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4 ALTARUM

5 DEPARTMENT OF HEALTH AND HUMAN SERVICES/HEALTH

6 RESOURCES AND SERVICES ADMINISTRATION

7 Meeting of the Advisory Committee on Heritable

8 Disorders in Newborns and Children

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11 8:30 a.m.

12 Thursday, January 21, 2010

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17 Washington Marriott at Metro Center

18 775 12th Street, N.W.

19 Washington, D.C. 20005

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1 COMMITTEE MEMBERS

2 Rebecca H. Buckley, M.D.

3 Bruce Nedrow Calonge, M.D., M.P.H.

4 Kwaku Ohene-Frempong, M.D.

5 R. Rodney Howell, M.D.

6 Jana Monaco

7 Piero Rinaldo, M.D., Ph.D.

8 Michael Skeels, Ph.D., M.P.H.

9 Tracy L. Trotter, M.D., F.A.A.P.

10 Gerard Vockley, M.D., Ph.D.

11 Duane Alexander, M.D.

12 Coleen Boyle, Ph.D., M.S.

13 Denise Dougherty, Ph.D.

14 Peter C. van Dyck, M.D., M.P.H., M.S.

15 Michele A. Lloyd-Puryear, M.D., Ph.D.

16 Frederick M. Chen, MD, MPH, FAAFP

17 Timothy A. Geleske, MD, FAAP

18 Michael S. Watson, Ph.D., FACMG

19 Thomas Musci, M.D.

20 Jane Getchell, Dr. PH.

21 Christopher Kus, M.D., M.P.H.

22 Bennett Lavenstein, M.D.

1 Mary J. H. Willis, M.D., Ph.D.

2 Sharon F. Terry, M.A.

3 Alan R. Fleischman, M.D.

4 Barbara K. Burton, M.D.

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

2 DR. HOWELL: Ladies and gentlemen, let me
3 encourage you to find a seat. Let me welcome
4 this very large and distinguished group to the
5 20th meeting of the Secretary's Advisory
6 Committee on Heritable Disorders in Newborns and
7 Children. And before the business of the
8 morning Dr. Puryear has some housekeeping notes.

9 DR. PURYEAR: And I apologize, I'm getting a
10 cold. When exiting the General Session the
11 restrooms are down the hallway to the left.
12 Altarum staff, Maureen, Rebecca, Tiffany will be
13 at the registration desk to direct and assist
14 attendees and answer any questions that may
15 arise about logistics.

16 Continental breakfast and lunch will be
17 provided to committee members and
18 representatives and presenters and will be in
19 the Junior Ballroom, Salon 1 on the 2nd floor.
20 On Thursday in Salon B; next to the committee on
21 Friday.

22 The dinner reservations for 6:30 at the Fire

1 and Sage Restaurant, which is located on the
2 lobby level here in the hotel. The restaurant
3 has asked us to please bring cash instead of
4 credit cards.

5 The pre-set menu has been chosen already and
6 can be viewed at the registration desk for a
7 total cost of \$46.00 per person plus tax and
8 gratuity, and of course alcohol is an additional
9 cost.

10 The sub-committee meetings will be held 3:00
11 to 5:30 today. Laboratory standards is in the
12 Junior Ballroom on the 2nd floor of Salon 1.
13 Follow-up and Treatment, Junior Ballroom, Salon
14 2 on the 2nd floor. And Education and Training
15 is in Salon 3, again on the 2nd floor.

16 If any of the presenters have changed their
17 presentations after submitting them, please save
18 the revised copy of your presentation on the
19 laptops and include your name and the title of
20 the presentation. We need that for the
21 committee website.

22 Committee members, organization
1 representatives, and presenters should stop by
2 the registration desk to upload the Briefing
3 Book supplement. And I want to right now
4 confirm that Dr. Skeels and Dr. Chen are on the
5 phone. Are you guys?

6 Unknown Male Speaker: Not yet.

7 DR. PURYEAR: Not yet?

8 Unknown Male Speaker: Not yet.

9 DR PURYEAR: Not yet. Okay, we ask that
10 you remove your Blackberrys from the tabletop
11 and the microphones --

12 Unknown Speaker: [Off-Mike.]

13 Dr. PURYEAR: Pardon me? Microphones are on
14 all the time, so remember that. Microphones are
15 not off; they're on all the time. And we are
16 recording this meeting so please bring the mike
17 close to you when you talk. And that's it.

18 DR. HOWELL: We have recorded all the evil
19 things you said before you were told the
20 microphones were on.

21 [Laughter.]

22 DR. HOWELL: Our last meeting was Dr. Duane

1 Alexander's last meeting and we certainly will
2 be looking forward to preparing some appropriate
3 recognition for him in the future. Duane has
4 been a member of this committee since its
5 inception and has been a very active and
6 important participant. And we will miss his
7 wise counsel.
8 However, we're extremely pleased that Dr.
9 Collins has appointed Dr. Alan Guttmacher as the
10 NIH representative to this committee. And Alan
11 will be here later today. He has some downtown
12 business to take care of this morning and this
13 afternoon, but he'll be here during the lunch
14 period and he'll be here all day tomorrow.
15 Dr. Guttmacher came to the National
16 Institutes of Health in 1999 to work in the
17 National Human Genome Research Institute where
18 he served a number of roles including Deputy
19 Director from August of '88 to 2009. And more
20 recently, during the past year as Acting
21 Director of that institute.
22 He has been particularly active in a variety

1 issues, but particularly the ethical, legal, and
2 social implications of human genomics. Alan
3 came to the NIH from the University of Vermont
4 where he directed the Vermont Regional Genetic
5 Center and was very active in working with the
6 Newborn Screening Program in Vermont.
7 Vermont, as you probably know, has a
8 centralized high risk program at the University
9 of Vermont. The only pediatric intensive care
10 unit is at the University of Vermont. And he's
11 been very active in this area and I'm sure he'll
12 be an active and interesting participant.
13 Before we get on with the business of the
14 day we need to review the minutes of 2009
15 September. And that's in Tab 5 of your book. I
16 have an honest to goodness book. For the rest
17 of the folks here, it'll be in Tab 5 on your
18 thumb drive.
19 Are there objections or changes to the
20 minutes that we need to note?
21 [Pause]
22 DR. HOWELL: Hearing no changes, can we have

1 a motion to approve the minutes?
2 DR. TROTTER: So moved.
3 DR. HOWELL: And second?
4 Unknown Male Speaker: Second.
5 DR. HOWELL: Those favoring?
6 [Chorus of Ayes.]
7 DR. HOWELL: Thank you very much. I might
8 point, as I think as everybody knows, the
9 minutes of the committee are posted on the
10 website. And judging from the comments and
11 questions I get periodically, there are a number
12 of people that do read our minutes and look at
13 them. So we need to be careful that they are
14 proper, et cetera.
15 We need to recognize in notes Committee
16 Correspondence, which is also included in your
17 Minutes. We have two letters from the Claire
18 Heine Foundation, Heine Foundation. One is a
19 request to form a group to discuss carrier
20 screening for SMA as well as other conditions.
21 And a copy of the letter from the same
22 foundation to the National Institutes of Health
1 concerning the same issue.
2 We also have a copy in your notes of the
3 letter on the Secretary's Stance on the ACMG report.
4 We have a letter from the Secretary in response
5 to our recommendations on legislation for
6 medical foods and formula.
7 And you have a final letter from the
8 Secretary that's included in your materials
9 today. Secretary Sebelius has been extremely
10 responsive to the material we have sent forward
11 to her. And we appreciate that a great deal.
12 The other thing is that you have gotten a
13 note about nominations for individuals to serve
14 on this committee. And let's have a lot of good
15 nominations that can be considered for this
16 committee to replace persons who will be leaving
17 the committee.
18 I might point out that we will discuss the
19 Heine Foundation request on carrier screening
20 when we discuss Sickle Cell disease tomorrow.
21 So if that's good with you. In your briefing
22 book you will see nomination forms and summary
1 of the reviews from the internal workgroup.
2 As you all very much remember, when a

3 nomination is reviewed by the staff at HRSA and
4 found to be complete, an internal review group
5 then looks at the documentation carefully to see
6 whether or not they would recommend sending this
7 nomination forth for evidence review. And
8 evidence review is a big deal.

9 So we would like to be certain if a
10 nomination is, would appear to be appropriate
11 for further consideration. And we have two to
12 consider today.

13 We have Hyperbilirubinemia and the
14 Congenital Heart Disease. Drs. Bhutani and
15 Koppel are said to be available by telephone.

16 I'm not sure that is indeed the case. But we --
17 Unknown Speaker: [Off-Mike.]

18 DR. HOWELL: Oh, Dr. Bhutani is here. So if
19 you have questions, he is here in the flesh so
20 that's great. And we also will be discussing it
21 so. First, Dr. Rinaldo will lead this
22 discussion. And the first nomination to be
1 considered is that of hyperbilirubinemia.

2 DR. RINALDO: [Off-Mike.]

3 DR. HOWELL: Wherever you would be
4 comfortable. Up here's probably a little bit
5 better.

6 [Discussion off the record.]

7 DR. RINALDO: Okay, good morning. I'm here
8 to present or summarize for the whole committee
9 the work done by the Review and Prioritization
10 Group. We were asked to consider two
11 nominations. And this is again, the work that
12 is best when presented in this light. Basically
13 when a nomination comes in there is the
14 administrative review from HRSA.

15 And eventually it will come to the
16 committee. The committee will decide if it
17 worth -- or is appropriate to send it to the
18 Evidence Review Group. And there is a back and
19 forth process. And eventually led to
20 recommendation to the HHS Secretary.

21 Now what we're talking about here is that
22 intermediate step where a sub-group of the
1 committee reviews the nominations and comes up
2 with really a recommendation to the whole
3 committee. There are six members, they're all
4 here.

5 And they, again, the job is to provide you
6 know, an opinion about the appropriateness of a
7 submission. And eventually, if there are more
8 than one submission, like we are dealing with --
9 the situation we are dealing with today, what
10 order of submission to, of the nomination to the
11 Evidence Review Group.
12 The form that has been prepared by HRSA, it
13 concludes six points and our overall
14 recommendation. And what I've done here is just
15 taken the summary of the comments of all the
16 committee members and just put it in a way that
17 not only would committee member, but everybody
18 else could actually be able to read it. Because
19 I don't think that showing this slide would help
20 a lot.
21 [Laughter.]
22 So we're just taking each and every piece.

1 And here, simply the reporter of the group, this
2 summaries were put together by Michelle mostly.
3 But I'm just going through the six point for the
4 two nominated conditions.
5 Again, the first one is bilirubin
6 encephalopathy and kernicterus. And it was
7 pretty much obvious consensus of the working
8 group that this is obviously a serious condition
9 that may cause permanent damage.
10 This is, again, an extension of the
11 discussion of the issue about perspective pilot
12 data from population based assessments are
13 available. And the answer is, yes prospective
14 studies have been conducted in the United States
15 and there are a number of very specifically
16 references.
17 And again, the numbers here refers to the
18 references listed in the nomination form that
19 are reference to work done in Pennsylvania,
20 Utah, and Israel.
21 Again, in case of these are the sort of the
22 titles of the three papers. They're all papers
1 published in Pediatrics that are easily
2 accessible through PUBMED or whatever you do for
3 your library.
4 The spectrum of the disorders, the third
5 question is; the spectrum of this disorder is

6 well described, to help predict the phenotypic
7 range of those children who will be identified.
8 And again, I understand Dr. Bhutani is here. So
9 I feel that probably we can allow to interject
10 if there is any relevant point to be made.

11 The issue is about you know, if all children
12 identified will eventually need treatment, and
13 the answer is no. But again, there is what is
14 now known as the Bhutani Protocol, a way to
15 clearly decide that. And there is a nomogram
16 that predicts the risk. And actually, this is
17 taken from his 1999 publication.

18 And I believe this is, as been described
19 repeatedly, as the gold standard in the field as
20 a way to assess the level of serum bilirubin in
21 the context of world risk there is for
22 encephalopathy and kernicterus.

1 The fourth question is, the characteristics
2 of the screening tests are reasonable for the
3 newborn screening system. Now here it's, in a
4 sense, is a very different world. Because we no
5 longer look at centralized testing but really,
6 of testing done at the birth place. And so it's
7 a different situation.

8 And eventually I think it would be an
9 interesting discussion for this committee as we
10 look at the existing testing done for hearing
11 disorders. And the possibility of screening for
12 hyperbilirubinemia and for critical congenital
13 heart disease.

14 So it would probably create an issue of how
15 this thing would be performed and perhaps
16 integrated. Again, no longer at the centralized
17 public health level but rather at the periphery
18 in each birth place.

19 There is here, again, the reference one
20 implies a false positive rate of approximately 2
21 percent. That could be a little of concern.

22 But certainly something worth monitoring very
1 carefully. And certainly something to ask
2 elements of your group to comment on it. And
3 again, this nomogram is used now very widely.
4 And so -- and again, it goes back to the gold
5 standard.

6 The fifth question is, if the spectrum of
7 disease is broad, those who are the most likely

8 to benefit from treatment are identifiable. And
9 there are risk factors. But the point is, that
10 these risk factors are now consistently
11 considered.

12 And as such, as you see at the end, the
13 infant most likely benefit is one whose risk
14 factor were not perceived during the short
15 hospital stay and who did not have a bilirubin
16 level measured. So again, the possibility of
17 things being there but not being adequately
18 considered is high.

19 And so, the treatment is well established,
20 phototherapy and exchange transfusion. These
21 are accepted practice in neonatology. So it's
22 really nothing new here.

1 So in the end, the recommendation to the
2 committee from the Review and Prioritization
3 Workgroup is summarized here. Gravity and
4 ability to prevent hyperbilirubinemia and
5 kernicterus are compelling reasons to screen in
6 the newborn period. The Internal Nomination and
7 Prioritization Workgroup recommends forwarding
8 the nomination package to the Evidence Review
9 Group.

10 I don't know if you want to sort of have
11 questions, discussions separately or for both
12 together. That's really up to you.

13 DR. HOWELL: I think, I would think we
14 should do them independently.

15 DR. RINALDO: Okay. So this is the, sort of
16 finest light related to this nomination. And
17 again, I'm here really as a reporter. I can
18 only say that the discussion of the group was
19 very much in consensus on certainly the validity
20 of submitting this to the Evidence Review Group.

21 DR. HOWELL: And the group that met, that
22 you are discussing, was consistent in it's
1 recommendation that it go forth?

2 DR. RINALDO: Yes.

3 DR. HOWELL: Everybody on the committee. I
4 see Dr. Bhutani here, and I think maybe we could
5 ask, since he's come from California and did the
6 nomogram that you referred to. Maybe we could
7 ask him to make a few comments before we have it
8 open for discussion. Dr. Bhutani?

9 Unknown Male Speaker: You might want to

10 come --

11 DR. HOWELL: You want to come to a
12 microphone? There seems to be one down here,
13 complete with a chair.

14 [Laughter.]

15 DR. BHUTANI: A very good morning to
16 everybody and to all of you and thank you for
17 this opportunity. Bilirubin screening has been
18 an issue that has confronted us pediatricians
19 for many, many years now.

20 And I think with the evidence that has been
21 gathered over the last few years, the expert
22 panel at the American Academy of Pediatrics that

1 comprised Dr. Jeffrey Maisels, Dr. Tom Newman,
2 and of Ann Stark, John Watchko, and myself, also
3 recommended when it was bilirubin screening,
4 based on the evidence that was available.

5 It has been practiced at most academic
6 hospital centers and most of the large regional
7 network centers across the U.S. And the data
8 that is forthcoming shows that it does reduce
9 the incidents of severe hyperbilirubinemia.
10 Whether it actually reduces the incidents of
11 kernicterus or not is too early to say. But we
12 do know now that the incidents of kernicterus in
13 the U.S., as reported in Pediatrics last year,
14 is about 1 in 38,000 newborn infants. So
15 clearly the disease burden is real. It is
16 highly preventable and I think the evidence is
17 very sound at this time. Thank you.

18 DR. HOWELL: Thank you very much Dr.
19 Bhutani. I wonder if we could have comments
20 from the members of the committee about this
21 recommendation that it move forward for formal
22 evidence review. Denise?

1 DR. DOUGHERTY: I have a question. Because
2 the U.S. Preventative Services Task Force
3 recently reviewed bilirubin screening and did
4 not recommend it, if I recall correctly; and
5 maybe Ned can explain. That wasn't included in
6 your overview here.

7 But I'm wondering, if we could get some
8 background on that to see if we really should
9 recommend this.

10 DR. HOWELL: Well the background can be

11 provided by the Chief of the committee. Ned.
12 DR. CALONGE: Well let me first correct the
13 wording that the finding of the task force was
14 insufficient evidence to recommend for or
15 against. One of the problems is, we don't have
16 any direct evidence, and we still don't have any
17 direct evidence, and we may not have direct
18 evidence.

19 And I think that our Evidence Review
20 Committee is going to actually have to deal with
21 the fact that the evidence is going to have to
22 be pieced together from non-direct, non-
1 randomized control trial purchase, which our
2 methods allow for and is completely appropriate.
3 I think the task force was struck by the
4 fact that, at the time, and already the evidence
5 is even changing, it was difficult to develop a
6 direct link between screening and prevention of
7 kernicterus. And that's the linkage I think is
8 a little tougher.

9 So when you heard a little bit around the
10 edges, there is kernicterus without
11 hyperbilirubinemia. There is severe
12 hyperbilirubinemia without kernicterus. And the
13 linkage of lowering bilirubins through
14 phototherapy is shown to reduce bilirubin levels
15 and additions from hyperbilirubinemia. But the
16 linkage to the actual disease hasn't been made.

17 So it's going to be something that this
18 committee will have to wrestle with I believe
19 the same way the task force wrestled with it.
20 But I don't think that's an inappropriate thing.

21 Plus, new evidence on the incidents, it's
22 surprising since the existing evidence was,
1 let's say, about 1 in a million; .9 per 100,000
2 I think was actually the number.

3 So getting your hand on what the burden of
4 the disease really is, and evolving the
5 information between this universal screening and
6 reduced -- reduction not of hyperbilirubinemia
7 but the condition we're interested in is what we
8 need.

9 I will caution the committee that that
10 evidence I believe is emerging and we may be
11 stuck with the issue that our evidence review
12 will precede the actual final answer. But

13 that's where the task force was.

14 So as I look at the review I think the
15 incidence issue is important. And the evidence
16 committee should start with the existing tough
17 evidence based practice review which looks at
18 all the recent data plus a bridge search from
19 where that stopped and where we are now.

20 DR. HOWELL: Thank you very much. Are there
21 further comments? Gerry?

22 DR. VOCKLEY: One question and one comment.

1 The question may well just be best put off until
2 the more extensive review, assuming it happens.
3 That 2 percent false positive that you referred;
4 was that -- how was that defined? Were those
5 individuals who had a high level and then didn't
6 have disease? Or was there something, something
7 wrong with their actual measurements?

8 DR. RINALDO: If I recall, but again, having
9 Dr. Bhutani here, perhaps it's easier to ask
10 him. I think these are based on the number of
11 readmissions because of elevated -- is that
12 correct Dr. Bhutani?

13 DR. BHUTANI: I didn't hear.

14 DR. VOCKLEY: The comment was that --
15 agreeing with Ned that this committee will look
16 at things slightly differently. Because we're
17 used to piecing together evidence that might not
18 in any individual component fit the definition
19 of true old, I'll call it old fashioned,
20 classical; there you go, classical evidence
21 based review. It doesn't mean that we can't put
22 it together. And so I do think it's worth going
1 forward.

2 DR. HOWELL: Ned, you had some comments?

3 MR. CALONGE: Thanks. Dr. Howell. I did
4 think that -- I mean my biggest interest in the
5 area of emerging evidence. Because the task
6 force does have, you don't just look at
7 randomized control trials. They were unable to
8 comfortably make the link.

9 The other thing I really want to stress,
10 were I think there's a gap and that we're going
11 to have to wrestle with; is the harms associated
12 with screening and treatment. Because you know
13 we've generated an industry of phototherapy that
14 takes a child away from the mom at least for

15 some period of time, has been shown to interrupt
16 breast feeding.

17 I really think we need to be able to
18 adequately capture both the potential benefits,
19 which you know, there are a few gaps in making a
20 link. But for goodness sakes, we should be
21 addressing the harms as well because this is not
22 a -- the number of children under lights will
1 greatly exceed the incidents of kernicterus.
2 And trying to find the right balance I think is
3 going to be an interesting journey.

4 DR. HOWELL: We have Tim, then we have
5 Tracy, and then we have Chris.

6 DR. GELESKE: Just as a general pediatrician
7 you think about this every day. This is bread
8 and butter pediatrics, daily practice. And I
9 believe that this is probably becoming standard
10 of care in most areas of the country, at least
11 in our area it is. So no matter what our
12 decision may be, I think a more thorough
13 evaluation of the subject is important.

14 DR. HOWELL: Tracy.

15 MR. TROTTER: I echo exactly what Tim just
16 said. This is what's happening. And the three
17 hospitals that my group practice in, two of the
18 hospitals it is the mandate; they are all
19 tested, and one is not.

20 And so if we look at nationally this is
21 going on but without data, then even more
22 important that we look at it. And I think the
1 amount of data that's accumulated probably in
2 the last five years is going to be pretty
3 striking.

4 Because there are so many people online
5 doing this now, there probably are some numbers
6 that don't make sense. And it is, it is huge
7 problem. And I'm not surprised by the incidents
8 data just from the number of legal cases I've
9 been involved with as an expert. It's easily 1
10 in 40,000 cases.

11 DR. HOWELL: Chris.

12 DR. KUS: Can you again; how does the
13 committee answer the question about there is an
14 effective treatment to prevent or ameliorate the
15 disease? I mean it doesn't sound, from what you
16 were saying, that that's strong there.

17 MR. CALONGE: Well the problem is, is what
18 we have is an intermediate outcome. And the
19 intermediate outcome is hyperbilirubinemia. So
20 what the task force found is that the screening
21 tests are great, they find hyperbilirubinemia.
22 The treatment is great, it treats
1 hyperbilirubinemia.
2 The gap is between treatment of
3 hyperbilirubinemia and the prevention of
4 kernicterus. Because hyperbilirubinemia is not
5 a disease, it's a lab test. It's translating to
6 neurological damage caused by bilirubin toxicity
7 in the brain. And that link was where the task
8 force and the Tufts Evidence Based Practice
9 Center had trouble finding the link.
10 DR. HOWELL: I think the one thing, this
11 committee is charged with doing rigorous
12 evidence reviews on which we make decisions.
13 But we take the evidence review and then we make
14 decisions around that.
15 I think these are the things that Ned is
16 addressing something we should -- I think that
17 unless there are other compelling things, I
18 think we've heard significant reasons that the
19 committee might want to send this forth. Can we
20 have a nomination to that effect? A
21 recommendation to that effect?
22 DR. TROTTER: I submit we move this forward

1 for evidence review.
2 DR. HOWELL: Is there a second?
3 DR. BUCKLEY: I second.
4 DR. HOWELL: Those favoring that, say aye.
5 [Chorus of ayes.]
6 DR. HOWELL: Any opposition?
7 [No response.]
8 DR. HOWELL: Anyone abstaining?
9 [No response.]
10 DR. HOWELL: So it's a unanimous
11 recommendation that this go forward. So thank
12 you Piero. Okay, and now we'll move on to the
13 critical congenital heart disease.
14 DR. RINALDO: This is the second nomination.
15 I believe should be somewhere in your packet.
16 And again, I'm doing the same thing, breaking it
17 down in individual pieces.

18 Again, here we -- I think operability
19 between the number of C's. I've seen critical
20 congenital heart disease and critical cyanotic
21 congenital heart disease. So I don't know if
22 there should be a third C.

1 But that actually is not a trivial issue.
2 Because again, one of the thing is how effective
3 the existing, the existing test would detect
4 known cyanotic cases. In fact, there is a
5 reference with a table that is quite
6 informative.

7 So critical cyanotical, CCHD in brief, can
8 result in a hypoxic encephalopathy, multi-organ
9 injury, and death. About a quarter are missed
10 at birth and the infant is discharged only to
11 return with this serious complication already
12 in, in full clinical manifestation.

13 And congenital heart disease is still the
14 most common cause of death in the first year of
15 life. And according to this CDC report,
16 combined prevalence, correlation and hypoplastic
17 left heart is about 3 per 10,000 birth. So
18 quite a high frequency.

19 The second question is about prospective
20 pilot data. There are several pilot studies
21 that have been performed over the last 10 years
22 in the U.S. and elsewhere. And there was
1 consensus report in pediatrics surmising the
2 analogies of 120,000 infants.

3 And the conclusion of that document was to
4 recommend performing pulse oximetry after 24
5 hours of life with already a defined clinical
6 cut off where the abnormal results would be
7 saturation less than 95 percent.

8 The spectrum of disease. Here is again, a
9 situation where we really have to -- and this
10 was part of the discussion of the working group.
11 Exactly how vast this group is and how many
12 conditions are included. There were actually
13 some requests for clarification to the
14 proponents.

15 And I think again, their response was,
16 referring again to this table published in
17 Pediatrics last year. And you can see, this
18 goes back to the issue about the fact that not
19 all of these conditions will manifest with

20 hypoxemia. And so you can see here, is a pretty
21 complete list of all the conditions that could
22 be detected by doing oximetry.

1 Then I'm splitting here the answer to the
2 summary of the fourth question. In two slides
3 there is a, again, the pulse oximetry is
4 actually described as a fairly simple thing. At
5 least something simpler of what is -- what are
6 the requirements for the current hearing
7 screening.

8 And there is a possibility of a false
9 positive results, but that again, there is a
10 very simple hyperoxia test to eliminate a large
11 number of these potentially abnormal results.

12 So with that technique in place, you can see we
13 have already some data about specificity of 99.9
14 percent; sensitivity of 70 percent; positive
15 predictive value, 47 percent.

16 So basically one of two abnormal results
17 would basically be informative. And false
18 positive rate, I don't know if that is expressed
19 as a percent. But again, this is all published
20 evidence. So at first sight, this seems to meet
21 the expectation of good performance.

22 There is also some discussion about the
1 cost. Again, it's something that we do or we --
2 I don't know as to what extent we want to deal
3 with it. But again, it's fairly simple. At
4 least using as a reference the only current
5 physical screening and that's the hearing
6 screening.

7 In continuation, the confirmation is
8 actually quite easily available. And that's
9 through a echocardiography. It's not
10 everywhere, available everywhere, but in most
11 places. And so that certainly seems to be
12 doable. Especially now with the possibility of
13 sort of remote tele-medicine consultation
14 wherever it's not available on site.

15 Time is important. And so it's likely to be
16 effective and be able to come up with at least
17 strong evidence of an abnormal results and also
18 of a possible diagnosis in a short period of
19 time.

20 And again, this addresses the issue about
21 obviously you don't want to go and tell a parent

22 that the child may have a hole in their heart
1 and then later say, oops. But this is being
2 mitigated as much as is possible.
3 And obviously, the intervention is most of
4 the time surgical with catheterization. And
5 obviously there are risks related to this
6 procedure that are inherent to their nature.
7 And so in not so many words, the working group
8 also had a consensus to recommend, the whole
9 committee, to send this nomination to the
10 Evidence Review Group.
11 But things at the last light, is well the
12 decision has already been made on the first one,
13 assuming that the decision has been made also on
14 the second one we'll have to do perhaps a little
15 more delicate job to decide which one goes
16 first.
17 I believe the Evidence Review Group has one
18 nomination in their hands now, the Thalassemia
19 Hemoglobin H. And so this would be who goes
20 second and who goes third.
21 DR. HOWELL: Thank you very much Piero. Dr.
22 Mathurin is here I believe and might like to
1 comment. Well apparently Dr. Mathurin is not
2 here. So we will go ahead and open up the
3 discussion for the committee. Any comments from
4 the committee? Tracy.
5 DR. TROTTER: Yeah once again, it's shocking
6 here's two things we deal with all the time.
7 [Laughter.]
8 DR. TROTTER: And I certainly feel strongly
9 that this should go forward. I think that the
10 down sides to this are much more clear cut and
11 much minimal. Telling somebody that their baby
12 maybe has a hole in their heart and then doing a
13 echocardiogram and saying no it's really not or
14 it's a little plate in the foraminal valley is
15 to me not a big deal.
16 We do that all the time because we hear
17 something. This just makes it more efficient,
18 quicker, at a time when somebody's not going to
19 be compromised. I think this is, in my mind,
20 even cleaner than hyperbilirubinemia. I feel
21 strongly it's a good -- it should go forward to
22 the Evidence Review.
1 DR. HOWELL: Tim and then --

2 MR. GELESKE: I agree. Our community
3 hospital looked at this five years ago after our
4 practice lost a baby with a double outlet right
5 ventricle and an interrupted aortic arch, who
6 had been seen four times in the first week and
7 decompensated day 10 as the duct closed. And
8 there wasn't enough information for us to
9 evaluate to go forward. So I think it's
10 important for the committee to look at it and at
11 least make a recommendation.

12 DR. HOWELL: Thank you. Ned.

13 MR. CALONGE: So my comment has nothing to
14 do with the nomination of the form, but Piero's
15 last comment. So we're already in the area of
16 exceeding our capacity for doing reviews. That
17 didn't take long, which one might expect it.
18 I think we are going to have to spend some
19 dedicated time about how to prioritize the
20 number of topics given the restricted resource
21 we have available for the evidence reviews.
22 And I would think that at some point, a sub-

1 group of the committee talking about topic
2 prioritization will be important. Because which
3 one should we do first and what should be the
4 inputs to doing that.

5 Now when there's only two with one already
6 being reviewed it doesn't seem like much. But
7 if remember right there might be another 82
8 potential conditions that might be screened for
9 with candle mass spec alone.

10 And I think the committee is really going to
11 have to think about a prioritization scheme that
12 allows us to weigh which goes forward in order
13 to use up our precious resource.

14 DR. HOWELL: I agree with Ned except for the
15 fact that the number of potential diseases will
16 far exceed 82.

17 [Laughter.]

18 MR. CALONGE: I was just talking about TMS,
19 that's all I was.

20 DR. HOWELL: That's the low side.

21 MR. CALONGE: Yeah.

22 [Laughter.]

1 DR. HOWELL: Are there further comments?

2 [No response.]

3 DR. HOWELL: And I gather that Dr. Mathurin

4 is not here.

5 DR. DOUGHERTY: I have a question about the
6 bilirubin and forgive my ignorance. But is that
7 a heritable disorder?

8 MR. KUS: Yes, some.

9 DR. DOUGHERTY: Yeah, so --

10 MR. CALONGE: Is that a scope question?

11 DR. DOUGHERTY: Yeah, it's a scope question.

12 MR. CALONGE: Now it's scope and
13 prioritization. So you've got all the problems
14 --

15 MR. TROTTER: A substantial number. A
16 substantial number. Hyperbilirubinemia?

17 DR. DOUGHERTY: Yeah.

18 MR. TROTTER: A substantial number of --

19 DR. DOUGHERTY: Well kernicterus.

20 MR. TROTTER: -- serious, of critical
21 hyperbilirubinemia is heritable diseases, yes.

22 DR. DOUGHERTY: Okay.

1 DR. OHENE-FREMPONG: I think what you're
2 trying to say that they have an underlying
3 heritable disease.

4 MR. TROTTER: Yes.

5 DR. OHENE-FREMPONG: Not that
6 hyperbilirubinemia itself that is inherited in
7 most cases.

8 MR. TROTTER: That's correct.

9 DR. OHENE-FREMPONG: But they have a disease
10 that predisposes to it.

11 MR. TROTTER: Yeah, that's correct.

12 DR. HOWELL: Any further comments about the
13 congenital heart disease at issue?

14 [No response.]

15 DR. HOWELL: I hear a sense of agreement
16 that this should go forward for review, is that
17 correct? And if so, can we have a
18 recommendation for that?

19 DR. VOCKLEY: Yes, I recommend we move
20 congenital heart disease forward.

21 DR. HOWELL: Second for that?

22 DR. RINALDO: Second.

1 DR. HOWELL: Those favoring that say aye.

2 [Chorus of ayes.]

3 DR. HOWELL: Any opposition?

4 [No response.]

5 DR. HOWELL: Did anyone abstain?

6 [No response.]

7 DR. HOWELL: So that's a unanimous
8 recommendation.

9 MR. CALONGE: Dr. Howell?

10 DR. HOWELL: Yes sir.

11 MR. CALONGE: Could I ask the committee to
12 entertain a nomination of prioritization? And I
13 would move that if that's appropriate that we
14 send congenital heart disease screening to the
15 committee, to the review committee as the first
16 priority and hyperbilirubinemia, which if it's
17 already the standard of care, or becoming the
18 standard of care, as a second line. My biggest
19 concern is that it would be really great to have
20 enough time to have published data on the
21 effectiveness of hyperbilirubinemia screening.

22 DR. HOWELL: Is there a second to Ned's
1 motion?

2 DR. BUCKLEY: I second.

3 DR. HOWELL: Dr. Buckley has seconded that.

4 So is there a discussion about the congenital
5 heart disease going first and the
6 hyperbilirubinemia going second?

7 MR. TROTTER: I think that sounds way too
8 logical --

9 [Laughter.]

10 MR. TROTTER: -- but still doable.

11 DR. RINALDO: Just for completeness, is
12 there anyway to have a sense of a time line?

13 DR. HOWELL: That was my -- I would hate to
14 have these things queued up waiting for six
15 months, eight months, a year. I mean I think
16 that's just too long. And I'm a big advocate
17 for having a line of procedure but I would hate
18 for them to be terribly slow.

19 DR. BOYLE: I guess I would go back to what
20 Ned said earlier in that a lot of the work for
21 the hyperbilirubinemia has already been done by
22 the previous committee. So I don't see a lot of
1 work, additional work there in terms of the
2 evidence based review. So I would actually
3 encourage that to go first.

4 DR. DOUGHERTY: But if you rely on the work
5 that's already been done we're going to wind up
6 with --

7 DR. BOYLE: But our committee has different

8 criteria then the other.

9 DR. HOWELL: Dr. Watson.

10 DR. WATSON: What does the pipeline look

11 like of reviews that are -- or of nominations

12 coming along. There's one in process now --

13 DR. HOWELL: Yeah, we'll hear about --

14 DR. WATSON: -- that just started?

15 DR. HOWELL: -- later today.

16 DR. WATSON: So there's one in process,

17 there's two coming forward. Are there more on

18 the -- that you're looking at to decide whether

19 or not they --

20 DR. HOWELL: Do you have others in house Dr.

21 Puryear? The answer is no.

22 DR. WATSON: There are no other nominations?

1 DR. HOWELL: There are no other nominations

2 in house as we sit here. So that the -- the

3 Thalassemia we'll hear about today and then

4 these are the only two on the docket. Jim.

5 DR. VOCKLEY: Ron I think the time line, the

6 question or the issue that you're raising is an

7 independent one and it's resource driven. So if

8 the committee wants to say that these should,

9 that the evidence reviews should come back no

10 later than one committee meeting after the,

11 after sending it for evidence review.

12 Then we just have to decide if we have the

13 capacity. If we don't, then we have to increase

14 the capacity. There's no other way of handling

15 that. So we'll have to ask our committee to

16 train another committee.

17 DR. HOWELL: I don't want fog the issue

18 about talking about time line, but that was just

19 a personal thing. Is I would hope that these

20 things would not lie around, et cetera. Because

21 I think they're both extremely worthwhile

22 nominations and I would hate for them to sit on

1 the shelf. So we'll have to work on that.

2 DR. PURYEAR: So, we have a motion.

3 DR. HOWELL: We have a motion and a second.

4 We've had a fair amount of discussion, unless

5 there's other wisdom. Any other comment before

6 we -- can we vote on that? Ned's nomination

7 that the critical congenital heart disease

8 nomination go first then followed by the

9 hyperbilirubinemia.

10 Those favoring that motion say aye?
11 [Chorus of ayes.]
12 DR. HOWELL: Any opposing?
13 DR. PURYEAR: Wait I need to see.
14 DR. HOWELL: Excuse me.
15 [Pause.]
16 DR. HOWELL: Any opposition to the motion?
17 [No response.]
18 DR. HOWELL: There's no opposition. Did
19 anyone abstain?
20 DR. PURYEAR: Yes, Coleen abstained.
21 DR. BOYLE: No, I'll go with it. I just
22 like the other one because it was expeditious.
0045
1 DR. HOWELL: We have --
2 DR. BOYLE: I'm not abstaining.
3 DR. HOWELL: We have three people
4 abstaining. Any further thing?
5 DR. PURYEAR: Three abstentions, is that
6 right?
7 DR. HOWELL: Yes.
8 Unknown Female Speaker: Yes.
9 DR. PURYEAR: Coleen, Tom --
10 DR. HOWELL: No, no, Coleen did not.
11 Unknown Male Speaker: She voted for it.
12 DR. PURYEAR: So it's two.
13 DR. HOWELL: Only two, only two abstentions.
14 You got it?
15 DR. PURYEAR: Yes.
16 DR. HOWELL: It carries.
17 MR. CALONGE: And again, I would recommend
18 that if it's not possible to increase the
19 resources that we do think about the criteria
20 upon which we make these kind of decisions at a
21 separate time.
22 DR. HOWELL: Yes. Outstanding. We're doing
1 well ladies and gentleman, thank you very much.
2 So that gives Sharon a lot of time. The next
3 presentation is from Sharon Terry and she's
4 going to be presenting the newly established
5 Clearinghouse for Newborn Screening Information.
6 The newborn screening saves lives of
7 2008 Amends the Public Health Act. It adds a new
8 section entitled Clearinghouse for Newborn
9 Screening Information. This requires the
10 Secretary through HRSA, in consultation with the

11 CDC and NIH to maintain a newborn screening
12 information clearinghouse.

13 Are you going to discuss the requirements of
14 that bill or do you want me -- oh I will not go
15 through what those requirements are. It has a
16 series of specific requirements that Sharon
17 carries out as a part of her contract. And so
18 we'll now hear about those and how she's going
19 to maintain quality data and performance
20 indicators on newborn screening that will be
21 publically accessible. Sharon.

22 MS. TERRY: Great, thanks very much. And
1 thanks to the committee for the time to share
2 this with you and the public. What I'm going to
3 do is present the clearinghouse both
4 conceptually with regard to the requirements per
5 the Act. As well as look at a beta site.
6 So I will be taking you on a tour of that.
7 That portion of the presentation will be
8 mimicked by our technical assistant for the
9 people who are looking at the web cast. So it
10 may not sync up perfectly and I'll try to be
11 very descriptive.

12 The vision for this clearinghouse, and the
13 vision comes from the Act, is asking that we
14 connect parents and healthcare providers with
15 resources and information. That we improve
16 understanding and informed decision making on
17 the part of both providers and parents as well.
18 That we facilitate information sharing.
19 That we enable data transparency, integrated
20 tools, technologies, and education and provide a
21 basis for follow-up. And that we provide
22 information on Federal funding for newborn
1 screening.

2 So all of those -- that is a lay
3 distillation of the Act. The Act actually was
4 quite clear about each one of these elements and
5 we are working on integrating each of the
6 elements. This is a diagram that has undergone
7 many, many iterations and is still really far
8 from perfect.

9 In fact, it's quite imperfect. And
10 essentially what it's doing is trying to say
11 that the clearinghouse is not going to exist in
12 a vacuum. But the clearinghouse is not going to

13 be everything. Even the term clearinghouse is
14 problematic.

15 In some sectors clearinghouse means a place
16 that decides what can be or can't be projected
17 to the public or given to the public. In other
18 places it means that it contains absolutely
19 everything.

20 And so we're, at this point, not even sure
21 that we'll keep the word clearinghouse per the
22 Act, but that we might consider other terms. So
1 we're very interested in both the committee as
2 well as the public's opinion on that.

3 Essentially the clearinghouse will in fact
4 interact with the CDC, HRSA, hearing data, and
5 also the NNSIS, HRSA newborn screening data for
6 the nation. It will also live in this kind of
7 cloud. And the cloud is a concept that's very
8 difficult for people to understand at this
9 point.

10 The cloud refers to cloud computing, grid
11 computing; all the sorts of things that we're
12 now interacting with without even knowing it.
13 So for example, Google, while we're all really
14 happy with how easily it retrieves information;
15 actually stores every single web page in the
16 universe that's every sought for on the Google
17 servers in the Google farm. And that's why it's
18 so fast for bringing information in. The
19 clearinghouse will not do that.

20 So it will not be a mimic of a Google kind
21 of system where everything is essentially owned
22 therefore by Google. But instead will be using
1 a more federated model where information will
2 still reside where that information resides and
3 it will link to that information but using a
4 kind of cloud system that allows it to link it
5 faster.

6 So some of the things that it is doing
7 certainly will be web 2.0 and we foresee some
8 web 3.0 kinds of interactivity. And I'll try to
9 describe that, but it again is pretty hard to
10 describe at this point in the sense that it
11 doesn't exist yet in some instances.

12 But the backbone for it is there, for
13 example Google Wave which maybe some of you have
14 seen, allows interactivity amongst all kinds of

15 applications that hasn't yet been kind of rolled
16 out to all of us.

17 In addition to the cloud, which includes for
18 example, and I'll show a little bit of this, the
19 coding and terminology standards that the
20 National Library of Medicine has been working on
21 with HRSA and others; includes the NCBI kinds of
22 efforts they are making around databases that we
1 are very familiar with like PubMed and perhaps
2 in the future a genetic testing registry, et
3 cetera.

4 It includes interaction with the HRSA
5 genetics collaboratives and the National
6 Coordinating Center. It includes coordination
7 and collaboration with the Newborn Screening
8 Translational Research Network. And then it
9 certainly includes a lot of interactivity with
10 existing resources like GARD, like March of
11 Dimes' PeriStats, et cetera; and I'll show some
12 of those things.

13 And then in the lower corner here I have
14 just the words congenital conditions because
15 there's also a cooperative agreement for
16 congenital conditions for information and
17 consensus kinds of guidelines that Genetic
18 Alliance also received from HRSA and will be
19 considering how to make sure that the Newborn
20 Screening Clearinghouse is expansive enough to
21 include that.

22 It's all sitting on the foundation of the
1 HHS Secretary and its interaction with this
2 committee since this committee makes
3 recommendations for data and data activities and
4 grant activities. And so there's certainly
5 going to be a lot of open and transparent
6 interaction. It's a cooperative agreement. So
7 we will be very responsive to both HRSA as well
8 as to this committee, as well as to the public
9 and iteratively improve it.

10 It's also the kind of project that isn't
11 just a project with a product like some others.
12 It's a project that is going to be iterative and
13 ongoing that needs to -- you know what we sit
14 here today and think about will certainly be
15 very different then two years, five years from
16 now; and we want to be able to integrate those

17 things as we go.

18 So the Act requires that it is centralized
19 and on line. And again, we're interpreting the
20 word centralized fairly broadly. We are not
21 interpreting it the way Google does. We are
22 interpreting it in a more broad way to say that
1 while everything will be centralized in the
2 sense of the public being able to find it or the
3 provider being able to find it, the resources
4 will still live where they live.

5 Which allows us then to be always accessing
6 current information and not updating a site that
7 has to store the information itself. In the
8 sense it will be a switch, not a store. It will
9 be research based information. Which is also
10 very tricky.

11 Genetic Alliance has another cooperative
12 agreement with CDC called Access to Credible
13 Genetics Resources Network during which over the
14 last four and a half years we've looked at what
15 does research based or evidence based
16 information mean. And we know how hard that is
17 with concrete science like genetic testing or
18 newborn screening. It's even more wiggly and
19 difficult with information.

20 And so we've set some standards in that
21 project that we'll be applying to this project.
22 It has to also include information on each state
1 is one of the requirements. It has to be an
2 interactive forum.

3 And right now, we consider interactive
4 forums, cutting edge ones, to be like Facebook
5 or Amazon in the way we order things. There are
6 interactive forums and technologies that are
7 coming down the line that are allowing
8 individuals to carry information with them
9 multiple, multiple ways.

10 I recommend that you watch something called
11 the Second 5,000 Days of the Web. Where Kevin
12 Kelly talks about how we're all going to be
13 interacting with information all the time. And
14 we kind of already do that when we carry our
15 Blackberry or our IPHONE.

16 But the idea that that would be ubiquitously
17 available to us and we'll be interacting with a
18 kind of web structure that we don't entirely

19 envision today. And we're anticipating that
20 particularly around newborn screening
21 information to families who are relatively young
22 and usually much younger than the people who are
1 making decisions about what should happen in
2 newborn screening information.
3 We'll also be looking at data. And we're
4 interpreting data fairly broadly. We've been
5 working a lot with HRSA about what data means
6 and how data information and resources actually
7 overlap each other. And we'll be looking at
8 that throughout the project as well as
9 understanding how to disseminate this
10 information.
11 Again, families preparing to have babies are
12 not always, and are not usually as old as many
13 of us in this room. And so we'll be looking at
14 what ways do young people receive information.
15 For example, texting or twittering, et cetera.
16 The guidance requires that the data,
17 information, and resources are liquid, that we
18 consider a meaningful use, accuracy, access,
19 information flow, and transparency. And I'll
20 talk a little bit about each of those.
21 So what we thought about in each of these
22 categories; and we have actually dozens and

1 dozens of examples that we put into the proposal
2 which we're happy to share with anyone, around
3 collection output and linkages for example in
4 regard to liquidity and the kinds of things that
5 already exist and that we will be bringing
6 together. And then the gaps that we saw and we
7 will be creating.
8 Same thing with quality. Really major
9 issues around meaningful use and accuracy.
10 Meaningful use, since the writing of the
11 proposal of course has taken on a whole new kind
12 of sense of -- sensibility in the country with
13 the issuance of the Meaningful Use Guidelines
14 that have come out of the HIT standards and
15 policy groups.
16 I'm sitting on the HIT Standards Group for
17 HHS; and so able to be really interacting with
18 them around what does meaningful use mean.
19 Right now, the meaningful use information that's

20 come out does not include newborn screening.

21 We've been discussing that both in the
22 committee.

1 And it's very important for the public and
2 perhaps this committee to make comments on that
3 so that newborn screening is in fact included
4 since it's a really good place, and I think an
5 easy place to talk about meaningful use.

6 And then the other issue around quality is
7 certainly accuracy, and we mean that quite
8 broadly. Again, bringing in all that we learned
9 in the CDC project. Access, really we're going
10 to be looking at information flow.

11 How do we get that information across to
12 individuals making sure that various sectors
13 have the same kind of access as other sectors.
14 And then transparency. This is a web based
15 project. Which right away denies access to some
16 individuals and we'll be looking at how do we
17 ameliorate that as we go.

18 Again, some of the really important things
19 to us are looking at new technologies that are
20 going to be pervasive. Certainly five years
21 ago, somebody might have looked at the concept
22 of an IPHONE or thought about Twitter and

1 thought that these things will not be
2 significant, they will be a flash in the pan,
3 they won't be important.

4 But what we're finding certainly is that the
5 places that young people aggregate themselves,
6 including young people all the way up to age 40,
7 45; are certainly now Facebook, MySpace, those
8 kinds of interactive even linked in spaces that
9 allow people to transfer information quickly,
10 transfer it the way they want to see it. And
11 I'll talk a little bit about how we might be
12 able to customize that.

13 So our activities for year one are landscape
14 analysis of newborn screening materials. And
15 that's certainly ongoing. It has been part of
16 Genetic Alliance's tasks to do that anyway
17 because of our newborn screening cooperative
18 agreements that we've had for now three years.
19 So we continue to do that.

20 The beta site which we launched in October,
21 and we're calling it a .9. So it's not even a

22 1.0 site yet, and you'll see it today. This

1 presentation, a workshop that we're going to
2 hold at the Association of Public Health
3 Laboratories' Newborn Screening and Genetic
4 Testing Symposium in May this year on a Thursday
5 in the afternoon. And you'll be getting
6 information about that as well.

7 And then the major activity certainly will
8 be the construction of the 1.0, 2.0 and 2.X. In
9 other words, on and on iterations of the site as
10 we go through the year.

11 We presented the Newborn Screening
12 Clearinghouse to it's national advisory
13 committee, the NAC. We had a lot of really good
14 interaction. Our project officer, Lenee Simon,
15 who's somewhere in this room. I'm sorry,
16 there's so many people. And we presented it to
17 the NAC and really got some excellent feedback.
18 We're working with Lenee to figure out how
19 to integrate all the comments that we received.
20 Some of the major comments, and there were many,
21 many so these are just a few were; how are we
22 going to prioritize information and what kinds
1 of quality filters would we create.

2 Again, the quality filter part we don't --
3 we're not so afraid of that question having
4 built the toolbox for quality materials that we
5 did with the University of Maryland and NCHPEG.
6 The prioritizing information is a tough one.
7 And that's always a question for all of us. We
8 are assaulted with enormous amounts of
9 information and how do we prioritize. Which
10 brings us to this idea of an interactive kind of
11 IGoogle sort of site.

12 So some of you may have seen it, you can
13 customize your homepage in Google and put on it
14 your gmail or your office or your feed from your
15 local newspaper. You can put on it quote of the
16 day. You can put whatever you want on that.
17 And we'll be eventually having this site be the
18 same way. So that you can come to it and
19 customize it the way that you need to see it.
20 Roles. Lots and lots of discussion about;
21 should there be one site? Should there be one
22 site with two portals? Should there be two

1 sites? The issues around consumers and primary
2 care providers, specialists, sub-specialists.
3 The issue around should all individuals be
4 coming through the same door?
5 Constant kind of dialogue between
6 understanding that consumers need one kind of
7 information; providers may need another kind,
8 but in many cases providers are happy to read
9 consumer information at least at first and then
10 move to a deeper kind of level.

11 So we're not sure yet will there be two
12 pathways or will there be multiple tiers. I
13 tend toward the multiple tier perspective
14 because even the literacy levels of the public
15 in some sense parallel those of providers in
16 terms of depth.

17 Lots of questions and good suggestions about
18 our interaction with HRSA Genetics
19 Collaboratives. The regional collaboratives are
20 a part of the project and they have subcontracts
21 with us to do work in the regions. And so we
22 will be working very closely with them.

1 And then lots of also questions about
2 inclusion of international perspectives and
3 issues. Obviously the issues around newborn
4 screening are global. When you get to issues
5 like data and aggregation of data, it's much
6 better to be global. Information resources
7 perhaps need to be global. I mean our first
8 iteration will certainly be much more U.S.
9 centric then we're used to being. But we are
10 being mindful about the issues around the globe.

11 I'm going to now take you on a short tour of
12 the website. Because again, it's not even its
13 first iteration. And for the people watching
14 the web cast, we will try to make sure that you
15 see pretty much the same thing.

16 Okay, so the resolution on the screen if I
17 bring the web site down to the size where you
18 can see the whole page, the normal size page you
19 won't be able to see it from your seats. And so
20 I've blown it up and I have to scroll down for
21 you to see the whole thing.

22 So right now, it's very simple and very
1 basic. It simply has nine blocks and quite a
2 few links in it to resources to allow us to

3 begin to conceptualize what will this thing look
4 like. Certainly home is the typical sort of
5 home page.
6 About simply describes the project and the
7 Act that it results from. And contacts just
8 give the individuals in our office that are
9 really working on this a great deal. Natasha
10 Bonhomme is the project director as she is all
11 things newborn screening. And she's also
12 sitting here in case you have any questions for
13 her.
14 The key things that we wanted to just show
15 you today are in certainly these blocks. But
16 also this little link here will allow people,
17 and it's not live yet because it takes a great
18 deal of coding to do this piece, but the
19 Iclearinghouse. And again, we're not sure we're
20 going to even use this name, allows people to
21 customize what you're looking at.
22 So if they don't like to look at some of
1 these resources they don't have to. And if
2 there are others they want to pull through they
3 can. So our thoughts here were to look at
4 newborn screening resources.
5 Genetic Alliance built the resource
6 repository which you can get to by going to
7 resource repository.org. In this case, you can
8 simply click the link that's on this screen.
9 The resource repository has been built with a
10 HRSA cooperative agreement for the National
11 Consumer Genetics Resources Center.
12 And so simply putting in a term, in this
13 case like PKU. I'm able to search documents,
14 video files, audio files, and links. This
15 repository has thousands, and thousands of all
16 of these kinds of materials in it; not just
17 related to newborn screening. But the structure
18 certainly works. I press search, and I come up
19 with search results that include 320 resources
20 that mention PKU.
21 I can edit the search, and I won't do that
22 right now. I'm working off this Sprint stick
1 that's kind of slow. But you can play with
2 this, you can edit the search and determine
3 things by the author, by the date, by where it -
4 - what part of the country the material is from.

5 Certainly in newborn screening an important
6 issue is that you're -- if you're in a state
7 you're using the state's resources. And we'll
8 build in filters that will allow you to come
9 in either via your zip code or via your region
10 so that you are, in fact, getting the right
11 resources for your region.
12 Another resource we have, here is
13 information for patients and providers. And for
14 right now this simply links to HRSA's
15 information for patients. That will be blown
16 out a great deal as we move through the project.
17 But right now is simply a bookmarked link.
18 Disease info search is another way of
19 looking at resources. And again, we're going to
20 be describing these much more carefully so that
21 parents particularly know what they're coming
22 to. In this case I've done a canned search,
1 again for PKU. This disease info search,
2 disease info search .org is again product of
3 Genetic Alliance through a collaboration with
4 HRSA, CDC, and NIH.
5 In this case what we're looking at is a new
6 kind of marriage between Genetic Alliance
7 resources and NCBI. We've taken the typical
8 NCBI kinds of things like PubMed and GeneTest
9 and put algorithms behind the page that filter
10 the results so that parents get just some of the
11 basics that they might need to see.
12 Or in fact, have filtered results on PubMed
13 articles or only review articles, that sort of
14 thing. So working with the folks at the NCBI as
15 well as some beta testing that we've done, we've
16 been able to limit what an individual might see
17 here so that they're getting quality
18 information.
19 This is undergoing radical reconstruction
20 for this project and there will be a different
21 face for this. This is too complicated and
22 still too many resources in our opinion. And so
1 we're working with NCBI on that.
2 Other things in here are the newborn
3 screening coding and terminology guide, which I
4 think many of you have already seen a project
5 again between HRSA, the National Library of
6 Medicine; looking at what should be the standard

7 language in terms of coding and terminology and
8 control kind of vocabularies.

9 Regions are connected here. The regions
10 right now are simply connected and linked to
11 their site. Eventually we will be looking to
12 link to the newborn screening resources on each
13 of these sites and make sure that those things
14 are tagged in the proper way. NNSIS, PeriStats,
15 I'm not going to open all these because I think
16 you guys have seen them. Same thing with the
17 committee's web site as well.

18 And then a very interesting part of this
19 project is that we are to aggregate all newborn
20 screening funding in the nation. And so right
21 now we're simply giving the links that will go
22 directly to the funding of each of the primary
1 agencies that are providing funding.

2 But what we're looking at right now is
3 building an aggregated filter search system that
4 will allow you to search across all agencies.
5 Because as either an individual, or an
6 organization, or a company looking for funding;
7 you're not so interested in what is the agency
8 providing the funding but where does the funding
9 come from.

10 And then last, but not least we have links
11 to the funding source, HRSA in this case. And
12 we are creative commons attribution licensing
13 the site. In other words, it is available for
14 whomever to use in whatever way.

15 And that's a fairly important thing too.
16 Because right now, I think as individuals who
17 have sort of used the web over these last, the
18 first 5,000 days of the web; we've been used to
19 going to a destination. The web is going to be a
20 place that is not a destination so much, but a
21 portable information source.

22 And so the way that we're going to construct
1 this is then this, and parts of it can be
2 integrated into other sites. And so there are
3 links that move back and forth throughout the
4 internet. And there are ways to carry this
5 information in mobile devices or in text forms,
6 et cetera.

7 So that is all I have in terms of a formal
8 presentation. I hope that it was not difficult

9 for people watching the web cast. I'm sorry
10 that we weren't able to do this live because I
11 needed to drive. But I'm happy to have
12 questions about anything that you've seen or
13 comments on anything that you think that I've
14 left out.

15 DR.HOWELL: Thank you very much Sharon.
16 Are there questions or comments for Sharon?
17 [No response.]

18 DR. HOWELL: Obviously a very ambitious
19 project. It should be extremely valuable I
20 would think when you're coming down the home
21 stretch. Well thank you very much Sharon.

22 MS. TERRY: Thank you.

1 DR. HOWELL: It looks like that you've
2 covered everything clearly.

3 MS. TERRY: Thank you.

4 DR HOWELL: This group is not only
5 extremely wise, but today has been very
6 efficient and so we're ahead of schedule. And
7 so what I'm going to do is I'm going to ask
8 Alissa Johnson if she would do one of her two
9 presentations before the break.

10 And Alissa, I'm going to suggest you do the
11 healthcare reform issue because that's a bit
12 briefer. And we should be able then to get to
13 our break right on time.

14 MS. JOHNSON: It's number 8.

15 DR. HOWELL: Yes. The policy brief on
16 Newborn Screening and Healthcare Reform for the
17 committee was presented in September. We have
18 received comments about that and the final draft
19 is being presented today for the committee's
20 approval. And Alissa is going to review that.

21 MS. JOHNSON: Okay, so if you'll remember
22 this is a paper that we put together for the

1 September meeting for you all to consider on
2 newborn screening and healthcare reform.

3 I'm just going to run through some of the
4 changes that we've made. But you should have an
5 updated version of the paper on the memory
6 stick. And I do apologize, it does say

7 September 2009 on there and that was just
8 envisioning a publication date at some point,
9 but it has been updated.

10 So I'm going to run through some of the

11 recommendations and the changes that we've made.
12 On recommendation one, if you'll remember in
13 September it said; ensure stable funding for
14 core and critical public health functions such
15 as immunizations and screenings.
16 And we had several comments that we might
17 want to revise that, remove immunizations. That
18 was referring to something from Trust for
19 America's Health. And I believe we had a
20 similar comment from March of Dimes when we sent
21 that out to them for further comment.
22 So it has been now revised to state; convene

1 an expert panel to establish a minimum
2 recommended standard of service and care for
3 each component of the newborn screening system;
4 education, screening, diagnosis, follow-up,
5 tracking and evaluation.
6 And if you'll remember another comment that
7 we had at the last meeting was that you know
8 there already was stable funding for of course
9 the screening itself and we needed to be clear
10 about what we were specifically referring to.
11 And then minimum recommended standard of
12 service and care is actually another comment
13 that we had had pre the last meeting that we
14 managed to work in to this recommendation.
15 Now recommendation 2 that's in the current
16 version of the paper is a new recommendation.
17 This was in the text but wasn't one of the
18 recommendations. But we wanted a way to tie in
19 the funding issue to accomplish -- for the
20 states to be able accomplish achieving that
21 standard of service and care. So that's what we
22 tried to do here.

1 So this language, like I said, was already
2 in the paper; develop national guidance on
3 creating public health budgets for newborn
4 screening systems in order to minimize
5 geographical disparities and highlight budget
6 alternatives that may better serve the needs of
7 a particular state program.
8 And then it goes on to say; the guidance
9 should incorporate the flexibility in funding
10 design that states may require and identify
11 areas that the federal government may target for

12 additional support to help states deliver the
13 minimum standard of service and care set forth
14 in recommendation 1.

15 Now I do note from the March of Dimes that
16 they wanted us to focus on you know, there is --
17 states do need some flexibility. They had
18 noted, and so we tried to incorporate that in to
19 this recommendation.

20 One question that I had for you all too is
21 just to note that it does the Federal Government
22 may target. And I don't know how strong you
1 want to be with that language. Should it say;
2 may want to target, or may target, or should
3 target? So that might be something you want to
4 think about.

5 Recommendation 3, which was previously
6 recommendation 2 is unchanged. So that's;
7 convene an expert panel to examine the billing
8 and payment practices for the cost of screening
9 services and to put forth recommendations that
10 enhance the standardization of health care
11 transactions.

12 Recommendation 4, which was 3 last time as
13 previously stated; Work with CMS to develop and
14 pilot a bundled payment method for providers
15 treating the same child with a disorder
16 diagnosed as a result of screening that can
17 serve as a model for all children with special
18 health care needs.

19 And we did receive some comments on that and
20 revised it. And rather than trying to tell CMS
21 you know, what kind of payment, the specific
22 kind of payment method they should be looking
1 at, we wanted to leave it more open.

2 So just to say; work with CMS to pilot a
3 payment method for providers treating
4 the same child with a disorder diagnosed as a
5 result of screening that incentivizes care
6 coordination. That way they have some leeway to
7 think about what they think would work best.

8 Recommendations five and six, which were
9 previously four and five. Recommendation five
10 is unchanged. Further define and adopt the
11 meaningful use case for newborn screening for
12 health information exchange endeavors by the
13 Department.

14 And six is also unchanged. Close gaps in
15 insurance coverage for medical foods and foods
16 modified to be low in protein as recommended by
17 the committee in April 2009.

18 I will say with recommendation six we had a
19 comment that should that really be directed to
20 the Secretary? Do we need to tweak that out
21 more because some of the recommendations that
22 were made with respect to medical foods were
1 directed to Congress. So that issue came up,
2 staff brought that up so we may need to reword
3 that.

4 Here are the additional comments that we
5 received with regard to electronic health
6 records. There was language added in summary
7 and in the text to state that -- this actually I
8 believe was from Jeanette -- to emphasize the
9 importance of electronic health records and the
10 opportunity that newborn screening provides.
11 We added; Newborn screening is among the
12 first encounters where health professionals
13 begin to compile medical information about an
14 individual and is thus a prime area for
15 introducing electronic health records.

16 Other comments. A suggestion to delete
17 textual references that suggest all states
18 should conform to a single design and financing
19 methodology. And we tried to do that in the
20 reworking of the recommendation that, I believe
21 it's number two now as far as making
22 recommendations about how to structure budgets
1 for newborn screening.

2 Regarding recommendation 2, the paper does
3 not build a case for an expert panel on billing
4 and payment. And now actually we say; work with
5 -- I'm sorry, yeah we do have work with CMS.

6 But the expert panel -- I'm sorry that does
7 still state that. I'm jumping ahead of myself.
8 So referring to; convene an expert panel to
9 examine the billing and payment practices for
10 the cost of screening services. We had a
11 comment that the paper didn't build the case for
12 the need for the expert panel. So that's
13 something for you to consider, whether you think
14 that should stay in there or not.

15 Regarding recommendation four, which is now

16 five. It is a good idea that needs, may need
17 more discussion in the paper. And that refers
18 to the meaningful use case for newborn
19 screening.
20 Also; add a recommendation on the urgent
21 need for educational materials and on a full on
22 national campaign to educate parents and health
1 professionals about the availability of and need
2 for newborn screening.
3 We do address in developing a standard of
4 service and care. The education is one of the
5 components. So I don't know if that's something
6 you want to flesh out more in the paper or if
7 you're recommending that a standard of service
8 and care is put forth in the -- what should be
9 available to the families and to healthcare
10 professionals regarding education, whether you
11 want to postpone that for that discussion.
12 Regarding recommendations five, which is now
13 six; medical foods should be discussed further
14 in the paper, and a proposal should be added to
15 convene a working group that includes the FDA,
16 CMS and Tricare representatives to consider
17 expanding federal support for public program
18 coverage of medical foods.
19 Now with the work you've already done on
20 medical foods, obviously I don't know if that's
21 something you want to think about or refer to
22 more in the paper. Other comments.

1 There was concern about creating an unfunded
2 mandate for state programs. And actually I do
3 need to tell you, we did have a discussion with
4 the National Coordinating Center and the
5 regional collaboratives, PI's. And I believe it
6 was in October or November. So I presented to
7 them the paper, the version of the paper that
8 you all had seen in September and these were
9 some of their comments.
10 So they had concerns about creating an
11 unfunded mandate for state programs. And it was
12 noted that recommending federal funding to
13 support programs that are not addressing
14 components of the newborn screening system might

15 prove a disincentive for states that are already
16 paying for these activities to no longer fund
17 them if federal funding becomes available.
18 So that ties in to the second recommendation
19 that we have added words that the Federal
20 Government might want to consider providing
21 additional support for certain areas.
22 Also from that meeting; a National Coverage
1 Decision by CMS related to newborn screening
2 might help to resolve some of the billing and
3 payment issues. So I don't know if that's
4 something you all want to consider more.
5 With regard to medical foods coverage, it
6 was noted that shipping often constitutes a
7 significant portion of payment costs. So there
8 was some concern, I don't -- this isn't
9 something that's discussed I don't believe in
10 the recommendations in the letter that you had
11 previously done.
12 I did take a look at the -- some legislation
13 that's been introduced and some state
14 legislation. And you know I don't know if
15 that's something that can be taken care of at
16 the regulatory level. But maybe it's something
17 that you would want to add or mention here.
18 That's it. Anybody have any questions?
19 DR. HOWELL: We need to discuss this paper.
20 We need to get a document sent to the Secretary
21 about the situation with healthcare reform and
22 newborn screening. Can we have any comments
1 about what Alissa has presented or about the
2 paper?
3 MS. GREEN: Can I make a brief comment?
4 DR. HOWELL: Yeah.
5 MS. GREEN: Okay.
6 DR. HOWELL: We're going to hear from the
7 folks here Nancy first. Mike.
8 DR. WATSON: So when you talk about national
9 coverage decision and billing and reimbursement
10 systems, are you talking about just the
11 screening part of this or diagnosis, follow-up,
12 management, treatment?
13 MS. JOHNSON: Well there wasn't a specific
14 discussion but that was a comment that the, one
15 of the PI's made from the regional
16 collaboratives. That they would like to see a

17 national coverage decision.
18 The current wording that we have is to
19 convene -- that they were I believe looking at
20 when they made that comment; convene an expert
21 panel to examine the billing and payment
22 practices for the cost of screening services.

1 And so we're not really specific there. So
2 maybe we need to be clearer in that and then you
3 can decide whether or not you'd like to add more
4 referring to a national coverage decision or
5 not.

6 DR. HOWELL: Well the first recommendation
7 does say education, screening, diagnosis,
8 follow-up, tracking and evaluation services.

9 MS. JOHNSON: Right, right.

10 DR. HOWELL: So that clearly is in the first
11 recommendation. It has the whole system.

12 DR. WATSON: I mean in the absence of
13 standards of care it's going to be hard to
14 establish an NCD, even an LCD on some of the
15 treatment follow-up, and you know what
16 constitutes an evaluation and all that kind of
17 stuff. I mean --

18 DR. HOWELL: Do you have some specific
19 suggestions for the text or the recommendation
20 that would cover that concern?

21 DR. WATSON: No.

22 [Laughter.]

1 DR. WATSON: I mean I can see where focusing
2 on the screening piece would be important
3 because I think you're recommending that
4 specific things be screened. There's enormous
5 variability in how the states approach that.
6 So I can see where getting some more uniform
7 approach and recognition about how you get
8 reimbursed and compensated for it would work.
9 But then you move in to you know, one behemoth
10 of a healthcare system for billing reimbursement
11 of diagnosis and care and everything else. And
12 that's a lot more difficult.

13 DR. HOWELL: Kwaku had his hand up I think
14 next.

15 DR. OHENE-FREMPPONG: Yes, I had just a brief
16 question. There's a reference to the electronic
17 medical record, the newborn screening might

18 provide an opportunity to develop it.
19 Can you elaborate a little bit on it?
20 Because it seemed to me most of newborn
21 screening data is stored in state health
22 departments. And how does it link to a child's
1 electronic medical record?
2 MS. JOHNSON: Right.
3 DR. OHENE-FREMPONG: What were they thinking
4 about?
5 MS. JOHNSON: Sure. Well I don't know if
6 Sharon wants to speak to that a little bit more.
7 MS. TERRY: Sure. So right, there is -- it
8 is not right now stored in any kind of medical,
9 electronic medical record. The idea is, and the
10 Office of the National Coordinator, several
11 other Federal agencies have been thinking about;
12 this is the first health exchange of information
13 even before vital records or birth certificates.
14 So it would be a prime opportunity to in
15 fact take that information and create the
16 beginning of an electronic medical record for a
17 child and would provide a way to move all U.S.
18 residents into such a system. There's some
19 proposals out -- in fact I'm not sure if the
20 proposal from ONC has circulated widely, I think
21 that it has.
22 To look at, there are some very simple web
1 systems that would allow this. There are some
2 link ups with things like Epic and DocSite that
3 would allow it. There are things that exist
4 already in some of the newborn screening vendor
5 software that would allow it.
6 And so the idea that we're looking at is, if
7 we do that and we see that as a primary instance
8 of health information exchange, then doesn't it
9 make sense for the nation, rather than trying to
10 take someone as old as me and put all my
11 information into a source, to begin right at
12 birth and begin with an electronic exchange of
13 that information.
14 And primarily in the beginning, simply to
15 allow the hospital to communicate with the state
16 public health lab, to communicate with the
17 pediatrician, to communicate with the sub-
18 specialist.
19 And then eventually, probably, and this is

20 what terrifies people, that parents would
21 actually be involved in the newborn screening
22 process in the sense of understanding what the
1 information was. Perhaps not in terms of
2 specific numbers but in terms of the overall
3 information.
4 And then eventually, to the issue around
5 residual blood spots and their storage and use.
6 And what are the issues when public health bumps
7 up against kind of private or research kind of
8 health.
9 So a very complicated scenario, but
10 certainly a place if we just started simply and
11 allowed the public health lab and the hospital
12 and/or pediatrician to communicate would make
13 life simpler for all those people.
14 DR. HOWELL: Ned, you had a comment.
15 MR. CALONGE: I was just really bothered by
16 Mike's comment that this practice pattern
17 variation means waste and ineffective care and
18 poor quality care. And then I thought maybe I
19 shouldn't say that because I don't have a
20 solution. I think -- I realize why we just take
21 screening on, because at least it's a parable
22 piece.
1 But this issue about not being able to
2 figure out what a common package would look like
3 because of practice pattern variation across
4 states. Means that we're really not doing a
5 very good job of addressing this issue.
6 DR. WATSON: You know I think the pieces are
7 being put into address it. It's NIH's
8 Translational Research Network that evolves the
9 evidence base on which standards of care can be
10 determined.
11 But in the absence, as you know, in the
12 absence of a good evidence base you either go
13 with expert opinion, which is where we are. And
14 we've had to make a lot of modifications on the
15 way we evaluate evidence because of the rareness
16 of the diseases. You know, which also makes it
17 very difficult to arrive at standards of care.
18 So you know, all those things make it a hard
19 process and Medicare, which is where a national
20 coverage decision is made. This is not a
21 Medicare population. So I mean there's some

22 interesting difficulties in NCD's around this.

1 DR. HOWELL: Coleen.

2 DR. BOYLE: Denise has a comment relative to
3 this. You can go first because mine's a
4 different comment.

5 DR. DOUGHERTY: I do. And I think what Ned
6 and Mike are talking about are at two different
7 levels. And Mike -- and I don't understand
8 quite how they fit together, but I think Mike,
9 you're talking about the clinical evidence.

10 And Ned, I think you're talking about there
11 is some patterns of practice that no matter what
12 condition it is, it's still messed up. And I
13 think the electronic health record can help a
14 lot. And that's what's being worked on.

15 So you know, if you have a child and you get
16 a newborn -- you know, you get a positive i.d.,
17 you should do something. Now you may not know
18 what the treatment should be, but you should do
19 something.

20 A referral or call the lab back or
21 something. And I think those things can be
22 specified without specifying exactly what the
1 medical intervention needs to be.

2 DR. HOWELL: Coleen.

3 DR. BOYLE: So I had more of a process
4 related question. And I guess I'm thinking
5 about this report and the next report that we're
6 going to discuss on newborn blood spots. And
7 that is, the committees, if they accept these
8 reports, they're making a number of
9 recommendations to the Secretary.

10 And so I guess I'm trying to understand what
11 the next steps for the committee would be. And
12 in the context of representing CDC, would this
13 be something that the ICC, the mandated inter-
14 agency committee would then somehow take
15 forward? Because I'm really trying to
16 understand the next steps in the process.

17 DR. HOWELL: Well as far as I'm aware
18 Coleen, the inter-agency committee has not yet
19 been developed, is that correct?

20 DR. BOYLE That's correct. But again, I
21 think we have a series of recommendations here,
22 which I think they're all very good. And I'm
1 just really trying to understand this

2 committee's role in trying to help in
3 implementation of them as well as what the, sort
4 of the inter-agency issues are.
5 DR. HOWELL: Well this committee's
6 recommendations would go directly to the
7 Secretary and would not be passed through the
8 Inter-Agency group. So we're looking at
9 developing a document that is comfortable with
10 this committee that would make recommendations
11 about newborn screening and healthcare reform.
12 We will not be able to solve all the issues,
13 but we can at least point the areas that we
14 would like to see addressed in reform and so
15 forth. But our job is to come up with a
16 document that this committee agrees would be
17 helpful and then we would send it forth to the
18 Secretary.
19 And by law, the Secretary will have to
20 respond to that within 180 days in some fashion.
21 And Secretary Sebelius has been actually very
22 responsive so far. So we need to come up with a

1 document that this group is comfortable with.
2 And I guess that's the next step. How do
3 you see moving ahead? You've heard Alissa's
4 review of some of the comments that she's
5 received on the document.

6 MS. JOHNSON: And one thing that might be
7 helpful to point out Dr. Howell is that we
8 received many more comments on the blood spot
9 paper. And so I think the time line, depending
10 on what you all want to do might, you know that
11 might be drawn out further.
12 So this might be something that could be
13 quickly turned around if you all wanted to. But
14 there were many more comments for you all to
15 consider on the other paper. So I don't think
16 those two will you know, be coming out right at
17 the same time.

18 DR. BOYLE: Maybe I'll just be a little bit
19 more specific. Recommendation one says, convene
20 an expert panel to establish a minimum
21 recommended standard of service and care.
22 Obviously, that's something that, you know,
1 being the Chair of the Sub-Committee on
2 Treatment and Follow Up --

3 MS. JOHNSON: Right, right.

4 DR. BOYLE: -- that might be something that
5 that committee, at least helps sort of jump
6 start.

7 MS. JOHNSON: Right.

8 DR. BOYLE: So I guess I'm asking the
9 committee, are we going to be active in some of
10 the recommendations that we're actually putting
11 forward?

12 DR. HOWELL: I don't see any reason why we
13 can't be Coleen, frankly. Is there any comment
14 about that? The committee had this paper I
15 might point out, on your stick and I hope you
16 had a chance to review it. Because I would like
17 to move ahead and get something on paper and
18 send it downtown as soon as we can. But being
19 prudent that we cover the comments you have.
20 Alan.

21 DR. FLEISCHMAN: I just want to follow-up on
22 Coleen's comment. I have the same question as I

1 read number one. And if I were the Secretary or
2 her staff reading it, I'd say well aren't you
3 guys supposed to do that? That's why I've got
4 an advisory committee. And do we want another
5 expert panel? Are you not expert? Or can't you
6 find some experts?

7 [Laughter.]

8 DR. FLEISCHMAN: So I just thought that we
9 might want to volunteer to help.

10 DR. HOWELL: So we have Coleen's
11 volunteering to be number one.

12 [Laughter.]

13 MS. JOHNSON: I'll write her name in here.

14 DR. HOWELL: And we have a second for Alan
15 thinking it's a great idea.

16 DR. DOUGHERTY: But I think the point is --

17 MS. JOHNSON: -- Right.

18 DR. DOUGHERTY: -- why write a
19 recommendation like that into a letter to the
20 Secretary when it's something that we could
21 recommend that with additional resources this
22 committee could do. Which would, I think, go

1 down a lot better than you know, telling her she
2 should set up an additional expert panel.

3 DR. HOWELL: Well would you like to take
4 number one out or put it in the document? I see
5 heads shaking. Sharon.

6 MS. TERRY: So I agree and I think that
7 probably, I mean it's interesting as we've gone
8 through this process some things have changed in
9 the atmosphere.

10 DR. HOWELL: A lot.

11 MS TERRY: A lot.

12 [Laughter.]

13 MS. TERRY: And so I think we can be more
14 explicit about certain things. For example,
15 that would be a good point to add. I wouldn't
16 take one out, I'd add that to one. And then I'm
17 thinking about the other ones only vaguely right
18 now. But I think there's other resources that
19 exist that could come to bear.

20 And the Secretary would appreciate us
21 saying; and we know that if you linked this with
22 this it would create this with only a slight

1 gap. So I think we should be as explicit as
2 possible. Especially where it would say
3 resources, but also explicit where it needs more
4 resources.

5 I mean I've seen too that she's very, very
6 responsive and that she sets up what needs to be
7 set up if some brilliant body like you all
8 figure that out.

9 DR. HOWELL: Jerry.

10 DR. VOCKLEY: But if we don't say something
11 to her she won't be able to react to it. And
12 every time we do one of these iterations it
13 comes back four months later and it's four
14 months out of date. So I mean I think we have
15 to -- I think we have to -- very, very specific
16 recommendations and what was, has already been
17 proposed for number one sounds reasonable.
18 Everything else, I mean if there are some
19 other really specific things, I'd say we could
20 handle that by e-mail or a conference call or
21 something. I don't think waiting to get this
22 thing until the next meeting makes sense.

1 DR. PURYEAR: So if we prepare a revised
2 recommendation by the end of today for number

3 one, can we then have a vote?

4 DR. DOUGHERTY: I think number four also
5 needs some word smithing.

6 DR. PURYEAR: Number one and number four?

7 DR. DOUGHERTY: Yeah. In the actual
8 document number four is a little vague and
9 confusing.

10 DR. HOWELL: Now if we -- so what I'm
11 hearing is that there is interest in having some
12 clarity on number one, a bit more. And Denise
13 has volunteered to work on number four, to
14 clarify that.

15 DR. DOUGHERTY: I would also like to know
16 what Frank said.

17 DR. HOWELL: And so if we have Denise's
18 recommendations in consulting with the other
19 people and other folks working on number one;
20 can these modifications be made today and get
21 back to you so we can look at them and vote on
22 this before the end of the day tomorrow?

1 DR. DOUGHERTY: Well who's going to tell me
2 what number four means? I mean does it mean the
3 medical home? Pay for the medical home for care
4 coordination? It's just --

5 DR. WATSON: I think it's --

6 MS. JOHNSON: Well that was --

7 DR. WATSON: I think it's different from
8 that. I mean it says a bundled payment for
9 multiple providers dealing with the same child
10 on a day of care or on a -- you know, at a point
11 of caring. And that collides big time with the
12 current health care billing systems.

13 DR. DOUGHERTY: Oh, okay.

14 MS. JOHNSON: Well we took out the word
15 bundled payment and we just called it a payment
16 method. So I don't know if you want to put back
17 in bundled payment.

18 DR. DOUGHERTY: And it doesn't say on the
19 same day either. So are you talking about --

20 Unknown Female Speaker: It doesn't say
21 anything --

22 DR. DOUGHERTY: -- a bundled payment for an

1 episode of care?

2 DR. WATSON: The variability of these

3 conditions is such that you can't predict on a
4 uniform basis what the care needs of any one
5 individual are going to be over the course.
6 DR. DOUGHERTY: Well there is an issue --
7 DR. WATSON: So it has to get --
8 DR. DOUGHERTY: -- where you know, kids can
9 only go to, if you're under Medicaid or
10 something you can only go to one doctor on one
11 day and then you have to do another appointment
12 even if you're in the same hospital clinic,
13 right? Is that still a problem?
14 Unknown Female Speaker: Yes.
15 DR. DOUGHERTY: So that's -- I mean that's
16 something concrete.
17 DR. WATSON: We learned long ago how to play
18 that system.
19 DR. HOWELL: Well maybe you could wordsmith
20 that to read so that it would be a little
21 clearer to cover all possibilities including
22 seeing multiple physicians on the same day or

1 whatever and so forth so that that will be.
2 Chris.
3 DR. KUS: To me the gist of the idea is that
4 there's a financial incentive for providing care
5 to kids that are more complicated. And I don't
6 know, it's gets complicated when you talk about
7 bundled and you talk about clinics on the same
8 day because you've got managed care and you've
9 got fee for service and they mix together.
10 My idea is really that you want to get, make
11 sure that people who are, particularly as this
12 relates to primary care doctors who are caring
13 for kids with chronic illness; that they receive
14 incentive for the level of care that they need
15 to provide. Now I don't know -- I'll work on
16 some words but that's what --
17 DR. HOWELL: Well why don't you work -- you
18 can be the co-chair of Denise's committee --
19 [Laughter.]
20 DR. HOWELL: -- and work on number four. So
21 Chris and Denise can work on that to be clear.
22 So we'll have a revised recommendation on number

1 four. And who else would like to comment about
2 other recommendations?

3 [Laughter.]

4 DR. CALONGE: You know I would point out,
5 not volunteering to work on it.

6 DR. HOWELL: I think you already have.

7 [Laughter.]

8 DR. CALONGE: Four looks reasonably vague
9 enough that I guess I'm not as concerned; with
10 work with and pilot.

11 DR. PURYEAR: Yes.

12 DR. CALONGE: Now actually Denise, I also
13 don't know exactly what it means but it doesn't
14 sound very threatening. And it says let's put
15 our foot in this water and think about piloting
16 something. So that's what legislators always do
17 when they can't get what they want, they pilot
18 it.

19 DR. TROTTER: I think there's value in the
20 fact that this paper is generic and somewhat
21 vague but hits the tops we want to hit. There's
22 no possible way we're going to be able to create

1 the detail to this that would make any -- all of
2 us happy about each section. And that is
3 probably right at this stage.

4 DR. DOUGHERTY: Then maybe it's just the way
5 the language is crafted, it needs to be a little
6 clearer.

7 DR. WATSON: Yeah, I think you can --

8 DR. DOUGHERTY: Still a lot of --

9 DR. WATSON: -- generalize the language --

10 DR. DOUGHERTY: -- dependent clauses.

11 DR. WATSON: -- and get around some of the
12 problems. I mean bundling has a very specific
13 definition in this world with payment.

14 DR. HOWELL: Yeah.

15 DR. DOUGHERTY: And care coordination, which
16 used to be there, screams out medical home. And
17 then -- but if you're only paying the primary
18 care provider, it's not enough.

19 DR. HOWELL: Chris.

20 DR. DOUGHERTY: Some something vague but --

21 DR. PURYEAR: That's the new version.

22 DR. DOUGHERTY: -- less awkward.

1 MS. JOHNSON: That was the September
2 version. This is new version. While everybody

3 thinking about that I did have a question about,
4 because that came up. And with regard to
5 recommendation three on convening an expert
6 panel to examine billing and payment practices.
7 Are you all the expert panel or is that someone
8 else?
9 And then also, it says for the cost of
10 screening services. And does someone want me to
11 reword that so it's clear we're referring to
12 screening itself?
13 DR. HOWELL: Any comments about that?
14 MS. JOHNSON: Not the other components of
15 the system. We touched on that before so.
16 DR. BOYLE: This recommendation?
17 MS. JOHNSON: Sorry, no recommendation
18 three. Do you want me to go to that one?
19 DR. BOYLE: This one?
20 MS. JOHNSON: Yes.
21 DR. CALONGE: So the problem is, it's really
22 so difficult to separate screening costs from

1 the costs of the system. Because no one would
2 ever do a screening test if you couldn't -- I
3 mean that's one of the things. Don't screen for
4 it if you're not going work on the results.
5 MS. JOHNSON: Right.
6 DR. CALONGE: So I don't know how to
7 separate them out. To me, our laboratorians
8 have allowed us platforms that have really
9 rached down the costs of screening for
10 multiple conditions. When we use new modalities
11 then the costs tend to go up. But I would never
12 think of the screening service in isolation of
13 what it costs to take care of the positives. I
14 don't know.
15 DR. PURYEAR: I think screening -- and we
16 need to define screening services. Because
17 screening services here meant that system, not
18 just the screening test. So it's probably
19 putting in those words, the newborn screening
20 system services and saying education, screening,
21 diagnosis, et cetera.
22 MS JOHNSON: But then we had the comment

1 that there was no standard of care. Do we want
2 to refer back to the recommendation one in that

3 then?

4 DR. DOUGHERTY: But there is, but the
5 standard -- there is a standard of care for all
6 that stuff --

7 MS. JOHNSON: Right.

8 DR. DOUGHERTY: -- at that level. Maybe not
9 for exactly what the clinical intervention is.

10 So I do think --

11 MS. JOHNSON: Okay.

12 DR. DOUGHERTY: -- that there is a standard
13 of care based on the work by the Short-Term and

14 Long-Term Follow-Up Committees --

15 MS. JOHNSON: Right.

16 DR. DOUGHERTY: -- and so forth and so on.

17 We'd say, we need to include education of the
18 parent, referral, blah, blah, blah, blah, blah.

19 DR. CALONGE: States are doing this now and
20 everyone has a sense for how much it costs in

21 the state. Now not everyone finances it the

22 same way. Colorado is completely fee based and

1 we just average the cost of all the program over
2 the fee and apply it to every kid that gets born
3 in a Colorado hospital.

4 Other states do it in different ways. They
5 mix general fund, but all of us have a sense of
6 the metric of what it costs. And I think, you
7 have 50 states you could -- and you have a lot
8 of experts around the table; I would believe we
9 would be able to come up with a point estimate
10 and a range for the cost of the entire system.

11 That would be my feel. I'm looking at Chris to
12 see if he agrees. It might be a wide confidence
13 interval but.

14 [Laughter.]

15 DR. KUS: We'll take it under consideration.

16 DR. WATSON: I think it's that mix of very
17 specific language and then sort of -- I mean
18 these are general principles. You can't argue
19 with what you said so I think it's a matter of
20 getting the language away from really very
21 specific things like bundling payments and
22 national coverage decision policy and addressing

1 it a bit more generically.

2 Because I think everybody agrees that we

3 have to have an organized system that goes
4 through short term follow-up and long term
5 follow-up. And we haven't even dealt with the
6 issue of you know, the 12,000 kids with chronic
7 disease we're putting in the system who are
8 going to turn 21 and it'll be a free for all.

9 DR. HOWELL: Chris.

10 DR. KUS: See to me that's the issue really
11 is that chronic disease. A payment methodology
12 for children with chronic disease, working with
13 some of those words there. Because I think
14 that's what our system doesn't do. There's not
15 an incentive for chronic disease, financial
16 incentive.

17 DR. MUSCI: Is this really what's going on
18 in number one? Isn't -- wasn't this concept
19 already stated in recommendation number one?

20 DR. PURYEAR: I think that if we combined
21 number one with number two and it's really
22 working with the recommended standard of care

1 and service developed by this committee,
2 developed national guidelines; would that work?
3 [No response.]

4 DR. PURYEAR: I'm asking the committee?
5 Coleen, do you think so?

6 DR. BOYLE: I think so.

7 DR. PURYEAR: Because we have already
8 recommended that. I can't even remember where
9 this recommendation came from.

10 DR. HOWELL : Let me ask a question. To go
11 back, we have this document, we need to make any
12 modifications and sign off on the thing so it
13 can go forward. And if we make the changes that
14 we've had discussion about; number one and two
15 and so forth. And Denise will think about
16 number a little bit more; and make those changes
17 and let you see it again in the morning. Are
18 you going to be prepared to vote on this?

19 Unknown Male Speaker: Yes.

20 DR. HOWELL: Okay, well what we will do --

21 MS. TERRY: There are people at the
22 microphone too.

1 DR. HOWELL: Okay, we'll have some brief
2 comments from the gallery. Nancy.

3 MS. GREEN: From the gallery, Nancy Green,
4 Columbia University. So Sharon largely
5 addressed my comments about the electronic
6 medical record. But I think this discussion I
7 think reveals that there too you need some
8 specificity of language because what's an
9 electronic medical record?
10 I think what you're talking about Sharon is
11 an individualized medical record that's
12 electronic that's integrated with the other,
13 both individual and public health systems. So
14 thank you.

15 DR. HOWELL: Thank you. John.

16 MR. ADAMS: John Adams. Thank you Mr.
17 Chairman, a brief comment. As the father of a
18 young adult with PKU there's one point I want to
19 make that I hope something doesn't slip into a
20 crack. Alissa identified the comment that in
21 previous activities and the draft of this
22 report; the question of the cost of delivery of

1 metabolic medical foods for chronic condition is
2 a barrier to access to the services.

3 And I'd hoped that we would find a way, some
4 language here by an amendment or a new
5 recommendation to include that in the scope of
6 this paper. I would happy to work with the
7 staff on some appropriate language.

8 And for the record, I say this as -- I just
9 came from the largest ever meeting of the PKU
10 community in the United States. And it is an
11 issue. And I say this comment as the President
12 of the Canadian PKU and Allied Disorders and not
13 on behalf of my employer, Oz Systems. Thank
14 you.

15 DR. HOWELL: Thank you John. So Alissa,
16 Michele will work with the folks who are
17 modifying these recommendations. And we'll have
18 a modified document tomorrow for you to look at
19 again.

20 And if you have not read this carefully,
21 please get out your memory sticks tonight and
22 refresh your memory. And so we will plan to

1 come back to this tomorrow. I think that it's
2 time for a break. We'll take a 30 minute break

3 and return.

4 [Whereupon, there was a brief recess.]

5 DR. HOWELL: We're going to move on now with
6 our next presentation which is an
7 extraordinarily important area and one that in
8 the newborn screening world has received an
9 enormous amount of attention in recent times.
10 I think much of the attention has been based
11 on some of the public information is not
12 accurate about how these spots are used and
13 their value and so forth. But as you know,
14 we've had a paper that the committee's been
15 working on about the proposed recommendations
16 for the use and storage of residual blood spots.
17 And in September we reviewed a draft of
18 that. And we have sent it to a number of
19 agencies. And in your book, under Tab 8 is a
20 list of agencies from whom we have received
21 comments. Several agencies made major comments,
22 extensive and so forth.

1 And I must confess, having read them, they
2 particularly was impressed by the NIH's comments
3 where they had obviously read this draft in
4 extraordinary detail, which was wonderful, and
5 made a lot of very thoughtful comments; as did
6 others.

7 And so we now have Alissa Johnson joining us
8 again. And she's going to present the current
9 status of that paper. And particularly focus on
10 a the number of important comments that have
11 been received. Alissa.

12 MS. JOHNSON: Thanks. I hope you're not too
13 tired of me. So I will not be taking up this
14 full time. Dr. Howell is going to lead a
15 discussion of some of the comments afterwards.
16 But just to let you know real quickly.
17 I'm going to run through first of all,
18 changes that we made to the paper after the last
19 meeting based on your comments and what was in
20 the transcript. And then I will be running
21 through -- we sent that version out and I will
22 be running through some of those comments that

1 we received, but focusing on NIH and OHRP.

2 And then also, I'm going to talk a little

3 bit about a pre-meeting that I had with Dr.
4 Howell and Dr. Puryear and some changes that we
5 thought might be a good idea to go ahead and go
6 forward with. So we'll present those to you.
7 So just quickly, I'm going to run through
8 the changes that we made prior to sending this
9 paper out to different agencies. We added a
10 statement at the beginning of paper regarding
11 potential to advance science and clinical care.
12 And that was based on I believe comments from
13 Coleen, that she had recommended.
14 We also added language that stated; a policy
15 in place that has been reviewed by the state
16 attorney general or other appropriate legal
17 authority; to recommendations 1 and 2. That was
18 a concern that was expressed by a couple of
19 people to make sure that the policies actually
20 call for things that the programs can do.
21 We also removed validation from
22 recommendation 1. So it now reads; the policy

1 should specify appropriate use and storage after
2 the completion of newborn screen testing and
3 verification of results according to laboratory
4 quality assurance procedures.
5 And then we also combined recommendations 3
6 and 4. And we'll come back to that, concerning
7 the educational process of the newborn screening
8 system and educating parents.
9 And that actually -- I'll take the fall for
10 that. I thought it might be easier to combine
11 the two rather than having two separate
12 recommendations about education. But we did get
13 some comments about that.
14 And then we kept the optional recommendation
15 in the paper to obtain additional feedback.
16 That was just something that HRSA had wanted to
17 do.
18 Now we're going to go to the responses
19 received. And there have actually been some
20 additional responses that we received that
21 aren't on there. But we did receive responses
22 from; ASTHO; CDC; CMS, which didn't have any

1 comments; NIH; Office of Civil Rights; and OHRP.
2 APHL actually sent some comments that were

3 just received so they're -- well I just received
4 them so they're not in on the memory stick. But
5 I guess we'll make those available at some
6 point. And then AAP I believe has additional
7 comments. I think Dr. Vilosick's going to speak
8 to that later.
9 We also requested comments from the American
10 Hospital Association; the Council of State
11 Governments; the ISONG; the Midwives Alliance of
12 North America; National Association of Attorneys
13 General; NCSL; and NGA.
14 So first I'm going to go ahead and run
15 through the NIH comments. And I have here at
16 the bottom of each slide, you'll see it says
17 page 1. So if you want to, if you have your
18 memory stick and you want to scroll to the NIH
19 comments; you can actually look at where they
20 are on page 1 of the comments that we're
21 referring to.
22 NIH urges the committee to become an

1 advocate for research use by setting forth
2 actual recommendations for States to consider.
3 When might consent for secondary use be
4 necessary and what mechanisms might be used to
5 ensure privacy and confidentiality?
6 Also on page 1, NIH said; the committee
7 could propose voluntary national standards,
8 including provisions for broad research use that
9 each state could consider for adoption.
10 In addition, on page 1; recommend that the
11 Secretary provide resources to facilitate a
12 national dialogue with the relevant stakeholders
13 across the states, perhaps through the National
14 Conference of State Legislatures.
15 Again on page 1 at the bottom; the issue of
16 education around newborn screening is critically
17 important and merits a fuller treatment.
18 Recommendation 3 should lay out the two
19 currently uninformed audiences; parents of
20 newborns and health care professionals who
21 provide them with pre- and post-natal care.
22 On page 2; also with regard to

1 recommendation 3, so that's referring to the
2 education. Recommendation; states may need

3 federal funding support to implement educational
4 programs. Why not recommend that the Secretary
5 provide funds for these activities? You can see
6 a theme maybe that we should be being more
7 direct.

8 Page 2 again. Although reference is made to
9 the use of opt-in or opt-out approaches in
10 recommendation 4, the paper does not discuss
11 these approaches or when they would be
12 appropriate. Support to States
13 might also be needed to help them address this
14 recommendation.

15 On page 2 again, if you're following on
16 there. Recommendation 5 calls for the
17 development of a model consent/dissent processes
18 for the use of residual specimens. A concerted,
19 nationwide effort is needed to develop a
20 national policy and best practices that could be
21 adopted by individual states.

22 Page 2 again. The committee should remove

1 the Optional Recommendation in the paper which
2 is in line with what you all recommended at the
3 prior meeting.

4 On page 2 again. The committee should
5 consider the potential benefit of suggesting the
6 creation of a voluntary national research
7 repository for blood spots into which parents
8 could voluntarily opt their children.

9 So those were some of the comments specific
10 to the recommendations. These were additional
11 general comments.

12 First on page 2; add information about
13 current state practices with regard to research
14 use of residual specimens. We noted in our pre-
15 meeting that that's information that the
16 National Coordinating Center has, in part.

17 Although it's informal so we would need to talk
18 to them about whether or not that might be able
19 to be cited in here.

20 Add information about examples of scientific
21 and medical discoveries made possible using
22 residual dried blood specimens. And in our pre-

1 meeting we did have a few suggestions that came
2 up that we already had that we might add for

3 that.

4 Then there were a list of topics that they
5 thought you should consider whether or not they
6 need further discussion. So I'll just run
7 through those on page 3.

8 Potential benefits and risks that screening
9 programs should anticipate as they approach the
10 use of residual specimens. Anticipated scope of
11 future uses of these resources; genetic vs.
12 genomic;
13 public health vs. clinical medicine oriented.

14 Again, more topics that may need further
15 discussion. The possible impact of increased
16 data generation and data sharing on privacy.
17 Ongoing governance and oversight of future
18 research using these specimens. So who would do
19 that? Oversight of distribution, including to
20 whom, for what, and how the specimens will be
21 distributed.

22 Additional topics for further discussion.

1 Policies for the return of various kinds of
2 results. More robust discussion of re-consent
3 once subjects reach adulthood, which is an issue
4 that relates back to the question of ongoing
5 oversight and the intention to give results.

6 Given that residual blood spots are finite
7 resources, what is the optimal approach for
8 allocating the resources among competing uses
9 and needs? Do policies for stored blood spots
10 apply to other types of archived newborn
11 specimens such as peripheral blood, buccal
12 swabs, urine specimens?

13 So those were some of NIH's additional
14 general comments. Now I'm going to run through
15 -- in our pre-meeting with Dr. Puryear and Dr.
16 Howell, some of the things that we agreed to
17 that we would go ahead and move forward with
18 assuming that you all are in agreement with
19 that.

20 In the executive summary; and I suggested
21 that we define consumers. We thought that would
22 be an appropriate thing to do. That's on page 3

1 of other comments. Under policy, ethical and
2 legal issues. Add international guidelines for

3 specimen repositories. That's on page 4.
4 Under ownership on page 5, it says add case
5 law. Under stewardship; we decided to move
6 ahead with defining stewardship; shorten the
7 discussion of examples in Michigan and Denmark.
8 And I understand that APHO actually received
9 some comments from the Michigan program about
10 that so we can work with them.
11 And remove discussion of a global
12 consortium. And NIH's comment about that is on
13 page 4 of their comments if you want to see. On
14 page 5 of their comments; privacy protections.
15 We actually had some good comments from the
16 Office of Civil Rights. And if we accept all of
17 those, that pretty much take care of those
18 concerns.
19 Under awareness and education; add a
20 discussion of the role of prenatal care
21 providers in educating parents and themselves
22 and cite more published references on the

1 subject. That's on page 5 of the NIH comments.
2 Under consent/dissent; pages 5 and 6 of the
3 NIH comments. Work with OHRP comments into the
4 paper and add text box explaining -- so we want
5 to insert a box into the paper that explains
6 anonymized, unidentified, linked with
7 identifiers, identifiable, completely de-
8 identified, private unless decoded and double
9 coded samples.
10 Under financial considerations, and that's
11 page 6 of the NIH comments. In the pre-meeting
12 we decided to shorten significantly that section
13 but include examples of the cost of storage and
14 retrieval. And I think we mentioned California
15 and South Carolina.
16 Moving on to the OHRP comments. That's the
17 only other comments we're going to review
18 specifically at the meeting. But the rest,
19 again, have been sent to you.
20 Now these were general comment and points to
21 consider regarding how HHS human subjects
22 regulations may apply in the context of newborn

1 screening activities. And I think if you do
2 move forward with perhaps a model consent or

3 dissent about this discussion this would be
4 something to keep in mind as well.
5 First they noted that the collection of
6 newborn blood spots would not involve research
7 under HHS regulations for the protection of
8 human subjects if the specimen collection for
9 the newborn screening is not modified in any way
10 for a research purpose. This is the case even if
11 it is known the specimens will subsequently be
12 used for research purposes. That's on page 1 of
13 the OHRP comments.

14 DR. HOWELL: That's a very interesting
15 comment.

16 MS. JOHNSON: Page 2 of the OHRP comments.

17 If the specimens were collected for solely
18 clinical purposes, then the retention of
19 specimens for future research studies may
20 involve research, depending on whether the
21 retention of the specimens is being altered due
22 to the plan to carry out research using the

1 specimens. If the retention of the specimens is
2 not altered by the future research plans, then
3 the retention of the specimens is not a research
4 activity.

5 If the creation or maintenance of a specimen
6 repository is a research activity and associated
7 individually identifiable information will be
8 retained with the specimen, then the existence
9 of the repository would involve non-exempt human
10 subjects research.

11 In this case, the repository would require
12 review by an IRB and the informed consent of the
13 subjects or the subjects' legally authorized
14 representative, unless the IRB determines that
15 informed consent may be waived.

16 Another consideration for such studies
17 involving newborns is that the additional
18 regulatory protections for children involved in
19 research will be applicable if the research is
20 conducted before the subject reaches the age of
21 majority.

22 Finally, the research use of individually

1 identifiable specimens from a repository would
2 involve human subjects research that would

3 require IRB review and considerations of the
4 informed consent requirements under the HHS
5 subject protection regulations, unless the
6 research meets the criteria for exemption under
7 45 CFR 46.101(b)(4).

8 If the research involves non-exempt human
9 subjects research and the subjects will not have
10 reached the age of majority when the research is
11 to be conducted, then the additional regulatory
12 protections for children involved in research
13 will be applicable.

14 And that is it as far as the comments that
15 we are presenting. So I think you do have
16 plenty of time for discussion. And now is it
17 moving on to Dr. Howell?

18 DR. PURYEAR: Do you want to hear the
19 comments from AAP?

20 MS. JOHNSON: Oh, yes.

21 DR. HOWELL: Tim.

22 DR. GELESKE: The paper was sent out for

1 review to the Committee on Genetics and the
2 Section on Genetics and Birth Defects. And it
3 was actually sent out twice.

4 The first time there were no comments that
5 came back. The second time there was some
6 comment from the Committee on Genetics which
7 kind of dovetails the comments from the NIH in
8 their second paragraph.

9 Which really encouraged that the paper make
10 recommendations and more strongly put forth a
11 recommendation to have a national repository for
12 blood banking and to support the use of the
13 samples for future considerations. They felt
14 that the opening paragraphs, while talked about
15 this that in the conclusions that that emphasis
16 was lost.

17 DR. HOWELL: Are there any other general
18 comments on this paper which has been around for
19 a bit, et cetera.

20 And I think that my take on the NIH
21 recommendations was that they were interested in
22 trying to ensure that the samples would be

1 utilized appropriately for research and that
2 they be preserved for that.

3 I think that was the big gist of what went
4 through there. I was very interested in some of
5 the OHRP recommendations about research which I
6 thought were interesting and very specific.

7 Sharon.

8 MS. TERRY: So I think the OHRP
9 recommendations have to be taken in context with
10 what we've all discussed repeatedly writing this
11 paper. And that is that while they're
12 technically correct given the current law and
13 the understanding of OHRP that de-identified
14 samples don't constitute human subjects
15 research.

16 That in our context there's also the whole
17 public trust issue and the things that we
18 address in the paper that I think should remain
19 and should reflect that this is in a context
20 that is different than the typical ones that
21 OHRP is considering.

22 DR. HOWELL: Thank you. Gerry.

1 DR. VOCKLEY: I think that regarding the 2 OHRP comments, especially the last two where
3 there were, where there was guidance about when
4 IRB approval was going to be necessary.

5 That somehow or other we ought to bring that
6 conversation back to the issue that that
7 essentially makes any sort of national
8 collaborative study unmanageable, undoable.

9 Because if you have to get an IRB approval
10 at every hospital where babies are born and
11 samples are going to be collected, to try to
12 establish a national research resource; it's
13 going to be dead in the water.

14 And so we've had this discussion about
15 what's a national IRB and how might we expedite
16 these kinds of studies on a national level be it
17 through the Newborn Screening Collaborative, or
18 the Translational Research Network.

19 But somehow or other, I think we need to
20 make the point that this kind of all
21 encompassing resource collection can't be
22 handled on a institution by institution basis

1 and make it work for informed consent.

2 DR. HOWELL: Any further comment from
3 members of the committee about this document?

4 Obviously this document addresses the more
5 contentious areas of the entire newborn
6 screening program. Coleen, you had a comment?
7 DR. BOYLE: Just I guess a quick comment.
8 And I appreciate the committee, or the Writing
9 Committee addressing my comment previously which
10 I think was in line with AAP comment and the NIH
11 comment of saying that.
12 I'm trying to highlight the importance of
13 this resource both for research as well as for a
14 lot of improvements to the newborn screening
15 system. And so the opening introduction for me
16 kind of gets lost in the recommendations. I
17 would have really liked it incorporated within
18 the context of the recommendations.
19 DR. HOWELL: Further comments about this
20 document? Sharon, do you have any further
21 comments? We obviously need to get this moving
22 along and send it along with recommendations and

1 so forth.
2 I think that we need to preserve these
3 spots. They are tremendously valuable. Do you
4 think the paper adequately addresses the value
5 of the spots at the current time?
6 MS. TERRY: I think it does. I think given
7 all these comments we can crisp it up even more
8 strongly. I think the climate again has changed
9 since we started writing the paper, you know
10 with the imminent destruction of all the spots
11 in Texas in our minds.
12 So I think this makes it more pointed. Some
13 of these comments make it more pointed and I
14 think we can make sure that that's clear and
15 that that introduction is part of the
16 recommendations as we go forward.
17 And I also agree though that again, we
18 can't, as Gerry said for the last paper, take
19 four more months and revise this again. I think
20 we need to get this out as fast as possible.
21 DR. PURYEAR: Do you want to talk about the
22 outline?

1 DR. HOWELL: I think that the -- Michele has
2 reminded me and I think that it will not
3 necessarily apply directly to this paper. But

4 the Institute of Medicine, interestingly enough,
5 they have a round table that's been in business
6 for some time that's looking at the integration
7 of genomics into healthcare and so forth.
8 And their oversight, the oversight body of
9 the IOM has just recently reviewed their work
10 over the past few years and interestingly
11 enough, has come back and said we would like to
12 see this committee work more on newborn
13 screening. So it shows great wisdom over at the
14 oversight body.
15 And in discussing some of the areas that --
16 the IOM does not want to get into the same area
17 that we're working in. But one of the areas
18 they have expressed some interest in is to
19 sponsor a workshop with this committee jointly
20 that would engage the public for comments on the
21 use and storage of dried blood spot.
22 And I think that would be valuable. But I

1 don't think -- that's just looking for the
2 future, but not a priority. I would agree that
3 this paper should proceed and it should have
4 strong --
5 I think the key thing is that it's most
6 unfortunate to see the destruction of these very
7 valuable spots for lack of awareness and from
8 lack of preparation and so forth. So we need to
9 avoid that going forth.
10 DR. PURYEAR: Right, and there's multiple
11 prongs of approach here. Genetic Alliance has
12 been engaging with the Plaintiffs and the
13 Defendants in Texas to talk about this.
14 But in addition, regarding the comment you
15 just made. I'm on the Steering Committee for
16 that IOM round table and we are not allowed by
17 IOM rules to make recommendations. So the
18 function of this committee is absolutely
19 critical.
20 DR. HOWELL: Yes.
21 DR. PURYEAR: And while the aerodyte study
22 of the IOM round table will be important we need

1 to move quickly I think.
2 DR. HOWELL: Yeah I would agree with that.
3 Any further comments about how to move this

4 paper along? It's amazing it's written in a
5 current language in view of the fact that it's
6 been in process so long.

7 [Laughter.]

8 DR. HOWELL: But is there any comments about
9 how we could get these important comments
10 together and get the thing out the door? What
11 would you like to do?

12 DR. VOCKLEY: Are we allowed to do an e-mail
13 approval? I mean I think a draft review and
14 approval without the need to be face to face
15 would make it a lot easier.

16 DR. HOWELL: That's not a problem to do as
17 far as I'm aware is it? Michele is sitting here
18 looking anxious.

19 [Laughter.]

20 DR. HOWELL: What would you -- I don't know
21 whether it's her cold or the anxiety.

22 [Laughter.]

1 DR. CALONGE: Public comment I guess was the
2 concern. Do we have to allow public comment?

3 DR. PURYEAR: Our plan as committee staff
4 was to actually revise the document, and this is
5 in your notes, revise the document based on the
6 comments that we got today and the comments that
7 we received from the various organizations.

8 Send it out for formal public comment within
9 a Federal Register notice. Because we need
10 formal comments from various organizations. And
11 then based on those comments have a final draft.
12 I'm hoping that can all be accomplished by May.
13 The IOM meeting is tentatively scheduled for
14 May 24th. So we promised them that that would
15 be part of the public comment process if they
16 could arrange it. So this -- and we want to
17 make sure that this goes through review from the
18 various HHS legal authorities; Office of General
19 Counsel too to make sure that what's being
20 recommended is correct.

21 DR. HOWELL: Ned.

22 DR. CALONGE: So Michele could I ask if

1 staff feels they have adequate input to revise
2 the document today and actually send it out for
3 simultaneous -- I mean start the review process

4 rather than even go through another cycle of us
5 reviewing it?

6 DR. PURYEAR: Yes.

7 DR. CALONGE: Because I think it's so close.

8 I think the points that were made are important.

9 I think you've captured them. I would just

10 revise it and let's get started on the review

11 process.

12 DR. HOWELL: Now is the committee

13 comfortable with having staff take the

14 considerations that we've had today, prepare a

15 document and send it then to the Federal

16 Register? Is that good? We should have a

17 motion on doing that.

18 DR. CALONGE: So moved.

19 DR. HOWELL: We have a motion. Do we have a
20 second?

21 DR. KUS: Second.

22 DR. HOWELL: And those favoring that?

1 [Chorus of ayes.]

2 DR. HOWELL: And any opposition?

3 [No response.]

4 DR. HOWELL: No opposition. Did anyone
5 abstain?

6 [No response.]

7 DR. HOWELL: So it was unanimous. So we

8 will expect the staff working with Alissa to

9 come up with incorporating the comments that

10 we've heard today. It will go out to the

11 Federal Register for publication and we'll look

12 forward to hearing from them.

13 MS. JOHNSON: I do have one quick question

14 though. They did mention specifically giving

15 examples of model consent or dissent processes.

16 And Michele and I had talked about possibly

17 instead of trying to reinvent the wheel and

18 coming up with something on our own, giving some

19 examples of what states do. So I'd want to know

20 if everybody would be comfortable like putting

21 on an appendix or something?

22 DR. HOWELL: Sharon.

1 MS. TERRY: And I'll also add to that, that

2 not only are there things states do currently

3 but there's already emerging technologies that

4 have rolled out since we started this paper that
5 do consent and assent through various technology
6 systems.

7 MS. JOHNSON: Okay.

8 MS. TERRY: So I think some examples of
9 those things would be great.

10 DR. HOWELL: Do you have an adequate number
11 of valuable uses of the spots, which was
12 strongly recommended to include in this
13 document?

14 MS. JOHNSON: Well you and I, we discussed
15 talking about adding some studies that have been
16 done.

17 DR. HOWELL: Right.

18 MS. JOHNSON: Yeah, so I can do that. And
19 then I was going to talk to Mike about whether
20 or not we might be able to include some
21 information that was done for the Coordinating
22 Center. Although, it hasn't been published and

1 it was informal, so I'm not sure about that.

2 But I will talk to him.

3 MS. TERRY: And Alissa also the workshop
4 that Mike and we put on, we're in the process of
5 transcribing some of that.

6 MS. JOHNSON: Okay.

7 MS. TERRY: So I mean it comes from Piero,
8 it comes from Sharon Cardea. But that had a lot
9 of richness to it in terms of what the benefits
10 would be as well.

11 MS. JOHNSON: Okay.

12 DR. HOWELL: Okay, so we have a plan I
13 think. We'll add those things and so forth.

14 MS. GREEN: Carol Green, University of
15 Maryland and actually Society for Inherited
16 Metabolic Disease. First of all, thank you very
17 much for a wonderful document.

18 And I'd like to come back to something that
19 I think Sharon just brought up. And ask whether
20 having you know, now looking at another four
21 months and public comment, whether there are a
22 couple of elements of the document that might

1 turn into, if the committee wishes it, a letter,
2 a very short letter to the Secretary talking
3 about how important this, these blood spots are

4 as a resource for children's health.
5 Also talking about how important are the
6 issues in public trust. But pointing out that
7 this can be used as a resource safely, that
8 OHRP; again being careful about the language,
9 has pointed out that it is legal, it's ethical,
10 there are ways to do this. Genetic Alliance is
11 working on ways to do this in a way that doesn't
12 violate public trust.
13 But I'm wondering if having just a short
14 letter might be something that could help Sharon
15 as she's trying to work with Texas and folks,
16 just an intent from the committee, something
17 that says this is valuable even if you can't yet
18 get to the whole thing. Whether a short letter
19 might be useful.
20 I would also point out that when you're
21 putting in the what good's come out of it, is go
22 way back. I mean we have CF screening because

1 people used stored blood spots in Colorado. Go
2 way back to galactosemia and everything else,
3 all the lives that are saved.
4 I just respectfully suggest that it could be
5 a, you know a one page letter that could be
6 useful in the discussion.
7 DR. HOWELL: Thank you very much. The
8 posting in the Federal Registry will only be 45
9 days. So it's not four months, fortunately.
10 And I would anticipate that with the
11 alacrity with which the staff at HRSA works, we
12 can get a document posted in the Federal
13 Registry very quickly. And so hopefully that
14 will not too long. They're very, very efficient
15 over there.
16 Are there further comments about this
17 document?
18 [No response.]
19 DR. HOWELL: I think this can be an
20 important document and I think the situation in
21 Texas is fairly settled. We might not agree or
22 disagree with the settlement but it's pretty

1 well along as far as what they have agreed to
2 legally and where they are going in the future.
3 Jane.

4 DR. GETCHELL: I just want to clarify. So
5 if we have comments on the recommendations how
6 do we, and when do we voice them?

7 DR. HOWELL: Now.

8 DR. GETCHELL: Right now.

9 DR. HOWELL: Right now.

10 DR. GETCHELL: Okay, well I do have a
11 couple. And on the recommendation specifically
12 I believe it's number four. Where it talks
13 about using anonymized samples for program
14 evaluation improvement and so forth. I had some
15 concerns with that.

16 We are using them basically for the purpose
17 they were collected. And by anonymizing them,
18 which I'm assuming is the same as blinding them,
19 and that's a question I had to, it sort of
20 defeats the purpose. Yeah it is, it's
21 recommendation four.

22 DR. CALONGE: And you're talking

1 specifically about quality improvement and --

2 DR. GETCHELL: Yes, exactly. Which is not
3 research and that's kind of the point.

4 DR. CALONGE: It's part of the laboratory
5 practice and the testing.

6 DR. PURYEAR: And according to OHRP's
7 explanation, this would have to be revised which
8 I think would address --

9 DR. HOWELL: So that will be addressed I
10 think in the revision with OHRP.

11 DR. GETCHELL: Okay.

12 DR. HOWELL: And I think that -- will that
13 satisfy your concern Jane?

14 DR. GETCHELL: Yes.

15 DR. HOWELL: Good. Do you have more than
16 one?

17 DR. GETCHELL: That was the most important
18 one I had.

19 DR. HOWELL: If you have a less important
20 one.

21 [Laughter.]

22 DR. GETCHELL: Well I think we're --

1 MS. JOHNSON: I have them and I can go over
2 them and e-mail yours if I want to make sure I'm
3 addressing them appropriately.

4 DR. GETCHELL: Okay.

5 MS. JOHNSON: And then they'll be sent out
6 everybody can see it again.

7 DR. GETCHELL: That would be great.

8 DR. HOWELL: Okay, and so we'll -- that will
9 come to be and it'll go to OHRP. Well the
10 committee has continued in it's usual active
11 and decisive manner and we're ahead of schedule.
12 But we are going to move on and pick-up one
13 of the Friday morning activities. And we're
14 going to ask Tracy Trotter to give his report on
15 the Response to the Council on Bioethics' Report
16 on Newborn Screening. Tracy, thank you very
17 much.

18 MS. JOHNSON: I just want to thanks and
19 thank you to the working group for letting me
20 edit your baby that I know you worked so hard
21 on. So I hope I'm not messing it up too bad.

22 DR. HOWELL: Well thank you Alissa for your

1 editing work and we look forward to even more
2 over the next few days. We'll get Tracy's
3 slides uploaded here very promptly.
4 Fortunately, he brought a copy with him.
5 [Discussion off the record.]

6 DR. TROTTER: Good morning. I was tasked by
7 Dr. Howell with reviewing the President's
8 Council on Bioethics' Report that was published
9 in December of 2008 entitled, the Changing Moral
10 Focus of Newborn Screening.

11 And to a group of us to come up with a
12 response from this committee regarding that
13 document. I borrowed liberally from all of
14 these folks. But the final product I will take
15 responsibility for in terms of how it's going to
16 come out today.
17 And our goal is to then have the committee
18 help me modify the comments today into something
19 that we can produce as a document, a written
20 document. And I thank all the people on the
21 slide though, without them this would not have
22 occurred.

1 A little background. The Council on
2 Bioethics, the membership of the council is
3 as noted up there. And there are eight

4 physicians, or people with M.D.'s on the
5 committee, and a scattering of other folks. I
6 think it's interesting to note the specialties
7 over there.
8 There's one of each, of each of these
9 specialties. And if one reads carefully this
10 document you'll see that it reflects the amount
11 of knowledge about newborn screening that you
12 would expect from that makeup.

13 [Laughter.]

14 DR. TROTTER: The purpose of this white
15 paper as I'm quoting from the report. "Is to
16 foster public awareness of the practice of
17 newborn screening, the ethical principles that
18 have guided it until now and the ethical
19 problems posed by its current and future
20 expansion."

21 This was about 400 pages. The first 10
22 pages covered the principles that guided it

1 until now. And the last 390 were the problems.

2 [Laughter.]

3 DR. TROTTER: So the overall, over arching
4 question is, what ethical principles should
5 guide the practice of newborn screening in the
6 United States? And their conclusions came down
7 to seven elements that are, that should be part
8 of, and I quote again; "an ethically sound
9 approach to public policy in newborn screening".
10 And we'll talk about each of those seven
11 elements. Although I'm going to really discuss
12 elements three and four because I think they're
13 the only ones that have, need our input, need
14 our response.

15 So we'll just go through them somewhat in
16 order, obviously. Element number is to reaffirm
17 the essential validity and continuing relevance
18 of the classical Wilson-Jungner screening
19 criteria.

20 As all of you and all of us in the public
21 health world know, this is a World Health
22 Organization document from 1968. It was

1 designed basically for adult chronic diseases,
2 but has been incorporated by almost everybody in
3 screening since then.

4 There are 10 W-J criteria for population
5 based screening. And is nicely summarized in
6 Alan Fleischman's excellent article that was
7 previously published commenting on this report
8 as "screen only if you can treat". And it's
9 pretty straight forward. If you use that you'll
10 figure out all the rest of the criteria.
11 Their second point is, however, only, and
12 note that I have only -- oops, that worked
13 pretty well.
14 [Laughter.]
15 DR. TROTTER: So much for that idea.
16 Anyway, only, and this is an important concept
17 that we're, that I want this room to work on
18 today. That only the Wilson-Jungner criteria
19 would be used to validate newborn screening.
20 The implications if one reads carefully are;
21 that the core panel may not meet those criteria.
22 That evidence based decisions are lacking. That

1 additions to the core panel may not meet the
2 criteria. And that other criteria have no
3 bearing in newborn screening.
4 It's carefully couched if you read the
5 article. They don't really say it doesn't.
6 They just say it may for 390 pages. So there
7 have been, amazingly for those of us old enough,
8 since 1968 a lot of things have happened. We'll
9 summarize a few of them.
10 1975, the Genetic Screening Report which was
11 a product of the National Research Council of
12 the National Academy of Sciences, broadened the
13 concept of benefit in newborn screening. And
14 this is, I think, much where most of the world
15 is at this point in trying to understand the
16 benefit to many of these diseases, many of these
17 problems.
18 Not only direct benefit to the child, which
19 has always been our number one concern. But
20 also to facilitate management decisions that
21 will clearly benefit a child whether you
22 directly have a medication or a procedure that

1 might fix them.
2 Provide supportive treatment, which is often
3 the most important thing pediatricians do with

4 many things. To inform subsequent reproductive
5 decisions for families. And all of had, in this
6 room have clearly dealt with those who have
7 identified second child, a second child
8 identified before the first child's diagnosed.
9 And provide knowledge regarding rare
10 diseases. And even more important in our venue
11 because of the rarity of what we deal with.
12 So if we look at the last 10 years, we can
13 look at really the explosion of progress in this
14 area I think. In 1991 ACMG coming into being
15 was very important in that it gave the medical
16 genetics world a forum and a group that could
17 speak for them as a sub-specialty and for them
18 as a science. And that's been very helpful.
19 And tandem mass spectrometry of course
20 showed up in the '90's and totally changed
21 newborn screening ending up with in 2003, the
22 Secretary's Advisory Committee coming in to

1 being. The result of that in 2005 of course is
2 the core panel.
3 And then in the last three years, there have
4 been at least four workgroup reports which have
5 further, after much work, further clarified I
6 think where one goes and what criteria need be
7 used.
8 I'll specifically talk about a couple
9 things. One is the initial ACMG expert group, a
10 member of the core panel. I love the concept,
11 as a pediatrician, that maybe the policy should
12 be driven by what is best for the affected
13 infant. If we all sort of kept that in mind I
14 think the rest of these actually become fairly
15 easy.
16 They felt that both the criteria of the
17 original classical criteria, if you will, and
18 the NAS/NRC criteria made sense and utilized
19 those to come up with their criteria, if you
20 will.
21 That we needed a specific and sensitive
22 screening test that applies to the, in a public

1 health setting. That there was a sufficiently
2 well understood natural history. And that there
3 was available and efficacious treatment.

4 In this case, treatment was expanded once
5 again to think of an infant. The infant
6 treatment which could be management, support,
7 and/or direct treatment; the family, the
8 reproductive decisions; and society in general,
9 knowledge about conditions, avoiding the
10 diagnostic odyssey.
11 Which not only as many of you parents in
12 this room know, is extremely expensive but also
13 extremely taxing emotionally to go through. And
14 that the states will make the final decisions.
15 This is a state based program as we all know.
16 I would then look at -- the next one I'm
17 going to talk about was a workgroup that I
18 participated in that came up with a report. We
19 lovingly call it the Calonge Report. I think
20 genetics medicine is going to change the name of
21 that Ned, I don't know. But we're disappointed
22 if they do.

1 [Laughter.]

2 DR. TROTTER: It will be published soon I
3 believe. And this was last year. You know most
4 of us in this room worked on this over a long
5 period of time to develop a method for
6 evaluating conditions nominated for population
7 based screening in the newborns. And it
8 understood that there are unique issues. And
9 those unique issues need to be dealt with in a
10 scientific fashion.
11 And those issues included many things, but I
12 noted multiplex technology; new information; and
13 the understanding that benefit is different in
14 conditions that have limited population based
15 controlled trials. Which again, we're going to
16 get in to more and more even with these newer
17 conditions that were nominated potentially
18 today.
19 So with all of that progress, we now can say
20 in response to element number one; is the ACMG
21 criteria actually I think do recommend, do fit
22 the currently recommended consistency with

1 previous criteria.

2 There is documented benefit to the affected
3 infant from early detection. And there is a

4 reliable screening test that is feasible in a
5 public health setting. In and of that
6 particular element I don't think there's
7 actually a question. Although there was an
8 implied question.
9 Element number two was that, and the italics
10 is a direct quote from the Council on Bioethics'
11 paper. So this is -- I'm just writing the seven
12 things that come on the last page of the summary
13 there.
14 So number two is; insist that mandatory
15 newborn screening be recommended to states only
16 for those criteria [sic] that clearly meet
17 classical criteria. Again my feeling is, 29
18 core conditions in fact meet that criteria.
19 If one wants to become very picky about it,
20 it becomes more difficult to say only Wilson-
21 Jungner, or do you include NAS/NRC. Again, I
22 think the ACMG expert panel chose the later in

1 that it made more sense with these conditions.
2 And I will hope that we all think it makes more
3 sense now.
4 Secondary conditions; which we think are
5 secondary that are picked up by basically
6 laboratory findings because we need those
7 findings to clarify the core conditions were
8 handled quite differently. And we're going to
9 come back to that because I think that's where
10 we're going to take departure from the Council
11 on Bioethics' thoughts.
12 So element number three, is they endorsed
13 the view that screening for other conditions
14 that fail to meet classical, re: Wilson-Jungner,
15 criteria may be offered by the states to parents
16 on a voluntary basis under a research paradigm.
17 So the classical criteria, just to remind
18 you, is limited to those criteria from 1968.
19 They cited the Massachusetts experience which
20 then used 10 core mandatory conditions that they
21 felt meet the criteria and all other conditions
22 were optional when they talked about it.

1 So here's where I can't go along with them.
2 I don't think we even shoehorn in there. I
3 think there is a need to move forward beyond the

4 classical, if you will, Wilson-Jungner criteria.
5 Newborn screening is a far different animal than
6 they would have ever considered in 1968. And is
7 in fact moved on from the NAS/NRC report in
8 1975.

9 And I think this committee has wrestled
10 with, and dealt with nicely, attempting to come
11 up with a process that is appropriately robust
12 in making this decision for criteria.

13 Having said that, when conditions do not
14 meet the expanded criteria, there is clearly a
15 role for research within newborn screening
16 programs. We need that to both enhance our
17 screening techniques and make them better and
18 better.

19 You need them to study disorders so that if
20 they become candidates in the future, which I am
21 certain is going to happen, that we have data on
22 them and we all have been struggling with that

1 in the last year or so here.

2 Their fourth element was to affirm that when
3 the differential diagnosis of some targeted
4 disorders entails detection of other poorly
5 understood conditions [that would not otherwise
6 be suitable candidates for newborn screening],
7 such results do not need to be transmitted to
8 the child's physician or the parents.

9 And their options with this recommendation
10 were that you would either suppress the
11 information that you had found. Or that you
12 obtain informed consent at the time newborn
13 screening was done. I'm glad to hear your
14 gasps, thank you.

15 So we have another problem here. First of
16 all, these are truly incidental and inevitable
17 findings that are an integral part of the
18 testing process for the core panel. The
19 implication of the Council on Bioethics' Report
20 was that this was a surreptitious way to advance
21 newborn screening beyond what it should be.
22 And as carefully worded as it might be, that

1 is the way almost anybody would read it. And I
2 think that's, number one, inappropriate. But so
3 what? We'll go on beyond that anyway.

4 Why not reveal the incidental findings?
5 More importantly, why should we? The number one
6 reason is the number one reason. It is patently
7 unfair and unreasonable to disregard these
8 results.
9 It is beyond my personal comprehension that
10 if the State of California knew my child was
11 affected with a rare disease that they would
12 choose not to tell me and I would think that was
13 okay. I think that's not okay. And I think
14 there's a lot of reasons beyond that. But just
15 patently, it's not all right.
16 Not only will we avoid the diagnostic
17 odyssey. It would inform reproductive decision-
18 making for my wife and I. It would allow us to
19 get in to an early supportive intervention for
20 both our child and ourselves. And it would
21 allow us to look for clinical research studies
22 might be available to us that could make a huge

1 difference.
2 An informed consent is not part of that.
3 Informed consent, in terms of picking up that
4 diagnosis and letting me know, I worry would get
5 in the way of getting newborn screening done.
6 So informed consent is not appropriate for core
7 conditions, no question about that.
8 It is required for research studies, no
9 question about that. But let's not be confused
10 by the incidental findings or secondary
11 findings. I do not feel that they fit that
12 criteria.
13 And if one were to attempt to get informed
14 consent for that while you're doing mandatory
15 newborn screening, I fear that would fall apart.
16 I may be wrong, but that would worry me a lot.
17 Number five is to encourage the states to
18 reach a consensus on a uniform panel of
19 conditions. What a great idea.
20 [Laughter.]
21 DR. TROTTER: We're here for you.
22 [Laughter.]

1 DR. TROTTER: All right, six. Use a
2 thorough and continuing reevaluation of
3 disorders now recommended for inclusion; yada,

4 yada, yada, yada. And the answer is, we do that
5 and we have multiple organizations who are at
6 the table today and a number who are not at the
7 table today who actually do that on a pretty
8 much constant and continuous basis. I think
9 that's well covered.

10 Okay, and number seven is; reject any simple
11 application of the technological imperative,
12 i.e., the view that we are screening for a
13 disorder merely because we can, because it's
14 detectable. And I think we clearly are not
15 doing that. And it has been clear to me as a
16 member of this committee, in fact I learned this
17 as a member of this committee.

18 That if all other criteria are met, and only
19 then, do we then review -- the review process
20 then goes to the technology and says, is there a
21 suitable test available? Can it meet public
22 health needs? Can it be done on a national

1 basis? And is it economically reasonable or
2 feasible?

3 And that's after it meets the criteria. I
4 don't think anything -- I do think we have been
5 driven by technology and we're going to continue
6 to be. And that is a good thing. It doesn't
7 make that the primary criteria. It makes it a
8 good thing that helps us go further.

9 So as you might imagine, I have a conclusion
10 or two. One; newborn screening is a state-
11 based, well established and very effective
12 public health program. It's actually the model
13 for early diagnosis and treatment. Something
14 that pediatricians would love to have for many,
15 many other things in our lives.

16 The Advisory Committee offers guidance
17 basically through its recommendations to the
18 Secretary. And then we have to allow the states
19 and those that make the final decisions to do
20 so. This Advisory Committee I think has moved
21 well beyond the seven elements noted in this
22 report.

1 I think we have created; I know we have
2 created a structured, evidence based assessment
3 that supports a consistently rigorous,

4 iterative, and transparent approach to making
5 these recommendations regarding broad population
6 based screening for rare conditions. And I
7 applaud our efforts. And that is my report.
8 Thank you.

9 DR. HOWELL: Thank you very much Tracy. I
10 wonder if there are comments to Dr. Trotter
11 about his review of this report? I think most
12 of the members, I assume all of the members of
13 the committee have read this report. Do you
14 have any comments about the report? Ned and
15 then Piero.

16 DR. CALONGE: Tracy that was great. My
17 comments have to do with the suppression of results
18 for poorly understood conditions. And I
19 understand your position and umbrage. And I
20 also understand that there is variation in that
21 position by both state and actually nations.
22 And I think that there are in depth

1 arguments on both sides that an underlying
2 feeling or basic value may not capture. I don't
3 have the best answer for this.

4 I am concerned that the detection through
5 screening of an underlying condition may not
6 fully capture the phenotypic expression of that
7 metabolic condition or whatever else we screen
8 for.

9 That some of the precursors that we look at
10 are not in a -- since we don't fully understand
11 the disease, we may be identifying a condition
12 for the pediatrician and therefore the family,
13 that's never expressed and yet the concern is.
14 I think perhaps the best route to find
15 compromise, and again, this is opinion based
16 because I don't have a good evidence base. Is
17 that if we move forward the strong
18 recommendation to not suppress results, there be
19 some approach to develop a uniform provider and
20 parent education around the lack of information
21 about this result.

22 I suspect that there may be persons in the

1 room who have received a report of a probably
2 benign mammogram. Which is one of the hardest
3 things for a provider to discuss with a patient

4 and for a patient to understand, what does this
5 really mean to me.

6 And I think that uncertainty has a value in
7 terms of you need to do follow-up. But it also
8 has harms, in the view that it's probably benign
9 but I can't say it's normal.

10 So I think trying to look at a uniform, or
11 at least a recommended approach to how to
12 provide these results where there's uncertainty
13 about expression or therapy, in a standardized
14 way to the providers of care for these kiddos
15 and the parents I think is just an important
16 part if we're going to take on the, if you find
17 it you need to tell them.

18 DR. HOWELL: Thank you.

19 DR. TROTTER: I would agree with that. And
20 I think the -- and I was obviously not clear in
21 my presentation. When I say detecting the
22 secondary conditions or results, in my mind I'm

1 separating out the variance of unknown
2 significance.

3 I mean we do get results in all kinds of
4 genetic tests that we don't know what to do
5 with. And I realize the huge problem that is.
6 From diseases, disorders we know about we just
7 don't know what to do about them.

8 I think there's a difference there. And I
9 think it's a big difference. And you're right,
10 some there need to be criteria to help figure
11 that out. Every -- if I got every single result
12 from every genetics that went out, my confusion
13 level would be higher than it is now.

14 DR. HOWELL: I think the follow-up along
15 that same line is that these conditions that we
16 -- these abnormalities or these variations about
17 which we know little, we should also be very,
18 very aggressive in setting in place research
19 efforts that would follow-up on these
20 abnormalities to see what indeed they do mean.
21 They may not mean anything, and there may be
22 underlying a significant problem.

1 DR. TROTTER: Correct, it's our one
2 opportunity to actually identify the cohort.

3 DR. HOWELL: Piero.

4 DR. RINALDO: I don't know if it's possible
5 to go back to that slide that says element
6 number four.

7 DR. TROTTER: Sure.

8 DR. RINALDO: And you had made a comment
9 about perhaps some --

10 DR. TROTTER: That part?

11 DR. RINALDO: The next one please.

12 DR. TROTTER: Okay.

13 DR. RINALDO: The point that I think has
14 escaped often in this discussion is that it's no
15 longer an issue of revealing. Because the
16 distinction between the condition we are
17 targeting and the other possibility will happen
18 only after the confirmatory testing.

19 So unless we truly believe that you can tell
20 a parent that I'm going to do a test on your
21 child but I will only tell you one type of
22 results but not the others. It's ridiculous.

1 So it's not an issue on fairness, of
2 unreasonability. It's an issue on realistic.
3 It's not realistic to say that you suppress the
4 results of confirmatory test because you're
5 already there.

6 You already recalled the patient. You
7 already communicated to the family that
8 something is going on. And that goes back to
9 the point that time after time we repeat. We
10 are not screening for conditions, we are
11 screening for markers.

12 And usually any marker has a differential
13 diagnosis. And so some of the things you will
14 detect are obviously more treatable and better
15 known than others. But it seems to me that we
16 are having a philosophical discussion about
17 something that cannot be changed.

18 DR. TROTTER: Thank you, I agree.

19 DR. HOWELL: Alan.

20 DR. FLEISCHMAN: Let me see if I understand
21 what you're arguing. Because this Council,
22 which by the way has sun setted and it no longer

1 is in existence. There will be a new commission
2 that is being developed right now by the White
3 House.

4 DR. HOWELL: I think sun setting is a polite
5 way of saying that Mr. Obama dismissed the
6 group.

7 [Laughter.]

8 DR.. HOWELL: For the record.

9 DR. FLEISCHMAN: But the reason that we're
10 entertaining this exercise is because this
11 report does exist and it is very evident if you
12 just do a Google search or whatever. And there
13 is need for comment on it.

14 But let me understand Piero, I mean I
15 believe this group would say to you; don't
16 confirm that -- I believe this group would say
17 in those secondary tests, suppress the
18 information completely. Don't confirm, don't do
19 anything with them. Or at least that would be
20 an option.

21 So Tracy's argument comes a step before the
22 discussion you're having. And that I believe is

1 what the Council said. I don't happen to agree
2 with them. But I think that's what they said.
3 Again, maybe you can give me a practical example.

4. Dr. Rinaldo: Because I can tell
5 you, for one thing; in the vast majority of
6 cases the evidence that will sort out between a
7 legitimate target and one of these, let's call
8 it incidental findings, is not done by a
9 screening laboratory. It's done by a diagnostic
10 laboratory.

11 So you really have no business to tell a
12 clinical laboratory that you will have to
13 suppress information. So the question is, in
14 the moment that you make contact and you ask for
15 something else, the issue if it's the primary
16 target or the secondary target is moot because
17 you're beyond that.

18 So I, I wear the hat, the screening hat and
19 the clinical lab. I don't think you just use,
20 oh I found this disease, oh but this is on the
21 black list so I call it normal. You want me to
22 falsify my report? It's just insane.

1 DR. HOWELL: Alan.

2 DR. FLEISCHMAN: Yeah, I don't want to argue
3 this issue.

4 [Laughter.]

5 DR. FLEISCHMAN: What I want to say is, I
6 think there are a few very critical issues that
7 this report that Tracy's authoring should focus
8 on.

9 The first I think should be that in fact,
10 the justification of the mandatory screening
11 program does lie in the ability to do
12 intervention and treatment. And we can broaden
13 what that definition is, but it lies in that
14 philosophical approach.

15 The second point is, the point that Tracy
16 brought up as an aside. And that was that the
17 Council didn't believe, didn't believe that the
18 secondary panel was not avoidable in the present
19 technological process.

20 They truly believed it was a surreptitious
21 way for the laboratorians or the pediatricians
22 or somebody to diagnose more diseases.

1 DR. RINALDO: That's there problem Alan. If
2 they are not knowledgeable it's there problem.
3 If they talk about things they don't know,
4 that's what they should get.

5 DR. FLEISCHMAN: Excuse me. So I think our
6 report should clarify that in no uncertain terms
7 what the reality is of these findings. That's
8 all I'm saying. I don't disagree with you.

9 DR. HOWELL: In a very simplistic way. I
10 believe that what Piero is saying, is that if
11 you look at a mass spec pattern and you find a
12 group of compounds that are abnormal or that are
13 outside the range that could indicate this child
14 has one of the conditions on the core panel but
15 it might be something else.

16 And so you do further studies. And you find
17 out, oh it's not one of the core, but it's the
18 other. And so you can't possibly not tell the
19 family the results.

20 DR. FLEISCHMAN: That's the third issue.

21 DR. HOWELL: Yeah.

22 DR. FLEISCHMAN: The second issue is to

1 clarify their misconception.

2 DR. HOWELL: Yes.

3 DR. TROTTER: Exactly.

4 DR. FLEISCHMAN: And that's what you were
5 just doing.

6 DR. HOWELL: And it's conceivably not
7 possible.

8 DR. FLEISCHMAN: But in our --
9 [Laughter.]

10 DR. FLEISCHMAN: Most neurologists,
11 neuroscience research, neurosurgeons, are
12 educatable. That's not our goal. Our goal is
13 not to change the opinion of this learned group.
14 Our goal is to write a report that stands out
15 there to clarify their misperceptions. And so
16 that if somebody would read this report it would
17 clarify the report that's out there for the --

18 DR. HOWELL: And I believe that can be done
19 by simply elaborating on Piero's comments about
20 how the system really works.

21 DR. FLEISCHMAN: And then the third most
22 important issue, is this issue of justifying why

1 this group, I think based on Ned's comments does
2 not believe in suppression of information to
3 families that might in fact impact on their
4 child and their lives that have been generated
5 through this ethical process that we've just
6 described in number two.

7 And I think those are the three issues that
8 are the most important for us to clarify based
9 on the misperceptions of the Council. And I
10 think Tracy's hit on those.

11 DR. RINALDO: I have one more comment. You
12 know the truth is that since the publication of
13 the appearance of a uniform panel. This
14 Bioethics, whatever it's called, Report is just
15 a combination of a campaign of disinformation.
16 Where people have deliberately refused to
17 understand the concept. That the fact is, the
18 marker has a differential diagnosis.
19 Many people in this room have turned blue in
20 the face in trying to explain it. And they
21 always were hitting a wall. So I'm just seeing
22 this wall showing it's ugly head one more time.

1 But don't tell me that we fail in our attempt to
2 explain it.
3 It was explained over, and over, and over

4 again. And you know, as they said the worst
5 type of deaf is a person who doesn't want to
6 listen.

7 DR. HOWELL: Dr. Watson has been very
8 anxious to say a word.

9 [Laughter.]

10 DR. WATSON: I wouldn't go so far as to say
11 anxious. But I think you can clarify this issue
12 for them by getting a little bit more specific.

13 There were 25 secondary conditions. 22 of those
14 are conditions where the marker identifies the
15 patient.

16 And in the course of establishing that going
17 through a differential diagnosis you don't end
18 up with PKU but you end up with one of four ways
19 of having a bipterin defect. Which is
20 important stuff to know clinically. Three of
21 the 25 are things that are identified because
22 the panel, our group agreed that only, any

1 clinically significant result should be reported
2 out.

3 So when you're running a tandem mass spec
4 profile of the aminos, you can see tyrosine and
5 you can see arginine. You might -- and even on
6 -- well just for those two, it was our decision
7 that those were clinically significant results
8 that should be reported.

9 You didn't have to see them if you were
10 using a form of tandem mass spectrometry that
11 filtered out those peaks because you had pre-
12 decided that they weren't significant. So those
13 are two of the three. The other is on the
14 acetylcarnitine profile is C5, that picks up
15 SCAD.

16 There's a lot of question about whether that
17 specific analyte should be seen or not on the
18 first run. But there's really just those three
19 conditions that one might identify by not having
20 filtered out all of the other peaks that you
21 didn't think you wanted to see.

22 So you know, at the end of the day 22 of

1 them are the differential diagnosis that the
2 physician goes through. And I don't think they
3 cannot tell the patient that they have a

4 clinically significant condition caused by
5 something other than the classical PKU mechanism
6 of phenylalanine hydroxylase deficiency. And
7 that's the lion's share of this stuff.

8 D. HOWELL: I think that Tracy did a
9 wonderful job in reviewing each of these. And
10 the plan is for this working, this writing group
11 to write a document that would include the
12 comments he's made and try to -- well put on
13 paper the descriptions that Piero has done.
14 It's important that this report have a
15 response because it's out there. It's as Alan
16 points out, you Google, you pick it up. And so
17 we need to have a response that clarifies some
18 of the misconceptions in this document.
19 Is there any -- would anybody have concern
20 about Tracy and his group proceeding to draft a
21 document that will come back to this committee?
22 But we should get it out there. Denise.

1 DR. DOUGHERTY: I don't know if you were
2 associated with this when the ACMG report when
3 through its torturous process here. But I think
4 it's not quite right to say that the ACMG report
5 did a careful review of the evidence for all
6 those aspects of the Wilson-Jungner criteria.
7 We unanimously adopted that report but it
8 was on the condition that the group move forward
9 and have a different approach the next time.
10 Which is why we have this nomination, evidence
11 review, all that process. Which is quite
12 different from the ACMG report even though we
13 started from the same list of topics.
14 So I'm not sure how to handle that in the
15 response. But I personally would not sign off
16 on something that said, yes we did follow all
17 these criteria in that first round.
18 I mean I think there's a way to say; they
19 make a point, we learned from that experience,
20 we've moved on. Look at how we're doing it
21 differently now and how rigorous we are. But I
22 would not sign off on anything that said, we did

1 it the right way the first time.

2 DR. HOWELL: Kwaku, you had a comment?

3 DR. OHENE-FREMPONG: Well actually it was an

4 example. I mean we are considering
5 hyperthlassemia hemoglobin h disease now. But
6 the marker for this condition has been available
7 for decades to all the newborn screening
8 programs. And either by default or by decision
9 most states don't even report the presence of
10 hemoglobin marks.
11 So it's not a very far fetched example where
12 something that actually, probably should have
13 generated some follow-up; and it's not an easy
14 marker to confirm because it decreases after
15 birth. So it doesn't lend itself to the
16 traditional confirmatory testing. In that we do
17 much more sophisticated.
18 But it is something that I think most
19 programs in this country don't report even
20 though it's a marker of hyperthlassemia for
21 most of these children. And I think it's by
22 design in most cases.

1 DR. HOWELL: Any further comments? I think
2 there's a sense that it's a worthwhile document
3 to prepare. We've heard a variety of comments.
4 And Tracy I think that you've gotten support
5 from the group to proceed with your work.

6 DR. TROTTER: I would appreciate everybody
7 who has comments, if you could send them to me
8 and maybe educate me about the ACMG process the
9 best you can. Because I think it needs to be --
10 everything needs to be there.

11 I mean I want this to be as factual and as
12 complete as we can make it. I don't think the
13 end conclusion's going to be any different then
14 probably what we've presented today. But we --

15 DR. HOWELL: This group spent a year
16 discussing the ACMG report. And I think that
17 many people around the table can summarize that
18 year briefly, hopefully.

19 DR. TROTTER: I don't want the year's
20 discussion. A paragraph would be lovely.

21 DR. HOWELL: Denise will be chairperson of
22 the summary committee.

1 [Laughter.]

2 DR. HOWELL: Are there further comments and
3 so forth? I think it's lunch time and we're

4 right on the moment. And so we'll return quite
5 promptly at 1:00. Now we have, fortunately we
6 have done some of the early afternoon stuff so
7 we'll plan to start right off after lunch on the
8 T-cell issue.

9 [Whereupon, a luncheon recess was taken.]

10 DR. HOWELL: But we have a series of very
11 important discussions this afternoon having to
12 do with T-lymphocyte defects, severe combined
13 immunodeficiency. And we're going to, in just a
14 minute hear from Dr. Jennifer Puck who will be
15 presenting her material remotely.

16 And Dr. Puck has submitted a revised
17 nomination form to the committee which is in
18 your folder. And it provides clarification,
19 particularly of the definition of severe
20 combined immunodeficiency.

21 There are important issues for the committee
22 to think about as we deliberate this particular

1 nomination. One is the clarification of the
2 definition of SCID.

3 The nominators and immunology committee
4 define SCID broadly. And when this issue was
5 discussed, when the committee first discussed
6 this nomination, committee members were thinking
7 of the definition of SCID to include all
8 lymphocyte deficiencies not just X-linked SCID.

9 The committee deliberations on SCID offer
10 the opportunity for the committee to consider a
11 mechanism or a model in which the committee
12 develops a means for approval or the addition of
13 the uniform panel either as a primary or
14 secondary condition that is contingent on
15 collecting data to monitor the screening
16 program.

17 As you recall, when the group reviewed this
18 nomination the first time, it was felt to be a
19 very strong recommendation and there were
20 certain specific things that the committee would
21 like to have available.

22 And so that will be -- and so we might well

1 define a sub-category in one of the
2 recommendations that would include this form of
3 situation where the condition is a important one

4 to be nominated. And the require or have as a
5 condition of that nomination the acquisition of
6 certain material.

7 And I would like now to ask Dr. Puck if she
8 is on-line to present her material. Jennifer.

9 DR. PUCK: Yes I am on-line. Can you hear
10 me?

11 DR. HOWELL: Very well, thank you. And your
12 slides are up. They look great. We know who is
13 working with you here.

14 DR. PUCK: Yes, so I would like to thank you
15 and the entire committee. And I am very
16 impressed with this process of evaluating
17 conditions and finding whether they're worthy to
18 be added to newborn screening panels.

19 I want to say that I've had help preparing
20 this presentation today. And you can see on
21 this first slide the people who have helped me.
22 And if we could go to the next slide.

1 I would just like to summarize the feedback
2 I got from you last year when SCID was first
3 considered by the full committee. And the
4 finding was shown here. The major weakness of
5 the nomination is whether there are sufficient
6 population based data to evaluate the clinical
7 validity of the TREC based screening test.

8 And furthermore, there were a series of gaps
9 identified. And in the next few slides I would
10 like to point out progress that has been made in
11 the past year to address some of these gaps. So
12 if we could look at the next slide.

13 This addresses the first objection or first
14 gap. Was that we have not seen prospective
15 identification of real SCID cases in pilot
16 screening trials. And of course, as everyone
17 knows, Wisconsin and Massachusetts have been
18 running state-wide pilots. And we're going to
19 hear a little bit more about those in just a
20 minute.

21 And in this slide I'd like to bring up that
22 SCID itself, or severe combined immunodeficiency

1 was the original primary target of TREC
2 screening. And this was how we presented the
3 nomination at first.

4 SCID is not a single entity. And here I
5 define it by very low or absent T-lymphocytes
6 produced by an infant such that ability to
7 resist infection is severely compromised. There
8 are over a dozen known and additional unknown
9 SCID genes.

10 And of course, when T-lymphocytes are not
11 functional or not present then they cannot help
12 B cells make specific antibodies. I think of T-
13 cells as the conductors of the orchestra of the
14 immune system. And there can't be any coherent,
15 adaptive, resistance to infections without an
16 appropriate number of good, diverse T-cells.
17 So in addition to the narrow definition of
18 SCID that we started with, it's now clearly
19 apparent that there are related conditions that
20 also have very low T-cells. And therefore, have
21 a risk of life threatening susceptibility to
22 infections.

1 And some of these are Severe DiGeorge
2 Syndrome, Severe Folate Receptor Deficiency.
3 Certain patients who have anatomical problems or
4 leaky GI tract that allows lymphocytes to be
5 sequestered and lost.
6 And in addition, there are conditions;
7 Omenn's Syndrome and SCID with maternal T-cell
8 engraftment. T-cells get in to the infant's
9 circulation during the birth process we believe.
10 And in these conditions, T-cells can be
11 found in the infant but they are alleloclonal.
12 They're not a good, diverse repertoire and they
13 don't do the job of conducting the immune system
14 orchestra.
15 So all of these conditions are characterized
16 by very low or absent TRECs. And I would like
17 to emphasize as I've put in bold at the bottom
18 of this slide, infants with any of the above
19 conditions should receive prophylactic anti-
20 infective therapy until their condition is fully
21 worked up and understood and addressed.
22 And in particular, what has turned out to be

1 very important, they should not receive their
2 live load of virus vaccine, which is now
3 recommended. And I actually pulled down from

4 the CDC website this morning the rotavirus
5 recommendations that are currently there.
6 This is a live attenuated vaccine that has
7 been made available in the last couple of years.
8 And now it is recommended for universal use.
9 The first dose is to be given at two months of
10 age. And depending on the brand, either two or
11 three doses are given at two month intervals.
12 The package insert does say that this
13 vaccine is not for infants with HIV/AIDS or for
14 patients with any disease that affects the
15 immune system. The only trouble is, we don't
16 have a way of knowing which infants might have
17 something wrong with their immune system and
18 thereby experience severe prolonged diarrhea
19 from this vaccine.
20 And I would call your attention to the
21 abstract that I included in the updated packet
22 for this year from Werther, et al., where a

1 rotavirus vaccine strain diarrhea was the
2 presenting complaint of a child with severe
3 combined immunodeficiency. And actually this is
4 not an isolated incident. Now there have been
5 additional cases of SCID with severe diarrhea
6 due to the vaccine strain rotavirus.
7 Just to finish up what's on this slide.
8 Infants with any of the above conditions can be
9 detected with very low TRECs. And I think
10 you'll hear about that from Dr. Comeau and Dr.
11 Routes shortly. But I also would like to call
12 your attention here to the two publications that
13 I included in the packet from Dr. Buckley's
14 group this past year.
15 In long term follow-up of patients with
16 SCID, it turns out that TRECs were a very good
17 tool to measure the ongoing production of T-
18 cells in these SCID patients who had been
19 effectively treated with a bone marrow
20 transplant.
21 And this publication, both of these
22 publications not only show the highly successful

1 treatment of SCID, but they also show that the
2 TREC test is a very good way to monitor the
3 production of new T-cells. And they correlate

4 with a diverse T-cell pool. Could we look at
5 the next slide?
6 So the other gaps, the willingness and
7 capacity of states beyond Wisconsin to implement
8 screening. As you know, we know have added
9 Massachusetts to Wisconsin and we hope to add
10 more states.
11 And also, I am running a targeted trial in
12 two hospitals in the Navaho Indian population
13 because they have found a mutation with a very
14 high SCID incidence.
15 And I think all of these trials are showing
16 that the tests can be run in a reproducible way
17 with a continued false positive rate of less
18 than 0.1 percent. So we do have new evidence on
19 that score.
20 Could we have the next slide? And at this
21 point I wonder if Jack could just stand up and
22 say a couple of words with the slides here about

1 his program in Wisconsin.
2 DR. ROUTES: Hi, good afternoon. It's an
3 honor to be here. I'm very happy to comment on
4 our experience in Wisconsin, which I believe has
5 been highly successful. Next slide please.
6 So what I'm going to talk about is our first
7 year's experience in screening newborns for T-
8 cell lymphopenia and severe combined
9 immunodeficiency. In total we screened 71,000
10 infants. And that isn't an error. For some
11 reason it's 71,000 infants, that was it. We
12 decided no more for 2008. Of the full term
13 infants, it's about 64,000. Premature about
14 6,600.
15 In the State of Wisconsin, under a current
16 algorithm, the way the newborn screening test is
17 done, they will continue to test abnormal
18 results from premature infants until they reach
19 the equivalent of 37 weeks of gestational age.
20 So what I'm going to do is focus on our results
21 on the full term or 37 week infants.
22 We had previously done a fairly large scale

1 preliminary study on about 6,000 newborn
2 screening cards to establish what we felt would
3 be a reasonable cut off for a TREC value in a

4 full term infant.
5 And based on that data, which was published
6 in the Journal of Allergy and Clinical
7 Immunology earlier in 2009, we had a TREC value
8 of approximately 25. And then we also had an
9 act in value that would determine that the
10 template was intact.
11 Out of the total, in essence 71,000 a little
12 bit under, we had a total number of 17 TREC
13 assays that were abnormal. And I must say this
14 was less than what we anticipated when we
15 originally set this up. We were a little bit
16 surprised.
17 Now then under our preferred algorithm,
18 because this is a, really a new assay somewhat.
19 And we really wanted to correlate the low TRECs
20 with the flow cytometry in numerating T-cells
21 and T-cell sub-sets. We really did try to push
22 the physicians to get flow cytometric evaluation

1 once the infant had a low TREC value.
2 That flow cytometry was done at our
3 institution, the Medical College of Wisconsin,
4 free of charge for all the infants that were
5 identified in the newborn screening process.
6 But nevertheless, four parents decided to
7 have a repeat card. And on those the TREC assay
8 was normal. One infant died before we were able
9 to numerate the T-cells due to a metabolic
10 cause. One parent refused a further evaluation.
11 And 11 actually went to flow cytometry. And
12 out of those 11, we identified eight infants
13 that had T-cell lymphopenia. In other words,
14 three out of eleven had normal flow cytometry.
15 We contacted the physician and those infants
16 were no longer followed up.
17 The remainder were all evaluated by
18 physicians. Three of the infants that we
19 identified had what we called third spacing of
20 lymphocytes or extravasation of the T-cells
21 outside the vascular bed.
22 We identified two 22Q, or DiGeorge Syndrome.

1 Out of those two, one of the infants hadn't been
2 identified at birth. And we've identified other
3 DiGeorge that hadn't been identified at birth as

4 well. We had two, what we termed idiopathic T-
5 cell lymphopenia.
6 And then we had, identified an infant with a
7 rare two mutation. Which is what my colleague
8 calls a combined, combined immune deficiency.
9 Because not only was this infant lymphopenic,
10 had a marked neutrophil abnormality.
11 And this infant underwent successful bone
12 marrow transplantation. And I am very happy to
13 say is doing remarkably well.
14 So just to summarize, our experience has
15 been fantastic with this assay. I mean we're
16 very pleased with how specific it is. In other
17 words, when we identify a low TREC, you know
18 really most of these cases are important causes
19 of T-cell lymphopenia.
20 The assay is cheap. It's about \$5.50 per
21 test, and as Dr. Baker can testify, this is
22 easily incorporated in the current algorithms

1 for newborn screening.
2 DR. PUCK: Thank you Jack. I wonder if we
3 can go right to the next slide and have Dr.
4 Comeau stand up and give us an update on the
5 Massachusetts pilot program.
6 DR. HOWELL: Before we hear from Anne, tell
7 me what the patient had that died of the
8 metabolic cause.
9 DR. ROUTES: I am actually not positive on
10 what the actual cause of death was. But there
11 were a number of abnormalities in terms of liver
12 function tests and things like that.
13 We are currently going back to all the
14 infants that died in the first year with
15 abnormal TRECs and trying to determine cause of
16 death. We recently got IRB approval at our
17 institution to do that. And Mae, Dr. Baker is
18 also IRB approval at the University of
19 Wisconsin.
20 So I, unfortunately can't give you a direct
21 cause. But according to the referring
22 physician, it was said to be metabolic of some

1 sort.
2 DR. HOWELL: We'll be interested to hear
3 about that. Thank you very much. Anne, if you

4 want to briefly review your experience.
5 DR. COMEAU: Thank you. Yes, I only have
6 two slides. And I wanted to draw your attention
7 to when we went forward with the implementation
8 in Massachusetts we did, as we did with other
9 conditions, we first established a wide working
10 group of transplantation specialists,
11 immunologists, infectious disease people as
12 well.
13 Our assay is a little bit different in that
14 the assay that we are using is a multi-plexed
15 assay such that the assay has an internal
16 control. Every single baby is tested not only
17 for TRECs, but also for a reference gene,
18 RNaseP. So it's a multi-plexed TREC assay.
19 Next slide please.
20 At this point in time I can report that
21 we've tested, since the beginning in February of
22 '09, about 77,000 specimens, about 68,000

1 infants. Our testing algorithm is similar to
2 that in Wisconsin. I won't say that it's
3 exactly the same.
4 And certainly, the vast majority of babies
5 who have suspect TREC results are babies from
6 neo-natal intensive care. 272 specimens
7 prompted a request for a repeat. But most of
8 those babies, as I said, were in neo-natal
9 intensive care.
10 Of the 272, only 51 of the 68,000 babies had
11 a recommendation for flow cytometry. And of
12 those 51 babies, 19 of them were shown by flow
13 cytometry to have T-cell lymphopenia.
14 Of the T-cell lymphopenias, we're not as far
15 a long yet in finalizing all of the diagnoses,
16 but we have seen I believe four partial
17 DiGeorge, Jacobsen Syndrome, many thymectomies,
18 and several of the babies who are still pending
19 final diagnoses. Next slide please.
20 This is the last slide. As part of our CDC
21 grant we were asked to train other state
22 programs. And this slide I think is a good

1 example of where we are at at this point in time
2 and that other state laboratories definitely
3 have the capability to move forward with a

4 complex assay such as a multi-plex TREC.
5 We have completed one weeks training of the
6 people from the Texas Department of Health, the
7 California Department of Health, and the
8 Minnesota Department of Health. And if you were
9 to take these babies -- excuse me.
10 All of these babies from these states, plus
11 Wisconsin and Massachusetts, that cohort would
12 represent, even though it's a small number of
13 states, 750,000 to about a quarter of all babies
14 born in the United States.
15 And the next training will be at the CDC in
16 early March. Wisconsin will also be doing
17 training of other states in this assay. And I
18 think that's everything that I wanted to say.
19 Thank you very much.
20 DR. HOWELL: You did a significantly large
21 number of flow cytometries then did the folks
22 that we just heard from.

1 DR. COMEAU: 51 out of 68,000.
2 DR. HOWELL: And they had --
3 DR. COMEAU: That's less than .1 percent.
4 DR. HOWELL: Jack how many did you report?
5 DR. ROUTES: 11.
6 DR. HOWELL: You had 11 out of 68,000 as
7 opposed to 70 something.
8 DR. COMEAU: Yes.
9 DR. HOWELL: Can you explain why there was
10 such a big discrepancy there?
11 DR. COMEAU: I think it probably is the
12 initial screening algorithm, not so much the
13 test as to what prompts a repeat TREC assay and
14 then what prompts flow cytometry.
15 DR. HOWELL: What's the cost of the flow
16 cytometry? I realize it was reported to be
17 free. But nothing is free. It obviously has a
18 specific cost.
19 DR. COMEAU: I don't know that. It's not in
20 my budget because it's charged -- do you know?
21 DR. ROUTES: For our flow cytometry that we
22 do in Wisconsin, it's an abbreviated form that

1 would pick up SCID and it's approximately \$100.
2 DR. HOWELL: Thank you very much. Thank you
3 to Anne very much. Before we get on with it,

4 apparently we have a bit of housekeeping.
5 DR. PURYEAR: We've been asked to ask you to
6 please lean in to your microphones, speak in to
7 it. So that you can be heard.
8 DR.HOWELL: When does -- Jennifer?
9 DR.PUCK: Yes.
10 DR. HOWELL: Do you have any comments after
11 these excellent presentations?
12 DR. PUCK: Well I could push on and show the
13 rest of my slides --
14 [Musical interruption.]
15 DR. HOWELL: Jennifer we know you're in San
16 Francisco, but I mean that was a bit much.
17 [Laughter.]
18 DR. HOWELL: You were going to push on
19 before we had this musical interlude. Can you
20 push on please?
21 DR. PUCK: Yes, could we have the next slide
22 please?

1 DR.HOWELL: Do you have a question of
2 Jennifer?
3 DR. RINALDO: Jennifer?
4 DR. PUCK: Yes.
5 DR. RINALDO: This is Piero, hi. Can you
6 tell us more about the study of the Navajos?
7 You said they had an incidence, so have you
8 found any?
9 DR. PUCK: So I can tell you I have not
10 found any yet. I was going to tell you a little
11 more about the Navajos and I had to ask the
12 tribal IRB for permission as they require of
13 every investigator doing research with their
14 population.
15 And the IRB meeting of the Navajo Nation was
16 cancelled due to a blizzard this week. So they
17 have not considered my request and I'm not able
18 to share details.
19 I can share that the test is being run
20 without any difficulty. We are using a face to
21 face informed consent. And we're not getting
22 100 percent participation. And we're running it

1 in two hospitals and we have now enrolled about
2 650 infants with no SCID infants.
3 And we do know that we have not missed any.

4 In fact, there have been SCID infants diagnosed
5 late who were not in my screening hospitals. So
6 that we know they're -- when there are cases on
7 the reservation we get them and we hear about
8 them.

9 The incidents of SCID is about 1 in 2,000
10 births on the Navajo Reservation due to a
11 founder mutation in the artemis gene, which is a
12 DNA recombination gene. So again, we don't have
13 a true SCID case. We don't have a single sample
14 that has been unsatisfactory up to this point
15 out of over 600, but the trial's ongoing.

16 DR. HOWELL: Thank you Jennifer. You would
17 like to proceed with your standardization?

18 DR. PUCK: Yes, just to wind up. Can we go
19 to the next slide to address the gap that was
20 identified that standardization and proficiency
21 testing would be needed. And the CDC has
22 stepped up to the plate here. Bob Voight has

1 worked on preparing quality control materials.
2 And although he was not able to come to the
3 meeting, he gave me these slides to share with
4 you. He will, I think it says here by April
5 2010, he will have QC materials available to
6 send out to any lab that wishes to have them.
7 And they have been circulated between
8 Wisconsin, Massachusetts, and also my own lab.
9 And these are samples that have high range, low
10 range, and undetectable TRECs. And I think that
11 people who run them in the different labs have
12 had very consistent results across the sites.
13 In addition, the training and education that
14 the CDC has taken on as a mandate has commenced,
15 as you heard with the first session already
16 taken place at Dr. Comeau's laboratory in
17 Massachusetts. Next slide.
18 And Bob Voight just also wanted to share a
19 typical series of TRECs. Calibrators run in his
20 lab. And you can see from this beautiful
21 straight line with a very nice R-value that from
22 run to run there's very good consistency in the

1 assay as being done in his lab. And I'd say
2 that this is true across the board. Next slide.
3 In terms of the costs. I think we've heard

4 from Wisconsin. My Navajo trial has a similar
5 cost. And I think the cost in Massachusetts is
6 stated to be similar to other screening tests.
7 In other words, even though this is a new
8 platform and DNA extraction, which could
9 potentially be a platform for many tests in the
10 future, it's sort of all being charged to the
11 TREC assay at this point. And even with that,
12 the test cost does not seem to be out of line.
13 And finally I wanted to bring up that there
14 is a new entity now, a funded consortium called
15 the Primary Immune Deficiency Treatment
16 Consortium. This was funded in September 2009
17 by the Office of Rare Diseases and NIAID.
18 And this is a program within the rare
19 disease network. And this group is dedicated to
20 follow-up of all infants with lymphocyte
21 disorders that are treated by cellular therapy;
22 that is transplantation or gene therapy.

1 And so this is a nationwide effort that will
2 now enroll and follow-up patients with SCID and
3 SCID variants so that we'll have a much better
4 handle than in the past on their outcome.
5 And finally in terms of cost I think we
6 should think about what is the cost of not
7 performing screening. And I think that during
8 the public comments we'll have an opportunity to
9 reflect on that. And I'd like now just to go to
10 my final slide.
11 So during the past few days, those of us
12 who've contributed to this presentation have had
13 a conversation and have brought other
14 immunologists into the conversation about SCID
15 and expanded SCID or T-lymphocyte defects.
16 And I don't think that it's necessarily our
17 place to tell you whether, whether to consider
18 the narrow definition of SCID or a broader
19 definition of T-lymphocyte defects perhaps as a
20 secondary target.
21 What I really want to leave this group with
22 is that there is a public health interest in

1 intervening in the lives of infants with low
2 TRECs. And in particular, right now, we need to
3 avoid potential harm from an otherwise

4 beneficial public health program, which is the
5 rotavirus vaccine program.
6 So that we should not be giving live
7 vaccines until a patient is evaluated by a
8 qualified expert in immunology who finds that
9 vaccinating with a live vaccine would be safe.
10 And the second point in this slide is that
11 we want to assure that infants with low TRECs
12 get the evaluation by such an expert without
13 delay. And third, that there also is a public
14 health interest in tracking the ultimate
15 outcomes of these patients to measure the
16 effectiveness of screening, of diagnosis, and of
17 management.
18 And so this is the end of my presentation.
19 I don't know if there are any questions for me
20 or if we should just go to the public comments.
21 DR. HOWELL: Are there specific questions
22 for Jennifer at this point? We're obviously

1 going to move along and so forth. We have a
2 series of comments to deal with today.
3 We're going to have some comments from Dr.
4 Guttmacher. Then we're going to have some
5 public comments. And then we're going to come
6 back to the committee where there'll be
7 additional comments and so forth.
8 I've asked Dr. Guttmacher to comment
9 specifically about the NIH initiative because as
10 you recall when this program was discussed some
11 time ago there were certain questions that the
12 committee felt needed to be answered and so
13 forth.
14 And Dr. Guttmacher, who I introduced earlier
15 this morning, as the Acting Director of the
16 Eunice Kennedy Shriver National Institutes of
17 Child Health and Human Development is involved
18 in a heavy way in this way and I think I'd
19 appreciate Alan's comment.
20 DR. GUTTMACHER: Thanks Rod. And I'd like
21 to begin just by saying what a pleasure it is
22 for me to be on the committee as a pediatrician,

1 medical geneticist, and for a dozen years, the
2 Medical Director of the Newborn Screening
3 Program in Vermont.

4 It's nice to be able to -- I was always
5 somewhat jealous when I was at the Genome
6 Institute, maybe envious is a more formal term,
7 of the fact that NICHD represented the NIH on
8 this committee. So now my, somehow my jealousy
9 is rewarded or something.

10 [Laughter.]

11 DR. GUTTMACHER: I like to think rewarded,
12 not punished. Rod had asked me to, I think for
13 some of you I'll be alerting you to this and for
14 some of you I'll just be reminding you of it.
15 And that is a solicitation which went out
16 from the NIH, and for those of you who are NIH
17 aficionados and would like to look it up, the
18 official solicitation number is NIH NICHD CD3
19 TM1014. And this has to do with an existing
20 contract with Health Research, Incorporated of
21 Rensler, New York for whom the PI is Ken Pass.
22 I have wonderful verbiage here describing

1 why Ken Pass is a guru of newborn screening, but
2 I won't embarrass Ken by reading it. I think
3 those -- the folks around the table know that
4 Ken has some expertise in this area.

5 The original contract had a focus to develop
6 a multi-plex assays for a variety of disorders
7 that included Galactosemia, biotinidase
8 deficiency, MCAD deficiency, hearing loss due to
9 connexin in the 26 mutations or cyto -- or CMV,
10 congenital hyperthyroidism, CAH, cystic
11 fibrosis, CRAC disease, and other
12 leukodystrophies, and SCID.

13 The original contract used Luminex or multi-
14 plex B technologies. And we're currently in
15 negotiations with HRI regarding the addition of
16 the SCID pilot that I can tell you something
17 about because it's in the public record already.

18 And that's -- the basic idea is to extend
19 the original contract to permit HRI and
20 collaborators, the collaborators is important,
21 to provide evidence and feasibility of
22 technologies related to severe combined

1 immunodeficiency in the environment of newborn
2 screening.

3 The extension of time is needed to provide

4 ample time for HRI to coordinate the evaluation
5 of a sample significant power to provide
6 evidence regarding efficacy.
7 Among the research priorities which are
8 being looked as we negotiate this with HRI is to
9 be able to look at appropriate screening
10 technologies that are either available
11 immediately or will be with a short set up
12 period, something like less than three months.
13 Be sure there is the ability to provide
14 immediate confirmatory test and procedures for
15 presumed positive results. That there is the
16 capacity and resources available for tracking
17 positive cases and for arranging appropriate
18 follow-up care and referral of identified
19 newborns with presumed SCID in a timely manner.
20 That there are administrative structures
21 conducive to prospective pilot testing including
22 the documentation and ability to obtain human

1 subject's approval in a timely manner.
2 I keep emphasizing this timely because the
3 idea is this is really trying to get the work
4 done and get done well but quickly. And there
5 should be adequate quality assurance and quality
6 control procedures in place for accurate
7 assessment of findings.
8 And the hope again is to have significant
9 power from this to be able to answer some of the
10 question that have been, we've been talking
11 about I think this morning in general, but
12 specifically be able to answer them for SCIDs.
13 I should also mention that we are also in
14 conversations about how we might be able to
15 extend or enrich this contract both literally
16 and figuratively in terms of public/private
17 partnerships. Other folks who have interests in
18 looking at these same issues, besides the NIH
19 that might be able to join in this either
20 formally or do some kind of supplemental funding
21 or something to see if the reach of this cannot
22 be extended even further.

1 DR. HOWELL: Thank you Alan. So I think
2 that you've heard that the NIH is working very
3 aggressively and rapidly toward putting in place

4 a system that will permit some of the questions
5 that we had asked before to be answered quite
6 promptly.
7 This afternoon we're doing something a
8 little bit different. And we usually have all
9 the public comments on Friday, as you know. But
10 since some of the public commentators had
11 specifically related to this particular subject,
12 we're going to now hear from four scheduled SCID
13 commentators.

14 And they've all assured me, hands upraised,
15 that they will be concise as well as very wise.
16 And we'll start first with Fred and Vicki
17 Modell. And Fred I think has been elected as
18 the spokesperson here.
19 MR. MODEL: So let me first say to you Mr.
20 Chairman and members of the Advisory Committee,
21 thank you for this opportunity. Most of you
22 know, Vicki and I established the Jeffrey Modell

1 foundation in memory of our son, who lost his
2 battle with one of the primary immunodeficiency
3 diseases at the age of 15.
4 Since our earliest days with the foundation,
5 we have had a very close collaboration with the
6 CDC and with the NIH on biomedical research and
7 the CDC on education and awareness activities.
8 Our work with the Appropriations Committee
9 in both houses of Congress has had a profound
10 impact. In the areas of research, public
11 awareness, and physician education. These
12 efforts have actually led to extraordinary
13 results for these often undiagnosed disorders.
14 But in recent days we have directed our
15 efforts and resources to implementing population
16 based screening for severe T-cell lymphopenia
17 including SCID.
18 We have always stressed the need for
19 earliest possible diagnosis. And we actually
20 believe, as most of you do, that newborn
21 screening is the ultimate path to reaching that
22 goal.

1 This committee has an opportunity today to
2 make history. The evidence based review that
3 Dr. Puck talked about was brought before this

4 committee a year ago, raised some very important
5 and very relevant questions about screening for
6 SCID.

7 Now, with general population screening of
8 all births well established in Wisconsin and
9 Massachusetts, and with programs ready to
10 launch. Ready to launch in New York,
11 California, Louisiana, Texas, Minnesota, and
12 Connecticut we can be assured that those
13 questions raised have been adequately addressed.
14 First, the review questioned the prevalence
15 of SCID. The NIH estimates prevalence at 1 in
16 100,000. There are other experts in the field
17 that believe it's closer to 1 in 40,000 once we
18 started screening. Without screening, newborns
19 with this disease will develop overwhelming
20 infections. With intervention, morbidity and
21 mortality is greatly reduced and many babies are
22 in fact totally cured.

1 Second, the review questioned the accuracy
2 of the screening. And Dr. Routes, who made an
3 eloquent presentation and also in the December
4 JAMA article, addressed that issue. And there
5 is specificity and sensitivity that was reached
6 with this test.

7 Third, the review questioned the feasibility
8 of conducting this screening. To date,
9 Wisconsin and Massachusetts have screened nearly
10 200,000 babies. Both states have indicated that
11 their respective laboratories can handle three
12 to four times that number. And they're willing
13 to make their protocols and their laboratories
14 available to the states. So as the states gear
15 up, feasibility is no longer an issue.

16 Fourth, the review raised the issue of
17 public acceptance of the screen. In
18 Massachusetts as an example, where families can
19 opt out, such requests are less than 1 percent.
20 There is nothing in this test that would
21 generate controversy or otherwise offend the
22 overwhelming majority of American parents.

1 Fifth, the review raise the issue of cost
2 effectiveness. Wisconsin and Massachusetts have
3 reported the cost at about \$5.00, \$5.50. And

4 the CDC, Newborn Screening Laboratory in Atlanta
5 has developed and even simpler method to run the
6 TREC assay further lowering the per unit cost
7 and the capital investment. Wider application
8 of screening will drive down the cost even more.
9 Sixth, and finally, the review questioned
10 the adequacy of available treatment centers.
11 The Jeffrey Modell Center's network consists of
12 79 research, diagnostic and referral centers at
13 leading academic teaching hospitals throughout
14 the United States. They have skilled and
15 experienced experts, and teams in place and are
16 fully prepared to respond.
17 Now let's think about it. Each day about
18 11,000 babies are born in the United States.
19 But only, as of today, only about 300 to 400 are
20 born in those states that screen for SCID. They
21 will be the lucky ones. They will be diagnosed.
22 They will be treated, often cured, and have a

1 good chance at life.
2 If on the other hand, they are among the
3 unlucky ones. If they live in 48 out of the 50
4 states that do not currently screen for SCID,
5 they will be sick throughout their entire lives.
6 And they'll be short lives.
7 I know that this Advisory Committee does not
8 mandate the states to adopt these tests. But we
9 can tell you from our experience, with meetings
10 we have held in states across the country, that
11 your actions, your actions are critical in
12 implementing this screening.
13 When this test is added to the core panel,
14 states will move forward. Screening programs
15 for SCID will be routine and precious babies
16 will be saved.
17 All of us in this room know that screening
18 for SCID is not only the right thing to do, it's
19 the smart thing to do. And in this case, the
20 word smart is a great acronym for all of the
21 essential elements required for a successful
22 newborn screening program.

1 Smart; specific, measurable, achievable,
2 realistic, and timely. Mr. Chairman and members
3 of this committee, this is our moment. We have

4 the technology to screen for SCID with 99
5 percent plus accuracy.
6 We have a success rate of over 95 percent to
7 treat these babies. The cost for this life
8 saving screen is \$5.00 or \$5.50. The investment
9 for the laboratory equipment, personnel, and
10 supplies at the state level has been addressed.
11 It has been resolved and it does not pose a
12 problem. And our foundation continues to commit
13 funding to jumpstart population screening in the
14 states using the TREC assay.
15 Tomorrow, another 11,000 babies will be born
16 in this country. Your decision today can give
17 great comfort and hope to those new mothers and
18 fathers who will not have to risk a tragedy and
19 a loss of their child to severe combined
20 immunodeficiency or lymphopenia.
21 Vicki and I accept the fact that science and
22 discovery did not come in time for Jeffrey. But

1 we are dedicated and committed to working with
2 you to help all of the Jeffrey's in the future.
3 This is our wish. This is our hope. This is
4 our dream. Let us go forward on this journey
5 together, beginning today. Thank you.
6 DR. HOWELL: Thank you very much Fred. Our
7 next person commenting is Mrs. Bornheimer, who's
8 a parent of a Wisconsin RAC2 patient. Ms.
9 Bornheimer, if you'll have a seat there that
10 would be great.
11 MS. BORNHEIMER: Mr. Chairman and members of
12 the Advisory Committee, my name is Missy
13 Bornheimer and I am here today with my family.
14 We come from Edgar, Wisconsin, it's a small town
15 in central Wisconsin with about 1,400 people.
16 And I would like to thank you for this
17 opportunity to tell our story.
18 We were thrilled at the prospect of
19 welcoming home our second child in June of 2008.
20 We were so excited and felt blessed to have a
21 new baby brother for Dillon. Mike and I would
22 say to each other, life was good.

1 Our son, Dawson, was born on June 12 of
2 2008. When the pediatrician called us 12 days
3 later with the news that our newborn baby

4 Dawson, may have a life threatening condition
5 called severe combined immunodeficiency, our
6 life was changed overnight.
7 Our dreams were shattered and we were
8 devastated. We learned that SCID, or boy in the
9 bubble disease, was a condition in which most
10 babies do not make it to their first birthday.
11 But fortunately, we were blessed.
12 Just a few months earlier, Wisconsin had
13 started screening every newborn baby in
14 Wisconsin for this disease in a program funded
15 by the Children's Hospital of Milwaukee,
16 Wisconsin Public Health Laboratory, and the
17 Jeffrey Modell Foundation. The doctors at
18 Children's Hospital told us that for Dawson to
19 have a chance at life he would need to have a
20 bone marrow transplant.
21 On the day of his transplant, every single
22 person in our Edgar School District wore a t-

1 shirt that said, Dawson has big dreams. And
2 with lots of prayers and support from family and
3 friends, the transplant was successful and his
4 life was saved. All of this because Dawson was
5 born in Wisconsin. The first state in the
6 nation to screen for primary immune
7 deficiencies.
8 And today, Dawson is the first baby in the
9 world born with a combined immunodeficiency who
10 was cured as a result of this newborn screening.
11 It is scary to think that if Dawson had been
12 born just six months earlier, he might not be
13 with us today.
14 We give thanks every day that we live in
15 Wisconsin. A drive from our home takes only
16 about two hours to go to Minnesota, Michigan,
17 Iowa, or Illinois; none of which currently test
18 for SCID. What if we chose to live just two
19 hours away? We would not have our beautiful
20 son, Dawson.
21 Mr. Chairman, I would personally like to
22 thank you and each of the members of the

1 Advisory Committee for giving Dawson and our
2 family a chance at life. You have played a
3 huge role in saving my baby's life. My days are

4 filled with smiles, laughter, and happiness
5 because of you. And I hope your days are filled
6 with the same knowing that.
7 Because of you, I get to be a mom to one of
8 the most wonderful babies in the world. And how
9 do you express thanks for something like that.
10 Our only wish is that young families like
11 ours in Minnesota, Michigan, Iowa, Illinois, and
12 all of the states can feel secure knowing that
13 if any one of them gets a call from their
14 pediatrician like we did, a program of newborn
15 screening can turn a devastating tragedy into
16 the kind of joy that Dawson gives us every
17 single day. Thank you.
18 DR. HOWELL: Thank you Ms. Bornheimer.
19 Thank you for bringing your family along. You
20 have great back up and assistance there I can
21 see. Our next commentators are Stacy and James
22 Barrett; who are the parents of a SCID patient

1 born in a non-screening state, and who was
2 diagnosed too late to survive. So Mr. And Mrs.
3 Barrett.
4 MRS. BARRETT: Good afternoon. On behalf of
5 Liam, our son, our family and the families
6 living with the effects of SCID, I thank you for
7 giving me the opportunity to speak.
8 As you all heard, my name is Stacy Barrett
9 and this is my husband James. We are Liam's
10 parents. Our son was diagnosed and passed away
11 from SCID. Liam would have been one on the 30th
12 of this month.
13 Liam was born on January 30th in Oregon, the
14 wrong state. If we had been in Massachusetts or
15 Wisconsin Liam would have been tested at birth
16 for SCID. If that had been the case, his
17 journey, our journey, may have had a different
18 ending.
19 Our families journey with SCID began on June
20 1st when Liam was admitted to the hospital for
21 failure to thrive. That was eight months after
22 this committee voted to delay acceptance of
1 universal newborn screening for SCID. 10 years
2 after the American Academy of Pediatrics called
3 for national newborn screening standards.
4 Six years after a expert on SCID, Dr.

5 Rebecca Buckley, testified at the first meeting
6 of this committee saying that SCID was a
7 pediatric emergency and should be included in
8 the uniform panel. Two years after SCID was
9 nominated and 18 months after Wisconsin began
10 screening for SCID.

11 At four months old, Liam was five pounds
12 below the weight for his age. During our
13 hospital stay the doctors ran several tests for
14 genetic diseases. All the while, Liam was
15 gaining weight at a steady rate. Because every
16 test came back negative, the conclusion was that
17 Liam was behind on weight because of a common
18 cold.

19 After 19 days in the hospital, we were sent
20 home with Liam on a feeding tube, antibiotics,
21 and physical therapy. We were told that this
22 would be a long haul, but he would eventually

1 fall back into the correct percentile for his
2 weight.

3 After five days at home and several more
4 trips to the doctor's office, we received a call
5 to take Liam back to the hospital to be
6 admitted; his blood count was low. A few days
7 later we received the news that he had SCID.

8 My husband and I were numb. How could
9 something like this happen to us. We had no
10 genetic trace of SCID in our family. We have
11 three healthy children that were born before
12 Liam that did not have SCID.

13 We started going through the process blind.
14 We had no idea where to take our son for care.
15 Little did we realize that this was only the
16 first step in our journey. During this second
17 hospital stay, Liam was diagnosed with three
18 more infections.

19 All together, he had four infections but no
20 immune system. He was only five months old.
21 His diagnosis was three months later than
22 published articles have state a SCID child could

1 be successfully treated with bone marrow
2 transplant after diagnosis at birth.
3 We then traveled to Seattle Children's
4 Hospital to await a bone marrow transplant which
5 we hoped would come from a sibling match.

6 Unfortunately, being diagnosed with four
7 infections prior to admission in Seattle; the
8 doctors were extremely cautious.
9 Good news came when we were told that Liam's
10 three year old sister, Riley, was a perfect
11 match. The only obstacle in our way was the
12 infections, which were now down to only two.
13 But the two left, PCP and parainfluenza 3, were
14 the most serious and life threatening.
15 Although the bone marrow transplant was a
16 success and he was ingrafting well with his
17 sister's marrow; Liam suddenly took a turn for
18 the worse. The infections in his lungs were
19 getting worse.
20 On August 16th, Liam's CO2 levels had
21 reached over 100, more than twice the amount of
22 an average baby. His heart rate was decreasing

1 and he was completely sedated into a coma.
2 As we watched his vitals decline, we believe
3 this was his way of telling us he was tired. On
4 the 17th of August my husband and I with the
5 help of Liam made the hardest decision in our
6 life, to let him go.
7 If our family were living in Wisconsin or
8 Massachusetts at the time Liam was born, Liam
9 would have been diagnosed with an immune
10 deficiency. Shortly after birth he could have
11 had a transplant with no infections.
12 If that were the case, statistically my son
13 would have had a higher success rate if
14 diagnosed at birth. Over 97 percent, as Dr.
15 Buckley testified before this committee in 2004;
16 statistics indicate our son would still be
17 alive.
18 Too many times our society's political in-
19 fighting creates delay in progress. My son is a
20 son casualty of bureaucracy. If we have the
21 means to test a child for disease, the means to
22 have a successful survival rate, what stops us

1 from doing it?
2 With immune deficiency, we cannot afford to
3 wait for this Board to decide whether it can be
4 statistically proven that screening for SCID is
5 cost effective and meets other rigid rules that

6 focus on population of newborns, instead of each
7 newborn as an individual.

8 Action needs to be taken now. While we wait
9 for numbers and testimonies, countless children
10 have lost their lives to this condition. It is
11 incredible that we don't know the numbers lost
12 to the disease because there is no national
13 database to collect this information and the
14 stories of those vulnerable newborns. Our son's
15 story, being one of the most recent and too
16 familiar.

17 It is society's duty to protect and nourish
18 the young children in our lives. It is the
19 responsibility of this Board to utilize its
20 power to save lives. What are we waiting for?
21 The statistics in Wisconsin may have shown
22 that classically defined SCID baby was not

1 diagnosed in the pilot, but they identified
2 other forms of immune deficiency that required
3 treatment. And we know that in Oregon, it has
4 been statistically shown that my son has died
5 from not being diagnosed soon enough. I guess
6 that statistic is one up on yours.

7 As you consider the updated nomination for
8 SCID and other immune deficiencies, please
9 remember that infants like Liam are born every
10 day in the United States and around the world.
11 We have the technology to screen and diagnose
12 and we have a treatment that is amazingly
13 successful.

14 But we do not have time to delay further.
15 It may take several years to start screening in
16 all 50 states. How many more stories like
17 Liam's can we bear?
18 When I learned I could have the opportunity
19 to speak in front of this committee, I thought
20 what a wonderful way to honor our son's life and
21 death by helping to see universal newborn
22 screening for SCID and other immune deficiencies

1 become a reality.

2 Please help me celebrate what would have
3 been Liam's first birthday, this month, and
4 support universal newborn screening for SCID.
5 Thank you for your time.

6 DR. HOWELL: Thank you Barretts for sharing
7 your story with us today. Our next commentator
8 is Barb Ballard from the SCID family network.
9 DR. PUCK: This is Jennifer Puck. While
10 Barb Ballard is coming up, can I make a comment?
11 DR. HOWELL: By all means. She's here but
12 we'll still hear your comment.
13 DR. PUCK: Oh, okay. The comment is that
14 the Barrett's have requested the leftover
15 material from the dried blood spot of Liam to be
16 sent to my lab and screened for TRECs. And I
17 performed this screening earlier this week.
18 And can tell you that there no detectable
19 TRECs in either the nursery or the two week
20 blood spot from Liam even though the control
21 template was completely intact. So indeed, this
22 would have been diagnosable with a TREC test in

1 either one of those samples.

2 DR. HOWELL: Thank you Jennifer.

3 MS. BALLARD: Thanks Jennifer I got that
4 news this morning that you had finished the
5 testing. My name is Barbara Ballard. And this
6 committee has heard me speak before.
7 Many of you may remember, I'm the mother of
8 a child with X-link SCID. I run a support
9 network for families with SCID. I'm also on the
10 Board of Trustees for the Immune Deficiency
11 Foundation.
12 I found it very apropos that we were able to
13 hear this morning a presentation on morality in
14 regards to newborn screening. Because I wanted
15 to bring up that subject today myself.
16 It was the philosopher, Peter Singer, who
17 queried society's morals by asking the question,
18 if you see a child drowning in a pond and you
19 can save that child without any risk to
20 yourself, other than you would ruin a \$200 pair
21 of shoes, would you save that child?
22 Basically everyone asked that question

1 almost incredulously answered, of course. But
2 when asked if they would write a \$200 check to
3 save 100 children, significantly fewer people
4 say they would write such a check.
5 The human psyche does not grasp the same

6 feeling of loss and grief on a large scale. We
7 cannot feel it viscerally. Even if the loss is
8 of 10 children, we do not feel 10 times the
9 grief and loss we would feel watching one child.
10 We do not even feel it twice as much.
11 In fact, when studied, we learned that the
12 higher the number of children lost, the less we
13 feel it because it no longer is a visceral
14 feeling that you can see and touch and realize.
15 We all need to remember that Liam Barrett
16 was that drowning child. And that you, the
17 members of this committee, stood on the edge of
18 that pond looking at your shoes.
19 When you next vote on whether or not to
20 recommend the testing for SCID as a universal
21 newborn test, I want you all to take a good look
22 at your shoes. And I want you to remember Liam

1 Barrett's face. And I want you to hopefully
2 grant him his birthday wish by casting your vote
3 to recommend universal newborn screening for
4 SCID. Thank you.
5 DR. HOWELL: Thank you very much. We're
6 going to continue the public comment briefly.
7 We have two people who need to do public comment
8 who've come all the way across the country and
9 will only be here today. And although their
10 comments don't relate to SCID, we're going to
11 hear those at this time.
12 After these comments, we will then come back
13 to SCID and have a committee discussion and so
14 forth. But I would first like to call on Silvia
15 Au, from Hawaii. Sylvia, who would like to make
16 the comment in this session.
17 MS. AU: Good afternoon. I wasn't planning
18 to make public comment. But on some of the
19 discussion that you've had today on newborn
20 screening, I just wanted to really come from a
21 state perspective. I'm speaking on behalf on
22 the Hawaii Department of Health and not the

1 Western States Genetic Services Collaborative.
2 I think that we really need to recognize to
3 the Secretary that newborn screening programs do
4 the best job that they possibly can. I don't
5 know any newborn screening programs that don't

6 try to do the best job that they can. And I
7 think that some of the things that are happening
8 with newborn screening programs aren't being
9 recognized.
10 We have a lot of pressure at the state level
11 right now. We have reduced budgets, we have
12 furloughs. You can throw all the money you want
13 to our programs, but we can't hire people.
14 So some of the recommendations to add this
15 disorders, add new programs would be great.
16 Totally support them, love families, want to
17 help them. But we are really in a situation
18 where we're having a tough time.
19 And you have to recognize the workload of
20 the newborn screening programs. And to say that
21 you can just add a disorder or add a program,
22 it's not that easy.

1 And I come from a state that went from being
2 you know, last in the country at screening two
3 disorders in the mid-90's to screening 32
4 disorders now. And we're doing two furlough
5 days a month. We've got lots of pressures on
6 us. You can't hire new staff.
7 So I just want the committee to be sensitive
8 to the newborn screening programs that really
9 work hard to do a good job for their families.
10 And your recommendations are going to impact us
11 because things like, if you have minimum
12 standards; I spend a lot of time arguing why we
13 pay for certain things.
14 We pay in Hawaii for all the treatment,
15 confirmation. We pay for DNA mutation analysis.
16 And they ask us why we're doing that because
17 that's a lot to pay for.
18 And if you come up with minimum standards, I
19 mean our administration wants to dive down. So
20 they're going to get rid of all the extra stuff
21 that we do. So you have to be careful for the
22 states that actually do more than we're required

1 to do. Because we love our families and want to
2 do good for them.
3 So you have to make sure that you're
4 politically sensitive to what's really happening
5 at the state level and not dismantle what we

6 have to advocate for every day. So that's all I
7 had to say. Thank you.
8 Dr. Howell: Thank you very much Sylvia. I
9 think that we are very sensitive to the issues
10 that are at the state level and so forth. And I
11 would like now to ask Anna Marie Seranin to come
12 forth.
13 And she is here to actually, to address the
14 nomination that we discussed this morning about
15 critical congenital heart disease. And so we
16 welcome Ms. Saarinen here for her remarks.
17 MS. SAARINEN: Thank you Dr. Howell and
18 committee. My heart goes out to the families
19 that are here today. And I'm feeling a little
20 challenged in speaking after you to be honest.
21 So bear with me, I'll do the best I can.
22 The good news is, I came here to sort of

1 lobby a little bit. Put on my lobbying hat and
2 convince all of you how important newborn
3 screening for CCHD is. And gratefully, I have
4 to do a little less of that thanks to Dr.
5 Rinaldo's very astute report and to the work
6 that's been done thus far.
7 So I'm grateful there were a lot of head
8 nodding around the table after Piero spoke.
9 Because this is such an entrenched belief for me
10 that this is the right thing to do.
11 So I'll give you just sort of a little bit
12 of background. I'm the mother of three. I have
13 a real job in public policy, so poor Sharon
14 Terry has had to see me twice during this trip
15 on health IT issues.
16 But my daughter, Eve, was diagnosed at two
17 days old with a severe mitral valve heart defect
18 and an enlarged heart. She was very nearly sent
19 home. Was in complete heart failure at four
20 days old.
21 In other words, she would have never made
22 her one week well visit. One of many babies I

1 soon found out are in that boat. One in 100
2 babies are diagnosed with a heart defect. That
3 is the most common of all birth defects.
4 And building on Dr. Rinaldo's comments, less
5 than a third of these heart defects are

6 diagnosed prenatally. That leaves two-thirds of
7 them that are not. I was in the two-thirds,
8 obviously because I had a daughter diagnosed at
9 two days old.

10 But of these, the data indicates that
11 routine newborn exams fail to detect, 25 percent
12 conservatively, Dr. Rinaldo and in some reports
13 go up to 40 or 50 percent depending on what
14 you're looking at.

15 So the pediatricians in this room, thank you
16 for your diligence in you know -- when you hear
17 that murmur not always saying let's check it
18 again at the one week well visit. If we have
19 the option to explore further testing, going
20 ahead to do that.

21 Murmurs often indicate the heart defect, but
22 serious defects, many of them don't present with

1 murmur immediately after birth. And even with a
2 murmur and a careful exam, additional measures
3 can help increase early detection. That being
4 pulse oximetry.

5 This simple, non-invasive test, which can be
6 done at an interval of 28 to 48 hours after
7 birth and detect those otherwise silent heart
8 defects. Pulse oximetry does increase the
9 detection of two CHDs over exams alone.

10 The important thing here is that the
11 earlier, as with many of the things you look at
12 on this committee, the earlier it's detected and
13 treated, the more likely the child will survive
14 and have fewer developmental delays and long
15 term health complications.

16 A baby coming back to the hospital in heart
17 distress is proven to have an increased chance
18 of death and a worse neurological outcome than
19 those diagnosed before discharge.

20 Obviously there are, you know the ripple
21 effects on the economy with kids that aren't
22 diagnosed soon enough and come back in that

1 acute situation end up in a longer term care
2 situation.

3 Or if they just don't make it, the families
4 are you know, forced to relocate often for
5 treatment; there are job losses; there's

6 divorce. There's all sorts of horrible things
7 that go along with you know, severe illnesses in
8 children.
9 And I think it's important to think kind of
10 outside just the single case of a child just
11 being sick to what the real impact on society
12 is.
13 There are many fine institutions in this
14 country that are already screening without
15 mandate using pulse oximetry, including Regents
16 Hospital in St. Paul, Mary Bridge Heart Center
17 in Tacoma, and Children's National Medical
18 Center right here in Washington.
19 We are actually in the process in Minnesota
20 of launching a very well planned pilot study.
21 It's going to be rather brief and rather
22 concise. 3,000 babies in about 12 weeks.

1 So compared to the huge numbers that you've
2 seen on some of the other material presented
3 today it's a small group. But so many pilot
4 tests have been done domestically and around the
5 world that the data is clearly there to help
6 your evidence review board.
7 And hopefully our data coming out of
8 Minnesota will be helpful in that regard as
9 well. And in the fact that it's very current
10 and very well thought through. Our outgo
11 evidence has taken into account many of the
12 existing studies.
13 So we've kind of tried to poke holes in the
14 things that have been problems in other studies.
15 And we also have been thinking a lot about the
16 number of deliveries outside of major medical
17 centers.
18 I'm a farm girl. A lot of my friends are
19 still in outlying parts of Minnesota. We have a
20 lot of deliveries in our state, as many do, that
21 are outside of major medical centers.
22 So we've been very careful about thinking

1 through what happens with those families if they
2 do indeed test low on a pulse oximeter
3 screening. That they won't be having to wait
4 for the echo or the echo read so that they can
5 get a quick diagnosis. Not always will there be

6 someone who's maybe well attuned to doing a
7 pediatric echo.
8 But they do have access to the machinery and
9 an echotech both in the major medical centers
10 have through, with the collaboration with he
11 Minnesota Department of Health, have committed
12 to using telemedicine to make sure there are no
13 outstanding wait times for diagnosis so that
14 parents aren't left to worry and wonder whether
15 their child does indeed have a heart issue or
16 something else.
17 I mean perhaps another respiratory or a lung
18 issue which is the other great thing about pulse
19 ox, is that it can identify things for these
20 babies outside of CCHD.
21 So I believe a one year challenge is an
22 evidence review. Most of the textbooks identify

1 more than 40 different defects. Many
2 cardiologists would not that there are probably
3 more than 100 different variants. Our
4 daughter's was very rare indeed. So many
5 congenital heart problems are different to
6 identify by fetal and neonatal ultrasound.
7 And I think the reach that you'll have in
8 implementing a pulse ox screening will have
9 exponentially greater impact in areas outside of
10 those major medical centers. And hopefully it's
11 going to be a lot easier and actually more cost
12 effective to implement as a physical screening
13 then even hearing screening was several years
14 back.
15 I understand the role of this committee is
16 ensuring that suitable newborn screening tests
17 are developed and safe, effective treatments are
18 available for implementation. Congenital heart
19 disease accounts for the majority of deaths for
20 congenital defects in children; six times more
21 than common then chromosomal abnormalities.
22 By any standard, when we have 1 in 100 kids

1 affected by a defect it's a public health need.
2 In the past three months alone, I personally
3 know of six families have had to bury their
4 babies to undiagnosed heart defects.
5 Eve's surgery happened within about a week

6 of her heart stopping. It was not going to work
7 anymore. I believe she's proof that medical
8 professionals can work their magic on these
9 babies if they are given the opportunity to do
10 so. They need to know there's a problem before
11 they can fix it.

12 So on behalf of the 40,000 U.S. families
13 will be diagnosed with heart disease this year,
14 and the 4,000 who will not live to see their 1st
15 birthday, I sincerely thank you for your
16 commitment to the health of newborns and for
17 considering moving forward to the next phase;
18 screening for congenital heart defects. Thank
19 you.

20 DR. HOWELL: Thank you very much Mrs.
21 Saarinen. We'll look forward to getting your
22 evidence review back, we hope, fairly soon.

1 Thanks very much.

2 We now come to the portion of our committee
3 where the committee will discuss what we've
4 heard so far about severe combined immune
5 deficiency from Jennifer and her colleagues, as
6 well as the persons who've commented publically.
7 Before we start with the general comments,
8 I'm going to call on Dr. Rebecca Buckley. The
9 committee is fortunate to have arguably one of
10 the leading experts on the subject as a member
11 of our committee.

12 And although she will not voting, because of
13 her activity in this area, she certainly -- we
14 will look forward to her comments on what we've
15 heard and where we are. Rebecca.

16 DR. BUCKLEY: Well I think that Jennifer's
17 presentation was very comprehensive and really
18 covers the current state of the problem. The
19 only comments that I would add would be that we
20 really don't know what the full spectrum of T-
21 cell deficiency is.

22 And I think that that's what Dr. Routes' and

1 his group's paper shows. That there are
2 probably other conditions that we don't even
3 know about that are characterized by defective
4 T-cell production that lead to death before a
5 diagnosis is made.

6 The other comment I wanted to make is that
7 as you saw from the baby from Oregon, these
8 patients look like the Gerber baby before they
9 get sick. And so there's no physical reason to
10 suspect this condition.
11 I'll just point out that this past August I
12 was referred a patient who had been in a major
13 teaching hospital for three weeks where the
14 multiple sub-specialties and multiple RAC
15 demographic studies performed before someone
16 thought of this condition.
17 So this was not a baby who was in a small
18 hospital. It was in a major teaching hospital.
19 Fortunately, the patient survived.
20 But, as with the baby in Oregon, most of
21 these patients acquire multiple infections,
22 usually that you can't treat like adenovirus,

1 for example where you can have overwhelming,
2 fulminating hepatitis and die before you can
3 even do a transplant.

4 So the information that's presented so far,
5 indicates that the test that's been proposed,
6 which is a TREC assay, can detect T-lymphocyte
7 deficiency. I would just modify a little bit
8 what they spoke about. Dr. Routes talked about
9 diagnosing T-lymphopenia.

10 And Dr. Puck, in one of her earlier slides,
11 she pointed out that Omenn's Syndrome, which is
12 characterized by clonal; it's like a leaky SCID,
13 where you have a clonal population of T-cells.
14 Often these babies can have very high lymphocyte
15 counts.

16 But the TREC assay would pick them up
17 because they don't have any recent thymic
18 immigrants. These are all memory T-cells or
19 clonal T-cells. It would also be effective in
20 picking up maternal T-cells.

21 Because as I'm sure you know, that if you
22 don't have any T-cells and the mother's cells

1 cross into the fetal circulation during inter-
2 uterine life, unless the baby can reject those
3 T-cells, these T-cells persist.
4 So the maternal T-cells that are in the
5 fetal circulation and in the newborn circulation

6 might confound a diagnosis just based on
7 lymphopenia alone. Whereas the TREC assay,
8 which picks up the memory type, the CD45RO
9 positive cells, would still detect these babies.
10 And then I guess the last comment I would
11 make would be about cost. You heard some
12 preliminary estimates of costs for screening.
13 But I would just speak to the cost for not
14 making the diagnosis.
15 We have data from our institution, which I
16 think was in the evidence review report showing
17 that if you can diagnose this condition before
18 the baby becomes infected, it is usually before
19 three and a half months of life, that the cost
20 of performing a bone marrow transplant can be
21 around \$50,000.
22 Whereas, if the baby doesn't come in until

1 around six months of age, which is the mean time
2 they come in, we have several one and two
3 million dollar babies who have been spending all
4 of their residual days in an intensive care
5 unit. So I think early diagnosis is cost
6 effective. And I think I'll stop there.

7 DR. HOWELL: Thanks very much Rebecca. I
8 wonder if there are -- I think that one of the
9 issues about finding additional conditions that
10 we don't yet know about is really the story of
11 newborn screening.
12 I think that any time you start screening
13 for something that you know all about you learn
14 once you start population screening, is oh my
15 goodness there are these other people that have
16 something that look like this but you won't know
17 about these until you do population screening.
18 Piero.

19 DR. RINALDO: I really have a question for
20 Jennifer, Becky, Anne, and all the experts here.
21 As you know, the uniform panel have this
22 structure, distinction between primary targets

1 and secondary targets.
2 And I keep hearing about all these unknowns
3 and things will emerge. I look at the slide
4 that Jennifer presented where she, herself, make
5 a distinction between SCID and related

6 condition.

7 So to what extent would be appropriate to
8 classify SCID as a primary target and other, I
9 don't know what the official term, known SCID T-
10 cell deficiencies are secondary targets knowing,
11 like we have learned before, that that's a
12 distinction that will really take place only
13 after the confirmatory testing is done and not
14 at the time that a low level of TREC is found.
15 Because these, I think could have quite a
16 significant impact. And so you know, is clearly
17 after what we have heard, you know I really feel
18 very strongly about where we should be going.
19 But at the same time, I'm concerned about the
20 issues of the precedence that could be created
21 about really having all of this untested.
22 I think this has been an issue before

1 conditions added to the primary uniform panel.

2 So is that applicable to talk about the primary
3 target and still under the definition group of
4 conditions. Anne you have your hand up?
5 DR. HOWELL: Anne, we're going to hear just
6 from the panel, just from the committee. Becky.
7 DR. BUCKLEY: I would just say that I think
8 it's just a matter of semantics because
9 hyperbilirubinemia we talked about this morning;
10 critical congenital heart disease, these are
11 multiple conditions that you're talking about
12 under one umbrella. And then SCID itself we
13 used to think was one condition.
14 But we now know it's due to mutations in at
15 least 13 different genes. So I don't have any
16 problem with the you know, classification of
17 this disorder as SCID where the secondary target
18 says other T-cell defects. But I think that it
19 really doesn't matter.
20 DR. HOWELL: Ned.
21 DR. CALONGE: So Piero I was actually going
22 in a different direction. And again, getting

1 back to what I've seen happen in other evidence
2 based groups. That as we moved forward, what
3 appears to have happened to me -- have happened
4 to me is that TREC, the test actually determines
5 more than the disease that we originally issued

6 the evidence review for.
7 Now I got to tell you, from a process
8 standpoint, that's concerning. Because the
9 review that we have is about SCID. It's not
10 about T-cell -- tri-detectable lymphocyte
11 abnormalities.
12 I actually have no problem with making that
13 the primary target. Because we're -- we're not
14 actually supposed to be screening necessarily
15 for diseases but conditions that are amenable to
16 treatment.
17 And so, I actually think nomenclature's
18 important. I think this is expanding the
19 recommendation not to test for SCID but to test
20 for TREC detectable lymphocyte abnormalities or
21 some combination of that.
22 Now so let me stop there and say, I'm okay

1 with that except we've now changed the case
2 definition and our evidence review is not
3 complete.
4 DR. HOWELL: Let me tell you what the case
5 definition was for the evidence review to
6 refresh your memory. For the purpose of this
7 review, severe combined immune deficiency is
8 defined based on the definition for the PubMed
9 medical sub-heading.
10 SCID is a group of rare congenital disorders
11 characterized by impairment of both humeral and
12 cell mediated immunity, leukopenia, and low or
13 absent antibody levels.
14 It is inherited as X-linked or autosomal
15 recessive defect. Children with SCID
16 universally have extremely low or absent T-cells
17 and may or may not have B-cells.
18 We have included some specific sub-types,
19 such as adenosine deaminase deficiency,
20 reticular dysgenesis, and Omenn syndrome in the
21 definition of SCID because they are
22 characterized by T-cells; but we recognize that

1 some groups consider these disorders distinct
2 from SCID.
3 And so that was the definition that the
4 evidence review used that we got back. I had
5 forgotten, I must confess. The reason I asked

6 Michele to pull this up as I had forgotten that
7 it had been so broad frankly in its
8 inclusiveness.
9 DR. CALONGE: So does that capture all of
10 the abnormalities that were detected in
11 Wisconsin and Massachusetts? Or were there
12 additional abnormalities?
13 DR. HOWELL: I --
14 DR. CALONGE: Rod, let me just tell you
15 where I'm going.
16 DR. HOWELL: Yeah.
17 DR. CALONGE: I think that if we expand --
18 if there's an expansion of the definition, I'm
19 actually okay with the current evidence review
20 and the evidence we've seen today on the benefit
21 side.
22 But I think that to be true to the process

1 we would want to do at least an interim search
2 on the potential harm of screening for those
3 conditions. And it could be, take as long as
4 you know, an afternoon of a literature search to
5 show we have identified no other potential harms
6 in screening for these other conditions.
7 But in order for us to stay true to the
8 process, of just screening with at least
9 moderate certainty lead to significant health
10 benefit, I would want to make sure that to vote
11 on it I have a good sense that we've covered the
12 down side to screening, which is always
13 inadequately considered.

14 DR. HOWELL: Let me ask the two states that
15 have screened; have you identified any
16 conditions that are not in the description I
17 read?

18 DR. ROUTES: Yes.

19 DR. HOWELL: I just read the description of
20 what was in the evidence review. And Becky, if
21 you --

22 DR. ROUTES. Well we identified infants that

1 would not be, fall under that umbrella,
2 including you know, at least one other infant
3 that was identified and her sister that has,
4 again, an atypical form of a naive T-cell
5 deficiency that will be transplanted.

6 Again, as a physician that sees these
7 infants, I'm sure it matters. When I said that
8 the RAC2 baby was a combined, combined, it was
9 actually in many worse than SCID because it was
10 a neutrophil defect coupled with a T-cell
11 problem. And that's not conventionally
12 considered SCID.
13 But as Dr. Buckley pointed out, it's sort of
14 arbitrary in a way. The baby certainly would
15 have died faster than a conventional SCID due to
16 the fact that it was a neutrophil defect in
17 conjunction with a T-cell problem. So Dr.
18 Howell, the answer yes we have.
19 DR. HOWELL: Yes you have. And Anne, what's
20 your answer? Yes or no.
21 DR. COMEAU: That's all I get to say.
22 DR. HOWELL: Not much more.

1 DR. COMEAU: Yes. But I do want to say,
2 that by screening for SCID, we will identify
3 infants with other primary immunodeficiencies as
4 has been stated without changing anything about
5 the screening, we're looking for TRECs. And so
6 an evidence base for the other, the other
7 diseases can be built.

8 And by screening for SCID, we can satisfy
9 finding infants with SCID and finding babies
10 with other deficiencies, build an evidence base,
11 and then you can expand the definition if that's
12 what you choose to do. So you don't have to go
13 backwards in evidence review.

14 DR. HOWELL: Gerry.

15 DR. VOCKLEY: Well I think Piero is correct.

16 I think we've identified a primary condition.

17 There's a little bit of looseness in the
18 definition and maybe some of the cases that have
19 been identified fall into a slightly different
20 category.

21 But if we keep our current definition and
22 say that's our primary target, in analogy to the

1 tandem mass spec, the other things are going to
2 come along for the ride.

3 We're not going to ignore them, we'll still
4 find them. But we don't have to -- if we define
5 them as secondary targets we don't have to

6 justify -- we don't have to say we're changing
7 process. I think we're -- I think we're just --
8 DR. HOWELL: Recognizing you'll find other
9 things.
10 DR. VOCKLEY: -- recognizing that we have
11 more that we'll need to learn. And I mean I
12 think that we all agree that this has to come
13 along with additional studies. But I am trying
14 to stay true to both the original application,
15 the evidence based review, and our requests for
16 additional information at the last meeting.
17 And it seems to me that if we -- that as
18 long we focus on the things that folks would
19 more or less agree fall into the definite that
20 Rod just read us, that we're you know we're --
21 we don't -- I don't think we're getting
22 ourselves into a problem with deviating from

1 process.
2 DR. HOWELL: Carol.
3 MS. GREEN: Sorry I'm borrowing the
4 microphone here. Thank you. And listening
5 carefully to the definite and deferring to the
6 experts that even with the technical definite of
7 T-cell and you know, X-linked, or autosomal
8 recessive; that there were some things -- I
9 think and so I will want to support what Piero
10 and Gerry were just saying.
11 I think deletion 22 doesn't fall under the
12 original definition. And it also wouldn't get a
13 bone marrow transplant, usually. So I think the
14 idea of -- I think the primary target would be
15 just larger than just ADA deficiency because
16 people were very wise about creating the
17 definition originally so the evidence review
18 would suffice for pretty much everything.
19 But I think we would recognize that we're
20 going to pick up some deletion 22 babies and
21 that would be a secondary target and nice to
22 find.

1 DR. HOWELL: Rebecca, would you like to
2 comment on what you've heard here?
3 DR. BUCKLEY: 22q11, if it's a complete
4 DiGeorge, is treatable by a thymus
5 transplantation. And it's urgent to make an

6 early diagnosis for that.

7 DR. HOWELL: So the treatment might vary,
8 but obviously an urgent diagnosis and treatment
9 and so forth. Chris.

10 DR. KUS: The question on process would be,
11 so we did have an expanded definition from what
12 you read then what we were initially thinking.

13 And we also put in --

14 DR. HOWELL: Excuse me, let me be clear.

15 That was the definition that was used for the
16 original evidence review.

17 DR. KUS: Right.

18 DR. HOWELL: Which, was we looked at it
19 again, to clarify our own heads, was broader
20 then -- I think for those of us who are not in
21 the SCID world, we think of SCID as a classic X-
22 linked SCID. And obviously, their definite was

1 more contemporary and included more things.

2 DR. KUS: So I guess the question to me is;
3 now we had a presentation that said, people
4 responded to the comments that we had made about
5 this. Does the next step, if we use the way
6 that process is, is the next step for the review
7 group to look at that and say whether it covered
8 those things? How would you -- how does it go?

9 DR. HOWELL: We're done with the review
10 group.

11 DR. KUS: Okay.

12 DR. HOWELL: The thing is, the decision is
13 at this table.

14 DR. L KUS: Okay.

15 DR. HOWELL: I mean I think that unless
16 there is some earth shattering thing that

17 happened we're at --

18 DR. KUS: So it's whether this group thinks
19 that things have been covered?

20 DR. HOWELL: That's correct.

21 DR. KUS: All right.

22 DR. HOWELL: I think that's where we are.

1 Denise.

2 DR. DOUGHERTY: I just have a question. I'm
3 looking at the articles now, which I should have
4 read before. But there seems to be more --

5 DR. HOWELL: Yes, you should have.

6 DR. DOUGHERTY: Yes I should have. So the
7 evidence review focused on the treatment by
8 transplantation. There's another, there's an
9 article, new article in the New England Journal
10 that talks about gene therapy and talks about
11 some harm. So if this committee were to
12 recommend screening, would it only recommend
13 screening and then treatment by transplantation?
14 DR. HOWELL: The committee to date has not
15 had specific recommendations on a treatment.
16 For example, we have not said you're going to
17 treat it this way. But certainly, I don't think
18 that we would recommend -- we would want it to
19 be treated by the most effective way.
20 But we also anticipate that, I would hope
21 that a year from now we'll have increased better
22 treatments and so forth. But I think you would

1 expect it to be the usual treatment, which has
2 clearly been transplantation to date. Ned.

3 DR. CALONGE: So --

4 DR. HOWELL: Ned's trying to keep us pure
5 here.

6 DR. CALONGE: And I don't want the perfect
7 to be the enemy of the good. So I want to ask a
8 simple question that would have helped me in the
9 presentation a long time ago. And I think I
10 know the answer. But I'm going to ask it
11 specifically.

12 So the RAC2 would fall within the definition
13 of SCID. So when we ask for a prospective
14 identification of a SCID case by testing, we can
15 say yes instead of a slide which never said yes.
16 We can say yes, we have identified at least one
17 SCID case, with our case definition, with
18 prospective testing.
19 Because of all the things we asked for, that
20 was the only slide I didn't have yes, we've done
21 this for you. So that's what I would like. I
22 would like -- that yes would help me.

1 DR. HOWELL: Rebecca, is that a yes?

2 DR. BUCKLEY: Yes.

3 [Laughter.]

4 DR. HOWELL: It is not possible to get a
5 more gilded edge yes.

6 [Laughter.]

7 DR. HOWELL: Jane.

8 DR. GETCHELL: I just want a clarification.

9 Screening is considered the TRECs assay, not
10 flow cytometry? Is that confirmatory? How do
11 we --

12 DR. HOWELL: It would clearly be a TREC or
13 -- TREC assay and so forth.

14 DR. GETCHELL: [Indiscernible.]

15 DR. HOWELL: Well I don't think that we're
16 mandating it what particular assay. You would
17 want an assay to be an effective, proven assay.
18 And the one that's been most proven has been
19 TREC. But again, I would hope that we will have
20 something even more specific and cheaper. I
21 don't know what that will be two years from now.

22 DR. GETCHELL: But the flow cytometry is not

1 considered part of the screening, it is a part
2 of the confirmatory process?

3 DR. HOWELL: It's only in Delaware where
4 they do flow cytometry where you have so much
5 money you would do it every day.

6 [Laughter.]

7 Unknown Male Speaker: No, it's
8 confirmatory.

9 DR. HOWELL: But clearly, flow cytometry I'm
10 confident would be a confirmatory type test and
11 so forth. And it would only be used in
12 following up babies who had an abnormal test.

13 DR. BUCKLEY: Actually, it's only one of two
14 types of confirmatory tests. The flow cytometry
15 tells you how many T-cells are there. But you
16 could lose T-cells, for example, through your GI
17 tract if you had intestinal lymphangiectasia or
18 some other reason where you were losing cells.
19 But the test that's most crucial is really
20 one of T-cell function. And so both of those
21 tests would be done before somebody would be
22 officially diagnosed with SCID or other types of

1 T-cell defects.

2 DR. HOWELL: And those would be routinely
3 used in the referral center about which we've
4 heard around the country. Are there further
5 comments or questions or suggestions or

6 anything?

7 DR. SKEELS: Rod, this is Mike Skeels.

8 DR. HOWELL: Oh good Mike, welcome.

9 DR. SKEELS: I just want to let you know

10 that I've been lurking for awhile. And I just

11 want to say that the last question that was

12 asked is of far more than just academic

13 interest. Because when we reviewed SCID before

14 it was on the assumption that TREC's were going

15 to be the screening method.

16 And I mean I think that all of our

17 conclusions and inferences were sort of built

18 upon that. And from the screening lab point of

19 view, we're going to have to be pretty clear on

20 what it is we mean by laboratory screening. So

21 I appreciate that question very much.

22 DR. BOYLE: Can I just have a clarification

1 of what the actual proposal is? I guess I'm

2 unclear are we a --

3 Unknown Male Speaker: A motion.

4 DR. BOYLE: Yeah, a motion here?

5 DR. HOWELL: Well I don't think there's been

6 a -- Coleen, there's not been a motion made. I

7 think that the purpose of the discussion would

8 be to review the previous information, to get

9 additional information from the to date

10 screening program.

11 And I think that the responsibility of the

12 committee then will be to come up with a

13 recommendation based on what we've heard. And I

14 think that, I think that the folks have done a

15 good job of going through the critique and saying

16 this was a problem and this was a problem and

17 how that stands today and so forth.

18 I think the second thing is that Dr.

19 Guttmacher has been very clear that the NIH is

20 in the process of providing funding along with

21 public and private consortia to answer some of

22 the questions that can only be answered with

1 large scale screening. The questions that we

2 had about some of the other stuff. And so

3 that's in place.

4 And so you've heard the follow-up about what

5 we know, what's been found. A SCID patient has

6 indeed been identified according to the
7 definition of our evidence review. And so now
8 we need to come up and make a recommendation.
9 Kwaku.

10 DR. OHENE-FREMPONG: Just a quick question.

11 The current algorithms that exist for
12 transplantation for SCID patients, about what
13 percentage could one predict would be covered
14 either full match sibling, unmatched, T-cell
15 depleted, about what percentage of the patients
16 would be covered by transplant?

17 DR. BUCKLEY: Theoretically it should be 25
18 percent. But in actual practice it's lower than
19 that that you would have a matched sibling. And
20 our experience has been around 16 percent of the
21 165 that we've transplanted at our institution.
22 So most of them don't have a matched sibling

1 so they have to have another type of donor. And
2 in our particular hands we've used a mother or
3 father as a donor by taking out T-cells and
4 using T-cell depleted marrow. So there are
5 other ways.

6 And then there are other types of
7 transplants that can be done such as cord blood
8 transplants, matched unrelated donor
9 transplants.

10 DR. OHENE-FREMPONG: So really my question
11 was, considering all those options, would you
12 consider that almost 100 percent of them would
13 have transplant one form or another as the
14 primary option for treatment?

15 DR. BUCKLEY: Yes, yes.

16 DR. HOWELL: So we could anticipate that the
17 situation is essentially 100 percent would be
18 able to be transplanted and so forth. Tom.

19 DR. MUSCI: Yes, I just had a question about
20 the assay very briefly. It may have been
21 covered at an earlier meeting which I was not
22 attended. But is there anything in the TREC

1 technology per say that's proprietary or has a
2 license associated with it? I just was curious
3 about how that would impact.

4 DR. HOWELL: I see lots of nodding that says
5 that it is not proprietary.

6 DR. MUSCI: It's clean.
7 DR. HOWELL: What?
8 DR. MUSCI: It's clean and generic.
9 DR. HOWELL: Well I'm not sure how clean but
10 it's not proprietary, et cetera, apparently.
11 DR. COMEAU: There may be some small
12 licensing associated with a particular enzyme
13 that's used. So it's not free and clear but --
14 DR. HOWELL: Oh sure, but it's that some of
15 the enzymes that are used in PCR and so forth
16 are of course proprietary and you would have
17 those charges. May would you like to make a
18 brief comment?
19 MS. BAKER: I seem to recall --
20 DR. HOWELL: Come to that microphone if you
21 would please.
22 MS. BAKER: The TREC assay, the sequence is,

1 it's published and I don't think any licences
2 associated with that.
3 DR. PURYEAR: May, can you give your name
4 please?
5 MS. BAKER: Oh, sorry. May Baker from
6 Wisconsin Newborn Screening Laboratory.
7 DR. HOWELL: Thank you. Piero.
8 DR. RINALDO: I would like to make a motion
9 to recommend to the Secretary of Health and
10 Human Services to add SCID to the primary panel
11 and to also add a generic description of known
12 SCID T-cell deficiencies to the secondary, to
13 the list of secondary targets.
14 DR. VOCKLEY: Second.
15 DR. HOWELL: We have a motion and a second.
16 So we know can have discussion.
17 DR. BOYLE: I guess I would like to have
18 some clarity from those of you who know a lot
19 more about this condition, about what the
20 benefits would be to going with this, as SCID
21 being a primary and the other disorders being
22 the secondary versus the primary being the T-

1 cell immunodeficiencies?
2 DR. RINALDO: Well in my view it reflects
3 discussions we had earlier and even this
4 morning. It really goes back to the fact that
5 we screen for markers and the markers have

6 complex differential diagnosis.
7 So this is actually a case of particularly
8 complex differential diagnosis but is in no way
9 different from what we have done before. There
10 is no -- it is unrealistic to expect a simple
11 straight correlation, one marker, one disease.
12 That doesn't happen in medicine.
13 DR. HOWELL: Ned has had his hand up for
14 quite awhile.
15 DR. CALONGE: I'd like to move an amendment
16 to the motion that we also recommend the
17 Secretary consider requiring a periodic review
18 of the experience of TREC testing or SCID
19 testing to see whether the diagnosis are made
20 and the outcomes associated with detecting and
21 treating those other conditions.
22 DR. RINALDO: I think for respect to the

1 procedures I think we can actually be specific
2 and say that the definite of SCID is the one
3 that was formulated in the evidence review.
4 DR. SKEELS: Rod, this is Mike Skeels. I've
5 got a question. This is a procedural one and
6 please forgive me for playing catch up here.
7 But Piero are you recommending that we change
8 the recommendation that we voted on the last
9 time we reviewed SCID?
10 DR. RINALDO: Yes.
11 DR. HOWELL: Yes.
12 DR. SKEELS: Okay, so this is the right
13 mechanism for doing this is to just say okay new
14 evidence has come to light, we feel differently
15 about it and we're going to change the category
16 into which we put SCID as a screening tool?
17 Excuse me, a disorder for screening?
18 And I guess part b of my question is; since
19 I agree with Ned that it would a lot, it would
20 be helpful to know more about the harms if in
21 fact we have an expanded definition. Is it
22 possible to do some sort of expedited or brief

1 evidence based review just to look at that so
2 that we can be a little more sure before we
3 vote?
4 DR. HOWELL: Okay.
5 DR. RINALDO: This is Piero. The only thing

6 I would say is that 90 percent of the literature
7 out there was probably written or contributed by
8 people in this room.

9 [Laughter.]

10 DR. RINALDO: So I think that we really
11 should not really go this far. I mean we
12 clearly have, you know direct access right now,
13 right here, to the people who can really say
14 what the evidence is. It's very easy, we can
15 certainly poll them, ask them, is there evidence
16 of harm for screening for one or the other
17 conditions?

18 DR. HOWELL: Mike let me make the comment is
19 that you unfortunately were not able to be with
20 us but we had had a considerable discussion
21 about the definition. And the definition that
22 was used in the original evidence review was

1 quite broad and included virtually all of the
2 situations that have been identified in the two
3 states. And so I think that was the reason to
4 put down SCID as the primary.
5 I believe, to take words out of your mouth
6 Piero, and recognize that there might be other
7 things. Now the -- we had had a potential
8 amendment to your recommendation. Would you
9 accept that amendment Piero?

10 DR. RINALDO: Yes.

11 DR. HOWELL: And would you Gerry? You
12 seconded it?

13 DR. VOCKLEY: Well I was wondering if it
14 would be more advantageous. I think if you look
15 at what we're supposed to be doing in this
16 committee, the kind of ongoing review of
17 conditions that are in the recommended panel is
18 actually part of our charge. So I don't know
19 that we have to move to have that specifically
20 added to this condition. I think it's
21 already there.

22 But what I do think might be helpful is if

1 we put some language into it that recognized the
2 need for additional studies and strongly urging
3 the responsible bodies to consider providing the
4 funding for that.

5 DR. HOWELL: I find that very attractive and

6 I think that some of us have thought about the
7 way the FDA approves certain drugs and so forth
8 for rare conditions. And they approve them for
9 use and marketing, but require a post-market
10 surveillance.

11 DR. VOCKLEY: Basically a phase four.

12 DR. HOWELL: And basically I think that, I
13 believe that that's what you're talking about
14 Ned, is that correct?

15 DR. CALONGE: Correct. Gerry, the only
16 language difference I would make is that we
17 expect, we don't encourage. And so I would want
18 to be really strong in this recommendation to
19 the Secretary. I wonder though, if I could also
20 answer Mike's question. Because it's an
21 important question and we shouldn't short
22 circuit it.

1 When we looked at SCID at the previous
2 review, we identified gaps in the evidence. And
3 we said we want to fill in these gaps. And I
4 think Mike what your asking for is an
5 acknowledgment that those evidence gaps have
6 been filled to the satisfaction of the
7 committee.

8 And going through the presentation, which
9 was very good except that one yes I was looking
10 for; I felt that those gaps that we asked for we
11 were provided sufficient evidence to say with at
12 least moderate certainty, that those gaps had
13 been met. So I'm comfortable with that.

14 And the one issue that I really want to get
15 was that, have we diagnosed a case
16 prospectively. Which just felt odd to mandate
17 universal screening before we had actually done
18 that. So I believe we've met the evidence
19 criteria that we asked to have met so that we
20 can revote it on the basis of the additional
21 information along the lines of Piero's motion.

22 DR. SKEELS: Okay, thanks Ned, that's very

1 helpful. I don't think our committee's been in
2 the situation before where we voted on something
3 and then we reconsidered it in light of new
4 evidence. And so I was just trying to
5 understand where we were. So thank you very

6 much.

7 DR. CALONGE: You know and it might be
8 helpful if we actually structure it that way in
9 the future. These were the gaps, these are the
10 answers when we're going to revote.

11 DR. HOWELL: There are several other
12 comments and then I want to come back and make a
13 suggestion. Carol, you've had your hand up for
14 a long time over there.

15 MS. GREEN: Thank you. And I think I'm
16 agreeing, especially with Gerry. And Rod I
17 think that the way I understand the answer to
18 Coleen's question about why do we have a primary
19 and a secondary is to be sure we are true to the
20 process because we have one thing that's
21 important to identify that doesn't fit under the
22 definition of the original evidence review.

1 And therefore, if we don't say primary and a
2 secondary target we have to go back and revisit
3 the evidence review which I think that's what
4 you were saying Rod I think?

5 DR. HOWELL: Yeah.

6 MS. GREEN: And then I want to very strongly
7 agree with Gerry and actually propose an
8 amendment to the amendment if that's allowed.
9 Just a little bit of a language change. Is to
10 say, that we need to you know, continue to
11 gather evidence but to explicitly say that we do
12 not intend to single out either the TREC assay
13 or T-cell depletion.

14 But just that the responsibility of adding
15 something to the core panel reminds us all of
16 our responsibility to continually monitor and
17 review the effectiveness and outcomes of
18 screening. But without necessarily singling out
19 each new one each time.

20 DR. HOWELL: We've had a motion and a second
21 and I consider -- I sense a considerable
22 consensus around the table. It had occurred to

1 some that we might find ourselves at this place
2 today. And there are a few -- I think it would
3 be helpful Piero, if you're comfortable, to be
4 rather specific in some of the things that we
5 might expect to come back and so forth.

6 DR. RINALDO: Sure. Actually, as we were
7 having this conversation I really was also
8 thinking of a very important comment made by
9 Sylvia Au. And that is, perhaps there is a new
10 concept that should emerge from this. That not
11 every state should do everything.
12 But we really should encourage, whenever
13 feasible, a developmental consortium of regional
14 networks. Some already exist. But
15 realistically, is it probably something that
16 would also help significantly when it comes to
17 the allocation of resources, the cost of a test.
18 You know and so that is also something that
19 people should really think about. That as more
20 things -- you know in a sense we are going to
21 get the break, the two other conditions being
22 considered are testing, a basum test done at the

1 periphery level. But we know there are other
2 things coming. You said many coming down the
3 pipe line.

4 So I think it will soon get to a point where
5 not even the most, best funded, and best
6 equipped program will be able to do all of these
7 things on their own. And so perhaps it would
8 make sense that somewhere in the western states,
9 you know one state will add SCID and do it for
10 the region, another state add whatever is next.
11 And just to start thinking in terms. But
12 going back to your point is -- Rod would you --
13 well many things have been said, would you like
14 to have something written up?

15 DR. HOWELL: Well we have something written
16 up kind of over here. And the thing is, is that
17 it would be helpful when the things go to the
18 Secretary to have some rather specific
19 recommendations so that we might help in.
20 And Michele has a few handy things written
21 here that she, that might be included in the
22 material. In other words, the nomination would

1 go to the Secretary if this is approved, that
2 this committee recommends adding this to the
3 core panel and the secondary panel.
4 And then in the correspondence, however we
5 would like to have some specific things that we

6 would expect or hope people would do that would
7 encourage is separate. And Michele you wanted
8 to say what?

9 DR. PURYEAR: So this is listening to what
10 others have said and some of the addendums.
11 Recommend adding severe combined
12 immunodeficiency disorders to the uniform panel
13 and other T-cell lymphocyte deficiencies to the
14 list of secondary targets as a comprehensive
15 entity with the stipulation that the following
16 activities also take place in a timely manner.
17 The National Institutes of Health shall fund
18 surveillance activities to determine health
19 outcomes of affected newborns with any T-cell
20 lymphocyte deficiency receiving treatment as a
21 result of prospective newborn screening.
22 Health Resources and Services Administration

1 shall fund the development of appropriate
2 education and training materials for families,
3 public health, and health care professionals
4 relevant to the screening and treatment of SCID
5 and related T-cell lymphocyte deficiencies.
6 And the Center for Disease Control and
7 Prevention shall develop and distribute to
8 performing laboratories suitable dried blood
9 spot specimens for quality control and quality
10 assurance purposes.

11 DR. HOWELL: That would just go -- that
12 would go with the material. In other words, to
13 amplify so that the expectations of the
14 committee are fairly you know, we would really
15 like these things done rather than just a
16 general comment and so forth. Would that be
17 acceptable?

18 DR. RINALDO: Yes, that would be acceptable.

19 DR. HOWELL: Any comments about the -- we
20 need to, then when we vote on the motion, that's
21 a separate thing. But before we get there, what
22 about the comments that Michele has written that

1 would accompany our recommendations? Are they
2 acceptable? Jane, you had a comment?

3 DR. GETCHELL: I do. And it has to do with
4 kind of what Becky said about splitting hairs
5 between primary and secondary conditions, SCID

6 and basically non-SCID. What we've heard is
7 that, SCID if you will, there's 1 in 100,000
8 babies is born with that. I'm not sure what
9 that refers to anymore.

10 And I can tell you in convincing my state to
11 add this testing, the more frequent we see this
12 condition, the more likely they are to go for
13 it. So that's just something to think about,
14 whether you split it into primary and secondary
15 or not.

16 DR. HOWELL: Well most of the things that
17 the states have detected so far would fall under
18 our evidence review of SCID.

19 DR. GETCHELL: Which is 1 in 100,000?

20 DR. HOWELL: No, no, no. No it would be --
21 I don't know, I haven't done the math.

22 DR. GETCHELL: What is it?

1 DR. HOWELL: Well they've detected four or
2 five in Wisconsin out of 70, is that right? So
3 it's one in 16.

4 DR. GETCHELL: So by lumping all those
5 together it's very powerful argument.

6 DR. HOWELL: It's a very powerful argument.
7 And they would be lumped -- and I think the
8 secondary thing is to simply accommodate those
9 things that we know are going to come up that
10 have not yet.

11 Are we ready to vote on this? Piero, your
12 motion was very straight forward so come again,
13 repeat it now that we've talked so much.

14 DR. RINALDO: The testimony read by Michele?

15 DR. HOWELL: Well that will just be an
16 accompanying document. You're just going to
17 make a nomination that we approve it.

18 DR. RINALDO: Okay, I make a nomination that
19 we approve the text that put together.

20 DR. PURYEAR: Recommend adding severe
21 combined immunodeficiency disorders to the
22 uniform panel and other T-cell lymphocyte

1 deficiencies to the list of secondary targets as
2 a comprehensive entity. And this was read with
3 the stipulation that the following activities
4 take place in a timely manner. And those I
5 outlined for NIH, HRSA, and CDC. So that's a

6 whole recommendation.
7 DR. RINALDO: So moved.
8 DR. HOWELL: Chris.
9 DR. KUS: Yeah I guess the comment I would
10 have is, that you've got those other
11 stipulations. So if those stipulations don't
12 happen in a timely manner then you're not
13 recommending that it should be a -- I mean
14 that's the concern I have.
15 If those things -- if states would say well
16 you're really not doing this and this so it's
17 really not recommending that I do this because
18 you haven't done the stipulations.
19 DR. PURYEAR: Well the NIH now has a
20 contract out for the first part.
21 DR. KUS: Then why have a stipulation?
22 DR. PURYEAR: Because I think Ned wanted to

1 ensure that, that the -- that these activities
2 were tied with the recommendation for screening.
3 DR. KUS: Yeah but I guess that's my
4 concern. Because again, somebody could say;
5 well yeah NIH did this but you had two other
6 stipulations and those aren't happening.
7 DR. CALONGE: Well I would point out the
8 recommendation isn't to the states it's to the
9 Secretary.
10 DR. PURYEAR: Yeah.
11 DR. CALONGE: And actually the Secretary can
12 adopt all of them or none of them. And the idea
13 is to give the Secretary the idea that there's
14 some other pieces of this that would be
15 responsible to follow through on, not that
16 states have to do that. I mean that's what I
17 look at, it's who the recommendation is to.
18 DR. PURYEAR: This is to ensure that the
19 Secretary follows through on these things, okay?
20 DR. HOWELL: But I think the core
21 recommendation is very clear that the condition
22 be added to the core panel and that the

1 secondary panel would be there for other T-cell
2 deficiencies that we haven't discovered. Carol.
3 MS. GREEN: And it's maybe too much word
4 smthing, but I agree with Chris. And I'd feel
5 a lot more comfortable if it didn't say, with

6 the stipulation that, but says we make this
7 recommendation and the responsibility of making
8 such a recommendation and all it entails reminds
9 of the critical need to.

10 Because otherwise it sounds like you only do
11 this if other things happen. And that doesn't
12 necessarily seem fair to me. But if people are
13 comfortable, I'll vote for it anyway.

14 DR. PURYEAR: Well you don't get to vote.

15 MS. GREEN: Oh, that's true. That's true.

16 I'm only here as a liaison. Good point, thank
17 you.

18 [Laughter.]

19 DR. HOWELL: But we really appreciate your
20 support.

21 [Laughter.]

22 DR. HOWELL: Any further -- Denise.

1 DR. DOUGHERTY: Is this our first positive
2 recommendation with the new process?

3 Unknown Female Speaker: Yes.

4 DR. DOUGHERTY: Okay I'm having -- so I'm
5 having a little bit of difficulty having now
6 scanned these articles.

7 DR. HOWELL: Oh goodness, after all the
8 trouble the President's had this week and you're
9 going to give more.

10 DR. DOUGHERTY: I won't send him an e-mail.

11 So I'm thinking that, and I forget exactly what
12 is in Michele's list. But I think it's
13 important when we make these recommendations,
14 and I'm reading about you know, there is an
15 increase in survival from transplant and
16 apparently from gene therapy according to these,
17 the evidence review.

18 But the thing is, there's still a high rate
19 of mortality. So I think by just saying you
20 should screen for it gives, could give the
21 impression to people that once you get screened
22 you're on a tract and your kid's going to get

1 all better. And I think it's important --

2 Unknown Female Speaker: [Indiscernible.]

3 DR. DOUGHERTY: Wait, wait, wait. I just
4 want to say, I think it would be important to
5 say to the Secretary, you know survival is

6 improved and so forth and so on but there's
7 still a need for treatment research.
8 DR. HOWELL: But I think --
9 DR. DOUGHERTY: That's what I want --
10 DR. HOWELL: Denise --
11 DR. DOUGHERTY: That's all I would like to
12 add.
13 DR. HOWELL: Denise, I think it's fair to
14 say that the survival data of your colleague to
15 your left, on the patients who were transplanted
16 in the first three months of life, are nothing
17 short of breathtaking. And it looks like her
18 pen got stuck when she was doing the Kaplan
19 Meyer thing because it just goes straight across
20 at 99 percent.
21 [Laughter.]
22 DR. DOUGHERTY: But then there's this

1 article in the New England Journal about gene
2 therapy --
3 Unknown Female Speaker: [Off-Mike.]
4 DR. HOWELL: Well --
5 DR. DOUGHERTY: Wait, wait. But that is New
6 England Journal, it's very influential. That is
7 arguing that there is a 37 percent to 70 percent
8 mortality rate with transplants.
9 DR. HOWELL: Well let me ask you --
10 DR. DOUGHERTY: That said that.
11 DR. HOWELL: If you were taking care of
12 child today with severe combined
13 immunodeficiency and you had an opportunity in
14 the first three months of getting a bone marrow
15 transplant at Becky Buckley's shop with a 98
16 percent 25 year survival or something
17 experimental, that would be the decision that
18 you would need to make.
19 DR. DOUGHERTY: But we're not --
20 DR. HOWELL: Sharon.
21 MS. TERRY: So I would say that the
22 treatment part is a liability we all live with

1 every one of these diseases and the other 6,000
2 or so and that the treatment is not perfect in
3 any case. And having some treatment is better
4 than no treatment. And there still will be
5 morbidity and mortality but that it makes clear

6 sense here given the data that we've heard to go
7 forward with this screening.

8 DR. HOWELL: I certainly agree. At a risk
9 of beating a dead horse, I don't know of data
10 that are as dramatic as the early treatment SCID
11 that Becky Buckley has published. They clearly
12 are the most dramatic of any disease I've ever
13 dealt with. Chris.

14 DR. KUS: I think the issue that by doing
15 the review, the review essentially says that we
16 feel that benefit outweighs the risk. And
17 that's inherent in these nominations.

18 DR. HOWELL: Absolutely. Thank you. Piero
19 and Jana.

20 MS. MONACO: Hi, I just wanted to agree. I
21 think that what we're going to get if we don't,
22 the mortality rate is going to be higher then

1 what it is without screening. But I think also
2 that applies, as the mother of two children with
3 a disorder, that applies to every single one of
4 these disorders. I have one with disabilities
5 like many do who was unscreened.

6 But those of us who have children who were
7 screened and are doing well, we know that the
8 risk every day is there that this child may go
9 into crisis and things just don't work out. So
10 I don't think we need to worry so much about
11 that as a criteria.

12 DR. DOUGHERTY: I just don't -- I mean I
13 think this happened with the breast cancer and
14 mammography screening as a recent example. That
15 because it was recommended people thought nobody
16 would die. I mean that's basically what
17 happened.

18 And I think there's a new movement out about
19 being clear that there are benefits but that
20 it's not perfect. And I think it's important to
21 let people know that. I just don't think
22 everybody would know that given the breast

1 cancer example.

2 DR. RINALDO: Can you tell me one thing that
3 is perfect?

4 [Laughter.]

5 DR. DOUGHERTY: I can't, but let Ned speak.

6 DR. HOWELL: Now that you've talked about
7 breast cancer Dr. Calonge's just going to have a
8 few words.

9 [Laughter.]

10 DR. CALONGE: I will tell you, and I
11 expressed concerns that -- and I am actually
12 pretty adamant about putting phrases in our
13 recommendation from here on out. Because quite
14 honestly, I'm not sure how good a job we're
15 doing with what we're supposed to be doing. But
16 let's be specific. Let's start putting it in in
17 every recommendation.

18 First of all I want to support my colleague,
19 because I think we got to recognize we're
20 sitting around this table to bring different
21 viewpoints. And we want to make sure we hear
22 all viewpoints and are respectful and we don't

1 jump down people's throats.

2 I think this issue about recommending
3 something and then finding out it didn't work as
4 well as you thought it would or worse, that you
5 know that the net benefit is small; is really
6 something that's a little difficult to deal
7 with.

8 And as I've talked about our methods and we
9 talked about provisional approval without the
10 definitive research; the criticism I got from
11 the colleagues in the evidence based world is,
12 are you really going to be able to go back and
13 say we're not going to screen anymore?

14 So I think we need to say, if we were faced
15 with that data, we have the ability to sit
16 around the table and say we're changing our
17 minds. And whoever's sitting around the table
18 at that time, because it will take years, are
19 brave enough to do that.

20 But I want to get back to Chris' point and
21 remember one of the reasons you develop methods,
22 you publish them, and then you try to adhere to

1 them is so that you can always go back and say,
2 what are we supposed to do.

3 And the issue is, do you have at least
4 moderate certainty that there's a significant
5 benefit, net benefit, that is benefits that

6 exceed harms in screening for SCID? And if you
7 do, then the appropriate vote for this motion
8 would be yes. If you are unconvinced you need
9 to either abstain or vote no. And that's really
10 -- I meant that's what our methods say.
11 And so what I appreciate is that we were
12 able to articulate at the prior meeting what we
13 needed. And the community had the resources to
14 step up to the plate and give us the information
15 we asked for. Which I got to tell you, does not
16 always happen.
17 And so I think we need to look at what was
18 given to us. Does it satisfy us so that we
19 believe our risk of being wrong is small, you
20 know so we have at least moderate certainty.
21 And we believe that there's a significant net
22 health benefit associated with this

1 recommendation.

2 DR. HOWELL: Thank you very much.

3 DR. CALONGE: Just to get us back to what
4 we're supposed to do.

5 DR. HOWELL: Anyway, we've had a motion, a
6 second, substantive discussion. The motion and
7 the words that Michele read to you are on the
8 board and so forth. And that's the deal. Are
9 we ready to vote.

10 DR. OHENE-FREMPONG: I just want to know,
11 can the word stipulation be changed to another
12 word?

13 Unknown Female Speaker: Yeah.

14 DR. HOWELL: What did you say?

15 DR. OHENE-FREMPONG: Stipulation, could that
16 be changed to just another -- continued
17 recommendation?

18 DR. CALONGE: How about expectation?

19 Unknown Female Speaker: Yeah.

20 DR. HOWELL: With the follow-up.

21 DR. OHENE-FREMPONG: Somewhat like it's a
22 condition.

1 DR. HOWELL: With the expectation rather
2 than stipulation. You would like to have
3 expectation rather than stipulation?

4 DR. CALONGE: Well that would be okay with
5 me.

6 DR. OHENE-FREMPONG: Something softer.
7 Because it makes it dependent and I'm not sure
8 whether
9 DR. CALONGE: Or understanding is fine.
10 Unknown Female Speaker: Yeah, understanding
11 is better.
12 DR. PURYEAR: With the understanding?
13 DR. OHENE-FREMPONG: I think sounds better.
14 DR. RINALDO: Additional recommendation.
15 DR. OHENE-FREMPONG: Or additional
16 recommendation.
17 DR. CALONGE: With the additional
18 recommendation.
19 Unknown Female Speaker: No, don't make it
20 additional recommendation.
21 DR. CALONGE: Okay.
22 DR. HOWELL: No.

1 Unknown Female Speaker: The Secretary will
2 have to parse it.
3 DR. CALONGE: Oh, okay.
4 DR. HOWELL: We'll have one quick comment
5 from Harry and then we're going to move this
6 along.
7 Unknown Male Speaker: The last time we said
8 something to the Secretary, not that we ever
9 heard from him, I think Michele told me there's
10 a new policy about things going to the
11 Secretary. Would you elaborate on that?
12 DR. HOWELL: The policy is the Secretary is
13 required by law, it's in the Newborn Screening
14 Saves Lives Act, to respond to any
15 recommendation that this committee sends to the
16 secretary no later than 180 days.
17 To either accept, to go away, whatever. But
18 the point is, we have to get a response. And I
19 must confess, that we've gotten more letters
20 from Secretary Sebelius then we got in the
21 previous seven years or whatever.
22 [Applause.]

1 DR. HOWELL: So for whatever reason, she is
2 much more conversant. I would like to move this
3 along. Understanding is there, is that good
4 with you Kwaku?
5 DR. OHENE-FREMPONG: I think that softens

6 it.

7 DR. HOWELL: Excellent, excellent. Those
8 favoring this motion?

9 [Chorus of ayes.]

10 DR. HOWELL: Let's see your hands, this is
11 an important vote. Rebecca Buckley cannot vote,
12 she's given great wisdom.

13 DR. SKEELS: Rod, this is Mike Skeels. I
14 vote aye.

15 DR. HOWELL: Thank you. Is there any
16 opposition to this motion?

17 [No response.]

18 DR. HOWELL: Were there any abstentions?

19 DR. PURYEAR: One.

20 DR. HOWELL: Where?

21 Unknown Female Speaker: Rebecca Buckley,
22 Dr. Buckley.

1 DR. HOWELL: Well she's abstaining, yes.

2 DR. CALONGE: She's recused, not abstaining.

3 DR. HOWELL: Excused not abstaining.

4 DR. CALONGE: Recused.

5 DR. HOWELL: Recused, she's certainly not
6 abstaining. She obviously is extremely
7 supportive. She told me that privately.

8 [Laughter.]

9 DR. HOWELL: I don't think I'm --

10 DR. CALONGE: Dr. Howell, I have to explain
11 to you the issue about recusal.

12 DR. HOWELL: But thank you very much.

13 That's an important vote and we'll look forward
14 to having great results from this. I think it's
15 very good. Thank you.

16 [Applause.]

17 DR. HOWELL: Before we go to our
18 subcommittee meetings, I'd like to introduce one
19 new face in the audience today. And over in the
20 corner, standing right in front of Carrie is Dr.
21 Carla Cuthbert. Carla, would you stand up?
22 Carla has recently joined the Centers for

1 Disease, whatever the CDC is.

2 [Laughter.]

3 DR. HOWELL: But Carla has been hired to
4 replace, if at all possible, Dr. Harry Hanin.

5 And so she is, the new person there. She is an

6 outstanding biochemical molecular geneticist and
7 I'm sure she'll provide great leadership to that
8 section. So congratulations Carla.

9 [Applause.]

10 DR. HOWELL: We are now going to our
11 subcommittee meetings after which we will
12 adjourn. And we'll see you as a group in the
13 morning.

14 [Whereupon, the afternoon session was
15 concluded.]

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

ADVISORY COMMITTEE ON HERITABLE DISORDERS
IN NEWBORNS AND CHILDREN

8:40 a.m.

Friday, January 22, 2010

Marriott Washington at Metro Center
775 12th Street, N.W.
Washington, D.C. 20005

ATTENDEES

COMMITTEE MEMBERS PRESENT:

Rebecca H. Buckley, M.D.
Bruce Nedrow (Ned) Calonge, M.D., M.P.H.
Kwaku Ohene-Frempong, M.D.
R. Rodney Howell, M.D., Committee Chairperson
Jana Monaco
Piero Rinaldo, M.D., Ph.D.
Tracy L. Trotter, M.D., F.A.A.P.
Gerard Vockley, M.D., Ph.D.

EX-OFFICIO MEMBERS PRESENT:

Coleen Boyle, Ph.D., M.S.
Denise Dougherty, Ph.D.
Alan E. Guttmacher, M.D.
Peter C. van Dyck, M.D., M.P.H., M.S.

EXECUTIVE SECRETARY:

Michele A. Lloyd-Puryear, M.D., Ph.D.

ATTENDEES - Continued

ORGANIZATION REPRESENTATIVES PRESENT:

Alan R. Fleischman, M.D.

Timothy A. Geleske, M.D., F.A.A.P.

Christopher Kus, M.D., M.P.H.

Sharon F. Terry, M.A.

Michael S. Watson, Ph.D., F.A.C.M.G.

Mary J.H. Willis, M.D., Ph.D.

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PROCEEDINGS

(8:40 a.m.)

CHAIRMAN HOWELL: We have a busy agenda this morning with a lot of most interesting and important areas to discuss.

One of the situations that was brought to my attention by several of you yesterday, as we were discussing Alissa Johnson's presentation about a letter we would write the Secretary about health insurance and changes that we have coming -- it was pointed out to me -- and I'm sure everybody on the committee is very aware of this -- that two areas of insurance that we really should comment about clearly are lifetime caps and preexisting conditions because, obviously, the patients that we diagnose in the newborn period will, by definition, have a preexisting condition that could be a lifetime stumbling block. So we need to be very careful in addressing that.

And the second thing is lifetime caps.

Again, although the conditions that we deal with are individually rare, so they don't impact the health insurance business in a big way, individually they can

be extremely expensive. And some of the treatments of the conditions that are screened for and identified in the newborn period would exceed most lifetime caps in literally a year or two.

Would the committee have any concern if we ask Alissa to add these two things into our document that would go forth to the Secretary? I think they were very good suggestions that we address. I see nodding of heads mostly going up and down in a proper direction and so forth. I only look at those that are going the right way.

(Laughter.)

CHAIRMAN HOWELL: But anyway, our agenda is obviously modified. You were so efficient and effective yesterday, we moved some things for today to yesterday. So we're going to begin with our subcommittee reports, and then we're going to have carrier discussion on sickle cell disease, and then we're going to have Dr. Zuckerman and then move on. But I would like at this time to begin with our subcommittee reports, and the first one on the list is the Subcommittee on Laboratory Standards and

Procedures. Dr. Vockley will report on that committee's activity.

DR. VOCKLEY: Can we have the next slide?

We spent a lot of the committee meeting this time doing a little bit of longer-range planning. We had the benefit of a new administrative support person, Sarah Copeland from HRSA. So we've been spending some time talking about where we would like the committee to go over the next couple of years. So the first thing that we did was to review our charge, which you see up here, and decided that this was way too wide for us to use as a template for the next couple of years. Maybe in the next couple of decades.

So we will just go to the next slide. We decided that really newborn screening applications and technology are likely to be all-consuming in the near future, that we just were not going to be able to deal with some other very interesting but equally overwhelming topics such as other age windows for screening. Can you do something at the 1-year finger prick when kids are otherwise getting a hemoglobin done or a hematocrit done? Can we do something at the 4- or

5-year-old kindergarten physical? So these are issues that are equally complicated to newborn screening. So ultimately somewhere along the line, we're going to have stop thinking of newborn screening and start thinking of age-appropriate screening, but not next week.

Next slide please. We looked a little bit at how the committee had been performing in terms of evaluating new applications for the screening panel and, in particular, how we were interacting with the initial review group that then recommends for or against the full evidence-based review and decided actually that it was probably okay. There were at least three members of our committee who were functioning on that initial review group, and we felt that there was adequate lab input to the decision. We felt that, for most of what we've looked at to date, the technology rarely was the deciding factor for or against moving forward, and even if there were some technological issues regarding a particular screen, they were not likely to scuttle it. So again, we decided that there really wasn't any need to push much

further on that.

However, given the likelihood that we're going to be focusing almost exclusively on newborn screening as we move forward in the near future, we do want to be sure or recommend to the full committee and the chair that that initial review group continue to maintain a member that is a laboratory and especially with experience in newborn screening implementation. That just makes sense to have somebody who is able to provide some real-world experience in that regard.

Next slide, please. So if the committee isn't going to be super-aggressive in being part of that initial technology review for moving applications to evidence review, what should it be doing? Well, we came up with some ideas that are summarized here. Perhaps first and foremost, what we started to do last time and will look to move forward on is really trying to keep kind of a 30,000-foot view on what's on the horizon. So overview of -- I chose to use the words either "enabling" or "disruptive" technologies, things that are really going to change the landscape in a big way. And there are some

examples, things like some of the microfluidics technologies that are coming down the road, in the same way that mass spec changed the scene in terms of ability to screen.

One of the suggestions that came out was that the committee, by reviewing existing technologies after a disorder has been recommended for screening, could play a role in reviewing, especially early on in the implementation phase, if there are various technologies that are available, how those technologies are being implemented, perhaps collect some comparative metrics on those, and then be able to make those data available to States that are looking to try to decide, well, you know, which one do I want to use.

Mike Watson this morning brought to my attention that a lot of the other committees and consortia that are involved in trying to implement and track some of these testing procedures and their implementation are actually doing this. So it really won't end up being a very costly, although it might be a little time-consuming, effort. We can simply mine data that other groups are collecting.

Then the final piece of technology-oriented information that might be useful for us to be commenting on, as they present themselves, are replacement technologies for existing members of the screening panel. So if suddenly there is another technology that looks a lot better than what's out there now, it is often difficult to get screening programs to shift gears and so some enabling from this committee might help that.

Next slide. There was some discussion about whether or not we could play a role in mediating what we ended up deciding to call State-to-State interactions, and this is more in the capacity of backup for emergencies, not full-fledged Katrina or that sort of thing, but you know, the pipes break and now you're down for a week while the Governor says, okay, you can fix it. How could that be formalized? And then one of the largest areas of discussion was the idea that as we move forward and the numbers of tests and technologies increase, is every State going to need to do everything or can there be regional or lab-specific specialization? So everybody

gets to be good at a handful of things and everybody uses that center for test A through G, and then the next set goes to another area. So it make sense, but it's actually not the way things work. Right now, States look at it mostly in terms of what they can implement. Then the committee potentially helping to play a role in disseminating technical information, and this kind of goes back to new technologies. It's, hey, there's something new you might want to take a look at. Do I have another slide? So this would be the last one. We have some of these things already on the slate for the next meeting but things that we're going to try to pay attention to going forward and generate at least some visibility for if not necessarily testing projects.

Looking at a survey of second-tier testing that's coming down the pike, we have a second test project that we're told will be ready for presentation to the full committee next time. So we're thinking about whether there's a reason to expand that to other disorders based on the results.

The thorny issue of suggesting tests for

removal from the panel. That's one that we've largely ignored up till now.

We spent a lot of time looking at molecular- and metabolite-based diagnoses. We haven't done much relative to hemoglobinopathies, and so going forward, that is something that I think the committee needs to familiarize itself with so that we can help with those discussions.

And a comparative look at the technologies for TREK assays now that that has been passed and really trying to identify if there are technical barriers for implementation at the level of the States.

And then I don't know what the last one meant. It's just kind of a general thing, I guess. So we'll stop there.

CHAIRMAN HOWELL: Thank you very much, Jerry.

Are there comments or questions of Jerry?

I had several questions, Jerry. So this committee has been extremely interested in the discussion of the second sample collection. As you are very much aware, certain States collect a second sample; others don't. I'm aware of the fact that

there's been a group working on that, and I'm now led to believe that we're going to hear from that group at your next subcommittee meeting. Is that correct?

DR. VOCKLEY: Jelili, are you still here?

CHAIRMAN HOWELL: Yes, he's just arrived. I saw him come in.

DR. VOCKLEY: You said you wanted to do it at the full committee. Right?

CHAIRMAN HOWELL: Can you come up to the microphone, Jelili? I would like to have this cast in stone about what we're going to hear.

MR. OJODU: Jelili with the Association of Public Health Laboratories.

Michele wanted me to actually give a presentation at this meeting, and I told her that we were still collecting data. States were putting things on pause because of H1N1, but hopefully by May 14, which is the next meeting, you will get an update of the status.

CHAIRMAN HOWELL: H1N1 is pretty much under control. So we can expect --

MR. OJODU: Well. (Laughter.)

CHAIRMAN HOWELL: We can expect your full attention. And that report, as I am led to believe, is going to focus considerably on some of the endocrine disorders. Is that right?

MR. OJODU: It is congenital hypothyroidism, NCH.

CHAIRMAN HOWELL: Right. So that's very important. The discussion around the table has been very straightforward: either everybody should be doing it or nobody should be doing it. So we will look forward to data that would support that. Well, that will be terrific. That will be great.

So the second thing is the issue of regionalization, how can your committee and this committee be involved, because it certainly makes sense as particularly some of the complex tests and confirmatory things are done to regionalize. Is that within the purview of this committee? Is that a part of the regional collaborative? How is going to work?

DR. VOCKLEY: Unfortunately, I think the

answer is yes to everything. Right now, I think that

the role that the Laboratory Subcommittee and, through it, the full committee can play is in raising awareness and putting this possibility on the radar screen in a way that individuals can't, so that if you or I or any of our individual committee members said, well, it should be regionalization, there always are openings to interpret that as, well, you run this laboratory and you're going to get the benefit from it. Whereas, if the committee comes up with a statement in some way, shape, or form that says -- you know, it sounds a little like apple pie and motherhood, but this is a good thing, it I think puts it on a little bit of a more solid footing and allows hopefully State health departments to look at that recommendation and say, well, okay, I can go back to my health secretary. I can go back to my lab and say almost we've been given permission not to do SCIDs. We can send it over to there. I would hope that that sort of enabling can make a difference at the level of State implementation.

CHAIRMAN HOWELL: I had three questions. I came to your meeting at the tail end, and one of the side discussions that I found very interesting and that

I would hope you all would look at is something actually that Piero is bringing up and that is that there are an increasing number of situations where the lower -- in other words, in medicine we always look for something that's elevated. In other words, we are looking for high cholesterol or whatever. And we tend not to look at things that are low. Looking at the exact same analyte is not doing anything new. And Piero pointed out that there are a number of conditions where you're not looking for it, but where the analyte is actually low, and I think that's a fascinating area.

Piero, would you like to comment about that?

DR. RINALDO: Sure. There are several of the tests that we perform now that could actually give us additional information. Now we screen for congenital adrenal hyperplasia and we look for a high level of 17-hydroxyprogesterone, but the resource for congenital adrenal hypoplasia that is really characterized as a phenotype by extremely low or absent 17-hydroxyprogesterone. So I think just mining the millions of data that are available everywhere probably would be some interesting finding.

It is possible to screen for the proximal urea cycle disorders by looking at low citrulline and some other related markers.

It is possible to screen for disorders of remethylation like MTHFR, cobalamin G, cobalamin E by looking at homocysteine. These are treatable conditions.

So it is certainly intriguing that we could expand the current panel of conditions by looking at markers at both ends. So I think that would be an interesting topic to discuss.

CHAIRMAN HOWELL: I found that very fascinating because you're not adding anything except you're looking at the other side of the coin and identifying conditions that are serious and treatable.

DR. VOCKLEY: It sort of comes under the category of mining the data you already have. That one is on my short list already. It wasn't up there because it came too late.

I was interested to hear that because as a non-laboratorian, I always just assumed that abnormal was abnormal whether it was low or high, and I was

surprised to hear that, for the most part, we're actually just looking at the high levels. So it's a good one to bring forward pretty quickly because it could make a difference pretty quickly.

CHAIRMAN HOWELL: Are there other questions or comments of the lab folks? Alan?

DR. FLEISCHMAN: I had raised with Dr. Vockley earlier the question of whether the committee might be interested in taking up the definition of what are the standards for quality assurance and enhancing laboratory techniques with the idea that we have argued that quality assurance is part of the newborn screening program and ought not be subject to arguments about storage and use of specimens after testing. Quality improvement is part of the program.

Yet, it is hard to find a clear and crisp definition of what that means, and there is some disagreement. And if I'm wrong and there is clear and crisp definitions of this, then please let me know. But it might be helpful, if the committee had such, this committee agree to it as a white paper minor report, not a big report, and that might be helpful at

the State level when States are considering their residual specimens and length of storage and use.

CHAIRMAN HOWELL: So you're suggesting that the Laboratory Committee look at how the samples are profitable or valuable in quality assurance activities for the laboratory.

DR. FLEISCHMAN: Well, I wouldn't have used the word "profitable or valuable," but that quality improvement and quality assurance is integral to the public health program and this is what that is, just defining the best practices in that regard so that there wouldn't be any confusion when perhaps a State was considering how long to store samples or whatever.

CHAIRMAN HOWELL: Any comments on that, Jerry?

DR. VOCKLEY: Well, I think actually it's a great idea because I think it can be done. It's one of those things with minimal work, literally just looking and seeing what the current standards are out there in the literature and the regulatory environment and then acknowledging that this is part and parcel of quality lab management in the newborn screening lab

environment. So I think we can do that with a minimum amount of work and actually maybe make a difference.

CHAIRMAN HOWELL: That's an interesting point. I think you're correct. We say that these are important samples and so forth, and you look for the literature on that and it's not there.

Carol?

DR. GREENE: I believe that it would be very useful to make it clear that there are legal requirements to save samples and to do that kind of quality assurance. The CDC staff that is staffing a work group that I chair that I will be presenting at CLIAC on February 8th I believe has looked over all that information. And there will be an opportunity for comment, and if we haven't made it strong enough, that would be a place to bring it up. Harry worked on that work group, and we can look back and, if it isn't clear, make some comments for addition.

I think it would be important to point to it, but I believe that probably APHL documents also have something to say about that, and certainly the CLIAC work group is going to present to CLIAC. CLIAC will

probably accept it, as they did the molecular document with some modification. And it is planned to be published as an MMWR. So in the meantime, it should be in progress and it should include exactly what you're talking about, but it might be useful to point to it.

DR. VOCKLEY: I think that's the indication here, is it's not that we have to reinvent the wheel. We just would like to have as an acknowledgement from this committee that this is important relative to newborn screening. So, Carol, if you could send those things my way as soon as they're publicly available, I would appreciate it.

DR. GREENE: They will be publicly available on February 8th when it's presented, but we can talk. We know some of the people who are working on it. We can review it with this liaison. I can look at it again with this in mind so that I can be prepared for comment. Mike just also pointed out that State law has something to say about it. So the document that we're working on is good laboratory practices, and then there is anything beyond CLIAC and then State law also has a role. CHAIRMAN HOWELL: I don't think you'd go to the State law issue that might have to do with this. I think you're looking at the importance of this as a laboratory quality assurance issue and not necessarily what the States have to say.

DR. GREENE: By that I mean that some States actually have laboratory quality assurance like New York.

CHAIRMAN HOWELL: Right.

We've got lots of things to do, but I think that would be an interesting thing to do. Regardless of the documents that are out there, it would be valuable for this committee to have a document because of its responsibility in newborn screening.

Let's go now to the Subcommittee on Education and Training. That's Jana Monaco and Tracy Trotter, and it would appear that Tracy has taken the speaker's seat.

DR. TROTTER: Yes. Jana and I would like to thank our subcommittee members and all of the guests who were there yesterday. It was a very chock-full

agenda that was so full we had to finish it at the bar,

which worked out okay. A lot of things going on that I'll try to update all of you on today.

Before I start that, here are our important players. We had two new members, Deborah Rodriguez and Jaimie Higgs, who joined us as new members of the subcommittee. Deborah is from the New York State screening program. Jaimie is with GeneDX and has been a genetic counselor for a long time in this area.

Before I start that, in reviewing the 811 pages of the briefing book for this meeting, I found that I have been clearly under-utilizing a number of important and unique adjectives and adverbs.

(Laughter.)

DR. TROTTER: And they are indigenous, I believe, to this area, the best I can tell. But I'm going to correct that with an introduction to our subcommittee report.

We will present a review of our subcommittee activity that is comprehensive, robust, synergistic, translational, and evidence-based.

(Laughter.)

DR. TROTTER: It will address and empower all

stakeholders in an inclusive, incremental, multi-directional, and transparent manner. Our rigorous and systematic deliberations were based on an iterative and facilitative paradigm.

(Laughter.)

DR. TROTTER: And our conclusions have a high degree of specificity and sensitivity.

(Laughter.)

DR. TROTTER: This report will be culturally and linguistically appropriate to Washington, D.C.

(Laughter.)

DR. TROTTER: Both HIPAA and GINA-compliant, we'll strive for analytical and clinical validity, and hopefully demonstrate clinical utility. Although our recommendations are only advisory in nature, we hope that they will have significant net benefit.

And by the way, we have voted to change our designation from "subcommittee," and we will now be known as your education and training medical home.

(Laughter and applause.)

DR. TROTTER: Yes, we did have wine with dinner. (Laughter.)

DR. TROTTER: The first on our agenda was a report from Natasha Bonhomme and the National Newborn Screening Clearinghouse which has been sort of a giant project that the Genetic Alliance has taken on in the last months with their partners. We talked about all of these factors that I think this project is going to continually improve. Most importantly is increasing awareness across all stakeholders and increasing educational efforts across the group, creating a more central linkage for data, resource sharing.

From a practitioner's standpoint, I really look forward to the possibility of point-of-service educational items helping me deal with that 7 minutes that I have to deal with it in the middle of Thursday afternoon when it comes up and to help us integrate the electronic technologies, which is of course a challenge for all of us in all of our areas.

Their Web site is now live and you're welcome to go and start fiddling with it. I think it will be sort of an ongoing project forever that has a very

impressive start. We really enjoyed that presentation.

We had a similar presentation regarding the Congenital Conditions Program, a very nice presentation from Joe McInerney and Emily Edelman from NCHPEG on the perinatal family health history, which is a NCHPEG, Harvard Partners, Genetic Alliance, March of Dimes, and HRSA project, very fascinating, point-of-care, interactive, tablet PC-based genetic history, family history with immediate feedback of response to it. Pretty exciting stuff. We saw -- I don't know -- a 10-minute demonstration of what they have so far. I really look forward to seeing that. I think we will all benefit from a little of that thinking outside-the-box technology and somehow getting this into the practitioners' hands. This is going to be for prenatal care providers, but I can see it expanding to cover lots of folks.

Dave Cotter from the American College of Medical Genetics Foundation talked about the summer internship plan, which is going to be targeted for the summer of 2011, which will target rising second-year medical students, so their summer after their first year of medical school, hopefully as many as 30

students, with an intense month of genetic immersion, shall we say, with an opportunity in the Washington, D.C. area that is obviously very rich in terms of the possibilities of clinical laboratory, public policy, et cetera to, at the very least, produce medical student graduates who are more versed and more excited whether they go on to become geneticists or not.

We had a report from our sister Secretary's advisory committee, the SACGHS. Kathy Camp and Sylvia Au were both at our meeting to talk about their educational task force report which will, they hope, be published by this summer. Very exciting. A lot of things that we had been looking at, a lot of information that we will need to use to implement some of the projects we've been working on. And Jana will join them at their meeting in February to report from our side, and we're going to continue to do that at each of our meetings, if feasible, so that we keep those lines of communication open.

We had a number of other reports from folks who tend to be at our meeting, which were good updates. The Genetics and Primary Care Training Institute, the

program that we've been shepherding along for the last year and a half, is now at, I think, the HRSA stage of just about rolling out for RFPs. And Genetics in Medicine we hope is going to publish a paper about that. So hopefully in May, we'll be able to give a more complete report about how that's going. Notable among the reports, the American Academy of Pediatrics has a cooperative project with ACMG looking at ACT sheets, something that I think most people in this room know about and for some reason was a pure mystery to most of the pediatricians who were asked about it even though that's who they're designed for. So it will be interesting to see. That's just getting started. Tim Geleske, who is on our subcommittee, is involved in that, so we will update you on what the end result of that was as well. We actually did not have time to go beyond that, but looking forward to in our May meeting, broadening the consumer representation in terms of presentations to the committee and trying to continually stay in touch with how do they want to know all this new information. We now likely will have one

more disorder to try to transmit information about and what's the best way of finding it and how do we tailor our education so that the ultimate end user, which is, of course, the patient and their families, gets what they need.

Thank you.

CHAIRMAN HOWELL: Thank you very much, Tracy.

Are there questions of Dr. Trotter?

You've got to realize that our 834-page agenda book is rather small for Washington. So that's very good. Actually Capitol Steps is a comedy routine right down the street, so you might go down there and apply for a job there.

(Laughter.)

CHAIRMAN HOWELL: As you know, they perform on the weekends in the Ronald Reagan Building right down the street.

Coleen, see if you can follow that act with your Subcommittee Follow-up and Treatment.

(Laughter.)

DR. BOYLE: I'm not sure I can. I was just going to say that. But if it's okay, I'm going to stay

here because I have my notes here for a presentation.
Is that all right?

CHAIRMAN HOWELL: Sure.

DR. BOYLE: Okay, great.

So similarly, we had a very active subcommittee meeting yesterday, sort of jam-packed, although we didn't finish our meeting at the bar, but maybe next time we'll do that. I'll be a little bit more verbose in my presentation.

But I did want to recognize our subcommittee members on the list here, as well as the skillful assistant of Jill Shuger who really helps us move forward as a committee. So I want to recognize her and all her work.

You can go to the next slide. I tried to summarize. We did have a lot of presentations, and I think last time in September, when I presented to you, we had just had a meeting the previous day focusing on the first issue here. You know our subcommittee has really been looking at the issues of long-term follow-up and trying to frame long-term follow-up, identify the roles and responsibilities of the major sectors

involved in long-term follow-up, and we've gotten now into the issues regarding how to measure the components of long-term follow-up. If you recall, those components are new knowledge discovery, quality assurance, evidence-based treatment, and care coordination. So we've been really looking at how to best measure that issue. In September we had a pre-meeting where we brought in a number of people in those sectors to discuss what they saw as the primary questions that needed to be addressed in trying to assure those functions.

Since that time, since September, Chris Kus in a working group of our subcommittee has really taken the lead on trying to move forward on those overarching questions, and he gave a presentation yesterday to the group. We did have some, I think, great discussion around the concepts and maybe how to expand those concepts and try to operationalize them a little bit more. I guess there are still some thoughts as to kind of what best to do with that, whether we should take this into a white paper. I wanted to sort of maybe get your thoughts on that and also mention the second

bullet up there.

Last time we also had a presentation to the full committee from NCQA in terms of their work that they do in terms of developing quality measures. So Michele and I followed up with Sarah following that presentation and thought that activity and that organization could really help our subcommittee in taking those overarching questions and actually developing quality measures for those overarching questions.

I know there are a lot of buzzwords here, and I'm hoping for the next time we can actually be a little bit more specific for you. I know that many of you that are in the practice world -- the issue of quality measures does ring true to you. But we're trying to do the same type of thing with newborn screening long-term follow-up.

So HRSA has a contract now with NCQA to really help our subcommittee in developing those quality measures, and they're going to help us sort of frame the overarching questions, as well as drill down to actually develop the quality measures. In addition to that work, we did get updates from a number of the projects that are ongoing in long-term follow-up. So we did hear a presentation from Sue Barry and she basically gave us a great summary of HRSA, as well as NIH-funded long-term follow-up projects. We did also hear from Cindy Hinton from CDC on the long-term follow-up projects that we fund.

The important piece there is that I think we're all recognizing the need to have common elements across all of these different systems that are being developed. I mean, obviously, there's a slightly different or maybe very different intent with the different projects, but there really is a need to have these common data elements. So we've been working. I know Michele and I have been working to really try to make sure that the projects that we fund complement each other with regard to the data elements.

We didn't hear about our longstanding issue on the medical foods. We didn't hear from Mary Kay Kenney because she has a critically ill family member, so she wasn't able to be with us. But I understand

she's well underway in analyzing the data from the

three-State survey. She has submitted an abstract to APHL and hopefully will be able to present there, as well as present at our May meeting.

Last time I mentioned that in our subcommittee in September we had a discussion on short-term follow-up issues. There were two issues that seem to come to attention that we felt the subcommittee might be able to at least provide some guidance to, and I've highlighted both of those in the bullets there.

One is the idea of whether or not newborn screening conditions should be State-mandated -- whether there should be mandated reporting of conditions through newborn screening. And the second one was the fact that in many States, most States, there isn't sort of timely, routine linkage of birth certificates and newborn screening information.

So we actually formed a small work group to take a look at both of these issues, and Debbie Freedenberg from Texas took the lead there, and Celia Kaye and Brad Therrell joined her in sort of thinking through this effort a little bit. They sort of tossed aside the issue of State-mandated reporting. I'm not

sure I agree with that entirely. In fact, we may have to think about it or maybe bring it to a larger group or a larger forum.

But they did sort of drill down on the issue of routine linkage with birth certificates and how this really could be a very important quality assurance mechanism. Only a minority of States link routinely. Several States actually include the newborn screening serial number as a field on the birth certificate. That would allow for very easy linkage between those two systems.

Then we did have some discussion about the fact that this field, the newborn screening serial numbers, is not right now a recommended field within the context of the standard U.S. birth certificate. As a subcommittee, we thought that sort of was a no-brainer, that that field clearly should exist as the suggested format. So we had some general discussion about this. Actually I asked Brad and Celia to come up with some proposed language that we could take back to you all, and maybe you could take a minute just to read this. So what we're proposing is that somehow we move forward on this language here, and the language is: "Newborn screening is an essential core public health activity required in every State. In order to facilitate verification that every child has received screening, the committee requests that the U.S. model birth certificate include a field for capturing the serial number of the initial newborn screening blood collection form." And then in parentheses, there's a suggestion that they can use the format that's actually described in the CLSI institute document. I guess Brad can provide you with more details on that specific aspect.

But we were a little unclear sort of how to move forward on this. Obviously, there is a committee that oversees the vital and health statistics and the standardized form. That's the National Committee on Vital and Health Statistics. We could send this recommendation to them. We could perhaps urge the agencies or the subcommittee to work with NCVHS to develop some field specifications, but clearly adoption

of this as a standard within the context of the usual

and recommended birth certificate format would really go a long way in terms of helping this become part of the structure at the State level.

Thoughts there?

CHAIRMAN HOWELL: Thank you very much.

I must confess I was unaware that there was a national recommended birth certificate. Is this recommended and the States then develop their own? How does that work?

DR. BOYLE: That's correct, yes.

CHAIRMAN HOWELL: So each State has a different birth certificate, but it's based on a national recommended. Is that correct?

DR. CALONGE: There are core elements that all States are supposed to use, and then States can add to that.

Nancy had a question.

MS. GREEN: Coleen, I think that's a great idea. Perhaps that concept could be expanded to include actually the results of newborn screening. There's so much effort on things like carrier results that are found through newborn screening but are not

transmitted. No? Okay.

CHAIRMAN HOWELL: There seems to be no support for that.

(Laughter.)

CHAIRMAN HOWELL: I haven't taken a vote, but I did hear all these "ohs" and so forth. Brad is going to shed some light on the subject. It strikes me as a wonderful idea, and I guess we need to figure out how we might be effective to do that. Brad, you had wisdom?

MR. THERRELL: So we did a short survey of States, and we asked, number one, do you have an electronic birth certificate; number two, does it have a field for a newborn screening serial number; number three, if it does, is it being used, and that sort of thing.

So it turns out that almost every State now has an electronic birth certificate. Not all, but almost all. And of the ones who are interested in this, there are now 11 States that actually have -- 10 States. There were 11 and Texas took it off their birth certificate five years ago. So there are 10

States now that have a serial number on their birth certificate. There are four more that are planning to add it in the next couple of years.

Most States commented that it would be helpful to have that, that it's difficult to get the State to adopt that because their birth certificate is already full of fields, and another field has to have a good reason for it. And so since this is now considered a core element in public health by ASTHO at least, we felt like this was an appropriate thing to now say it's a core element of public health. Let's put it on the birth certificate so that we can validate that it's being done on every baby. Then that allows the States to make these linkages and so on.

The first thing they're going to ask is, well, what does the format look like? There is a format recommended in CLSI's standard LA4-A5 that specifies how a unique number should be formulated, and if States would use that, then that would be helpful too.

CHAIRMAN HOWELL: I guess the question that we must address -- Kwaku? DR. OHENE-FREMPONG: Texas had it for how many years and then why did they take it off?

MR. THERRELL: Texas had it for about six or seven years. The staffing changed and there wasn't the push. When I was there, I was pushing for it, and that's why it got put on. After several years of fighting, they finally agreed to put it on.

Now, the trouble was it wasn't required that it be filled out. So in the hospitals, they said, well, it's just another field. It's not required that we fill this one out, and that data is down the hall somewhere. So it's going to be difficult. So they didn't do it. So over the years, nobody was pushing for it, and so they needed some more space. And I'm told that in 2005 they took it off.

DR. BOYLE: I was going to say I think there are two issues. One is, obviously, getting the field as part of their standard recommendation for the U.S. certificate, but the other part, at least, if I'm understanding Brad correctly, is sort of the requirement at the State that it gets filled out.

CHAIRMAN HOWELL: Ned, you had a question or

comment?

DR. CALONGE: The standard birth certificate is changed rarely. I don't know whether they may be moving to a strategy where you can change it more often, but it gets changed like every 10 or 15 years. It's a major issue when it gets changed. This last time, it just was changed maybe 4 years/5 years ago, and then all the States wrestle with changing their systems to adopt the new standard.

I just want the committee to understand I think this is a worthwhile endeavor, but you shouldn't expect that the recommendation will change the national standard overnight. I think it's a good thing to set up in the queue and just understand that it's going to take a while to filter down into actual practice.

CHAIRMAN HOWELL: Mike, you were --

DR. WATSON: I say this with some trepidation since it's one of those projects that's been sitting on my desk for a long time. But if the problem is that you don't have a standard for filling out that field, you know, we've already engaged with the Joint Commission on Hospital Accreditation. They were

interested in establishing standards around newborn screening because they clearly recognize that we know a lot more about a tumor than we do about a baby in a hospital because there are standards for registries and everything else about tumors and every form of cancer that occurs, but not for babies.

So the Joint Commission required -- Brad and I had some conversations with them a couple of years ago. They then required -- because the American Hospital Association would be against any new standard ever being imposed on hospitals, they asked us to do a complete analysis of all litigation related to newborn screening to identify where hospitals had been held liable. So our law firm did that the summer before last. I think it was that recently. So we have all that data, and there's extensive liability that's demonstrated when a case gets to the merits of the case in court. They rarely get there. Institutions settle these things, when they're involved in newborn screening, way before you get to the merits of the case. So you don't see it in case law. But there's enough there that I think the

Joint Commission would be very interested now in following up on setting standards for newborn screening which would improve your ability to find a baby after screening results came back. They have a critical results requirement that if a critical result comes back, you have to be able to communicate that on down the chain.

So perhaps somebody on your work group -- I talked to Alex about this previously. We didn't follow up. But perhaps somebody would like to work with me to finalize that interaction with the Joint Commission. I think it works better through this committee to be having a more direct communication pathway with them than just me. So I'd be happy to work with you on it. We've got most of the pieces aligned I think.

CHAIRMAN HOWELL: Carol?

DR. GREENE: I think this is a great idea and I hesitate to say this, but all but one State, I think, now allows people to decline newborn screening and not all babies are born in hospital. And a birth certificate -- you got to have it, and that's obviously the reason we don't want to put results on it because

it's your birth certificate that you show when you want to go get a passport and the passport folks don't need to know if you're a carrier for sickle cell.

Having said that, it's all going to be linked. There's going to be electronic records. It's going to be a different world. But right now, although I think this is a lovely idea, I think we also need to be sure that if you say that it's a field that has to be filled out before you can have a birth certificate, there also has to be a place for there's no number because the family declined or what happens if you're being submitted by a lay midwife who delivered a baby at home. So I love the idea but there are some other things that would have to be addressed.

CHAIRMAN HOWELL: Ned wants to respond to that, and then we have interest on this side.

DR. CALONGE: Because I deal with birth certificates all the time, I just think people need to understand the process. Very little of what is actually collected is printed on the birth certificate. So the data set is much more extensive. The birth certificate you have printed out basically has your

name, your date of birth, and even what's printed out varies from State to State. So that's a document used for identity verification.

So we have many, many more fields on every birth from the mom's occupation, dad's occupation, all this stuff. And to be honest, many of those fields that we want to collect have missing data. So there's no ramification other than you have to have a name, you have to have a birth date. There are very few elements that will, if missing, preclude you from printing out a birth certificate. So I want people to understand.

So you actually could put the results in and folks should know that and suppress them and they could be there all the time. The two choices are to put them in the data set or to build a permanent link and never delete your newborn screening data. So those are the two ways to think about it.

Again, I think setting this up as an expectation for whenever they revise the standard session is something we should support and just kind of understand how it would actually play out.

CHAIRMAN HOWELL: Alan is next and then

Chris.

DR. FLEISCHMAN: I just wanted to say that I think this is an extremely important recommendation that we ought to move forward on, and it's telling, Dr. Howell, that you didn't know this crisis in America about the lack of uniformity of vital statistics and the problems that we have actually in ascertainment because of that.

But having said that, there have been a lot of national organizations and meetings, the Surgeon General's Conference, Institute of Medicine reports that have argued we need to strengthen the vital statistics starting with the uniform birth certificate, and we could and we should. And this is the right time to do it since there have been a lot of changes. I think this is an important part of getting in that queue that Ned talks about so that we're sure that we're represented when, in fact, these changes occur.

CHAIRMAN HOWELL: Chris?

DR. KUS: I totally agree with Alan about the idea that there's a real difference between States and everything like that. I think given Ned's comment

about moving on the national guidance, the other part is the States -- it's their birth certificate, so they could make a change. You can really work with States. You can do it faster.

But to just highlight the complication, in New York State, there's a New York State birth certificate and there's a New York City birth certificate, and there are some slight differences.

CHAIRMAN HOWELL: It's clear that the group would like to have some input on this, and I guess the question is what would be the most effective way to proceed here. Peter, do you or Michele have some wisdom on this?

DR. van DYCK: I think there should be a small paper developed by a group, if there isn't so far -- I'm not hearing that there is -- that suggests exactly what should happen, and then I think, working with Mike -- he should be a member of that committee -- to mine everything that's been done --

CHAIRMAN HOWELL: And then --

DR. van DYCK: Then it can come forward as a recommendation to the Secretary because, obviously,

vital statistics is under secretarial review.

CHAIRMAN HOWELL: So your thought, as far as the mechanism, would be for the appropriate people to get together, come up with a document that we could send forward to the Secretary since the vital statistics program is under her purview. Can you work to do that?

DR. BOYLE: Yes.

CHAIRMAN HOWELL: Are there any further comments, Coleen, on your program?

DR. BOYLE: No.

CHAIRMAN HOWELL: Would you like to go back to that recommendation and have the committee formally endorse that recommendation?

DR. BOYLE: No. We could come back with the white paper next time.

CHAIRMAN HOWELL: I think that you've certainly got the sense of the committee that it's very interested in doing that.

And I will have to ask Ned why it takes people so long to change it. I know Florida's birth certificate is linked, and apparently they just did it.

But anyway, let's move along.

DR. CALONGE: If you don't want to do something, one reason is as good as another.

(Laughter.)

CHAIRMAN HOWELL: Well, thank you very much to the subcommittee.

We're a bit ahead of schedule, which is great. Not much but a bit. And we're now going to move on to a discussion of carrier screening for sickle cell.

I think that most of you are aware from our previous discussion that the NCAA recommended recently that sickle cell carrier screening be done in athletes.

The Sickle Cell Disease Association of America, in collaboration with HRSA, the NIH, and CDC recently had a meeting to review the level of evidence for sickle cell carrier screening and current screening practices for prenatal and newborn screening.

We are sorry that Dr. Jordan was unable to travel for personal reasons today, but we're going to hear from Dr. Lanetta Jordan who is representing the Sickle Cell Disease Association of America. We,

obviously, have the great benefit of having Dr. Ohene-Frempong, who is a member of this committee and is an expert on the subject and this area, and he will comment about that.

Now, keep in mind, as we are talking about sickle cell disease, I would like to engage the committee, after we've finished with the sickle cell, to discuss carrier screening in a broader sense. We have some correspondence about that. So we will move on to discuss that after that.

Dr. Jordan, I believe you're on the phone.

Is that correct?

DR. JORDAN: Yes, I am, sir.

CHAIRMAN HOWELL: Great. Welcome and so forth. We're sorry you're not with us, but I'm sure you're enjoying the weather in Florida considerably more. Okay, thank you very much.

DR. JORDAN: Good morning, everyone. It's a little hot today in Florida.

(Laughter.)

DR. JORDAN: But thank you so much for allowing me to present online. I actually had minor

surgery last Friday, and although I tried to sneak out of town, as most of you there who do know me, you know that I do travel a lot but my doctor absolutely prohibited me from traveling. So I am online. So thank you and I would like to thank Dr. Lloyd-Puryear for inviting me to present at this meeting.

In June of 2007, the National Athletic Trainers Association posted a statement or a position related to sickle cell trait in the athlete. Their consensus statement was to promote screening of sickle cell trait in college athletes. They did ask SCDAAs to participate in this consensus meeting that they had. SCDAAs did do so. At that time, our chief medical officer was Dr. Betty Pace, and after much review, SCDAAs did not support the NATA consensus statement.

In June of 2009, secondary to litigation, the NCAA recommended that member institutes move forward with testing student athletes, and that was certainly based on the recommendation from NATA in 2007.

So there was a lot of media exposure, a lot of anxiety, a lot of questions from parents and trainers, coaches, and the SCDAAs national organization

and their member organizations started to receive increased calls from around the United States. They wanted recommendations and wanted recommendations right away.

What we did -- at SCDA we have a medical and research advisory committee. We discussed what some recommendations could be and how best to approach going about developing those recommendations and realized that we needed some partners. So we sought the assistance of the CDC, HRSA, NHLBI. We, therefore, had a meeting in December of 2009, and that meeting was centered around the scientific and public health implications of sickle cell trait.

I'd also like to mention that in October of 2009, the AAP news did release a statement by Drs. Hord and Rice on the NCAA's position for athlete testing. They did not support testing but did emphasize taking common-sense precautions for safe training.

So the meeting focus certainly is more of a public health agenda. It involves the epidemiological research approach with the emphasis on services, policy, cost effectiveness of sickle cell trait

screening.

Today, I will outline four areas: one, the state of evidence for health outcomes associated with sickle cell trait; two, screening, follow-up, and health education for sickle cell trait; three, ethics, stigma, and discrimination; and lastly, the recommendations from the Sickle Cell Disease Association of America.

So the variants that we're interested in related to carrier screening are hemoglobin AS, AC, and AD.

When we think about carrier status, certainly being a carrier was thought of as a benign condition, but we have heard and certainly seen cases where the carrier status is not benign. In 2009, published in the American Journal of Medicine, there were some associations that were made, exclusively cumulative evidence that did support some associations, probable associations and some that were very possible. The ones that are certainly noted that have received public awareness are the cumulative evidence, which do have some convincing associations. I would like to

highlight. Out of that group of six under cumulative evidence is the exertional rhabdomyolysis and the exercise-related sudden death. Those are two that certainly have gained great public awareness and that's where the NCAA has focused some of its attention when it comes to screening of student athletes.

As we continue throughout the presentation and have some discussions afterwards, I hope, I would like for us to keep in mind that worldwide, there are 300 million people who are carriers for sickle cell and 3 million in the United States of America. That would certainly have some cost implications that we would certainly need to consider.

So when we think about the state of this evidence for health outcomes associated with sickle cell trait, we can think in terms of relative risk.

Dr. John Kark has published this information extensively. He did a retrospective analysis from 1977 to 1981 where he analyzed out of 2 million military recruits who experienced nontraumatic death who had hemoglobin S hemoglobinopathy had a relative risk of 30 compared to recruits without hemoglobin S, a relative

risk of 3. So certainly this was alarming, at least to the point of needing to gather more information and make a determination if there is an absolute risk that we needed to be concerned about.

So this ensued into an interventional trial occurring between 1982 to 1991, and the hypothesis was that if you were able to prevent exertional heat illness, it would reduce the mortality for all recruits and significantly so for the excess deaths seen among those with sickle cell trait. So there were 1.8 million basic training recruits. The intervention was a strict protocol to prevent exercise heat illness or injury, and having followed that strict protocol, none of the 13 predicted deaths occurred.

So the conclusion was that prevention of exercise-related deaths did not require identification of sickle cell trait as prevention, diagnosis, and treatment of exercise heat-related illness or injury are unrelated to hemoglobin type. Also, exertional heat illness is a preventable factor contributing to sudden exercise-related death in persons with sickle cell trait.

Well, certainly if policies are created, policies are constantly changing as they're being reviewed and updated based on the evidence. So the military continues to evaluate their policies, and they have concluded that there is evidence that does support sickle cell trait as an increased risk for exertional heat illness or injury but with the understanding that there are also other contributions from unidentified genetic polymorphisms.

So the thought is that it's not sickle cell trait or hemoglobin S in and of itself, but there really needs to be a good examination of some of those genetic markers.

And two, sickle cell trait does not exclude military personnel from duty in the Army. However, there is a minor exception in that in the Air Force, the Navy, and the Marines, the recruits can be selected not to participate in some certain military occupations such as diving or flying. So they do have some criteria to discuss that with those individuals who may fall into that category.

And thirdly, preventive measures can reduce

exertional heat illness or injury. That's really the operative phrase that we certainly can carry forward, that there are preventive measures and we certainly want to be sure that recommendations do include those preventive measures.

So when we think about screening, follow-up, and health education and how this information is reported, you've heard this morning that there are variations across States, and within New York, there are even variations there. Clinically significant hemoglobinopathy results are reported to the physicians. So newborns who are screened through the universal newborn screening program, those who test positive and are confirmed are certainly plugged into those physicians.

However, when we do assess carrier trait reporting findings, we do see variations across States where 48 States report to primary care physicians, and you see those exceptions there: Florida, Georgia, Louisiana, New Jersey. And 27 report to birthing hospitals; 17 report directly to families; 12 use the sickle cell community-based organizations; and 6 of the

States notify hematologists.

We have had universal hemoglobinopathy screening since 2006. However, 90 percent of the newborns were screened since 1993, and that screening primarily was for disease. We needed to identify confirmed cases to initiate medical care and to vaccinate against those pneumoniae and influenza and meningococcus infections. We also wanted to make sure that we could educate parents on health maintenance and also on the health risks associated with sickle cell disease.

However, carrier screening follow-up and health education has certainly been varied. Screening in symptomatic individuals for genetic predisposition or for a disease condition, which was thought to be benign -- and we know that it certainly is not absolutely benign, but because of the State variability in carrier status, recording of the tests, maintaining and reporting those results to the parent, we do have some gaps in follow-up and also some gaps and some opportunities in education.

Additionally, because there is a lack of

agreed-upon clinical evidence defining the health risk associated with carrier status, it certainly makes it more challenging to develop protocols that will be adopted across the States for carrier follow-up and education and when we think about the cost-benefit, you know, who exactly will provide the education, the follow-up, the long-term follow-up, who would monitor that those are occurring correctly.

So if we take just a glimpse at the cost, looking at athletes, so if we look at a snapshot of collegiate athletes -- and some of this information can be found by Hord and Rice in their AAP commentary -- if there are 400,000 collegiate athletes at any point in time and we perform a hemoglobin electrophoresis at a cost of \$50 -- I know that some are proposing the \$10 Sickledex test and if that is positive, then they can move on to the electrophoresis. However, if you're going to perform the test, you need to certainly perform the correct test.

But if we look at 400,000 college athletes, we're talking \$20 million, and if that trickles down to the high school level where there are 8 million

athletes, we're looking at \$400 million.

We are not just now talking about newborn screening, but we're talking about rescreening because more likely than not these athletes have already been screened during the newborn period. So the rescreening is certainly going to be costly, and these are funds that could be use, I would think, more wisely.

But if we actually did perform such tests at these costs, what would likely happen is that rescreening would result in only screening those targeted groups, and so those targeted groups, for the majority of individuals, would be African Americans and African American males. So we are certainly concerned about pulling out that targeted group on a national level at SCDA.

We're also concerned that we know that the screening is occurring within athletic programs, but we certainly do not have any information about the referral process. The results -- we've received reports -- are going to the coaches, but beyond that, are there other experienced professionals and resources available to these athletes? Do they receive genetic

and family planning counseling, for example? Is there any type of consent form? And if they choose not to have testing done, are they then excluded from participation? Are they told about the potential benefits and risks of carrier testing before and after the test? Is their privacy protected?

We certainly are concerned about the possibility of stigmatization of the carrier by the community and certainly would want that to be minimized. We were assured by the NCAA that student athletes were not stigmatized. However, through discussions, we did learn that there were times during practice, the students without hemoglobin S would have one type of conditioning and the students with hemoglobin S would have a different type of conditioning. So that does in a way certainly stigmatize them.

In terms of long-term follow-up, what is that mechanism? Is this only for the benefit of while they're practicing and have a scholarship and once that's over, they have no resources?

In terms of maintaining the medical record

and access to that information, will they have access to their testing results?

To elaborate a little more on carrier screening ethics, discrimination, and stigmatization, is there a moral obligation to act for the benefit of others? Certainly if we are talking about carrier screening, although there are no intentional discrimination practices, there certainly are some unintentional discrimination and biases that will likely occur over time. There's certainly the potential for racialization and stigmatization. We also could be faced with issues of workforce discrimination in this population and health insurance discrimination.

Again, we're concerned about privacy. Is there informed consent? Is this a voluntary process? And I did hear a discussion that some States have made newborn screening a voluntary process with parents. And is there respect for an individual's rights? Overall looking at justice, are all individuals treated equally and fairly? I would certainly question that, given that those with

hemoglobin who are carriers for sickle cell may not be treated equally or fairly if they're already experiencing loss of scholarships and have different types of practice patterns compared to the other athletes.

And when we think back in time at what happened in the '70s -- next slide, please. I came across this, and I must say I have learned a great deal during this process. But apparently because of legislation that supported sickle cell screening by Dr. Charles Whitten, which some of you I'm sure know quite well, termed sickle cell disease was the new "ghetto hustle" because now that screening was endorsed by the legislation, we now had sort of mom and pop and fraudulent screening centers that were popping up all over. So we certainly want to keep our eyes open for the situation that if there is an opportunity for individuals to feel that they can sort of jump on the band wagon and offer carrier screening, again we have no controls in place to ensure that it's being done correctly.

So the Genetic Information Nondiscrimination

Act of 2008, GINA, certainly has a section that does discuss sickle cell testing. In orange, I'll just read that section. "This form of discrimination was evident in the 1970s which saw the advent of programs to screen and identify carriers of sickle cell anemia, a disease which afflicts African Americans. Once again, State legislatures began to enact discriminatory laws in the area, and in the early 1970s began mandating genetic screening of all African Americans for sickle cell anemia, leading to discrimination and unnecessary fear. To alleviate some of this stigma, Congress in 1972 passed the National Sickle Cell Anemia Control Act which withholds Federal funding from States unless sickle cell testing is voluntary." So I would like for us to keep this information in mind as we do move forward with recommendations for carrier screening for sickle cell.

What GINA will do, in terms of protection and the types of tests that are protected -- right now, we do see that sickle cell is among the protected in the carrier screening disorders section. But it does not apply to members of the United States military, to

veterans obtaining health care through the Veterans Administration, or to the Indian Health Service. So again, as we continue to educate our client population, we certainly would like for them to be aware of what GINA will do and what GINA will not do related to carrier screening.

And GINA does not include protection from genetic discrimination in life insurance, disability insurance, or long-term care insurance. Certainly from my experience with the adult population -- and I know this is not carrier screening, but adult population of sickle cell disease, trying to obtain life insurance and disability insurance is nearly impossible.

So the recommendations for carrier screening from the Sickle Cell Disease Association of America.

There are 10 points, and it's small on my screen, so hopefully you have a better view than I do.

But one is screening for sickle cell hemoglobinopathy should be part of established universal newborn screening legislation.

Two, genetic information should be protected by HIPAA privacy laws. I certainly support the idea of

information being portable and some type of linkage with the electronic medical record. And if the Joint Commission can assist with that effort, I certainly think that will be a worthy cause because the results of newborn screening certainly somehow need to be accessible down the line for individuals who have been screened.

Three, hemoglobin testing should be done using HPLC.

The referral process should have experienced professionals who are culturally competent, and professional resources to carriers should also be available.

We would like to see a consent obtained.

We certainly would like a process in place where there are standards in terms of the potential benefits and risks of carrier testing communicated to individuals who are carriers and also those with disease. Just as States are varied, I can tell you that the community-based organizations are also varied with the information that is given to clients around the United States. So we would like a better process

for that.

Stigmatization of the carrier by the community should be minimized.

And universal precautions should be implemented to prevent exercise-related illness or injury. Thus, the need for sickle cell carrier status need not be identified and that information remains private with that individual or that individual's family.

Continuing professional education and awareness in all disciplines should be ongoing, and this certainly medicine, sports, education, and public health.

An appropriate carrier research agenda that complements sickle cell disease research should also be pursued. And I add "complements sickle cell disease research" because we don't want to lose sight that sickle cell disease is a major disorder and we don't want funds shifted away from sickle cell disease and only applied to or more applied to carrier screening or risk associated with being a carrier. But I think a complement to overall sickle cell disease is certainly

appropriate and we do need more research for sickle cell disease carrier status.

The next step for the SCDAA is that the CDC is having a blood disorders meeting in March, and we are taking about 10 of our community-based organization executive directors to that meeting. The CDC will have a work group with those individuals as we put in place a process of really understanding how the community-based organizations can work with the States and the physicians and the CDC and HRSA and NIH to have a unified message related to disease and also to carrier testing and what those recommendations actually are. Also, in June, June 3rd and 4th, the NIH will have a meeting related to sickle cell carrier status and setting a research agenda for sickle cell carrier status.

Thank you and before I guess I move into questions, Dr. Ohene-Frempong will, I think, have a few slides and some comments that he would like to make.

CHAIRMAN HOWELL: Thank you very much, Dr.

Jordan, and you will stay on the phone with us. We

will ask Kof to make a few comments. DR. OHENE-FREMPONG: Thank you very much. If

I can have my slides. I must say, in the spirit of disclosure, I'm actually biased on this subject.

(Laughter.)

DR. OHENE-FREMPONG: I have sickle cell trait. I found out I have sickle cell trait just before I was supposed to represent Ghana in the 1968 Olympics as a high hurdler. I played soccer all my life and track at a very high level all my life. This discovery came late. So it was somewhat disbelieving that it could affect you in any physical way.

When I was a resident, a boxer named Francisco Rodriguez died in New York City the first time he stepped into a boxing ring. The chief medical examiner in New York at the time attributed his death to two things. One was cardiomegaly. His heart was about twice normal, and they also found sickle cells in his blood at the postmortem. So they attributed sickle cell trait as part of the cause.

You can move on through these slides.

So I wrote a letter to the News and New York

Times. I wrote a letter arguing that it was not likely

that sickle cell trait actually contributed to his death, first, because sickle cell trait would not make your heart twice as big. Sickle cell trait -- individuals don't have anemia and they certainly don't have heart failure. And also everyone with sickle cell trait who dies, unless if they die from maybe carbon monoxide poisoning, will have all their blood cells become sickle. So anytime they look at postmortems and they find sickle cells in your blood, that is really most likely the postmortem effect.

So one of the things I know about me is that when I die and if I have an autopsy, that I would have died from sickle cell trait plus anything else. If I jump out of an airplane and my parachute does not open, don't worry. Just before I hit, all my cells will sickle. I will be dead before I hit. We have tried to explain this to pathologists for a very long time, but it never sticks. And I'm willing to tell you that about 90 percent of the cases that you read about where they're attributing death to sickle cell trait, it is a postmortem discovery.

This is not to belittle this subject. Clearly, the military study shows that there is some increased risk for untrained military recruits. During basic training, there is increased mortality for those with sickle cell trait. It's hard to put it in perspective because even the John Kark article that Dr. Lanetta Jordan just went through, if you just hear about the risk ratio between those with sickle cell trait and those without sickle cell trait, the denominator gets lost. In the largest review, there were 6.5 million military recruits, and I think there was something like 31 heat-related deaths and out of the 31, 14 of them have sickle cell trait. The death rate among all those recruits was much lower. Less than half of the death rate expected in the general population in the same age group. So even where there is an increased rate, I just don't want people to lose sight of the fact that we're still talking about a very small risk.

So for the individual athlete or potential athlete, if you are going to advise them of their risk, in total it's a very small risk. It needs to be

understood.

I think that Dr. Jordan made the point that research needs to look at this. In my mind, this suggests that there may be a linkage between sickle cell trait and something else that we have not been able to find. We think that we know that people with sickle cell trait have a higher risk of getting dehydrated because they have hyposthenuria. We don't concentrate urine as much. So if you are in a situation where you get dehydrated, one could postulate that they be at higher risk for heat-related injury because they are likely to get dehydrated fast. And there are some experimental studies in which people would exercise after a little bit of water deprivation and their body temperature rose. In the same individuals, when they were allowed to drink water liberally, their temperatures did not rise as much. So I think that certainly in sports, NCAA controls so much of college sports that they have the true opportunity going forward to actually study this very carefully, work with trainers and coaches, hematologists, exercise physiologists to try to understand what happens to some of these people. But I

really don't think that blanket screening at a second level is the way to go.

Also, there is something strange here.

Everybody knows that football players are not really the best conditioned athletes most of the time. But most of the increased mortality related to sports seem to happen in football. There are several countries in Africa where 20-25 percent of the general population have sickle cell trait, and they field soccer teams that play in heat and get dehydrated, and they don't report any increased mortality. In this country, basketball doesn't seem to have the same degree of mortality associated with it. Certainly not track or soccer in this country, but football.

Some of the physicians associated with NCAA themselves have described some of the training methods in football as, to use their word, "insane." But NCAA does not want to look in there.

The military looked at their training, made recommendations on how to hydrate recruits, and in the 10-year prospective study, after they changed their hydration practices, as was shown, the increased

mortality was wiped out completely. All they had to do was monitor body temperature and enforce water drinking at frequent intervals and that did it.

So I think there is something that if they look carefully, we could learn something about it and maybe put into practice something that has worked in the military, also in the sports.

Just to broaden the subject a little bit, as Dr. Jordan said, there are over 300 million people with sickle cell trait in the world. So if there are any health implications of sickle cell trait, they have public health implications. It's a major thing. One cannot understate it, and we have the opportunity to learn what it may be if we carefully do some studies so that we can make recommendations. The U.S. certainly has led much of sickle cell disease research in the world. So something that other countries may have missed because of other mortality rates that are higher, and so one sort of loses sight of whatever sickle cell trait may be adding to those risks. We can learn something and hopefully make it available. My final point also is that in our context

sickle cell trait certainly could be a non-important issue in the sense that people in the U.S., from a large study done in the veterans study where they looked at 65,000 African American males, the rate of sickle cell trait in them was about 8 percent. That was about the same as the general population. And there was no stratification of the rate by age, meaning that those with sickle cell trait lived as long as those without sickle cell trait. Many of the major causes of death that were examined and hospitalization were the same.

The only two things that they found that seemed to be increased was that there was increased gross hematuria or essential hematuria and also pulmonary embolism was increased. But other than that, there was no general indication that people with sickle cell trait were at much risk. So there may not be much certainly benefit for having sickle cell trait in the United States.

But if you look at it on the other side of the pond in Africa, even today since malaria still kills about a million children in Africa, having sickle

cell trait offers 90 percent protection against severe malaria. For children between about, I think, 6 months to 16 months in one report -- this is the highest risk of malaria deaths, by the way -- all-cause mortality was a 55 percent reduction by sickle cell trait in African children in that age group. So one needs to have that in perspective also before you tell countries to sort of do massive activity to try to either change the epidemiology of this gene. Maybe once malaria has been cured and we have a vaccine, then one can look at sickle cell trait from a different perspective. That's my final point.

CHAIRMAN HOWELL: Thank you very much, Kof. What suggestions do you have for this committee concerning the NCAA recommendation and what should be the response or commentary or whatever of the committee?

DR. OHENE-FREMPONG: You know, I think under tab 11, I wrote something for SCDA, and there are some recommendations there as far as the sports issues go. But since, at this point, all young people in the United States have been tested for sickle cell,

certainly those in high school and many of those in college and those who are coming up, that as Dr. Jordan suggested, if there could be some linkage between the newborn screening results and when they reach the age -- or whenever they are going to participate in sports, I believe that the counseling and the clearance of athletes for athletic activity in high school or college should go through their health care system. As it is now, you get a form that your doctor is supposed to sign before you go, and physicians, nurses, and others involved in that sort of counseling should include the potential risk for people with sickle cell trait, that even though it's not clear, has been documented so that they will be careful about hydration, resting when they're tired, and also that the athletic departments should be educated to include in their training practices the same thing that the military learned, that is, to allow athletes to get well hydrated. I think that to me will be sufficient. But to actually screen athletes at a secondary level because they're going to play football I think is too discriminatory. I think there should be

a more general approach to this. Whatever is done for the sickle cell trait athlete, as was done for the military recruit, in a general way seems to benefit everybody. When the military used new hydration methods, there was a mortality decrease in both those with sickle cell trait and those without sickle cell trait. So that was of benefit, and I think the same approach could be taken here.

But we do screen for sickle cell conditions in this country. Every child with sickle cell trait should know it. It's probably more important for them when they reach the age of reproduction than it is for athletics, and that counseling I think should be part of general public health activity.

CHAIRMAN HOWELL: The general plan had been -- the committee staff has been working to put together a writing group that would include you, Dr. Jordan, and others, to draft a document that would include comments we've heard here today and have it reviewed by the committee here and send a letter to the Secretary making recommendations of what this committee would suggest. Is that still consistent with what you think

we should do?

DR. OHENE-FREMPONG: Yes.

CHAIRMAN HOWELL: Could we have some comments on the committee about this? This is an important issue obviously. It's also a visible issue. NCAA is a very large and active group around the country. Piero?

DR. RINALDO: I would like to ask Dr. Jordan for a clarification. The slide that showed the recommendations, the first point was about that if any screening happens, it should happen for newborn screening. But later down, the recommendation was there should be informed consent. The slide is now in view. So number 5. So are you implying -- are you suggesting that we should sort of have informed consent at the newborn screening level?

DR. JORDAN: Not at the newborn screening level, but certainly for the adolescent or the young adult, there should be some form of consent which we actually obtain in our health care system before we do any screening.

CHAIRMAN HOWELL: I think that's an important clarification because I think that we would certainly

not want to make a specific recommendation about informed consent.

Are there any other comments we might proceed to the working group? The plan would be for this group to put together a document, and we will have a document for the next meeting that we'll send to the Secretary on this issue.

Chris, Carol?

DR. KUS: Yes, I think the big point here is if you look at number 8, the universal precautions implemented, I think this is a time to say that that's what really needs to be done. Is there a definition of the universal precautions implemented to prevent exercise-related illness and injury? What is that?

DR. JORDAN: Yes. The NATA actually has it posted on Web site exactly what those precautions are. So it is very similar to what has been done in the military. But what NATA states is that it's very challenging for them to have the coaches comply with the precautions. Basically there seems to be a lot of testosterone running around on the field, and so the coaches push the players and the players push

themselves. So the universal precautions are not followed strictly.

CHAIRMAN HOWELL: Chris has a continuing comment.

DR. KUS: Well, I think that this is a point with whatever the communication is to emphasize that because I think that gives the idea that it's clear in reviewing it that people should be using reasonable precautions when they're dealing with athletes.

CHAIRMAN HOWELL: The document we send forth should be clear about what those might be so they will be well defined.

DR. JORDAN: And very explicit, yes.

CHAIRMAN HOWELL: Thank you very much. Carol had a comment.

DR. GREENE: Thank you. My comment was going to be the same as Piero's, and Rod has already pointed out the importance of it. So my question is a process one.

These wonderful carrier screening recommendations from the Sickle Cell Disease Association of America. Is there any possibility --

because it is possible to read them in a way that you did not intend, is this already complete or is it possible to asterisk it or say for adolescents? Is it possible to make it clear in the way that you just clarified to us?

DR. JORDAN: Oh, most definitely. And these have not been distributed. This is the first viewing of these. So certainly it's brought to this committee for review and so that we can revise them as needed.

CHAIRMAN HOWELL: Excellent.

Peter, did you have a comment?

DR. van DYCK: I just had a question. So it's a recommendation that we've heard this morning that in newborn screening both disease and carrier status are identified. Should that be communicated then uniformly or universally to parents?

DR. JORDAN: Yes. We see the variation between the States. The CDC has reported that nicely. So they know the variations of carrier status reporting. I think if there could be uniform reporting of disease and carrier status, that would be beneficial. Here in my health care system, when we invite parents in who test positive for trait, they have no idea really that they can have subsequent children that have sickle cell disease. So because they have trait, they're sort of lost. No one really talks to them, and they think, oh, I'm fine. I have no risk here. And two, three children down the road, they then can come back and say, well, what happened? Why wasn't I informed?

So I think there has been that focus on disease, and certainly that focus then and those energies and dollars needed to be there, but we are certainly now at the level of, I think, advancing the initiative to carrier follow-up.

CHAIRMAN HOWELL: We have some commentators at the microphone. Would you please introduce yourself, as well as your comments?

DR. HASSELL: Certainly. I'm Kathy Hassell, adult hematologist from the Mountain States Genetics Collaborative and Director of the Colorado Sickle Cell Center.

DR. JORDAN: Hi, Dr. Hassell. DR. HASSELL: Hi, Lanetta.

I have two comments, one of which has just been touched upon.

As we saw earlier, there's inconsistent reporting of carrier status throughout newborn screening programs, and if one is to build a platform of notification or at least information around this area, one has to thoughtfully consider whether this committee or a process would attempt to standardize notification, not just disease, but carrier status.

The second is this is timely. I'm in receipt of an email from the Arizona Department of Health who hastily convened, as we meet here today, in Arizona all of its athletic associations to tell them what to do about this. They've sought the educational information. They made the assumption that this is a vetted, understood, codified, and clarified area. So departments of health are becoming entangled, shall I say, in this entire controversy around testing of even pre-high school athletes in Arizona. So timely action, if something is available from this committee, would be seen as very helpful.

CHAIRMAN HOWELL: Thank you very much.

MS. WARNER: Good morning. I'm Ellen Warner from the National Heart, Lung and Blood Institute at NIH.

As part of the Healthy People 2020 initiative, CDC, HRSA, and NIH proposed and got approved a new focus area in blood diseases and blood safety. One of our approved objectives is to increase awareness among carriers of their trait status. And of course, the obligation is upon us federal officials to now measure progress in this area. So data will be required.

And part of our implementation strategy will have to address the issue not just of informing parents, but health education through critical milestones in the developmental process so people, as they mature, can carry this information about their trait status with them so when they go to school, participate in athletics, and reach reproductive age, they should be aware of their trait status.

CHAIRMAN HOWELL: I would hope that with your new expertise and interest, that you can participate in

this writing group that will work on this document. We will share your wisdom.

I think that the notification of carriers in the newborn screening period is a significant issue.

There's great variation in how to deal with that.

Obviously, it will not just be sickle cell. If we make recommendations about notification of carriers, you immediately turn up cystic fibrosis, among others. So that's not a trivial consideration to consider.

Are there further comments about this?

So we will expect this distinguished group of spokespersons to have an eloquent document for us to review at our next meeting and send something forth.

There are a lot of issues here, but it seems to me the important thing is to get this on a slightly different track than has been recommended as far as screening all the athletes. That doesn't seem to be the right way to go.

The second thing is that you have in your folder -- I mentioned it briefly yesterday -- a letter addressed to this committee and a similar letter that was sent to the NIH from the Heine Foundation urging us

to consider carrier screening for spinal muscular atrophy in the broad concept of carrier screening. It seems to me -- a personal opinion is that carrier screening is going to become a much bigger issue as the technology becomes inexpensive and there are a number of untreatable conditions that would benefit at this point in time from carrier identification, not unlike what has been suggested for cystic fibrosis. And a recommendation recently came from the American College of Medical Genetics about carrier screening for SMA. There was a recent meeting at the National Institutes of Health that was sponsored by several institutes to discuss this issue.

And I'd be very interested in your thoughts about looking at carrier screening in a similar way. It's a very different process, but it certainly would fall within the broad purview of this committee. Can we have some comments about that?

And the first specific disease condition that the committee would be looking at, I believe, might be SMA since there's been so much discussion and work and research and technology in that area. Sharon, you had a comment.

DR. TERRY: Yes. I was at the NIH meeting, as you know. I felt at the end of that meeting, that we had only begun the work and that probably the proper place is an ongoing committee like this one to look first at this disease and then others as we go forward.

And then the interesting thing I think is to bring together the right players, certainly the family groups because there was some disparity between what various groups thought, and then also the professional societies because there was also some discord between those societies at least in writing and it might be good to understand the intention behind the various guidelines.

So I think that it's a bit of heavy lifting, and I think this is the proper place for it to be done.

CHAIRMAN HOWELL: Well, I think you're correct. For those of us who were at the NIH committee, there are a variety of issues that are very important. Number one, professional societies that would have to deal with implementing this prenatal

testing and so forth. That's a substantial issue and

it adds a considerable burden.

There's always been the concern among groups that if you do carrier screening, you might lose your interest and attention to identifying treatments and cures for these children because if you have a really effective treatment and a cure that really works well, well, then carrier screening doesn't become very key if you can identify the children. So I think that we would have to be very cognizant of these competing interests and so forth, but it's an important area.

Alan?

DR. GUTTMACHER: Someone should probably speak who wasn't at that meeting, but I also was at that meeting and have had numerous discussions about this. I heartily agree with both Rod and Sharon. This clearly is a coming -- it's already here in many ways, but a tidal wave that is soon going to engulf us, particularly with new technologies making this screening eventually when we sequence everyone's DNA, in fact a matter of course. And we're not that far away from that world, I would remind us. I think that this is a very good group

because this is a very complex issue, and it has the kind of multiple issues that require multiple perspectives and a lot of the nuance is very similar to the nuance that we've just been discussing here the last couple of days, et cetera. So I would think this would be a very wonderful thing for us to be taking on.

CHAIRMAN HOWELL: Jerry?

DR. VOCKLEY: Just to remind us all that the kind of conventional wisdom to date has been that we don't give carrier screening that doesn't have immediate clinical applicability to individuals who are not of an age to consent. So in other words, giving an SMA result or any carrier testing result -- CF -- to a family about a child eliminates the ability of that child to decide later on whether or not they want that information.

So relating that back to one of the things that I mentioned in the Lab Committee report, which is that right now we're focused on newborn screening, but there are other ages where there is essentially universal contact with the health care system, that we should not just look at this issue in the context of

newborn screening but talk about it in the context of age-appropriate screening. And it may provide a slightly different view on when something like this might be appropriate, and even if we say, well, maybe the newborn screening isn't the right time to do it, but some time later might be, it adds a level of opportunity that might make it less complicated to deal with in the context of newborn screening.

CHAIRMAN HOWELL: One of the things that comes up is that as we move into carrier screening, there is some very heavy lifting, as Sharon says, but one area that there's a lot of work to be done in is certainly the ethical and legal and social area. We have been contacted by the other Secretary's advisory committee, the Secretary's Advisory Committee on Genetics, Health and Society, about having some joint conversations about overlapping interests. I think that would be very prudent to do. If this committee would think that appropriate, we can certainly begin dialogue with them to say that this is an area we're interested in and we would like to work with you in discussing. We'll obviously come back to this

committee. But if the group agrees with that, we will plan to have some conversations with Sarah Carr and try to work on that a bit as we go down.

Alan?

DR. FLEISCHMAN: I too was at that meeting.

It's the same cast of characters. You can line them up.

But I think Dr. Vockley's point is very well taken. When we consider preconception or prenatal screening, that's within the individual health care context. When we talk about newborn screening, we talk about it in the public health mandatory testing context. And these are different. They're very different, but they're both very important and have complicated LC issues. And as Dr. Guttmacher points out, we're rapidly coming down that road with preconception and prenatal testing.

I think this group would be a good group to do this if it were expanded not just with the community of interest, but there's some expertise that isn't represented around this table at this point in that specific area. So it might be that combining with the

-- I don't want to call it the parent committee, but the other committee would be a good way to do that. But I do think it's going to take some very hard and complex thinking and advice to the Secretary about the future of preconception and prenatal testing in America.

Just to throw something into the minutes, I mean, my own personal feeling is that it is not a disease-by-disease argument. It's really a conceptual argument that needs to be made in the voluntary dyadic relationship between patients and doctors, which is different than what we've been doing, for the most part, in the last two years on this committee.

CHAIRMAN HOWELL: I agree. It's not a disease-by-disease. I think that we will benefit in our work, however, with examples and so forth. With regard to the other committee, I think that they will provide great expertise. But let me remind you there's only one congressionally mandated genetics committee and that's us.

(Laughter.)

DR. TERRY: I was waiting for you to say

that.

CHAIRMAN HOWELL: I try to remind you all the time.

(Laughter.)

DR. TERRY: Right, yes.

I would recommend --

DR. FLEISCHMAN: I stand corrected, Dr. Howell.

CHAIRMAN HOWELL: Thank you. Let's put that in the minutes.

DR. TERRY: I would recommend that we take the proceedings from that very rich meeting -- it was quite an astoundingly rich meeting, the one that was at NIH -- and then use that as a basis for the work that this committee needs to do in part because we're going to hear the same conversations over and let's, instead, move the ball farther than that meeting did.

CHAIRMAN HOWELL: Dr. Guttmacher is working very hard on a summary of that meeting, and it's progressing at a federally slow level. But anyway, we'll try to get that back and --

DR. GUTTMACHER: I would like that stricken

from the record.

(Laughter.)

CHAIRMAN HOWELL: Some of us are contributing mightily to its slowness.

It's break time. So let's take a 30-minute break and we'll return and finish the morning.

(Recess.)

CHAIRMAN HOWELL: We're now going to move to a presentation by Dr. Alan Zuckerman. He's going to tell us about the progress of implementing the newborn screening use case since he last presented to the committee's September meeting. He can also address the need for this committee to comment on CMS and ONC documents on the meaningful use. As you know, the newborn screening case was not included as a stage 1 use case.

You've heard from Dr. Zuckerman over the time, but he's been a member of the Commission on Certification of Health Care Information Technology Interoperability Work Group -- there are all sorts of good terms -- since it's creation, as co-chair of the new Interoperability Work Group this year. Alan, let's hear about the interoperability specifications and your comments about what this committee needs to do.

DR. ZUCKERMAN: Thank you very much. A great pleasure to be here at the committee at this pivotal point in time that's the culmination of several years of work in developing the HITSP/IS92 newborn screening interoperability specification. But what is really happening when this is voted in on Monday is that it's creating new roles and responsibilities for this advisory committee as we move out of the phase of developing and endorsing standards into the phase of actually moving them forward.

Now, of course, as we've discussed before, the initial work deals primarily with the transfer of newborn screening of lab results into electronic health records in hospitals and practices, and it's building on capabilities that are going to be part of every certified record that is out there. And over the next few years, this will become a predominant mode of practice, and it's the responsibility of this committee

to supervise activities at NLM to define the

vocabularies and the content of these messages for newborn screening. So as new conditions are discussed, as suggestions are made about reporting back to both patients and providers, these need to be included in this evolving specification.

Of course, the other key area for the committee is that having electronic reporting should improve the efficiency and accuracy of gathering the evidence to make decisions about the long-term impact of newborn screening. And we have opportunities now to look not just at reported cases but at entire populations based on the content that will go into these electronic reports.

The final thing we're going to consider today is the interim final rule from the Office of National Coordinator of HIT and the NPRM, the notice of proposed rulemaking, from CMS on incentives for meaningful use of EHR. And of course, we would like very much for newborn screening to be part of that. We're not in there in phase 1 this year, but we have a short window of opportunity, perhaps 18 months, to get this into the phase 2 quality measures and requirements of the

Medicaid programs. Again, the final interoperability specification is up earlier this week. It's up for a vote and is anticipated to be accepted on Monday. It's worth remembering that this activity began back in 2007 from the Personalized Healthcare Workgroup at the AHIC that Peter van Dyck and others were involved in chairing the subgroups on newborn screening. But at this point, the work is finally ready to go into practice and use. There are several vendors in the room here who have expressed interest in beginning implementation very quickly. We have several States with HRSA support or cooperating with them that are going to be actually putting this into practice over the course of the next year. But it's actual rapid adoption and moving into generally accepted practice over the next two years that's going to make electronic reporting of newborn screening part of the measures that may be required in phase 2 of meaningful use for EHR. And it's also worth remembering that this use case was only one of four of the recommendations out of the AHIC. There's also a privacy document. You've

seen and will continue to see the coding and terminology standards. But one fourth area that this committee hasn't really looked at before is monitoring and promoting the adoption of electronic data exchange, both for initial screening and for follow-up. Hopefully, this will become more of an ongoing activity defining the data that we feel needs to be gathered. We didn't provide copies of the specification to you because it really is hardly worth reading. It's a very technical document that delegates and refers and invokes other materials. But I'd like to review some of the key substance, and what we did give you are two very important documents that illustrate the practical impact and how people will begin to use it. Again, the primary focus is on initial screening, but the broad scope goes much further. The content mechanism is a particular version of the HL7 labs, and it's the kind of message that every lab, every electronic health record is sending. So newborn screening and hearing screening are becoming a special case of what is becoming dominant technology. And for those who don't have electronic records -- sorry. The

slide was just out of synch.

DR. DOUGHERTY: I was just asking -- I don't know if we can interrupt, but I think it would be helpful to some of us, even some of us who have the 500-page document on their desks, to explain what the meaningful use exercise is before getting into the use case. My understanding is that some quality measures are set up, and if you agree to measure those measures, collect the data on those measures in your practice and you have 20 percent of kids on Medicaid, you can get a payment incentive.

DR. ZUCKERMAN: Well, there are several sides to meaningful use. Let me perhaps divert there because that may be of even greater interest.

The first part of it is meaningful use is about incentive payments from the Stimulus Act, and it's a substantial amount of money divided between practices and hospitals. To get these payments, there are several preconditions. You have to be eligible. So to be an eligible provider under Medicare and Medicaid, there are different rules. To be an eligible hospital, there are different rules. There are also two sides to the equation.

One is if you're selling the products, you have to be certified and meet certain certification criteria, provide certain standards, and make use of certain content standards and vocabulary standards. So there's a definition of what is an eligible EHR, who is an eligible potential purchaser, but then to actually get the money, you have to demonstrate that you're using it in a meaningful way to change health care. And the way in which you normally demonstrate it is to use it to gather and report quality measures.

So as we get into our comments and discussions, we need to look at both sides. What's the definition of an eligible electronic health record, that is, one that provides the capabilities that will support newborn screening, and on the other side, when someone purchases that product and wants incentives, what do they have to do to demonstrate that they're using it to support activities which we want to defend? Again, one of our key points of concern is how to get newborn screening into that equation, particularly

given that we're kind of behind the curve in not having

evidence-based measures that people are using newborn screening appropriately. So part of our 18-month agenda is to get the product out there. It's also to get evidence on measures of what is appropriate use of these newborn screening reports.

In the first phase that's beginning now, it's simply moving data. In the second phase, you want to measure and report quality. In the third phase, you want to demonstrate improvement in outcomes and practice.

And our focus today is to get ready for phase 2. But before we get there, we need to have the codes. We need to have the way to move the hearing events. And I just wanted to point out that the interoperability specification also covers areas like delivery of educational materials and collecting of patient consents.

We can say that things are ready because we've gone through a process of inspection testing and people trying to develop messages and samples that use it. What you see in front of you today are two documents, one showing sample application of the

messages and one showing a vocabulary that's intended to be reasonably comprehensive but which is still a work in progress. These documents were in the briefing book. Both documents were in the briefing book that provide guidance on how one would create a report that can report at a detail level, that can carry quantitative results.

Among the other things which need to be done with newborn screening is to capture the data from the filter cards and move that in electronically. In these documents are examples of data to be entered and sent by the hospital or entered at the labs that originate on the filter paper. These all need to be reviewed carefully. Some have their own codes. Some are already part of the standards like the various demographics and information about the laboratories.

One of the things that we're trying to do is develop a library of typical reports to illustrate the variations in what States do between each other, what they may do for individual patients with normal or abnormal results, and what might be done to send additional data for research purposes to one of the

regional collaboratives. And these reports will join the two documents that you see here and be available on the Web site. And the traditional PDF documents with logos and other format, as long as they're carrying the same data, may persist in some States, and the messages that are intended for electronic records also can be translated into Web-viewable documents or printable documents to assist people in viewing the data.

All of these will be available on a special new HL7 tab out at the NLM Web site for newborn screening codes that's been added. The material that was distributed in the briefing book is also downloadable and will undergo continuous revision.

It's important for the committee to look at those documents and request changes and request differences based on the topics such as the several you discussed at this meeting, which should result in changes in the kind of information to be reported back either to providers or patients or to programs for quality improvement program maintenance.

Just to go quickly through some of the elements of the sample message document, the one that

begins this way, which is again in the briefing book, first it begins by taking data off the filter card, moving it into the message, such as information about the mother, the patient, and areas like the quality of the specimen or the reason that the test was done. Throughout the sample document, we try to give representative examples and examples of the choice list for things like risk factors for hearing loss, the types of quality assessments. And these need to be aligned with the data and evidence that you want to be able to capture on populations.

An example of reporting test interpretation is there's an overall interpretation of whether any conditions have been found, and then there are lists of conditions. It might have positive markers, equivocal markers, and other types of interpretation. So within these lab reports and like many others, there's both reporting of the primary quantitative data or reporting of the interpretation by the laboratory typically with comments.

Here you see, for example, how one would represent a normal amino acid profile and address

additional comments to providers. And this may be all that the physicians see.

But in addition, you may want to send on to particular referral groups or to your regional collaborative the detailed quantitative values of the amino acids that were measured, or you may do a combination when a disease is suspected, provide the evidence for the amino acids which are abnormal. As the library of reports will be illustrating and as the capabilities built into the specification allow, you can custom tailor the reports for the amount of data to be represented in different clinical settings.

Turning now to the other document, which is the LOINC panel, this document is split into two halves. The first half lists all the possible LOINC codes, and here we're dealing with initial screening, so it has many different anchor points for presenting interpretations, presenting quantitative data, presenting data that came from the filter cards. In the future, there will be similar collections of LOINC codes for various follow-up databases, for confirmatory testing, other things. The scope of this document is

to try to be a global inclusion of what States are currently doing.

And the codes also capture the methods that were used. So whether you're using IEF or HPLC for the hemoglobinopathy, pattern recognition is expressed within the codes. Again, our main concern is that these lists are as inclusive as possible and changes can be made with relatively short notice to make sure that nothing has been left out.

The second half contains the answer lists.

Some codes may be associated with a value, like a measurement of an amino acid. Others, such as conditions with positive markers, will represent a list of one or more items chosen from the list, and the lists that are described in the document are intended to be as comprehensive as possible and to cover all of the primary and secondary targets that States are testing for. So as we add new target conditions, as new test methods come into use, we need to be sure that the answer lists reflect the kind of data which should appear on the reports.

I also wanted to mention that we are moving

into a new phase of rolling out these activities by partnering with an organization called Integrating the Healthcare Enterprise and HIMSS. Every January, this voluntary organization, primarily of vendors that is trying to promote health information exchange, holds an event called the Connect-a-thon, and this is where vendors come together in the same room and demonstrate that their software is able to move data back and forth. We're very pleased to announce that newborn screening and newborn hospital discharge are on the work program for next January and that we are in the process of developing integration profiles for these activities. And if all goes well next January, we will have laboratory vendors and hospital information system vendors sit down in a room and illustrate that you can move data back and forth.

The newborn discharge summary is a particularly exciting area linked to perinatal work flow because this document that's intended to go from a hospital electronic record to the office record is fed by the antepartum record containing tests that were done on the mother during pregnancy, the labor and

delivery summary, the vital records birth certificate fields, and of course, newborn screening and other labs.

This represents a new form of routine data integration that we hope will become a standard operating procedure. One of the events that we hope will happen is that the newborn's record -- and we're dealing here only with normal newborn, short-stay discharges for the first year, that the record that's created in the hospital will move into practice and will open a new ambulatory electronic health record with the newborn screening results integrated into it and with data from the mother's record from other key events automatically populating the office-based records. So we hope this will also begin to engage hospitals in sharing results with patients and with physicians in the community.

Most of you know newborn screening results for normal newborns often arrive at the hospital after the infant has gone home, but with the advent of electronic reporting, these can be added automatically and immediately filed in the record, update the

summary, and the summary can be then made available both to parents and to other providers when it's needed. Some of the regulations going into these capabilities are that patients get electronic access to data within 96 hours of when it's provided to the hospital. This means that we're going to eliminate the delay of filing newborn screening results into hospital records after the infant leaves and that when the parents can identify where the infant was born, which is a lot easier than identifying which physician the infant is going to be seeing when they show up for their 2-week or their 1-month checkup, that you'll be able to use that information of where the infant was born to ideally get the results. This isn't going to happen instantly, but this is our vision for the next five years as the way in which data will flow between different devices.

So what can we be doing here to move this forward? Although public comments are closed, the comments that are submitted to NLM will continue to refine the messages and codes to make sure that they meet your need. Encouraging participation of vendors

will get this into a very public showcase at the HIMSS convention next spring.

And as has been mentioned before by Sharon Terry, new exploration is going on for the nationwide health information network to make moving data easier to find. This is going to be based on directories of hospitals and physicians, have point-to-point things. The goal is that some day secure electronic mail of medical information should be as easy to implement as the U.S. Postal Service mail is today, with the addition of appropriate security constraints. You should be able to locate people. You should be able to get a message to someone, unlike what email represents today being neither secure nor having a fixed structure of how to find people and know if they participate. Of course, as we mentioned before, encouraging CMS to get newborn screening into regulations of meaningful use will be a big driver for adoption. One of the things that the advisory committee might consider is sending letters to States to try to accelerate the process of adopting and implementing these electronic specifications. Every

opportunity to assist them should, of course, be encouraged. One of the most important opportunities is getting State Medicaid regulations to require the use of electronic newborn screening and to put in place quality measures which would report back completion of hearing screening, review of newborn screening by appropriate points of time.

Again, the other important next steps that can be occurring are going to be in the form of comments on the regulations and taking action to encourage the adoption of the specification. A very important part of that will be recognizing we're in the middle of a 60-day window of opportunity to respond to two sets of regulations that were issued, one from ONC on the certification criteria and standards and the other by CMS on the incentives. These came out on December 30th, as required by the legislation, and they're going to control a significant amount of funds disbursement that will be starting in October.

While we didn't make it into the phase 1 area, these incentives are going to be able to drive forward change if we're ready to get them into the

2013. A set of draft responses was prepared and has been circulated to the committee. One of the key issues we need to consider is does the committee want to make a formal response and are the suggested responses here appropriate.

First, we suggest that there be raising awareness of the background of why newborn screening should be considered part of meaningful use. The committee's comments deal with specific recognition that the standards will work and can be applied to newborn screening, in particular, incorporating lab tests into electronic records, providing patients copies of records, giving them timely electronic access, and providing care summaries capability to exchange key data.

We also need to respond to two sets of questions: one from ONC, one from CMS.

ONC asked about relationship to other Federal law, and we can connect meaningful use of EHR incentives to the needs to collect evidence under the Newborn Screening Saves Lives Act.

They also asked about the feasibility,

maturity, and prevalence in the industry as to whether this is going to be ready for 2013 regulations. Our comments to them were equally comments to ourselves about the role we're willing to take and what we believe is going to happen to make this feasible. Part of that will also involve preparing quality measures that can be used for accountability, and the Long-Term Follow-Up Committee discussed yesterday some of their activities to get evidence about quality measures that could be implemented.

CMS took a somewhat different position, and we're, I think, in a very strong position there.

They're asking for comments on what to do next in 2013, and they've already targeted very specifically newborn screening as one of the activities. And they also at three places in their report acknowledged the gaps in newborn screening, make a commitment to develop quality measures, but they also caution State programs not to impose barriers on physicians if the cost would be too high in areas such as connecting to a newborn screening registry.

Again, here I think we need to both encourage

CMS and encourage the States that this is something we can do on a 2013 time frame. We can have State Medicaid programs ask physicians to report back to public health what happens with hearing screening, with completion and review of newborn screening results and their indications.

So let me stop here, take some questions and comments. Perhaps first we should deal with the specification and then get into the issue of our preparation to comment back to ONC and CMS.

CHAIRMAN HOWELL: Questions or comments for Alan?

DR. ZUCKERMAN: In particular, you raised the possibility of do we want to send a letter to the States to encourage them to move forward. Do we have additional comments or review on the data for things --

CHAIRMAN HOWELL: At your desk, you have a letter that has a January 22 date on the top, and it's from me as chair of this committee. This addresses a number of the things that Alan went through as far as the requests and so forth. If the group is so inclined, this letter would go to the Secretary but

also could be posted to the ONC site and the CMS site specifically responding to questions that they asked. I think Alan has been fairly clear about those, but you might want to go through those.

Does APHL have a position that they've responded to, Jelili, on these recommendations?

MR. OJODU: Yes, we do have some recommendations or some comments to the recommendations, and we plan to submit them prior to the deadline.

DR. LLOYD-PURYEAR: Are they public?

MR. OJODU: No, not yet. I think we can share them with you eventually I guess.

CHAIRMAN HOWELL: Are they consistent with the document -- have you seen the document that we have before us?

MR. OJODU: I'm not sure exactly what you're looking at.

CHAIRMAN HOWELL: Why don't you look at that and maybe we can comment?

Sharon?

DR. TERRY: So I agree with this approach and

think that Alan did a very good job of laying out the issues on the HIT Standards Committee, so I've been in the weeds on all of this stuff. Genetic Alliance will be providing comments and they're consistent with this as well.

The other thing we've done is worked with the HIT Now Coalition which is a coalition of consumers and companies, vendors, to take on newborn screening as their example of what should be done and use it all the way through the immense documentation to make comments. So that whole coalition will take up newborn screening.

CHAIRMAN HOWELL: Well, it certainly seems very sensible. And the comments that the Alliance has made -- are they consistent with what you've seen here?

DR. TERRY: Yes, they are very consistent.

CHAIRMAN HOWELL: So they're not divergent. Denise?

DR. DOUGHERTY: Just a couple of clarification things that could happen in here. I think it's very good. I think there's a little confusion I have about when it says a measure of

newborn screening because we often talk about the newborn screening system. So where would that measure be collected? Would it be collected at the public health laboratories or in the primary care provider's office or some other care provider or both? That's not clear to me from just a quick read.

CHAIRMAN HOWELL: Alan, can you clarify that?

DR. ZUCKERMAN: The measures inherently have to come from the user of the electronic health records as part of meaningful use, but one of those measures is sending data to public health. So one of the things we can ask practices to count is that they have sent back information to public health on the outcome of a repeat hearing screening in infants who left the hospital with their last screening saying that they were referred, that they didn't pass. So one can count what percentage of infants who were being seen in a practice whose last hearing screening says refer for retesting, who got retested, and if the results of the retest went back to public health.

In a similar fashion, one can count just how many people opened and signed off on a newborn

screening report. We talked today about sharing carrier states for sickle cell with families. That is an example of a quality measure that can be counted. You can count if the results of the newborn screening is in the electronic record. The system can count how many children in a period of time were detected with sickle cell trait, and you can look at what the practice did and what they can document they did to inform the parents.

DR. DOUGHERTY: So the first one, let's say, the primary care provider -- I'm not sure if you're talking about hospitals or primary care providers.

DR. ZUCKERMAN: Well, we're talking about both because there are programs for both.

DR. DOUGHERTY: So for that to happen, realistically there will have to be this connection between -- some automatic connection. I'm trying to figure out what the measure would be, the actual measure. What measurement people want to get away from is just clinicians checking something off on a box because that doesn't always mean that it happened.

DR. ZUCKERMAN: For example, if we define a

cohort of infants who were seen in a practice under 30 days of age, one can go through and determine if the practice obtained a copy of their newborn screening report and if that is part of their electronic medical record. And we can set performance criteria for what percentage of children reach 30 days of age without having their newborn screening results filed in the chart. And there may be accountability for why not that would be allowed, as often is.

But the first step in most of these quality measures is the ability to collect the data, to report back how many diabetics you have in your practice. Well, here the same approach. How many children with various metabolic or hearing diseases and is that recorded on their problem list?

And one of the things we've worked towards is getting a comprehensive list of SNOMED codes, other codes to enter data on the problem list, and we can go through and audit records for the number of children with conditions detected by newborn screening that are known to the practice.

DR. DOUGHERTY: So that seems very feasible

for people who get the incentive and have the electronic health record.

But the next piece where the provider reports back to public health is where I'm having a little trouble figuring out how you measure that that actually happened.

DR. ZUCKERMAN: Oh, very easily. One of the capabilities in the certification criteria is the ability to send the lab data to public health where it is required. Every time you send something out of your electronic record, you're required to keep a privacy log of who you disclose that data to. So it is very feasible to find how many children have had newborn screening done, how many of them may have been referred on hearing screening, and how many hearing screening reports were sent to public health by counting.

Now, we're not sure what the performance will be, and part of what we as a committee here need to do is to have evidence-based tested measures ready in 18 to 24 months that have the credibility for CMS to accept them as a legitimate request to make of providers. DR. KUS: Can I just comment on that? With immunization registries, practices already do that now. So the idea is that if you give an immunization, you've got to report it back to the registry. So it's a matter of how you structure these ongoing things. So it's not like it's not happening.

DR. DOUGHERTY: But not everybody has an immunization registry.

DR. KUS: Correct, but that's ongoing in development. It says that you can do that.

DR. ZUCKERMAN: And not every State's immunization registry can accept data from a practice in EHR. But part of what we're moving towards and part of what I think we have an infrastructure to create, particularly in the area of hearing perhaps, is that capability.

DR. DOUGHERTY: Okay. I think just as a matter of clarification, as I said, I think it's important to lay out those steps and the specific measures and then give the example of the immunization registry, saying this is already happening. So

applying it to newborn screening is not a big deal.

DR. ZUCKERMAN: We didn't say it's not a big deal.

(Laughter.)

DR. DOUGHERTY: It is not something entirely novel that has not been tried before at least, and you have some data on the immunization registry and how successful that is and how many get reported. Right?

DR. ZUCKERMAN: Without the data on newborn screening, CMS can't introduce this into the 2013 regulations.

CHAIRMAN HOWELL: The inclusion of newborn screening in the electronic revolution, shall we say, seems to me to be a very important effort. This document that you have before you, as you can see, was worked on by staff with input from Alan. It has a description of newborn screening which I think this committee obviously knows and then has a few very specific comments to the ONC and CMS in response to their things.

If you would agree to send this, I think everybody has had a chance to look at it. It's a brief document. If you're comfortable with sending it

forward, we will move as a committee to send this forward.

DR. BOYLE: Can I just ask a question?

CHAIRMAN HOWELL: Yes.

DR. BOYLE: I just read the first two pages, not the rest of it, the comments there. But it's not clear to me what was missing from newborns based on these comments, you know, what needs to be done still.

DR. ZUCKERMAN: Well, that's where we get into the second question. We need quality measures that are validated and that are nationally recognized that can be added to the list of data that practices have to provide to collect their incentives. And the other thing we need is the proof of industry readiness. We need to know how many States are able to send their newborn screening reports to EHRs. And remember, we're not going to have a different custom program in each State in each practice. One has to work nationally for the products. We have to have this presence in the community. So those are the two things. We need validated measures that can be required to get your

incentive, and we need to demonstrate that the industry is ready to send data to the hospitals and to the practices.

CHAIRMAN HOWELL: Carol?

DR. GREENE: Do we have the appropriate people in the room to be confident that the States are ready? It's been a long time since I had much conversation with the States about their electronic interoperability, and I know that every newborn screening lab person I've ever spoken to works hard to work with their State folks and would like to have better computer systems.

CHAIRMAN HOWELL: We certainly have some State expertise in the room, if that's your question. Jane, would you like to comment or Ned?

DR. GETCHELL: I think it varies by State certainly. I can tell you for Delaware, we are working toward it. It's interesting. The complicating factor is the number of parties that are involved and the different expertise, and that really does slow it down and complicate it a lot. But 2013 is what we're aiming for. DR. ZUCKERMAN: Well, 2013 begins in October 2012.

DR. GETCHELL: Oh, dear.

DR. ZUCKERMAN: And regulations have to be issued. So the 2011 regulations will be out this June, in June of 2010. That's why I say we're thinking 18 months. My hope is that the seven States that are already participating with HRSA and a number of States like yours that are working with them that will benefit from the early adopters are, I think, going to make it feasible to reach some level. But I think we have an important role in making people aware that we're playing catch-up to get ready.

DR. GETCHELL: The other thing I want to comment on is we were talking about immunization registries, and labs are also working on interoperability with a whole host of other areas, infectious diseases being a very important one right now. So, yes, we are working toward it. I can't tell you that we'll all be there by 2013, though.

CHAIRMAN HOWELL: Carol?

DR. GREENE: So as a follow-up to this, I'm

reading the letter and thinking, oh, yes, this is great. We need to be going in this direction. But now I need to ask another question. If this is tied to incentives, are we going to be setting up something where because a State is not an early adopter and has a legislature that meets only every two years and isn't ready to give the State the money that they need to do what they do, that all of a sudden the pediatricians in that State are not going to be eligible for an incentive because they haven't got any system to participate in? Sorry. I'm ready to say this is great, let's do it, but I figured I better ask.

DR. ZUCKERMAN: Yes. There are a lot of pediatricians very worried about that, very worried about that for immunizations, and they will be for newborn screening when they hear about it. The issue is that Medicaid in each State will set the final set of rules within that State. Medicare is done nationally and they're setting their set. So there's guidance from CMS about not asking something in your State such as connecting to a newborn screening registry, that's not widely available or that would

represent a barrier to providers getting incentives. Part of the substance of the comments is saying that we want to work to see that this doesn't happen and that we don't opt out because we think we can be ready because the capabilities are there.

DR. GREENE: For me that's a full answer and would completely solve the problem for me.

DR. GETCHELL: A question that I had, are there incentives for the State as well as incentives for providers?

DR. ZUCKERMAN: I wish there were explicitly. There are pools of money for health information exchange. So I think there are ways that States can, in fact, get incentives, but they're not tied to the meaningful use objectives. These incentives go to hospitals. They go to practices. There is a program of assistance to the States, but it's very different.

CHAIRMAN HOWELL: Chris?

DR. KUS: I think there's incentive money through Medicaid for State programs to build data systems, and there has always been the discussion about how that applies to people who aren't on Medicaid. At

least in our State, the answer we're getting is that as you develop this, it will have applicability. So to me there is some dollars out there if you work with your Medicaid agency pretty closely as they're putting together their plan.

DR. ZUCKERMAN: As I presented to the Health Information Policy Committee, one of the big differences between Medicare and Medicaid is that once you turn 65, you go on Medicare. You never come off it. But in Medicaid, it's a revolving door and people go in and out. And at the State Alliance for E-health at the National Governors Association, there was widespread recognition that there are certain State programs in HIT that have to be applied to everyone because eligibility and movement in and out of Medicaid and transfer between different State programs is so widespread that people will lose benefits and that many of the benefits of these programs come only when you have a lifelong record and transfer of the data and that taking someone out of a registry because they lose their Medicaid eligibility in a particular month is most unfortunate.

But as far as these funds go, you have to have a certain percentage of patients in the practice. The minimum is 20 percent rather than 30 as it is for Medicare.

CHAIRMAN HOWELL: The question for the committee, do you want to -- we have a commentator from the audience.

DR. HASSELL: Actually a point of clarification. Kathy Hassell from Colorado and Wyoming Hemoglobinopathy Confirmatory Testing and Newborn Screening Follow-Up Program.

CHAIRMAN HOWELL: You're going to have to get an acronym.

(Laughter.)

DR. HASSELL: Yes, I think so. Most importantly I distinguish only because I don't speak for my department of health laboratory, but I'm obviously integrated into the work we do together. The terms, as you've outlined them here, will not be implementable in Colorado and Wyoming based on the testing we do for hemoglobinopathy. So my point of clarification is, as you push this out to the States,

is there opportunity to change the lines that are not apropos?

DR. ZUCKERMAN: Yes, absolutely. That's what I said. I want to emphasize again and again. The comment field is always open on the NLM Web site. Even though the LOINC and ROMA database revisions take place once every six months, we continuously add anything that's missing often within just a week or two. So we are very strongly committed to filling in anything that States need to implement, and we know the only way we're going to learn is when people develop a detailed plan. And using these documents we feel is also going to improve communication between the programs and the vendors and others that are working with them because it provides a framework to accurately document what you need to be able to say on your report.

So whatever is missing, please make a request. We will try to satisfy them as quickly as possible, even if it's only a single State that's involved. And since almost all of the data is optional, people are not required to address every single element in those two documents. CHAIRMAN HOWELL: Are there further questions or comments of Alan? If not, can we have some further comments about this and a recommendation that we send this forward?

DR. van DYCK: So moved.

CHAIRMAN HOWELL: Dr. van Dyck has so moved.

Can we have a second?

DR. VOCKLEY: Second.

CHAIRMAN HOWELL: We have a second.

Any discussion further?

(No response.)

CHAIRMAN HOWELL: Those favoring our sending this forward, please raise your hands.

(A show of hands.)

CHAIRMAN HOWELL: I see every hand, I believe, up.

Any opposition to sending it forward?

DR. DOUGHERTY: It could be edited.

CHAIRMAN HOWELL: It could be edited a little.

And no one abstained from that vote. So we

will proceed with that.

Thank you, Alan. Are there further comments that you have?

DR. ZUCKERMAN: No, just to thank you so much for all of your support and cooperation over the last few years, and we look forward to seeing an impact hopefully in 2013.

CHAIRMAN HOWELL: Well, we'll see you back I'm sure.

Jane?

DR. GETCHELL: Who is this going to be sent to?

DR. LLOYD-PURYEAR: To the Secretary.

DR. GETCHELL: Only the Secretary?

DR. LLOYD-PURYEAR: No, and to the public comment site for the Office of National Coordinator and CMS.

DR. GETCHELL: So it's not going to go to States?

DR. LLOYD-PURYEAR: No.

CHAIRMAN HOWELL: No. It will go just to those three sites: the ONC site, the CMS, and the Secretary. DR. LLOYD-PURYEAR: Jelili assures me we're in consensus with their comments.

CHAIRMAN HOWELL: Thank you, Jelili.

DR. DOUGHERTY: Well, just a question. Will it be posted on the advisory committee Web site?

DR. LLOYD-PURYEAR: Yes.

CHAIRMAN HOWELL: So that States can get it then.

DR. LLOYD-PURYEAR: So I have an announcement. Oh, go ahead. Another question? Oh, okay.

We are passing down the line -- or have you already passed them? So what's being passed around is an update to the briefing book. It has the PowerPoints and the documents that were received after the first one was sent to you.

And if you want to keep your thumb drive, you're welcome to this time. We discovered the proper language. And if you don't want the thumb drive, just leave it at the registration desk outside.

For members of the audience, if you would

like to receive an email of all the presentations,

please sign up at the registration desk.

CHAIRMAN HOWELL: The thumb drive your downloading only contains 2 terabytes of materials.

(Laughter.)

CHAIRMAN HOWELL: But I see everyone is using a contemporary system today.

Yes?

MS. HARRIS: If the committee wants to upload the thumb drive they have, they can go to the registration desk and they'll just add that. We're still working this out. We will have it perfect by the next meeting.

CHAIRMAN HOWELL: For those of you who don't remember, as you know, the first time we got the thumb drive, there was a great discussion about whether or not the committee members could really legally get it because it was a gift of tremendous value.

(Laughter.)

CHAIRMAN HOWELL: I think it's worth about 59 cents at Target.

But anyway, Michele in all of her wisdom solved that. Did you buy them? What happened? (Laughter.)

DR. LLOYD-PURYEAR: No. We resolved it.

They are office supplies.

CHAIRMAN HOWELL: Oh, they're office supplies. Well, that's good.

I realize lunch is upon us, but I would like to spend a few moments on committee business. Then after lunch, we can get back and hear about the nomination of age.

Let me remind you of the calendar for the rest of this year. We'll be meeting on May 13th and 14th where the highlight of the meeting will be Jelili's presentation on the second spot, and the September 16th and the 17th will be our second meeting of the year.

The other note I have is that at the last meeting, we decided that we would have a work group of the advisory committee to focus on developments relating to coding and terminology and electronic transformation. And we had asked Piero and Coleen to chair that group, and they apparently have had

discussions with HRSA and decided that a more focused

work group with specific skills would be needed. And they would like to add Harry Hannon, John Eichwald, Alan Hinman, and obviously Alan Zuckerman and Mike Watson to that group.

Do you all have any comments about that?

Apparently you're going to comment at our May meeting.

Is that right? At least, that's what my notes say.

Okay, we'll have you on the May meeting.

I think the other thing is that if there are suggestions of what this group that will be monitoring data and so forth should do, let us know.

Are there any other suggestions and so forth?

I think the other thing -- after this meeting today, you're going to get an email from Altarum, which is the vendor that's setting up this meeting, asking you to comment about the logistics of the meeting. We obviously will be interested in agenda items for the May meeting. A number have already surfaced during the course of this, as we've discussed frequently. So let us know.

The other very important thing is that there's a notice in the Federal Register that announces

that this committee will be receiving nominations for two members who will be leaving the committee. So please send recommendations to Michele of anybody that you think would be an excellent person to serve on this committee.

As I think you know, we have two pending additions to this committee that were required in the Newborn Screening Saves Lives Act, a medical ethicist and an infectious disease expert, and those recommendations have been vetted and sent downtown some time ago. So hopefully, we will hear from downtown about those before our next meeting so those folks can be seated at our next meeting.

Is there any more committee business that we need to do?

(No response.)

CHAIRMAN HOWELL: Well, why don't we go to lunch and please try to get back because we're going to be hearing the evidence review from Alex Kemper on the work group of hemoglobin H, which was our last thing that we sent forward for evidence review. So let's have lunch and we'll be back promptly at 1 o'clock. (Whereupon, at 12:05 p.m., the meeting was recessed, to reconvene at 1:00 p.m., this same day.)

AFTERNOON SESSION

(1:05 p.m.)

CHAIRMAN HOWELL: The committee will remember at earlier meetings we had agreed that we would send forward for formal evidence review the nomination for hemoglobin H disease. And that evidence review has been completed, and Alex Kemper will now review that for us. Thank you.

Alex?

DR. KEMPER: Thank you very much. I'm pleased to come here and present on behalf of the Evidence Review Workgroup. But as Dr. Howell mentioned, I am going to be talking a little bit this afternoon about the preliminary findings from the hemoglobin H evidence review. Before I move further on this, I want to emphasize that the evidence that we're going to be talking about today is purely from the peer-reviewed published literature, not any data that we've been able to get from experts in the field. But before I move on with that, I just want to update everyone with our other activities. First, in terms of Krabbe disease, our final

report was presented here in 2009, and it was revised and formally submitted in December. There's a manuscript for that work that is now undergoing the clearance process, and we plan to submit that to Genetics in Medicine.

The other thing is that we now have a overview paper describing the Evidence Review Group's process that's in press in Genetics in Medicine as well, as well as brief summaries from the three final reports that we've done thus far.

Again, I'd like to acknowledge and thank my fellow work group team members. I think Dr. Perrin has done just a really fabulous job of gathering together a bunch of very smart people who are also a lot of fun to work with. So it's a great honor to be a member of the work group team.

So now let me start with the hemoglobin H disease findings.

So as you all quite aware and especially after Dr. Ohene-Frempong's excellent overview at the last meeting, hemoglobin H disease is an inherited hemoglobinopathy. It's a type of alpha-thalassemia. It's caused by either deletions or nondeletional mutations of three of the four alpha-globin genes, and I'm going to show some pictures to illustrate that in a little bit.

It has a variable clinical course with symptoms including anemia, hepatosplenomegaly, cholelithiasis, growth retardation, and other problems as well.

And one of the things that I want to make sure that I say at the outset is that there are certain mutations, such as the constant spring mutation, that are associated with worse health outcomes than the simple deletional form of hemoglobin H disease.

This again is just to summarize what goes on with the development of hemoglobin H disease. So you begin fetal life with two alpha and two globin genes, and normally shortly after birth, you make the transition to the adult form of hemoglobin which consists of two alpha chains and two beta chains, and that's the normal circumstance.

With hemoglobin Bart's there's a deficiency

in the amount or the functioning of the alpha-globin

subunit, and so children with hemoglobin H disease present in early infancy with hemoglobin Bart's which is a tetramer of gamma chains simply because there aren't enough alpha around. Then shortly after early infancy, it switches over to a tetramer of beta chains. Hemoglobin H is the disease that's associated with a tetramer of beta chains, and hemoglobin Bart's is the tetramer of gamma.

So this is a further illustration. If you are normal, you have four functioning alpha-globin genes and your genotype is alpha-alpha/alpha-alpha. If you're a silent carrier, you might have, for example, one deletion. So you'd have a deletion in alpha and then two other alphas on the other gene. Alpha-thalassemia trait is associated with two deletions which can either be cis or trans. Both deletions could be on one gene or on the other. Hemoglobin H, if it's deletional, is associated with having three deletions. So you have one functioning alpha across the two genes. And then with nondeletional, typically what you have is two deletions and then one mutation.

There are many different mutations that have been described leading to hemoglobin H disease, but the one that we think of most commonly, because it's often considered to be both the most common of the mutations and one of the more severe mutations, is the constant spring mutation. So in the example here, hemoglobin H disease with constant spring, there would be two deletions and one constant spring mutation.

And finally, hemoglobin Bart's hydrops fetalis occurs when there's no functioning alpha gene whatsoever. So, for example, four deletions.

So how did we get into the position of being able to review this disease? Well, first, individuals with hemoglobin H disease may experience significant anemia and growth retardation. So we know that hemoglobin H disease is associated with significant adverse health outcomes.

Presymptomatic identification of infants with hemoglobin H disease may improve health outcomes.

And third, newborn screening is possible using dried blood spots. California has been doing this since 1999. Other States have also been screening

for hemoglobin H disease, and I'm going to discuss that in a little bit.

The second and I think one of the most critical things to recognize too is that newborn screening occurs in a critical window for hemoglobin Bart's detection, that is, before you switch over to the adult form of hemoglobin, in which case you would be looking for tetramers of beta chains instead of the gamma chains.

Finally, current-state hemoglobinopathy screening technologies can be used to detect hemoglobin H disease, and as I mentioned before, there are a number of States that are actually doing this, in addition to California.

So in terms of our methods for evidence review -- I hope that this is now getting familiar to you all -- first, we conducted a systematic literature review to summarize the available evidence from the peer-reviewed published literature. Then our plan is to use this as a springboard to talk with experts in hemoglobin H disease, including investigators, advocates, and clinicians, to just find out what the

sources are from published data.

DR. VICHINSKY: This is Dr. Vichinsky. I don't know if it's appropriate for me to make comments and when you would like me to. I was the one who proposed the hemoglobin H screening. Would it be better for me to wait until you finish?

CHAIRMAN HOWELL: I would think it probably would, if you'd be willing to sit tight for just a bit.

DR. VICHINSKY: No, no. I just want to have some direction.

CHAIRMAN HOWELL: I think once Alex finishes his presentation, if you could comment, that would be particularly helpful.

DR. VICHINSKY: All right.

CHAIRMAN HOWELL: Thank you.

DR. KEMPER: Okay, thank you.

So the topics I'm going to discuss today include incidence, natural history, what we know about testing, treatment, economic evaluation, and critical evidence needed. One of the things that I hope to get from this group is guidance about specifically the critical evidence needed. As you may have noticed from

looking at the book and the conversations I've had with you, there's a lot of knowledge that's not been published, and as we approach the experts, I want to make sure that we gather the information that's most helpful to your decision-making process.

In terms of the materials included in the preliminary review, in your book we have a detailed literature review methods description, a summary of the evidence from the literature review, tables highlighting key data from the abstracted articles, a separate table of studies that were excluded because they were based on four or fewer cases, and a comprehensive bibliography.

Our systematic literature review encompassed the time period from January 1989 through October of 2009. We looked again at the sources we normally look at, including Medline, OVID in-process to find articles that might not have been indexed yet in Medline, and other non-indexed citations. We looked at English language studies only and restricted them to human studies. We reviewed the references on the nomination form and the bibliography of the papers that

were selected for review as well.

We initially identified 1,362 abstracts for preliminary review. Based on a first-pass review of the abstracts, 88 were selected for an in-depth review, and 19 of these articles met the inclusion criteria for data abstraction.

This is a summary of the papers that met our review criteria. Based on our initial search, only 19 studies actually met the criteria, and nearly all of them were case series. There were 12 of those, and we also identified six cross-sectional studies.

Now, moving forward, we used the quality methods that we described previously, looking at individual study designs, and we can talk more about that later if you want to. But let me move to what we actually learned.

So if you look at issues related to natural history, there were 18 studies that addressed that in particular, and three studies that addressed the incidence, and 12 studies that were genotype-phenotype correlation, and three that were just kind of other natural history disease papers.

CHAIRMAN HOWELL: Alex, do we know whether or not Dr. Vichinsky can see your slides? Elliott, can you see these slides?

DR. VICHINSKY: Yes, thank you.

CHAIRMAN HOWELL: Okay, thank you very much. Great. I just want to be sure.

DR. KEMPER: And just to make sure that we're on the same slide, I'm looking at the one that says "Natural History: Incidence," and I'll let you know as I move forward.

So in terms of the incidence, there are two things I want to highlight. Both of these were from the California screening experience. The overall birth incidence of hemoglobin H disease as reported between 1998 and 2000 was 1 in 15,000, and then in a subsequent report covering the period of 1998 through June of 2006, the incidence of hemoglobin H disease was 9 out of 100,000 which is fairly close to the 1 in 15,000 number, and there was a separate incidence of .6 per 100,000 for hemoglobin H disease with the constant spring mutation.

This slide summarizes the balance between

deletional and nondeletional hemoglobin H disease. The first thing that I want to point out is that only the California study is a population-based study. The other studies up here were based on findings from referral clinics. And I think that explains why there's variation in the proportion caused by nondeletional hemoglobin H disease, and of course, there's variation across different populations as well. Again, in California the ratio was 78 percent deletional and about 23 percent nondeletional among the cases that they found, but in some populations, it's been reported to be much higher, for example, in northern Thailand where more than half of the hemoglobin H disease was nondeletional. Moving to the next slide, in terms of the natural history, we talked before about how newborns can develop anemia, also significant jaundice, and hepatosplenomegaly, especially with the constant spring mutation. And there are reports of babies who were born with hemoglobin hydrops fetalis, including from the California screening experience, and typically when we think about hydrops fetalis, we don't normally think

of those babies as surviving. So I think that, at least to me, was surprising.

In infancy and childhood, individuals with hemoglobin H disease can develop significant pallor, growth retardation, again anemia. We saw described pulmonary function defects, mild cardiac anomalies, and again hepatosplenomegaly. And then there were numerous reports in adults of significant iron overload and cholelithiasis.

Again, I really want to emphasize the differences between deletional and nondeletional hemoglobin H disease because I think that plays into how you think about this condition. It's clear that children with nondeletional hemoglobin H disease are diagnosed at younger ages because of the worst course that they have. They have higher rates of anemia and require blood transfusions earlier and more often, and there are also higher rates of hepatosplenomegaly.

Next I'd like to talk about screening. There were three articles overall that we include here in screening. Let me describe a little bit about the screening process, and again, Dr. Ohene-Frempong at the

last advisory committee meeting described this quite eloquently. So hopefully I'm doing a good job of echoing what he said.

The first-tier process is detecting elevated levels of hemoglobin Bart's, and then the second tier is diagnostic testing to confirm why the child has hemoglobin Bart's.

Because California has published so extensively on their screening program, I'm going to spend some time talking about that.

There was a trial period between 1996 and 1999 where they began measuring hemoglobin Bart's level by HPLC. Initially they started with a cutoff of 14 percent, but they realized that the lowest amount of hemoglobin Bart's in a newborn confirmed to have hemoglobin H disease was 27 percent. And so their cutoff level was increased to 25 percent in August of 1998, and that was to minimize the number of referrals that were being made. And then in California, hemoglobin H disease newborn screening was mandated in October of 1999, again using the cutoff that they established. These are data from the 2001 publication that covered the period from 1998 to 2000. There were about 1,300,000 children screened. It's always surprising to me when I look at California numbers because they're so much bigger than everywhere else. Certainly more than Delaware I would assume.

During this period, they identified 101 newborns with elevated hemoglobin Bart's level. 89 of these were found to have hemoglobin H disease. Nine were found to have alpha-thalassemia trait. One was a carrier and -- this is where I was leading before -- one child with hemoglobin Bart's hydrops fetalis and one normal.

I have this as sort of a caveat on the bottom of the slide because most newborns with hemoglobin Bart's level below the cutoff value didn't have confirmatory testing. An undetected case of hemoglobin H disease in that range couldn't be ruled out. But again, that's no different than any other screening test that we typically think about.

Let's talk now about diagnosis. Certainly

there are multiple strategies for alpha-globin

genotyping that have been described. The California newborn screening program uses a multiplexed gap-PCR assay -- and I hope nobody asks me the details about how that works -- to detect common deletional and nondeletional alpha-thalassemia mutations in newborns with elevated hemoglobin Bart's.

In terms of the effectiveness of treatment, this is where we had some problems. There were no studies that looked at the effectiveness of early treatment of hemoglobin Bart's that we could identify in the peer-reviewed published literature. And I want to emphasize that that doesn't mean that knowledge about the benefit of early intervention isn't out there, and I think that that's one of our unique challenges coming up.

Dr. Vichinsky, I'll announce this slide.

This is follow-up and treatment. So again, we found no peer-reviewed publications regarding presymptomatic treatment, and there are no data published on follow-up of children identified in California. But from talking to the folk in California, it sounds like there is a wealth of data out there that we have to now go and

systematically gather.

Again, you're not going to be surprised in terms of the economic evidence, that there's no peer-reviewed publications relating to costs or the cost effectiveness of screening and treatment, and we have insufficient data available now to discuss any sort of economic analysis.

So to summarize, our key findings were that compared to children with deletional hemoglobin H disease, those with nondeletional hemoglobin H disease more often had jaundice, hepatosplenomegaly, growth retardation, and required blood transfusions.

Most published natural history evidence is from studies on clinically identified populations in older children and adults, so referral clinics and that sort of thing.

The California data suggests that HPLC for elevated hemoglobin Bart's is feasible and that there are validated methods for the diagnosis of hemoglobin H disease by confirmatory genotyping.

So again, this is where I'd particularly like your help. There are two key questions that we have to

go back and evaluate, and that is the natural history during the newborn period in the first 5 years of life to get a better understanding of what the opportunities are for early intervention, and then the second related thing is what are the benefits of early diagnosis. So that will include us looking at what treatment methods are available and also looking at the effectiveness of treatment.

Now, one thing that I don't have on the slide that I would also like to bring up is that I've had conversations with many of you here about what States are currently doing because many States screen with a process that would identify hemoglobin Bart's. For example, I spoke to Sylvia Au -- and I'm looking for her, but I don't see her right now -- who said that Hawaii has been screening for hemoglobin Bart's but just hasn't reported those data. I'm not sure what States currently do, and I think that that needs to be systematically evaluated. And I learned yesterday that the CDC is now actually planning to collect those data. So I think that will be very helpful as well. So again before I end, I have a long list of

experts that we plan to speak to, and I'll just leave the names up there. But I think that that list is going to have to also expand to include individuals from those State public health laboratories that are now actively screening for hemoglobin H disease to learn more about what their experience has been. So thank you very much.

CHAIRMAN HOWELL: Thank you very much.

I wonder, Dr. Vichinsky, would you like to make some comments about Alex's brief overview of where they are?

DR. VICHINSKY: Yes. First of all, it was very clear and the data she presented was largely accurate in my opinion and I appreciate it. The few things I'd say is that because the way the literature searches were done, I think key and important information that's published in mainstream journals wasn't included that were significant, and I'll give you some examples. I published in Pediatrics. And I think it has to do with their search titles where they put "H" into the title. But we published 1,000 genotype-

phenotype correlations in the PCRN, and I published as a first author in 2005. Of that data, we published 119 hemoglobin H patients with their genotype-phenotypes and clinical picture.

In addition, because of the search time line, we published this fall, actually November 1st, in the American Journal of Hematology the details of the clinical pictures of 50 hemoglobin H constant springs.

I also published in 1996. The title of the paper was The Clinical Cause of Hemoglobin H Constant Spring, in which 50-60 percent of the kids were transfusion-dependent and had splenectomy versus H.

I think it has to do with the search engine didn't include things that were more generic in terms of entry. You know, like our paper said the epidemiology of thalassemia in North America. So I think there are articles that would -- you know, they won't change, I think, her analysis, but they will add some other data. For instance, in the data that I'm mentioning and others, when you try to determine outcomes, the mean ferritins in the children with the H's was 400 by 12 years old. And in the data that I published -- here's another example of it. I wrote a paper -- this was in Pediatric Blood and Cancer -- where I said serum ferritin underestimates liver iron concentration in transfusion-independent thalassemia patients. A significant percentage of those patients studied were alpha-thals. And what I found was the serum ferritin was falsely low compared to the liver iron in that group.

Then in the recent paper that Kidd and Hoppe and our group published, we actually updated the epidemiology of the newborn screening program in terms of more detailed analysis with genotypes, as well as being the national pilot reference lab for the region. We updated in that the consults referred and how many of those individuals -- I think 1,400 consults -- were H mutations. That was published in the International Journal of Lab Hematology. I think it came in December.

So I think the search engine could be more sophisticated, but I don't think it's going to change a

lot right now in what you said. It will just give some

other evidence-based points that show that the H's have iron overload when they're young and that splenectomy was done in infants and that they had thrombosis as complications.

In the paper we reported recently on the 50 H constant springs with T.D. Singer as the first author, we had sepsis in 7 percent of the children and we had thrombosis in like 5 percent.

I'll send you all those data. Actually I think Dr. Hoppe may have sent most of them in her letter response.

DR. KEMPER: Yes. So I should say, first of all, from a purely evidence review perspective, I really appreciate all the work that you've done in this area. You've been very helpful in laying out the issues.

The papers that you discuss we actually did identify in our literature review. So we have those.

DR. VICHINSKY: But they weren't listed in your bibliography that I got.

DR. KEMPER: Yes. Well, to the bibliography -- you know, it summarizes those articles that were

subsequently then used in the literature review. The challenge is -- you know, our mission is looking into evidence for the benefit of early intervention.

Although most of those studies that you described are very helpful in terms of describing the natural history and the epidemiology, the particular issue of learning more about what happens early on and the benefits of --

DR. VICHINSKY: Well, I would think you'd like to know what the ferritins were in 10-year-olds.

DR. KEMPER: I'll leave that to the advisory committee.

DR. VICHINSKY: I think that would be useful data.

Anyway, I appreciate your work. It's similar and I don't think it changes your analysis. So it just would expand on outcome points, but it's not going to change things. I do think they're worth looking at.

I will send you some other data too. Ash

Lawell who is here has been tracking over many years the database from birth on in the H constant spring patients. He just pulled it out, and we're going to send it to you. It will hopefully be accepted. But it

basically demonstrates the natural history of H's over the 25 years and shows basically the H constant springs -- all of them land up being transfused by adulthood or 23 years of age.

CHAIRMAN HOWELL: Obviously, Dr. Vichinsky will be an important expert.

DR. VICHINSKY: I'll send you that data, but I have nothing else other than praise to say for your presentation.

CHAIRMAN HOWELL: And you will certainly be on the interview list that's coming out. So that will be an opportunity to see and review the materials that he has had here and so forth.

Kof, do you have comments about this?

DR. OHENE-FREMPONG: Is Elliott still there?

CHAIRMAN HOWELL: Yes.

DR. OHENE-FREMPONG: Elliott.

DR. VICHINSKY: How are you?

DR. OHENE-FREMPONG: Fine.

Can you remember how many, maybe percentage-wise, of the H babies started chronic transfusion therapy or even episodic transfusion therapy in the

first year of life?

DR. VICHINSKY: I have from the studies, but we've been looking at -- in our own natural history study, not the stuff published, but in our natural history database that Ash has just pulled on the computer data -- we're hoping to get accepted. And it's broken out by year of birth on, and in the H constant spring group, it looks about 20 percent of the patients land up on transfusions in the first two years and it continues to increase. By five years, it's 45 percent, and by 20 years, it's 100 percent. So it's 20 percent, two years. Anyway, that's the data we have. So these are on 23 constant springs followed up on. And the problem in that data is that when we talk about 100 percent of the patients being transfused by adulthood, that's not on a that major transfusion program. Those are patients who required intermittent transfusion or chronic transfusion. I actually have that broken out. So it's about 20 percent in the first two years. Ash is producing for me for you the data that you wanted. Many of the transfusions were precipitated

by an associated viral illness. Only about 22 percent of them are sort of like that major transfusion patients. The rest are intermittently transfused.

Okay?

DR. OHENE-FREMPONG: Okay, thanks.

CHAIRMAN HOWELL: Are there further comments?

Ned?

DR. CALONGE: So I think two big areas of concern. One is I still don't feel I have a great idea of the natural history of screening-detected disease. I appreciate California's experience. I'm trying to wrap my arms around the natural history in the cohort of children that have come to the attention of a center and therefore followed over time for 25 years, which is helpful. But is that an accurate representation of the 89 kids that were detected in the California project? So that's one gap that's hard for me.

It's interesting because it reminds me a lot of hemochromatosis screening in that all we know is the extreme phenotypic expression of the condition, and trying to track that back to the number of people with high ferritins at a certain age is actually remarkably

difficult and confusing.

DR. VICHINSKY: I think these points you make are right, but I want to just add into this the public health issue. The diseases are occurring in immigrant populations that are growing dramatically, a 2000 percent increase in population over time in our screening programs. And the census data underscored that projections are increasing dramatically and will continue to change the epidemiology of the country. Now, the problem with this population is the only easy time to diagnose them is in the neonatal period, and then they leave the neonatal period. The only way to diagnose them is in the neonatal period, and then once they leave that period, it's very difficult to diagnose them because of the loss of the simple diagnostic infrastructure, as well as the fact that the tetramers are so unstable, they're not picked up. In fact, yesterday I saw a woman who's actually Italian who developed cardiomyopathy from iron overload treatment because she was an H that was missed, and the labs were sent out to Quest and they were just giving her iron.

The easy time to capture them is in the neonatal period and then track them, and it's very difficult after that. They're a multi-ethnic group that is very hard to help once they're out of the newborn period.

In fact, in the State screening consults that were sent to us a reference lab for the country during our contract period, the main cases that were sent to us -- almost all of them were for other newborn screening programs, not other community programs. Most importantly, another reason why I think the data I published already is important is that 75 percent of the constant springs we reported in our papers had an E-beta mutation with them, which really modifies the disease significantly. We started doing alpha-beta mutations. So I think the diseases are complicated and the natural history may be more than one thinks from other parts.

So anyway, I think it's a good time to at least begin to think about where the country is going in epidemiology and immigration and when you can diagnose them. There's no question from the data from

China and other places that when they're older, they're going to have iron overload. I guess the question you want to know is can intervention make a difference when they're very young.

I just want to underscore that splenectomy is very effective in changing transfusion needs, and I have that data. The problem is it carries with it a substantial thrombotic rate in these patients, which I'm not sure of the exact etiology.

So anyway, I'm going to shut up.

(Laughter.)

DR. CALONGE: Rod, can I continue?

CHAIRMAN HOWELL: Please.

DR. CALONGE: So I think you've actually gotten to the other issue, the issue of the effectiveness of treatment over time in preventing the complications and which complications exactly are we trying to prevent.

There are two issues, one that you're close to answering, which is early detection in the neonatal period does give an opportunity for a treatment difference than waiting till some other time to

diagnose the problem. So that's a useful piece of information.

The fact that the intervention is splenectomy or could be splenectomy or one of the interventions could be splenectomy I think is remarkable to think about. Again, of the kids who are screening-detected, what percentage of those would be expected to have all of the problems that are associated with the cohorts that have gone to referral centers? And I think that's a gap in evidence that's going to be a little interesting to try to figure out a way around because the intervention is pretty dramatic and carries with it more than just thrombosis as a risk factor, but multiple other risk factors associated with a major surgery.

So, Alex, I think those were the questions you were asking and looking at the interplay behind the natural history not of center-treated disease but screening-detected disease is essential. We've heard some hints that early detection provides a window of identification which could be important, and then the issue is that what are the benefits of the treatment

and what are all the treatment options available and are we providing substantial net health benefit.

CHAIRMAN HOWELL: Dr. Watson?

DR. WATSON: This one sort of reminds me of yesterday when we were talking about the uniform panel and the different kinds of secondary targets where the vast majority of ours were part of a differential of an analyte.

When we did the uniform panel, there's a real disparity in that we looked at the hemoglobinopathies. We said the S allele was the core, and we look at variations around other things with an S. And we got a few of the Bart's that way.

But for this one, it fits the clinically significant result that you can see on HPLC, and even though we're thinking about it as a primary core target, there's a lot of patients already being informed or pediatricians being informed of this result straight out of the newborn screening lab because if they use HPLC, they see the 20 or 25 or 30 clinically significant variants out of the 600 or 700 globin variants that can be found. So even if you don't think

it's a core, we've still got a lot of interesting issues to think about because it's being reported out of newborn screening programs already but not in a really well coordinated way.

DR. KEMPER: So if I can just echo that with a personal experience. I live in North Carolina and I've seen on newborn screening reports the presence of hemoglobin Bart's when you look it up in the computer, but there's no guidance about the next step, about what you should do with it, and it's not quantified in terms of the amount of hemoglobin Bart's.

DR. WATSON: Well, ACT sheets are done and will be on the Web site in the next few weeks for about nine of the non-S allele-related hemoglobinopathies. Since they are being reported out, we thought we needed to do that.

The second part that's hard is I think for a while Oakland Children's was funded by HRSA as a center for mutation detection, but it seemed to me that people just aren't bothering to get it done or they're not being told that they have a result that needs to be sorted out, so that they're not even functioning as a

center for mutation testing for hemoglobinopathies anymore. And it sounds like a lot of these just aren't being done.

CHAIRMAN HOWELL: Elliott, would you care to comment about Dr. Watson's --

DR. VICHINSKY: Yes. In terms of the laboratory issues, I think it's very important because you got to standardize those, what's being reported and whether they're meaningful or not.

I'd like Dr. Hoppe to just say a few words, if I could, around that specific point, who runs our DNA newborn screening hemoglobin lab with Dr. Kidd.

DR. HOPPE: I think the one point I'd like to add is -- we had piloted with the National Newborn Screening and Genetic Resource Center a study to look at unusual or ambiguous variants coming from newborn screening programs that couldn't further identify them. So we were getting a lot of hemoglobin H patients or cases, babies from the west coast primarily, and we're continuing that.

So in our recent publicatio, we showed that we had 1,200 or so referred samples from other States

that were either trait or hemoglobin H precisely because of this reason that, A, they don't know what to do with an elevated Bart's on their HPLC on their primary screen, and they don't know what threshold to use, which again is going to be lab-specific.

So I just wanted to point that out. Hawaii wanted us to start doing their whole family testings, and we were doing all of this for free. So we said, look, we'll just do the newborns, but we're not doing your entire extended family. So they've built a program around that. Now they're doing it independently. But I think the need is there. Certainly to add to Mike's comment that there's information out there that isn't being disseminated fully or comprehensively and people need to be educated.

DR. VICHINSKY: And because Bart's is being reported, there hasn't been a standardization really of what the thresholds in each of those programs, I think, are that make a uniform diagnosis of hemoglobin H versus not and which should be further worked up. So the fact that that is being sent out without a clarity

on it is an issue for some program and particularly for pediatricians.

CHAIRMAN HOWELL: Have you heard enough comments to assist with your further and final deliberations?

DR. KEMPER: It's been very helpful except for Dr. Calonge has got his hand raised.

DR. CALONGE: I had forgotten while I was talking. I would hope, Alex, that you don't see peer-reviewed publication of whatever treatment data somebody can put together as an essential element. I mean, I think trying to look at what reports on treatment effectiveness can be put together in time for your consideration, you will end up being the peer review of the quality of the data itself, and we need to be comfortable with that. If there's some discomfort, Jim, in the practice center, I think recognizing that you can actually get other people to look at the same report and give you an idea of the quality so that you're not both the judge and the incorporator I think could be useful. But I think you're going to have to get that treatment information

and whatever we can get together because that's a gap I don't think we can get around if we don't have some measure of treatment of effectiveness.

DR. KEMPER: I totally agree.

DR. VICHINSKY: I'd just like to make one comment. I was relatively involved in a central way with the development of newborn screening for sickle cell disease, and I know that there were a lot of programs that were against it because, really, the thing that made a difference in sickle cell disease was really education and training of the families about fever and infection and complications, how to feel the spleen, when to come in for fever, things like that. But the screening programs really launched onto the study, which I was an author with people on both the penicillin studies. And that was really used as a tool to initiate newborn screening.

But in fact, that is not the main benefit -- or it's part of the benefit of newborn screening for sickle cell. Actually, if you look at the published data, actually a large percentage of children don't even get the penicillin or it's a problem.

So the major benefit -- where I have a difference with newborn screening programs that really deal very straightforward with PKU or hypothyroid is that the benefit to hemoglobinopathies is a complex multi-organ problem, and it really requires counseling and education and family training. Having a magic treatment bullet, you know, is what you're asking about, and it's really intervention and education and counseling and things like that that will change prognosis and outcome.

CHAIRMAN HOWELL: That will be helpful.

Jim, Dr. Perrin, did you have a comment?

Could you come to the microphone please? Dr. Perrin is here listening to this elegant evidence review that he's been overseeing.

DR. PERRIN: In response to Ned's very helpful comment, we obviously can do the quality of the evidence review. We tend to bring in content experts in every case to help us really review the clinical literature and make sure we're not missing something in that context.

CHAIRMAN HOWELL: Ned, you wanted to respond

to Jim.

DR. CALONGE: Yes, sorry. I would just add one other methodologic issue on the previous comment which is we did say in the methods that there might be times where we had to look to a like condition because we had inadequate evidence for the condition in front of us. So to the degree that you believe hemoglobin H disease looks like sickle and we would expect similar benefits from family counseling around issues as we found with that, I think that's evidence you could also bring in to the committee to help us make a decision.

CHAIRMAN HOWELL: Thank you very much.

And Jane had a comment.

DR. GETCHELL: Yes. On the method that's used, I think many programs are still using IEF and probably not quantitating it. So those programs would be unable to report percentage of Bart's. It would be an interesting piece of information to have.

DR. KEMPER: Those are data that are being gathered.

CHAIRMAN HOWELL: So you'll have that information. Are there further comments that would help guide Dr. Perrin and Dr. Kemper in concluding this nomination, which we anticipate will be --

VOICE: I just want to also say I think an important aspect is also to get that population base data about outcomes. I'm not sure if people in the room are familiar. We're starting the hemoglobinopathy surveillance system within the next few weeks, and we should be in a position to at least get some of the population-based data on rates of splenectomy and things like that that might actually inform the decision about the outcomes related to people with hemoglobin H because we are going to target all of the hemoglobinopathies, including hemoglobin H.

DR. KEMPER: You're number two after Dr. Vichinsky.

DR. CALONGE: One more issue, if I could. It gets to the population question, and that's the issue that I don't know quite what to do with. But what I heard was that the changing demographics due to immigration were actually increasing the amount of this

condition which to me sounds like an identifiable risk

factor. And I don't know that anyone has looked at screening at any age, including newborn based on risk factors. I understand that's a different issue, but again if a clearly identifiable population has 90 percent of the disease, I would wonder if that's something that you could look for evidence in as well.

And I just made those numbers up. I don't know.

CHAIRMAN HOWELL: Kof, you had a comment?

DR. OHENE-FREMPONG: Yes, two comments.

I think one of the concepts that maybe the committee may have problems with is a clear presymptomatic treatment plan for the patients. I think people are not sure what the symptom is and what the treatment for it is. We've hinted about transfusion and splenectomy as if maybe these are things you do in order to prevent some symptom of this disease from showing up, and it's not clear what those are.

And the second point is minor. IEF, isoelectric focusing, per se is not a method that cannot be used to quantitate. If you scan the IE band, if you get an isoscan, you can determine the percentage

of the bands that you get. So I don't want us to recommend that people, if they want to know the percentage of Bart's, that they should use HPLC. They could just add a little equipment to what they have now and still be able to determine percentage.

CHAIRMAN HOWELL: Mike?

DR. WATSON: Yes, only to say that it might be worth stepping back and looking at the hemoglobinopathies because they are very disparate from the way we approach tandem mass spec. If you agree that H disease is clinically significant, then even if you don't know everything about it, you'd say it's probably a secondary target that should be reported out. And it's really inconsistent in how we approach it in two different groups of diseases.

So it's probably worth looking at it from that sense because that actually may drive you to getting the data you need if you can do those things in a controlled environment like we talked about yesterday for one condition where we approved it, but we recognize that we need to get follow-up information and other things in an organized way. CHAIRMAN HOWELL: The difference in that is that the condition we approved yesterday would require the institution of a new technology rather than to use a current technology and say report it out.

DR. WATSON: Well, it was a core condition, and nobody is going to nominate themselves to be a secondary target, I don't think.

CHAIRMAN HOWELL: It would be hard if you don't have a test on the panel.

Carol?

DR. GREENE: And in that spirit, I wonder if it would be reasonable maybe even to make a motion that instead of at the moment going forward with continuing this evaluation for addition as a core condition and with the suggestion that there could be some unpublished data that we could find, but then we get into all the morass of is it peer-reviewed enough -- would it be appropriate to say this should be named as a secondary target? It should be reported, and that will lead us to getting all the information that we need.

CHAIRMAN HOWELL: I don't know whether it's a

formal nomination, but I would think that the process is quite far along and we would need to reach that conclusion once we see the final data. I think it would be unusual to stop in midstream here.

DR. GREENE: Well, maybe rephrase it. I probably said it very badly, but not to say stop the process, but is there enough to say it is a secondary target?

CHAIRMAN HOWELL: I don't think we know that until we see the data.

DR. WATSON: California is reporting the data and we've done ACT sheets on at least eight non-S allele-related hemoglobinopathies that are being reported out as well.

DR. GREENE: Forgive me because I have not been a part of the process formally before, but for the secondary targets, did we do formal evidence review before they got named to be secondary targets? So do we have to have a formal evidence review before we say something is a secondary target?

CHAIRMAN HOWELL: They had the same degree of evidence review as the primary targets. They ended up

on the secondary.

I think that your point is well made, and I would not deny that could be a recommendation. But I think that we now have the questions that have been answered I think for Alex and Jim to proceed and to get the evidence done.

Will you be back for the May meeting?

DR. KEMPER: Yes, I will.

CHAIRMAN HOWELL: With all the data finalized?

DR. KEMPER: All the data that's fit to present.

(Laughter.)

CHAIRMAN HOWELL: And you will have interviewed all the key persons on that list?

DR. KEMPER: Yes, sir.

CHAIRMAN HOWELL: Okay, good. We will try to find time after the APHO report to include your report.

I was just joking.

Carol?

DR. PERRIN: As well as other nominations you may have for people. We would like any other

suggestions you have for people for us to interview.

DR. VICHINSKY: I left out one important area, and it will take a second. Hemoglobin H is an unstable oxidative sensitive hemoglobin disease. And so when they get viral infections is when they die. What happens with H is they're well and then they catch a flu and they drop 8 grams. It's those sudden, unexplained events that are morbid-driven and that education of the family during could make a big difference for those -- and their doctors. So it's somewhat similar to the big drop you see in Gestic's BD. You know, they get the same list of medicines to avoid. So these sudden life-threatening events education would play a big role in.

CHAIRMAN HOWELL: Well, it seems to me that you obviously have access to a lot of material in California in particular that this evidence review group will want to go through and assess and work with you. I'm sure that Alex and colleagues will soon be on your doorstep.

Are there any other comments before we go ahead? Carol has a comment. Kof also has a comment. DR. GREENE: Just that it was pointed out it already is a secondary target.

CHAIRMAN HOWELL: It's already on the panel, yes.
Kof?

DR. OHENE-FREMPONG: A question about babies with fetal hemoglobin F only. Is that on the secondary target? I'm just asking because somebody may come back and look for the same information.

CHAIRMAN HOWELL: Mike, can you answer?

DR. VICHINSKY: You know, I got to underscore. Actually, when I spoke about your committee, there was actually some discussion where they thought I was going to propose a standardization for beta thal because, frankly, as Kof brings up, there really isn't a laboratory-based, clear diagnosis for beta thal diseases in newborn screening programs. And as you look at the COIN data, a lot of the F stuff is not right and not standardized so that many of them are not thal majors. So I never even addressed that, but it is related. We really have a bigger issue even with

the beta thals. F and E, yes. F and E like in California has become -- you know, there are a thousand cases of EE and FE reporting. I just want you to know these changing immigration issues is not just the age alone. I singled that out, but it's happening in many programs in the country, including inner-places like Minnesota as immigration has.

So I don't think you can do it at this committee meeting, but I would agree with Kof. We need to look in the newborn screening panel of what we do with that other data. That's all.

CHAIRMAN HOWELL: Thank you very much, Dr. Vichinsky, and thank you very much, Alex. I think we've heard enough about this.

(Laughter.)

CHAIRMAN HOWELL: So we will now move on so that we can finish this meeting in an expeditious fashion.

We have two persons who would like to provide public comments, and the first person on my list is Andrea Williams. If you would please go to the microphone, Andrea. MS. WILLIAMS: I'm going to try to read a little slower than I did the last time.

CHAIRMAN HOWELL: Well, don't read too slow. We may leave.

(Laughter.)

MS. WILLIAMS: Okay.

To the chairman and advisory committee, my comments today regard sickle cell trait carrier testing. As a research assistant to Dr. Luchsman and Christian Murdy, I've been involved with the follow-up of families with children identified as sickle cell trait carriers by the newborn screening program since 2005. The program has been successful in providing genetic counseling using a certified genetic counselor via phone to more than 97 percent of those families who are able to be contacted. A smaller number of them come in for confirmatory testing and further counseling.

In 2009, there were approximately 700 children born with sickle cell trait in western Pennsylvania. The 17- and 18-year-olds who are leaving

high school, depending on their birth day and its

relationship to the September 1992 start of newborn screening in Allegheny County, may not have been screened via the newborn screening program.

As you guys know, I wear many different hats.

So as the executive director of a community-based organization, I have been afforded the opportunity to collaborate with sickle cell providers in western Pennsylvania and have established a community outreach program that focuses on awareness, education, screening in many different venues, schools, universities, health cares, and community events and religious organizations and churches. One such was on the University of Pittsburgh campus. We had a small lunchtime health fair where 42 students came by the table and 27 of them continue to be tested and followed up with genetic counseling.

So the need is there and the response is clear. Your continued education to resources around sickle cell trait awareness, genetic counseling, and education and proper screening and coordinated follow-up is beneficial to everyone. A starting point may be to use the newborn screening program and those

identified through this program as having sickle cell trait carrier status and then moving into education and screening for everyone.

Keeping in mind that there's a growing population that is entering their child-bearing years that is likely ignorant of their sickle cell trait carrier status, to neglect to properly design and fund education, screening, and follow-up for everyone is to neglect the next generation of parents who will have children with sickle cell disease though will undoubtedly feel the shock that accompanies a diagnosis when one or both parents lack the knowledge of their trait status. They will feel the pain that I felt when my son was diagnosed at birth, having had two children previously identified as having sickle cell trait and then learning later, after the fact, that my husband is a sickle cell trait carrier.

I feel constrained to give a voice to all of those who aren't aware of their trait status and their possible risk for having a child with sickle cell disease. My comment is to recommend that a funded program of awareness, education, and screening that is

carefully designed for the successful implementation. This that I propose is a huge project considering the history of what has been attempted in the past. The time is now and here's the reason. We know have the technology to systemically bring about awareness and education of screening, knowledge, and proper screening methods, and the protections provided by GINA. This system will become the model for other genetic diseases as we move forward, and I am confident that you will make recommendations that give voice to everyone to serve and provide for and protect us for generations to come.

Thank you.

CHAIRMAN HOWELL: Thank you very much, Andrea.

And a second and final commentator is Mickey Garsky.

MS. GARSKY: Hi. As always, thank you very much for the opportunity to present public comments to the committee and the chair, Michele, Dr. van Dyck. I will be very expeditious.

Thank you for nominating the SCIDs group of

disorders to be added to the core panel. It's what the consumers are looking for, and I think you deserve to be applauded for the work that you've done to accomplish that.

My second comment is you earlier today asked for possibilities of recommendations of who might else be invited to sit at the table. And I've thought for a while as a consumer, that with all the education that the genetic counselors do, that they might be given that opportunity with their valuable service that they provide to consumers.

So thanks for adding SCIDs. See you.

CHAIRMAN HOWELL: Thank you very much, Mickey, for those comments.

Let me thank the committee for an excellent and very productive two days here. I think that a lot has been accomplished. A lot is on the table with presentations.

Let me ask you to think about one area that we've not discussed and that is the conditions we have previously reviewed and have not recommended to be added at this time but to go ahead and to do certain

studies and so forth and come back -- those folks are obviously very hard-working to come back. And I think that it would be helpful, if you have ideas about how you would like to see that return and so forth, what you would like to see when they come back -- obviously, they would need to address in a systematic way the gaps that were there. If there are other things that you would like to see, why don't you contact Michele? I think that the SCID folks did a great job.

I think that as Ned and others pointed out, it would have been handy if perhaps we had the evidence review that applied to the specific area right before us to refresh our memory. I think that that would have just been one thing.

But let's think about that a little bit as we expect, well, specifically the issue with Krabbe disease, the issue with Pompe disease. Those conditions will obviously return to us, having answered or worked on the areas where we felt gaps existed. So think about that.

Let me thank you all for your hard work and have a safe journey home. Chris, do you have a quick word before we leave?

DR. KUS: Yes, actually just to follow up on one of the things you charged us with, which was one of the recommendations for health care reform that related to the payment method. Denise and I worked with a group of folks and we have a recommendation, and I can give it to you and I can read it quickly.

CHAIRMAN HOWELL: Read it quickly.

DR. KUS: Okay, sure.

The recommendation is to work with the Centers for Medicare and Medicaid to develop and pilot a payment method for an integrated system of care coordinated through the medical home for children diagnosed as a result of screening.

CHAIRMAN HOWELL: Thank you very much.

Again, the other two things that we will include in the document, as we discussed earlier today, were being certain that the folks picked up the newborn screening because they have a preexisting condition -- that will have to be addressed importantly -- and also a lifetime

cap. Thanks very much for your attention and have a safe journey home.

(Whereupon, at 2:10 p.m., the meeting was adjourned.)