U.S. DEPARTMENT OF HEALTH & HUMAN SERVICES
HEALTH RESOURCES AND SERVICES ADMINISTRATION
(HRSA)

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ADVISORY COMMITTEE ON HERITABLE DISORDERS
IN NEWBORNS AND CHILDREN

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MEETING

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FRIDAY
AUGUST 26, 2016

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The Advisory Committee met in the Terrace Level Conference Room, 3635 Fishers Lane, Rockville, Maryland, at 9:00 a.m., Dr. Joseph A. Bocchini, Jr., Chairperson, presiding.

MEMBERS PRESENT
JOSEPH A. BOCCHINI, JR., MD, Louisiana State University; Chairperson
DON BAILEY, PhD, MEd, RTI International
MEI WANG BAKER, MD, Wisconsin State Laboratory of Hygiene
JEFFREY P. BROSCO, MD, PhD, University of Miami
FRED LOREY, PhD, International Society of Neonatal Screening
STEPHEN MCDONOUGH, MD, Retired Pediatrician
DIETRICH MATERN, PhD, Mayo Clinic
ANNAMARIE SAARINEN, Newborn Foundation
BETH TARINI, MD, MS, FAAP, University of Iowa
CATHERINE A.L. WICKLUND, MS, CGC, Northwestern University

EX OFFICIO MEMBERS

CARLA CUTHBERT, PhD, FACMG, FCCMG, Centers for Disease Control and Prevention (CDC)
KELLIE KELM, PhD, Food and Drug Administration (FDA)
MELISSA PARISI, MD, National Institute of Child Health and Human Development(NICHD), National Institutes of Health (NIH)
JOAN SCOTT, MS, CGC, Health Resources and Services Administration (HRSA)

ALSO PRESENT

DEBI SARKAR, Designated Federal Official, HRSA
NATASHA BONHOMME, Genetic Alliance
AMY COCHRAN, PhD, University of Michigan
SIOBHAN DOLAN, MD, MPH, March of Dimes
CAROL GREENE, Society for Inherited Metabolic Disorders
ADAM KANIS, MD, Department of Defense*
YVONNE KELLAR-GUENTHER, PhD, University of Colorado School of Public Health
ALEX KEMPER, MD, MPH, MS, Duke University Clinical Research institute and Department of Pediatrics
CHRISTOPHER KUS, MD, Association of State and Territorial Health Officials*
JENNIFER M. KWON, MD, MPH, FAAN, Golisano Children's Hospital, University of Rochester*
ROBERT OSTRANDER, MD, American Academy of Family Physicians
SHARMINI ROGERS, MBBS, MPH, Missouri Department of Health and Senior Services*
SUSAN TANKSLEY, PhD, Association of Public Health Laboratories
CATE VOCKLEY, National Society of Genetic Counselors
MICHAEL WATSON, MD, American College of Medical Genetics and Genomics (ACMG)

*via telephone

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

9:03 a.m.

CHAIR BOCCHINI: Thank you, good morning. Welcome, everyone, to the second day of the August 2016 Advisory Committee on Heritable Disorders in Newborns and Children meeting.

We'll start by doing a roll call. Don Bailey?

MEMBER BAILEY: Here.

CHAIR BOCCHINI: Mei Baker.

MEMBER BAKER: Here.

CHAIR BOCCHINI: Jeff Brosco.

MEMBER BROSCO: Here.

CHAIR BOCCHINI: Carla Cuthbert.

MEMBER CUTHBERT: Here.

CHAIR BOCCHINI: Kelly Kelm.

MEMBER KELM: Here.

CHAIR BOCCHINI: Fred Lorey.

MEMBER LOREY: Here.

CHAIR BOCCHINI: Dietrich Matern.

MEMBER MATERN: Here.

CHAIR BOCCHINI: Steve McDonough.

MEMBER MCDONOUGH: Here.

CHAIR BOCCHINI: Melissa Parisi.

MEMBER PARISI: Here.

CHAIR BOCCHINI: Annamarie Saarinen. I know she's here. Okay. Joan Scott.

MEMBER SCOTT: Here.

CHAIR BOCCHINI: Beth Tarini.

MEMBER TARINI: Here.

CHAIR BOCCHINI: And then Cathy is not able to be here today. Debi Sarkar?

MS. SARKAR: Here.

CHAIR BOCCHINI: And then the organizational representatives. Robert Ostrander?

DR. OSTRANDER: Here.

CHAIR BOCCHINI: Michael Watson.

DR. WATSON: Here.

CHAIR BOCCHINI: Joseph Biggio by phone. Susan Tanksley.

DR. TANKSLEY: Here.

CHAIR BOCCHINI: Chris Kus by phone.

DR. KUS: Here.

CHAIR BOCCHINI: Adam Kanis by phone.

DR. KANIS: Here.

CHAIR BOCCHINI: Natasha Bonhomme.

MS. BONHOMME: Here.

CHAIR BOCCHINI: Siobhan Dolan.

MS. DOLAN: Here.

CHAIR BOCCHINI: Cate Vockley.

MS. VOCKLEY: Here.

CHAIR BOCCHINI: Carol Greene.

DR. GREENE: Here.

CHAIR BOCCHINI: All right, thank you all.

Today we're going to start with a couple of presentations related to newborn screening timeliness.

And first we have Yvonne Kellar-Guenther who's going to discuss newborn screening timeliness, the Collaborative Improvement and Innovation Network, the CoIIN

Network.

Dr. Kellar-Guenther is an associate professor at the Colorado School of Public Health. She is program evaluator for NewSTEPs and is the associate director for NewSTEPs 360, both HRSA funded projects.

She also was the lead for the NewSTEPs timeliness CoIIN initiative.

In addition to her work on NewSTEPs Dr. Kellar-Guenther is the program evaluator on several public health projects and teaches program evaluation at CSPH.

So, welcome. I look forward to your presentation.

DR. KELLAR-GUENTHER: Thank you. So thanks for inviting me to speak this morning. I'm very excited and very honored to share with you the work that we did as part of CoIIN, and then to also tell you about some of the other timeliness work that we're doing at NewSTEPs.

So first I'm going to start with what

is a CoIIN. So it's a lovely acronym and I forget it each time so I have to read it.

It's a collaborative improvement and innovation network. And the idea, CoIIN is a learning collaborative.

So we brought together seven states and they have to share. They share resources. They share successes, but they also share failures.

So the other part of CoIIN is that the emphasis is on quality improvement, not quality assurance. So together we learn. We learn from what's going well, what's not going well, and share all of those things.

So the other part of CoIIN is that we use technology. So we met via teleconference, but we started meeting face to face.

Because if you're going to tell people what's not going well, and what's not working you need to actually kind of see each other to kind of get some trust and some relationships going.

So this was a 15-month program and it

was unfunded for the states. So they put in an application, said yes, please, I'd like to do work with you but unfunded for 15 months.

And so we had seven states that joined us.

And we required the states to have teams, and their teams were three to five people.

But we required an interdisciplinary approach. So we had to have a newborn screening laboratorian, we had to have a newborn screening follow-up, and we had to have the hospital involved.

And so we've been hearing throughout this meeting newborn screening is a system. We're very interested in having the parts of that system there as part of the team.

So, these should look very familiar to you. So these are the timeliness recommendations put forth by this committee.

These came out a month after we started. But we still adopted most of them as our benchmarks

and I'll tell you where we kind of deviated from what you suggested.

But we were looking at activities that would improve the percentage of children whose findings were reported out no later than five days of life for critical conditions, no later than seven days of life for all the reports from the newborn screening.

These are the other parts of the recommendations. So we were very interested in how people could get the collection from 48 hours of birth, you get that first blood spot collected, and then also how quickly could it be received at the lab.

So, we actually didn't go with 24 hours at collection because I said this came out after. We were looking at 48 hours of collection. So that's one of the places that we deviated.

And we used the NewSTEPs quality improvement indicators to kind of look at the different pieces of the system.

So we were very interested in the time it took from birth to collection with an emphasis on that 48 hours.

We were interested in the time it took from specimen collection to receipt by lab which we used as 48 hours.

We were interested in the time it took from specimen receipt to reporting out complete out of results.

And then of course, the big one, from birth to complete out of results.

So, what did we learn? So, for the first indicator, specimen collection before 48 hours of life.

So this graph actually represents how the states did as a group. So it's all seven states, it's the median for each month of the percentage of dried blood spots that were collected within 48 hours of birth.

We have some high-achieving states. So we started at 91.6 percent and as a group we were

able to meet our 95 percent benchmark. So, as a conglomerate we reached that goal.

This actually shows the individual states. And so you can kind of see it hiding in there.

At the 95 percent is a bar, a purple bar, and that's the goal. That's where we were going.

And so as you can see there were four states that were where we wanted, at that 95 percent, and other states had definitely shown progress.

What's important is we started this and we didn't tell them that they had to actually -- this wasn't one of the goals that we mandated. So five states really were working on this.

So these are the five states that were spending their efforts trying to improve collection within 48 hours of birth.

And what you should notice is they all have progress. So, in a short period of time people were able to really make some great strides.

And people started low. So, some people were under 80 percent and were able to get up close or have a big jump closer to 95 percent.

So, how did they make these changes? So, it's a learning collaborative. We talk about barriers. We talk about how to overcome those barriers.

So, one of the first barriers is hospitals don't actually know the recommendations. And again, given the timing that makes sense of when this occurred, but we have to actually let hospitals know here's actually the bar that we're looking for.

And when they did know the bar they didn't actually know how well they were doing.

And so one of the things that came out was to provide hospital reports.

And so this is a sample report. We had several states do reports, but this is a sample report from one of the states.

And there's a lot of things that I like

about this report. One is it's very clear to see where the state average is, it's the blue bar, and it's very easy for this hospital to know where they are. So they're the yellow bar along the bottom.

But you could watch this. In this state you could actually -- the hospitals could see their bar move.

One thing to note is this state chose to de-identify -- or to keep it de-identified. So you can see numbers, but you don't actually -- they don't know who's in the top, they don't know who's in the bottom which is important. Some states chose to make it identifiable, some did not.

The other thing that you'll notice about this report is you see red, yellow and green.

In one of our first early learning sessions we brought in a data visualization expert who talked to us on the phone about layout, colors. So is it horizontal, is it vertical. And so this report really kind of reflects a lot of things that we learned from a data visualization expert.

The other thing I like about this report, this team worked very closely with the hospitals and they'd keep bringing back versions to try to make sure it was clear.

So it's not just get it out there, it's get it out there in a way that makes sense and at a glance people can kind of see where they are and where they need to be going.

So, report cards were awesome, but they don't always make it to the people who actually need to see the report. So that was another lesson learned.

So people were sending it to different roles within the hospital, and sometimes they got shared and sometimes they didn't.

And so there was a lot of education to hospitals about the value of sharing the report. And there was a lot of discussion about who you aimed to get to the report out to.

So, you get it to the nursing supervisor. She may or may not share it with staff

and that would be great.

But it turns out if you bring in risk management at a hospital they might add a little more buy-in.

And so it really was hospital to hospital, but the states spent time kind of figuring out who should get the reports.

And often they added to the list versus substituting people on the list so more people were getting the report.

Three of our states actually did surveys to hospitals to find out what they knew, where they were at with things.

One of the things that came out for one state was just slightly more than one-third recalled watching the CLSI video. All hospitals got it. It's there in the hospital somewhere, but people aren't pulling it out to educate.

And so what this state decided to do was do point of care messaging. So they created posters that got hung up in the nursery, in the NICU

so that people doing it right there and then could see and be reminded of the message.

And so this is one of the posters that was created.

And this was very innovative. They worked with their local university to actually get this done on a very, very good budget.

And it highlights everything. On this poster I know when to collect, I know how to long to dry, I know when it's supposed to be shipped to me. So it's all right there and I can place it.

And it doesn't matter if I'm the night shift, or the morning shift, I've got it there in front of me.

The same program also created another poster where they were emphasizing demographic information. Because blood spots can arrive, but if you can't find out how to contact them about the results you're still kind of missing that end piece.

And so this was another poster that they

had. And for one of their own benchmarks they were looking at accuracy of information.

Another barrier, big barrier is state legislation. So, we're saying hey, you really want to get it no later than 48 hours of life.

For this state when we started their state legislation said that the blood specimen should be collected between the second and sixth day of age. So they're saying not to even start until after 48 hours.

And some hospitals are willing to say, you know, the state's saying 48, I'll go with it. And some are saying no way, the legislation says don't start until 48. I'm not going for it.

And this won't shock you - in the 15 months they didn't get it changed, but in 19 months they did.

So as of July they have new legislation. And right now it reads a specimen collection shall occur after 12 hours but no later than 96. But the good news is it's open comment period and they're

working to get that down to 48. So that's a hard change to make, but they were able to do it in 19 months. So that's our collection time.

Another thing that we looked at is specimen receipt. And it's really interesting. I was talking to Stan yesterday, Stan Berberich, and we were talking about timeliness.

You know, you focus on the things that really affect the whole continuum, but there are changes that you can make that make changes in days instead of just hours.

And this quality indicator really is a place where you can start making some changes in days.

So, we're looking at specimens received at newborn screening lab within 48 hours of collection.

So, as a group, so this is all seven states as a group the median was 68 percent when we started, and we were able to boost it up to 80 which is a pretty big jump.

And what you see is there was a lot of movement here. And so there are activities that we found that really helped to increase this.

So, one of the biggest barriers still is the education. So hospitals don't know what they're aiming for.

So this is another state who provided reports. And if you look at those purple dotted lines that follows the months that reports were released.

So this state released reports and they did it in an identifiable way. So you knew where you were and everyone else knew where you were.

And you see that that really leads to action for a few months. And so all of a sudden they would get a lot of calls. People were very interested in education.

And then you see there's a little bit of a plateau. And so they released another report. And again they got some action.

And so the timing of reports is

something that we see our 360 sites kind of looking at is how often do you report because you do get movement.

One of the ways to make a big change is to change laboratory hours. So, some of the states that came on to the CoIIN in that first day when we were meeting and we were talking about root causes of the problem of timeliness, they identified their lab only being open five days a week as a major problem, major barrier to them hitting their timeliness goals.

So, two states were impacted by this lab that were in the CoIIN. And in March this laboratory began to be open six days a week instead of five days.

And this is important. They were open on the sixth day to receive and to process, which is different. Some labs just open to receive but not to process. So this one was open to receive and to process. The indicator was more about receipt.

But you see that for one state they went

from 12 percent being received within 48 hours to 53 percent being received within 48 hours. And then the other was 45.

The goal line is orange because here is a place that we deviated. You are recommending 24. We looked at 48. So our bar is a little different than what this committee has recommended. So I didn't give us a purple bar there.

So, changing the laboratory hours was great and we got a big bump, but one of the big lessons learned is opening an extra day is not the silver bullet that takes you from zero to 95 percent. And I think that that's important.

There's a lot of other ways that you can kind of get that extra movement, but from a quality improvement standpoint one of the things that you see is this change is important and it has a big impact, but it plateaus.

And so they were able to get very high, you know, they're at 70 percent, 53 percent. Iowa has allowed me to de-identify them for this.

Iowa actually is open 7 days a week, 24 hours a day, and they were our only state at the 48 hour to actually be over that 95 percent benchmark that we set.

And so by doing that they were able to reach the 95 percent.

But here's an important message that I think people may want to consider. Iowa isn't at 95 percent for the 24 hours. For specimens received within 24 hours they're at 50 percent.

And what I'd say is maybe -- the 48-hour is potentially a benchmark that should be considered because Iowa is at 100 percent for results reported within seven days of life, and at 100 percent for critical results reported within five days.

So they're meeting the true end goal, but they're not meeting this one benchmark. And so that's just something to think about as we think about the different benchmarks moving forward for timeliness.

So, being there to receive it is great, but it has to get there. So the other big change that we saw here was courier service.

So, specimens spend too much time in transport. The mail is a horrible way to get specimens. And so one of our sites began a courier system and then other sites expanded their courier system.

So this is actually from a site that began a courier system. And they rolled it out within three regions of the state. So they cut the state into three pieces.

And what you see is the total hours from before the change of how long it took for specimens to get to the lab versus after the change.

So in the eastern part of this state it took 84 hours to get to the lab, but they were able to drop it to 44. Not 24, 44.

You've got the same with the 64 to 39. It went from 89 hours to 49 hours. So adding a courier statewide got them within that 48-hour

benchmark that we set for CoIIN.

This state actually had a courier system, but they still don't have it statewide, and they didn't have it statewide.

But one of the things that they did is they added more birthing centers. And so they added 25 percent more facilities to their courier program and you see that in that addition they're able to get up and get a little bit of a bump.

So the couriers definitely help meet that timeliness as we've set it in terms of collection to receipt by lab.

Another one of my favorite lessons learned from CoIIN.

So we had a state who had courier service and in their contract they had Saturday courier pickup. But time had passed and they realized that the courier wasn't actually running on Saturdays.

And so a very easy thing to change. And when they came together for that face-to-face

meeting they were like oh, that's interesting, we actually have Saturday in our contracts but it's not happening.

And we figured that out in January, but it didn't get changed till June because while it sounds easy to just say it's in the contract, do it, it's not.

Because part of the problem was the hospitals were saying don't come. And that was because the hospitals thought they were paying for the courier even though they weren't.

So there was education to the hospitals, you're not the one actually paying for this, and they need to come even if you don't have anything. And so it took a while to get that systems change.

But again, once it got reinstated then you see more samples getting to the lab in a timely manner.

Another thing that we ran into just kind of talking to the states is the way the courier

works they have a route.

And so one state was looking at which hospitals weren't working and they were looking at that 24-hour goal. They were looking at who wasn't meeting that 24-hour goal.

And they found that it was the ones that were earlier, closer to the state health department but earlier on the courier route were having a hard time kind of getting the specimens ready for pickup.

So, a lot of our states have actually worked very closely with hospitals. Like we said, there was a hospital lab and they've talked about how to troubleshoot.

This specific state hasn't figured out the 24-hour piece, but in terms of the 48-hour piece people talked about having -- some hospitals have laboratory staff gather the specimens instead of nursing so they can do it at a specific time.

One hospital actually changed where the pickup occurred.

So for this hospital -- this is a hospital. For this hospital the nurses were busy and they couldn't get the dried specimens down to the lab for the courier.

And so they had a meeting, they talked and they were like let's just have the courier go up to the birthing unit.

They went from over 30 percent being late to less than 10 percent being late. So that little change had a big impact for that hospital.

So that communication and really working with that system is important as we troubleshoot and think through timeliness.

Just like laboratory hours couriers hit a plateau. So it's really helpful, but you kind of hit a spot where you need a little bit more to get past.

And one of the things to think about is actually the number of days that the courier picks up.

So this is a state that went from no

courier to courier. And it was a huge jump from under 40 percent to close to 80. They really thought that the courier would get them to 95, but the courier's coming six days a week. So one potential thing to think about is could it be seven.

And this is Oklahoma's data. So Oklahoma is part of our 360 project and they just presented to us on their courier system.

And we noticed something interesting when they were presenting. They do two graphs, one for their hospitals that are on seven-day and one for their hospitals that are on five.

And you can see that they actually -- they have allowed us to share this -- they actually identify their hospitals.

So, for the seven-day they have a 95 percent benchmark within 48 hours. And not all of them are making it, but there are some that are making it.

And five-day, no one is making it. And so kind of thinking about how to get the specimens

there, how often to get them there and are people there to receive them and to run them.

So, our next piece of the quality indicator that we looked at was results reported out within three days of lab receipt. And now we're going to start to see some drop-offs.

So, the last two pieces were hard for all of our states to give us data because of what was being collected when we started this project.

We aimed for three days and that was made by us. So, what we did is we took the timeline of when we wanted things reported out, we took the other recommendations.

So they had 48 hours to collect the specimen. They for us had 48 hours to get it in. So if they were going to report out in seven days they really had no more than three from when they received it to when they were reporting out.

So again our benchmark is orange because it's one that we set. But you can see there was a lot of progress for this one, but we hit a

peak and then came down. So some interesting things were happening.

So as a group for the four we went from 25 percent to we ended up at 57. So what's going on?

So these are the individual states. And so you can see that the green state has some ongoing things that are happening. So one month they have it, one month they don't.

And then I'll de-identify the purple state because they've allowed me to. That's California. And one of their changes is they brought on SCID -- well, they had SCID, sorry, they had SCID while they were doing CoIIN.

But in California they have regional labs and then they have a state lab. And when a new condition comes on if there's no FDA-approved test then it has to go to the state lab.

And so they can release most of their results in a timely fashion, but that one result takes a little longer when they have to go through

the state lab.

And so the minute they got it FDA approved they shot up. But that was the problem for them. They're going to roll out new testing soon, so they expect to see a repeat of this.

The other state that has a line that looks like it was a struggle, they had some personnel, so they had a shift in personnel.

But then when the SCID testing began for them in January they took a dive just because they were short-staffed, it's the holidays, and they have a new test. So they have a lot of things that they're trying to work out.

So we should expect that as new tests are being rolled out that there's going to be some hit to timeliness in terms of the reporting out.

We don't know enough about this yet, but NewSTEPs just received an award for New Disorders Cooperative Agreement from HRSA and so we'll be kind of exploring that as we move forward with that work.

The other thing, one of the states that was on here had -- they were kind of at zero and then they have a peak. So they actually go up during the holiday season.

That's the other thing that we heard is holidays are a killer. But I've got to say that most months have a holiday so we really need to figure out how to deal with that holiday killer.

But November is especially hard because you have Veterans Day and you have Thanksgiving.

And so this state who has a lot of experience with quality improvement said let's try something different.

We know this rush is coming. Let's try looking at what's going on and staffing differently.

So they get specimens throughout the day, but they get two primary times that specimens come in.

When a specimen comes in it's not necessarily just ready to run. You're going to

have to do some work on it. You have to get it ready.

So, what was happening was the later afternoon would come in and they'd be ready right when people from the laboratory were going home. So specimens are sitting there and they're not being tested.

So they shifted the laboratory hours back so that they would have time to run that second set before they went home. And they saw success.

And they are, again, a quality improvement state. They get it. This is their PDSA cycle. This is their study.

And so in July they started their act which is to actually now they do this as their new way of doing business. And we're looking forward to the data to see what that impact is long-term.

So, the last piece of quality indicator that we looked at was results reported out within seven days of birth. And we didn't do five days for critical because we only had one state that

could provide that data.

So, we have two states that can provide this data.

And so you have one state that did very well. They were above the goal line.

But there's room for improvement. They went from 98 to 100 percent. So they were still doing activities that could improve.

This other state had amazing growth from 9 percent to 32 percent. So what were they doing?

So, this was a state that had already been doing some activity, but what they decided to focus on for CoIIN was poor performing hospitals.

And before this they had been kind of looking at poor performers, but they'd been looking at large hospitals that were poor performers. For CoIIN they looked at all hospitals regardless of size.

And they did some very targeted education efforts. And then they looked at their

courier service and tried to see if there was a way that they could get to these poor performers, or figure out a way that the poor performers could get to a courier.

And so between those efforts they were able to get a 20 percent plus boost.

So, how did we do? Well, we moved the needle, yay, but we're not there. And so there's work to do.

But we made a lot of progress in 15 months. All states made some progress. All states improved.

In terms of their own goals three states met at least one of their goals, but -- that tells you that we're high achievers when we write goals.

But it was great. The states all can show improvement.

So, now what? So, NewSTEPs got some funding, NewSTEPs 360. This is a HRSA-funded project that began almost a year ago to the day.

And to me it's like CoIIN on steroids.

So we took the CoIIN model and we kind of blew it up.

So, instead of working with 7 states, right now we're working with 20. And on the airplane ride home I will be reviewing applications for round two of funding. And we meet next week.

So in September we'll have more states that are joining us and doing efforts to try to improve timeliness in their state.

The goals are the same. So we're really aiming for that 95 percent of the timeliness goals.

Mostly it's the same. There's a few differences. Now we give the states money which is a huge difference to help them start some of their efforts.

Their efforts have to be sustainable when the funding ends. So we're not paying for a service that when the funding goes away they can't continue to pay for.

And then for CoIIN I would call states

periodically and talk to them, but now we're much more targeted in our support and our coaching.

So all states have a coach, a CQI coach, who calls them either every month or every other month and kind of helps them along.

And in that call we get data. So now we have more rigorous data and we're really going to understand those peaks and those troughs because of the way that we're collecting data this time.

But it's still a sharing of resources. It's still looking at the quality indicator data.

So, we've had some stories -- we've had success, but I have a few stories people allowed me to share with you.

So, I had shown you Oklahoma. They recently presented on one of our webinars. And before they were part of CoIIN they had started this effort Every Baby Counts, and they're expanding it as part of CoIIN.

But one of the changes that they made is how often those hospital reports come out. So,

you really need to look along the bottom. And it's Quarter 1, 2016. That's where you see the change.

So, they made some progress on their Every Baby Counts, and they were hitting a little bit of a plateau. By going from quarterly reports to monthly they now have a higher percentage of their hospitals having their specimens arrive within two days of collection. So that's what they're measuring there. So that one changed.

Virginia has made a lot of changes. So, they have more hospitals to their route. They added a Sunday courier. So they're six-day. They went from a five-day to a six-day.

They also did report cards, but theirs are quarterly.

They started doing some education efforts with some of their poor-performing sites.

They put information in the report cards about changes to highlight success stories and let people know what can be done.

And then they also are working on their

LIMS system to capture some of the data that we need to track.

So, this is the three months prior to joining 360, CoIIN on steroids. So, what they marked is the ones in reds are the ones that are taking over three days to get specimens to get to the hospitals, the ones in green are the ones that are making our two-day mark and the ones in yellow are the coming in the right direction.

This is three months after joining CoIIN. So, in that time of six months they had changes from six birthing hospitals. Three were able to come down, and perhaps more importantly, three were able to be within two days. And so their efforts, they're already seeing a change very quickly.

So, Wisconsin is another program that was funded by 360 and they're actually focusing on getting results into the hands of providers faster.

So, instead of mail, they are moving to faxing. And their goal is by December to have 80

percent of their providers receiving faxes.

So, what happens is they have 95 percent of the results verified by the seven days of life. But when you mail those results now you're adding another three days for that report to actually get in the hands of someone who can do something about it.

By faxing you're adding a few hours to get those results into the hands of someone who can do something about it.

But faxing is not easy. It takes a lot of time. There's a lot of things that have to happen.

But here is the success that they're seeing as a result of the change that they're making. So, they're going from less than 10 percent being in the hands within seven days, and now they're over 50 percent. So in a few months they've made a big change just by faxing to the ones that they can reach, and as they add more providers that number will grow.

And then finally for NewSTEPs 360 we have some federal partners. And one of our federal partners is Baby's First Test.

And one of the things that they did for us, for 360 is they conducted a focus group during the AWHONN meeting.

So, Natasha led the focus groups. There was 14 people and they had 8 states represented.

And so here are some of their findings. It really reinforces what we heard from CoIIN states and then also provides some new insight.

So, it turns out getting a blood specimen isn't as easy maybe as we think it is. And I think as we heard yesterday from Jackie that some of the midwives really struggle with how to do that with the equipment, how to do it well.

We've got the different shifts having different information which is we've got the one state that's doing the point of care education so that might be a solution for that one.

Thinking through how to fit newborn screening into the workflow. Those are those conversations that people are having with hospitals. You can't go tell them you need to work with the system.

And our states have found a lot of success by asking them how to make it fit in.

Getting that buy-in. Some of that is who you send the reports in to, but some of it's probably education at the hospitals as to why it matters.

Lots of things are happening. We've got lots of competing priorities. And so trying to get back to that and finding the champion.

And then the sharing of those personal stories. It's interesting, when we do site reviews people go out and we share the reports which are great. But even as we know here those personal stories are really touching and sometimes you have to remind people of who they save as a result, and maybe when things didn't go well so that they

understand the importance. Because that gets lost in the day-to-day routine.

So they're going to submit an abstract to AWHONN to share the findings. So in a qualitative sense they're going to do member checking and share it with the other members, and then have a publication.

So, we are doing great things. We are not there yet. I look forward to in a few years giving you an update again on 360 activities.

So, as with everything that everyone has said it takes a village to do this. So, this is our NewSTEPs team who has helped with CoIIN and is helping with 360.

And these were our amazing, amazing states that were part of CoIIN. I cannot thank them enough for learning with this. They really got to start from the ground up. So, thank you.

(Applause.)

CHAIR BOCCHINI: Yvonne, thank you very much. That was an excellent presentation.

It shows really a remarkable, a wonderful approach and excellent results in a relatively short period of time.

So, very good. We look forward to another report in another 18 months.

Let's start with the discussion. So, Steve and then Joan.

MEMBER MCDONOUGH: I want to thank you for an absolutely outstanding presentation, and I want to thank you so much for the important work that you're doing. You're benefitting many children.

I've only been involved with this committee for five years and many of you have been here longer.

But five years ago when I first came here the first advocates that I met were the parents of children who had died because testing had not been performed adequately.

And to see five years later the process of the Milwaukee Sentinel newspaper doing the

brilliant reporting that they did.

Congress which seems like they do nothing actually got involved and assisted our committee and the public health lab people who were working on this issue.

Our committee made some recommendations a year and a half ago.

I also have to compliment Iowa who does our North Dakota testing, and Stan Berberich and the leadership that he has provided in setting that benchmark for states to get up to.

And just to see the rapid progress that's being made in resolving this issue. It's just so impressive.

Going back where we were five years ago and the parents coming to our committee and where we're at right now.

So I just want to thank you so much for the work that you're doing. And you do an excellent job of presenting that information as well.

I have one question. A year and a half ago in February 2015 when we voted on this issue we set an objective of states -- encouraged states to have 95 percent meeting the objective of test results, time critical in five days and all reports in seven days.

And there was supposed to be a database set up where states were encouraged to report their results.

The question I have I guess for the Genetic Services Branch or MCH is what progress is being made and who they are going to be reporting that information to.

So, thanks so much for what you've done.

DR. KELLAR-GUENTHER: So, I think the database may be the NewSTEPs Data Repository which is -- it's up, it's running. States are entering data in it.

Not all states have MOUs, but many states. And I'm looking out, I don't remember the number that have MOUs. So, 31 states have MOUs and

are entering data.

And we just did a report for the GAO and states submitted -- some that didn't have MOUs were able to submit data to us via Excel files. So we have some of that data.

MEMBER MCDONOUGH: Thank you.

MEMBER TARINI: Yvonne, that was excellent.

Quick question. The term "courier" I find gets used loosely. Not by you, I'm just saying in general.

And I looked it up in the dictionary recently because I said what is a courier. And it literally, my understanding is it just means it's a transport system.

So like, even the mail is technically a courier.

So, do you -- and my understanding also from Dr. Berberich who has educated me on this topic is that outside the mail you then have scheduled couriers in which they are running routes and you

are basically contracting them.

And either they have your route on their route or they don't, and they'll tell you what time they can pick up which tends to be UPS and FedEx.

Or you can contract with a courier in which you can design much like a computer. Like, I would like you to be here at this time, economic.

Do you have any sense of the distribution of those types of couriers amongst the states?

DR. KELLAR-GUENTHER: So, I can't tell you for all the states.

I can tell you that for the CoIIN states they were mostly using state-run courier systems, and so not -- some were using FedEx. There was only a few though. And I don't have an exact distribution.

The ones that brought it on brought on state-run courier systems, and then the ones that expanded were state-run couriers.

MEMBER TARINI: And so the states can

decide when the pickup comes and when the drop-off happens.

DR. KELLAR-GUENTHER: They have contracts with those couriers. I don't know how they're negotiated.

But, so we had a discussion recently for 360 and we were talking about that change in lab hours.

And someone pointed out, look, if you have a contract with a courier it's easier to change that contract than to change the workforce and deal with the union.

And so -- but that's all I can tell you. I don't know, so again I'm looking out to my little NewSTEPs village. Does anyone out there have a better sense?

I know when we collect the data on courier it is up to them to define courier. And that is a discussion we had two days ago about trying to think through how to define that better.

Okay, no one stood up.

CHAIR BOCCHINI: Other questions, comments? Jeff.

MEMBER BROSCO: I join Steve in thanking you for a great presentation. Wonderful work.

Yesterday if I understood correctly we learned from at least one of the states that as they're adding new kinds of tests, particularly genetic and genomic sorts of tests, that it may be harder to meet the deadlines of five and seven days.

Is there some mechanism that you have for figuring that out and either changing the deadlines, or making special dispensation? How does that change?

DR. KELLAR-GUENTHER: So, we haven't had to deal with that yet but under the New Disorders grant we will.

And we're not looking at timeliness per se under there, but we have a readiness tool that we're collecting.

And so we're trying to track the time

that these steps take.

Because right now when people fill out about what's the impact or how long it's going to take it's a guess.

And so we're actually going to collect real-time data to get a sense as to when it starts and how long it really takes.

And there's going to be variation, right, depending on the type of test.

So, my answer is I don't know yet, but ask me again.

MEMBER BAKER: I can comment a little bit because we are experiencing this right now for the CF.

So, the interesting thing we're doing is when they have all the test results available except CFTR mutation we send preliminary report, and also tell them CF mutation test pending.

When we have CF mutation available we send another report. So we're trying to do that.

Another thing is the CF haven't affect

our overall time, 95 percent that much because you only have top 4 percent undergo.

So by going forward that's the issue we need to think about, like Beth said yesterday.

DR. GREENE: That seems like -- again, thank you for a great report. And that seems like a great solution.

Anybody paying attention knows that you've just told them the IRT was abnormal. Because if the CFTR is pending and you're only doing it on the top 4 percent you've just told them the IRT was normal if they know what you're doing.

MEMBER TARINI: Except I don't think most physicians know any of the tests.

I agree with you --

(Simultaneous speaking.)

DR. GREENE: -- you will know, and the pathology will know. And the question is you can see a parent asking questions about that one.

MEMBER TARINI: We're working on this at Michigan because at Michigan they were giving

out the report, positive, presumptive positive, but they weren't giving mutation data.

And the physicians didn't even know to ask for the mutation data.

In addition, when we surveyed the physicians in the state, the primary care physicians, many of them got it wrong, like upwards, if I can remember, 40 percent when we asked them if the screen had two mutations how likely the child was to have CF.

So, I think that -- I agree with you. I am suspicious that the primary care physicians have enough understanding of (a) what's going on, and even if it's there the comprehension of the implications unless they're flat out told to sort of pick up on that.

DR. GREENE: I completely agree. What I am anticipating is farther down the line depending on the state's criteria. And if you decide that you're going to call it negative if it was mutation negative, and then somebody starts

questioning, well, the IRT was positive and another state would have just done a sweat test.

So, it's just -- I mean, to say that it's pending I think -- I've had experience with another state that changed the newborn screening form and actually didn't realize that they were conveying information that they hadn't intended to convey.

So, it does convey additional information to anyone who knows what to look for which could be a lawyer later.

DR. KELLAR-GUENTHER: So I -- and getting back to your point of by saying it's pending it's still not all results. And so it's still not within the seven days, I think. And so that's something that I think we need to work on.

MEMBER BAKER: Yes, I think that's for this specific disease, not for others.

DR. KELLAR-GUENTHER: Right.

MEMBER BAKER: Another thing that I want to be measuring very, very carefully is the CF screening. The algorithm is two steps. Even

you have a top 4 percent I wouldn't convey the information you may -- it's a screening positive. That's not our state educated people.

Because largely people in this top 4 percent is normal. The reason is because you have a second step you allow yourself a little bit liberal.

So, we wouldn't let people think because it's pending potentially -- I mean, 94 is not higher, you have CF.

CHAIR BOCCHINI: Natasha?

MS. BONHOMME: I'll be real quick. Thank you, Yvonne. What a great presentation. I feel really excited that Minnesota is participating in the expanded NewSTEPs 360.

And you'll forgive me for texting during your presentation because I was messaging Amy Gaviglio in the State of Minnesota about are we on six days, or are we on seven days. Like I legitimate didn't know and I wanted to hear what our hurdles were.

It seemed from your presentation that this 24-hour benchmark, and correct me if I'm wrong, it really seems almost unachievable in some ways.

And I don't say that often because, listen, we're in a world today where I can click on Amazon Now and get 40 packs of toilet paper delivered to my house on Christmas Day within an hour.

So, I think to your question about what's the definition of "courier" we have so many innovative new options available to all of us, including the public sector, that might require just a little bit of exploration.

It could be like on our NewSTEPs CCHDTA calls where we provide here's some new recommendations on how you can do this better. Just that whole idea of what transport looks like and how might the mechanisms that are available to us today at not exponential cost to the public health system be available to hospitals. So that

was one thing.

But I wondered about the standard and what may or may not change as a result of this newly funded work.

DR. KELLAR-GUENTHER: So, the recommendation won't change. We'll continue to get data.

And we have a new benchmark. Obviously for 360 we'll use the recommendation versus the other.

I don't know -- so, me not speaking for anyone other than me, I represent no agency, I do wonder if it's unachievable.

But I also wonder does it matter. I mean --

(Simultaneous speaking.)

MEMBER SAARINEN: If you're meeting the five or seven days --

DR. KELLAR-GUENTHER: Right. That's the one that really matters to me, and if that's what's being met then that's -- the rest that goes

into it.

So we use it as a way to kind of say where is there room in the system to improve.

But if 48 hours is the room in the system to improve and that's okay, then yes, I think as long as we meet the five to seven that's the important benchmark to me.

MEMBER TARINI: I just want to quickly -- the five to seven is the metric we're meeting. And I'm going to talk about this too.

But that metric was defined by this committee. And I want to point out that that's a metric we defined.

And if we end up with a child that could have been detected on day four, but we created a system that we're like, well, all we have to do to get to five rather is as fast as we can within reason of cost we are making ourselves -- we are playing to an arbitrary metric.

I'm not saying it's not a good place to start, I'm just saying be satisfied with five if

four is achievable or three is not necessarily acceptable.

DR. KELLAR-GUENTHER: Absolutely.

CHAIR BOCCHINI: And I think that before -- clearly with the timeliness workgroup, what they did was they turned around the question and said what do we want to achieve. And the achievement was seven day results with five days for time critical illnesses, or seven days for time critical.

Then they worked backwards as to what would be needed to make that happen.

And so we're still within that time frame, that's one thing, but I don't think we're at this point ready to change any guidance.

Natasha.

MS. BONHOMME: Just to add to what Beth was saying I think that's really important because as we know, so much of what started this really important work was those articles, or those articles that came out.

And I think some of those stories in those articles even under all this great work that we've done, those children would not -- it still wouldn't have changed the outcome for those children.

So I think that's just important because this was really spurred by a public if you will media push, and that that's something to keep in mind because I'm sure someone somewhere is working on a report saying where are we now based off of where we were then.

And I just wanted to comment or add a little bit to the focus groups that we did with those nurses.

We really targeted nurses who were either shift leaders, or they felt responsible.

And what we found even from that it wasn't necessarily someone with an official title, but it was someone who was oh, I'm the person that brings all the educational materials back to my unit.

Or I'm the, you know, things that we would never have known without actually having those conversations.

And so I really kind of commend this structure and really can't wait to see how the structure of really being collaborative and speaking to the people who, you know, we're all on the front line in different ways but they are really on the front line in a very specific way.

And even just getting information back of -- no one even asked us, the nurses, about newborn screening. No one asked us about our experience around it and how important it was, and how empowered they felt by even just having one focus group to be able to say, wow, I'm going to go back and actually really think about this.

You know, people come in and talk to us about all sorts of other issues. No one really talks to us about newborn screening, even down to no one talked to us about changing the filter paper and the information on it. And that has completely

messed up our flow. And just all those little things.

So I really think this is really important work and that there is even more important work that could be done.

CHAIR BOCCHINI: Anne, last comment.

MS. COMEAU: Anne Comeau from Massachusetts. Thank you for a very nice presentation which I think gave a peak at the complexity of this situation, and very nicely showed a variety of cooperative solutions, and quite a variety.

That said, I think that when it comes to evaluation I'm going to really advocate for much less variety, and for very careful definitions of what it is that we're looking for.

When we are looking for what is our benchmark for reporting a newborn screen, well, what is a screening result? Is it a screening result that is totally all encompassing? Or is it a screening result plus supplemental information?

Very different timelines that you're going to get from people.

Shouldn't we be also looking for the time critical results of out-of-range results going out?

So, I think that despite the kinds of variety that you displayed I'm hopeful and I think that most newborn screening programs would be able to say that when they have an out-of-range metabolic result, or an out-of-range any kind of result that gets out the door probably the same day that it comes in.

And that would be a good measure. But I think we have to very carefully define what it is that we are going to require newborn screening programs to aim for.

So, I also will advocate for revisiting the guidelines. The five- and seven-day were good places to start, but in order to make a difference to the sick kids that we need to find we need to be able to standardize the report so that all of

us can understand where we can have improvements.

And if we don't standardize it we won't know where to go. Thank you.

CHAIR BOCCHINI: Thank you. Yvonne, thank you very much again for your presentation and thanks for the discussion.

Next on the agenda is a presentation on the Robert Wood Johnson project on newborn screening timeliness.

And Beth Tarini, committee member, will be joined by Amy Cochran, research assistant professor at the University of Michigan.

Dr. Cochran is the T.H. Hildebrandt Research Assistant Professor in the mathematics department at the University of Michigan.

Her research interests are in mathematical biology, especially in computational psychiatry.

She has focused on the psychiatric disorder bipolar disorders and on describing mathematically the volatility of mood that is

characteristic of this disorder. Welcome.

MEMBER TARINI: Thank you. Dr. Cochran is right here. I'm going to start the presentation and then Dr. Cochran will take it home.

I want to thank you all for having me present today on our preliminary findings so far and on the project in general.

I want to thank my team which is larger than the two of us. And also thank the Michigan Department of Health who has helped us with this project and who is on the line, my team members Mary Kleyn and Lois Turbett.

So, they may be able to answer additional questions if I am unable to, and/or add their perspective.

So, this is a project that is funded by the Robert Wood Johnson Foundation through the Public Health Services and Systems Research Network.

And the title is Improving the

Efficiency of Newborn Screening from Collection to Results.

And this is our research team. And you can see the names here. Dr. Sontag's on it and has been very helpful as a consultant.

And the team here is very multidisciplinary. This is one of my take-home points, that as has been mentioned this is a complex process, it involves multiple stakeholders and therefore -- and as we've seen in Yvonne's presentation involves the melding of multiple experts to sort of get it done.

And that's what we've done here. We have health researchers, applied mathematician, quality improvement expert, healthcare operations engineer, newborn screening researcher and health economist.

And this is our advisory committee because not everyone can fit on the research team. And so we meet on a regular basis.

And on this committee you can see we

have representation from several states' newborn screening programs, hospital health association. We're working with NewSTEPs closely.

And this has been an incredible resource in terms of helping us sift through the data as well as thinking about things in ways that -- how things run on the ground.

So the goal today is to present the project design and goals, review some preliminary results and discuss next steps for the project.

So, this is to get sort of agreement and buy-in which I think we probably already have, this is a complex process.

It requires coordinated and timely collaboration between multiple stakeholders -- Yvonne demonstrated this very nicely -- that is within and between clinical medicine and public health.

And there are different ways to organize and deliver newborn screening. Each state program we know designs its own process.

I want to be clear that different designs can be equally effective. Different does not equal bad as long as the objectives can be achieved in a cost contained manner that the program can afford.

So different is not bad. Different makes it difficult to assess the processes across states where leverage points might be useful.

So, this is a plug for health services research slide.

This problem is very well suited to health services research because it talks about system factors, many of them here, that affect the access, cost and quality of care which ultimately affect the health of newborns and can be at all levels from the population down to the individual.

This is a just general approach we took of trying to educate those in public health outside of newborn screening about the general sort of steps that are going on.

We talk about in our group the

collection, the transport and the processing as three major steps, and what is happening within each of those steps, where they're happening and what's happening from a timing, from a staffing, from a frequency and availability piece.

And as we just noted the goal right now is five to seven days depending on the result.

So why did we do this project if CoIIN exists and NewSTEPs 360 exists?

Well, this project was motivated by my being part of the committee discussions as the AAP liaison to think about is there a role for taking a broader perspective of this process to perform a systematic analysis of the broad process and identify leverage points where you can potentially intervene and improve process efficiency.

Here's an example. We can focus very tightly on areas in the process where we know there's a problem. We can focus very tightly on the hospitals. We can focus very tightly on the courier.

We can make incremental progress on each of those steps I showed you in making the length of time shorter.

But, and I'm not saying this is bad, I'm just saying this is part of the motivation of this project. At some point it doesn't matter how fast you are in the hospital if you're waiting for the courier to pick you up.

So, from an opportunity cost perspective you've exhausted your ability to make it even shorter.

From the subway analogy if the Red Line is coming at noon it doesn't matter if you get there at 11:59 or you get there at 11:30, you're going to get on the bus.

And so the question is this is where the broader perspective comes in of the total process and where the potential leverage points are that then lead to the total process becoming more efficient.

So, the goal of the project was to use

innovative dynamic simulation modeling -- that's why I have Dr. Cochran here -- techniques to systematically identify a potential process of proven strategies for reducing the time from collection to test results, and then assess the tradeoff between timeliness and costs for the strategies identified.

You don't always want to build a Porsche if you don't have the money if you can build a Civic and get there just as fast. So you must have an assessment of what is the incremental cost of changing the system and what are you getting for what you're investing. Cost, not just dollars but resources.

So, simulation modeling, for those in the audience just a brief overview, is a statistical method for identifying the steps in the process that can be modified.

And the implications are by running multiple simulations with data input.

The implications are it's a systematic

and efficient way for assessing the timeliness of a state's process, and can as I said identify those steps in the process that can be linked to significant timeliness leverage points, and can be tailored to state-specific process.

I think the potential here is it can get us out of the weeds for a moment in that many states know where some of their problems are.

There may be other points in that process which are not seen, but can be lifted to the forefront with a modeling analysis that looks at the entire process.

Some early challenges and barriers to the project which we've already discussed and many of you are aware of.

This is a complex process. Not only is each program different, each hospital is different potentially.

So, now you have 83 agents collecting specimens in potentially different ways going to a newborn screening lab.

And you have to understand how those processes work. Yvonne has demonstrated this nicely that it's not easy.

There's variability in organization and implementation at the program and hospital level.

Who collects, as Natasha said? Who does what job and what their title is depends on the hospital that you're talking about.

And the availability of data is difficult because not everyone is collecting all of the data that is useful for this type of model.

And then as I mentioned just a few minutes ago what is the health outcome gain of less than five days.

So, at the end of the day I can tell you the cost to get incrementally hours below or to five days, but ultimately anyone would ask me the last piece on that health services model which is so how many lives did you save.

It is difficult to actually I think give

you an assessment of how many babies present less than five days.

I don't know if people -- this is also a plug. If there are those in the audience that have that data I'd be -- systematic data, that would be very helpful.

If we knew what percentage of MCADs present at three or four days that could be built into this model.

This is difficult data to get because it may not be systematically collected.

So, I'll turn it over to Dr. Cochran to present our preliminary model results.

DR. COCHRAN: All right, thank you. So, I'm going to focus on the data analysis that we did.

And I'm particularly focused on the part of the process that starts at birth and ends when the lab kind of starts processing and they issue receipt of the starting of the process.

The data that we looked at is collected

from the Michigan Newborn Screening Program. So this is run by the State of Michigan.

And we have nearly 100,000 NBS specimens as collected over a year across the State of Michigan. So, 83 birthing hospitals.

And I'm going to particularly focus on those newborns that were not born to a NICU or a special care unit.

And in this data we have several characteristics that we'll look a little bit more closely - hospital ID, the time and date of birth collection, and the receipt of the lab arrival, as well as mileage to the lab, hospital, and pickup schedules as well as actually the lab hours of the state.

So, kind of the first thing that we do is always just take a look at the data to kind of get a better insight into what we have.

And so these are the distributions of if you look in the top left this is the distribution of births across the days of the week.

And so kind of very -- this is averaged over all those NBS specimens that we have.

And what we find is that, and this maybe is no surprise, that during the weekdays births are more common than they are on the weekends.

In addition, throughout the day births are more common in the morning around 8 and then that slowly declines until at night they're actually less common.

And this is averaged over the hospital, but we see similar patterns between hospitals too.

So what does that mean as far as timeliness?

Well, if births are more common on the weekdays, and given that in Michigan you wait 24 hours before you start collecting, then collection is going to be more common one day shifted over.

And so you can see this in the data, that from Tuesday to Saturday that's more common than it is from Sunday to Monday.

So if you're thinking about staffing,

or how much effort to put into collection you have to think about the fact that it's going to be more common from Tuesday to Saturday.

The hours of collection are a little bit -- don't have such a nice trend. And we'll look at more carefully why perhaps that might be.

So, from there we just took the process and we split it up to two parts.

So, first the part from birth to collection, and then we looked from collection to arrival at the lab and the starting of the processing.

And as far as birth to collection what you can kind of see, again, they wait 24 hours before they start the collection, but nearly 70 percent of specimens are collected within 24 to 26 hours in the State of Michigan.

So it's very tightly controlled. They're doing a great job getting collection. And in fact, over 99 percent of the specimens are collected within 36 hours.

Now, what that means is if you then go a step down and look at the collection to lab time you can immediately see that there's a greater variability in the times.

And so from a systems perspective then perhaps our resources are better spent in the collection to lab time and trying to improve that because of the higher variability.

And so one thing that will come up again is this pickup. And I think we've talked about it before, but this courier pickup.

And so this is all the hospitals when the couriers are typically picked up. In Michigan they're typically picked up six days a week. So, every weekday and around about 6 p.m. is probably the typical weekday pickup.

And then they'll have a pickup on either Saturday or Sunday. So, Michigan, in the Upper Peninsula they're typically picking up the specimens on Saturday. And then -- because that's farther away from the state laboratory. But then

most of the other hospitals are picking it up around 6 p.m. on Sunday.

So, in Michigan it's important to note that there's kind of a fixed courier route. So they pick up specimens and then they travel not directly to the lab, but perhaps to other hospitals before arriving to the lab.

And in fact we do have two hospitals that have their own courier and they go directly to the lab. And they're able to really cut that time by about seven hours.

And in fact, the results that I present, how long it takes is going to be an important factor.

So, from here we really wanted to understand a little bit better where that variability comes in the collection to lab time.

You noticed there's kind of three peaks. They're all separated by day.

And so we did just kind of the simplest model you can get which is just a linear model, a

linear regression to see what factors are important to that collection to lab arrival.

So, one of the things we looked at was hospital volume. And this is just in terms of how many births they're handling.

And this wasn't significant, to our surprise. In fact, the size is not either making it faster or not slower.

However, what was important was the time of collection.

And so you can stare at the Tuesday collection and look at the estimate. That's in hours.

And so what this is saying is that a Tuesday collection on average is about 12 hours faster than a Saturday collection. So this is all relative to Saturday.

And in fact, a Friday collection is about three hours longer than a Saturday collection.

We can also look at time of day. And

this also contributes to the kind of timeliness.

So, early morning collections are about three hours faster on average than the evening collection.

Mileage to laboratory. This is very intuitive that that would contribute to the timeliness.

That number actually -- it means about two minutes per mile if you were to kind of do the reciprocal. So, that kind of makes sense.

Now, since collection time both throughout the day as well as across the week is an important factor you may ask why. Why is Friday and Saturday so much slower than the other days of the week?

Well, in Michigan we have a six-day schedule for the lab. And so on Sunday it's closed.

So, if you're picking specimens up on Saturday and it arrives to the lab on Sunday it's going to wait there till Monday before processing

begins.

And so that perhaps could be contributing to the delay.

And this is where simulation comes in. Can we explore this hypothesis further? So, could collection time be so important for the NBS timeliness through its relationship both to those courier schedules that we talked about as well as the lab hours?

And so we used this data to create kind of a realistic simulation to try to capture all those parts of the system from birth to lab arrival.

So, we took the data and we kind of reproduced those patterns of birth. We included uncertainty so there's a little bit of randomness involved in the simulation.

Then we kind of took those birth to collection times to also generate some sort of time.

From there we modeled the collection to pick up, allowing for four hours of drying in our

simulation, and then a fixed transit time.

And then we assumed that the processing begins once the lab's open, so once the NBS specimen has arrived and the lab is open.

As far as this 10-hour fixed transit time, this is just capturing kind of the experience from the people that we work with in Michigan who say, so given about a typical pickup of 6 p.m., those specimens arrive between 3 and 4 a.m. So I'm just going to assume a 10-hour schedule.

Now, of course the results will depend on that fixed transit time, and we have looked at other, say a shorter transit time and how that might affect things.

And so, with this simulation we can start to explore what you might want to actually implement before you actually implement it. So, it's a nice kind of what-if scenario to see what the tradeoffs are.

So, we'll particularly focus on what happens when we change the lab hours as well as what

happens when we change the pickup schedules.

And so the lab hours are on the bottom for the State of Michigan for point of reference.

So, here let's fix the lab hours and see what happens when we change the pickup schedule.

So, our baseline is going to be this typical 6 p.m. Sunday to Friday pickup. And this is what's returned from the simulation, and it looks very similar to what the actual data is. We have three peaks and this kind of wide variability.

Now, you might say, well, we have six days. What if we switch our Sunday pickup to a Saturday pickup?

So, in the upper right we're looking at that scenario.

And what you find is if you look out towards the 86 hours, in the 6 p.m. Sunday through Friday you have a lot less specimens that are collected at that very delayed time when you compare it to the 6 p.m. Monday to Saturday.

And again, that makes sense. If you

switch your pickup to Saturday, they pick it up on Saturday but then they wait on Sunday until the lab opens. So, it makes sense that switching that would actually delay the process further.

There's other things we could do. So rather than maybe searching a day we could say delay the pickup by about six hours. So that's our 12 a.m. Monday through Saturday pickup.

And if you compare that, kind of the two histograms, so the upper left to the bottom left, you can see that the curve is kind of shifted to the left. So you've improved timeliness for the majority of those specimens.

So, we can look at that a little bit more carefully with numbers.

So, we ran the simulation. We tried 35 different simple pickup schedules. These are six-day schedules, 12 a.m., 6 a.m., 12 p.m., 6 p.m., 9 p.m.

I do want to say we also tried seven-day schedules. But again, because the lab isn't open

on one of those days you actually don't create improvement. So that's an important thing to note. Just if you go from six-day one day a week to seven-day one day a week.

So we had some sort of ranking system. And you can see the 6 p.m. Sunday through Friday, that's going to be our baseline again.

So, if we switch from the 6 p.m. Sunday to Friday to say, a 12 a.m. Monday to Saturday you get on average about a four-hour improvement.

You can also look at those kind of really long delayed NBS processes. So we can look at those specimens that take longer than 60 hours to go from birth to when they are issued a receipt.

And you can see a reduction from about 14.6 percent to 32 percent. So, about 14 percent less specimens are collected -- or arrive to the lab after 60 hours of birth.

So again, this is just ways to kind of compare beforehand what would happen if you changed your courier schedules.

I do want to say that this is a caveat. I'm only focusing on timeliness. And so in fact when you go from a 6 p.m. - 12 a.m. that might affect other things.

So, the 10 a.m. transit time, those 12 -- if you pick them up at 12 a.m., they're arriving to the lab at 10 a.m.

However, our lab opens up at 7. And so they're starting their processing later. And as a consequence by the time they finish processing it might be too late in the afternoon to contact your primary care provider. And that's a big concern that Michigan is focusing on.

So, you could say actually do a 9 p.m. in which case those arrive at 7 a.m. right when the lab opens. And you actually get similar results to that 12 a.m.

So these are all things you kind of can explore a priori before you actually change it in the system.

We also looked at changing the lab

hours. I know a lot of states are thinking about what happens if I go from a five-day to a six-day schedule, what happens when I go from a six-day to a seven-day schedule.

The upper one is the current one in Michigan so that's kind of the baseline.

And we considered all these things. We also considered shifting the lab hours. So Michigan is thinking about shifting it earlier for that exact reason of trying to get to the primary care provider early enough.

And when we do that we can see little changes. So that second to last row, 5 a.m. to 3 p.m. actually has similar results to the current lab schedule. So that might be beneficial from the perspective of contacting a primary care provider.

So, kind of just our broad conclusions. So, because Michigan is doing such a good job with the collection the bottleneck now is that time from collection to lab arrival.

And we kind of narrowed in through

simulation and regression on the pickup schedules as well as the lab hours, and how we can adjust them.

And kind of the general guidelines that we come up with is first, recognize that there are patterns of birth. And so you might want to consider a system that takes that into account. As well as when the lab is open. So if the specimens are just sitting there waiting for the lab to be open that's not actually improving the process.

And simulation, you know, I'm a modeler so I'll always plug simulation. It can give us some ideas before we actually change.

Of course this is not capturing everything. And we also didn't really focus on the lab processing which will also have probably other bottlenecks to consider.

So I'll turn it back over to Beth.

MEMBER TARINI: Thank you, Amy. And so as Amy pointed out this is the first sort of step with Michigan allowing us to utilize their great data that they have to get a model running and see

how it actually works.

And so the next step is to refine the model with additional data from surveys of other hospitals and state newborn screening programs.

And of course I'm sure you are all thinking like, that's great, I can change and open my lab, but what am I going to do and how much is it going to cost me.

So, that's another goal of ours is to get data on cost.

Of course we all know from the preliminary discussions we've had with the cost workgroup that those are no easy feats to find that data, and who's actually paying for it is a whole other piece.

And then before I end I have on the line Mary Kleyn who was state epidemiologist at Michigan, and Lois Turbett who is the newborn screening nurse coordinator.

And so I want to give them a chance if they have any comments before we go into the

question period. I think their lines are open.

MS. KLEYN: Hi Beth, this is Mary. Can you hear me?

MEMBER TARINI: Yes, we can.

MS. KLEYN: Okay, perfect. I don't think I have anything to add. I think that was a great presentation, really interesting to see all the different simulation models.

So, I'm just here if anybody has specific questions about our process. I'm happy to answer them.

MEMBER TARINI: Great. Thanks, Mary. And Lois?

MS. TURBETT: I just have one comment.

MEMBER TARINI: Sure.

MS. TURBETT: In working with hospitals one of the other bottlenecks to consider is their send-out department.

So, when you collect them on time, if you put the courier pickup time later in the day there may be no hospital personnel to actually

package and log the specimens for the courier.

MEMBER TARINI: That's important. Thank you for reminding me.

And it gets back to Dr. Cochran's point that you can't take the model and go. You have to with any data sort of take the model and say, okay, this is what we might do.

And then consider given the content expertise around the table what are the other opportunity costs that we're going to run into, or the other problems we're going to create.

It's like when you do something you have to see what the sort of collateral damage could be from your intervention. You can't presume it's null.

So, thank you, Lois. And I'll now leave it open to questions.

CHAIR BOCCHINI: Dietrich.

MEMBER MATERN: Great work, great presentations. Thank you very much.

I sit here and I wonder whether one

should revisit the issue of when the sample is actually collected.

So, in the NewSTEPs we heard because California is part of it as one looks at 12 to 48 hours as collection. In Michigan you looked at status quo.

MEMBER TARINI: Well, they did 24 to 36.

MEMBER MATERN: Right. And the data show that they're trying to meet the 24 hours at least.

MEMBER TARINI: Yes.

MEMBER MATERN: But what could you model it for 12 hours? And again, looking at how the OBs are delivering the babies, and I assume it's not biology that dictates the weekends.

So, and then the delivery is mostly in the morning. So, as 12-hour collection would mean they collect in the evening, and would that make any difference. That would be I think interesting to know.

And maybe the NewSTEPs. And maybe you add California to the states you want to look at. But I think that might be worthwhile looking at.

MEMBER TARINI: So, that's exactly -- we can certainly model that.

And one collateral piece to then look at, and I know Lisa, I don't know if Lisa Feuchtbaum is here this time, but the paper that was published out of California talks about what happens when you get those 12 hours.

And my understanding from the paper was you don't see a significant shift in the metabolic, but you do see an increase in the false positive rate of the hormone test.

So, you pick up another piece that you might have to sort of look at.

MEMBER MATERN: Yes. And as I said last time, Piero Rinaldo is looking at this with CLIA and can adjust the results by birth wait per hour.

MEMBER TARINI: So if we can do that

then we can address that problem that would be created by the current state of affairs. So I think that's very helpful. Thank you. Thank you, Dieter.

DR. GREENE: The one comment that I was going to make was the answer.

MEMBER TARINI: Took the words out of your mouth.

DR. GREENE: You did perfectly, that the CHH and thyroid false positive rate goes up dramatically.

The other thing I wanted to sort of reinforce -- first of all, that was fabulous, and clearly a way that we hopefully all ought to be able.

I'd be also interested to know how much it actually costs to do that kind of simulation. Because that is clearly the right way to be going about solving every problem.

And how much can that approach be -- can it be scaled to be used by people without a grant

from the Robert Wood Johnson Foundation. So that's one question.

And the other is dealing with the other laboratories sometimes introducing old-fashioned technology.

If you actually want the courier to go to the birthing center to pick up the samples you're actually putting your hospital lab at a major, major risk unless there's a solution introduced there because that's not JCAHO and that's not CAP because they have to have the specimen accession and you can't have satellite laboratories anymore.

And actually, CDC could probably tell us more about that.

But one solution that was used in one place is send the sample out directly, but make a copy of it. And then the lab can actually accession based on the copy while the sample goes directly.

So there are solutions but you can't always bypass the laboratory.

MEMBER TARINI: So, to your first question about the cost this is sort of the beauty of health services.

You're not buying a machine, although that's a sunk cost. You're buying the expertise of the individual who may have other expertise as well.

So, there's no reason -- now, Dr. Cochran has a Ph.D. in applied math. Am I right, applied math? Yes.

So, for a grant I get the best of the best to fight for the dollars.

Now, this modeling practice I believe, correct me if I'm wrong, that there can be ways to do this. There can be ways.

I'm in Iowa. Dr. Cochran is in Michigan. She works on the data remotely for me. So, she doesn't have to be in my lab.

I utilize her time and pay her for that time. So there is both an access and a cost issue that I think potentially could be solved.

I'm not saying that all the states need modelers. Let me just qualify.

I'm just saying there can be creative solutions, to Annamarie's point, to get at this utilization of skills.

To your second point about the courier I'm not sure I understand. So if the courier comes to the hospital directly and picks them up? If they go on the hospital grounds it's a problem?

DR. GREENE: If the physical sample isn't in the laboratory. The laboratory -- it is my understanding that a hospital laboratory -- we used to have satellite laboratories all over hospitals. And they've really stopped that. And it's related to JCAHO and CAP.

And the laboratory has to have control over all of the specimens. It has to be accessioned.

And the laboratory can change its workflow within the laboratory, but if the sample never got to the laboratory, if it was picked up

from the birthing center --

MEMBER TARINI: Oh, I see, from the floor.

DR. GREENE: Yes, exactly.

MEMBER TARINI: Now, I'm going to ask Lois who's on the line, are there hospitals in Michigan, the smaller hospitals, where they go to the laboratory? Or are they accessioned on the floor, or do you know?

MS. TURBETT: I do know. It's a mix. There are many hospitals where they're picked up from the floor.

And they have their own way of keeping track. Some do it well, some don't.

And then -- this is the first time I've heard of this as being a concern, so when we have our training in the fall it's definitely a question I will ask them.

MEMBER TARINI: Right. And so this gets to the other issue which is it's a mix.

So, when I go to design -- this is where

it's the people on the ground all the way up to the 30,000 foot view of the modeler.

I have to understand what each process, or the program has to understand what each process is on each hospital.

And once those hospitals, those processes, that first of the three sections is tightened, then you can look at these other pieces to get at them.

To your point about the costs, that is an important piece that we're going to look at.

And I have -- Dr. Berberich has done, when Iowa, my understanding, and Stan, correct me if I'm wrong, that Iowa did a cost analysis before this all happened. They went 7 days a week, 24 hours a day.

And my understanding is that, and Stan will correct me if I'm wrong, that the argument made to the public health department, the NC that would decide, whoever that may have been, was in dollars only. I'm not talking about the actual ability to

have someone run the lab on a Sunday, or to hire people, or to have them run it at night.

But in terms of dollars it's on par potentially with adding a new disorder. And I just want to put that out there as a sort of thought.

We don't think too much -- well, I should say this. We don't discuss in this committee explicitly the dollars spent when we add a disorder, but we talk about the dollars spent when we are running the lab and timeliness.

I'm not saying that's right or wrong, I'm just pointing it out.

So, if we are having dollar conversations about timeliness which affect all of the disorders why are we not having those conversations about adding a disorder if those are comparable costs?

And one affects one disorder, and one affects 50.

MEMBER BAILEY: Don Bailey. Thanks so much for a great presentation and I love the

sophistication of the analyses. Just a couple of observations and a question.

So with respect to cost, you've got like a key cost is getting the actual raw data to begin with.

MEMBER TARINI: Correct.

MEMBER BAILEY: Michigan seems to have a very good system of time stamps essentially for when all these things happen.

MEMBER TARINI: Yes, time stamps, that's correct.

MEMBER BAILEY: I don't know how many other states have that level of data.

I mean, I can see from Yvonne's presentation and understanding endpoints or the outputs of this, but to actually have the --

MEMBER TARINI: That is correct.

MEMBER BAILEY: -- the timing of this is the only way you can actually do the modeling in any kind of cost-effective way.

MEMBER TARINI: You have to track the

specimens, more than just how many got here, X percent arrived at this time. That's correct.

MEMBER BAILEY: Exactly, exactly, yes.

I did want to ask Dr. Cochran if there is -- and this is just a question for my own interest. Is there a difference between mathematical modeling and simulation in what people would do in operation, for operation science?

I mean, you're a very sophisticated at a mathematical model. My understanding of operations researchers is really taking it and saying, okay, now we have this system. We've got 27 elevators going up and down in a large building. How do we program those elevators in a way to maximize efficiency.

Are you in a program that actually does that kind of work as well?

MEMBER TARINI: Well, before I get to that, I want to ask Mary Kleyn, if she will know, how difficult is it to time stamp these data? How

difficult did you find it to do that? What were the barriers and the challenges?

MS. KLEYN: So, this is Mary. I got fairly lucky because the system was already designed with a time stamp before I went to pull the data.

So in terms of on our newborn screening card we collect the birth date and time, and the collection date and time.

So when that's received in the laboratory we have data coders who enter that into our LIMS system. So that was already available.

For tracking the laboratory receipt date and time what happens is that when the scientist or the technician logs into the computer in the morning which is attached to a bar code scanner they use.

As soon as the card is scanned then that date time stamp is automatically added to our accession number which is a unique identifier we use to track the sample throughout the whole

testing process in the laboratory.

So, all of our date time stamps were already routinely collected and tracked in the software.

MEMBER TARINI: So you make a good point, that not every state can do this now. But I think it's reasonable to consider the ability to aspire to it, especially since it has other potential downstream --

MEMBER BAILEY: A good example of how that kind of data --

MEMBER TARINI: It already exists.

MEMBER BAILEY: Yes.

MEMBER TARINI: And you can have data. In Michigan oftentimes we say oh, well, we can ask so and so because they're collecting this. So it's basically sort of an exponential piece. But I'll let Dr. Cochran comment.

MEMBER BAILEY: Without a whole description of the field.

MEMBER TARINI: She's, by the way,

potentially hirable. So should anyone be looking for this skill set.

(Laughter.)

DR. COCHRAN: I just want to say, so one of our collaborators who's actually my husband is an operations researcher.

And so we worked very closely with everyone on the team, and the two of us were the ones sitting at the computer doing this very closely together.

So he has a lot more expertise modeling the process steps, you know. It's not my background as you know. So he was really guiding, making sure that was the proper way. Yes.

MEMBER BAILEY: Thank you. My only other question, or it's really just an observation is I love the systems approach as opposed to looking at each individual piece.

It helps to see. And your analogy of the subway I think is a very good one.

Taking those data and actually making

changes assumes -- in the easiest way assumes you have control over each step of that process. And different people have controls over different steps of the system.

MEMBER TARINI: Correct.

MEMBER BAILEY: So, the state lab doesn't really control what goes into the hospital. The hospital doesn't really control what the courier does, et cetera.

So, I love the systems approach. I think then modifying a whole system is different from modifying one piece of the system.

MEMBER TARINI: I agree, and I would counter that we modify a whole system when we add a new disorder.

So, we are not -- it is not new to us to modify the system when it comes to certain things. But this is certainly an area in which I think the programs as you saw from Yvonne, who knows where the contract is, who knew that the contract was modifiable.

These pieces, and I have found this in newborn screening in general. And it's not bad, it just is. When we've done our surveys for my team is that there are many people involved and they are very good at what they do.

And sometimes the information, understanding -- they all know who does what, but trying to understand and connect those people, and understand the larger picture is difficult which makes actually knowing if you can affect it one step. And then actually effecting change a second.

So, I think you're right, this shows you the potential leverage points. Then you must go into the reality of are they cost-effective, rewarding, and how much juice do you get for the squeeze, and can you actually do it.

CHAIR BOCCHINI: I'm going to give you the last comment.

MEMBER BAKER: I just have a question. Again, I like this because I feel we are going to

evidence-based decision-making.

One thing I was wondering, other than modeling can it become a template?

MEMBER TARINI: Yes.

MEMBER BAKER: Because each state, you base on the Michigan data. Now, we have other data, but different like a courier coming in --

MEMBER TARINI: Yes.

MEMBER BAKER: So, the answer is yes, which is encouraging.

MEMBER TARINI: Well, the goal and the way this was posed to the RWJ was that this would build a process model in the sense of a process model that can be manipulated.

You can put in different steps into it and then input the data so that the technique can be tweaked for the states, and that is the opportunity from the grants perspective to effect change. It's a tool that can be modified and used.

If you want to comment more on the sophistication.

DR. COCHRAN: Yes, I think really what it seems like the next step is to take this and turn it into some sort of app where someone could input their own data.

MEMBER TARINI: That's good.

DR. COCHRAN: Oh well, you have the money to do it, right?

(Laughter.)

DR. COCHRAN: This is beyond my expertise. But really, you know, so that a different state could put in their own data and then model the whole process.

I think that would actually be pretty straightforward and something that's normally done from my perspective.

MEMBER TARINI: Good work. Look at that.

MEMBER BAKER: So, I hope NewSTEPs can be --

MEMBER TARINI: You can be a pilot. I will call you. Okay, we'll discuss after.

CHAIR BOCCHINI: All right, well thank you very much both Beth and Amy for the presentation. We really appreciate it and look forward to the next phase of your study.

So we are just five minutes from behind. So we're going to come back at 10 minutes to 11. A short break and then we'll be back for the next speaker. Thank you.

(Whereupon, the above-entitled matter went off the record at 10:41 a.m. and resumed at 10:55 a.m.)

CHAIR BOCCHINI: All right, let's welcome everybody back from the break. We're ready to start the next presentation. And the next two presentations are going to be by individuals who are presenting to us by telephone.

The first is Dr. Sharmini Rogers. Dr. Rogers is the chief of the Bureau of Genetics and Healthy Childhood for the Missouri Department of Health and Senior Services.

She's going to talk to us today about

Missouri's experience implementing lysosomal storage disorder screening and follow-up for Pompe, Gaucher, Fabry and MPS-1 as well as Krabbe disorders.

Dr. Sharmini has been with the Missouri Department of Health and Senior Services for a number of years.

She has overall responsibility for the newborn screening program, genetics program such as cystic fibrosis, hemophilia, sickle cell and formula program for individuals identified with a metabolic disorder.

Dr. Rogers' schedule made it impossible for her to travel, but she's kindly agreed to share her experience by phone. So, Dr. Rogers, we're ready when you are.

DR. ROGERS: Thank you and good morning to all of you. And I would like to thank the advisory committee for inviting me to share this experience.

I also want to say up front that all the

information that I share this morning is the hard work of many people in the state lab, my follow-up staff and our contractor genetic samplers. Without them we would have no study to tell you this morning.

My goals for today are really to provide the legislative background, our process, screening results, how we implement our short-term follow-up and determine our confirmatory results.

I'd also like to take this opportunity to share some challenges we continue to face and lessons learned.

As many of you know Missouri's legislation came right behind Illinois's legislation and followed the same language.

The law was named after Brady Alan Cunningham who had infantile Krabbe.

Brady was born on April 16, 2008, and died a year later. When Missouri was screening for over 67 disorders but sadly not Krabbe.

It passed in August of 2009 and we had

until July 2012 to start screening.

Even though they specified which of the LSDs to screen they actually gave us an option to add others if we chose to do so.

I just wanted to show you Brady's parents, Bob Evanosky, when they came to testify. Bob is carrying Brady.

When the law passed the state actually explored how they were going to screen and finally decided to use the digital microfluidics method.

However, as the time came nearer to implementation we discovered that we really were not ready to screen for Krabbe, and we were getting lots of pressure to start screening.

And so we contacted New York to do our Krabbe screening. Missouri owes its deepest gratitude to the Wadsworth Lab, especially to Drs. Joe Orsini, Michele Caggana and Carlos Saavedra.

A task force was then created in early 2012 to develop follow-up guidelines and reporting.

We met regularly by conference call and occasionally face-to-face. And as soon as the pilot started we actually had monthly calls to go over the cases.

New York began screening August of 2012 and Missouri began the population-based pilot for Pompe, Gaucher, Fabry and MPS-1 January 2013 with the intention of screening for Krabbe in-house which we began in June of 2015.

This is a little background on the workload in Missouri. We have around 78,000 births annually and the lab actually screens about 92,000 samples given the repeats and unsat specimens from that which average to about 375 specimens daily.

The lab has two full-time employees dedicated to the screening for LSDs and the follow-up staff has one full-time FTE which actually breaks down to two staff working on the follow-up so that we have backup.

The lab too has other staff

cross-trained to provide backup.

And then Missouri has four contracted centers to provide the follow-up and confirmatory testing.

I just wanted to show you all what the digital microfluidic platform looks like. We have eight. So we have two staff men for machines each.

And they are affectionately named Snow White and the Seven Dwarfs. I'm not sure which one of those eight is Snow White.

But you can see they are small platforms that do not take up much space and can very easily handle the 375 daily specimens.

This is a schematic diagram to show you the workflow for the screening using digital microfluidics.

From the flow chart you can actually see that the testing does not take very long. All in all for one run it takes about five hours.

These are our current cutoffs. Over the course of -- over three years that we have been

screening we have changed our cutoff several times. And it's closely monitored by the lab with input from our task force and genetic center.

This graph just depicts the effect of age on the results with Krabbe screening. The red depicts preemies and blue full-term babies.

You can see here that there is some difference, but not very much.

And this one is for Fabry showing really a marked difference in the results in age between the preemies and full-term.

This slide shows all enzyme median activities together by age of collection. They all show some differences that you can see clearly that Fabry shows distinctive differences.

Based on this data age-related cutoffs were developed early on to help us with reducing false positives.

So we also looked at the enzyme activities between male versus female and we didn't really see much difference. They are pretty

similar except maybe the females are a little higher. But it didn't warrant any different cutoffs.

This diagram gives us a clear picture of why screening for multiple disorders together provides important and useful information.

The enzyme profile helps us weed out obvious compromised samples and false positives to reduce the referral numbers.

This is no different from when we use our tandem mass where babies with high phenylalanine due to PPN feeding are not referred.

So in summary of screening for the four lysosomal storage disorders Pompe, Fabry, Gaucher and MPS-1 we do meet age-related cutoffs for all the babies.

The premature babies can show altered enzyme levels which is why repeat screens would be useful.

Multiplexing has great advantages for assessing reliability.

We really need to watch out for seasonal variation. I didn't show you any slides, but it is different in high heat and humidity, especially for the carriers in phenyl deficiency.

This is no different from when we do the GALT assay.

The lab is very pleased using the digital microfluidics method for its ease in installation as well as screening method. And you saw earlier that it really didn't take that long to run using that method.

Now specifically for Krabbe screening. As I said earlier in order to follow the law to begin screening by July 2012 we had to develop an agreement with New York to screen our samples as we didn't have a method that was really at that point.

After all the testing was completed daily in Missouri the samples were sent to New York via overnight FedEx.

New York then tested the Missouri

samples exactly the way they tested their own which was retesting anything less than 20 percent of the GALC mean.

DNA testing, the analysis was less than 12 percent.

Then they continued DNA testing and LH GALC feed was less than 12 percent. They notified Missouri for referrals if mutations were found.

New York then sent the samples and results back to Missouri and we followed our usual referral protocol to the genetic center.

New York screened 266,189 samples for Krabbe from August 2012 to July 2015. They reported 42 with just polyphormisms and these were not referred.

In this time frame there were also 54 referrals and none were infantile Krabbe. They detected 6 genotypes of unknown significance, 3 genotypes of unknown onset and 42 with one known Krabbe mutation.

We had three families that refused any

follow-up.

In April of 2014 Missouri began validation for in-house screening for Krabbe using the fluorometric bench assay and molecular analysis for early detection.

The screening was done in tandem with New York screening same samples.

We requested 34 of previous Missouri positive Krabbe referrals, 4 with two mutations and 30 with one mutation. And Missouri was able to flag all as normal except for one carrier of the Y303C mutation which happened to be slightly above our proposed cutoff.

They also tested 29 of previous Missouri polymorphs only and that flagged as abnormal.

They tested positive samples just provided by New York and they were able to flag that as well.

So I just wanted to show you the equipment used. You can see it's just a small

equipment on the table, just a very small amount of space that's needed.

This is just a fluorometric bench method. You can see by the process not many steps. It's very simple and it can be done within 24 hours.

The lab has a fixed cutoff for the DNA prompt. And as I said earlier we only look for the 30kb deletion.

They also have a failsafe cutoff level to refer at low levels that no mutation is found.

There are several circumstances also when we request a repeat screen. The list is the lower level without going to DNA testing.

And this is when we get a result that's inconclusive and doesn't seem that other LSDs that are also flagged, or when we cannot provide a result because it's a premature infant, a transfused baby, or the specimen was collected early.

And finally, borderline cases where the GALC sees a borderline range but not low enough to meet our DNA prompt.

I just wanted to show you all the first day of parallel testing with New York. And it is really incredible how well they match using different methodologies.

So Missouri contracts as I said earlier with four genetic centers in the state to provide confirmatory testing and follow-up of infants identified by newborn screening.

We actually began contracting with these centers in 2005 after we expanded screening to include disorders through tandem mass.

This map just shows you were the centers are situated and how our state is divided for coverage. Region 1 is on the western side of the state, region 2 the central area, and 3 the eastern side.

We have two centers on the eastern side of the state and we divide the infants by giving St. Louis Children's the last names that begin with A to M, and Cardinal Glennon gets the infants with the last names beginning N to Z.

Why, you may ask? Nothing scientific about that. We just thought it would be an even distribution and less confusing for the lab to determine where to send the referrals in that region.

So during the implementation phase we did not provide results on the abnormal screens for the lysosomal storage disorders. We just phoned and faxed the centers, and they then contacted the clinic provided to coordinate the care with the family.

At the completion of the implementation phase and LSD was fully adopted the infant's family care physician was then notified along with the centers of the negative result per our regular newborn screening protocol.

I just wanted to show you all our schematic diagram of how a test comes through the lab, and when it's identified to be abnormal how it gets referred and followed up.

So for the lysosomal storage disorders

our LSD task force developed guidelines for the diagnostic testing for confirmatory tests.

And we require them to report certain results back to the state once the results are obtained.

Evaluation by the centers for Pompe typically occur within 24 hours of receiving a referral. Genetic evaluation and genetic counseling is provided to educate the family on newborn screening and Pompe disease.

Then the information that is reported back to the state is the date of initial clinic visit, the leukocyte GAA activity results and the date that it was collected, confirmatory laboratory used and their reference ranges, and then all the following tests as required for Pompe.

Finally, to let us know what the diagnosis is, what is the date that they confirmed the diagnosis, and what the treatment and follow-up plan.

For Gaucher confirmatory testing is by

checking the GBA enzyme activity. If it is low DNA mutation analysis is done.

This is handled by the centers as a non-urgent referral for assessment and testing. Critical exam with a geneticist is usually helpful since babies with type 2 and 3 Gaucher are symptomatic from birth.

The information that's reported back is again the date of initial clinic visit, the GBA enzyme activity, the confirmatory laboratory used and its reference ranges, the results of the mutational analysis, diagnosis date, and treatment and follow-up plan.

The confirmatory testing for Fabry is the GLA enzyme activity. And for males if it is low then DNA is done. For females enzyme activity and DNA is done at the same time.

If baby is confirmed to have Fabry the centers schedule them and assess available clinic slots in genetics for evaluation and genetic counseling.

The mother is then tested along with evaluation of other family members.

And the information that is reported back to the state is the same, date of initial clinic visit, the enzyme results, and the labs used and reference ranges, the mutations, diagnosis, date of confirmed diagnosis, treatment and follow-up plan.

So for MPS-1 the confirmatory testing includes the IDUA enzyme activity which reflects the DNA analysis. If abnormal then a urine GAC screen -- is consistent with MPS-1 then go on to do the mutational testing.

The results reported are similar to what I've already said previously.

When New York was doing the testing confirmatory results for GALC enzyme activity was sent to a confirmatory lab, and a repeat newborn screening and the parental carrier testing was completed through New York.

If the results are confirming that the

baby may have Krabbe disease, that is low enzyme and two mutations, baby is seen within 24 hours by genetics and neurology.

If neurology is normal, then lumbar puncture and MRI, nerve conduction velocity and brainstem auditory evoked response is done.

If the GALC enzyme is low and only one mutation is identified with or without polymorphism baby is seen as soon as possible by genetics, but neurology is not consulted at this time.

And the confirmatory information sent back is basically whatever testing they have done, and diagnosis, and their treatment and follow-up.

When Missouri, however, began screening the centers treat the abnormal results the same way by seeing the baby within 24 hours and confirming the GALC enzyme activity and mutational analysis through a confirmatory lab.

Mutational analysis along with parental carrier testing is completed if baby was

referred with an heterozygous 30kb deletion or was referred under the failsafe cutoff.

All other tests are completed if neurology is abnormal and reported to the state with the standard information.

So since I've made this presentation we've had two more confirmed cases. For optimal and three years at screening for lysosomal storage disorders, and screening for 276,000 births we have 141 infants confirmed with an abnormal lysosomal storage disorder.

The two additional confirmations were one classical Pompe and one late-onset Pompe, bringing the Pompe to a total of 36 instead of the 34 listed on the table.

Gaucher is still five that have been confirmed. Fabry is six confirmed. The MPS-1, three confirmed. Krabbe, 10 confirmed positives but no infantile Krabbe.

And no infant was confirmed with a multiple LSD, though they were referred with a

screen positive.

So, as I said we have 36 confirmed positive Pompe cases. We now have 8 infantile and 20 late-onset Pompe. Six are confirmed classical infantile and two non-classical of which the seven are CRIM positive and we have one CRIM negative baby.

The baby with CRIM negative has two nonsense variants. They have this baby on ERT as well as immune separation. The baby is now two and a half months old and is doing well.

The remaining five classical infantile cases were started on early biweekly ERT infusions. One was weekly and then moved onto biweekly.

And at the annual follow-up since milestones are normal.

Two of the non-classical infantile who are siblings were put on treatment, but the younger sibling did not tolerate the infusions and so the infusions were stopped.

The family moved out of state to North

Carolina and so no follow-up was done in Missouri after the year.

But they have recently moved back to Missouri and will continue care at one of our centers.

The late-onsets are being followed up regularly and to date all are fine.

For Gaucher five babies were confirmed positive, three were diagnosed as Gaucher type 1, and one of the three developed hepatomegaly at 16 months and was started on infusions every other week. The other two type 1 are not on treatment.

One diagnosed as Gaucher type 3 presented with hepatosplenomegaly and thrombocytopenia at birth along with a family history and was started on weekly infusions.

The third was a genotype of unknown significance and that was not on treatment but is being followed up annually. All of the symptomatic cases are in treatment.

For Fabry 86 were confirmed positive

with 83 diagnosed as Fabry. The other three were diagnosed as genotype of unknown significance.

Seven confirmed were female. One of the confirmed Fabry males was diagnosed as classical Fabry, as having the same genetic mutations as the mother who is currently a Fabry patient.

The A143T allele has been associated with non-classical Fabry disease and appears to be common in Missouri, found in 61 percent of the cases.

Questions have been raised regarding the pathogenicity given the prevalence in Missouri.

Due to the advanced screening new numbers were identified with Fabry and we now have four family members that have been put on treatment because of newborn screening and following up with the family.

For Hurler we've had two confirmed severe cases. The first child had multiple

abnormalities besides Hurler and died with complications from a bone marrow transplant.

The second baby underwent stem cell transplant and is doing well.

To date we have not seen an infantile Krabbe, thank God. The centers are following up on the unknown onset and genotype of unknown significance, and to date none have shown any symptom.

The incidences that I've listed here are just for confirmed disorders with known disease-causing mutation in the infantile period except for Fabry as they are all later onset.

I will share incidences that includes the late-onset Pompe and the genotypes of unknown significance and unknown onset.

From the time I sent this presentation out for Pompe, the 1 in 39,000 that I show here, because of the additional baby that was identified the infantile confirmed incidence is actually now 1 in 34,500.

For Fabry only if you see 1 in 3,300. However, if you combine Fabry with the genotype of unknown significance for both sexes it's 1 in 3,200.

If you just look at males it's 1 in 1,800. If you just look at the females it's 1 in 20,000.

Then for Pompe as I said with the addition it's now 1 in 34,500 just for infantile.

For the late onset alone it's 1 in 15,000. If you combine the infantile and late onset it's 1 in 9,800.

If you look at the genotype of unknown significance or unknown onset it's 1 in 35,000.

If you combine them all it's 1 in 7,600.

For Gaucher you can see on the table it's just Gaucher, it's 1 in 69,000. If you were to look at just the genotype of unknown significance it's 1 in 276,000. And if you combine them it's 1 in 55,000.

For MPS-1, the severe type is 1 in

138,000 and if you combine it it's 1 in 92,000.

For Krabbe it's, well, zero. And for the genotype of unknown significance along with the unknown onset is 1 in 31,000.

So as you can see Missouri is definitely seeing many more cases than was expected from the population incidences.

So, I'd like to tell you some of our challenges. I guess you all can guess what would be the first major challenge is seeing the number of referrals, confirmed cases than was expected.

You can imagine the centers' feeling of being overwhelmed with the patient volume as it was definitely more than what was expected.

The centers really felt that they needed one person to just follow up on the infant and abnormal screen for LSD to ensure timely assessment and evaluation.

In planning to implement centers actually thought they needed to develop a good team, and then to educate other specialists as well

and get them prepared for this.

The advice from the centers on confirmatory testing is to send tests to labs that are familiar with newborn screening, especially due to the differences between labs on how results are reported and interpreted.

There's definitely four genotype and phenotype correlations that we've all seen. As you can see from the table I showed previously we have many variants so unknown significance and genotypes of unknown onset. It's very hard to decide what to do with them.

Missouri is finding a significant number of pseudodeficiencies, especially with MPS-1.

We have seen a 2 to 3 percent among the African-American population, and for Pompe we are seeing at least 4 percent in the Asian population with pseudodeficiency.

So, since Missouri has been the pioneer for these lysosomal storage disorders screening,

and treatment history is really based on symptomatic patients there are no guidelines on following up asymptomatic patients.

So the question is do we have sufficient evidence to say that the patient with pseudodeficiency will not develop disease later on in life.

Are we just increasing the patient's anxiety and making their asymptomatic children fragile?

But in actual fact, when we talked to the families instead of all these unknowns when you ask parents when you confirm diagnosis of their kids they prefer to know their child's status to prevent a diagnostic odyssey.

But there's real concern with the clinicians that the family will be lost to follow-up if the onset for symptoms is -- since they occur much later in life and the children are asymptomatic.

I mean, we have already seen in this

three years that we have lost families that we have not seen in the usual newborn screening for other disorders.

So, a word on Fabry. The newborn screening patients and the affected family members, as you can see the numbers have tripled.

The Fabry population you see 61 percent have the A143T allele.

We have identified a lot of relatives that only a few are symptomatic. This raises interesting questions for a clinician following these babies.

How are we going to plan to test these asymptomatic at-risk relatives? Do we see them in clinic, or do we just order a test without having them come in? Or can they actually be seen by a genetic counselor alone?

Overall, the Fabry -- number of patients of Fabry that the centers have seen are pretty overwhelming.

I think many discussions have been had

with the ethical dilemmas of screening because of the identification of a lot of carriers and late-onset conditions.

We know that there may be the possibility of losing that parent-child bond. But I think we can address these with education.

But the inability to get life insurance, and long-term care insurance, and disability insurance is definitely a barrier, and we need to find a way to bridge this.

But the one thing that is very important is to address the support for these parents.

The families of newly diagnosed newborns have no support group because we have to first identify all these infants.

And neither do the healthy children who have late onset diagnosis. So parents have nobody to talk to to see what to expect or what not to worry about. So we really need to be thinking about that.

These are some of the lessons learned,

that it is really important that we create a task force to help us, that we follow guidelines that really need to be flexible.

We have learned quite a bit. We don't have all the answers. And for screening for over three years the follow-up so far has been really going smoothly with no real major hitches that we have seen to date.

So overall we've really been very pleased with the screening methods. And as you all saw the incidences are much higher than the published incidences. False positives are similar to other newborn screening tests.

We have confirmed 141 cases to date. The good news is after screening for three years we have not reported an undetected case that presented clinically for any infantile disorder.

So the road is still windy but uncharted water, and unknown. But I think we have made great strides, and the families of children we have identified and go on to treatment are very

grateful.

I'd just like to acknowledge all these people. None of this work would have been done without all their hard work, especially the lab staff, our follow-up staff, our genetic centers, our advisory committees.

I would like to take the opportunity to thank all of them, and most importantly the patients and families that we have identified and treated. Thank you. Questions.

(Applause.)

CHAIR BOCCHINI: Thank you for that presentation. Really you're breaking ground with your work.

Let's open this to the committee. Dieter.

MEMBER MATERN: Thank you very much for that presentation. It's a little sobering when you're part of the committee and you approve these conditions, and then you see what happens, and that there's potential harm that can be there.

And I think it is mostly driven again by false positives. And I think the carriers of pseudodeficiencies and those that have no genotypes consistent with disease are really false positives.

I would like to -- maybe it's something for the Lab Standards Committee to address first, is to really define what a true positive is, and also see whether we can identify a means to reduce it.

Of course there is next generation sequencing, all this stuff, but I think we see clearly the genotypes of uncertain variants are not helpful.

Now, I can disclose that I have probably a conflict of interest although I don't think any more money because I have a lab that can offer second tier testing for some of these conditions.

And we're screening Kentucky babies for three lysosomal storage disorders including Krabbe disease because that's on their law and they asked

whether we can do it and we said yes.

But we also screen for Pompe and MPS-1. We've been doing this since actually the Secretary sent that letter out that she endorsed MPS-1 and XLD. So at six months for 25,000 babies.

The first week we screened we identified one MPS-1. The second week we had a false positive for MPS-1 and we didn't have a single one since because we added a second tier test for dermatan and heparan sulfate. So we do not report anyone with a low IdoA activity and normal glycosaminoglycans.

For Krabbe we use psychosine which I'm surprised that we still don't talk about psychosine at least in terms of follow-up.

Of course not everything is closed with respect to how useful psychosine measurement is in the follow-up of patients, but so far I think any symptomatic patient with Krabbe disease at any age with have elevated psychosine.

So I think it should be helpful to at

least identify the early infantile cases in the newborn period.

There is a problem with late onset cases. It's difficult to overcome as we've heard here again, and as we know from New York, but we should consider whether the late onset are secondary targets.

For Pompe disease we're working on a second tier which I think if it works out will be very easy for any lab to implement.

So I think we should address it and help the state labs and particularly also our follow-up people and the patients to better define what the goal of the screening programs are.

CHAIR BOCCHINI: Thank you. Additional questions or comments from the committee? If not, Natasha and then Carole Greene.

MS. BONHOMME: Natasha Bonhomme at Genetic Alliance. Thank you for that presentation. I think it's a lot of data and a lot

of information for us all to mull over.

One question I had. First, I really appreciate you talking about where this puts families in terms of this is a new experience in terms of being identified with these conditions but through newborn screening.

And it's something that we of course are very interested in.

You said that they don't necessarily fit into the established advocacy groups or support groups that are out there.

Have you seen them come together in any way? What kinds of supports are they given? Or if you could just elaborate on that a little bit more.

I will say that is something that we're hoping to be able to learn a little bit more about through the new conditions program that was recently awarded to APHL and being a partner with them on that.

But it would be great just to hear a bit

more about what you've heard in terms of what families are doing because this is kind of new territory even on that advocacy support group page.

DR. ROGERS: Well, Natasha, I think clinicians, our centers could give a better picture.

But from what I've heard is that I think there are only a few babies that have been identified to have the infantile disease from the disorders that we are screening. And so families don't have -- they're not necessarily from the four different centers, and they're not necessarily brought together to know who the other families are and to be able to talk to each other.

And the cases that are out there that you may have a Pompe support group and a Gaucher support group, these were all people identified later in life. And so they just don't feel they fit.

And I was talking about those that were identified with late onset. These are families

that have healthy children and they're going to be healthy for many years to come.

But yet I think they want to feel connected some way to other parents who also have these fears and these apprehensions I guess to come together.

CHAIR BOCCHINI: Melissa, and then Carol.

MEMBER PARISI: Thank you for that presentation.

My question is really about Fabry disease and the definition of carriers. I was struck by the fact that it didn't appear that you had identified any female carriers of the condition even though this is an X-linked condition.

I'm just wondering if maybe you're defining carrier differently than what I was expecting given this heterogeneity with regard to presentation with symptoms for those who do happen to carry mutations in the gene. Could you give me a little more feedback on that?

DR. ROGERS: Basically the centers are sending us a diagnosis for females as Fabry disease and not as carriers.

Andrea, you are on the floor. Do you want to say something?

CHAIR BOCCHINI: She's coming to the microphone.

DR. ROGERS: Okay.

MS. ATHERTON: I have to start this off by saying I unfortunately am no longer at Children's Mercy as a genetic counselor and I work for Shire now.

But going back and speaking with -- about how the centers in Missouri would do the follow-up for Fabry disease we didn't use a terminology carrier for Fabry disease. They were heterozygote or, well, Fabry male.

So the females that were identified as phenozygote for Fabry disease were classified as Fabry disease, knowing in fact that with X-linked disorders when females are concerned we're not

going to pick up every heterozygote female through an enzyme screen.

So there's probably a fair number of girls out there in the State of Missouri who are carriers, carriers in the sense of being heterozygotes for Fabry disease, that have normal enzyme function and therefore were not referred through newborn screening to be identified.

DR. GREENE: Carol Greene, SIMD. And I had two questions for follow-up.

But to continue on that theme, this may be coming back to what Dr. Matern said just a moment ago about needing to have a common language.

And it would make sense that if somebody's enzyme activity was low enough that you might call it Fabry disease recognizing you didn't pick up other heterozygotes.

But just because your blood level is low doesn't mean you're going to have a low enough level to actually get symptomatic.

So I think that brings back to what Dr.

Matern said about needing a common language.

So again, I want to add my thanks for a great presentation. I have two questions that have to do with the follow-up.

Earlier you mentioned some anecdotes that the families were grateful to have the information. I think you were referring to those who were symptomatic.

And then later you mentioned that many of the families who are -- the term of art now seems to be patients in waiting, that are very anxious.

And so one question that I'm wondering is is there any formal evaluation of the psychosocial impact on those families.

So, thinking about finding them support is great, but I wonder if there's any formal evaluation of the impact on the families.

And my second question is just speaking as a clinician and knowing when you get the positive newborn screen and you know exactly what testing needs to be done, and the insurance doesn't cover

it, and we compromise a lot. You know, can't get a sample to the right laboratory.

Do you have information about the experience of the clinical centers actually getting this testing done?

DR. ROGERS: For your first question about the evaluation we have no formal evaluation.

But the centers have told us that the families that have infants who have been confirmed with the disease that are in treatment are grateful, but those with late onset are also grateful.

Because once education is given to them and they understand what the disease is they truly are grateful that they know and they don't have to worry down the road at some point that their child's going to get sick and they're going to have to go from doctor to doctor to find out what that child has. So, they are grateful.

And of course you're going to have some parents that really are upset about this.

For your second question -- I'm sorry, I've already forgotten what the second question was. Could you repeat the second question, please?

DR. GREENE: What's the center's experience actually getting insurance approval to see the neurologist, to have the spinal tap, to have the DNA testing done, to have the enzyme assays done.

DR. ROGERS: From what I know in Missouri we have no problems with Medicaid because there's as long as a newborn screening is done for that particular disorder they will approve all the tests.

Tricare has had some problems with paying for certain tests.

We at the state have given each of the centers some seed money, not very much, to help if insurance doesn't cover it.

And usually for what insurance doesn't cover, tests like parental testing. And so the

Children's Hospital finds that difficult to get that testing done, so we have provided funding for that.

And I wanted to also say that all our centers are sending samples for psychosine. They weren't doing that in the beginning because at that time, Dieter, it was a research project. But now all of them are sending samples for psychosine. It was not something that we initially created in our form to report back.

CHAIR BOCCHINI: Thank you. Sharmini, thank you very much for your presentation and your comments. We appreciate it.

We're now going to go onto the next presentation. This is by Jennifer Kwon. And Dr. Kwon is also on the phone.

She's associate professor of neurology, pediatrics, pathology and laboratory medicine at the Golisano Children's Hospital of the University of Rochester.

Dr. Kwon is a child neurologist with a

strong interest in improving clinical outcomes in children diagnosed with rare disorders by newborn screening.

She is a member of the Evidence Review Committee and the Registry Committee in the American Academy of Neurology.

She's going to talk to us about long-term follow-up for Pompe disease. Dr. Kwon?

DR. KWON: Thank you. I hope you can hear me. I'm in a local Canadian holiday town and in order to ensure good screening of the high definition video and a clear cell signal I found this ideal location, except it's near a bar. So if you hear some background noise that's what that is.

(Laughter.)

CHAIR BOCCHINI: We can hear you. Go ahead.

DR. KWON: So, in terms of disclosures I am a paid consultant for Genzyme, and I'm the psych PI for the Genzyme registry.

And I am not a Pompe disease clinical expert. I mean, I am a clinician who is interested in improving long-term clinical outcomes and those who have been diagnosed with rare disorders via newborn screening.

I'm not quite sure why the clinical experts in Pompe disease aren't giving this talk instead of me, but I have reviewed the slides with Amy Brower and Mike Watson of NBSTRN/ACMG as well as Melissa Wasserstein and Priya Kishnani.

And I really thank them for their assistance with these slides.

I also am sure that they will appreciate it if I stress that any views that I express are my own.

But you should be aware that those clinicians who are following children identified by Pompe disease newborn screening converse regularly with LSD experts and Pompe disease experts.

So, the background of long-term

follow-up in Pompe disease is that even though newborn screening was added to the RUSP to improve outcomes in those with infantile Pompe disease by allowing them to have early treatment we have always known that newborn screening is likely to identify far more infants with late-onset Pompe disease, anytime from early childhood to adulthood.

And based on the evidence review, I didn't put these numbers on the slide, but on the evidence review that was conducted for the advisory committee a few years ago about Pompe disease we predicted that annually we would identify about 40 cases of infantile onset Pompe disease in the U.S., and about 90 plus cases of late onset disease.

So, in preparation for how best to follow the Pompe disease patients we looked at the landscape of information that we already had at the start of newborn screening.

And this is the listing provided by the ACMG that highlights that NICHD and NBSTRN

supported pilot screening of Pompe disease in three states, Georgia, Wisconsin and New York.

There were also a number of NBS carrier resources needed to have monthly calls of the pilot centers as well as state newborn screening labs in states that were interested in implementing screening.

And other states have joined on who are thinking of becoming interested later.

Just recently we've developed a clinician focused call to deal with long-term follow-up issues.

In addition, NBSTRN also sponsors a specimen repository, an analytical and clinical validation tool through Piero Rinaldo's project as well as a long-term follow-up tool and data set which is really supposed to be the heart of where the long-term follow-up registry data resides.

The following slides I'll go through relatively quickly in the interest of time, but this is again to show the wealth of guidelines that

were available before newborn screening began.

First, we had the ACMG ACT guidelines, ACT sheets, which really gave a lot of early information about how to diagnose the condition once a referral is made as well as emergency management guidelines.

The next guideline was an ACMG practice guideline specifically for Pompe disease which was published in May of 2006.

There is a more recent guideline being developed for newborn screening follow-up which has not been published yet.

And then the May 2006 one was published in Genetics and Medicine.

The following ACMG standards and guidelines are more broadly for lysosomal disease in general, including pre-symptomatic management of a variety of lysosomal diseases including Pompe disease.

And that came out in Genetics and Medicine in May of 2011.

And the final set of guidelines which were not an ACMG product, but were a product of neurologists interested in establishing some sort of care guidelines specifically for late onset Pompe disease patients.

And this appeared in Muscle and Nerve in March of 2012.

And really my reason for showing you all of these -- I'm sorry, we're going to go through the slides for the lysosomal disease and then the consensus guidelines for neuromuscle.

And then the next slide which I think is slide number 10 is really my way of saying that while guidelines are really very helpful and useful to give you the general gist of what we're trying to avoid, or the serious harms we're trying to prevent in diseases they're not necessarily well suited for the ongoing clinical interactions that take place between doctors and people who are identified as being at risk for Pompe disease.

So, to that end we have recognized that

the providers who are actually seeing Pompe disease newborn screening referrals, especially those who are thought to be late onset, who are supposed to have their presentation later in life, but we don't know necessarily how much later in life.

There have been a number of discussions among those providers.

So, as we said before NBSTRN has recently started sponsoring provider calls. And I think I may be -- there is a time lag on my HD video so I think I may be a slide ahead. So if we could go to the next slide which starts with clinical follow-up initiatives.

The NBSTRN sponsored calls, and we began recently in June. In states such as Missouri they have provider based calls regularly to talk about issues with their whole lysosomal screening program.

And really those calls have been very helpful for other states like New York. So we looked at the Pompe disease guidelines, for

example, produced by Missouri.

In addition, there are Genzyme-sponsored workshops. As you are aware the treatment for Pompe disease, enzyme replacement therapy, the ERT is produced by Genzyme.

And they have a number of helpful workshops for clinicians following pre-symptomatic patients of Pompe disease.

But as you can imagine these discussions tend to be expert driven and standardized approaches are really not present yet. So they are evolving.

So, this table is really meant to give you a sense of the New York State Pompe disease guidelines, and just sort of in a quick and dirty form.

Basically, the only mandated testing or clinical diagnostic follow-up occurs at diagnosis, so at the time of referral.

But for late onset patients, in other words, patients who appear to be asymptomatic as

infants, the follow-up really depends on the eye of the observer.

So there are a lot of things in the column marked as clinically indicated.

And if any one of those follow-ups happen to be abnormal that is considered a trigger for at least considering initiating ERT.

So, in New York, this is data that I recently got from Joe Orsini, we screen about 400,000 infants. And of those we think we've identified 2, possibly 3 infantile cases, and possibly 28 late onset cases.

So that's just -- it's not meant to be a statistic to carry away, it's just to give you the scope of the issue of late onset disease follow-up.

So the question to ask is how do we actually follow these late onset patients. Do we ask people to come when they're worried about their child? Do we check them regularly and decide if we're worried about the child before doing testing?

There's been a real clamor for having maybe a more standardized and clearly defined protocol for follow-up.

And of course the questions that arise are what are the optimal surveillance frequency and testing, and at what point should we really think of pulling the trigger and starting a patient on enzyme replacement therapy knowing that when a children is started on enzyme replacement therapy which is every other week infusion it is very likely that this treatment will be continued for their lifetime.

And so to that end there are Pompe disease newborn screening registry efforts underway to at least collect data about clinical practice that hopefully we can go back and look at and evaluate.

And these are taking place between NBSTRN and individual states. And also Genzyme has been collecting some newborn screening data as well.

CHAIR BOCCHINI: We've lost the sound.

DR. KWON: Hello? Can you hear me?

CHAIR BOCCHINI: We can hear you now. We lost you for a little while.

DR. KWON: Okay. I'm sorry. So I think I actually may have just gone ahead a few slides.

So we were talking about the New York State Pompe disease guidelines. And did you hear me talk about the numbers of infantile and late onset patients?

CHAIR BOCCHINI: We did.

DR. KWON: Okay, all right. So then the next slide after that.

CHAIR BOCCHINI: We're on the slide Recent Questions Raised about Long-term Follow-up.

DR. KWON: Okay, I'm sorry. I'm looking at the video. There's a lag. So thank you very much.

So, the recent -- just an example of some recent questions that have come up about

long-term follow-up that the clinicians keep asking is, first of all, how frequently should we be following these infants.

And then when isolated abnormalities arise how should they be addressed. There are many of us who are seeing infants who have elevations in CK. Many of us are seeing infants and young children, or siblings of infants identified with late onset Pompe disease who have fatigue, weakness, headache, or pain.

And there are also infants who have more involved follow-up and who may have perhaps minor abnormalities, not abnormalities that suggest serious disease, but possibly something that may suggest multiple involvement.

The other question that arises is that as you know in certain populations there is a GAA splicing mutation which is felt to lead to a more benign phenotype.

And some of us have seen patients who are homozygous to this splicing mutation who we

would like to follow less frequently because the data suggests that these patients should do better.

And so that's been sort of one of the questions that has also been raised. That's just to give you an example.

So in our last provider call, and we'll go to the next slide which is entitled When Public Health Meets Rare Disease Care.

In our last provider call it was suggested that for a Pompe disease newborn screening and clinical follow-up registry we really consider what the CF Foundation registry does and how they work.

And so -- and I've long been a proponent of using the CF disease foundation and their registry as a model for improving clinical outcomes in rare disease.

And the reason for their successes we think are due to the fact that they have a system of ongoing evaluation or clinical outcomes in their centralized national registry, that the registry

oversight is conducted by an advocacy organization whose board and members are really committed to clinical quality improvement over the lifetime of the patient.

So these aren't researchers necessarily. These are people who want to make the lives of people with CF better over the course of their lives.

And of course, in doing so they're raising important research questions. They're generating impetus for important clinical trials.

But the one thing that we often forget about the CF Foundation and their registry is that their registry has access to sources of funding that are really unheard of in the rest of rare disease care.

And it also makes it a non-starter, the quantity of money that's available for this one disease-specific registry. And that's what makes it so difficult to replicate this for other rare diseases, even a rare disease like Pompe disease

which has had, as many of you know, fairly heavy industry sponsorship.

So, in conclusion, and this is my final slide, our long-term follow-up efforts are -- we're trying to develop a registry because we understand already that we have no idea what we're doing when it comes to following patients with late onset Pompe disease.

I should say we do know the serious consequences we're trying to prevent. We do know that we don't want people to -- have end stage muscle damage.

But we're not really sure of the best time to start ERT to prevent that.

And so even though we have these guidelines about not starting ERT too late we're not necessarily sure when the optimal timing is.

We know a lot about the genotype/phenotype correlation, the GAA gene. There are resources again that Mike Watson wanted me to mention like ClinGen and other research going

on to follow up better biomarkers.

For me just at a classical level I find the NBS care and sponsor provider calls a great resource for clinicians just to air their immediate concerns and issues that hopefully we will find that these questions lead to more targeted registry work.

And so that's where I will end my talk. Thank you.

(Applause.)

CHAIR BOCCHINI: Jennifer, thank you very much. We appreciate your presentation.

Can you give us an idea of how many providers are on the Newborn Screening Translational Research Network calls?

DR. KWON: So, I think the Georgia call there was pretty impressive attendance. And we're going to make the calls quarterly.

I would say that overall the calls are not just for providers, they're also for other newborn screening stakeholders. So it's hard for

me to give you a number of the providers.

But I do think that we all manage to stay in touch with each other, especially as these common questions arise.

CHAIR BOCCHINI: Thank you. Any questions or comments? Starting with the committee. Jeff.

MEMBER BROSCO: This is Jeff Brosco. I think we heard from a couple of presentations that there are certain ethics issues that are going to come up from newborn screening that we can anticipate.

And Aaron Goldenberg and I along with the NBSTRN group are putting together a paper that sort of lays out what are the common ethics issues that come up for probably any candidate condition that probably should be thought about before we get too far.

So that we don't end up screening for a condition saying, oh, we suddenly found this. Now what do we do? Trying to at least think about

what the approach might be before we get to that stage. Hopefully we'll be able to share that with you at subsequent meetings.

CHAIR BOCCHINI: Thank you. Other questions or comments from the committee? Joan.

MEMBER SCOTT: This is Joan Scott. Thank you for that really good overview.

Jennifer, do you happen to know if the CF registry is done only under informed consent? Is it a patient-entered registry and data, or is it clinician-entered?

DR. KWON: So it's a clinician-entered registry program. And all patients whose data are entered, they do consent.

MEMBER SCOTT: And do we have a sense of where there is screening for Pompe what clinicians are doing about encouraging -- because the NBSTRN is done under informed consent to collect data and enter the follow-up data into their -- is that not correct? I'm looking at Mike. He's nodding his head.

DR. KWON: That is correct.

MEMBER SCOTT: So, do you have a sense that clinicians who are now seeing individuals with Pompe are asking patients for informed consent around being part of that long-term follow-up database?

DR. KWON: So, I would say yes, they are. But first I should make it clear that there is right now -- there are plans to develop a Pompe disease newborn screening long-term follow-up registry with NBSTRN.

And in order to make those plans a reality we will have to figure out some way of instituting some consent procedure.

But even without that many centers that are already Genzyme registry sites are already entering newborn screening data into the Genzyme active patient registry.

And again, they can only do that with patient consent. So there's still no way around the fact that this activity is an activity that

requires patient consent.

MEMBER SCOTT: Yes, that wasn't a question that it shouldn't be. I just was trying to get a sense about whether or not the families who are being identified through newborn screening are being told of these registries and encouraging participation.

Because it's the only way we'll be able to systematically collect the data that we need.

DR. KWON: And I think that because -- so, I'll just speak for myself. So, I know about these registry efforts that are underway, but I have two late onset follow-up patients that I follow and I haven't really presented the registry as an option for them yet because I think that this is still early days in terms of the registry process.

When I feel like the workflow is a little clearer and that the structure of registry oversight is a little clearer I think all clinicians will be more than happy to enter data

into a registry.

CHAIR BOCCHINI: All right, thank you. Jennifer, thank you very much for your presentation. I think there are no other questions or comments at this point in time so please go back and enjoy the rest of your holiday and your location. Thank you.

DR. KWON: Thank you.

CHAIR BOCCHINI: So that will conclude the morning session. We have until 1 o'clock to return following lunch.

I would like committee members before you head for lunch to meet at the lectern. We're going to take a photograph. Group photo. Okay, thank you. We'll see you back all promptly at 1.

(Whereupon, the above-entitled matter went off the record at 12:10 p.m. and resumed at 1:07 p.m.)

CHAIR BOCCHINI: All right, let's go ahead and do the roll call. We do have some early leavers and some late returners, so let's see who's

here. Don Bailey? MEMBER BAILEY: Here.

CHAIR BOCCHINI: Jeff Brosco.

MEMBER BROSCO: Here.

CHAIR BOCCHINI: Carla Cuthbert.

MEMBER CUTHBERT: Here.

CHAIR BOCCHINI: Kelly Kelm.

MEMBER KELM: Here.

CHAIR BOCCHINI: Dieter Matern.

MEMBER MATERN: Here.

CHAIR BOCCHINI: Melissa Parisi.

MEMBER PARISI: Here.

CHAIR BOCCHINI: Annamarie Saarinen.

MEMBER SAARINEN: Here.

CHAIR BOCCHINI: Joan Scott.

MEMBER SCOTT: Here.

CHAIR BOCCHINI: Debi Sarkar?

MS. SARKAR: Here.

CHAIR BOCCHINI: Joseph Biggio on the phone. Susan Tanksley. Chris Kus.

DR. KUS: Here.

CHAIR BOCCHINI: Adam Kanis.

DR. KANIS: Here.

CHAIR BOCCHINI: Natasha Bonhomme.

MS. BONHOMME: Here.

CHAIR BOCCHINI: Siobhan Dolan.

MS. DOLAN: Here.

CHAIR BOCCHINI: Cate Vockley.

MS. VOCKLEY: Here.

CHAIR BOCCHINI: And Carol Greene.

DR. GREENE: Here.

CHAIR BOCCHINI: All right, thank you all.

So, this afternoon session we have four reports from workgroups. The first is the Cost Analysis Workgroup Update. This will be presented by Alex Kemper.

Alex is the leader of the Condition Review Workgroup. He is at Duke Clinical Research Associate and department of pediatrics. Alex.

DR. KEMPER: Thank you very much, Dr. Bocchini. I know that right after lunch at 1 o'clock what everyone really wants to do is hear

about cost assessment methods so I'll do my best to go through this.

And really the key things I hope you get out of this presentation is both what we can do and what we cannot do. Because I think that understanding both of those things is equally important.

So, this is a list of the membership of the workgroup. And I won't read through all the names, but I'd like to thank everyone here and also point out that several members of our workgroup are now sitting at the big table. So in a sense we're kind of the proving ground is the way I like to think of it.

So, our charge was to consider methods to assess the cost of newborn screening expansion.

And I think as most people in this room know this is part of the Newborn Screening Saves Lives Legislation. So we're really required to do this.

So, just to recap where we are with this

work. If you remember last time I talked about doing a pretest to assess the feasibility of cost assessment methods.

And we were looking at two target conditions, MPS-1 and Pompe disease.

Both these tests can be done on multiple platforms and they can also be multiplexed with other screening tests.

But as you'll see I'm trying to really simplify some of the details of the analyses that we're doing.

So we're not estimating costs for each possible screening strategy, but just trying to look overall at the cost.

And our strategy has been to gather estimates and ranges that can be useful for states as well as the advisory committee, but at the same time minimizing the burden on respondents to gather this information.

And obviously we're not being prescriptive about how these data will ultimately

be used.

So, one of the first tasks we did was to look at the various categories for cost that play into the cost of doing the screening test and the follow-up.

And I'm going to talk about the follow-up in more detail in a second. But if you just think about sort of the general categories, there's equipment and consumables.

And there's different ways of going about getting this stuff. You can either go and purchase it, and purchase the supplies, and the reagents, and that kind of thing. Or you can have a reagent rental agreement where material is supplied to the laboratory.

There's this group of other laboratory expenses which depending upon the program that we're talking about are things that aren't already included in the equipment and consumables.

So, things like maintenance, repairs, installation, or update of the laboratory

information management system.

There's obviously labor and how labor is costed out depends upon the number of people that we're talking about, the particular position and of course what their salary and fringe benefit rate is.

And then there's this issue of confirmatory testing and referrals, sort of the short-term follow-up.

And this is organized differently by different newborn screening programs. And so some newborn screening programs are, you know, do a lot of work in this short-term follow-up and others don't.

And so it introduces this element of variability when you look at costs. Again, I'm going to illustrate in more detail in a second.

And then of course there's issues of overhead and indirect cost which can do things like pay for the space or the building as well as utilities and all the other things that go into

overhead.

So, we as a group developed a template. And the components -- so this is the kind of thing that while working with an individual newborn screening program we can try to elicit this material.

So, factors to include are the number of specimens that the newborn screening program evaluates.

And we really focused on specimens because that's different than the number of individuals that are screened. Because, for example, some states are two screen tests, some states are one screen tests.

And then there are some babies that will have repeat screens done for other ways. So, even in the single screen state it's never one per one.

So anyway, looking at the number of specimens that the newborn screening program does annually, the platform, the specific test that's done.

And then equipment, consumables, other lab expenses. The labor that we talked about. Issues of confirmatory testing and overhead as I just talked about before.

So, what I want to do is just show you an example of a spreadsheet that we filled out.

And just to minimize the number of slides that I'm showing you, you'll see that I have states compared, you know, I'll have state A, state B and the next slide as you might guess we have C and D.

The fact that they're next to each other, I would really avoid sort of comparing across the lines.

That's because the number of specimens that are tested annually might be different. The platforms are different. The number of tests that are done, the multiplexing is going to be done.

But if you just look at -- and just so you don't ask which state is which, states really asked us to maintain confidentiality because a lot

of these numbers are really proprietary in terms of how they do contracts and that kind of thing, and just didn't want the names of the states divulged. And so I won't be revealing that here.

So, here we have two states, one with 100,000 specimens tested and the other 180,000. You can see different platforms.

You can see one state has a reagent rental agreement and the other state has purchased equipment.

The number of conditions that are tested using each platform are different. So one is a fourplex and the other is six.

The state that had this rental reagent agreement didn't give us any cost for additional consumables, but the one that used tandem mass spec did.

There's this other laboratory expenses. We didn't -- I should have dropped that 461,000 for state B one level down, but you can see the big differences in terms of laboratory

personnel.

One state did not provide us with overhead or indirect costs.

And so if you do this math you can figure out what the cost per specimen is, and that's the number on the left in each column, and then the cost per specimen per condition where I just took for state A and divided it by four, and for state B divided it by six.

But it's not like there's this linear association between the number of things that you screen for and cost. So that's, I mean, it's a simplifying assumption but it's really, you know, in reality it doesn't make sense because you invest a lot to get the screen test and then there's a small, probably incremental cost for each additional one.

But I wanted to be able to at least put it on some sort of standardized framework.

And then here is -- you can see state C which is a smaller state and state D which is a

little bit bigger, but also smaller.

And then as I showed you, 80,000, 98,000. You can see the state, the 98,000 gave us both a rental reagent agreement and in addition a large amount for consumables and other laboratory expenses, and labor which state C didn't.

And you can see where the numbers boil down in the end.

So, things that I just want to point out from this is that newborn screening programs do a lot of work.

And figuring out the exact cost for our purposes is not something that's part of their job.

So, in a sense it's not surprising that it's hard to elicit the numbers and get them into the buckets that we want them to be in.

And so it just brings into how accurate are these numbers really.

The other thing that I want to make sure people appreciate is that the number of specimens that are done in a state has impact on what the

overall costs would be.

So if you're a smaller state, you have a fewer number of newborns to test, you're taking your startup costs and putting it over a fewer number of babies being tested.

So one way that some newborn screening programs do that is they partner with other programs and have more centralized testing.

But there is this factor about the number of specimens that are tested and ultimately what costs are.

The other thing, and I alluded to this before, is that different newborn screening programs take different tacks to how they do long-term follow-up and the degree to which they do things like genetic testing and that kind of thing.

So that's sort of borne differentially by states.

So one of the simplifying things that we did was really focus on the cost of testing the

specimen and not those other follow-up costs. Which my guess is they probably are much smaller than the actual screening tests anyway. I'm going to revisit this again in a second.

And then one point I wanted to make sure that I drew out too. The different platforms and different testing strategies in general are going to have different numbers of false positives too. And so that's going to affect this follow-up cost as well.

So again, we made a lot of simplifying assumptions and just kind of tried to do the best we could.

So, highlighting what I just said before, I said all states incur some sort of follow-up cost but only one state reported a follow-up cost in the costs of confirmatory testing.

So, even though newborn screening program may not be bearing a lot of these costs, clearly the system societally does.

So, Medicaid covers a lot of follow-up testing in most states. So it is something that's absorbed somewhere.

So, everyone knew this is like -- Cate actually came up with this. I need to give her credit. But really I felt like we were comparing apples to apples and there's just so much variation.

If you leave with nothing just remember this slide for the amount of variation.

Of course when she said that we were like comparing apples to apples that's what I thought of at first. But it's just the geeky person inside of me.

So anyway, we had a lot of assumptions that we had to build in, and it's important to understand the context.

So there's this huge variation in state annual birth rates. There's variations in the number of specimens per baby. We talked about two versus one states.

There's issues of who pays for what. There's the issue of timing. So, when you first start things out there's a lot of upfront costs and there's different people that may be involved in paying for this.

And then, over time too there become screening efficiencies. And so we wanted to have this two-year projection but I think really in the end we probably know more about the initial startup costs.

And then there are all sorts of other things that are happening in the state that impact like who pays for what and where costs appear.

Again, all these other sources of variation that this committee thinks a lot about in terms of screening algorithms, different laboratories' access to specialized services, issues related to the condition.

One could go on and on thinking about things that would cause costs to vary.

So, as I think everyone is aware that

when a condition goes for review there's a nine-month period for that review to happen. And so there's limited time for collecting data.

And if you really wanted to get to these costs it would require a fair amount of attention.

I really think that the newborn screening programs would need assistance like how the CDC can get involved with doing these very careful evaluations within newborn screening programs.

But that's just not going to happen within the short period of time that we have to get to that level of detail.

And as I said before this is not what the newborn screening programs sit around and think about. But we just need to work with them to get it where we can.

Estimates are going to represent what's going on with the early adopters. They're going to be the ones that have the information.

I mentioned before this issue about

costs being higher for states with lower testing volumes.

And then one of the things that was very interesting that I didn't appreciate before we started gathering information was that the privacy issues that newborn screening laboratories face in terms of details that they can share with us.

So, again, thinking ahead what are we going to do if no U.S. state has started screening or is in the planning process of screening.

So, for example, there's a pilot study that was done in Australia or somewhere like that that was enough to move something to evidence review.

So at that point we'd have to work with vendors and researchers, but that may not reflect what's going on.

And then of course there are these other things that happen in terms of the price of the equipment, FDA approval issues, new screening technology, all sorts of things that are going to

muddy the water.

So, what do I think we can provide? So as long as there's at least one state that's doing it, or is in the planning stages and is willing to provide us constant information I think that we can get at least in a sort of broad sense the overall estimate of startup screening and laboratory costs, and then make other estimates based on the unique characteristics of the state or states that we're able to access.

Again, our cost assessment plan is going to be focusing on the budget impact from the state newborn screening perspective.

Hopefully we'll be able to as a primary source of data go to states. In terms of the estimates that we hope to generate it would be cost per specimen to add the particular condition.

And one thing, and I have to thank Annamarie who pointed this out as I was putting this slide together is that everything I've talked about so far reflects traditional dried blood spot

screening.

So we'll have to reconsider how we're going to do things if a point of care newborn screening test is under consideration.

So, we will put together a narrative description at least summarizing what we know in terms of the requirements for screening, the assumptions that we made, and the sources, the methods of getting the cost estimates. So at least when you look at these numbers you can understand where they came from.

And so our next steps are going to be to finalize this approach and submit a report as well to the advisory committee. And then we'll be ready to incorporate this as we're able to into the condition review procedures and the overall timeline that we have.

Now, I'm going to go and open up the floor for questions, but I'd like to invite Scott Grosse to come up.

So, Scott's been incredibly helpful in

doing this. And he's like the real card-carrying economist. I just play one for the advisory committee.

But I think it's important to have him up here because if you ask a really specific economic question I want to be able to make sure that we're giving you a good answer.

So, now that he's up I can open the floor to questions.

CHAIR BOCCHINI: All right. Thank you, Alex, and thank the CDC for lending Scott out to us. I think that's been great, a big help.

I want to thank you and the members of that workgroup for all the work that you've done to try and standardize this in some way that it's going to be beneficial to the committee and provide the data that we need when the condition backs to us with all of the evidence.

So let's open this to any questions or comments from the committee. Joan.

MEMBER SCOTT: Thank you very much.

That was really helpful. And it again illustrates how difficult cost can -- mean so many different things.

And there are so many variables in when you do this kind of analysis.

So, when it is done and that information is provided to the committee as part of that rubric along with the evidence review and the public health impact what are the dangers that the committee should be aware of in considering that information? Does that make sense?

DR. KEMPER: No, that totally made sense because it informs how you weigh that.

So, I have a couple of observations. And I'd like to get Scott's input.

So, first of all, we're only looking at one side of the equation, right? So we're looking at the costs for doing the screening. We're also not even looking at the diagnostic test and so forth.

So, it's just -- I hope it gives you

insight into what the impact might be on what the newborn screening laboratory program would have to invest to screen for those things.

But it's kind of an unbalanced equation.

That being said though, oftentimes we hear that various preventive interventions are cost-saving.

And that's rarely actually the case because these are rare conditions and so every specimen of every baby gets this cost, but the benefits are narrowed down to a certain number of individuals.

But that doesn't mean that it's a bad thing to do.

And so we will do as best we can to articulate where we're certain about the numbers and where we're not. And I think it's going to be more not than certain.

But I'm sure that the advisory committee when they figure out how to use these

numbers it will be just one teeny bit of information. But I think we need to be careful about this.

And one of the things that worries me too is that whenever you present something on the slide in the committee or wherever with all the caveats around it people lose track of all the caveats, and the number gets out there, and people just kind of fixate on that like it's the truth. And that just happens all the time.

And so I just feel very strongly that we need to be careful about how much weight we put into this and the way it's used.

That's sort of my 30,000 foot level. But Scott?

DR. GROSSE: One of the issues Alex mentioned is that the cost of the test may change. With FDA approval costs may go up.

So, typically we have the cost estimates for the home brew before there's an FDA approved test. So who knows what the cost will be

eventually that most states will have to pay.

We did not include any cost to the state health department for organizing the process of establishing a condition. Adding to the panel all the committee meetings, all the staff time that's taken.

The biggest omission is that there's no cost for the long-term follow-up not just of the infants who are diagnosed, but all the infants with the late onset, asymptomatic kids that have to be followed up which we heard about this morning.

MEMBER BAILEY: Just echoing Joan's words how much I appreciate what you've done, and also recognizing -- helping us see the old thing about what you put in is what you get out.

The data coming into this are going to be quite variable.

I think one danger might be that we come up with a cost for the next condition, and then the next condition after that we look at it and say well, this condition is costing a lot more or a lot

less than that one.

This is why what you're doing is so important. We want to make sure that we're feeling like we're using the same approach to making that estimate on both of them.

But it might be worth thinking about something like what we're doing. I don't want to create another matrix, but maybe saying, okay, based on the data we think this is typical of what you would expect to add a new test.

Is it a lot more expensive? Is it going to be cheaper than usual? That would help me I think in the long run to think more about how we make a decision in the process.

Because then you look at well, it's eight dollars per test, what does that do for us. So anyway, I would just throw that out for us.

DR. GROSSE: One way to do this would be to look at SCID as a sort of a -- for a stand-alone test. Like six to eight dollars per infant. And say anything that's less than that would be

considered relatively inexpensive.

DR. KEMPER: I mean, I totally agree with that. It's just it's hard because we're also looking at one side of the equation and not the whole thing.

And so I just don't want this to become $50,000 per quality which is something that's just kind of made up.

MEMBER BROSCO: What I'm going to say is a follow-up, following on Don's comment. Because you could also wonder too about getting us a sense of how uncertain.

I mean, you said you were very uncertain about things. But there might be some times where you say look, this is what the test costs. People are pretty sure. Just, it's adding one more condition, it's not a big deal.

There might be others where you might say we're so uncertain you really shouldn't even look at this number, even though we have to give you a number. So that might be helpful too.

MEMBER SAARINEN: I actually was going to say something very similar. You know, that's why God created asterisks because this is exactly -- you can't just shove everything into the same bucket and say this is a cost analysis and this equals the same thing.

And even taking CCHD out of the equation I think there was this similarity between CCHD screening and SCID in that we knew there were going to be secondary and non-target conditions that were going to be picked up by a test. That's generally -- the test is the cost of the test, right?

But if you were going to try to evaluate the cost of care, short-term follow-up, long-term follow-up, then it opened up -- it wasn't a can of worms, it was just simply like how are we going to demonstrate both potentially costs saved on the clinical side through earlier detection versus extra dollars having to be expended both by the public health and the clinical side for all these additional conditions that are being picked up that

weren't originally the target conditions.

As you suggest, there will be some I imagine that will come before this committee that are quite straightforward. Here's the assay. There's nothing else it's going to find. It is what it is. And then you can find your apple within your fruit basket there.

Thank you to both of you for your leadership, by the way. I've learned a great deal on your workgroup.

CHAIR BOCCHINI: Thank you both very much. We look forward to the report.

All right, next we have a summary of the activities of the Education and Training Workgroup. And Natasha Bonhomme is going to give that presentation for the leaders of that workgroup.

MS. BONHOMME: Thank you. Both Cathy and Beth had some travel limitations so I am happy to present for this group. I'm happy to take questions, but I don't promise that I can answer

all of them. That's their job.

So, just in terms of our agenda we did our typical updates from our members, then spoke about the nomination and education project.

We also reviewed some of the workgroup projects that have been discussed here. And then closed the session discussing some additional education needs and project ideas.

So, first an update on the nomination education project. And this is something that we have discussed before, but really the need for parents and really anyone thinking of nominating a condition to have a better sense of what is that process, what do the forms mean, what are the steps, what order are the steps.

And so this is a project that we have undertaken with Dr. Kemper and his team.

And in the past I'd say four or so months we've worked -- sorry, when I say "we" I mean Genetic Alliance -- have worked with Dr. Kemper and his team to really create both the text that would

go along with this as well as a graphical representation because we know people are typically very visual and wanting to actually see what is the pathway.

So at the meeting we presented that and are also exploring some of the technological capabilities and issues in terms of putting that up on the HRSA site, on the committee's website.

So the end goal is to have something very easy for people to walk themselves through in terms of the nomination process on the advisory committee's website.

So as a reminder the project one for this workgroup that was discussed when we did the reformatting of the different workgroups was to create a tool that provides primary care providers with guidance and tips for discussing a positive newborn screening result with parents, something that could be used with the ACT sheets.

As we know the ACT sheets are really useful and they do a good job of laying out what

the condition is. But the idea around this project was almost more of a communications accompaniment, really something in terms of how do you talk to families when they're in that situation.

So, I have been working with members of ACMG, particularly Alicia Keen and Dr. Flannery have been extremely helpful in thinking about how do we incorporate the work that was started a number of years ago with Genetic Alliance and Dr. Carol Greene around issues of talking to families who were experiencing a false positive, and what are the communication strategies around that.

And combining that in some way with the ACT sheets.

So we have met and had a number of emails exchanges, and have identified particular people who have experience working on the ACT sheet working group through ACMG to come together and think about how would we create something that's very easy that could be a companion piece for the ACT sheets.

So, more to come on that at later meetings, but that is moving along.

The committee also will probably help us in the way that would be most useful which is really to review whatever we end up coming up with.

So, the work will be done between Genetic Alliance and ACMG, and then what comes out of that will go to the committee for review and comment.

There was also discussion about how do we incorporate this idea of the actual communications strategies and working with families who are going through that process. Again, not just the condition itself, but the how do you talk to families in a range of different arenas.

AAP resident education project. There's a pediatric resident education curriculum that Dr. Tarini is working on that she is going to look and see how to incorporate maybe a case study around this in that. So, there will be more to come

on that.

That discussion led to another discussion around parent handouts to be used at a time of notification of positive newborn screening results.

The idea being that yes, you can give a tool for providers to use, but wouldn't it be helpful to have something that parents can go to when they are about to have that conversation. They key questions to ask, things like that.

That's something that we've seen in other areas of medicine when people are getting results back and saying remember to ask this. Because we all know that experience of having zero questions when you're getting the news, and then you walk away and 15 minutes later you're like oh, here are all the questions I wish I had asked.

So there was some discussion about that, but it really circled back to the challenge isn't that this information isn't out there, it's actually how do you disseminate it, and how do you

get it into the hands of people once they need it.

So, the discussion was really to hold on that endeavor, focus on the practitioner residency side, but then also use the work of other groups to really think about not creating anything new, but really thinking about what are the channels that we've seen that actually get information into the hands of parents.

So they know when they're getting that information they know to go here, wherever that here is.

Project two as a focus area for the workgroup is the educational outreach project. And the idea around this was mapping of educational resources.

So, the idea that there are so many resources out there, there are so many materials that are out there, and they're all targeted to different people whether that's prenatal, or new moms, new families. Whether that is in general newborn screening, false positive, after the test,

all these different pieces.

The idea of really mapping that out and seeing what's available.

The format would be to have a matrix with characteristics that were seen as important. So the audience, the location. Is this something that can be used regionally? Is it something that's state-specific? Is it dependent on whether the birth happened in the hospital, or birthing center, or at home? So, a range of different pieces.

But like all great ideas when there isn't funding available it's really difficult to know where to move forward.

So, there's a lot of energy and passion I would say around this, but the workgroup members really thought about how to use kind of organizational relationships to start thinking about at least pulling in together more of the educational materials that are out there. Baby's First Test, the Newborn Screening Clearinghouse is in the process of launching our resource center.

And through a number of listservs maybe some of you have seen we're asking for resources to come in. So that's kind of a first step in this endeavor, but this obviously would be a much bigger and separate project that the group is interested in but is still thinking about how to move forward on that.

Another discussion that came up was midwife education. There was discussion about whether that should be a particular priority area for the Education and Training Workgroup.

It was decided that it should be -- we should wait on that a little bit in terms of really figuring out what else is out there, what other groups are doing this work.

I know different groups, different organizations and also states are looking at how do they reach midwives and reach those who are doing home births.

So really the decision was to wait, see what other projects are out there and then see how

the workgroup could leverage those efforts.

Timeliness came up in terms of what are the opportunities for education. The group will reach out to some hospital associations, really again trying to get this on their radar.

One really great suggestion that came from Don Bailey was to explore connections with phlebotomists and their associations. Maybe even inviting them to present to us in the future to see what are their processes.

I think similar to when we we're thinking about nurses we need to learn a little bit more about the workflow and the process of people on the ground who are involved to get a better sense of how we can be helpful.

I think that's the last slide.

CHAIR BOCCHINI: Thank you, Natasha. That was a good summary of lots of different things going on in that committee.

Any questions or comments? Annamarie.

MEMBER SAARINEN: Thanks, Natasha.

That was a good presentation.

So, when you said you want to wait on the midwife piece are you waiting for information to come out of another entity that's involved with this committee or one of the other workgroups?

Or is someone actually taking a look, doing a landscape of what has been done out there?

And the reason I bring it up is I feel like over the last couple of days we've heard pretty consistently about that there are issues with home deliveries, and to some degree maybe a little bit of spillover into birthing centers, but primarily with midwives being able to execute on newborn screening in a consistent manner.

And while I am all about wonderful education materials to the degree they're available to every baby's family I also know that for the large part babies being born in facilities, in hospitals are getting the tests when they should get the test. And follow-up has been pretty fairly well done.

So this seems like one area that we're having trouble not just with education, we're having trouble with actual execution of screening and screening care delivery.

And so I would elevate that on the priority list versus pushing it off. I hope I can say that being not on your workgroup. But that's my comment.

MS. BONHOMME: I think that makes sense. Again, I can't speak for the co-chairs because I'm not them.

I think in terms of the conversation that we had it was really to see how does that workgroup best know how to leverage its efforts, and to really focus in on what we can do.

And I definitely of course look to the other people who were there to chime in.

So, I think the idea of waiting wasn't so much a this is not a priority, but as an assessment of what could that group really do and would be really useful.

And so now I'm stepping out of that hat and into the Newborn Screening Clearinghouse hat in terms of the work that Jackie presented during the public comments and seeing those trends, hearing that there are other teams looking at this issue, and really trying to think how do we address that.

I don't think that there's necessarily a halt on that. I think people are really trying to think of how do we reach it.

And I think your point is exactly right. Oftentimes when we talk about education we think that means a material or just awareness building, but I think what we're really seeing is here's a true gap.

You know, when we say we have 98 percent of babies screened, we're now talking about that 2 percent that may be falling into that category, and it's because of kind of the environment of where they're being born.

So, I would say that the waiting again

wasn't necessarily this isn't a priority, but it was really to get a better assessment of what is out there, how is this a priority for the committee. Because the workgroup priorities are connected to the committee overall priorities as well. And to kind of keep a watch on it, and be able to have a further discussion about it at our next meeting.

I don't know if that covers it, or if anybody else wants to.

MEMBER SAARINEN: No, I appreciate that, Natasha. I think I was wondering if you had taken on the charge of making that assessment, or if you need outside support from other entities to help do that sort of landscape assessment, to help with pushing to the next place with the midwives.

MS. BONHOMME: I think yes to all of that, all of the above. All of the above needs to happen.

And I think that that could be something that whether within the context of this group, or other federally funded projects, or state-based

projects to really think about, again, like you said it's something that's come up quite a bit, I think particularly with timeliness.

What is the next step in that. What should be happening.

CHAIR BOCCHINI: Okay. Thank you very much.

Let's hear from the Follow-up and Treatment Workgroup. The update will be given since Dr. McDonough had to leave early, Carol Greene and Alan Zuckerman will present an update on the activities of that workgroup.

DR. GREENE: So, we're going to hand back the slides back and forth because really it was a very lively discussion and Dr. McDonough had put together the slides. So we'll have to trade off just a little bit.

So, first of all it was a great discussion. We have two major projects.

The first slide just reviews for the medical foods sub workgroup. And just for full

disclosure the head of that sub workgroup also could not be here or Sue Barry would be standing up doing this presentation. So, I am one of some of her co-chairs along with Kathy Camp and Christine Brown.

So, the charge from this committee, and I think one thing that will hopefully save me from needing to go into a full review is there's several new members of the committee.

One, Beth Tarini not only apparently not here at this moment but actually knows the whole history of it because she's been listening to the prior discussion as a liaison and two other new members of the committee were actually there for the discussion.

So, you on the committee remember the charge that you gave to this sub workgroup. And that based on a presentation at a prior meeting from Kathy Camp the committee wanted to see some other information added and see us develop a white paper, a policy brief, a review, a state of the issue

document.

And also to pull from that history of the problems with access to medical foods what has been done historically and to lay out what are some of the options.

And if we can come up with any recommendations to bring to this committee that this committee would then want to bring to the Secretary.

It's part of the reason that the discussion was so lively is at the same time the workgroup's process is informing some of the actions of many of the organizations that are sending people to the workgroup. So there's a lot of interest going on.

This committee had asked us to include some information about the IOM report. And there is a draft of this paper in process. Sue Barry has done a lot of work.

We're including information on maternal PKU, considering options. So all of

this, we're attempting to put this into the draft and to have a draft to this committee before the November meeting in hopes that it could be completed if we can get it all to you in time.

And this is just to remind you that the chair is Sue Barry. Co-chairs, a lot of members, lively discussion.

And in order to work on this we've had three phone call meetings since the last meeting of this committee.

And we are in the middle of drafting, incorporating the discussion from this committee. We'll bring it back to you.

DR. ZUCKERMAN: Thank you. The quality measures workgroup has a hard task in defining exactly what quality measures are and how we got here.

But it is really the next logical step in the prior work of the Long-term Follow-up Committee and the connections became very apparent yesterday.

Our refined charge is going to bring to this committee a report highlighting the state of the art of quality measurement, identifying opportunities to use quality measures for the long-term follow-up of newborn screening.

We will be illustrating that by developing a set of case studies that demonstrate the value of work that's already been done, and highlighting different approaches which different groups are using.

And to help deal with the problem of efficient use of existing resources and get more people engaged in long-term follow-up in quality measurement we'll be including how-to guides illustrating the process developing, implementing quality measures and particularly identifying resources for assistance such as steps to get a measure approved at the National Quality Forum.

I chair this group as a primary care pediatrician working with children with special needs and as a board certified clinical

informatician.

My co-chairs represent the other dimensions of the problem. Amy Brower brings expertise in both research informatics and also in public health.

Jana Monoco is bringing the consumer perspective on quality measurement, advocacy organizations.

And Kathryn Hassell is a clinician who also has extensive experience working with the regional genetics collaboratives.

And much of our discussion now look at the different approaches to quality measurement in the public health sphere among specialty and primary care providers and the need for consumer definitions of what is quality and the value of consumer generated data.

We have a large membership bringing together different components of the quality measurement process. People who have had experience in a range of process.

And we're also looking forward to input from Kamila Mistry, a committee member here who is at AHRQ working very much in this area.

The Long-term Follow-up Workgroup has sort of split its activity so that we are holding separate monthly calls for each of the two projects, and then coming together quarterly for discussions across the full workgroup.

At the meeting yesterday we had some very animated discussion about the emerging key findings for the executive summary which deal with three areas that are the changing environment, the available resources and opportunities.

There is a great deal of interest and incentive to engage in quality measurement and that I think was very apparent here at this meeting where it came up repeatedly.

But connecting to prior work, it's important to remember back in 2008 the long-term follow-up subcommittee published a paper emphasizing the need to engage in the same kind of

questions we're talking about more, one from a learning healthcare system perspective of acquiring and discovering new knowledge, and then bringing evidence-based treatments into practice.

Modern EHRs no longer just record care. Their purpose is to generate new guidelines and understanding of care, and then to bring those guidelines into the process and change what happens during an encounter.

We also back in 2008 stressed the importance of coordinated care in a medical home and continuous quality improvement. So we're basically right on target there.

There are resources coming forward from NewSTEPs, NBSTRN and the regional collaboratives as well as from CMS who we think can make this process easier and more cost-effective in the future.

And there are many opportunities for things that are needed that no one has engaged in, particularly the custodianship and advocacy for

measures.

One of the very interesting case studies we discussed a little bit yesterday was a project at Mountain States using an MCAT checklist integrated into an EHR.

An alternative to paying people to collect data. A process for collecting data during an encounter as well as prompting clinical decision support to get people to cover key items with patients.

And this has now been transferred to some of their other conditions.

Other items that we hope we will bring to you in May will be a description of the connection between quality assessment, quality improvement and clinical decision support.

We also want to get more people familiar with the efforts at ONC, AHRQ and CMS to develop new standards for integrating quality measurement into care, including the electronic quality measures to define what is done on the QRDA, Quality

Reporting Document Architecture, to get physicians to communicate with public health and payers.

And the quality data model to facilitate extraction of data directly from EHRs without duplicate data entry.

DR. GREENE: So, the other things going on outside this committee and the workgroup that we just wanted to be sure -- that were discussed during our sub workgroup meeting and we want to be sure the committee is aware of them have to do with medical foods.

It is important to know, and I really want to say it again in front of the full committee, that access to medical foods is not the only issue in long-term follow-up.

There are major issues with access to care. A great example was given during our meeting and I just want to put it on the record for the full committee that children with congenital heart defect don't always have access to the medically recommended care and monitoring for follow-up for

those children.

Medical foods has been an important issue for decades now and this committee has decided to put some attention to it.

And at the same time that the sub workgroup is working on this policy paper this seems to be a particularly good time to have such a paper.

The American Medical Association has just passed a resolution brought by the American College of Medical Genetics that says the AMA is solidly behind coverage for nutritional -- for medical foods for treatment of inborn errors of metabolism.

I won't get into all the details of part two of that resolution, but it does mean that they have made a powerful -- that a powerful organization has made a statement that coverage is needed.

New York is working on such a resolution. They intend to bring it to the Academy

of Family Physicians nationally.

AAP I understand is possibly working with AFP. And very important, the military has made some progress in this.

So this is an area receiving some national attention. Hopefully -- people are talking about approaching legislators.

And so this is one of the reasons we're in such a hurry to get all this background out there and get a good executive summary that people can take around as talking points so that people who are trying to make progress will be informed.

DR. ZUCKERMAN: And finally, Dr. McDonough regrets he can't be here himself to share with you some of the important ideas he keeps bringing back to our workgroup.

If you can measure it and you don't measure it, it's not important.

We really don't know how many states are not doing long-term follow-up and what they're missing.

And an interesting intersection between medical foods and quality is the unknown percentage of pregnant women with PKU who have good control during their pregnancy, and whether we're seeing a return of maternal PKU syndrome that's almost the step backwards from where we began newborn screening 50 years ago.

Many other areas of medicine, regional variation in outcomes and utilization of health services have been important guides.

And perhaps we need to know more about how outcomes vary in different parts of the country and why, and what are best practices for dealing with the conditions detected by newborn screening.

And again, to thank the committee for your attention to long-term follow-up Dr. McDonough wanted to share a picture of maternal-child interaction taken on his recent trip to Alaska.

CHAIR BOCCHINI: Thank you both very much. Nice presentation. Questions? Comments?

There was also a lot of activity in this workgroup as well, so thank you both very much.

Laboratory Procedures and Standards Workgroup. Kellie Kelm will present this update. Oh, Susan Tanksley as well. Okay.

MEMBER KELM: We're actually both still here. So, we had a very atypical workgroup meeting, but it was actually extremely interesting.

So, here is our current workgroup roster. We actually realized as we were discussing yesterday we have lost a few to retirement in the last year or two. So we're definitely looking forward to working with Debi on finding some new members. So, a pitch for anybody out there.

So, the two projects that our workgroup were recently tasked with from the committee was, number one, to explore the role of next generation sequencing in newborn screening, and number two, to review data related to the timeliness goals, and

to look at things such as implications of earlier testing window than 24 to 48 hours, and unforeseen consequences, and other items as well.

When we were talking about this meeting and realized that all these presentations were actually going on with the large committee we thought that what would be interesting for us is the lab -- most of us are lab people -- getting together and talking about the presentations.

And that we didn't need any additional ones because the committee meeting was really covering all these topics. So that's what we did.

We actually had two hours of just discussion. So I'm going to summarize some interesting points that came up that we got to talk about.

And so we started in terms of next gen sequencing, both that as well as the NSIGHT presentations.

So, some of the discussion that was inspired by those presentations was -- what came

up in part was a little bit of discussion of non-newborn like childhood period testing and whether we could play a role there.

And I think we've talked about that before in the committee, it was a few years ago, but that came up again as we talked about some of the things that people are interested in thinking about and testing for, and whether or not -- if they're not approving it for the newborn phase is there another time that we could test.

But then is there another time when we can have all children tested if we consider it a public health activity which is always the concern.

So, that was really interesting and that also wound up leading into some discussion of whether or not there was a role for drafting guidelines for laboratories in terms of using older data.

Here we wound up touching on a few things, both the requests for sickle cell data that's coming to a lot of labs when they're asked

about really old data, 20 years old.

Talking about how long we keep the data, and whether or not -- especially as technology and knowledge changes, even though we're required -- some states are required to keep this information for a period of time whether it can create a liability.

You know, DNA raw data, 20 years from now the technology is going to change, our knowledge is going to change.

So is there some -- I know no one likes to discard data, but in some ways is it a liability to have it. Is it cheaper to retest. Will practice and technologies change so much that that would actually be the most appropriate thing.

And lastly, Carla brought up 20 years from now -- we're so dependent now on interpreting all these things with software. We may have software that won't talk to the old software. So it might be a moot point anyway. Did you have any other thoughts?

So, Scott Shone was with us. So we also talked briefly on his presentation as well as the committee's vote on having one prospectively identified case as we consider conditions for evidence review.

And although we just came up with the cost data there was another discussion about whether or not we almost need a matrix for the nomination process. So, I think we have a lot of matrices here.

And here was another interesting conversation I think. There was discussion of the frequency of the condition that we could screen for. When you're considering costs of screening that's just another factor I'm sure a lot of programs must think about.

And that of course we always have the discussion of how it's going to be harder to do pilots when conditions are more rare to find the one case or more.

But some others in the group argued that

we can't lower the bar when that happens. And so some interesting thoughts.

And it was brought up that laboratorians are used to a process, a checklist if you will. And bringing up that it's important to remove subjectivity from the process.

And once again, what was brought up is not to bypass the follow-up testing piece of the whole newborn screening process.

DR. TANKSLEY: So, multiple times yesterday -- so although the timeliness discussions were today, timeliness was brought up in some of the discussions yesterday.

So it was brought up during Michele Caggana's talk. One of Michele's slides showed that what they've hypothesized is that by adding next gen sequencing it would add a minimum of two days to the process.

And so we talked about timeliness and not just the impact of molecular testing, but previously when Kellie and I presented for the

timeliness workgroup 1.0 -- we didn't know we were 1.0 at the time -- but during the presentation of the recommendations of the workgroup we had said that you really need to use caution in these recommendations because you don't want to do more harm than good.

By focusing on meeting the goals you may actually say well then, we don't need to do the second tier testing. And then you have increase in false positives.

We talked a little bit about that issue earlier today.

And so that's really where our discussion led. So, we thought we may need to revisit the recommendations as we get more data.

And I think that was mentioned earlier today, that we need to be able to capture the impact of that second tier, or additional testing that's performed, and how that may impact the actual time that it takes to get to a result.

We also talked about I'll call it

regionalization. So, currently there are several regional programs that do newborn screening and that's been chosen by the states and it's working very well where there's one lab doing testing for multiple states.

I think Mei mentioned yesterday that as they look at next gen sequencing in a state the size of Wisconsin it's very expensive. And so they may have to batch, or they may not be able to do next gen sequencing every day. They need to find a more economic way to do it.

But when they look at performing that testing for additional states as well it actually becomes more economical and actually improves their timeliness.

And so there's some consideration as more and more states -- as there's a higher uptake on more and more molecular technologies that that might be beneficial for some states.

And then finally, kind of getting to the point of timeliness. So, when we put together the

recommendations those recommendations really focus at the end of a lab result.

So, getting a report out, it doesn't go to diagnosis. And so some of the second tier testing that's done may actually decrease the time to diagnosis and ultimately that's what matters.

So, we shouldn't be bound by our recommendations. And maybe at some point we can figure out what is a percentage that we should actually be meeting so that we're not doing more harm than good.

We also had continued discussion about just some of the pre-analytic issues that we're still seeing.

So, the timeliness recommendations came out February of '15. And there has been a huge emphasis throughout the states. And you heard talks about the CoIIN projects and NewSTEPs 360 and some of the progress that's been made.

But you also saw data that show that despite all those efforts it's still very hard to

achieve the recommendations.

And one of the issues, newborn screening programs often try to take on the entire role of the newborn screening system, yet they only really have impact on the things that they can touch daily.

And so we need to figure out how to achieve those better partnerships with the hospitals, and birthing centers, and midwives who are collecting those specimens.

And then that's a very short window in a child's life. And then you have the entire spectrum after that. So, the follow-up, diagnosis and treatment of those, long-term follow-up.

There are issues with turnover at hospitals. So, a program may be able to go in, and in a small state may be able to educate at every single facility every year, but there's still going to be new staff every time they go in.

And so we need to figure out a way to maintain the improvement that happens at

hospitals, and birthing centers, and whoever collects the specimens.

We talked about needing to find a champion. How do you find the person that's going to be able to engage, and continue that engagement, and be able to not just train one group, but have a train the trainer within each facility.

We talked a little bit more about courier. You know, it's expensive. And even if you have a courier system in place you're able to pay for that in a program, there are still some issues with couriers.

One of the states talked about how they have a person dedicated to basically watching the shipments that are supposed to be coming in, comparing that with what's actually come in, and trying to pinpoint and figure out where those shipments are that are lost somewhere at a hub.

We tried with timeliness 2.0 to get -- and we had a call with Joint Commission, but there's still a need for a role with the Joint Commission.

And so we need to try to figure out how we get in there further and have some further conversations.

And then we also talked about transparency in the timeliness data available to the public.

So, in some states it's been able to be published on a website and it's transparent. And in other areas that's still not available.

And if anyone has any questions we'll attempt to talk you through our freeform discussion we had yesterday.

CHAIR BOCCHINI: Thank you both very much. Any questions or comments related to the presentation?

Clearly a lot of work going on in this workgroup as well so thank you very much. Appreciate it.

So, we are scheduled to adjourn at 2:15 but a last item is if there's any new business to come before the committee. And I'll certainly

entertain any items that people want to bring forward as potential new business for the committee.

I think we've heard a lot of things that are already going to be incorporated into new business going forward and so -- but are there any questions, comments coming? Okay.

All right, well then based on that I think this has been a very informative meeting. I think it's very clear that our new members are already integrated into the committee and have already played a role in making things happen.

So I appreciate the work of the entire committee as well as HRSA with getting things organized and Debi for her role in making this all happen. And the organizational representatives and everybody else who's contributed to this meeting.

So with that I want to thank you all and we look forward to our teleconference meeting in November. Thank you. I'll conclude.

(Whereupon, the above-entitled matter

went off the record at 2:17 p.m.)