesn't bode very well if  
20 we are not able to stick to our guidance.

21 And there's a lot more. In other  
22 conditions there's a lot more that you would

1 identify when you prospectively screen.

2 This might seem very simple because my  
3 goodness, you find them, you treat them, they're  
4 better. That seems very, very apparent.

5 But for other complicated diseases my  
6 concern is that it would not be so simple. And  
7 that's why there's a great tension with making  
8 this decision.

9 But again, I still support what the  
10 Nomination and Prioritization Committee says.

11 MEMBER MATERN: However, if we don't  
12 move it to the evidence review it will -- I mean,  
13 we're not adding it to the RUSP today. It's just  
14 a question whether we're moving it to the  
15 evidence review.

16 And the evidence review will have to  
17 look at everything we discussed today. They will  
18 have to look at whether the test as it would be  
19 implemented in a public health laboratory.

20 One of the things that I'm a little  
21 bit concerned about is what is happening in the  
22 screening labs right now when it comes to X-



1        adrenoleukodystrophy. You can identify X-ALD by  
2        using lysophosphatidylcholine with a separate  
3        assay, or along with the lysosomal storage  
4        disorders, or as has been proposed you can also  
5        add long chain acylcarnitines to the  
6        acylcarnitine panel and pick it up that way.

7                    But I don't know how easy it will be  
8        to add GAA creatine and the long chain  
9        acylcarnitines if you use MRMs because at some  
10       point there's only so much you can do at a time  
11       even with a tandem mass spec.

12                   So that is a thing that I don't know.  
13       I don't know if anyone from Perk & Elmer is here  
14       who can tell us what their plans are, those kind  
15       of questions.

16                   MEMBER CUTHBERT: So, I can't speak  
17       for Perk & Elmer. This is Carla Cuthbert  
18       speaking again.

19                   I can't speak for Perk & Elmer  
20       particularly, but I do know that Perk & Elmer is  
21       coming out with a modified neobased kit soon.

22                   They did a presentation earlier this

1 year at the APHL newborn screening symposium.  
2 And they did indicate that they are including  
3 several new markers specifically to address X-  
4 ALD, SIMD ADA and GAMT is specifically not on  
5 that.

6 Now, perhaps they were not given a  
7 heads up about this so they had been working on  
8 what they knew had been added to the Recommended  
9 Uniform Screening Panel and that they recognized  
10 -- they're also looking to improve the detection  
11 of succinylacetone which has been a problem  
12 historically.

13 So, when we did ask them about GAMT  
14 they said that they were not planning on doing  
15 this again. They're listening to this  
16 presentation. Perhaps they will consider  
17 differently.

18 How that additional marker performs  
19 with their current expansion which they are  
20 working at to try to get to a sufficient level of  
21 acceptability before they roll that out is  
22 anybody's guess.

1 I don't know that, you know, we can  
2 ask them whether or not they can put this in, but  
3 that would be a hard request.

4 MEMBER LOREY: This is Fred. I spoke  
5 to them last week and it seemed they're not  
6 working on it.

7 MEMBER BAILEY: So I'm going to  
8 recommend we take a chance and move it forward to  
9 evidence review. I feel like we have a very  
10 strong evidence for benefit for these babies.  
11 The low cost of screening and relative to a lot  
12 of the other conditions we've got a pretty strong  
13 case already.

14 I actually don't think we'll learn  
15 much more from the evidence review, frankly, but  
16 in the meantime I think what we'll get is the  
17 APHL review of state capabilities.

18 We can ask the advocates to come  
19 together quickly and pull together some consensus  
20 guidelines for treatment.

21 These pilot studies are already  
22 ongoing. We'll potentially have more data. And

1 we'll know in nine months whether we can make a  
2 decision or not.

3 I mean, I realize we're going to pay  
4 Alex the big bucks to do the review, but I  
5 frankly think in -- okay, the small bucks -- I  
6 frankly think in this case that we've got a  
7 strong candidate here and that we should take a  
8 chance and move forward with the evidence review,  
9 recognizing that it may fail at the end, but I'm  
10 willing to take a chance on it myself.

11 MEMBER BOTKIN: Second.

12 MEMBER SPONG: So, Don has actually  
13 answered a couple of -- part of the question that  
14 I had. And again, some of it is education for  
15 me.

16 If I understand correctly the pilot  
17 criteria that we went through before lunch was  
18 the first time we kind of outlined what that was.  
19 So that isn't even really final yet, although one  
20 of those comments was that you needed to have a  
21 positive in order to move forward. But we  
22 haven't totally hammered those all out.

1           So, say this was the last meeting.  
2           What would be the harm in going ahead and moving  
3           this forward, getting that information?

4           I appreciate that you're not going to  
5           get a whole lot as Don just kind of reinforced to  
6           me, at least not from the evidence-based review.

7           But maybe while that process is going  
8           on and getting everything else that you would get  
9           in that nine-month period you would get other  
10          information that would be helpful rather than  
11          waiting for that one case and delaying the whole  
12          thing by not moving forward.

13          So, education is what I'm after here  
14          to understand and make an informed decision.

15          CHAIR BOCCHINI: Yes, the only  
16          difficulty is if we get out nine months out and  
17          we don't have the key data that's necessary a  
18          decision will have to be made to reject the  
19          packet.

20          MEMBER SPONG: So then could you not  
21          reconsider it at a later date if something  
22          positive did come up?

1 CHAIR BOCCHINI: Right, but that's the  
2 same thing as doing it -- by following our own  
3 criteria for including it.

4 But I understand your point. Cathy?

5 MEMBER WICKLUND: I was just going to  
6 say that I wonder if that would set us back even  
7 farther. Like if you move it forward through  
8 evidence review, you go through that process.  
9 I'm just trying to think about time-wise, but I  
10 don't know if we'd save time or not. Or if you  
11 would just almost set back the whole process even  
12 further. I don't know.

13 MEMBER BOTKIN: Jeff Botkin. A couple  
14 of thoughts.

15 And I think as the pilot group sort of  
16 thought about this identify one baby, I think  
17 that really was intended for a couple of things  
18 that may be worth unpacking here.

19 One was just to try to give some ball  
20 park for the sort of size of study we're talking  
21 about. As we talked a little bit earlier, it  
22 wouldn't be appropriate to say you have to have a

1 prospective population-based study, but you're  
2 done after the first thousand babies.

3 Or on the other hand it wouldn't be  
4 appropriate to say well, we kind of like 20 or 30  
5 affected babies followed over 5 years because  
6 that would really give us some excellent data to  
7 make a decision. You have to find something in  
8 the middle.

9 So, I wouldn't necessarily personally  
10 consider that to be a hard and fast condition and  
11 be a deal-breaker in this situation when there's  
12 other information.

13 But the question I would have is  
14 whether there's other information that might be  
15 fostered by a recommendation to look for more  
16 data before formally going forward.

17 One's sort of the natural history.  
18 And I do think the fact that you've got lots of  
19 negatives with a million babies without false  
20 positives is very helpful.

21 If you had had 40 false positive  
22 babies in the first 100,000 kids that would be

1 very informative. So the fact that we've got  
2 zero, that too is informative in a good way.

3 I don't have a good feel for  
4 population prevalence at this point. You know,  
5 at 110 babies in the literature there's got to be  
6 lots of babies out there that never made it to  
7 the literature. Is there a way to collect  
8 information from clinicians who are likely at the  
9 bottom of the referral pattern for these kids to  
10 get a better estimate on what the population  
11 frequency is for this condition.

12 And then it sounds like with Nicole's  
13 other publication there's additional information  
14 that might be reviewed in terms of the test  
15 performance as well as potentially some short-  
16 term fairly quick studies that could be done  
17 retrospectively with blood spots.

18 So I guess my question is would an ask  
19 for more data decision by the committee at this  
20 point prompt that additional data to come  
21 together in a way that a going to evidence review  
22 decision wouldn't.



1                   MEMBER MCDONOUGH: This is McDonough.  
2                   Second Don's motion.

3                   MEMBER MATERN: Just one comment.

4                   MEMBER BAILEY: I didn't really make  
5                   a formal motion, but I will eventually. When  
6                   it's time I'll be glad to.

7                   MEMBER MCDONOUGH: I thought I --  
8                   okay. That's my fault. When he does I'll second  
9                   it.

10                  MEMBER MATERN: While you find the  
11                  microphone if I might just point out that in the  
12                  paper here there is also a mention of this kind  
13                  of registry that they wanted to implement.

14                  Now, this was published in 2014 and if  
15                  you click on this it will not get you anywhere.

16                  I sent an email to Dr. Stuckler and  
17                  asked her whether this is close to being live and  
18                  I didn't get a response yet.

19                  MS. GREENE: Carol Greene, SIMD. Two  
20                  things. The quicker one first.

21                  To contribute I hope to the  
22                  committee's discussion about whether or not to

1 accept the recommendation of the review  
2 committee.

3 And that is the recommendation had two  
4 parts to it. One was based on the judgment that  
5 treatment was not yet. And I really do feel  
6 strongly that there needs to be some further  
7 guidance about what's meant by that because I  
8 really do think, and I think all the clinicians  
9 would say treatment is a yes on that one.

10 So that the recommendation wouldn't be  
11 based on something to do with the pilot and  
12 having guidance for treatment, but I would take  
13 off that for the treatment.

14 I think there is enough to go forward  
15 with treatment. That's just speaking as SIMD  
16 trying to offer that for the discussion of the  
17 committee.

18 The second thing is that perhaps what  
19 I'm hearing people trying to do with the studies  
20 should have at least one positive, but yes, of  
21 course if your positive is in the first thousand  
22 you can't stop there.

1           That maybe if the language of that was  
2 perhaps rewritten to say something like that the  
3 sample size should be sufficient, should be twice  
4 the expected prevalence or something so that  
5 you'd have a good chance of picking up at least  
6 one, and you'd know something about the false  
7 positives.

8           And I think what are the chances in  
9 the first million you don't pick out one of the  
10 four in that million that would be affected? I  
11 don't know the number, but it's a reasonable  
12 number.

13           So maybe if instead of sticking with  
14 the first positive you say that the pilot study  
15 size should be roughly twice your expected  
16 prevalence. And then you will have data, and you  
17 combine it with the historic and you'll have that  
18 data.

19           And the reason that I put that forward  
20 in this context is because I really want to  
21 support those who have said if you don't stick  
22 with your own guidelines you're going to lose the

1       credibility and the sense that you are -- I  
2       forget which group came and said that we're going  
3       to depend on you to do our evidence review.

4                If we don't stick to our own  
5       guidelines you lose that. And that's why states  
6       don't accept it. They want to do their own  
7       evidence review because we don't follow our own  
8       rules.

9                MS. TARINI: Beth Tarini, AAP. Quick  
10      question.

11               The previous examples where there were  
12      no children identified from prospective  
13      screening, was that vote for evidence review?  
14      Dieter brought this up I thought, but wanted  
15      clarification.

16               Were those votes for evidence review,  
17      or were those votes for nomination to the RUSP?

18               The reason I ask is because if it's  
19      the latter then this is not necessarily a  
20      deviation from procedure that we're voting to add  
21      to the RUSP when those votes said come back after  
22      you find a case.

1           MEMBER MATERN: I think it's all about  
2 determining whether we send it forward to the  
3 evidence review.

4           MS. TARINI: My point is the  
5 conversation here is about concern about  
6 deviation from protocol. And I'm trying to  
7 determine if this actually matches the protocol  
8 we think we're deviating from.

9           In the past when there was no case and  
10 we said no, come back when there's a case, were  
11 we saying no to evidence review, or were we  
12 saying no to addition to the RUSP?

13           MS. SARKAR: So, this is Debi. For X-  
14 ALD it was no to move it for evidence review.

15           MS. BONHOMME: Natasha Bonhomme,  
16 Genetic Alliance.

17           My comments kind of go to some of the  
18 things that have already been said. More so not  
19 whether this should be in, or whether this should  
20 move forward or not, but really the issue of  
21 communicating this out.

22           I think the fact that we've had about,

1 what, a 30-minute or so conversation about is  
2 this consistent or is it not is something that  
3 should be noted.

4 And that whatever the communication is  
5 that goes back to the nominators and back out to  
6 the public around this clearly lays out why this  
7 does or does not go, and clearly the next steps.

8 Because this is an issue that has come  
9 up with other conditions that have gone through  
10 the process. And to have the parents and the  
11 public become really frustrated with this process  
12 because it seems very convoluted and not clear  
13 when you have people who say this seems like a  
14 slam dunk, or this seems like a go, but it isn't.

15 I think we just need to be really  
16 careful about the communication that goes along  
17 with this because I think there could be an  
18 opportunity for clarity, but also clearly an  
19 opportunity for more confusion out to the public  
20 in terms of what is this process in terms of  
21 adding conditions to the RUSP.

22 And then also our having conversations

1 of why are advocates going straight to states to  
2 get these things. Shouldn't they go through the  
3 RUSP.

4 But clearly that's -- even for a  
5 condition that some would say is very obvious  
6 it's not clear.

7 And so I just really want whatever the  
8 communication is that goes back out to the world  
9 around this that there's just real attention to  
10 clarity in terms of why you choose what you  
11 choose to do, and the right next steps for  
12 families to follow up, or for the nominators to  
13 follow up.

14 MEMBER LU: I guess this will come  
15 down -- this decision to move it forward will  
16 come down to whether or not there is a case of  
17 true positive.

18 And I'm getting increasingly concerned  
19 whether that is misplaced.

20 I guess the argument I hear, one is  
21 that it helps -- having a true positive helps  
22 establish prevalence and predictive value. And

1 if you think about it, how valid is it to have  
2 one case as a numerator to help you establish  
3 that population prevalence, or predictive value.

4 And then the second is to establish  
5 that in terms of treatment efficacy and what  
6 Carol's saying. Again, I'm not sure how much  
7 information treatment efficacy from one case will  
8 tell you versus all the other information that we  
9 already have.

10 So again I think, I know that's the  
11 guidelines that we have around pilot studies, but  
12 I'm wondering whether we're placing too much  
13 confidence in waiting for that one case of true  
14 positive.

15 CHAIR BOCCHINI: So, I guess the  
16 important thing is would everybody be comfortable  
17 to approve something to be placed on the RUSP  
18 without having any baby identified by newborn  
19 screening?

20 I mean, to me that's the crux of the  
21 argument. And I think that was part of the  
22 argument for SCID as to why it wasn't recommended



1 for the RUSP until that positive occurred.

2 I think that's the one question we  
3 need to feel comfortable with if you're going  
4 forward and then don't have that.

5 MEMBER MCDONOUGH: This is McDonough.  
6 Yes, I would be. And if we have to eventually  
7 get to the point with such conditions that are so  
8 rare to say, okay, we think the evidence looks  
9 good. We're going to try this. We're going to  
10 give it three years. And if we haven't picked up  
11 any cases then we'll stop doing it.

12 I would rather that this committee  
13 work on identifying cases to help these kids and  
14 families out, and err maybe on the side of, well,  
15 maybe we shouldn't have done this. As long as  
16 it's not causing harm.

17 Again, if California was doing the  
18 pilot study, was doing their state we would  
19 probably have evidence pretty quickly where there  
20 are a large number of births. But if it's just  
21 going to be Utah it's going to take a long time.

22 So, I would answer yes to that.

1 Looking at the preponderance of information that  
2 we have with these rare conditions that we need  
3 to take that leap forward, that we have faith in  
4 our public health labs that they can do the  
5 testing appropriately.

6 And if we did it wrong and we didn't  
7 pick up cases that we can back off from that.  
8 But that's better than letting these kids not be  
9 diagnosed and being damaged because that's the  
10 thing we don't -- the longer we wait, we don't  
11 have these families coming back.

12 And you're taking a look at the kids  
13 and saying okay, we didn't do this and this is  
14 what happened. We don't see that.

15 MEMBER BAILEY: So, just to follow up  
16 on that a little bit.

17 And this shows how complicated these  
18 decisions are for us really, and especially again  
19 for rare conditions.

20 If you think about some of the other  
21 conditions we've reviewed. So if this disorder  
22 had a very expensive laboratory test, if it made

1 a lot of errors in the test, if the treatment had  
2 to be a stem cell transplant or some other  
3 particularly dangerous treatment, or if it  
4 identified children with many different severity  
5 types that we didn't know whether to treat a  
6 child or not treat a child, having to make all  
7 those complicated decisions, then I would say  
8 yes, we need more -- I would feel less confident  
9 about screening for a condition, adding a  
10 condition that we never had.

11 But we're not talking about that here.  
12 So I would feel, and I'm not voting to put it on  
13 the RUSP yet, because I think we still need to go  
14 through this process and get a little bit more  
15 data.

16 But I still feel what I said earlier  
17 that I'm willing to take that chance and move  
18 forward for the evidence review.

19 CHAIR BOCCHINI: Well, I think if  
20 we've completed the discussion then we are open  
21 to take a -- if someone wants to make a motion.

22 MEMBER BAILEY: Well, does the

1 recommendation of the nominating committee not  
2 constitute a motion?

3 CHAIR BOCCHINI: It does not. It  
4 opens the opportunity for discussion. The  
5 nomination needs to come from the committee. I'm  
6 sorry, the motion needs to come from the  
7 committee.

8 MEMBER BOTKIN: Yes, Jeff Botkin. I  
9 just recognized how very difficult this is for  
10 everybody. I'm going to move to support the  
11 recommendation of the Nomination Committee.

12 MEMBER KELM: Second.

13 CHAIR BOCCHINI: Moved and seconded  
14 that the recommendations of the Nomination and  
15 Prioritization Committee be accepted.

16 We'll now do a -- no, no, there is  
17 time for discussion before vote.

18 MEMBER WICKLUND: Is this implying  
19 also that there has to be an identified case? I  
20 mean, what I'm saying is that in order to move it  
21 forward is this recommending that there has to be  
22 an identified case before they can bring it back

1 to us?

2 CHAIR BOCCHINI: It does. But in  
3 addition, I think based on the discussion we  
4 certainly can add that additional information can  
5 be brought forward. If there is a repository  
6 that has blood spots that can be looked at  
7 retrospectively and other things that were  
8 mentioned, that that can come forward as well.  
9 Dieter?

10 MEMBER MATERN: Well, I think we know  
11 already now that there is a repository, so what  
12 are they supposed to tell us? As you've just  
13 heard already at the meeting there is a  
14 repository.

15 CHAIR BOCCHINI: So, the  
16 recommendation does certainly continue to include  
17 the finding of a case.

18 MEMBER BAILEY: Call the question.

19 CHAIR BOCCHINI: So, the motion is to  
20 accept the recommendation of the Nomination and  
21 Prioritization Committee that we do not initiate  
22 external evidence review, but that we recommend

1 that the proponents work with other experts to  
2 formalize treatment guidelines. And that  
3 certainly doesn't mean that treatment guidelines  
4 -- I mean, it would certainly just improve the  
5 consensus, but it doesn't mean that treatment is  
6 not appropriate. But we can discuss that.

7 And encourage continuation of newborn  
8 screening prospective studies in Utah and  
9 Australia, and then report as soon as possible  
10 when a patient has been identified prospectively.  
11 And that the plan would be to move, if that's  
12 accepted, then move that forward to evidence  
13 review upon achievement of that milestone.

14 MEMBER MATERN: One more. So, if you  
15 were against it does it mean automatically if  
16 there was a majority to vote against this motion  
17 that it would motion towards the evidence review?

18 CHAIR BOCCHINI: No, it would mean  
19 there would need to be a second motion for that.  
20 So, Don Bailey.

21 MEMBER BAILEY: No.

22 CHAIR BOCCHINI: So, I'm going to vote

1       yes.   Dr. Botkin?

2                   MEMBER BOTKIN:   Yes.

3                   CHAIR BOCCHINI:   Carla Cuthbert.

4                   MEMBER CUTHBERT:   Yes.

5                   CHAIR BOCCHINI:   Catherine Spong.

6                   MEMBER SPONG:    No.

7                   CHAIR BOCCHINI:   Kellie Kelm.

8                   MEMBER KELM:     Yes.

9                   CHAIR BOCCHINI:   Fred Lorey.

10                  MEMBER LOREY:    Yes.

11                  CHAIR BOCCHINI:   Dieter Matern.

12                  MEMBER MATERN:   No.

13                  CHAIR BOCCHINI:   Steve McDonough.

14                  MEMBER MCDONOUGH:   No.

15                  CHAIR BOCCHINI:   Kamila Mistry.

16                  MEMBER MISTRY:   Yes.

17                  CHAIR BOCCHINI:   Michael Lu.

18                  MEMBER LU:       No.

19                  CHAIR BOCCHINI:   Alexis Thompson.

20                  MEMBER THOMPSON:   Yes.

21                  CHAIR BOCCHINI:   And Cathy Wicklund.

22                  MEMBER WICKLUND:   I'm going to say no.

1                   CHAIR BOCCHINI: Okay. Well, thank  
2 you all very much. I know that was a very  
3 important but very difficult and complicated  
4 decision to make.

5                   I have seven yes and five no so the  
6 outcome is that -- six, I'm sorry. All right,  
7 just to be sure, seven yes. Okay.

8                   So, I think the important thing is  
9 that we all feel this is a strong nomination and  
10 that we would like to have the data necessary to  
11 move forward as soon as possible. So thank you  
12 all very much for that.

13                   And we want to thank the families for  
14 being here to make the case of how important this  
15 is for us.

16                   So with that that will conclude this  
17 session. We do have the workgroups meeting. And  
18 Debi, do you want to go through where the  
19 location is of each of the meetings for the  
20 workgroup?

21                   MS. SARKAR: Just before, do you want  
22 to just clarify what the final vote is?



1                   CHAIR BOCCHINI: Okay, so the final  
2 vote was in favor of the recommendation of the  
3 Nomination and Prioritization Committee to -- not  
4 to initiate external evidence review at this  
5 time.

6                   MS. SARKAR: And we will follow up  
7 with the nominators with next steps.

8                   CHAIR BOCCHINI: Right.

9                   MS. SARKAR: So, we will have our  
10 three standing workgroups meeting this afternoon  
11 until 5 p.m.

12                   The Education and Training Workgroup  
13 will be meeting here in this building. The  
14 Follow-up and Training Workgroup and the  
15 Laboratory Standards and Procedures Workgroup, if  
16 we could all meet upstairs by the café within the  
17 next 10 minutes we need to walk across the street  
18 to 5600 Fishers Lane.

19                   You'll need your driver's license, a  
20 picture ID. You'll have to sign in, go through  
21 security. We will have HRSA staff there to  
22 escort you to the meeting rooms.

1                   So, Laboratory Workgroup and Follow-up  
2                   and Training Workgroup members, please meet us  
3                   upstairs in 10 minutes. Thank you.

4                   (Whereupon, the above-entitled matter  
5                   went off the record at 3:09 p.m.)

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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  
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Court Reporter

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