The Advisory Committee on Heritable Disorders in Newborns and Children

Day One

HRSA Meeting

Rockville, MD

November 8, 2017

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A P P E A R A N C E S

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JACKIE SEISMAN, M.P.H., (for Natasha Bonhomme)

C O N T E N T S

P R O C E E D I N G S

DR. JOSEPH BOCCHINI: Good morning, everyone. I'd like to welcome you all to the fourth meeting of the Advisory Committee on Heritable Disorders in Newborns and Children for 2017. This is the 47th meeting since the committee was first formed in 2004. I want to take this opportunity to introduce some new members of the committee who are joining us today for the first time as members.

First is Sue Berry. Dr. Berry is a Medical Genetics physician with special interest in outcomes for individuals identified through newborn screening. She is Board Certified in Medical Genetics and Pediatrics. She received her medical degree at the University of Kansas, completed a residency in Pediatrics at the University of Minnesota. Dr. Berry is Professor in the Department of Pediatrics at the University of Minnesota and currently serves as Chair for the Newborn Screening Translational Research Network. She has been a member of the Advisory Committee Followup and Treatment Work Group since 2009 and has participated

in a number of projects and publications from that group. Dr. Berry also serves as Co-Principal Investigator on a project funded by the National Institute of Child Health and Human Development to examine long-term outcomes of individuals who have inherited metabolic disorders identified through newborn screening. Dr. Berry has special expertise in long-term followup of individuals with conditions identified through newborn screening, and she has assembled a dynamic database of clinical information about individuals with these conditions in order to improve their treatment. So, we welcome Dr. Berry to the Committee.

The next new member is Dr. Cynthia Powell. Dr. Powell is also a Clinical Geneticist and Pediatrician and a Genetic Counselor with 28 years of experience working in the field of Clinical Genetics. Dr. Powell received her medical degree at the Medical College of Virginia and completed her pediatric residency at the Children's National Medical Center in Washington, D.C. She is Board Certified in Pediatrics, Clinical Genetics, Cytogenetics, and Genetic Counseling. Dr. Powell is an Associate Professor of Pediatrics and Genetics at the University of

North Carolina, Chapel Hill, where she also served as Chief of the Division of Genetics and Metabolism in the Department of Pediatrics from 2004 through 2014. She is also the Medical Director of the Cytogenetics Lab at UNC Hospitals and Director of the Medical Genetics Residency *Program. She has the lead in a research study examining the use of new technologies to expand the number of conditions that can be detected with newborn screening. She has also served in leadership positions on National Boards and Associations in the field of Medical Genetics and Genomics including serving on the North Carolina State Newborn Screening Advisory Committee. Dr. Powell, we welcome you to the Committee.

The third new member is Dr. Scott Shone. Dr. Shone is Senior Research Public Health Analyst at The Center for Newborn Screening, Ethics, and Disability Studies at RTI, International. He received his Ph.D. in Molecular Microbiology and Immunology from the John Hopkins Bloomberg School of Public Health and joined the New Jersey Public Health Laboratory in 2005 through the Association of Public Health Laboratory Centers for Disease Control and Prevention, Emerging Infectious Diseases, post-Doctoral Research Fellowship Program. Dr.

Shone spent 9 years as the Director of the New Jersey Newborn Screening Laboratory. During his tenure, the program expanded screening from 20 to 55 disorders, upgraded the laboratory's information management system, installed and validated multiple pieces of new equipment, expanded molecular testing, increased efficiency, and reduced cost through implementation of LEAN processes, and maintained central services during multiple states of emergency. Currently, Dr. Shone is working to develop private public partnerships and evaluating different models for technical assistance. He provides newborn screening system technical guidance and leads the Information, Technology, and Data Quality Assurance Activities for Early Check, RTI Statewide Voluntary Screening Program. So, Scott, we welcome you to the Committee as well.

Then, we have Laura Kavanagh, the new HRSA Ex-Officio member.

Dr. Michael Lu, the Associate Administrator for the Maternal and Child Health Bureau, has left Federal Service to take a new position as Professor and Senior Associate Dean for Academic Faculty and Student Affairs at The School of Public Health at George Washington

University. We thank him for all that he did for this Committee and for HRSA during his tenure here.

To represent HRSA, we now welcome Laura Kavanagh, the Acting Associate Administrator for MCHB. Ms. Kavanagh was the Deputy Associate Administrator for MCHB since 2015, has been in the Bureau for many years overseeing MCHB's Applied Research Workforce Development and its Autism Initiative. So, Laura, I want to thank you for joining the Committee as well.

I also want to thank Dr. Fred Lorey. Dr. Lorey was asked to continue an extra period of time on this Committee when we were waiting for the complete -- to bring the new Committee members on board so that we could continue to have a quorum to do our work. So, Fred volunteered and was willing to stay an extra time, and we want to thank him for all of his contributions to the Committee and his willingness to accept additional time serving on the Committee when we had actually told him his term was finished. [Laughter.] And, again, he participated quite actively at the last meeting. So, Fred, I understand you're on the line, and I wanted to thank you again for all of your contributions over the years not only to this Committee but to newborn screening

in general and all the work and accomplishments you had during your tenure in California. And, certainly if you would like to say a few words since you're on the phone, we'd be happy to hear them.

DR. FRED LOREY: Thanks, Dr. Bocchini. I just want to thank everybody -- the Committee and everybody else associated. My time there was really enjoyable and the learning experience -- I'm really happy with the new Committee members. So, thank you all. I made lots of new friends through this process.

DR. JOSEPH BOCCHINI: Thank you, Fred. So, I also want to mention that we have a new Designated Federal Official for the Committee. Debi Sarkar has also taken a new position. She is serving as Chief of the Genetic Services Branch, and as such will not be able to stay on as our DFO. However, the Genetic Services Branch will continue to provide support for the Committee, so she will still be involved with Committee activities. I want to thank her for her dedication to the success and the support of this Committee, and she served as this Committee's DFO since 2013. She successfully guided us through major transitions, helped the Committee navigate procedures, and insured that our meetings ran smoothly.

So, Debi, a personal thank you for all that you've done to make this Committee successful. And, we wish you the best with your new administrative responsibilities.

So, Dr. Catharine Riley, who is to my right, she has served as the Acting DFO for the past 2 meetings and will now serve as DFO for the Committee moving forward. Dr. Riley is the lead for newborn screening in the Genetic Services Branch at HRSA. She received her Ph.D. in Public Health Genetics from the University of Washington, School of Public Health, her MPH in Health Administration and Policy from the Mel and Enid Zuckerman Arizona College of Public Health, and her BS in Molecular and Cellular Biology from the University of Arizona. Prior to coming to HRSA, Dr. Riley served as a Health Scientist on the Rare Disorders and Health Outcomes Team in the National Center on Birth Defects and Developmental Disabilities at the CDC. She has 17 years of research and practice-based experience in a combination of Public Health Genetics Newborn Screening, Rare Disorders, Health Policy, and Public Health Infrastructure, Health Education, and Workforce Development, and certainly has already made contributions to this Committee in her work as the Acting DFO. So, we welcome her formally as the

Formal DFO.

So, now we'll open the Committee meeting with the roll call. So, representing the Agency for Health Care Research and Quality, Kamila Mistry?

DR. KAMILA MISTRY: Here.

DR. JOSEPH BOCCHINI: Mei Baker?

DR. MEI WANG BAKER: Here.

MR. BRADLEY: Susan Berry?

DR. BERRY: Here.

DR. JOSEPH BOCCHINI: I'm here. Jeff Brosco?

DR. JEFFREY BROSCO: Here.

DR. JOSEPH BOCCHINI: Center for Disease Control and Prevention, Carla Cuthbert?

DR. CARLA CUTHBERT: Here.

DR. JOSEPH BOCCHINI: Food and Drug Administration, Kellie Kelm?

DR. KELLIE KELM: Here.

DR. JOSEPH BOCCHINI: Health Resources and Service Administration, Laura Kavanagh?

DR. MS. LAURA KAVANAGH: Here.

DR. JOSEPH BOCCHINI: Dietrich Matern?

DR. DIETRICH MATERN: Here.

DR. JOSEPH BOCCHINI: Cynthia Powell?

DR. CYNTHIA POWELL: Here.

DR. JOSEPH BOCCHINI: National Institute of Health, Melissa Parisi?

DR. MELISSA PARISI: Here.

DR. JOSEPH BOCCHINI: Annamarie Saarinen?

MS. SAARINEN: [No audible response]

DR. JOSEPH BOCCHINI: Annamarie has not yet arrived. Scott Shone?

DR. SCOTT SHONE: Here.

DR. JOSEPH BOCCHINI: Beth Tarini?

DR. BETH TARINI: Here.

DR. JOSEPH BOCCHINI: Cathy Wicklund is unable to attend this meeting. And then, our DFO, Catharine Riley?

DR. CATHARINE RILEY: Here.

DR. JOSEPH BOCCHINI: And, then our Organizational Representatives in attendance. American Academy of Family Physicians, Robert Ostrander?

DR. ROBERT OSTRANDER: Here.

DR. JOSEPH BOCCHINI: American College of Medical Genetics, Michael Watson?

DR. MICHAEL WATSON: Here.

DR. JOSEPH BOCCHINI: American College of

Obstetricians and Gynecologists, Britton Rink?

DR. BRITTON RINK: Here.

DR. JOSEPH BOCCHINI: Association of Maternal and Child Health Programs, Kate Tullis?

DR. KATE TULLIS: Here.

DR. JOSEPH BOCCHINI: Association of Public Health Laboratory, Susan Tanksley?

DR. SUSAN TANKSLEY: Here.

DR. JOSEPH BOCCHINI: Webcast Association of State and Territorial Health Officials, Chris Kus?

DR. CHRISTOPHER KUS: Here.

DR. JOSEPH BOCCHINI: Department of Defense, Adam Kanis?

DR. ADAM KANIS: Here.

DR. JOSEPH BOCCHINI: Genetic Alliance, Natasha Bonhomme?

MS. NATASHA BONHOMME: Here.

DR. JOSEPH BOCCHINI: March of Dimes, Siobhan Dolan?

DR. SIOBHAN DOLAN: Here.

DR. JOSEPH BOCCHINI: National Society of Genetic Counselors, Kate Walsh Vockley?

DR. CATE WALSH VOCKLEY: Here.

DR. JOSEPH BOCCHINI: Society for Inherited Metabolic Disorders, Carol Greene?

DR. CAROL GREENE: Here.

DR. JOSEPH BOCCHINI: Thank you, all. So, the first Agenda Item is a review and a vote on the August minutes. The Committee received draft minutes prior to the meeting, and several members submitted changes. I think we had more over the last 12 hours than we've seen before. They were all sort of minor edits, and you have been given a copy of the now formatted final version of the minutes of the meeting.

Are there any additional additions or corrections to be made to the minutes?

DR. MEI WANG BAKER: Mei Baker. Actually, I am going to correct a mistake I made. So, this page is 13, and when I put my editing in, I meant to say, "We are running a parallel study of using both the traditional cutoff method and CLIR, and so far --". I missed the "far." So, it should have been, "so far, they are agreeable" -- just adding the "far" there.

DR. JOSEPH BOCCHINI: Okay. So noted. If there are no addition -- additional additions or corrections, I will entertain a motion to approve the

minutes, and certainly the individuals who were not members at the last meeting will not be asked to vote on the minutes.

DR. BETH TARINI: Motion to approve. This is Beth Tarini.

DR. JOSEPH BOCCHINI: Okay. Is there a second?

DR. JEFFREY BROSCO: Jeff Brosco, second.

DR. JOSEPH BOCCHINI: All right. All right, then.

We will now vote on the meeting minutes from August. Mei Baker?

DR. MEI WANG BAKER: Approved.

DR. JOSEPH BOCCHINI: I approve. Carla Cuthbert?

DR. CARLA CUTHBERT: I approve.

DR. JOSEPH BOCCHINI: Jeff Broso?

DR. JEFFREY BROSCO: Approve.

DR. JOSEPH BOCCHINI: Kelli Kelm?

DR. KELLIE KELM: Approve.

DR. JOSEPH BOCCHINI: Dietrich Matern?

DR. DIETRICH MATERN: Approve.

DR. JOSEPH BOCCHINI: Kamila Mistry?

DR. KAMILA MISTRY: Approve.

DR. JOSEPH BOCCHINI: Melissa Parisi?

DR. MELISSA PARISI: Approve.

DR. JOSEPH BOCCHINI: Beth Tarini?

DR. BETH TARINI: Approve.

DR. JOSEPH BOCCHINI: Okay. So, the minutes are approved as corrected.

So, next on the agenda are a few announcements. Our next meeting will be held February 8th and 9th of next year. This meeting will be in person, and it will at the same location and also available by webcast. Additional meeting dates have been set up through 2020 and can be found on the Committee's website, so for long-term planning, you know when we are going to meet.

We also have 3 Work Groups, and each work group has members completing their service on the Committee next month. We are currently accepting nominations for the following 3 Work Groups: Education and Training, Followup and Treatment, Laboratory Standards and Procedures. Self-nominations should include a statement of your interest, your CV or your resume, and nominations must be E-mailed to Alaina Harris -- her E-mail address is up there for you to see -- by November 20th.

A few Committee members will be completing

their terms in 2018, and we are looking for nominations for individuals to replace these retiring members to fill these vacancies. So, a call for nominations will be announced soon in the Federal Register.

So, today we are going to hear presentations first from APHL on working toward newborn screening timeliness goals. We are also going to have a panel discussion on implications of detecting carriers through newborn screening, and we're going to have a Phase 2 report on the SMA evidence review.

On day 2, we will hear Work Group updates, as the Work Groups will meet this afternoon to complete their work. They will update us on day 2. We will also hear another panel discussion, this on Clinical and Public Health Impact of SCID screening.

So, now I would like to turn this over to Catharine for some additional information. Catherine.

DR. CATHARINE RILEY: Thank you, Dr. Bocchini. The Advisory Committees Legislative Authority is found in the Newborn Screening Saves Lives Reauthorization Act of 2014. This legislation established the Committee and provides the duties and scope of the work for the Committee. However, all Committee activities are

governed by the Federal Advisory Committee Act or FACA, which sets the standards for the establishment, utilization, and management of all Federal Advisory Committees. As a Committee member on a Federal Advisory Committee, you are subject to the rules and regulations for special government employees.

I have some standard reminders, just to go over with the Committee. I wanted to remind Committee members that as a Committee, the Committee is Advisory to the Secretary of Health and Human Services, not to Congress. For anyone associated with the Committee or due to your membership on the Committee, if you receive inquiries about the Committee, please let Dr. Bocchini or myself know prior to committing to an interview.

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

When a vote is scheduled for an activity or an

activity is proposed and you have a question about a potential conflict, please notify me immediately.

So, according to FACA, all Committee meetings are open to the public. If the public wishes to participate in the discussion, the procedures for doing so are published in the Federal Register and announced at the opening of the meeting. For this November meeting, in the Federal Register we said there would be a public comment period, which there will be today from 11 to 11:30. Public comment is only with advanced approval of the Chair or DFO. Public participants may ask a question of Committee members or other presenters if they do have the approval of the Chair or the DFO.

Public participants may also submit written statements, and this is done through the online registration process. Also, public participants should be advised that Committee members are given copies of all written statements submitted to or submitted by the public, and we do state this in the Federal Register Notice as well as the Registration website.

Any further public participation will be solely at the discretion of the Chair and the DFO.

So, I wanted to know if we have any questions

from the Committee members.

Just a couple of logistic reminders for those that are attending in person. First, welcome to all of those who are able to attend with us in person today -- we have a full house here -- and, also, welcome to all of those who are attending via the webcast. We know there are lots of folks attending via webcast as well.

For those attending in person here today, just know as visitors you do only have access to the fifth floor of the building, so that's the floor that we're currently on, the pavilion, the cafeteria, the rest rooms, and then the meeting room areas this afternoon. So, all other areas of the facility are restricted and do require an escort by a HRSA staff member. There are no exceptions for this.

If you need to leave and re-enter, you will be required to go through security again when you come back in, and we will have -- an escort will be able to escort you. So, we will have escorts available toward the end of lunch if people need to leave and re-enter during the lunch break.

If you need to leave and re-enter for any other -- at any other time -- please notify one of the HRSA

staff so we can help you with that.

With that, I'd just like to welcome you, and I'll turn it back over to Dr. Bocchini.

DR. JOSEPH BOCCHINI: Thank you, Catharine. Our first presentation today relates to timeliness in newborn screening. As you know, it is very important for Newborn Screening Program to be successful in reducing disability, morbidity, and mortality. The process from specimen collection through diagnosis and treatment must occur within a short window of opportunity between birth and the onset of clinical symptoms. So, based on that, the Committee reviewed and reaffirmed the Newborn Screening Timeliness Goals, which are listed here, and I'll just briefly go through them.

Presumptive positive results for time critical condition should be communicated immediately to newborn's healthcare provider, but no later than 5 days of life.

Presumptive positive results for all other conditions should be communicated to the newborn's healthcare provider as soon as possible, but no later than 7 days of life.

All newborn screening tests should be completed within 7 days of life with results reported to the

healthcare provider as soon as possible.

In order to achieve those goals, initial specimen should be collected at the appropriate timeframe for the newborn’s condition, but no later than 48 hours after birth, and specimen should be received at the laboratory as soon as possible, ideally within 24 hours of collection.So, since that time, HRSA has funded an initiative to improve Timeliness of Newborn Screening diagnosis. Through this award, NewSTEPs 360 was developed to improve the time to diagnosis and treatment for babies undergoing newborn screening who receive a presumptive positive result and facilitate and coordinate collaborative learning and quality improvement activities by Newborn Screening Program using strategies that will improve Newborn Screening Timeliness.

Joshua Miller is here with us today to present an update to the Committee on where states are with regard to the Timeliness Goals and share examples of how states have utilized quality improvement activities to improve timeliness and other aspects of newborn screening process. Mr. Miller is Research Instructor in the Department of Epidemiology at the Colorado School of Public Health and is currently the Project Manager of

NewSTEPs 360.

After Mr. Miller's presentation, there will be time for Q&A and Committee discussion.

So, welcome you here and look forward to your presentation.

MR. JOSHUA MILLER: Thank you, Dr. Bocchini. And, to the Committee, a quick note. I am picturing you all naked right now to help ease my nerves. So, no pressure to the Committee at this time. [Laughter] But, I would also like to thank the Committee for this opportunity to present to you the status of the Timeliness in Newborn Screening and how Newborn Screening Programs continue to save lives through successes in improving timeliness.

And, how I'm going to present this to you today is by utilizing data from the NewSTEPs Data Repository. And, the way I'll do this is essentially two-fold. I'm going to start by presenting to you how the distribution of data has shifted over time since 2012 at an aggregate level as it relates to working toward achieving the Committee's recommended Timeliness Goals. And, then I'm going to transition into the Newborn Screening Program's specific level and how implemented changes in activities

by the Newborn Screening Programs have impacted their timeliness measures and resulted in improvements in those measures. And, then hopefully I'll start the conversation on how we can continue to continue these improvements moving forward and how to sustain those successes once they're achieved.

But, before I get into the data, I would like to do a quick summary of NewSTEPs and NewSTEPs 360 and how we have worked to create a collaborative paradigm to improve Timeliness in Newborn Screening.

So, for those who don't know, NewSTEPs is the Newborn Screening Technical Assistance and Evaluation Program funded by HRSA. It's a collaboration between the Association of Public Health Laboratories and the Colorado School of Public Health. It provides data services, technical assistance, training the Newborn Screening Programs, and assists states with quality improvement initiatives. And, part of the data services we provide is providing a data repository for Newborn Screening Programs.

In this database, we collect newborn screening data on state profile information, case data, as well as quality indicator data for the purposes of quality

improvement at the program level.

In order for programs to enter data into the repository, it is required that they have a fully ratified Memorandum of Understanding with APHL, and even after the MOU is fully ratified, it is still completely voluntary in order for them to enter data.

NewSTEPs 360 is one of those quality improvement initiatives that very much falls under the umbrella of NewSTEPs, and it is a separate funded cooperative agreement through HRSA in which funding began in September of 2015 and is scheduled to end in August of 2018. It is still very much a collaboration between APHL and the Colorado School of Public Health, and this is a snapshot of our governance chart. And, Scott Shone, who was our previous Chair of the Steering Committee, and Mei Baker, who is our current Chair, I think will be very happy to see that in the solar system that we've created for our governance chart, the Steering Committee is the central star with the highest level of density in which all these other things revolve around.

So, as you can see, the biggest planet in the solar system is NewSTEPs, but I want to draw your attention to the dark red planets above the sun there.

That is known as the Steering Committee. In terms of SCID, NewSTEPs, and NewSTEPs 360, these are quality improvement initiatives funded by HRSA that receive funding separate from the larger NewSTEPs cooperative agreement, each with their own purpose. NewSTEPs 360 is one of those with the purpose of working with Newborn Screening Programs to improve timeliness.

And, you may note there are a couple of asterisks under NewSTEPs 360. That is because NewSTEPs 360 is the only quality improvement initiative right now where funding funnels directly through the Colorado School of Public Health, making us the lead institution on this initiative.

So, this is a map of current NewSTEPs 360 participants. As I mentioned earlier, funding began in September of 2015, and by January 1st, 2016, we had 19 state Newborn Screening Programs who started to receive funding and began their activities to improve timeliness, and 1 Territorial Newborn Screening Program, for a total of 20, and these are highlighted in purple on this map.

And, then 1 year later in January of 2017, we had an additional 8 state Newborn Screening Programs join the project, for a total of 28 state Newborn Screening

Programs, and those are highlighted in orange.

So, we have a lot of partners for our NewSTEPs 360 who are helping us and states move toward improving timeliness in newborn screening. That includes Natasha and Genetic Alliance's Baby's First Test in helping us provide educational resources, NICHQ who helps us to provide [cut off], CQI continuous quality improvement training resources both to us as a team and to Newborn Screening Programs, as well as many other national partners who provide services for the project.

NewSTEPs 360, as I mentioned, is a HRSA-funded initiative that is modeled under the -- what they call the COIN model, which is the Collaborative Improvement and Innovation Network. And, I'm glad I got that right. I rehearsed that more than anything else, actually. [Laughter] So, this is the logic model based on that continuous quality improvement logic model, and I want to draw your attention to the bottom half of this because we believe that one of the strongest outcomes thus far for NewSTEPs 360 has been the ability to build the relationships on collaborations for a venue of collaboration for the NewSTEPs Newborn Screening Programs to come together and learn from one another to improve

timeliness.

Each state is assigned to one Continuous Quality Improvement Coach, and those coaches are personnel from the NewSTEPs -- or staff in the NewSTEPs 360 project. And, so each state is assigned to a coach, and each month, that coach meets via webinar with those states to talk about the current PDSA cycles, how they can improve on those PDSA cycles, how they can potentially correct anything, if there are obstacles in the way, or even identifying new activities that may impact their timeliness measures.

And, then once a month we also have an all-state webinar every month in which all state participants come together on one big webinar. And, recently we've also started doing electronic breakout rooms in these webinars to really focus down on topics of timeliness, so that way they can really interact and collaborate to create some synergistic results in terms of successes they've had in improving timeliness and working together to develop methods to overcome barriers that may impact timeliness.

And, any of the states participating in 360 focus on one or many of these focus areas, which include

hospital education, expanding courier services, expanding operating hours, improving internal laboratory processes, improving short-term followup processes, and implementing health information technology to improve timeliness.

So, the NewSTEPs Data Repository collects a total of 8 quality indicators and many of their sub-parts. The data that I'll be presenting to you today is based on Quality Indicator 5, which measures all of the different parts of timeliness that Dr. Bocchini mentioned in terms of the recommendations.

We collected the annual level, so basically states that have a signed Memorandum of Understanding with APHL can voluntarily enter this data aggregated at the annual level into the repository. And for NewSTEPs 360, when we started we realized that we need to be able to track progress in timeliness a bit closer than just by year. So, we added another part to the repository that collected this timeliness data on a monthly basis. And, whether they're entering data on an annual or monthly basis, the data is entered as the number of specimens that fall into a specific time interval category. So, for instance, if a state were entering data for September of 2017 for collection times, they would enter the number

of specimens collected within 12 hours of birth, the number of specimens collected within 12 to 24 hours of birth, 24 to 48 hours of birth, so on and so forth. And, that is then reported as it is in this presentation as the percentage of total specimens.

So, how many Newborn Screening Programs have submitted data? So, as I go through the aggregate data here starting on the next slide, you are going to see two different types of data.

So, the first will be based on annual data, and this is based on a Timeliness Report that we developed to submit to the GAO. So, in early 2016, we were contacted by HRSA, who was contacted by the Office, also known as the GAO, to develop a report based on the data we collect in terms of timeliness measures.

So, in the spring of 2016, we sent out a request to all 53 Newborn Screening Programs requesting that they provide us with that data, and we ended up receiving data from 38 Newborn Screening Programs, 20 of which had a signed MOU, 18 of which did not, but submitted it via an Excel spreadsheet, which is then aggregated on the back end afterwards. And, then in August of 2016, we submitted that report to the GAO,

which, of course, they then published that in December -- their own report.

For NewSTEPs 360, we have 28 participating programs, and to this point, we've had 22 programs that have submitted data for NewSTEPs 360.

It is important to keep in mind that the data submitted -- so that 22 is not going to be consistent across measures because -- just because a state may have submitted data for collection times but may not have submitted data for transit times or reporting time-critical results, and this is because of various complications and obstacles with developing the queries and extracting that data from the LIMS system within various states.

Okay, so without further ado, I would like to being presenting to you shifts in the data in terms of -- at an aggregate level in terms of timeliness progress.

So, Timeliness recommendation 1 is reporting presumptive positive results for time-critical disorders within 5 days of life for 95% of initial specimens. And, what the table is showing you in that first row is the recommendation in a tabular format. And, that second row is basically informing you of any differences in the way

that we collect that data in the repository compared to what the recommendation is.

So, in this instance, the only difference is that in our repository, we collected as 95% -- we look at it as 95% of all specimens and not initial specimens, as we felt that what the important part was reporting those time-critical results from birth whether it was -- without differentiating between whether it was an initial specimen or repeat specimen.

So, this is the first of many box plots I'm going to be showing you. The percent of specimens is always represented on the Y access, XX always represents time and units of years for these box plots, and above each box and whisker plot, you'll see a number, which represents the number of programs that submitted data for that particular measure for that particular year. What's great about box plots is it really shows you the distribution of the data.

And, so I just want to point out that the middle line within that colored box represents the median, but equally as important as the median change is how that entire box shifts -- that distribution. So, the bottom is represented as the 25th percentile, and the top

of that box is represented as the 75th percentile, also known as inner quartile range, and it also can be interpreted as the middle 50% of your cohort. Knowing how that shifts is equally as important as the median. So, what this box plot is showing you is that the median percent of specimens with the presumptive positive result for time-critical disorders reported within 5 days of birth increased from 23% in 2012 to only 24% in 2015. But, what's important to note here is the distribution of that middle half of the cohort moved upwards and also grew, right? So, in 2012 the middle 7 of the 14 programs were reporting 12% of 48% of time-critical results within 5 days, and that shifted to about 18% to 68% in 2015.

This box plot is showing you essentially the same thing you just saw. So, the two box and whiskers on the left are what was presented in the previous slide, and the two on the right representing 26 in 2017 is the monthly NewSTEPs 360 data aggregated at the annual level. And, so there are some limitations to this in that in many of these slides, the number of programs that submitted data represent a subset of those that submitted data for the GAO report. But, nonetheless, it gives a good picture of how these timeliness measures are growing

over time.

So, what this shows you is that with the NewSTEPs 360 cohort in 2016, the median percent of specimens with the presumptive positive for time-critical disorder reported within 5 days of birth was at 40% and then improved to 50% in 2017, and that the inner quartile range has actually shifted upwards as well in 2017, showing that 25% to 75% of those specimens with time-critical results have been reported within 5 days.

These bar graphs are showing you how many of the programs have achieved that 95% goal set by the Committee. And, each of these bars represents one Newborn Screening Program. And, the summation of each bar is the sum of each of those time categories as we collect them. So, essentially the top of each bar represents those specimens reported within 5 days.

So, what this is showing you is that in 2016, one program achieved reporting 95% and then in 2017, there was also one program that achieved reporting 95% of time-critical results within 5 days of birth. But, again, it’s important to notice that in each of these Newborn Screening Programs, the bars appear to be growing taller, and progress is being made in working towards

those goals.

Timeliness recommendation 2 is reporting presumptive positive results for non-time-critical disorders within 7 days of birth for 95% of initial specimens. And, again, for NewSTEPs, we collect this in a manner that does not differentiate between initial and repeat specimens.

For the data that was submitted to the GAO for 2012 through 2015, this is showing you that the median percent of specimens with the presumptive positive for non-time-critical reported within 7 days of birth increased from 52% to 55% in 2015. And, again, that distribution of the inner quartile range shifted upwards to where the center 8 of the 16 programs were submitting 40% to 80% of specimens within 7 days for presumptive positives for non-time-critical results.

Again, this is adding on the NewSTEPs 360 data to the previous slide. In 2016, you can see the NewSTEPs 360 cohort was reporting a median of 65% of non-time-critical results within 7 days, and, that again increased in 2017 to a median of 82%. And, again, please note how the distribution also shifted upwards.

For this measure, 3 of the Newborn Screening

Programs participating in 360 achieved the 95% goal in 2016, 2 achieved it in 2017, and the third almost made it there. But, again, it's important to note here how each of these bars is growing, representing how each Newborn Screening Program is making progress towards reaching those goals.

Timeliness recommendation 3 is reporting all results from all tests within 7 days of birth for 95% of initial specimens. We collect this the exact same way in the NewSTEPs repository. So, for the data submitted to the GAO for this measure, the median percent of specimens for all results reported within 7 days of birth increased from 45% in 2012 to a median of 59% in 2015, and also again note how that distribution of the middle 50% rose up to a range of 20% to 90%.

When adding on the NewSTEPs 360 data, in 2016 we had a median of 83% of all results reported within 7 days, and that increased in 2017 to 89%. And, what's also important here is not only that the distribution of inner quartile range is going up, but that it's actually tightening, right? So, instead of having this big range for this measure, we're actually tightening that distribution. By 2017, the NewSTEPs 360 cohorts who

provided data for this measure were reporting 70% to 98% of specimens with all results within 7 days of birth.

Again, showing you how many have achieved the 95% goal, in 2016 for NewSTEPs 360, we had 4 programs achieve reporting all reports within 7 days of birth, and in 2017 we had 7 programs. And, again, please note how each of those bars appears to be increasing as everyone is making progress.

So, timeliness recommendation 4 is the first recommendation that supports the reporting recommendations. This is that all specimens -- 95% of initial specimens being collected within 48 hours of birth, and we collect this in the exact same way in the data repository. This box plot is showing you that this is by far the highest performance measure in timeliness for programs. The median in 2012 was 86%, and then that rose to 93% in 2015 in terms of specimens collected within 48 hours of birth. And, also note how tight that distribution is.

And still, even with that high level of performance, when you add the NewSTEPs 360 cohort to this, you can still see that there are still improvements being made and that in 2016, the median was 95%, and that

still rose to 96% in 2017, still with those tight distributions. And, at this point on average, what this is showing you is that on average, Newborn Screening Programs are collecting -- or at least the hospitals are collecting -- greater than 96% of specimens within 48 hours of birth. In 2016, 11 participating states achieved this goal, and in 2017 11 also achieved the goal.

Timeliness recommendation 5 is a little trickier. This is receiving 95% of initial specimens within -- at the laboratory within 24 hours of collection. For our report to the GAO, we -- because we hadn't analyzed the data yet, we said ideally this is what we're going to use as our benchmark as well to align with the Committee's recommendation. After analyzing that data and after working with states that are participating in NewSTEPs 360, we realized that this 24-hour mark seems to truly be an ideal and may not be a realistic goal to attain for a lot of these program. And so, for that reason, we then kind of shifted the benchmark to 48 hours.

But, then we also realized that through NewSTEPs 360 that many programs have some complications

with recording this in their LIMS systems in units of hours. And so, we then shifted this to collecting it in units of days. And, to parallel that 48-hour mark, we said realistically that we'll use this benchmark of realistically that all specimens should be received at the laboratory within 2 days of collection. And so, as I move forward with this through this presentation, that's the benchmark that I'll be using for the most part.

So, these are the exact same box plots -- types of box plots that you were seeing before, except on the left, you're seeing the aggregate data submitted to the GAO in terms of this percent of specimens received within 24 hours of collection. And, on the right you're seeing the percent of specimens received within 48 hours of collection. And, this is just to give you a comparison. That 24-hour mark seems to be a very challenging benchmark and that the median increased in 2012 only increased by 4% from 2012 through 2015 to a median of 7%. But, when you look at the 48-hour benchmark, there's a significant increase there in which the median was 36% in 2012 and rose to 53% in 2015.

So, this is a little trickier of a plot because

I'm plotting hours from 2012 to 2015, and I'm plotting days for NewSTEPs 360 all on the same plot on the left and right, all right?

So, 2012 and 2015 on each of these plots are what I just showed you on the last slide. 2016 to 2017 are there to show you the difference in terms of collecting in days versus hours, right? So, on this first one on the left, it's showing you that -- those first boxes on the left are showing you the same as what you saw before and that the median was 4% in 2012, went up to a median of 7% in 2015, but when you collect in units of hours, there's always that possibility that the baby is born late at night, and then they cross over that midnight point into another calendar day. And so, what this one day is inclusive of is day 0, which is same day as birth, and day 1, which is the next calendar day of birth. So, it's a combination of those. And, so you can see that because of that, you have a higher -- a higher performance for this in which you increase from 35% to a median of 36% in 2017.

The one on the right is comparing the 48-hour mark that I showed you to the 2-day mark. And, so the plot on the right is showing you that the median percent

of specimens received within 2 days of collection in 2016 for the NewSTEPS 360 cohort was 75%, and that increased to 78%. And, again, notice how much tighter the distribution is for those measures than it is for the 48-hour mark.

In terms of achieving receiving specimens within 2 days of specimen collection, there was one program each year that achieved the benchmark -- the more lenient benchmark of within 2 days of collection. But, again, note how progress is being made across those bars.

So, now I would like to transition from the aggregate level, which kind of shows you how those distributions are shifting over time, to presenting to you direct examples from Newborn Screening Programs who are participating in NewSTEPs 360, and how those implemented changes are resulting in and impacting their timeliness measures.

So, Virginia in early 2015 began implementing hospital site visits at -- educational hospital site visits that included the quality of the specimen collection, the transit times -- you know -- where the drop-off locations are, and they would actually go over each of the hospital report cards to indicate specific

areas that a hospital might be struggling with and to focus on those areas based on the data.

Then, in February of 2016 -- those hospital sites concluded by the end of 2015 -- and, by February of 2016, to continue that momentum, they decided to begin doing direct outreach via phone call to nurse managers at the hospitals. So, based on the data that they were extracting from the LIMS, they would analyze that data, notice areas for improvement at each of those hospitals, reach out to them directly for education, and -- for instance -- if hospital one was struggling with transit times, they would call up that hospital, educate them on the importance of why getting the specimens to the lab in a timely fashion was important -- you know -- and assuring them that getting those specimens to the courier pickup locations was important.

And, what this graphic is showing you is that based on those activities, how their timeliness measures increased. So, this is a reference point run chart or a line graph. And, the juxtaposition there at the 0% mark is basically a point in time. So, what that is showing you is that by the end of those hospital site visits and at the exact month when they started those direct

outreach to those nurse managers at the hospitals, from that point, they had a 4% increase in the number of specimens collected within 48 hours of birth and over 16% increase in the number of specimens received within 2 days of collection.

This is that exact same graph except with a lot more measures added to it, right? So, the red line -- the orange line and blue line are still there in terms of collection and transit times. But, what I wanted to show you here was how making those improvements in those pre-analytic measures based on those educational activities had a multiplicative increase in their report times. So, that top line there is showing you that the percent of specimens with non-time-critical results reported within 7 days of birth increased by almost 63% and that the percent of specimens with time-critical results reported within 5 days of birth increased by nearly 55% based on those educational activities.

Montana, participating NewSTEPs 360, has focused on extending their courier services. And, they have unique challenges in terms of just having a large geographic space to deal with in terms of delivering specimens.

So, in March of 2016, they added a 6-day courier on Sundays for their larger facilities on the courier route. And then, for those smaller facilities not on the courier route, they provided overnight UPS shipping. And, what this did when they implemented this in March of 2016, was it increased their percent of specimens with all results reported within 7 days by 8% and increased their percent of specimens received within 2 days of collection by 17%. And, it just so happens as well that the end of those lines in April of 2017 coincides with Montana's first time of being able to achieve reporting 95% of all results within 7 days of birth.

Indiana is also focused on adding that Sunday courier, but they are also focused on extending their Saturday operating hours. And, they began their activities with NewSTEPs 360 in January of 2017. So, in 2016, this is showing you their performance in terms of percent of specimens with all results reported within 7 days of birth. And, independent of NewSTEPs 360, they were flirting with that 95% benchmark, right? So, they were almost there, and then they would go down, then they would almost hit it, and come back down again. As they

began their activities in 2017, this is showing you that in March, they began -- in March of 2017 -- they started a pilot in which they opened up a Sunday courier to just 6 pilot hospitals, which is there you can see they kind of first hit that 95% mark. And, then in June of 2017, where you see that they finally went over that 95% mark, it was due to -- because they extended that Sunday courier to all of their hospitals in Montana and simultaneously opened up for Saturday operating hours. And now they are -- at least with the data we have -- it looks like they are consistently reporting all results within 7 days of birth for greater than 96% of specimens.

Texas, in July of 2016, independent of their other NewSTEPs 360 activities to improve timeliness, conducted an internal Quality Improvement Project to identify areas within the lab that could improve timeliness for Texas. And, as a result of this, what they found was that if they shifted their staffing hours to 7 a.m. to 4 p.m. to 8 a.m. to 5 p.m. daily, that would insure that those specimens received at the 2 p.m. delivery time could be accessioned and tested on the same day as delivery instead of the next day. And, what this did was it increased the percent of specimens with time-

critical results reported within 5 days by 126%, and those with non-time-critical results reported within 7 days by 56%. And, this was by a simple change of just shifting staff hours by one hour every day. Not so simple -- but it seems simple.

Alaska -- so, each state has barriers that are unique to their state. And, Alaska has some barriers like none other. They have some very large geographical challenges. They are one-fifth the size of the lower 48 states. They engulf -- they can swallow Texas whole. So, if you think they do things big in Texas, they do them even bigger in Alaska. They have 1800 named islands, which means there are many unnamed islands. They have 39 mountain ranges, which contain 17 of the 20 highest peaks in the United States, and 5% of the state is covered by ice fields. They also have challenges unique to just the program in addition to those geographic challenges.

So, the Newborn Screening Program is located in Anchorage. They have 20 birthing hospitals in Alaska, and only 10 of those are connected by the road system, which means the other 10 have to be accessed by airplane. Of those 10 that are -- that can be accessed by the road

system, 4 of them are one to six hours' drive to the nearest airport. In addition to that, all of their specimens are tested at the regional lab in Oregon, which means once the specimens arrive at Anchorage, they still have to travel about 2,500 miles to get to Oregon to be tested -- and, this is on a daily basis. So, they have some timeliness challenges.

Alaska joined the NewSTEPs 360 Program, and they started their activities in January of 2017. They began educational efforts in January of 2017, which included developing or adapting a video that was created by the Colorado-Wyoming team to educate birthing centers on the importance of timeliness in newborn screening.

In September of 2016, they were at about 33% of specimens received within 2 days of collection. Once they began those educational efforts, this is showing you that their performance on this measure began to increase to almost -- by April of 2017, they were at about 48% of specimens received within 2 days of collection.

In June of 2017, they began to expand to commercial air service courier -- commercial courier air service to their hospitals. The courier that they had been using -- which was also an air service -- did not

function on weekends and did not function on holidays. And, in addition to that, instead of flying the specimens to Anchorage, they would fly the specimens directly from those hospitals all the way to Oregon, and you would say that probably saves time, right? But, it actually created problems because the program in Anchorage was having problems tracking all those specimens coming from all those hospitals, and Oregon was having issues with that because they were receiving several shipments a day at different times, and so some were missing the cutoff and some were not. So, by expanding to this other commercial air service -- this commercial air service somehow Sabra in Alaska was able to convince this air service that we should -- that they should fly 7 days a week every day of the year, including holidays and weekends, which is fantastic.

And, so now, in June of 2017, once they started expanding that, this data is showing you that there was a huge peak in their data, and as of September of this year, they are reporting Oregon laboratories receiving almost 64% of specimens within 2 days of collection. Keep in mind that those specimens are traveling 2500 miles in addition to the 200, 400, 600, 800 miles the

specimens have to travel to get to Anchorage first to then go to Oregon, because now the specimens are going to Anchorage so that way they can collate all the specimens into one package and then send those on to Oregon via another overnight airline service, which then arrives at the Oregon laboratory by 8 a.m. every day.

And, I also wanted to point out that in May of 2017, there was a dip in the data. And, that was because -- as I mentioned -- that courier service was not functioning on holidays or weekends. And, so what you see there is three straight days of a courier not being able to function. And, so you see that dip in May of 2017, but in September where there's Labor Day, you actually -- you don't see that dip anymore. And, that was eliminated because of the 7-day commercial air courier.

So, this graph to me is just insane. So, Alaska has made such vast improvements for their pre-analytic processes. But, in addition to that, the Oregon Newborn Screening Laboratory has made internal improvements that includes hiring a Quality Improvement Specialist, refining their hemoglobinopathy screening processes, and reallocating resources to help improve

timeliness internally at the Oregon lab. So, there is an additive effect of what Oregon is doing and what Alaska has done in their pre-analytic processes and has resulted in a 538% increase in the number of specimens reported within 7 days of birth.

So, Iowa functions on a separate philosophy to timeliness in that all babies should receive the same benefit every day regardless of the day of the week they were born. And, this is because they looked at -- Iowa looked at their birth data and noticed that there is a disparity caused by the discontinuation of the birth continuum and the Monday through Friday lab operating model. So, in other words, babies don't care when they're born. They're going to be born every hour of the day, every day of the week, and that's probably not always going to coincide with a Monday through Friday operating model. And, this can be compounded by the fact that in Iowa, at least, that distribution of births by day of the week is not random. And, this is what this graph shows.

So, let's say hypothetically that the Iowa laboratory was not open on Saturday and Sunday and they didn't have a courier operating on the weekends, which is

very not true. But, hypothetically we'll say that. And, let's say that me and my wife had a child in Iowa that was born on Thursday. So, based on the Monday through Friday model, optimally that specimen would be collected on Friday. But, because there's no courier service Saturday or Sunday, then that specimen would be delivered probably on Monday, and then tested probably that same day or on Tuesday, and then that result may be reported out Tuesday or Wednesday. So, you're looking at a 5-6 -- you're looking at a 6- or 7-day report time. And, if my child had a time-critical result, it would require much more urgent attention than that.

And, what's compounded by the fact is that showing this Iowa data, the distribution of birth by day of the week is not random, right? So -- and, this is because that those weekend days -- there are 80% less births than on the weekdays, and this is because of scheduled cesarean sections and induced births that are purposely scheduled to avoid the weekends. So, it increases that risk because more babies are born on that Wednesday and Thursday, and if that Saturday and Sunday nothing -- there are no activities -- then that increases the risk of those infants born on those days.

So, what Iowa has done based on their data is develop a system to eliminate that disparity as best they can.

So, for one, Iowa really focuses their educational efforts not only to the hospitals but to the couriers themselves on why newborn screening is so important. They want to make sure that they tell these -- they want to make sure that they inform the programs and the couriers that what they're doing is they're delivering a package -- not just a package -- but, they're delivering babies' lives in their hands.

Additionally, they provide a same-day courier, 7 days a week, 365 days a year, and their laboratory is open 20 hours per day, every day of the year. And, this data shows that this eliminates that disparity and that greater than 96% of specimens are collected within 48 hours of birth and that greater than 96% of specimens are received within 1 day of collection. And, I've been showing you within 2 days of collection. So, this is greater than 96% within 1 day of collection.

It also gets rid of that batching effect that can happen on the weekends if there is no activities -- limited or no laboratory activities on the weekends. So,

a lot of educational activity is focused on the batching effects that can occur at the hospitals.

But, Iowa focuses also on the effect of batching specimens at the laboratory itself. So, if there are no activities on Saturday and Sunday, then you have specimens kind of piling up and getting rid of that batching effect, as a result this data shows that greater than 90% of time-critical results are reported within 2 days of receipt and that greater than 96% of non-time-critical results are reported within 4 days of specimen receipt.

Eliminating this disparity between the birth continuum and the Monday through Friday operating model allows all specimens to be delivered on the same day as pickup, tested the same day as delivery, and allows results to be reported the very next day, no matter what day of the week. And, as a result of that, greater than 99% of time-critical results are reported within 5 days of birth, greater than 96% of non-time-critical results are reported within 7 days of birth. And, you'll notice that there's a dip there in that data in quarter 3 of 2016. And, this is because of the Hologic recall and discontinuation of the CFTR agents, which shows you that

no matter how high performance is for timeliness, Newborn Screening Programs are still subject to external influences that can affect their data.

So, I want to go over quickly ten important takeaways from the data that I've shown you today and lessons learned from NewSTEPs 360 to this point.

So, first is that improving timeliness takes a combination of all those focus areas that I presented before, right? So, it's educational activities, it's expanding courier, expanding operating hours, improving lab processes. All of that positively interacts and positively impacts timeliness. And, when you look at the aggregate level, you notice small improvements at that macro level. But, when you zoom into the Newborn Screening Program level, you're actually seeing massive improvements based on the activities that they're doing.

And, so moving forward, it's how do we continue making those improvements so that way we can start seeing that success at the larger aggregate level more quickly.

Even incremental improvements can require a lot of time and effort for Newborn Screening Programs, and each state -- as I showed you with Alaska -- has barriers that are unique to them. Just like Iowa states, they

want to examine their own data to assess the differences in their own distribution of births by day of the week and perhaps sit down and try to work on an operating hour and courier model that best fits the model for their own state.

And, my presentation has gotten mad at me. Yep, there it goes. So, I've been cut off. Thank you for your time. [Laughter.] Thank you. There we go.

Number 6 is something I didn't go over in the presentation but continues to be a challenge nonetheless, and those are essentially out-of-hospital births still pose a change for improving timeliness. That includes midwife births, babies in the NICU, anything outside of your standard well-baby unit birth.

I bolded 7, 8, 9, and 10 because I think they're the biggest takeaways, and I'm going to start with 8. I think one of the greatest outcomes from NewSTEPs 360 so far is that Newborn Screening Programs have been able to collaborate to develop methods to overcome obstacles in timeliness in that they've been able to reach outside of the black box -- of their artificial black box formed by their state barriers and work together and share ideas to improve timeliness

within their own states.

And then, so moving forward, efforts should be focused on continuing to make these improvements at the newborn screening level so that way we can see those big aggregate changes in the data for timeliness and also how to sustain that success once it's achieved because one thing we've learned is that timeliness requires constant and continuous attention and effort and that even the slightest competing priority can affect the data.

And, so, then how do we work with programs and develop a system to where timeliness can be focused on while still focusing on implementing new conditions, which is still very important, any other competing priorities, in terms also with the limited resources that they currently have, limited staff capacity. All this can have a negative impact on timeliness. So, how -- how do we develop a system that allows programs to focus on all of this at once.

And, in spite of all of these competing priorities and all of the busy schedules of these Newborn Screening Programs, they continue to on a daily basis avoid adverse outcomes and save lives for babies.

And, I want to go through very quickly an

example of how an infant was saved in New York through the timely actions that occur every day across every state in the country.

So, on day zero, a baby girl is born during the week-long Jewish holiday known as Sukkot. At just over 24 hours of age, the specimen is collected, and just over 43 hours of age, the specimen has already arrived at the New York Newborn Screening Laboratory. At almost 49 hours of age, the specimen has been at the lab for a whopping total of 5-1/2 hours and they've already screened positive for galactosemia, and the lab staff has already created a referral.

At age 49 hours, followup calls out the result to the Specialty Care Center; however, they cannot get hold of the family. In the following -- in the next 3 hours, the following happens. They contact the birth hospital, but they find out the baby has already been discharged. They contact the Specialty Care Center nurse handling referrals and provide the nurse with all the numbers that were provided to them by the birthing hospital, and voicemails and texts are left at all of those numbers. Followup then calls the pediatrician's office, which is closed for the Sukkot holiday. The call

is transferred to the answering service, and an on-call doctor was paged. However, they do not receive a response from the on-call doctor, as they find out that the doctor is out for the Sukkot holiday. However, they then do reach the office secretary, who then requests that they fax in the results and that the doctor will return their call in a few days after the holiday.

The program then sends the fax as requested, but in bold state, “This result is life-threatening. Act quickly.” And, they also include a fax sheet on galactosemia in case they are unfamiliar with the disorder.

They then contact the police, and on the second request, the police go to the family’s house to try to find the family, but they’re not home, and they ask the neighbors how the baby is and where they might find the family. They then re-contact the hospital for any emergency numbers that weren’t given to them before, and they are given the grandma’s number, and they do reach the family at the grandma’s house.

At 5:30 p.m. on day 2, at age 52 hours, and ambulance is sent to the grandma’s house. They arrive at the emergency department at the Specialty Care Center.

The baby is admitted to the PICU and survives. And, the Specialty Care Center is quoted as saying, “If it had been one more day, the outcome would have been bad.” But, it wasn’t, right? The baby was saved. And, that’s telling us success.

This is what Newborn Screening Programs do every day. They put aside all the competing priorities in their busy schedules because they dedicate their professional lives to saving the lives of infants and newborns every day.

So, in conclusion, every Newborn Screening Program participating in NewSTEPs 360 has made great improvements in timeliness. Since activities began for NewSTEPs 360 in January 2016, over 74,000 additional newborns have had specimens collected within 48 hours of birth that otherwise wouldn’t have. An additional 62,000 newborns have had specimens received within 2 days of collection that otherwise wouldn’t have. An additional 378 newborns have had time-critical results reported within 5 days of birth. An additional 2,000 have had a non-time-critical result reported within 7 days of birth that otherwise would not have. And, over an additional 117,000 newborns have had all results reported within 7

days of birth. And, now we need to focus on continuing this momentum and sustaining success.

I would like to give a big thank you to all the Newborn Screening Programs for doing all the great things that they do every day to saving the lives of infants. And, I want to thank the programs who provided data to us for the sake of the Timeliness Report to the GAO. I want to give a big thank you to all the programs participating in NewSTEPs 360 who continue to provide us with endless amounts of information no matter how busy their schedules are. And, a big thank you to the entire NewSTEPs and NewSTEPs 360 team. This was a huge team effort, and it also will be a true team effort. So, thank you. Thank you for your time today.

[Applause.]

DR. JOSEPH BOCCHINI: Joshua, thank you for an excellent presentation that certainly shows the value of quality improvement but all the work that you have put into it to make that program. And, I agree that the screening programs deserve a lot of credit.

So, we're going to open this up for Q&A and discussion. First will be the Committee, and then the organizational representatives. So, operator, if you

will open the line for Committee members and org reps on the conference line. And, so when speaking, please identify yourself so that they have it for the record, and speak closely to the microphone as I have been. I guess I'm doing better today. Okay, good. All right. So, Committee members -- Cindy.

DR. CYNTHIA POWELL: Cynthia Powell. Thank you very much for the presentation, and I applaud this really important effort. And, thanks to APHL and NewSTEPs and everyone else involved with it. I've always said in our state that -- you know -- if we can ship almost every item imaginable overnight -- you know -- tennis shoes, what have you -- you know -- there's no reason why we can't do this for dried blood spot cards. And, unfortunately, every year or two -- you know -- we will have a baby with -- let's say -- MCAD who dies -- you know -- where they could have been saved just through -- you know -- the awareness. And, I'm wondering if you specified to the participating states the time-critical conditions, or was that for them to determine?

MR. JOSHUA MILLER: So, we -- we have a list on our website that categorizes them as time-critical or non-time-critical based on the ACMG -- I believe --

recommendation. I forget who that was. Okay, yeah -- that. Sorry. So, based on that. But, there are states that still determine what they consider to be time-critical and non-time-critical, right? And, so we are encouraging them or to work with them to kind of categorize it in their LIMS system as we -- as we have it categorized as time-critical in our repository in addition to how they categorize it -- if the disorder is time-critical.

DR. JOSEPH BOCCHINI: Beth?

DR. BETH TARINI: Followup. Two questions. One -- this is Beth Tarini. A followup to Cynthia's, which is participation and standardization of the data. It seems that one barrier is that you have about half of the programs participating. And, in addition to that on a microlevel beyond that, you have them submitting different data metrics, and then you have beyond that of them defining the data metrics differently. So, it seems that going forward, this is a tremendous inter-convergence for making a difference. What can the Committee do to help NewSTEPs and 360 succeed in this regard? Because, if you don't have the full-on complement of data and the data you have is not consistent, we will

hit a barrier -- a significant barrier.

MR. JOSHUA MILLER: Yeah. That's a great point, and I agree with you. There are a lot of challenges to getting this data and standardizing it. I think what the Committee can do to support NewSTEPs -- the NewSTEPS HIT Workgroup over the last couple of months has started working toward developing a common data model, and basically what the process is is requesting data dictionaries from Newborn Screening Programs on the way that they select their data. So, that way we can look at all the different fields, how it's formatted, and then work towards developing essentially a common data dictionary as a recommendation for how this data should be collected, not only for the purposes of putting in the repository, but also to help in terms of how this data -- other data is reported across Newborn Screening Programs whether it's to NewSTEPs or just internally or whatever it is. So, that way when Colorado calls up Massachusetts, they can talk about the same data points type of thing.

And, so this is a very fresh idea and one that is just getting off the ground, and I think -- you know -- any support from the Committee on in the future maybe

making recommendations on a common data model based on this work --

DR. BETH TARINI: Correct.

MR. JOSHUA MILLER: -- or giving us -- you know -- $12,000,000 to do it. [Laughter.]

DR. BETH TARINI: Well -- you know -- we ask for the Federal Agencies -- we have in the past requested money that doesn't -- that's a challenge.

MR. JOSHUA MILLER: Yes.

MR. BETH TARINI: I would argue our biggest push comes in setting recommendations that then the programs -- treading lightly on unfunded mandates -- but helping with a guiding hand of how they can best collect data that will contribute to our ability to get the appropriate care in a timely manner to the children.

So, if that is something that would be useful from the Committee, we make a lot of recommendations. If that one is a useful one, I think the Committee should look into this. Because if we can make your job easier, then we can make the Federal dollars we pay to you go further.

MR. JOSHUA MILLER: Agree.

DR. BETH TARINI: Thank you.

MR. JOSEPH BOCCHINI: So, that's a good point. But, just to mention, as you know, with our reauthorization, timeliness is a responsibility. Following this is a responsibility of our Committee, and the Laboratory Standards Workgroup is responsible for continuing to follow this. So, I think interaction between that workgroup and NewSTEPs is certainly important for us to continue to evolve a better understanding of how to continue the momentum and perhaps provide funding and so on.

DR. BETH TARINI: Agreed, agreed. And if -- but, if the Committee sets forth a, this is our request and puts it in writing, it could have yet another layer of oomph, if you will.

DR. JOSEPH BOCCHINI: Right. Agreed.

DR. SCOTT SHONE: Scott Shone. I echo re sentiments -- Joshua did a great presentation.

MR. JOSHUA MILLER: I'm sorry. Who are you again?

DR. SCOTT SHONE: I'm a new Committee member. A lot of date well presented. So, thank you.

I want to sort of echo of what Beth said that this is a problem we're seeing beyond just timeliness,

but in terms of getting data for followup -- short and long-term followup. The kind of threat here is resources. I don't think it's always just money. I mean -- I think that's obviously a big issue, but the broader topic that I think we need to address that will help -- to help all these topics from timeliness to implementation of new disorders, to followup and tracking is provision of resources. And, I think that NewSTEPs and your colleague at NewSTEPs 360 -- Sarah McKasson -- has a great toolkit that just came out on expanding services where it talks about the system effort, and, you sort of alluded to this. And, I don't think it comes down to programs.

The initial discussion a few years ago was this is not a new program problem, it's a system issue. I think one of the beautiful things about Iowa is that their system is open 7 days a week -- not their laboratory -- not their followup program -- their system. I think -- so, so we need to attack all of those on a system issue whether it's getting -- having resources for -- for docs to put in data into followup or for the programs to put in their data on quality improvement.

So, I guess my concern -- and, it echos Beth's

-- what recommendations can the Committee -- can we look at in terms of sustainability. Sustainability for this in the scope of -- there are three disorders that added that most states aren't screening for. There's another one that we'll hear about coming up. So, there are huge challenges to doing all of this with no additional resources -- human, financial, or otherwise. So, I think that's probably the issue to tackle for the programs.

MR. JOSHUA MILLER: Yeah, I agree. And, to tie in that with Beth's point is that there are so many of those competing priorities at the system level that a lot of states just don't have time to provide us with the data. I mean -- that's one of the issues, right? It's just they're already stretched too thin. And so -- you know -- NewSTEPs is -- we would like to make this a standard process to where it becomes a routine part of their workflow where they provide us with data in the repository voluntarily without receiving any money, but just because of the kindness of their hearts they want to give us their data. And, we're doing our best to provide that type of environment, but it's -- you know -- it really has worked to this point where -- you know -- we get a request, and then we put out a request to the

programs -- you know -- a rushed request that says, oh, please, give us all your data by Tuesday type of thing -- you know? But, yeah. So, working on that, I think, Scott, that's a good point.

DR. JOSEPH BOCCHINI: Dieter?

DR. DIETRICH MATERN: Dieter Matern. I agree that data is always great to have and to collect, but I think you've shown pretty nicely that actually the way that Iowa does it gets the job done the way we would want it to be. So, why can't we just recommend that everyone does it like Iowa does?

MR. MILLER: Yeah, I think that would be a tough recommendation to make based on resources allocated. The great thing about Iowa is it seems that their system supports that type of 24-hour, 7-day, 365 days a year process. I don't think the resources are there for every state, and it would be a huge challenge to do that, and may cause a slight revolution at the Newborn Screening Program level. I think it's definitely worth -- you know -- a conversation. But, again, I really think it's up to those programs to develop a courier and operating hours. I think what we've -- one thing that we definitely found out, which I didn't really

go over in this presentation, but when we analyzed the data for the report that we sent to the GAO -- you know -- we found one significant statistical result, and, that was that reporting results significantly associated with operating hours. And, we didn't collect courier service in the appropriate way to be able to analyze that in a way that would show the significance as well, but I would imagine it would be.

And, so I think we've established at this point via the data that Monday through Friday probably isn't going to cut it for timeliness and that to some level of degree, we need to include activities and couriers at least one of those days of the week -- one of those weekend days. But, I really think it's up to each program and then analyzing their own data to see what type of system best fits their own data. But, I agree that the Iowa model is great and that the data supports how successful it has been to this point.

DR. DIETRICH MATERN: A followup, if I may. I mean -- again, I -- Newborn Screening in the US is state-based, so we are a Federal Committee, and we can recommend to the states to follow best practices. And, it seems to me that the Iowa practice seems to be the

best right now, and looking at what they're doing, it seems -- it's not surprising that what they do works. I think there is some competition between states to do the best job, so I think states will actually look at what we discuss today and say, well, what can we do to get to the Iowa stage? I think there is public awareness. I mean -- the reason we're talking about timeliness again comes back to a family that came here and complained about timeliness issues, and then it was picked up by the press, and that put a lot of pressure on the states. And, actually if you indicate where that article came out over the timeliness discussion, you will probably see that the increases are probably not just driven by the 360 NewSTEPs process, but actually to a significant amount by the pressure from the press. So, I think this comment you can make a recommendation to do something that Iowa is doing, and the states will follow either because we suggested or because someone picks up and writes another article, or families go to the Advisory Committees on the state level to put pressure on them.

MR. JOSHUA MILLER: Yeah. Thank you, Dieter, and I would suggest that if the Committee wants to seriously continue with that conversation that beforehand

they invite Stan Berberich to present before the Committee on -- in more detail on what the Iowa model is. He would have much more detail than I do.

DR. JOSEPH BOCCHINI: Mei, Beth, and then Jeff.

DR. MEI WANG BAKER: Well, it seems when we talk about it, I'm just adding on a quick reply -- my comments. Talking about the Iowa model -- if we do ask Stan to come to present, and I would like to also hear how the clinicians will accommodate this 24 and 7. I think in the end that you want to be sure the clinicians react, right? You see the sample come in before time -- do they have 24/7 to take a normal newborn screening, and that will help because comparing the end -- the patient can be cured way earlier than others. So, I think it's an important fact.

So, coming back to my comments originally that I want to make -- we talked about resources, we talked about priorities. Indeed, we have to take this into consideration. One thing, since Scott and I work on the Steering Committee, we have encouraged NewSTEPs to really do something useful for the state, not just ask for data. So, the one thing is to use like incentives. I think if they done a very good job in terms of infograph. So,

what I'm trying to do actually, I use this for two purposes. One is I submit the data, but also I am able to use the data for my own Committee to the summary to report. Because if you said that you needed to do that, can I just do once and get both? I think this would help the state because your graph is very pretty. So, people tend to want to use it and go back to our annually report can utilize it.

I think that activity, I would continue to encourage, and also you get feedback for the data because the data is not just for data -- you want to use the data like Dieter was saying. You analyze, have the good recommendation and utilize -- you know -- find the best practice.

MR. JOSHUA MILLER: And, what Mei is alluding to there in terms of the graphics is that NewSTEPs had -- NewSTEPs 360 is utilizing Tableau 2. Currently right now we have about up to 15 infographics that are completely interactive online that update automatically based on the data entered into the repository. That allows users or programs to filter the view how they want to, create a data dashboard that they want to. For timeliness, they can look at all these measures and compare themselves,

identify to all the other programs participating in 360.

DR. MEI WANG BAKER: And to utilize.

MR. JOSHUA MILLER: Exactly. That requires a log-in. And, then the state profile once their opened and de-identified completely -- you know -- available to anybody. And, in addition to that -- you know -- you can use that for your own reports and do whatever you want to. But, in addition to that too, we've also been working on -- I worked with Montana to develop -- you know -- they were able to provide me with their de-identified specimen level data in Montana. And, I was able to develop for them interactive infographics specific to hospital level data for them. And, I'm currently working with North Carolina to do the same thing and develop a dashboard to make a hospital report card. And, so that's kind of going above and beyond what our initial task was in terms of the data. But, it's something -- it's a need that's out there for the programs because they don't always have that specialty to work with the data -- to pull it from the LIMS, to develop the queries, to clean the data, to create reports.

And, so we're trying to help out with that the

best we can, but to grow and expand on that, I think more resources would be required to allow us to help with that across all the states. Go ahead.

DR. JOSEPH BOCCHINI: Beth?

DR. BETH TARINI: This is Beth Tarini. To follow up on Mei's comment. We were having a side comment that this incentive is an important piece, and the value is in the eyes of the state. Each state will have a different value or different incentive to participate so one place to start, and it may not require much resources -- it may -- it may not. And, so one place to start is to ask the states how can we make this as valuable for you as we can.

The other point I wanted to make is Iowa is not -- is it like Wobegon where like everyone is brighter, happier, taller? [Laughter] Like -- you know -- above average. Thank you. We may be above average, but we're not above average all of the time. We -- you know -- I do work in the state now for almost the last two years, but we are not wealthy. You can look in the state papers. We are not wealthier. We have a rural population. We have a low birth rate. That means we collect less money for our fees, if you do the math. We

don’t have physicians that work 24 hours a day, up all night waiting for their newborn screen. So, I just want to pause or push back on any exceptionalism like somehow this state is a magical kingdom that was able to get this done because they’re magical. They likely -- although I’m not speaking for the program right now -- Stan can speak for the program -- they likely have set their priorities in such a way that with the limited resources they have had, they structured the program to get this done this way and have made tradeoffs in other ways. So, I just want to put that out there. It is not a magical kingdom, although a nice place to live.

My question is this.

MR. JOSHUA MILLER: And, I’m sorry, Beth, if I implied that.

DR. BETH TARINI: No, no, no. This is not what you have -- and I didn’t mean to imply you implied that. [Laughter.] This is a common thread that I hear that Iowa is not magical -- it’s not the word used -- that it is special in some way.

DR. MEI WANG BAKER: Like somehow this state is a magical kingdom.

[Laughter.]

DR. BETH TARINI: So, it is a more sort of widespread, I think, common thought.

My specific question is to push back a little on the conclusions of the success of the program NewSTEPs. Can you go back two slides to number 2 -- or a few slides?

MR. JOSHUA MILLER: Twenty slides.

DR. BETH TARINI: Yeah, there you go. So, I think -- let me just say that this work is incredibly valuable. My personal perspective is the value is in -- the greatest value is in the states reflecting on what -- from a systematic perspective -- what they can do to improve at their level on sort of a PDSA cycle. That forced -- if you will -- or encourage for reflection -- is huge. I think it creates -- it is sort of kindling for greater -- greater improvements.

But, I will push back on number 2 saying that improvements small at the aggregate level are quite large at the program level. It depends on what you're talking about with small, because the numbers are the same. Small is small. It doesn't translate across. So, it's about the number of specimens. It's about the number of babies. And, I'm not saying these aren't qualitatively

large improvements, but to your original slides, you are getting 2% to 3% changes. And, so those aren't huge -- they are certainly a starting point.

MR. JOSHUA MILLER: But, there are a lot of babies.

DR. BETH TARINI: There are a lot of babies. Correct. And, one life is one life. But, we are looking at 95%, and every life gets counted the same.

MR. JOSHUA MILLER: Um-hum.

DR. BETH TARINI: So, because we can't assess ahead of time who's the one that's going to turn positive. So, 2% to 3% is important because across a large population, it's a lot of numbers. But, there -- and, as you said -- this is a start, and there's a ways to go.

My concern with those initial slides are that you had -- from a data perspective -- two or three states or programs added. The question I have is, is the improvement that you saw related to the states that existed improving or did you have additional states come on that were already high performers? So, is the delta due to the existing states, the new states, or a combination?

MR. JOSHUA MILLER: Yeah, it's definitely a limitation of those box plots at the aggregate level, and that is because I would have loved to have used annual data for the larger NewSTEPS. The 2017 data hasn't been entered for the annual data yet because 2017 is still happening.

DR. BETH TARINI: But, you know in the first box plot which were the 12, the 14 --

MR. JOSHUA MILLER: Through the 15.

DR. BETH TARINI: Correct.

MR. JOSHUA MILLER: Yeah, those are the same. So, 2012 to 2015 -- those were the same states that submitted with maybe one or two that didn't submit. So, those are using the same states.

DR. BETH TARINI: So, they're not different states.

MR. JOSHUA MILLER: No, they're not. So, when you look at 2012 to 2015, it's the same states. But, when you look -- when you add on the 2016, 2017 -- those are NewSTEPs 360 states, and so those could potentially represent a different cohort of states. And, so yes. Those are not directly comparable.

DR. BETH TARINI: Are the same states in the

box plot to the left as to the right or are they different states? It's like the second or third slide.

MR. JOSHUA MILLER: All right. So, if you look at this one -- these are 2012 and 2015. Those are the exact same states.

DR. BETH TARINI: Keep going. There's another one there. This.

MR. JOSHUA MILLER: I wish I had your photographic memory.

[Laughter.]

DR. BETH TARINI: Sometimes it serves me well -- sometimes not. So, 16 -- there's 16 states. There's 14 in 12 and 16 in 16.

MR. JOSHUA MILLER: Um-hum, yeah.

DR. BETH TARINI: You see the jump. Or there's 12 in 15.

MR. JOSHUA MILLER: Yeah.

DR. BETH TARINI: What are the 2 states that were in 16 that weren't in 14?

MR. JOSHUA MILLER: Yeah, so based on some of the MOUs that are signed -- so, if a state signed an MOU in 2014 --

DR. BETH TARINI: Right.

MR. JOSHUA MILLER: Some of them state that they will not provide data prior to the signing of the MOU. So, 14 of those states are the exact same, and it just adds on 2 additional onto that 14.

DR. BETH TARINI: So, that's my question. Are the 2 states that you've added on -- are they --

MR. JOSHUA MILLER: Are they high performers? Is there a bias involved? It's very possible.

DR. BETH TARINI: You don't know --

MR. JOSHUA MILLER: I don't know right now, no.

DR. BETH TARINI: Is it a knowable piece of information?

MR. JOSHUA MILLER: Yes, it is knowable. Absolutely.

DR. BETH TARINI: Okay. That would be helpful to know, I think. Then, the Committee will have a sense of, was there improvement on the 14, to what degree, and/or what degree is attributable to new high-performing states.

MR. JOSHUA MILLER: Okay, yeah.

DR. JOSEPH BOCCHINI: Two last comments.

DR. JEFFREY BROSCO: This is perfect because Beth is asking the kind of question I was trying to

figure out in this data. This is Jeff Brosco. Thank you. Because I was trying to think of which states were 2015 and so on, and it sounds like there are new states added. And, is it true that in 2016 to 2017, it's only NewSTEPs 360's states?

MR. JOSHUA MILLER: Yes, in these box plots. That's correct.

DR. JEFFREY BROSCO: So, these are states who voluntarily wanted to participate --

MR. JOSHUA MILLER: Absolutely. So, there's a bias there, right?

DR. JEFFREY BROSCO: It's a really different kind of cohort.

MR. JOSHUA MILLER: Yeah.

DR. JEFFREY BROSCO: Do you have any data on states that didn't participate during those same times?

MR. JOSHUA MILLER: We don't, no.

DR. JEFFREY BROSCO: So, in NewSTEPs, data like that is not entered at all? There's no other repository for that information?

MR. JOSHUA MILLER: So, we collected on an annual basis from all states with a signed MOU. But, again, providing this data is completely voluntary, and

so we don't get data from every state. So, it's really hard to compare for those states who didn't.

So, NewSTEPs 360 -- they're highly motivated to provide us with data. And, 2016 data has been entered for the annual timeliness data, so that could be looked at more closely. Annual data will be entered for 2017, of course, next year in 2018. So, at that time, we can look at it and be able to separate it by states to compare those. We still have to keep it -- you know -- de-identified unless we receive permission from all the states to identify them in this manner. But, yeah -- it is something that needs to be looked at more closely.

For the purposes of the GAO report for that 2012 to 2015 data, we did do that. I mean it was a full 72-page report that really broke down the data and who submitted what for what year, for what measure. And, that's available on our website to download it if you would like more information on that.

DR. KAMILA MISTRY: So, I work a lot with CMS on the Child Core Set, and I think there are some good lessons learned sort of across, and we work on working with the states to report Medicaid data on certain core measures for quality. And, so I think that issue that

Mei and I think Beth brought up about -- you know -- really making this a value for them and really reaching out to them and really trying to understand. And, I think this also relates -- I want to connect two thoughts -- which is the standardization piece of it. The standardization piece is a big limitation. And, I think really trying to understand how you could make that happen -- whether that's talking with states about what are the best practices and really thinking across with folks, and what are the barriers and limitations to that.

But, standardization does have a value, I think, in thinking about things more broadly. In terms of dashboard and some of the things you've talked about in terms of tools and providing that information, I think can have a broader impact -- you know -- across states. And, so, I think -- you know -- I think just connecting those two dots I think is going to be important in terms of recommendations and next steps.

Secondly, I think related to some of the thoughts -- I think it's important going forward with this work -- to really think about limitations. You're -- I mean -- it looks great in terms of what we're doing, but what are the things we're not doing whether it's who

are the states that aren't coming in, what are the sort of downsides of not standardizing, and what can we really say. So, it's kind of like the implications and the caveats all do become really important. And, while it's important to highlight the great and the promising, it's also just as important to think about what isn't working, what isn't quite right, and what are those nuances that we really need to be working on and can help with as a Committee.

MR. JOSHUA MILLER: I agree.

DR. JOSEPH BOCCHINI: Kellie, we'll give you the last. Then, we're going to have to move on.

DR. KELLIE KELM: Kellie Kelm. Having worked on the Timeliness Report where we decided proactively to define recommendations with end-points -- if you will -- that no states were really even able to collect at the time that we felt was the best way to look at timeliness, we knew that programs -- some programs were going to be more able to change their computer programs -- their software -- in order to get some information, and some states were just unable and were going to need to go through -- unfortunately sometimes -- bureaucratic processes to -- you know -- have to jump through hoops to

do that, and then, of course, work with their software providers to do that as well because in many cases we are told they couldn't collect.

And, I think -- what's interesting to me and as I look at the data and I think it's going to be really interesting to unpack it in our Committee and our workgroups -- sorry -- is I still think there are probably a number of states that aren't even collecting on time-critical. The number is much smaller than just the overall. And, it's interesting. Obviously, I see the collection -- collection and transport is where we're succeeding the most. The reporting results by 5 days and 7 days is where we're still lagging the most. And, I'm sure -- you know -- we can unpack that and see what the cases are. But, of course, it's -- you know -- second-tier testing. We've heard a lot about this. We talk about it a lot, and I think we can continue to do that. But, obviously, we also just have a smaller number of people that are -- you know -- and, I think it looks like the presumptive positives are the ones where we're struggling the most with the timeliness, and we might want to think about that in our workgroup and continue to have discussions on that.

MR. JOSHUA MILLER: And, I think having more data for those would be very helpful because what we found is that it's very difficult for states and their LIMS to record whether a disorder is time critical or not. Everything is recorded at specimen level, and it could be -- it's usually by analyte. And, so it's -- you know -- they're not able to change that within the program normally. They have to go to their vendor to pay their programmer time to create new variables and to collect the data in a different way. Laboratory information systems were not developed to report data to NewSTEPs, right? So, that's one of the -- or it's a -- you know -- even for the most part -- for a lot of the quality indicator improvement measures that they need internally.

And, in terms of those pre-analytic measures, those are where we're showing the greatest improvement, and based on the data, you can see that the collection times are stellar -- and, they have been stellar. And, so those probably aren't affecting any challenges in timeliness currently. But, it goes to show that it's not just looking externally to improve those things. It's also looking internally to improve internal laboratory

processes or extending those operating hours, and it's interaction of all of those that really lead to improvement in timeliness.

DR. KELLIE KELM: And, I wanted to add one note, that you have defined transport to the lab differently than what we did in the recommendations.

MR. JOSHUA MILLER: Um-hum.

DR. KELLIE KELM: And, we obviously then don't have that data and how the recommendations went out. And, it's just something that we're going to have to consider as we review it, and as we present it to the Committee is that it doesn't match the recommendations and what we might want to do about that going forward.

DR. JOSEPH BOCCHINI: So, we're going to give you the last, last question or comment.

DR. MELISSA PARISI: Okay. I have a question for you. This is Melissa Parisi. And, this is related to the actual point at which you say done, when we've actually reported those critical results or non-critical results out. Your New York State example was an interesting one, and I wasn't sure when the clock stopped. Was it when the pediatrician's office was notified? Was it when the ambulance went and picked up

the baby and took her to be treated for galactosemia, or was it at an earlier time point? And, do all the states record that information in the same way?

MR. JOSHUA MILLER: Yeah, we're trying to standardize that as well. So, for time-critical and non-time-critical presumptive positives, we want to define the time of report out as the moment, right? Because almost every Newborn Screening Program doesn't wait until they receive a final report with all the results on it -- you know. They see a presumptive positive for time-critical, and they're on the phone calling immediately. And, that's the point in time that we want that measure.

For all results, we're talking about when that final report is created and shipped out. But, equally as important, which is something we don't measure, right, is -- at least for the quality indicators at this point -- is the time between when that report is sent and when someone who is supposed to be reading the report is reading it, right, which is a much harder measure to actually collect. And, not for the quality indicators, but for a case data we collect -- that's all de-identified -- each case that's entered by a state also has the same timeliness measures recorded on a continuous

scale, and there we also report the time from report out to medical intervention, which is really what matters, right? And, so -- then we get that at the case level.

DR. JOSEPH BOCCHINI: Okay. Joshua, we have to move on to the next subject. But, Joshua, thank you very much. We appreciate that.

[Applause.]

DR. JOSEPH BOCCHINI: So, we are a little bit behind schedule, but we want to give each of the individuals who have asked to provide public comments the opportunity to do so. So, I would ask each of you to keep to the time that you were assigned in terms of the duration of your presentation. You will need to come up to this podium to make your comments.

The first on the agenda is Dr. Darryl Devivo, the Sidney Carter Professor of Neurology and Pediatrics at the Neurological Institute at Columbia University. His comments will address the compelling need for newborn screening now that there are -- there is an FDA-approved effective therapy for spinal muscular atrophy.

Oh, he'll be on the phone? Okay. If you'll open up Dr. Devivo's line.

DR. DEVIVO: Good morning.

DR. JOSEPH BOCCHINI: Great. We can hear you. Go right ahead.

DR. DEVIVO: Good morning, good morning, Dr. Bocchini and the members of the Advisory Committee. I thank you for the opportunity to testify today. As just mentioned, my name is Dr. Darryl Devivo. I am the Sidney Carter Professor of Neurology and Pediatrics, Director of the SMA Clinical Research Center, and Director Emeritus of the Pediatric Neurology Service at the Columbia University Medical Center in New York City.

Our clinical site is the largest in the United States. We have treated over 250 SMA patients. Additionally, we serve as a trial site for all of the SMA candidate drugs in the United States including the first approved drug for SMA called Spinraza or otherwise known as nusinersen. We also treated the first human being in the world with Spinraza in December 2011.

My testimony this morning focuses on the timely nomination of SMA to the Recommended Uniform Screening Panel.

During my fifty years of caring for children with neuromuscular disorders, there has been continuing efforts to develop an effective treatment for SMA. Until

recently, all of these efforts met with failure. Clinical trials of Spinraza started in December 2011 and culminated 5 years later in the broadest approval by the FDA. On December 23, 2016, the FDA officially approved Spinraza as the first effective disease-modifying treatment for this devastating genetic disease. Data from the randomized, sham-controlled, phase 3 trial in infants called ENDEAR showed a statistically significant reduction in the risk of death or the need for permanent ventilation in infants with SMA. These trial results were just published in detail in the New England Journal of Medicine on November 2, 2017.

Natural history studies both in humans and in model mice show that early drug intervention is required for the greatest effect in SMA. The natural history data indicates that there is only a limited window for optimal intervention for SMA type 1, the most common and severe form of the disease. This degenerative process is aggressive within the first six months of life. Motor neurons cannot be restored after being lost. Putting it another way, this is a true medical emergency where every day counts. This fact is supported by the recently reported ENDEAR trial in symptomatic infants where 75% of

infants receiving drug prior to 12 weeks of age gained motor milestones. In contrast, only 32% of babies treated after 12 weeks of age gained motor skills. The average age of clinical diagnosis for type 1 babies in the Cure SMA database is 4.9 months -- clearly unacceptable now that we have an effective treatment for this condition.

In addition, early results of Biogen's ongoing open-label study of presymptomatic infants called NURTURE demonstrates that infants treated proactively while clinically healthy achieved normal motor milestones in contrast to symptomatic infants who were started on treatment after the onset of symptoms. I have had the privilege at Columbia of caring for three of the infants in NURTURE, and they all are developing normally at ages 30, 18, and 16 months of age. Amazing as it may sound, all three are walking, running, and developing normally.

A recent pilot study of SMA Newborn Screening in New York State, supervised by Dr. Wendy Chung, now in it's second year, enrolled newborns from three hospitals in the New York Presbyterian Health Care System. Of the 3,826 babies screened in the first year, 1 infant was identified with a homozygous SMN1 deletion and 2 copies

of the SMN2 gene. This genetic profile allows one to predict the severe type 1 SMA phenotype as the likely clinical outcome. This infant was enrolled in the NURTURE clinical trial and treated with Spinraza at age 15 days. She is now age 16 months, meeting all normal developmental milestones, and free of any respiratory issues. In fact, she is now walking and running. This performance is in stark contrast to the natural history of SMA in which type 1 infants never make any motor gains after initial presentation, and significantly better than the recently published Endear trial results of symptomatic infants, as discussed earlier in my testimony.

In closing, timing of disease-modifying treatment has a profound effect on the expected outcome for SMA patients. Simply stated, early treatment leads to a better outcome. In fact, we have known about this rule since the early days of newborn screening and the treatment of phenylketonuria. Therefore, it is critical that SMA be added to the Recommended Uniform Screening Panel to permit presymptomatic infants with genetic SMA the best chance for a normal life when they are free of the weakness, the respiratory distress, the spinal

curvature, and the threat of death that predictably emerges postnatally in this untreated infants.

I strongly urge the Advisory Committee to approve the SMA nomination now that we have an effective treatment for this devastating disease, and now that we have clearly demonstrated the benefits of early therapeutic intervention. I thank the Committee for the opportunity to address you today and urge you in closing to nominate SMA to the Recommended Uniform Screening Panel. Thank you very much.

DR. JOSEPH BOCCHINI: Thank you, Dr. Devivo, for your comments and certainly your career of working with children with neurodevelopmental disorders. As you know, we'll hear an interim report today about the evidence review and our expectation is that that will be ready for the Committee to review and vote on in February. So, thank you.

DR. DEVIVO: Thank you.

DR. JOSEPH BOCCHINI: Next is Maria Spencer. Ms. Spencer is the Vice President of Policy and Advocacy at Cure SMA. She will discuss adding SMA to the RUSP as well.

MS. SPENCER: Good morning, everybody. Again,

my name is Maria Spencer, and I'm the Vice President of Policy and Advocacy for Cure SMA.

I'm testifying on behalf of the Spinal Muscular Atrophy Patient Community regarding the nomination of SMA for inclusion in the Recommended Uniform Screening Panel. This Committee is authorized under the Newborn Screening Saves Lives Act to make evidence-based determinations to add new conditions to the Recommended Uniform Screening Panel -- RUSP. In order to be added to the RUSP, a condition must: 1) Be identifiable within 1 or 2 days after birth; 2) Have a screening test available; 3) Benefit from early detection and intervention; 4) Have an effective treatment. We believe the application currently under consideration for SMA meets each of these criteria. We hope that the Committee's favorable report -- favorably reports SMA be added to the RUSP.

If one considers the fact that over 4 million babies are born in the United States, and nearly every one of them is screened for serious and life-threatening, heritable disorders and medical conditions, then imagine what adding SMA to state panels will mean for those babies newly diagnosed today.

In a little over a month from today, we mark

the anniversary of the FDA approval of Spinraza. Currently, no babies treated under NURTURE, the trial testing Spinraza is in -- testing Spinraza in pre-symptomatic infants has died or required permanent ventilation, while 39% of those treated in the trials after showing symptoms did. And in 68% of those in the control group, 100% of the babies in NURTURE are sitting and 10% after showing symptoms, and may are reaching age-appropriate milestones.

Children across the country are being treated by this life-changing therapy, which has shown positive results for disease, which is the leading genetic cause of death for children under the age of 2.

However, infants with type 1 SMA are currently diagnosed at about 4.9 months of age, after several months of a diagnostic journey. Therefore, Cure SMA, families, researchers, and others who have come before this Committee over the last year have said overwhelmingly that newborn screening combined with early therapy is the best chance to have -- is the best chance to have a change in the lives of many impacted individuals for the next generation and beyond.

In conclusion, we know there is a life-saving

treatment for SMA that has been shown to be even more effective when delivered pre-symptomatically. It is of the utmost importance that SMA be added to the RUSP to insure that patients receive treatment as early as possible to obtain the best outcomes and to save lives.

I want to thank the Committee on behalf of our community for the opportunity to address you today. Thank you so much.

DR. JOSEPH BOCCHINI: Thank you, Ms. Spencer, for your comments. We appreciate that.

Next is Cheryl Yoder, parent of a child diagnosed with SMA type 1. She will be sharing from her family's experience with SMA and the impact of having her son tested at birth and receiving Spinraza by 3 weeks of age. Welcome.

MS. YODER: Good morning, Dr. Bocchini and members of the Advisory Committee. Thank you for the opportunity to testify today. My name is Cheryl Yoder. I'm Mom to five kids, but I'm going to be talking about Ariel and Jace today.

I'm testifying on behalf the Spinal Muscular Atrophy Patient Community regarding the nomination of SMA for inclusion on the Recommended Screening Panel. Our

third child was born in December of 2012. Her two brothers, daddy, and I were so excited and in love with finally a baby girl, we named her Ariel Joy. There were no signs at birth that anything was wrong. She was perfect. However, it was during her first month of age that I just began to feel a nagging concern about Ari's well-being. It was small things at first. I couldn't really pinpoint it. By the -- it was at a well visit when she 4 months old that I expressed my now real concern to the doctor. Ariel wasn't holding her head up very well. She hadn't rolled over. She just seemed weak. By the time she was seen by Dr. Tom Crawford, a pediatric neurologist at Johns Hopkins, around 6 weeks later, there was really no question that something was seriously wrong.

In another 2 weeks, at 6 months of age, test results finally confirmed Dr. Crawford's assessment -- our girl had SMA. Ariel was with us for 16 precious months.

In July 2015, Jace was born. We had blood drawn immediately for testing, and when he was 8 days old, we learned that he too was affected with SMA, and we were devastated. But, timing could not have been happier

for Jace. Biogen had just opened a new clinical trial and it is the NURTURE study that has been mentioned for children just like Jace -- those who were diagnosed with SMA but as yet without symptoms.

He passed screening and received the first dose of Spinraza on the 25th day of his life. I could go on and on telling you of his exploits. He has -- we have celebrated milestone after milestone. He is now independently walking, talking, he climbs the steps, he sings, he is a very busy 2-year-old, and he has his sights set on running. You can imagine our delight and joy in this incredible journey that is worlds different from what we experienced with our daughter, only 4 years ago. We prayed to Jesus for a miracle, and we're watching in unfold in Jace.

I'm here today because it's my hope that pre-symptomatic treatment could be the starting place for every family that has to hear the words spinal muscular atrophy attached to their child's life. We knew to test Jace because of Ariel, but many children, like Ari, are months older before their diagnosis is made.

Scientific literature shows that children with SMA type 1, the most severe and most common form of SMA

and also the form that both Ariel and Jace have, don't get correct diagnosis until nearly 4 months after symptom onset. This robs them of the most important window for effective treatment, which is before significant motor neuron loss has occurred. Every day past without treatment increases the impact of SMA on that child and their family -- think of it -- for life. Because time is of the essence in treating children like Jace, newborn screening is the key to giving these children their best chance to thrive.

So, thank you for your time today and for the opportunity to address the Committee. Thanks for considering our nomination.

r: Thank you, Ms. Yoder, for your presentation and sharing your family story. We appreciate it.

Next, we have Ms. Kristin Stephenson, Senior Vice President and Chief Policy and Community Engagement Officer at the Muscular Dystrophy Association. For comments, we'll address long-term followup care and support for newborns identified with neuromuscular disease through newborn screening. Welcome.

MS. STEPHENSON: Thank you so much for the opportunity to be here today and to address the Committee

again, and welcome to those of you who are new to the group. My name is Kristen Stephenson, and I serve as Chief Policy and Community Engagement Officer for the Muscular Dystrophy Association, and I'm pleased to be here with you today as so many exciting opportunities in screening are moving forward for neuromuscular disease.

As an umbrella organization representing more than 40 different neuromuscular disorders, MDA is committed to the screening diagnosis and treatment of multiple diseases; Pompe, SMA, muscular dystrophy, and other disorders. And, we're proud to be working collaboratively with the clinician, research, and advocate community on screening for these three diseases and looking at other candidates as they become appropriate to bring to this Committee and to meet your vigorous review standards for consideration for addition to the RUSP.

What I would like to share with you today really builds on what you've heard about the importance of seeing SMA added to the panel and asking you to think about the very significant and strong support network and infrastructure that's already in place to help this community of newborns once they are identified.

For SMA specifically, as the evidence review process continues, and as you look at critical factors such as the treatment algorithm that's in development, we would ask you to take into consideration as well this infrastructure. One critical piece of that infrastructure is the network of care centers. MDA supports over 150 care centers around the country that are equipped to handle specific neuromuscular disorders including Pompe, SMA, and muscular dystrophy. And, those care centers are led by some of the thought leaders and some of the leading clinical researchers in the SMA and neuromuscular disease space and are the same locations where many of the clinical trials take place, where potential therapies are investigated for SMA and other diseases.

Thousands of individuals living with neuromuscular disease are seen annually in these clinics and hundreds have been dosed with the new treatments that are coming on market for disorders like SMA. While administration of these drugs can be complex and complicated, this system is in place, and we are working to help support the clinicians and the care centers to ensure that they have the resources that they need to

move forward with seeing newborns.

While there is work to be done, it is in process, and we eagerly await additional newborns being seen in the care center structure.

In addition to the care center structure, MDA has a disease registry that captures provider-entered data at 26 different care centers in 16 different states around the country that includes capturing data on spinal muscular atrophy. The purpose of this registry is to collect longitudinal disease information to help accelerate and drive therapy development and also to improve standards of care and clinical care.

The development of the registry has been a community effort that has engaged multiple stakeholders and thought leaders in this space including in SMA and which we look forward to sharing information from with this Committee and with the community.

This same care center and registry network supports SMA, Duchenne, muscular dystrophy, and other disorders, and we think it’s imperative that as you’re thinking about the big picture of services and support and what will happen to newborns identified in the SMA screening process, that there is a robust knowledgeable

body and network out there ready, willing, and able to help support this community from day one.

This is a community working together toward the common goal of newborn screening, as you've heard from the prior testimony this morning and in other meetings. We're very proud of the work that we have all been doing together and look forward to continuing that going forward. We hope that soon SMA will be added to the list of conditions on the RUSP and that additional neuromuscular disorders will follow. Thank you for your time and for your consideration, and I look forward to the conversation later today regarding the evidence review phase of SMA.

DR. JOSEPH BOCCHINI: Ms. Stephenson, thank you for your comments and presentation. I appreciate it.

Next, we have Annie Kennedy, Senior Vice President of Legislation and Public Policy at Parent Project Muscular Dystrophy. She will provide updates on activities of the National Duchenne Newborn Screening Effort.

MS. KENNEDY: Hi, good morning. On behalf of Parent Project Muscular Dystrophy -- PPMD -- I would like to thank the Committee for providing me the opportunity

to address you here today. My comments are on behalf of myself, on behalf of Michele Lloyd-Puryear, and on behalf of Dr. Jerry Mendell from Nationwide Children's Hospital, who together have been providing leadership for our National Duchenne Newborn Screening Efforts.

We are pleased to be presenting today on behalf of the more than 8,000 individuals estimated to be living with Duchenne muscular dystrophy in the US. But, more it is with an increasing sense of hope and urgency that I am here today on behalf of the thousands of babies who are yet to be born with Duchenne.

Duchenne muscular dystrophy is one of the most common, fatal, genetic disorders diagnosed in childhood, affecting approximately 1 in every 5,000 live male births. Because the Duchenne gene is found on the X chromosome, it primarily affects boys. However, carriers can manifest symptoms that range in variability from mild muscle cramping to cardiomyopathy to girls with the classic Duchenne phenotype.

While Duchenne is still a 100% fatal disease, we have demonstrated that immediate identification and early clinical interventions can add years, even decades, to an individual's lifespan. In the last year, our

landscape has changed and advanced significantly. We now have two therapies approved for use in Duchenne in the United States, and a third approved outside the US and currently under review by the FDA. We have a robust pipeline of investigational therapies advancing within clinical testing, and three separate gene therapy programs which are moving into the clinic within the coming weeks. Our Duchenne community's research pipeline is both robust and hopeful.

Prior to today's meeting, we submitted a written comment to the Committee that included a detailed update of our Duchenne therapeutic pipeline. From my oral remarks, I'll provide highlights from our National Newborn Screening Efforts only.

For the last three years, PPMD has convened experts in both Duchenne and newborn screening to build a National Duchenne Newborn Screening Infrastructure aimed at developing the evidence to support Duchenne newborn screening. The Duchenne Newborn Screening Effort has established the partnerships required to research, highlight, and implement nationwide newborn screening for Duchenne. Through these efforts, we have begun to create information technology tools to support the development

of screening and diagnosis technologies as well as to enable longitudinal studies to understand the health outcomes of newborns diagnosed and treated early.

Once developed and implemented, the tools will be available for population-based newborn screening and state newborn screening program implementation.

We have also been active in legislative efforts around the reauthorization of the Newborn Screening Saves Lives Act and Federal funding for US Newborn Screening.

Last month, PPMD convened a meeting of our Duchenne pharmaceutical and Duchenne community partners. The intent of the meeting was to provide attendees with the background needed to define the next steps for Duchenne newborn screening and outline a meaningful collaboration. We were also very fortunate to have representatives from two state laboratories as well as Biogen and Sanofi participate in the meeting and our discussions to provide perspectives from other relevant conditions outside of Duchenne and other pilot experiences.

To date, our efforts have focused on insuring that all families and clinicians have access to uniform educational and training materials and that those

diagnosed and treated are followed long term. We believe that the use of the centralized and established infrastructure for newborn screening pilots will accelerate the generation of evidence, the submission of a RUSP nomination packet, the review and recommendation for RUSP status, and ultimately nationwide newborn screening.

We will continue to remain committed to supporting infrastructure and leading policy efforts around Duchenne, and we are currently pleased to report that the outcome of last month's meeting was that our pharmaceutical industry community has expressed a desire to move the pilot forward as a consortia and those plans are currently underway.

Our Duchenne Newborn Screening Efforts have benefited significantly from the great expertise and generosity of experts and leaders within NIH, HRSA, FDA, CDC, ACMG, and the Newborn Screening community as well as our Duchenne community. This is an important inflection point for us in our community and one that we recognize we would not have reached without the guidance and support of all of you, and we are grateful.

Our Duchenne community is hopeful, but we also

know that we have an extraordinary amount of work that we must do to transform our existing National Duchenne Care and Support infrastructure into one that fits within the public health model for newborn screening, and we are working hard to accomplish this. Thank you for your efforts and for your time today.

DR. JOSEPH BOCCHINI: Thank you for your presentation. Thank you for providing an update to the Committee. I appreciate that of current activities and progress.

The next presenter is Ernest Shu. He is the Cardiovascular Product Manager at Admera Health and would like to present comments on genetic testing for inherited cholesterol and diabetes. Mr. Shu, is your phone line -- do we have his phone line open?

MR. SHU: Yes, sir.

DR. JOSEPH BOCCHINI: Great. We can hear you. Go right ahead.

MR. SHU: Thank you for that introduction, Dr. Bocchini. Contrary to the other public comments this morning, I am not talking about SMA or spinal muscular atrophy.

Good morning all, members of this Advisory

Committee, and members of the public.

My name is Ernest Shu and I'm the Cardiovascular Test Portfolio Product Manager at Admera Health, a CLIA-certified and CAP-accredited laboratory based out of New Jersey that utilizes Next-Generation Sequencing technology to advance personalized medicine. We focus our efforts in three main disease areas: pharmacogenomics, non-invasive cancer screening, and inherited cardiovascular diseases. Physicians and patients receive diagnostic test results in a distilled and manageable report, giving them the relevant information to make more informed treatment decisions.

A colleague forwarded me this invitation to attend the webcast and make some comments during this public comment period.

Along with the aforementioned clinical test offerings, I wanted to take the time to also announce that we recently launched two, direct-to-consumer tests on the Helix genetic testing marketplace. One test is for inherited high cholesterol, which tests for familial hypercholesterolemia, and the other is for inherited diabetes, which tests for Mature-Onset Diabetes of the Young or MODY. What's especially relevant to this

discussion and for the committee is that these tests can be used as screening tests to seek out those who are afflicted with these disorders.

Furthermore, the FH Foundation had their annual global summit in Miami about a month and a half ago, and they have openly made it their mission to advocate for screening at an early age. Our diabetes test is especially relevant right now because November is diabetes awareness month. Now, these diseases are often underdiagnosed or misdiagnosed because family doctors may not know about these diseases.

These two tests are currently available at a low price point of less than $150, without the need of insurance approval as well. In the near future, we will also launch tests for Alzheimer’s disease, Pharmacogenomics, and sudden cardiac death, which is important because we hear stories about these kids who die after their hearts just give out after overexertion from exercise or sports.

The Helix marketplace also offers products from other partnering companies in areas such as familial carrier screening, nutrition, fitness, ancestry, and entertainment.

I am aware that this committee may not openly advocate for any commercial test or company. On a personal level however, if anybody attending this two-day Advisory Committee on Heritable Disorder's meeting is interested and would like additional information, I welcome them to visit www.admerahealth.com or contact me directly at 908-222-0533. Thank you very much.

DR. JOSEPH BOCCHINI: Thank you for your presentation. We appreciate it.

That will conclude the public comments. We are running a little bit late, so we're going to delay returning, so you have a chance to eat, until 12:40. But, we want to start promptly at 12:40 because we have a busy afternoon agenda.

And, to close, Catharine has a couple of comments for you.

DR. CATHARINE RILEY: Yeah, thank you. Just some reminders. Again, there is a cafeteria right here across the pavilion for your convenience, and if you do need to exit the building at lunch, there will be escorts at the security from about 12:15 to 12:45 -- maybe a little bit longer -- since we're coming back. As Dr. Bocchini said, we're going to start promptly at 12:40.

We have a lot on our agenda for this afternoon, so we'll get started then, and thank you.

[Off the record for lunch at 11:50 a.m.]

[On the record at 12:47 p.m.]

DR. JOSEPH BOCCHINI: We're ready to start the afternoon session. And, we're going to start with a roll call.

Kamila Mistry?

DR. KAMILA MISTRY: Here.

DR. JOSEPH BOCCHINI: Mei Baker?

DR. MEI WANG BAKER: Here.

DR. JOSEPH BOCCHINI: Susan Berry?

DR. SUSAN BERRY: Here.

DR. JOSEPH BOCCHINI: I'm here. Jeff Brosco?

DR. JEFFREY BROSCO: Here.

DR. JOSEPH BOCCHINI: Carla Cuthbert?

DR. CARLA CUTHBERT: I'm here.

DR. JOSEPH BOCCHINI: Kellie Kelm?

DR. KELLIE KELM: Here.

DR. JOSEPH BOCCHINI: And, we have Joan Scott for Laura Kavanagh.

DR. SCOTT: Here.

DR. JOSEPH BOCCHINI: Dieter Matern?

DR. DIETRICH MATERN: Here.

DR. JOSEPH BOCCHINI: Cynthia Powell?

DR. CYNTHIA POWELL: Here.

DR. JOSEPH BOCCHINI: Melissa Parisi?

DR. MELISSA PARISI: Here.

DR. JOSEPH BOCCHINI: Annamarie Saarinen?

MS. ANNAMARIE SAARINEN: Here.

DR. JOSEPH BOCCHINI: Scott Shone?

DR. SCOTT SHONE: Here.

DR. JOSEPH BOCCHINI: Beth Tarini?

DR. BETH TARINI: Here.

DR. JOSEPH BOCCHINI: And, Catharine Riley?

DR. CATHARINE RILEY: Here.

DR. JOSEPH BOCCHINI: And, for the organizational representatives, Bob Ostrander?

DR. ROBERT OSTRANDER: Here.

DR. JOSEPH BOCCHINI: Michael Watson?

DR. MICHAEL WATSON: Here.

DR. JOSEPH BOCCHINI: Britton Rink?

DR. BRITTON RINK: Here.

DR. JOSEPH BOCCHINI: By phone.

DR. BRITTON RINK: Here.

DR. JOSEPH BOCCHINI: Thank you. Kate Tullis?

DR. KATE TULLIS: Here.

DR. JOSEPH BOCCHINI: Susan Tanksley?

DR. SUSAN TANKSLEY: Here.

DR. JOSEPH BOCCHINI: Chris Kus by webcast?

DR. CHRISTOPHER KUS: Here.

DR. JOSEPH BOCCHINI: Adam Kanis?

DR. ADAM KANIS: Here.

DR. JOSEPH BOCCHINI: Natasha Bonhomme?

MS. NATASHA BONHOMME: Here.

DR. JOSEPH BOCCHINI: Siobhan Dolan?

DR. SIOBHAN DOLAN: Here.

DR. JOSEPH BOCCHINI: Cate Walsh Vockley?

DR. CATE WALSH VOCKLEY: Here.

DR. JOSEPH BOCCHINI: And, Carol Greene?

DR. CAROL GREENE: Here.

DR. JOSEPH BOCCHINI: Thank you all. We're going to start the afternoon session with the panel discussing the implications of detecting carriers through newborn screening. And, this has been a subject that has -- that we have talked about at the last couple of meetings, and I think it's important because with varying procedures, and in many cases infants who are --

individuals who are carriers may be identified along with infants who have a particular condition.

So, since it's come up in the context of our previous conditions we reviewed and the current conditions we're reviewing now, this -- we decided that we would put a panel together to review the implications of carrier screening or carrier identification.

So, I'm going to introduce the individuals who are part of this panel. We're going to let them all speak and then start with the Q&A after they've completed their -- their subsequent presentations.

Our first presenter is Dr. Mike Watson. Dr. Watson will be offering the clinical perspective of carrier identification and reporting carrier status in the context of a population-based screening program. Dr. Watson led the efforts and developed the original Newborn Screening Panel. He is currently an adjunct Professor of Pediatrics at Washington University, School of Medicine, and the Executive Director of the American College of Medical Genetics and Genomics. He is also the ACMG Organizational Representative to this Committee.

Following Dr. Watson, we have Dr. Aaron Goldenberg. He will be providing an overview of the

potential ethical, legal, and social implications of identifying or not identifying a carrier in the context of newborn screening. He is an Associate Professor of Bioethics and Directive Research, Department of Bioethics at Case Western Reserve University, and he serves also on our Education and Training Workgroup.

Our third presenter is Dr. Michele Caggana. Dr. Caggana will be sharing New York's experience with the potential identification of carrier status in their SMA Pilot Study. Dr. Caggana is the Deputy Director of the Division of Genetics and Chief of the Laboratory of Human Genetics at the Wadsworth Center. She has been Director of Newborn Screening Program there for over 10 years. She is also involved in many national newborn screening efforts working with the CDC and the Association of Public Health Laboratories.

And then, as I said, after presentation, we'll open this up for questions and comments.

So, Mike, we'll turn the floor over to you.

DR. MICHAEL WATSON: Thank you. Thank you, Dr. Bocchini and Committee. You said the one word, and I actually have it here, and it's probably a misnomer, which is, we're not doing carrier screening. We're

actually doing newborn screening and finding carriers, and the goals of carrier screening and newborn screening are very, very different, and that's where the problems come in in figuring out really what we ought to be reporting out and following up based on really the things that are going to impact that infant clinically. And, it's really challenging once you look at the many ways by which carrier situations arise in the population.

So, we're each going to do about 15 minutes. I get the thrill of sort of the basics -- all these different ways you can be a carrier, depending on modes of inheritance and such. And, then just some nominal information at a clinical level about some of the conditions that raise issues in some of these different forms of inheritance. But, much of that clinical context will be in the next presentation that Michele Caggana does, talking more about this in the context of SMA, where it's clearly an issue we're dealing with and is up for Committee decision.

So, I have no disclosures to make. I'm not even allowed to have them in my job. I'm going to go through just the basics of what constitutes carrier status and different modes of inheritance, both

traditional Mendelian forms, which basically are how we defined carriers originally, but we have a lot of non-traditional ways for people to be carries and nonsymptomatic -- no signs and symptoms that have come with other modes of inheritance have been identified over the years.

We'll talk about the uses of this kind of carrier information. Clearly, your ability to detect carrier status is going to be dependent upon the technologies used in screening -- newborn screening that may or may not be definitive or have a high positive predictive value that they have identified a carrier state in an individual.

And, then we'll talk a little bit about some of the policy implications that many of the states have dealt with and will continue to deal with as other types of conditions come into newborn screening.

So, we'll go through -- I'm not going to cover every form of inheritance in 15 minutes -- we're not going to -- we don't have that much time. I'm going to try to touch on the ones that are most applicable in a newborn screening context right now, so the autosomal recessive traits where mostly we're thinking about single

nucleotide variance in individual genes, autosomal dominant traits we'll discuss briefly, but much of that's not in newborn screening, though they're coming and are starting to spread, X-linked traits clearly are becoming increasingly important with linked adrenal leukodystrophy being a newborn screening, Fabry disease, and then we'll talk about some of these non-traditional ways by which someone can be asymptomatic but still be "a carrier" different than the Mendelian forms of carriers. But, we have germline mosaicism in Duchenne muscular dystrophy -- no evidence -- it's a somatic mosaicism that isn't identified in any other cells but identified as a germline risk based on recurrence in a family. We have copy number and genetic phasing of genes that are -- we see in conditions like SMA. And, then we have repeated sequences where essentially the pre-mutation version of a Fragile X triplet repeat expansion puts somebody in this "carrier state" and at high risk for expansion and having affected offspring.

And, some conditions actually bring more than one of these into play. Certainly, SMA has both the phasing issues of the genes as well as single nucleotide variations, and both of those in about 5% of cases. So,

we'll touch on some of those. This is like back to basics 101.

Autosomal recessive -- I think everybody is reasonably familiar with this. Both parents are carriers, have one copy of a gene with a pathogenic variant in it, and when presented homozygously to the -- to the fetus -- would have an affected individual 25% of the time. Two carriers in that next generation are the risk factors, and then one that would have the homozygous for the normal version of the gene from those two parents.

Newborn screening comes at this often, typically biochemically where sometimes we actually can differentiate based on activity of the enzyme that a carrier exists. But, most of the time, there is a fair bit of overlap with either the abnormal population or with the normal population that makes it much more difficult to be definitive about carrier status.

Where more often it is coming into play nowadays is when we have a molecular test as a second tier. So, IRT and cystic fibrosis screening go into a molecular test at the second tier, begins to detect carrier states, and it's very much more difficult for the

states to deal with this kind of a problem because we have a huge problem of variance of uncertain significance. So, if you have one definitive pathogenic variant -- so you had IRT that got you into that next step -- now, you have one clear pathogenic variant and now you're probably going to be told that you have at least one -- you may have a variant of uncertain significance, and you're going to have to go to a more definitive test in the diagnostic center to try to sort that out.

We also have the lysosomal storage disorders coming into newborn screening, most of which have a second tier of a molecular test. Unlike many tests where that second tier has not -- well, it's a second tier for me when it's in the newborn screening test algorithm. More often, it's tested in a diagnostic setting where it wouldn't be considered a second tier, because once you've told the family, you're in a different setting. The Newborn Screening Programs may deal with it in the newborn screening as a second tier in order to hone down -- hone down on the number of people who are going to get reported out of the program.

All right. So, the autosomal dominance --

there are actually not a lot of those involved in newborn screening yet. These are things like Huntington's disease as an example of an autosomal dominant. Familial hypercholesterolemia is one of those we may eventually see in these kinds of programs. Neurofibromatosis. Right now, we don't have to deal with much of this in the newborn screening context, but in this context, all it takes is one chromosome with that pathogenic variant in the gene of interest that gets passed to a child for that child to be clinically affected with the disorder.

Penetrance is big in autosomal dominant disorders, unlike autosomal recessive disorders. So, we have much more variable penetrance has been documented clearly in the autosomal disorders, and among those who are non-penetrant, they may be clinically -- they're clinically unaffected, but we also have a much higher new mutation rate in the dominant disorders, so the parent won't always be a demonstrable carrier of the abnormal gene. Because of this new mutation rate, it might arise in their germ cells.

X-linked recessive is one that's beginning to hit us more frequently now with Fabry in many states increasing and others sort of candidates for newborn

screening. This is a situation where in the carrier female -- and this is probably one of the more complex issues we're dealing with in some of the lysosomal storage diseases and other X-linked disorders -- the female carriers who have one copy are at risk for disease because of the lionization effect of X chromosome and activation. You know -- you can imagine a bell curve of cells in an individual -- in a female where half of the cells may have one X chromosome active -- the other half the other X chromosome active. But, it's a bell curve, so there will be some people in which the luck of the draw left them with the abnormal -- the X chromosome with the abnormal gene being much more predominant in their cells and therefore more likely to express the disorder, and then the other end of the spectrum where they got the luck of the draw of having mostly the X chromosome with normal allele on it being expressed at most of the cells and therefore clinically normal. And, these are often milder because of that sort of distribution of cells in X in activation. The disease is often more mild in the females than it is in the males.

And that actually can be one of the central themes of problems in figuring out what carriers are

important and trying to understand both which ones are clinically relevant because they can certainly have a severe form in a female, but there's lots of milder forms that may be present, and we begin to have to think about really what is the target of screening. Some of these decisions are already being made about some of these that some types just don't get reported out and others do.

So, in the non-traditional carriers, think of something like Fragile X. It's not in newborn screening but has been proposed as a candidate at times. The individuals who have pre-mutations in these triplet repeats are at risk of myotic instability and generating that full mutation that can lead to a Fragile X child. But, what we've learned over the years -- actually much more recently -- I did a lot of Fragile X research early in my career, and the number of families I sat across the table from and never saw fathers with ataxia and having these neurological disorders in the grandfathers of these families. It wasn't until much more recently that they were sorted out. But, it's clearly something that occurs in many -- in the pre-mutation carriers of Fragile X, and it's something we'll have to think about. So, it's going to be a disorder by disorder kind of process to figure

out what are the associated conditions and the severity, and do we want to find them in newborn screening or not because carriers are obviously much more common than the clinically affected individuals.

Another version of this non-traditional carrier status arises in spinal muscular atrophy. It's actually a situation where this part of the Chromosome 5 has the SMN1 gene and the SMN2 gene that's missing a critical X on that makes it much less functional in the vast majority of the cells. But, because of the similarity between those two genes, we get a fair bit of recombination in the geno that can leave you with two copies of the SMN1 gene on one chromosome, no copy on the other one. You do a molecular test, and they look clinically normal because they've got two copies, but they are at risk of having a child -- because of that chromosome that has no copy of the SMN1 gene on it. And, the same phenonemon occurs with the SMN2 gene, which modifies -- modulates the clinical severity of the presentation of SMA when you have two SMN1 gene problems. The more SMN2s, the less severe the condition becomes. And, those range from 0-5 in individuals -- the number of SMN2 genes they might have because of this -- this

recombination between repeated sequences that can occur.

Somatic mosaicism I mentioned earlier, but this is -- we see this in Duchenne muscular dystrophy, which is a condition that's becoming a candidate for newborn screening where they carry the gene of -- the gene mutation in only cells in the germline. There are also versions where you can see it in other cells, and it's a mosaic in other somatic cells, but there's a subset where it's only in the germline cells that have predispose of the risk, and these became apparent when an individual in whom you couldn't document that they were carriers ended up having another affected child, and it sort of gave us a recurrence risk that we present to these families when they come for genetic counseling.

So, as I said, the real issue that we're going to have to deal with is the clinical issues. They are milder conditions often when one is a carrier than in some of these modes of inheritance than others. So, figuring out in sort of that newborn screening model where the goal is to identify the individual or the infant that you want to detect because you have an intervention available -- much less concerned about whether or not there are reproductive or familial

implications of finding that carrier status because the goal is not carrier screening and carrier identification -- it's newborn screening to identify the infant that needs to have intervention that could ameliorate the clinical phenotype.

So, that clinical relevance, I think, is the -- is one of the things to the individual that distinguishes the newborn screening perspective, but certainly this information is valuable in a familial context where reproductive decision-making is often what one wants to be able to empower with knowledge of a carrier situation in a couple where both are carriers and may be at risk of having an affected child.

But, it also has implications for cascade testing. You know -- I really recoil when I hear people use the words cascade screening. Cascade basically means you've identified an affected individual in a family that now makes that family at very much higher risk for other individuals having whatever it is you might be looking for so you can cascade out through the family to get at others. And, it turns out for those who have suffered through the Hardy Weinberg Equilibrium, it basically ends up saying that the rarer a condition is, the more likely

that you find a carrier or an affected individual -- that you'll find a much larger portion of that individual -- of individuals with that condition within that family. The more common it becomes, the more distributed it is across the population.

So, cascade sort of testing is most effective when --it gets more and more effective as the condition gets rarer and rarer because you're able to detect more people from having found one person who has the condition or is a carrier of the condition.

And, then I've already mentioned -- you know -- why we do newborn screening. It really is starting in that infant who is treatable. And, it sort of leaves you with the ethical dilemma that's been talked about infinitum, and I'm sure that Aaron will touch on it when he speaks. But, it's basically, if it's not clinically relevant to the individual, do we either withhold that incidental information that's been detected in the newborn screen, which might be labeled as paternalism -- or do we require somebody to possess that information, and both are difficult choices to have to make. And, sometimes sort of the facts of how everything is playing out as we collect data will inform us about which is the

preferred outcome. You know -- if we're going to bury the system in carriers, we may make a financial decision about them, and we certainly have significant workforce issues arising already with many carriers of XALD and other conditions being put out into the clinical genetic community for followup, and those workforce issues are already leaving many clinical geneticists to dread the next condition that comes into newborn screening that's going to continue to increase the demands on that relatively small workforce.

So, when is carrier status clinically relevant to the individual? So, in the autosomal recessive, this is actually a typo here that can be severe form was supposed to be on the line below. But, in the autosomal recessives, they -- they rarely show clinical phenotype related to the condition. You may be able to show biochemical evidence, but rarely will you -- much less frequently will you show any clinical evidence.

The X-linked recessives are the ones that's really hitting the community because of the clinical implications for those females who are carriers -- some of whom could be severe and many of whom will be milder forms of the disease or unaffected. Significant

portions, though, of them may have some milder form of the condition, and -- you know -- it leaves us having to weigh the balance of whether we want to identify them or not. Are they the target of newborn screening or not? And, those are the issues, I think, that are going to have to be sort of considered in every condition that you review in the future for inclusion in Newborn Screening Programs.

And, then we have these pre-mutation repeat sequence issues of later-onset disease. And, certainly many of these milder forms that we may see in females may be later onset of the condition than you see in the classical form that you may see in the male -- certainly the Fragile X tremor-associated syndrome that you see in many of the older males and females, frankly, who have pre-mutations for Fragile X -- the females sort of having that pre-mutation on one of their Xes and then getting that luck of the X inactivation draws to which of the two X chromosomes is active and the males having the pre-mutation with this later onset version of Fragile X tremor associated syndrome.

So, when you think about this a bit, I just -- I'm not going to try to cover every way carrier screening

may have implications in newborn screening -- and you'll get a lot more information from Michelle when she speaks. But, I just wanted to give you a few examples so you understand how it can impact the workforce and the population that we screen.

Sickle cell anemia -- 8-10% of African-Americans are carriers for an S allele, so a very large population potentially that could be -- that's an autosomal recessive that could be brought to the clinical community. Most Newborn Screening Programs establish a program -- at least those that report out these -- only report out the carrier status. You know -- there's certainly questions as to whether we should be identifying them. If we could actually identify them and capture them in electronic health record environment where that information was available at the time they decided to go into -- you know -- high-exertion sports and exercise -- which seems to be where there may be some risk associated with that carrier state for an S allele -- you know -- it would be valuable information. Our EHRs are a far cry from being able to provide that service yet.

Back in the 1980s, the Foreign or the Counsel

of Regional Networks, which has been replaced by a couple of other things that are now the Regional Genetics Networks that HRSA funds -- they recommended that the carrier status for sickle cell be reported, and it was for interesting reasons. Part of the reason was that they were concerned about the access to health care of this population. And, they even made the information available to both the providers and to the families for concern that they weren't getting into health care services.

And, then there is certainly the -- you know -- I've already mentioned the high-exertional exercise issues that carriers in high altitudes, which led to enormous problems with sickle cell screening back in the 70s that I won't go into.

Cystic fibrosis -- you know -- we report on the second-tier molecular results where we have with the one clear pathogenic, sometimes two clear pathogenic variants, which are more straightforward. But, when you have one and then you have -- you know -- every condition that seems to go into newborn screening, we have not gotten to the point yet where we're able to have curated that particular gene variance for their pathogenicity.

And, it's something -- I'm one of the participants in the ClinGen Resource Project, which is targeting really the curation of -- the clinical curation of variance in genes to try to get a better handle on what's pathogenic, what's benign, and reduce that number of variance of uncertain significance that causes a huge problem in the Newborn Screening Laboratories when they have to deal with this molecular information.

And, there is a lot of variability in conditions based on ethnicity of groups or the population background or origin of that particular group of people that make the incidence quite different. Cystic fibrosis -- 1 in 30,000 in a Chinese population; 1 in 4,000 in a Caucasian population; so very different risks of being carriers for the same condition in different groups.

X-linked adrenal leukodystrophy -- we mentioned -- 1 in 17,000 births, about 20% of females have some symptoms by adulthood. So, it's that whole clinical issue of are we -- do we need to bring them in as positives in the newborn screening, and most are -- they're being referred out -- and, certainly in California.

And, then, I think it really does boil down to

the clinical issues associated with the individuals who are carriers understanding what proportion of them may have that severe form that it was the reason we screened in the first place versus those that may have one of these milder forms of disease, and then whether whatever form they have is actually the treatable form. And, then the issues of whether or not our workforce is going to be able to digest the volume that's coming to it because right now, as I said, we need to -- we're going to have to find ways of boosting this workforce or sharing some of the labor in ways that will reduce the impact so we -- because certainly the number of conditions that are candidates for newborn screening right now are pretty -- a pretty steep curve to get up, and our capacity is really quite limited.

So, general recommendation has been not to test children unless the test result is of direct benefit to the child. But, we do newborn screening, obviously, on children or making decisions about whether or not we're going to report out these carrier statuses or not. And, typically the decision is made around whether there's direct benefit to that child by having been identified as a carrier, so we're back to those clinical issues.

I think I already mentioned how most of the Newborn Screening Programs approach reporting of carrier status. So, on that, I'll stop or else I could go on all day, but I won't.

DR. JOSEPH BOCCHINI: Thank you, Michael. We're going to bring you back up after the other presentations.

DR. GOLDENBERG: All right. I'm a little shorter, so I've got to move the mic. Nope, no problem.

All right. Thank you, Dr. Bocchini, and thank you to the Committee for having me today. Nothing says post-lunch excitement like ethics. [Laughter.] So, we're going to do some ethics.

My goal is not to be here as an ethicist to say this is what we should be doing or should not be doing. That's not going to be helpful for our conversations thinking about SMA or thinking about other conditions. What we think will be helpful is for me -- and the goal for this presentation is to give the Committee and for all of us to think about some tools to have conversations about bioethics and carrier screening to give us some language that we can be using as we start talking about whether or not it's appropriate to be giving carrier

status back.

Mike just gave a really amazing talk looking at all the complexities regarding the kinds of carriers that we may be returning results to and how much that complexity may affect our decision-making at the state level.

I'm going to start by really simplifying that very complex conversation by looking at this kind of dichotomy here, which is to return carrier status or not to return carrier status. Clearly, those decisions are going to be condition specific. Clearly, they're going to be mediated by the probability and severity of the potential health impacts of knowing that information, the potential reproductive and family planning options that may be available to families who receive carrier status, treatability of those conditions, patterns of inheritance which we know are going to be complex for many of these conditions, and actual age of onset. But, again, I think finding our way in kind of an ethical, legal, social world between these decisions of whether to return or not means needing to be very careful about these other mediating factors or moderating factors that will help us to guide those decision processes.

So, I want to start here by saying we need to think about the complexities of this spectrum about whether or not to give or not give when thinking about ethics.

So, let's start by just looking at a couple of kind of what I'm calling primary ethical principles that I think are crucial for thinking about whether or not to give carrier status back in Newborn Screening Programs.

First, we talk a lot about autonomy, right? And, we'll talk a little bit about parental autonomy. I'll actually end the presentation talking a little bit about parental autonomy. I want to talk a little bit about A Child's Right to an Open Future, an ethical concept that has been -- did not start with genetics, but has been -- you know -- used frequently to think about -- for example -- adult-onset testing in childhood. We'll talk a little bit about best interest standards. And, the hope is that as we kind of go through the potential ethical implications of giving this information back, that we can use these three kinds of ethical principles to kind of guide our conversations.

But, I want to start by thinking about the social implications. I'm going a little out of order in

my ELSI, but I want to start by talking about the social implications, because I think it's the things that I think we're most familiar with. It's the -- it's the area that I think there's been the most research, even though there's not a lot.

And, I want to start by talking a little bit about -- Mike mentioned the sickle cell screening in the 1970s. This was a program that started as a National Initiative to try to put more attention on sickle cell screening here in America, and it led to 12 states creating mandatory laws regarding -- regarding sickle cell screening. Unfortunately, many of those laws were written without adequate education, without adequate counseling, without adequate information for people using that, and it led to a lot of stigmatization and confusion among both African-American families and others about what it meant to be a carrier. It led to -- for example -- carriers being excluded from military service in some cases. It led to a number of other stigmatization problems, and I think we can take a look at history and make sure and I'll -- you know -- I think it has to start with that education, and it has to start with that communication because we don't want to repeat some of

those mistakes if we decide for various conditions that we want to be returning carrier status.

So, that kind of leads to the second point, which is the potential stigmatization or impact on families by either knowing carrier status or having misunderstandings about carrier status. There is some potential for impact on self-esteem or self-image. We know there is potential worry about discrimination based on even -- you know -- based on disease status and potentially carrier status. We do have GINA -- the Genetic Information Non-discrimination Act -- a very good law that protects people against discrimination based solely on genetic information. But, there are some limits of GINA.

So, for example, it doesn't cover long-term disability insurance. It doesn't cover life insurance. If you work for a company that has less than 15 employees, you're not covered. It doesn't cover certain parts of the military, right?

So, we need to be very careful about our relying on particular state or federal laws that will protect people against discrimination for two reasons -- one, because there are limits, and two, because even if

there are laws that protect people, the empirical evidence shows that many people who undergo genetic testing are still concerned about discrimination. And, I think when we think about carrier status, we need to remember that.

There are other potential psychosocial and psychological impacts. There have been a couple studies. So, this study that was done in the UK found increased anxiety among parents who received carrier status results from newborn screening for CF and sickle cell; although, I think it's interesting to get back to this question of education. When you look at what that anxiety was tied into, much of it was not tied into the actual carrier status per se, but rather the method in which it was returned -- the method in which it was given back, and that's something that I think we need -- that we'll come back to at the end of the presentation. But, it's clearly an important piece of giving information back in an ethical -- in an ethically justified way and is in a way that actually helps parents understand the information and feel comfortable with the information.

Another more recent study by Don Bailey, one of our close colleagues and his colleagues and Cindy Powell,

found some levels of increased anxiety among -- among mothers who received pre-mutation carrier from -- through -- in a potential newborn screening situation. But, when compared to a group of non-pre-mutation carrier mothers, that -- there was no -- there was no statistical significance in terms of the increased anxiety.

But, these are some of the only studies that are out there on this, and I think there's a need -- a really crucial need for more research on the potential impacts of this information to make ethically justified decisions.

So, let's take a step back and think about the different kinds of outcomes that Mike talked about in terms of the potential impact of carrier status on -- on newborns and families, the first of which -- and, again, I'm simplifying this just for us to kind of think through some of these issues -- would be what happens when you have carrier status where you -- where you will potentially have health benefits in childhood, right? So, you have carriers that may have health effects in either early childhood or later childhood. And, so we could make the argument that there's still the benefit of early detection. You can do better screenings and

interventions. You can think about cascade testing for families. And, that would be an argument to return carrier status when there's a potential for health benefits in childhood.

Others might say, well, we have all these other things that we talk about -- the potential harms of misunderstanding of that status, potential discrimination, unnecessary screening, potential anxiety or worry. But, I feel like within kind of the context of ethics, that the best interests of the child would override any of those concerns based on the kind of ethical guidance that we have as newborn screeners in giving information back that will help families -- that will help children. And, so I would say that even if we were worried about all these things like discrimination, like stigmatization, best interest standards would probably in almost every case override that if we can show that the health benefits in the child may be there. And, here's where uncertainty comes in, right? And, there's always an issue of uncertainty when we think about ethical decision making. What happens when we don't really know? What happens when we're not sure whether or not those health benefits will be there, and

how do we make decisions with states to do those things?

So, it gets a little bit more complicated when we start thinking about potential health benefits in adulthood, right? So, I think we can all make arguments that we want to return carrier status if we think there may be potential impact on adults. It increases awareness of risk. We think that's a good thing. It can potentially increase screening or potential interventions for adults. But, we also have, again, the same kinds of things that we talked about before -- the potential harms of misunderstanding, potential discrimination, unnecessary screening potentially, and potential anxiety and worrying knowing that information early in life before one becomes an adult. And, this is where a very commonly used ethical discussion happens, which is the Child's Right to an Open Future.

And, I want to talk a little bit about Child's Rights to an Open Future because I think it will help us as we start thinking about the potential use of information for potential health benefits in adulthood, all right? So, the Child's Right to an Open Future is not a new concept. It was first discussed by Joel Feinberg in this book on *Child Rights and Welfare* in

1980. The idea behind the Child's Right to an Open Future is that we as adults -- we as -- and as government officials or as clinicians -- need to hold particular rights in trust for children that should be saved until they're an adult. That their autonomy -- their adult autonomy -- is not well developed yet -- they're children. But, that doesn't mean that we can make decisions that may impact their decision-making as an adult, right?

So, it's focused on autonomous decision-making of the child when they reach adulthood, right? The most common use of this in medical fields is when parents may refuse -- for example -- chemotherapy for a child who is sick based on religious reasons. We typically will not allow those decisions to be made, because it infringes on the child's right to make those decisions in adulthood. In 1997, Dena Davis, one of my colleagues at the time at Case Western, talked about applying this idea of an open future to genetic testing. And, it's been used quite frequently to make arguments against allowing for testing -- for example -- children for adult-onset conditions based on the idea that we're taking away the child's autonomous right as they grow to make decisions about

understanding genetic information about themselves when they come of age, right? And, so that decision would be taken away if we were to give that information to -- for example -- to a parent and would take away a child's autonomous right to make decisions about genetic testing in the future.

Many organizations -- ACMG, AAP, and others -- have discouraged returning carrier status without health benefits to children based on the idea of a Child's Right to an Open Future -- the idea that withholding that information promotes choice as adults.

But, I want to take a step back, and I want to problematize that a little bit in rare disease. When we're talking about -- for example -- breast cancer or heart disease, I think you can make a very good argument that a child, when they reach a certain age, can make decisions about screening on their own. But, if you have a child without a particular family history, the idea of screening for rare diseases when you reach adulthood may not be there. So, for example, if you're thinking about X-linked adrenal leukodystrophy or you're thinking about other conditions, the argument for the Right to an Open Future, I think, is lessened given the fact that children

may not think to get tested as an adult. It's not going to be something that's going to be in their face, and it may only occur when symptoms happen. And, so the idea of getting tested pre-symptomatically, I would say is problematized within the context of an open future given how rare disease screening happens.

Now, this is changing a little bit because -- please ignore my creative use of screen without my typo there -- so, the question is, will adults get screened for these rare conditions without a family history or particular group membership where you see higher rates of a particular condition. We are seeing higher rates of what people are sometimes calling Universal Carrier Screening or Expanded Carrier Screening. So, rather than just doing a small -- for example -- Ashkenazi Jewish Panel or a panel of three or four conditions -- many families are choosing to have carrier screening before having children for a hundred or two hundred conditions.

Many -- actually, I think all of the major companies that are offering Expanding Carrier Screening have included many of the conditions for which this Committee has either already decided or is in the process of deciding or potentially in the future will decide

whether or not those should be on the RUSP. Those include CF, Pompe, MPS1, X-linked adrenal lipodystrophy, Fragile X, Duchenne, and SMA. All of the major providers of Expanding Universal Carrier Screening have those conditions on them. So, it could be that as more people start using this kind of information that they will get screened as an adult, so we don't have to worry as much giving that information in childhood.

Although, I would like to just raise some equity considerations, right? Some of those tests can be expensive. Not everyone has access to that -- that information. And, not everyone has access to genetic services necessary to understand that information afterward.

So, this slide kind of goes up and down a little bit in terms of its ethical implications, but I do think that we need to confront how rare disease affects this idea of an open future and how rare disease may put us in a situation where an argument for an open future isn't as strong when we're worried about adults who would never think to get screened as adults, let alone being aware of the potential risk.

So, one of the maybe more stickier ethical

issues has to do with carrier status when reproductive decision-making is either the only or one of the only benefits to gaining this information, right?

So, arguments to return carrier status when reproductive decision-making is the key aspect of that return of that information, right? So, there may be reproductive benefits to parents and families to make decisions about adoption, pre-implantation genetic diagnosis. There may be reproductive benefits for newborns as they grow and make choices for their own lives about reproduction. But, the concepts -- you know -- this works if we agree that we can think about expanding benefit in newborn screening to include reproductive benefits beyond just benefits to newborns.

There are potential social implications of this, back to -- you know -- the kind of social implications we were talking about early on -- potential harms from misunderstanding, discrimination, potential anxiety or guilt about this. And, I guess the question is, does this information -- if it’s focused on reproductive decision-making -- move us away from ethical justification for mandatory Newborn Screening Programs in states if the information is purely about reproductive

choice.

A number of my colleagues in the Ethics Watch just a few years ago published a paper where they kind of problematized this issue of expanding newborn screening towards reproductive benefit, and they kind of weighed both sides. While there's clearly potential benefits to families, they did question whether or not this moves us away from some of the core values that newborn screening was based on as we move away from potential benefits to individual newborns.

But, I think this is an open question, and I think it's important for us to think about the family all together and what the information can do for families.

I would like to talk a little bit about parental autonomy and rights. So, in ethics and in some of the conversations that I know you all have had, we talk about the right to know versus the right not to know. And, one of the questions that has been raised by ethicists thinking about carrier status not just in newborn screening but generally in other screening programs is, can programs force parents to know their carrier results, right?

If we don't have a consent process and this

information is giving back information to families, are we subsequently taking away a parent's right not to know this information? And, I think when we see potential health benefits for newborns, we're maybe not as concerned about maybe violating that right not to know. If I give you information about a child who potential has a serious condition, you may find something out about yourself. But, for best interest of the child, we don't worry so much about giving that information given the importance of that information for that newborn.

So, yes. Parents will understand that they're carriers and have that information whether they wanted it or not. But, the goal is to protect that newborn. If that goal is not there, and the carrier information is purely for -- you know -- purely for just knowing carrier status -- if there's not a potential condition involved -- are we potentially violating a parent's right not to know their genetic information? And, I think this raises a question of paternalism in public health and whether or not states are in a position to say, we think this information is important enough to override one's autonomy.

That happens quite a lot. It's not -- you know

-- sometimes we think about autonomy as this core value -- and, it is -- that can't be violated, and that's not true. We -- we have a variety of public health programs, a variety of situations where we override one's individual autonomy when we think there's common good -- for example -- when we think this information could save lives.

And, so one of the question is, when do we make that decision in newborn screening to potentially override and make -- basically force families to understand this information, or should we be thinking about this as a consent process. And, the question is, if we were to move toward a consent process for carrier status, would that solve all these problems?

So, for example, what about parents who have the right to know? We want to kind of impose their right to know. People might say, look, I'm a parent, I want to know this information both about myself and about my newborn. And, then we have to kind of get into some of the questions that Mike was raising about personal versus clinical utility, and who gets to decide and what that information is used for.

A recent study in the UK that did focus groups

with parents about whether or not they had the right to know carrier status from cystic fibrosis screening in newborn screening found some very interesting information. All of the members of the focus group -- so, every participant in the focus group -- said they would want to know carrier status. Every one of them said, absolutely, we would want to know carrier status from newborn screening. But, all of them also said, but we think it's our right that if we didn't want to know to make that choice. And, that's an interesting conundrum for us to be in, which is that many parents want to know this information, but they also want to have that choice. And, I think that's where we kind of get into this question about whether or not it's -- this would be a time where consent processes would be appropriate.

So, this gets back to this original question that I had, which is to return or not to return, and, questioning whether or not there are some possible middle roads.

So, one I know that's been raised by some -- by some scholars is to only screen targeted groups. That raises all sorts of questions about the universal nature of screening and I think raises some potential concerns

about that. There is potential implementation of a consent process for carrier status where you don't consent to the newborn screening but you would consent to receiving carrier status. There's a proposal in a few papers to put carrier status in medical records that would be revealed later -- not revealed to parents at the time of screening.

But, I think we need to think about conditions and specific policies given how different these modes of inheritance may be for conditions and what the potential impact of that information may be.

But, this is related to, I think, an important programmatic question that I know many people in the audience and many people on the Committee may be thinking about is that there's a difference between the right to know or not to know and the right to return or not to return versus to detect or not detect carrier status. I know that's something that programs can struggle with. I think Michele is going to talk a little bit about this after.

And, so the question is it is ethical -- for example -- to filter out carrier status, and is it even possible with some new technologies. Some work that Beth

Tarini and I have done on genomics in newborn screening, I think relates to this question. So, these quotes are really about genomics, but I'm putting them in here because I think they're apt for what we're talking about, which is potentially a conflict within professional ethics. Where in our study, we found many program officers of Newborn Screening Programs felt very clearly that we shouldn't just be giving certain information back -- we need to be very clear about the definition of an actual result. We need some guidelines about what our actual results understand -- that just because we can do a test doesn't mean we're prepared to deal with the results. Maybe we shouldn't test public health systems -- a little bit more concern about what to give and what not. While we also had quotes from people who said, ethically I think most programs feel that they need to report what they find -- and, as a laboratory and you report what you find. To window something out means to me that you're maybe missing something that might be a very key piece of information for a family, and how do you live with that?

So, I do think there's a potential in professional conflict, which is what do we -- what

decisions do we make about detecting versus not detecting carrier status, and I hope that with Michele's talk, we can have an open conversation about that.

I'll end by saying that balancing whether or not to give carrier status needs to be mediated by a number of things. One -- and, I think most importantly -- is communication and education. We have to do a better job of educating the -- you know -- both our -- our own community and parents about the potential impact of carrier status. Information technology as it changes, the ability to put -- for example -- carrier information that might be revealed later in a medical record would be important to understand, and to understand the potential for consent processes.

This paper, which was just published a number of years ago, looking at 270 parents who received either carrier status from cystic fibrosis or sickle cell found about 35% had very negative responses to receiving the information, and about 31% to 32% had very positive reactions to receiving carrier status. When they looked at the factors associated with either negative or positive anxiety or reactions to carrier status, it was incredibly dependent on the kinds of messages that were

given during the educational procedures -- the traits of the provider, the atmosphere and the setting in which the carrier information was revealed. So, we know that the impact of this information can be changed based on the kind of information given to parents, how that information is conveyed, and who is doing the conveying.

So, I do think that this idea of -- the importance of education cannot be understated in dealing with some of the ethical implications of revealing carrier status.

And, finally, I would just like to say that -- you know -- there are four, five, six papers on these issues, but it's clearly not enough, and it's definitely not enough if you want to start thinking about condition-specific ethical implications. There is a need for more ELSI research, and I think there's a need for doing that kind of ELSI research as part of newborn screening pilot studies.

There's an upcoming NBSTRN paper that Jeff Brosco and Michele Puryear, and the NBSTRN Ethics and Legal Workgroup has been working on, laying out ethical questions that could be asked within the context of newborn screening pilots. Our hope is that I can come

back maybe in -- you know -- the future and talk about that paper, which is a much more general paper. But, I do think that it's time to include many of these questions in the pilots that we're using to make informed decisions about adding conditions to newborn screening.

I'll thank my collaborators and end there. Thanks.

[Applause.]

DR. JOSEPH BOCCHINI: Thank you, Aaron. That was great.

DR. CAGGANA: Good afternoon. I wanted to thank Dr. Bocchini and Committee for inviting me to talk about our pilot study and sort of carrier screening in the context of newborn screening and how we deal with them in the various tests that we do, and also to Aaron and Mike for setting the stage for me, and for Dr. Kemper and Lam for their continuing evidence review.

So, I do have a disclosure, which is rare for a government employee. This study -- our pilot study was funded by BioGen, and we have recently published our results in Genetics and Medicine, and I want to also thank Dr. Denise Kay at the New York State Department of Health for giving me a lot of the slides that I'm going

to show to you today.

So, spinal muscular atrophy has been talked about a lot in the context of this meeting and other webinars that have been done. And, just remember that there are several different types, and they vary in severity from type 1 to type 4. Mostly, it's a disease of motor neurons, and it is the most common genetic cause, as you heard earlier, of infant and toddler death, with an incidence of about 1 in 6 to 1 in 11,000. So, the expected carrier frequency is about 1 in 50 to 1 in 60.

The defect is in the SMN1 gene, and -- as you know -- it's deleted. The exon 7 deletion is the most common mutation. And, I just want to emphasize that for this talk and for our pilot, we concentrated on chromosome 6 type SMA. We are not looking at the other different forms.

So, this is just a diagram that shows the SMN2 gene that Mike talked about where it is a truncated form of the gene, and it has some function, but it's not as functional, obviously, as the primary SMN1 gene. And, as he mentioned also, there's variable genomic copies of SMN2, and that impacts the severity of the disease. We

are looking for homozygous deletion in the SMN1 gene in our studies.

So, you also heard about some of the new treatments that are -- the new treatment primarily that's available, and there are several others in the pipeline. And, as you also heard from one of the parents, this is really a game changer for SMA and really brought it into the newborn screening kind of sphere, because now we have this treatment, which prior was only really a palliative treatment for these kids, and we expect other types of treatments to become available in the near future.

So, the question that I was -- the question that I was posed with is to talk about carrier status and newborn screening, and should it be reported to families. And, as you've heard in the previous two talks, currently it's really not recommended to subject minors to carrier screening. In the newborn screening, you think of carrier status almost as an incidental finding.

So, our pilot study has been ongoing now and began in January of 2016. It's at three hospitals. You heard from Dr. Devivo earlier -- he's from Columbia. And, it's at three of the hospitals in their system -- the New York Pres, Morgan Stanley Children's, Weill Cornell

Medical Center, and the Allen Hospital.

And, the goals of our project were: a) To develop an SMN1 assay that can be used in a Newborn Screening Program in context and to demonstrate the feasibility of doing that in a high throughput manner, and to offer the screening, assess uptake, and outcomes, and one of those was to see how parents felt about getting back a carrier result.

The hospitals are up there on the slide for you, so we expected in a year or two of screening, we might find one child that had SMA. The recruitment model is an opt in. This is a requirement of the IRV at the GOH. We can't have an opt-out model, so we had to get consent from each of the parents. We have coordinators at the hospital, and their job is to describe the study to parents. We have a video that's actually on You Tube, and we can also have a pamphlet that parents can look at. And, they give consent by a tablet form.

When the screening card comes to the program, it's marked with SMA on the side there, and you can see it sort of how it looks, and the cards get sorted out, and someone does the SMA test in our lab. Primarily Ritu Jain is the one in the lab that does this. And, then

from there, the results are put into the Red Cap system, and we have access -- Denise has access to Red Cap, so we can monitor that we didn't miss a consent from a parent and that we were testing only parents that did consent. So, we have those checks and balances in place.

For the pilot, we run our assay in triplicate. This was just to be overly cautious in developing it and making sure that everything worked properly. And, SMA testing, as you know, is sort of the first genomic DNA test, but we have the luxury of having already DNA extracted from our SCID test. So, when we go high throughput, we would do a combined multiplex assay.

The DNA gets extracted from the dried blood spot because we're only testing the babies now from parents who give consent. And, we set up a TaqMan qPCR, originally on the 7900s, but we've moved it over the QuantStudios, and we actually use a delta-delta CT to calculate copy numbers. So, by doing that, we get affected homozygous deletions, we get carrier status, and we also have equivocal categories where we would repeat tests.

Doing this, if we decided to mask carriers, we would not do the delta-delta CT, and we would only really

look for presence or absence of the exon 7 material in the assay. We do not sequence for carriers. So, if a parent -- if a child has a deletion in exon 7, it gets reported out as a carrier, if it's homozygous deletion, it gets reported as effective, and if we find two copies present, it's normal.

So, Denise had prepared this for ASAG, and at that time, about a month ago, we had 8,167 infants that were screened. Of the parents approached, 93% of them opted in to testing, and I have a little bit of information about some of that.

We expect with 250,000 or so births -- we would expect about 24 to 40 cases annually, and the data is up there for the various hospitals and the various carrier frequencies, and we had actually the one baby who was affected with SMA.

Currently, using the carrier frequency we have, we expect to find somewhere between 13 and 14 carriers a day if we didn't do the -- if we did not mask them somehow, and that equates out to about 3500 annually. We do see variability in the carrier status based on the parents' ethnicity, and I'll talk about that in a bit as well.

So, early on we were receiving somewhere in the neighborhood of about 15 to 20 samples a day, and, again, they were tested in triplicate. And, now we're up to about 35 samples per day.

So, the low carrier frequency in New York we think is actually related to a bias in the hospitals and the individuals -- the race and ethnicity of individuals at those hospitals because of the 2 plus 0 genotype that Mike talked about -- it's high in Hispanic populations, and it's also high in Ashkenazi. And, there was a paper out in 2014 that looked at the Ashkenazi haplotype at Mount Sinai patients, and they found a SNP downstream that you could use to determine whether it was a 2 plus 0 or not.

So, in those cases, if you have 2 plus 0, you have 2 copies of SMN1 on one of the -- one of the copies of the chromosome, and the other one has 0. So, that parent really is a carrier, yet in our assay, they would look like they were normal. So, we have the potential to miss those kids.

So, we designed the assay, and then we started to enroll individuals. We offered genetic counseling to parents who had a newborn with a carrier result, and

about 16 out 113 of those agreed for a genetics referral, so they agreed to come in and actually speak. Of those, 11 out of 16 actually made an appointment, and 8 out of 11 actually maintained the appointment. And, so out of the ones that actually made the appointment, the uptake was fairly high, but overall the uptake was low on actually coming into the center and getting a genetic counseling session.

At the time, most of the parents expressed concern, but then after speaking with the counselor, they understand -- they understood the difference between being a carrier and -- or the baby being a carrier and the baby being affected.

Interestingly, almost 47% of the parents who came in already knew that they had the potential to be a carrier because they had been found to be a carrier themselves during the prenatal screening. So, that group of patients was actually a little less concerned and had better understanding, obviously, because they've already heard this twice.

The other thing that -- the way we do the assay is -- or the way that we do the screening for the carriers is we have the report that's available as part

of the newborn screening test report. So, as soon as that is available, it is up on our website. So, the data is sort of out there. They also get a phone call, and then they get a followup letter as well explaining what the results mean.

I have some information -- and we talked to the genetic counselor at Columbia -- and I have some information from her on things that she had sort of come to understand as she went through this.

We did have the one affected baby. The expected natural history -- you probably all well know -- you've heard it multiple times -- but, this little baby now is almost 2 years old. She'll be 2 years old in the beginning of 2018. She has -- milestones have been met. She is running, walking, and talking, and she's being followed in the clinic by Dr. Wendy Chung.

So, some of the conclusions from the pilot is that in the context of newborn screening, SMA testing is feasible. We calculate about 20 cents per baby, but I have an asterisk on that, so stay tuned. Ninety-three percent of the families have opted in based on those that are approached. Our overall carrier rate in New York is a little bit lower, and this population, again 1 in 72.

And, we had one infant that was predicted at type 1. When we did these screens, she was brought in, had an SMN2 test done, had the SMN1 test repeated. Everything indicated that she was a type 1 infant. She began treatment at 15 days of life, and, again, she is asymptomatic at 21 months. That 20 cents is the lab cost only, and that's because we could multiplex it with SCID. We don't have to set up a new assay, a new test -- we already have the equipment. It's really the cost of the probes. Followup, education, all those other things are not included in that price.

So, what do we do with carriers now? So, the biggest carrier frequency population we have is hemoglobinopathies. We do those by reports. We don't do any followup in New York on those kids. We don't do any further action. They don't go see the specialist or the hematologist. We started not too long ago doing a letter and a brochure to parents after the newborn screen result is available. So, about 2 weeks after the newborn report is available, we send a letter home and say, your baby had a screen, the baby was found to be a carrier, here's some information, and we have a brochure called The Family Connection.

I have numbers for you on another slide so you can see. For CF, we also do carriers by report, but those individuals are followed up, and they're required to have a sweat test. So, the reports prompts action. It says it's a screen positive result. The Specialty CF Care Center is notified, and we require the sweat test.

But, when we start doing full gene analysis for CF, we are going to handle our CF carriers more like the hemoglobins.

Adrenoleukodystrophy is the newest -- one of the newer results that we have. Again, these are carriers by report. We do require followup. So, these kids also get referred.

So, the only one up there does not get referred for followup diagnostic testing right now are the hemoglobin carriers.

So, this is the volume of hemoglobin by birth, and you can see why we don't send them all out to the center. Roughly 72 to 7300 infants per year in New York have a carrier-type result for hemoglobinopathies.

Again, we started several weeks ago sending a letter and a brochure to the parent's address -- the mother's address -- when we get those types of results

because we weren't convinced that the message was getting to the families in light of all of the NCAA requests as well.

Cystic fibrosis volumes by birth -- again, we refer kids whether they are 1 or 2 mutations, and we also have very high IRT values. So, we refer 800 kids, and about 600 of those are carriers. Our overall carrier frequency in New York is about 1 in 400, and our expected is about 1 in 35. So, clearly by newborn screening, we are not finding all the carriers that are out there.

And, lastly for ALD, because it's a low referral-type test, this is data on almost 900,000 infants. We have referred out 25 carrier girls and 1 carrier boy. He was a Klinefelter. He was heterozygous for an ALD mutation. And, so we have 26 carriers in that population out of the 69 referrals. Those kids do get followup, and the incidence rates are in line with what is actually published when you look at the overall data.

So, the issues that are related to carrier detection in context of newborn screening, for that topic I send a note out to our IMD specialist -- our genetics specialist -- and said, should we report SMA carriers or not, and give me feedback on what you think. And, so

they all think that they will end up getting a higher volume of calls from the outside providers -- the pediatricians and primary care and families -- and to have to manage this with a dearth of counselors, so they see that as an additional burden.

Two of our providers thought we should report carriers, and the rest said no. So, we have a total of 9. I don't -- I believe 8 responded. Some did say it was good for family planning. Interest in carrier screening of the siblings, we find, particularly for kids where we find a mutation and a new condition, and there may be family members or older siblings at home that didn't have the benefit of screening.

The question that Aaron brought up about the mission of newborn screening was one of their comments, and many providers both calling me and calling the specialist have difficulty interpreting what it means to be a carrier. They say do I need to do anything? What do I need to look for?

The professional community, as you heard, has not yet reached consensus on reporting carrier status in the context of newborn screening. Those recommendations haven't been made. And, again, our carrier frequency in

Hispanic population is about 1 in 100, and that introduces in our minds some health disparities because we're going to miss those kids with our screen if we report carrier status.

Ashkenazi Jewish families also have that 2 plus 1, and a proportion of families actually refused the newborn screen because of the increased uptake and the recommendations on SMA prenatal carrier screening. Again, 47% of the carriers already knew when we called them with the carrier results that they were carriers.

So, the counselor gave us some other little bits of information that she's collected. In her hospitals, the update for prenatal screening is high, but it is variable depending on which hospital you look at individually, and that population does not necessarily come in for newborn followup because they already have been told about their carrier status.

Based on the followup survey data -- so, part of this study is to send a little survey back out to families and ask how they sort of felt about the carrier experience -- 4 to 5% of those that they sent surveys to didn't recall the status of the newborn or that they had been called by a genetic counselor. So, that was kind of

interesting.

Prenatal care screening feels different to parents when it affects them but it doesn't affect their baby. So, they have a better -- they sort of -- they're not so bad, they're adults, they're good, they feel okay, they know it's not bad. But, when you give that same result to their baby, it's -- it's felt differently.

And, she said a lot of parents will ask what I should look for despite trying to reassure parents that this is a carrier result. The chance they have SMA is quite low. She said that few parents actually do request followup sequencing. They do talk about it, and very few of them actually request that sort of, okay, I have a carrier, let me see if there's another point mutation on the other chromosome to determine whether or not that individual actually has SMA. And, she said there's some phone counseling caveats. It's hard to read body language. Parents are often distracted, you can hear other kids in the house, and she doesn't feel like she has the same attention on a phone consult as she does seeing them in person.

And, she said each consult takes about 15 minutes, and that could be a time sync when you're

churning out 13 or 14 of them a day.

And, then parents that are making appointments after carrier screening are offered carrier screening for both parents if they hadn't had it already. So, if they have a newborn with a positive carrier screen, she offers testing to the other parent who hasn't yet been tested, if that's the case.

And, so we're here to talk about SMA and screening and other states are obviously going to provide us with more information. Things that we're talking about in New York State -- we have to amend our reg if we add this full scale. We're trying to get together a Care Center Network of neuromuscular docs to help see these kids, and the multiplex qPCR with SCID in our lab is 20 cents to add the test. We typically don't get funding for education and followup, but we get it for the laboratory piece. And, the question of carrier reporting obviously has to be resolved. And, then other considerations we're worrying about are detection of late-onset and how that gets managed, false negatives -- the babies that have point mutations, the cost of treatment and when to initiate it, and the additional treatments that are coming down the pike.

So, the work we do takes a village for sure -- the lab, Denise, Colleen, Ritu [phonetic spelling] and Sandra do the testing and look at the data every day, our providers, and the people who are involved in recruiting the families, everybody involved in BioGen and the Health Department for helping fund this. So, thank you very much.

[Applause.]

DR. JOSEPH BOCCHINI: Thank you, Michele. If our other two speakers would come back up, and then let's open the questions and comments first to Committee members. Sue?

DR. SUSAN BERRY: So, some of this decision is upon us, as you've already described, in a practical sense with most CF newborn screening and a lot that we get carrier information that I think almost everybody gives back because you send a kid in to get sweated and lo and behold, they were heterozygote, and that is sort of part and parcel with it. So, whether we wanted it to be here or not, it's already a part of how we have to operate. The same thing is true with ALD and that whole cascade thing -- it's not the future, it's now.

So, I guess the thing I end up worrying about

is that we have all these ethical questions, but they're already -- they're already in our lap, and who -- where is the people power to handle this? You said 15 minutes per call, and I'm sort of making the mental adjustment about how many hours of genetic counseling time we would need to be able to handle even the most superficial of conversations. I'm a bit overwhelmed by the idea of how we're going to accomplish all of this, and who is going to keep track of it forever? Because -- I'm wondering because I have like 50 questions written down here, but it's an overwhelming resource issue -- people power, knowledge power, data retention. I don't even know where to start with the complexity that comes here beyond the ethical issues -- just the practical issues of accomplishing this.

So, the rhetorical -- it was sort of a rhetorical question in the sense of where do we see ourselves as a Committee and as a community being able to address these questions. What do you -- what recommendations would you have for the Committee about where we can tackle this?

DR. MICHAEL WATSON: So, the rhetorical answer might be that certainly we've made an assessment of the

public health capacity when we look at a new condition. We may have to look at the capacity of the health care system itself if we're also taking on these patient loads.

DR. JOSEPH BOCCHINI: Jeff?

DR. JEFFREY BROSCO: Jeff Brosco. While you were talking, I did a back of the envelope calculation, and if we have 200,000 births per year in Florida and you assume the 1 in 70 carrier rate and 15 minutes per, that ends up five FTEs if you talk to everyone for 15 minutes. So, you're right -- it's not possible.

I think part of the reason why we have this panel -- and, thank you for putting it together -- is that yes, as Aaron laid out, there are a lot of critical ethical issues, and the principle is very helpful. And, what we hope at the end of the day is that our policy matches our values. But, it could be hard just to do this in a value-based way. As we pointed out, there are lots of different conflicting values. So, here's where research comes in, right? And, I think that part of what Aaron and I and Michele are saying is, if in an SMA pilot we randomized families to get results or not and followed up with them to see what were the results of that -- do

they need to talk to someone for 2 hours or not? Maybe the vast majority of families don't even care that they get the results. And, so it's a moot point. Maybe you send out these 30,000 letters, and only 3 people really care -- you need to follow up with a -- I'm sorry -- or maybe 100,000 need to. So, just finding out the facts -- that's the first step. And, so I don't know if you want to make any comments about that.

DR. GOLDENBERG: Yeah, I would just agree -- I think that the data does point to less anxiety, less worry, less distrust when there is a good conversation that happens with either a primary care physician or someone else who can kind of explain what being a carrier actually means for families. But, I also think that at least in the more general genetics and genomics literature beyond newborn screening, the ability to do that effectively for thousands and thousands of patients is not there. So, we, I think, as both a newborn screening community but also just generally as a genetics community, are in a position where now is the time where we need more research on what we can do that would mediate some of that concern that doesn't involve a 3-hour consent process, right? And, you're seeing that

with exon and genome sequencing in clinical centers that are increasing their numbers. They don't have the counseling capacity. They don't have the time to do it.

And, so there's a lot of empirical research looking at what will satisfy parental needs or patient needs in terms of getting at some of those questions. But, we're not there yet, and I think that we don't do it sufficiently in newborn screening research, right? This is, I think, one of the points that we're making in our papers that the pilots -- just like yours -- is a perfect place to have more of these questions answered.

I was really happy to see some of the qualitative data from your work. We don't see that as much, especially for disease specific, and we need to be able to do that more effectively to hear from families about what this means because I don't think it needs a 3-hour conversation, but I do think that making those distinctions for families, talking about what carrier status is can go a long way for alleviating those kinds of anxieties and those kinds of concerns that we, as a community, might be really worried about.

DR. JOSEPH BOCCHINI: We have Mei, then Beth, and then Joan.

DR. MEI WANG BAKER: So, the one thing I want to mention to you -- I want to mention here is Aaron said it well -- once you report carrier or you detect carrier is two different things. So, then getting back to SMA, and I don't know exactly Michele how they do that -- they use delta CT? So, our experience is in the current setting for the SCID, you will not be able to tell if it's a carrier or "Y-type." So, when you do the delta CT, you have to have controlled samples so you know the SMN2 or SMN1 copy in order to do the calculation. So, I think Michele would do it the same way.

So, I think that's interesting. Then, we assess do you detect or not. Then, if you detect it, what's the benefit for this child -- for the family. To me, the only thing I can think is because if you use the exon 7 deletion, homozygous, your sensitivity is 96 to 98%. So, that's the CF because we use the first RT. We upfront do that, and I feel okay because the only benefit I feel like you report one copy SM1 deletion gives you the opportunity to detect another allele, so you have a point of mutation. So, this is the only benefit.

Another thing I want to comment is when it was a carrier -- I think because Fragile X has been mentioned

a couple of times, I think Fragile X, when you have less than 200 CGG copies, we use the term carrier, but I think it's way different because no matter if it's a male or female, you carry this beyond 54, and lower than 200, eventually you either have premature function at all ataxia. So, that has some consequence. So, I think we treat it a little bit different. So, I just wanted to mention that.

And, I think in the newborn screening concept, in my mind at least, is -- it really is autosomal recessive inheritance when you have a carrier largely do not have a health consequence. Of course, we are facing in terms of X-link. So, I think it's another thing that's different.

DR. CAGGANA: I mean -- I agree. In order to do the delta CT, we use RNase P. And, so you do sort of a macro to calculate that out. So, in the case where we decide -- if we decide not to report carriers out, we would just really do a CQ threshold and do positive or negative and be done with it.

With Fragile X, as discussed, if you're looking at copy number, you're going to find the pre-mutations, and what do you do with those as well, but that's for

another day.

The other thing that I was thinking with the -- relaying this information, I always look to Amy, who does really good infographics. And, I think that something like that has to be done so that you can push that out to your providers in an easy way that they could give that information to parents without having them go to the specialist to get the same information from a counselor if you go the path of reporting out carriers. But, there has to be a clear sort of tested way to do that out in the community with many different types of people to assure that your message is clear to them. It's really hard to do, and I think that's where the challenge is.

DR. JOSEPH BOCCHINI: Beth?

DR. BETH TARINI: To follow up on that, I think that this could be looked at as an opportunity for disruption, if you will, in the genetics counseling community. You've gotten to the point where what we've done along -- not genetic counseling -- but, what we've done all along is not going to carry us through. So, do we change or do we make a decision about what we're going to give and not give.

So, a comment, and then a question. A comment

to Jeff's point -- I think the RCT is in treating ID, and I think we don't leverage other studies in parallel or nested within these pilots that are focused heavily on lab and outcomes. I do caution us to be careful what we wish for because depending on what we find, we could end up saying, you know, carrier screening -- carrier counseling has a benefit. What are we going to do with the 5,000 hemoglobin carriers? We can't then back out of the corner and say, well, but SMA is different. Hemoglobinopathies are different and they're not generalizable. They all have to be counted the same.

And, for that reason, I'm -- this is not on New York because I don't think they're alone in this -- in that we talk about mitigating the anxiety of the differential between carriers and cases as if those who have hemoglobinopathy as a carrier sort of are birthed with the understanding that they are a carrier and that they don't have sickle cell disease, and they have no signs or symptoms of sickle cell, and they're not the least bit confused about their carrier state despite the fact that it is a situation that disproportionately affects those who are under-privileged and under-resourced.

So, I think it's a bit of a slippery slope when we presume this -- that differentiating a carrier versus a case conversation that ends up in a carrier counseling is different anxiety than being birthed and knowing you're a carrier, but being okay with it because many people have sickle cell trait. So, I just put that out there as a thought for the Committee.

DR. CAGGANA: I agree.

DR. BETH TARINI: I guess it's not a question, sorry.

DR. CAGGANA: That's okay. I'll answer your non-question. So, we thought a lot about that in our state because some states do provide counseling. They do a lot more for hemoglobin carriers, and we have a large number of them. And, we felt that a lot of the community was not being told that maybe the report was stuck somewhere or downloaded, but that the message wasn't getting across to the families. And, so that's why we opted to go ahead -- even though we're trying to reduce the amount of mail we send out -- we actually thought it was beneficial to send a letter to explain it -- talk to your baby's doctor, and here's what this means -- and, that we were communicating better with the family. There

are numbers on the brochure, and that way, at least, they were more confident they got that message.

DR. JOSEPH BOCCHINI: Joan? Okay. Cynthia?

DR. CYNTHIA POWELL: Cynthia Powell. Yeah, I was thinking the same thing as Beth in terms of -- you know -- we've been screening for sickle cell and reporting out trait for over 40 years now, and -- you know -- while we could use a lot more research about it, there haven't -- there hasn't been a ground swell of, oh, this is horrible and -- you know -- all these poor outcomes -- you know -- based on people knowing that they're carriers. They certainly don't -- you know -- remember it very well, because that's why they contact the screening lab when they have to -- you know -- get ready to play sports, and they're required to -- you know -- have that information.

But, we found in our CF newborn screening that -- you know -- similar to what you reported, Michele, for the low uptake for -- you know -- people wanting genetic counseling that -- you know -- while they're given a brochure, if -- you know -- they've got a negative sweat chloride test and they're presumed to be a carrier, but very low uptake of -- you know -- meeting face-to-face

with a genetic counselor.

And, I also think that -- you know -- the workforce argument, while it is important, but it's not enough to say we shouldn't be doing it because I think nowadays in our -- you know -- with so many different media outlets for conveying information that -- you know -- we need to start thinking beyond -- you know -- the need for a face-to-face newborn screening session -- I mean genetic counseling session to -- you know -- get that information. There's other ways that that could be done.

DR. JOSEPH BOCCHINI: I have Mei and then Sue.

DR. MEI WANG BAKER: Mei Baker. Finally, I remember to tell my name. I have a quick question for Michele. And, you have three sides in the carrier testing. One side is 1 in 142, and any explanation different? I didn't do the calculation because if the report is 1 in 54, and your other two are more close to this number and different -- I'm wondering --

DR. CAGGANA: It has to do with the types of individuals that come to those hospitals, and we think that a higher proportion of them have the 2 plus 0 genotype. So, the carrier frequency we're detecting is

actually lower than we expect. So, we don't know if we can extrapolate that out to the entire state. So, it's probably somewhere in the ballpark of what's obviously in the literature in reality.

DR. SUSAN BERRY: I guess part of the problem is there's not a very effective genetic literacy amongst the population. If we had a better understanding generally of what being a carrier actually meant before it was sort of a point of worry for you as an individual, we might have a simpler road. So, can you comment, Mike, perhaps on what the college or other professional organizations might be doing? I know this is a longstanding problem, and a lot of work has been done to try and think about improving genetic literacy.

DR. MICHAEL WATSON: I'm not certain of the question.

DR. SUSAN BERRY: Well, my question is, what efforts have professional organizations done to be able to enhance the understanding of the general public about genetics so that when they're confronted with this idea that they're a carrier, they don't even know what a chromosome is.

DR. MICHAEL WATSON: Yeah, I -- we don't do a

lot in the general population, I'll admit that. They do access some of our more general information that we make available to non-genetics trained physicians who in that much a different place than many of -- a bunch of the public. But, I -- you know -- I have gone out to our Committees as I was thinking about getting this -- this talk organized to start thinking more about the issues of carrier. When is it appropriate clinically to bring these carriers out of the Newborn Screening Program into followup services, and -- you know -- I think we only deal with the -- you know -- a subset of these conditions. There's a lot of other specialists involved with other conditions in newborn screening. So, it's a much broader question than just what the genetics community is thinking, but, yeah, I think we're going to have to get on it.

DR. GOLDENBERG: I would just add to bring that point together with a couple other points that have been made that I think a lot of the literature and a lot of -- some of the educational materials tend to bundle carrier status into a kind of one monolithic issue that people need to think about. And, what we've seen today is that being a carrier, being heterozygote means a lot of

different things for a lot of different people and a lot of different conditions. And, as we start thinking about potential impact -- potential health impact on children, potential health impact on adults, incomplete penetrants, some of these different patterns of inheritance, we need to be thinking, I think, more broadly about condition-specific policies or condition-specific educational materials. And, I agree, Cindy, that we haven't seen a lot of anxiety currently with sickle cell information. But, it was a long, bumpy road in the 1980s to get there, and there were a lot of problems with some of those programs -- not so much in newborn screening -- but in other state policies. And, I think it took a long time to get there.

While I agree, I don't think we need massive education. I think that as we look at different implications of being a carrier and what it means, I think it's important for us to think about what kinds of questions we need to ask. Even, for example, understanding the difference between the potential impact on the newborn who has that information in early childhood versus parents who get that information and now learn something about themselves. And, I think one place

that has been thinking a lot about this is our neighbors in the prenatal world, who has Universal Carrier Screening, Expanded Care Screening has become more common, are dealing with this every day. So, the question, for example, do you have enough counselors, how do you do counseling for this adequately. Prenatal genetic counselors are dealing with this quite frequently with -- you know -- a huge uptick in numbers of people coming to them with carrier status information. I think there may be some lessons to be shared across the pre- and post-natal world that I think could be really helpful for us to kind of think about what's going on in the prenatal world about carriers.

DR. JOSEPH BOCCHINI: Scott?

DR. CAGGANA: Could I just comment? The other thing that's important to remember, I think, too in the prenatal setting is what actual count -- what type of panel or what you're getting as your carrier screen. We had a case in New York where a woman was prenatal, had a carrier screen, was negative. They never partner-tested the husband. The baby came back with 508 and another rare variant, which the mom had. So, the baby actually had CF. She was totally blindsided. So, that's another

piece of education that we have to remember to include.

DR. SCOTT SHONE: Scott Shone. So, a couple different thoughts about sort of Beth's comment about you treat all carriers the same. We talk about hemoglobin -- hemoglobinopathy, CF, SMA, and perhaps DMD -- we had the discussion about DMD -- but, do we go back to galactosemia? We identify galactosemia in carriers and all the other carriers for other disorders, and it makes me think about -- you know -- to detect or not detect. And, when it comes to genetic assays, it's fairly clear in terms of are you a carrier or not, but with these biochemical assays, we struggle with and we're still immersed in the cut-off and and post analytic tool analyses. Do we have to reconfigure all that thought process to now, okay, well we need to adjust everything to now identify carriers, and then we're shifted to -- and then we're shifted to -- not only because you have a spectrum -- you have a spectrum of babies who have disease, and you're going to have a spectrum of carriers who have whatever. And, they're going to overlap in an ugly fashion. And, it's then going to shift everybody to more second-tier testing or have a lot more diagnostic testing.

And, so I don't mean to make a slippery slope argument, but I'm wondering that's -- you know -- there's been a lot of discussion in the last hour on the post-analytic part of it, and returning that, and how do you handle that. But, the analytic part of it and it's generating in the Newborn Screening Program is a behemoth as well.

DR. CAGGANA: Yeah, and I would sort of disagree that we need to treat carriers the same as -- you know -- you said maybe condition-specific treatment for the -- because a baby that has a trait result and our lab gets IF. And, so, if a baby has isoelectric focusing as the second-tier newborn screening test, than that individual, we're pretty sure they are just a sickle cell carrier. There's not that risk that they're going to have something else. And, that's where the difference comes in, and that's why the other conditions get acted on as well, and this overlap burden of the curves overlapping -- it's treated differently in the hemoglobinopathies, I think, because we're more sure they're carriers in the hemoglobinopathies.

DR. JEFFREY BROSCO: Jeff Brosco. So, at our next meeting, there's a chance we're going to have to

decide about SMA -- whether to add it to the RUSP when there's a carrier rate of something between 1 in 40 to 1 in 70. And, if we have to think about what the benefits or harms are of adding something to the RUSP, this is something we want to know about, right? And, to the degree that we knew there was significant harm or at least significant resources, that would be important for us to know. And, if there weren't, then that would be helpful as well. So, that's it. I'm just going to say that. I'd love to know.

[Laughter.]

JOAN SCOTT: Inquiring minds want to know. I'm not sure if you said it, Michele, but if you're -- for the individuals that you're reporting out as carriers -- and you said most of them don't go on for additional sequencing to make sure that there isn't a point mutation. So, what is the number of potential SMAs that might be missed without doing that?

DR. CAGGANA: I think it reports the residual risk as 1 in 1,000 that the baby has -- less than 1 in 1,000 that the baby has a point -- would have SMA with a deletion, and it's 1 to 2,000,000 that they have 2 point mutations in the screen.

JOAN SCOTT: Okay, thank you.

DR. JOSEPH BOCCHINI: Dieter, I'm going to give you the last question.

DR. DIETRICH MATERN: Yes. Dieter Matern. Thanks, Joan, for bringing that up because I was concerned about it as well. So, in New York, you consider these babies as carriers, but there is still a chance that they actually may have SMA. So, how does that set you up in terms of liability, which is the least concern here, but is a concern.

DR. CAGGANA: The reports call it -- they say it's positive for one copy -- one deletion copy of SMN1, and then the report goes on in the interpretation to talk about the other possibilities that this baby most likely is only a carrier of the exon 7 deletion and that there's this risk that they're affected. And, so that's an explanation that's in the interpretation.

DR. DIETRICH MATERN: So, counseling then the families about this little detail can be done on average, I guess, in 15 minutes, but some patients or families may need more time to grasp that concept.

DR. CAGGANA: Yes, and it's also whether or not they've been exposed to the prenatal SMN1. And, again,

because once ACOG recommends that, it gets offered, but there is a certain proportion of people that uptake that prenatal test. And, so people that have heard it twice -- have heard the same result twice understand it better. So, it's -- repetition is good for the soul kind of thing. And, so to be clear and be able to describe what that means in a way that maybe it's only a few minutes conversation or maybe not a conversation -- call if you have questions. That's the hard part we have to figure out if we choose to go that route. And, it's a challenge we have in everything else that we do.

DR. JOSEPH BOCCHINI: All right. I want to thank Dr. Caggana, Dr. Goldenberg, and Dr. Watson for excellent presentations and stimulating the discussion that we had related to this. It's very important.

Next, we have a presentation on the status of the -- where are we -- right here -- the status of the SMA Evidence Review, Dr. Alex Kemper, who is Division Chief of Ambulatory Peds at Nationwide Children's Hospital, Professor of Pediatrics at Ohio State University, College of Medicine, who also serves as a Condition Review Workgroup Lead. He is going to give us a presentation on the status of the evidence review for

SMA. And, as you know, it's already been stated that we're working on our 9-month schedule with the goal of having evidence review completed and presented to the Committee for its evaluation and determination of whether the condition is appropriate for being placed on the RUSP in February. Alex?

DR. KEMPER: So, I'm hoping that magically the slides are going to change or do I have to do something? Oh, I have to click, okay. I thought they were going to put a different presentation up. That shows you what I know.

So, thank you very much for this opportunity to give everyone an update about the status of the review that we're doing for you all on spinal muscular atrophy -- SMA. And, I have with me K.K. Lam, my partner in crime, without whom none of this stuff would come together.

I know we're running a little bit late, and so what I want to highlight as I go into the presentation is I just want to give you a general sense of where things stand right now, and also find out from you if there's something in particular that we should make sure that we gather for the time that devoted in February. I don't

necessarily think we need to do a deep dive on the evidence, though we're certainly prepared to do that and happy to do so, and I'd also like to thank Dr. Matern and Dr. Tarini for being the liaisons to this project, who have certainly given us a lot of food for thought about things that we ought to look for.

My final sort of observation before I go into things is that things are rapidly evolving in the world of SMA. Dr. Caggana thanked me earlier before her presentation, and I actually had to thank Dr. Caggana for keeping me -- keeping us up on sort of the moment-to-moment evolution of what's going on with New York and her patients with us.

But, I would also like to highlight that just last week, there were two major articles that came out in the New England Journal of Medicine related to SMA -- one related to the treatment with nusinersen and then the other with the novel therapeutic approach with gene therapy in a viral factor.

So, I'm not going to specifically talk about those two studies today, but I just do want to highlight how fast things are moving. And, so we're going to do our best in February to really give a good picture of

where things are, and I certainly think that we'll have enough for the decision then.

I would be remiss if I didn't thank the rest of the members of the Condition Review Workgroup, many of whom are here in this room, and Dr. Lisa Prosser listening in the phone, and I'm calling her if technology is our friend.

So, again, my main goal is letting you know where things stand. This shows our various activities with the goal of finishing within 9 months, and I'm happy to say that we're hitting our benchmarks actually really quite nicely.

We've had our second tech meeting. We're still working on issues related to followup interviews -- that process is sort of lagging as we learn other information.

But, things, you'll see, are moving ahead nicely with the decision model, the evidence review, and with public health impact component of things. Jelilli is in the back of the room, and I may call on him if there are any particular questions about that as well.

So, again, we have three components. There is evidence review, where, again, I want to highlight the major outcomes that we're looking at. I'll talk a little

bit about the decision analytic model, and I can show you a draft of the tree and sort of blank tables about what we hope to fill in there, and then I can give you a quick update on the public health system impact assessment. And, again -- you know -- each moment I can feel like a new survey being submitted.

So, this is the so-called PRIMSA table, which shows our literature review and sort of where we've come down on things. You can see that the bottom line -- there are 221 studies that we did retain for review and extraction. The key thing is that most of the published studies are not about treatment outcome. Those treatment outcome studies are just emerging. So, we have a lot of presentations that have been made in a lot of places, and, of course, now we have that recent in the Journal of Medicine study that I talked about before. But, a lot of the studies about treatment are still in the process. And, then a lot of the studies are around screening. And, I talked about screening more at the last meeting, and I'm not going to focus on that here -- are also unpublished. And, again, we lean on the results from New York, and then our CDC colleagues have been incredibly generous with their time.

So, in terms of -- you know -- where things are in the United States regarding newborn screening for SMA, there is New York that we talked about. There was a Utah and Colorado project, which is now finished, and I'm not going to talk about that. From what I can tell, it's not going to add much data to what we're learning from New York. There's been legislative approval in Missouri and Minnesota, and then there are other states that at least we know of that are considering SMA screening, and they're listed here.

And, as we talked about before, the CDC has developed screening methods and has available proficiency testing material, which is -- you know -- obviously critical to our rolling out newborn screening, if at least you're going to use that.

So, I'm just -- you know -- I hope that nobody asks me about particulars being non-laboratory and -- you know -- when I look at these kinds of graphs, it reminds me of being a kid and spirograph.

[Laughter.]

But, their focus is on real-time qPCR for SMN1 exon 7 deletion -- you know -- original iteration that is focused on the intron, but now it's the exon. It uses --

you know -- specific probes to increase the specificity in the presence of SMN2 so you don't get faked out by the SMN2 that's there. Those of you who are laboratory, I'm sure are cringing at my definition.

But, the key thing -- the important thing to know about the CDC methods is that -- and, I'm going to show you some of the work that they've done -- but, it's a highly accurate way to identify exon 7 deletions in both alleles, and it will not identify carriers. Dr. Caggana spoke eloquently before about the potential benefit of picking up carriers in terms of the -- you know -- potentially being able to find these other cases, although it would be rare.

So, that didn't come across very well on the screen, but the CDC has looked at using an anonymized dry blood spots and basically they can discriminate those individuals with SMA based on samples. Again, these are anonymized versus unaffected carriers, and it's really not designed to identify carriers themselves.

Other important things -- it can be multiplexed with SCID screening. The cost to multiplex it with TREC screening has been estimated by individuals at the CDC to be around or less than 10 cents a sample. I almost

hesitate to put up that number less than 10 cents a sample because that's just like -- you know -- the reagents and that kind of thing, not -- oops, I almost spilled my drink on the machine -- but not the -- the bigger process, okay? So -- you know -- take that 10 cents with -- you know -- in perspective.

And, again, I mentioned before that the CDC has material out there and has offered consultation and technical support for those interested in using it.

In terms of treatment, I've listed up here until last week the peer-reviewed scientific publications, of which there are a handful, and then, of course, we have a lot of great literature that we found -- these are unpublished presentations. And, I'm going to be -- again, certainly in the interest of time -- I think I'm going to dive deep into the ENDEAR study, which is the one that I think is going to be most relevant for the decisions that the Advisory Committee is going to have to make.

This is a slide that just shows the range of different projects that have been done. And, again, I'm happy to go back and talk about this further, but I think that it makes sense to just move on to the ENDEAR

studies.

So, the ENDEAR study is a phase 3 randomized trial of nusinersen in infants with SMA. It's important to understand the eligibility for this study, okay? So, it includes infants who have a genetic diagnosis of SMA, infants who have two copies of the SMN2 gene who developed symptoms prior to 6 months of age, and who were 7 months or younger at the time of study screening for eligibility and infants who did not have hypoxemia in terms of not having respiratory compromise at the time of screening to participate in the study.

So -- you know -- this is -- you know -- these are not infants that were identified through newborn screening, but these were infants who -- you know -- had symptoms early on and were referred at an early age to participate in the study.

So, this is -- we have -- this is our -- you know -- the great literature version of this whole thing, but this is what was published in the New England Journal of Medicine, and fortunately it matches with the slides that we're about to show.

This was presented in a meeting, I think, in France as well. No, no, this is the Boston one. I was

going to say I was going to hope that in the future the Advisory Committee would be able to send us to France for these kinds of presentations.

So, what I'd like to highlight in this is that if you dichotomized the period of disease before entry into the study at 12 weeks of age, there appeared to be better outcomes. And, I'm going to show you that on this slide. So, during the public comment period, there was mention that if individuals got referred by 12 weeks of life -- it was actually 12 weeks of duration of symptoms, which is an important nuance. But, again, these children were -- you know -- less than 7 months of age when they were referred to the study, so they were still in infancy, but it wasn't really 12 weeks of life -- it was 12 weeks of duration of symptoms.

And, so maybe what -- so, if you look at this slide in the middle -- the slide on the right -- I think that this -- these two slides do the best job of pointing out what the issues are.

So, if you look on the slide that's labeled B -- disease duration -- let's say it goes to 12 weeks -- you'll see a blue line. That's the individuals that were enrolled in the ENDEAR study. If you look at the black

line that has that precipitous drop-off -- that's compared to historical controls, okay? No, that's the same treatment -- I'm sorry -- I was thinking about a different state. This is the same treatment. So, the individuals that didn't get the treatment. And, then if you look on the right, this is individuals who had disease that was 12 weeks or longer, and you can see that they more closely match what was going on with the sham treatment.

So, let me say this again because I misstated something earlier. The middle slide is less than 12 weeks of age and compared to sham treatment. The one on the right is disease treatment greater than 12 weeks comparing treatment to sham treatment. And, you can see that there does seem to be an important effect when you look at intervening less than 12 weeks of age. And, this is on event-free survival. But, they're similar graphs that have been drawn.

UNIDENTIFIED FEMALE SPEAKER: Less than 12 weeks.

DR. KEMPER: Yeah, of disease duration.

So, I'm going to move from -- so, we talked about screening. We talked about what we -- you know --

the kinds of stuff that's emerging around treatments. And, what I want to do is just give a quick update about the public health system impact assessment.

So, as we've done in the past, we had a kickoff webinar where we talked about the kind of information that we would need, and we prepared a fact sheet. We had a webinar on October 4th. It was live and recorded. If you want to go and watch it, you can. I think it's up on Netflix now.

[Laughter.]

And, you can see -- you know -- we addressed the usual topics in terms of what's new and about screening, treatment, outcomes, what would be involved with short-term followup -- all that kind of stuff.

The survey is now open, and it will close on November 17th. And, I know that Jelilli wants to comment on sort of where we are. I don't know know if he can where we are today, but -- you know -- 13 days after the webinar, we had 12 completed surveys. If past performance is a guide to -- to what happens in the future, usually as we get closer and closer to the day being closed and we send of little -- you know -- nastygram [sic] emails, we get more response.

And, then we'll be doing followup interviews with states who have a mandate to screen to understand what kind of process they're going on to implement things, and, of course, to have them estimate costs using the tool that we developed in the past.

And, then the third component that I just wanted to talk about briefly was the modeling and where we are with the modeling. So, the goal of the modeling again is to quantify what might happen if you were to screen all 4 million newborns born in the United States compared to what might happen with clinical identification. Certainly -- you know -- we can look at things like mortality or -- you know -- with or without combination with the need for mechanical ventilation. And, then there's more data that is now coming out regarding motor deficits. There is one particular scale -- the Hammersmith -- what's the NE -- I can never remember -- neurologic examination -- HINE.

UNIDENTIFIED FEMALE SPEAKER: The HINE.

DR. KEMPER: The HINE, exactly. That how I refer to it all the time. So, it's unclear whether or not there will be sufficient data in there to model that in a meaningful way, but we'll think about that.

I will tell you it's been an interesting conversation thinking about what kinds of things that we would want to model. So, for example, one of the things that came up early was the need for a G-tube to get fed that way. But, there's so much variation at what point somebody might decide to put in a G-tube that that just didn't seem to be like a reliable thing to model on.

But, I -- you know -- do feel confident that in terms of the -- you know -- really bad outcomes in terms of prevention and mortality and those kinds of things that we'll be able to get to.

Now, in terms of the modeling, our focus throughout -- and, I'm going to show you the model in a second -- has been on type 1 SMA. And, that's on the next slide. Let me just show you that -- you know -- this gets to two issues. One is what's the goal of screening? So, I would argue that with screening, what we want to do is identify -- you know -- the most severe cases that are most likely to benefit from therapy. And, then the other issue is just what's the volume of data -- you know -- the quality and reliability of the data that are out there to be able to model the effect on some of the other forms of the other types of SMA that may -- you

know -- be very clinically important, but -- you know -- just may not be able to get there.

So, this slide just shows you -- you'll be looking at a hypothetical cohort of newborns and comparing newborn screening to clinical identification. And, as usual, we'll look at the outcomes of positive screen and negative screen, and for negative screens, look at -- you know -- whether or not there could be false negatives. Again, at least looking at the data we have from the CDC, it seems like the false negative rate is going to be very low. And, you can see that we can also incorporate copy numbers as modifying effect on the whole thing.

So, again, if there are more detailed questions about the modeling and what we plan to do, I'll bring Lisa Prosser into the call. This is a slide that drills in with some of the outcomes, and we talked about those before, so I won't belabor that. And, then ultimately what we plan to have is a table like this, and you should be used to these tables because we've generated them in prior reports where we can compare what might happen with newborn screening to clinical identification, and we can have a -- you know -- the expected number as well as the

range based on the available evidences. And, given the amount of evidence we expect to find, it's going to be the range that's really going to, I think, be most helpful, and -- you know -- all of the tables that we've provided in the past.

So, the next steps in terms of where we are with this is developing the estimates for modeling parameters, so a lot of that is coming from the work that we're doing to extract evidence from the published and unpublished studies. And, then once we have that, we get our Technical Expert Panel together again. We have a meeting scheduled for December 13th, and what we do is we walk -- for this particular call -- we're going to walk through the model and walk through the estimates and get a sense from the experts about whether or not the -- the input parameters we have make clinical sense.

I will tell you the two previous Expert Panel meetings that we've had were just absolutely fabulous in terms of learning and understanding about the condition, and -- you know -- there are things that you read in the literature and you think that you have a good grasp on, and then when you talk to the experts in the field, you realize it's a really moving field and people are

learning things rapidly. And, so it's been critical.

So, an example of that would be -- you know -- issues around copy number and how copy number informs treatment. So -- you know -- my sense of things now is that if you have 3 or fewer copy numbers -- I'm looking at K.K. to make sure I don't misstate this -- that most people at that point would move ahead with treatment. But -- you know -- if there's 4 or more, there's sort of more debate and observation involved at that point.

UNIDENTIFIED FEMALE SPEAKER: Right, and there appears to be evidence available for -- for -- I don't want to say type 1 -- but symptomatic SMA patients with copy number up to 3 based on ENDEAR and CHERISH, which is not yet published, but is -- has come out in conference literature.

DR. KEMPER: I have to say that the people doing all the SMA trials have like the best names for some of these. I'm like very jealous of their ability to come up with acronyms, but it also makes it hard to sort of keep track of which one is which. But, CHERISH is the longitudinal followup one.

So, I'm going to stop there and leave it open for questions. And, again, in terms of questions,

there's sort of like two buckets of things. We're happy to talk more about the evidence if you'd like to talk about that. But, more importantly, if there is anything that we haven't touched on that you think would be helpful for February, I'd really like to hear about that.

DR. JOSEPH BOCCHINI: Thank you, Alex and K.K. Questions and comments from the Committee. Joan?

MS. JOAN SCOTT: So, you started to touch on it a little bit briefly here at the end, but I guess it would be helpful to know how clear the followup treatment protocols are and how much consensus there may be or not amongst the clinicians who -- who will be seeing the children who are identified about when to treat and when not to treat and the potential harms both of treating too soon or treating too late because that's going to put -- you know -- the ability to identify, but then what happens afterwards is just as critically important.

DR. KEMPER: Okay, we'll make sure to do that. That's a great point.

DR. LAM: Yeah, and I might add also -- we actually just got this -- I guess it was yesterday -- a beginning summary piece. There is a -- what is it -- an MVS Treatment Consensus Group of Experts who are

currently as we speak working on this very issue.

DR. KEMPER: Yeah, so Cure SMA is -- has -- is leading that, and they have a Delphi process. But, it will be interesting once this comes up too to find out like -- you know -- this is what the experts in the field are really doing as well.

DR. JOSEPH BOCCHINI: Jeff?

DR. JEFFREY BROSCO: Jeff Brosco. Alex, could you go back to the slide that has the -- I guess it's the ENDEAR study where you have before 12 weeks and after 12 weeks, and just a quick question about that, if you know. Yeah, that's the one.

So, is there a possibility that the difference between them is that the group C -- the greater than 12 weeks -- had a more severe form and that's why they had symptoms for a longer time? Do we know the age at which they started treating or is that something you can figure out?

DR. KEMPER: Yeah. So, there's likely to be a million confounders, and I don't know if we can really comment on that.

DR. LAM: Yeah. At this point, this particular secondary analysis -- so to speak -- of the ENDEAR study

was from a conference, and while it was pretty detailed, those are very good questions, and we have wondered are there age issues and what not. We don't know at this point. So, that's one slight limitation as a gray-lit piece. But, yes.

DR. JOSEPH BOCCHINI: Okay. I have Dieter and then Sue.

DR. DIETRICH MATERN: Yeah. Dieter Matern. Two -- two -- one question and one comment. The question is also relating to this type of data. Given that patients have been identified because of an affected older sibling -- I mean -- shouldn't there be data coming out now that indicates how patients fare that are really picked up through newborn testing? So, I think that would be important.

And, my comment -- on October 10th, the Minnesota Advisory Committee that advises the Commissioner in Minnesota met and for whatever reason, a vote happened, and SMA was recommended to the Commissioner to be included in the Minnesota Panel. But, as far as I know, there was no legislative action taken 2 days later unless Amy Gaviglio or anyone from Minnesota can --

[Speaking off mic.]

DR. DIETRICH MATERN: So, Minnesota is waiting for the Commissioner to respond to that?

DR. LAM: You're absolutely right. Yeah.

DR. JOSEPH BOCCHINI: Beth?

DR. LAM: If we can just briefly report -- I believe also, in terms of your first question, the NURTURE study is the current trial with pre-symptomatic infants. It's at an earlier stage, but some interim results have come out that do seem very positive. It's -- I think it's 20.

DR. KEMPER: It's not a trial in that everyone is getting treated.

DR. LAM: Right.

DR. KEMPER: So, they're comparing -- yeah, it's an open label trial. So, they're comparing it to historic norms.

DR. JOSEPH BOCCHINI: Okay. Sue, then Beth. Okay. And Annamarie, and Mei.

DR. SUSAN BERRY: So, Sue Berry. Yeah, I think all three of the missions -- like this -- when anybody says anything about legislation because that's not how it works. It also shows how we're overrepresented, sorry.

So, the question that I -- that I wanted to kind of toss out here -- I don't think it was part of what you reviewed here or maybe even what we'll discuss. But, the cost of the treatment -- we were kind of doing a back of the envelope calculation based on how many babies would be born in a given state. And, it's a pretty stunning number. Is that going to be an element of our discussion or our review?

DR. KEMPER: Well -- I mean -- certainly, you're free to discuss anything. But, in terms of -- you know -- our scope and mandate in terms of costs, we're really limited to the costs that it would take for the Newborn Screening Program to take it up. I appreciate that there are -- you know -- concerns about access to the therapy -- you know -- which is expensive. But, in terms of that component, that really goes beyond -- you know -- what our particular mission is. And, although most of the other things, I think we'll be able to get to. I think that is going to be our goal.

DR. LAM: Yeah. We won't -- it won't be part of the -- you know -- as we -- we said from our cost assessment methods development -- it won't be a full part of that. But, there are articles -- not fully studies --

not cost studies per se -- but, there are articles that document it. It's quite well known the pricing of nusinersen, Spinraza, etc. And, so we will be able to address it in the narrative context and background.

DR. KEMPER: Right. So -- you know -- that's a contextual issue, so we can provide you with that information. But, there's going to be no new -- you know -- analysis about that from our side.

DR. JOSEPH BOCCHINI: Dieter, did you want to respond to something that was said?

DR. DIETRICH MATERN: Yes. Dieter Matern, again. So, at the Minnesota Advisory Committee meeting in October, there was discussion about this as well, and the members of the Committee were informed that BioGen actually has a program to provide treatment for anyone, even if they can't afford it, which of course I then suggested they should give it to free for everyone. So, I repeat that suggestion here.

DR. JOSEPH BOCCHINI: So, before we do the next questions, we're going to move this to webcast at 3:00. So, we have just a few minutes before it ends, so we're going to try to complete these questions. And, if there are additional questions, we certainly can get them to

the workgroup through our two representatives who are on the workgroup as well as directly with Alex.

DR. KEMPER: Yeah, and I could just add in -- again, if there is something in particular you think is really critical that we address, and you think about it later, send us an E-mail. But -- you know -- pretty soon we're going to have to close the door in terms of our ability to gather new evidence so that we can complete things in time for February and have it -- you know -- really evaluated by peers and that kind of thing.

DR. JOSEPH BOCCHINI: Okay. Beth?

DR. BETH TARINI: [No audible response.]

DR. JOSEPH BOCCHINI: Pass? Okay. Then, Mei. She's okay. And then, Annamarie?

MS. ANNAMARIE SAARINEN: Do you want me to go first? Sorry.

DR. JOSEPH BOCCHINI: Yes. They all passed.

DR. KEMPER: They ceded their time to you.

MS. ANNAMARIE SAARINEN: Wow. That's awesome.

Why do we as part of evidence review need to be talking about how we dictate clinical followup? And, I'm not questioning really Joan's question -- I'm just glad

she raised it, actually, because it reminds me a little bit of how we're just kind of trying to find it because we've shown through that evidence review that it's appropriate -- you know -- recurrence rate does not follow all the reasons that we put something forward for evidence review. At the point of being able to find an SMA1 or SMA2 case, I really -- I do think these things kind of pass out of newborn screening hands a little bit -- open communication, outcomes, and those sorts of data reporting things. But -- I mean -- we're not really doing that as part of this process, are we? Question -- sorry -- that's one.

Two. Who's -- I don't need to know the names -- but, among your Expert Workgroup -- do you have any advocates or parents just even one or two?

DR. KEMPER: Yes. So, let me do the second one first. We have a parent advocate who we've invited to the Technical Expert Panel. She was on the first one. She had a conflict for the second one. But, she has a child that's being treated with nusinersen, and we actually think it's really important to have that voice in our process, even though -- you know -- at the end of the day, we're just trying to look for the -- you know --

the facts, being able to understand that things to look for is helpful and is something that we really strive to do.

Going back to your first question -- you know -- I understand what you mean in terms of like -- you know -- we're not developing clinical guidelines for people. We're looking at whether or not newborn screening -- you know -- the relative balance of benefits and harms. But -- you know -- in all the other projects we've done, we always look and see if there's some sort of consensus about what to do once you identify a case, because -- you know -- it informs how the Newborn Screening Programs -- you know -- operate and whether or not there is -- you know -- the benefit that we see from studies could be translated to care. I mean -- maybe you can even think about that on the -- you know -- the feasibility side of doing things. You have to kind of know what you do when you find a case. It's not -- you know -- having full consensus from everyone. You know -- it's up to the Advisory Committee about -- you know -- how much of a factor that is. But, at least understanding whether or not people know what to do with cases that are identified through newborn screening is important.

MS. ANNAMARIE SAARINEN: Right. I think -- I think that access to care issue is -- is a bigger concern, or ought to be maybe a bigger concern for this Committee than once they get access to care -- how those decisions are being made based on that specific clinical case because it's just so -- there's no vanilla box. I imagine there isn't for SMA. We only have -- you know -- we have friends who lost a child to SMA at 18 months old, and I just know how torturous that journey was for them, but, yet their daughter's case was different.

DR. KEMPER: So, if I could just build on something. I didn't really mention this before, but we -- we are focused on nusinersen as the treatment. But, nusinersen is a component of a much more complex therapy that individuals affected with SMA get in terms of -- you know -- the -- you know -- all the -- you know -- the pulmonary evaluation they get, the physical therapy that they get -- you know -- OT/PT thing -- that kind of stuff. I mean -- there's a much bigger package. But, the reason that we focus on nusinersen alone is that it's the really -- it's the thing that it's the thing that's changed the care so dramatically, and it's the one where there are systematic trials we can look at. So, I think

that gets to your point as well.

MS. ANNAMARIE SAARINEN: Can I -- I'm so sorry to -- I have my four-tiered questions here. But, the other one was when you mentioned that we're targeting the most severe cases of SMA, obviously that's true. I'm looking forward to the final report and seeing if you're going to be able to touch on that the screening is also -- that it's not a bad thing that we're identifying clinically significant -- whether those are considered secondary targets or however they're being framed in the conversation. I just -- I know you and I have had this discussion a few times before -- but, I think it goes to equity a little bit. I mean -- when you have cases that might not be life-threatening in the immediate phase or might not need that sort of intense treatment in the immediate phase, but once those children that have severe cases -- we just worry about whether they're going to get the care they need.

DR. KEMPER: Right, and if I -- I'm just going to magnify your point too. We know that it's what -- about 60% of kids have type 1 SMA, which means that 40% have a different type. But, it's really where the data are for those -- you know -- most of the data is

concentrated on those more severely affected individuals. So, again, I don't mean to give short stick to those that are less severely affected.

MS. ANNAMARIE SAARINEN: I think the three studies will help kind of fill it out, and hopefully you'll get some more data before the next one as well.

And, just for Dr. Bocchini, I will just say this having been at the meeting in October, Dr. Matern sort of mentioned that we're not sure why we took the vote. From my perspective, we didn't as a Committee take that vote in Minnesota because we were in any way discounting the important work of this Committee, in fact we paid very, very close attention to the work of this Committee. So, I just wanted to say that for the record.

However, we have a process. We only meet twice a year. I think we are in a unique position in the state of Minnesota to have treatment studies happening. We have experts at our three hospitals in Minnesota that have been providing our Committee data for 18 solid months, and we felt fairly in a decent place to make the recommendation to the Commissioner, having SCID multiplex in place as well was a consideration. But, I do think we just felt with the timing of things that this might maybe

put us a little bit ahead of the game knowing that the Commissioner had time to consider and that there may be action taken, and he may, indeed, decide, and probably will decide to wait to sign anything until after our next meeting. So, I just wanted to put that out there.

DR. JOSEPH BOCCHINI: Have we lost the feed? Do we still have the webcast, or is it gone? I just wanted -- if we're going to lose the webcast, I just wanted to remind the people on the webcast -- oh, we have two minutes? Perfect. I want to remind people that we start again at 9:30 tomorrow morning and that those of you on the webcast who are going to call in for the workgroup meetings, the workgroup meetings will start in about 10 minutes from now, and you can call in at that point.

DR. SCOTT SHONE: Scott Shone. So, just thinking of what Annamarie said, I wonder if making sure that the data in the evidence review that was used in the Minnesota decision is also part of the one that you guys are doing -- if it was -- like she mentioned -- the data that has been provided to that Advisory group also comes to this group. But, that wasn't my point.

My point is from the systems impact -- and,

this might be something for Jelilli -- but, I went back and looked. So -- you know -- SCID was recommended at the beginning of this decade. Forty-four states are screening for SCID. Pompe at the beginning of 2015 -- only 7 states. MPS1 and X-ALD earlier last year -- 5 and 7 states respectively. And, I know many of our colleagues are working diligently to get these disorders added, but that's the landscape of the Newborn Screening Programs at the moment -- trying to add these. Joshua Miller presented -- had a wonderful talk this morning about the challenges of timeliness.

So, I'm wondering if -- not in the scope of whether or not the disorder should be recommended in February -- but, as part of the information process presented to the Committee if, as going forward, is part of a gaps analysis and recommendations we can make to the Secretary of here's the challenges, and here's additional resources -- again, not necessarily all fiscal -- but, here's additional resources to help move the ball forward because this is now on top of four or five other mandates recommendations, but -- you know -- carrying a lot of weight that this Committee has put forward.

And, so, I don't believe the public health

system impact looks at that, but I wonder if there's an ability to gather some of that data over the next several months through the new disorders work that NewSTEPs is going or some other mechanism to look at how this fits into the broader picture of what all these programs are already facing.

DR. KEMPER: Yeah. I mean -- certainly we've talked to our NewSTEPs colleagues, and we'd be interested in finding out if they have any more. We're a little bit stuck in terms of the range of things that we can ask about in the Public Health System Impact Assessment and part of it because the OMB process that we have to go through before we can send surveys out to the states to the degree that we can get this when we do the deep-dive interviews, we can find out about that. But, I do think that -- you know -- in the future, there's -- you know -- a significant argument could be made for revisiting the kinds of questions that we ask states and how we go about doing that. I think that we're sort of stuck where we are right now with the kind of data that we can get.

DR. JOSEPH BOCCHINI: Beth?

DR. BETH TARINI: Beth Tarini. A quick response to Annamarie's point about treatment. I agree

that I don't think we are in the position to sort of be in the room with the patient and the provider when they're making decisions about the treatment, but at the same time, when we recommend mandating meaning requiring by law that the child be screened despite parental choice and override that choice or the opportunity for that choice, I think we do have some degree of responsibility to insure that there is at least some consensus -- they don't have to be perfect -- on how that child is going to be treated. One -- simply I think from an ethics perspective that we've mandated this, so we should have some sense that the people that are giving treatment that they sort of have some consensus on. And, two -- the equity argument that's been long used in newborn screening that birthed this Committee -- no pun intended -- that is that there can be an inequity if you are in a state in which one provider or one set of providers believe one way is the right way to treat it, and that ends up not being the right way -- that child does not have any access to appropriate care. And, if you get divisions and/or inequities like that -- I think that could be problematic for the cases -- the children and their families who identify.

So, I think it's a judgement call, of course, and some degree of consistency is, I think, what we're looking for.

DR. KEMPER: I lost my clicker, and I feel like my power is gone.

DR. JOSEPH BOCCHINI: Okay. Thank you, Alex and K.K., thank you for the Committee. I think good discussion.

We're now ready to initiate the workgroup meetings a couple of minutes behind schedule. This slide shows you where each of the three workgroups will meet -- which rooms you'll be in.

And, then last meeting we began the process of asking each of the workgroups to give us a timeline for completion of current projects and begin the process of thinking about what additional needs, gaps, barriers, and challenges that are identified within your workgroup area to begin to propose potential projects and other things moving forward that you could bring for consideration by the Committee.

And, so this is a template that we put together. So, as you think about each potential program or project or other thing to consider, what would be the

purpose, who would we be educating and assisting Newborn Programs in the individual states, would we be providing information, etc., what's the need for this, the gap that exists, the barrier and challenge that the activity is addressing, what kind of activity would it be, and/or what is the intended final project, and then product for the project, and then an estimated timeline. So, if you'll begin that process, and then perhaps when you report tomorrow, if you have additional things, we'll begin to look at it as a Committee and then begin the process of considering which might be the most important.

So, with that, Catharine, are there addition things to bring forward?

DR. CATHARINE RILEY: Thank you, Dr. Bocchini. Just some logistics for those who want to attend the workgroup meetings. There are signs just out here in the atrium for each workgroup. There will be an escort by those signs. We also have the room numbers here. If you can make your way to those rooms if you're in one of these workgroups. They will be starting the workgroup meetings at 3:15.

So, thank you so much, and we'll reconvene tomorrow at 9:30 a.m. Thank you.

[Whereupon, the above-entitled matter was concluded at 3:08 p.m.]