Secretary's Advisory Committee

on Genetics, Health, and Society

Twenty-second Meeting

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Secretary's Advisory Committee on Genetics, Health, and Society

June 16, 2010

I N D E X

I N D E X (Continued)

Keynote: "---" indicates inaudible in the transcript.
"*" indicates phonetically spelled in the

transcript.

M O R N I N G S E S S I O N

(8:02 a.m.)

Opening Remarks

by Steven Teutsch, M.D., M.P.H.

DR. TEUTSCH: Oh, is that Mara on the phone?

MS. ASPINALL: This is Mara, yes.

DR. TEUTSCH: Good. Well I am glad you could join us. We actually have a lot to cover today but before we get too far into it, I want to thank Paul Billings, who I assume will be here soon, and Charis who should be here somewhere for helping to organize the session yesterday.

I heard from many of you that it was one of the best sessions that we have had and we clearly had some terrific speakers. In addition, we had, I think, some very productive discussions. So thanks to Charis, thanks to Paul, and for those who don't know, Cathy Fomous was the staff person who put it all together. So thanks to all of you.

So this is the second day of our meeting and today we have an update from FDA, some sessions on genomic data sharing, issues related to carrier screening, residual dried blood spots, and we will get into all of that over the course of the day.

One just housekeeping matter, we have a slightly different format for lunch today.

(Whereupon logistical matters around lunch were

discussed.)

DR. TEUTSCH: Charis, we just thanked you, even though you were not here for the terrific session yesterday.

So we want to get into the meat of the matter this morning with an update from the Food and Drug Administration. I think we will have a chance to hear from Liz Mansfield who we all know and love.

(Laughter)

DR. TEUTSCH: I think after this presentation we will love her even more because she has some really exciting things to share with us.

DR. MANSFIELD: I am waiting for my slides.

DR. TEUTSCH: We have a little time? While we wait, are there any other items that anybody wants to raise?

DR. TEUTSCH: All right. Well we will proceed. Are you good Liz?

DR. MANSFIELD: Yes.

DR. TEUTSCH: All right! Liz, take it away.

Updates from the Food and Drug Administration (FDA)

by Elizabeth Mansfield, PhD.

DR. MANSFIELD: Oh, Okay. Thanks as ever for having FDA here to address the Secretary's Advisory Committee. I do have some rather exciting things to say today and I am available to discuss, but I do have to leave at 9:30 to go to the DIA meeting. So catch me quickly.

(Slide)

As probably, if you read the newspaper, the internet, anything like that, you will know by now, there has been a large discussion going on for several years now about oversight of direct consumer genetic testing.

We have had calls from many quarters, including this body, to implement or increase oversight of direct-to-consumer genetic testing, partly because there are medical claims being made. Many people believe that the clinical value of some of the claims is quite poorly established.

Many people are concerned that it does not require intervention of a health care provider. I think we heard a lot of this already in the direct-to-consumer discussion.

(Slide)

Again, unless you were asleep, you probably read or heard about the Pathway/Walgreens story in which Pathway Genomics and Walgreens stated that they intended to market direct-to-consumer genetic tests that included pharmacogenetic tests. I am sorry, there is a typo in here.

They were going to do this directly to the public through Walgreens by providing a sample collection device that would be sent to Pathway and the results would be returned to the consumer.

FDA became very concerned about this particular method of marketing and sent an “It has come to our attention”

letter to Pathway and told them that they are not a laboratory developed test. That is not the only issue, but that is the current regulatory hook. Walgreens has since abandoned their marketing plan.

We asked Pathway to come in and talk to us and because it is an ongoing compliance issue, I cannot tell you anymore about it.

(Slide)

There has been a lot of Congressional interest lately. The congressional investigation is going on through the Energy and Commerce Committee. They have sent letters to a number of direct-to-consumer firms requesting information about their tests, specifically their analytical and clinical validity and other information.

I am aware that they sent an additional letter to 23andMe following on the news that there had been a sample mix-up in which patients received results that were not their own. Congress is clearly interested. There is the possibility for a hearing this Summer on the subject.

(Slide)

So we got the hint. We sent out on the tenth, five untitled letters to the companies listed there. The reason we sent them to these was because we had previously spoken with these companies about what they were doing. This does not mean that this is the limit of what we would do on direct-to-

consumer testing. It was just that we had spoken to these companies and we knew what they were offering.

Our letters request the firms to work with us. We believe there may be some claims in their tests that do not require oversight because they are not medical claims. Then certainly some of them, as the tests are currently configured, are medical claims and we would like to work with them on figuring out how they are going to submit the information to get all of these clearly approved.

(Slide)

So that was direct-to-consumer. There is outside a printout of the Federal Register Notice announcing that we are holding an open public meeting on array-based copy number testing which has become a standard laboratory procedure almost now. The meeting is going to be on June 30. It is a very short timeline. We have to work fast to cram it into the time between an ISCA meeting and an ACMG meeting on similar subjects so that we would have all the expertise in the room.

It is open to the public, but you need to register. You can make five-minute presentations. We are requesting that your presentations are designed to answer the questions that are asked in the Federal Register Notice.

Our intent is to gather information on regulatory approaches to non-targeted testing. We talked about this a little bit yesterday, I think, with the whole genome

sequencing where you can see everything without necessarily having asked to see everything. We realize that our regulatory approach is going to have to be a little bit different than it has been for single analyte targeted testing.

We are going to have a panel. They are going to address the six questions in the FR notice. The docket -- well the docket stays open all the time. You can always send things to the docket, but we are requesting comments by July 30 and that is the docket site if you are interested. I think Kathy is handing out the printout right now.

So I think this will be of interest for the array community as well as probably the whole genome sequencing community because many of the issues are the same. We know now that array testing for copy number has now supplanted cytogenetic testing in many labs. I believe ISCA is recommending it as possible first tier testing. So we are hoping to get a handle on this and make sure that the public health is served.

(Slide)

This committee -- I am not sure how much we have talked about this in the past, but I did want to let you know that FDA is working on companion diagnostic draft guidance that will define what a companion diagnostic is, and that is a diagnostic that is required for safe and effective

administration of a drug.

We intend to explain when regulation of such a test is required in order to assure that the treatment plus diagnostic combination is safe and effective or safe and efficacious in the case of the drug. Hopefully, it will get out in 2010.

In addition, we are preparing a much more complex document which addresses the issue of co-development of a treatment and a diagnostic. This has been requested by many, many different people, pharmaceutical companies, different industry interest groups, and so on. We intend to make it informational and not directive.

If you have been in this field at all, you will know that every situation is very different from every other situation so we don't think we can build a path that says do this and this and this and this because everybody is going to have a different way of approaching it.

But we will address differences in the regulatory strategy and review issues and so on that is different from normal drug development, normal diagnostic development. It is planned to be published this year. I hope that happens.

(Slide)

I think Alberto told you last time that we have developed, after a SACGHS meeting in which a patient advocate made a complaint about Myriad Genetics, we did develop a new

product code for laboratory developed tests that enables anybody who wants to to report an adverse event, make a medical device report, to FDA for a laboratory developed test.

Previously, there was no way to do that. We realized that that was probably not a very good idea and so we put a product code in there and we have actually received several MDRs from the public recently on this. So we think it may help us keep tabs on people -- at least people who feel they have been harmed. We investigate it and so on. So that was another success coming out of the SACGHS meeting.

(Slide)

Probably many of you are aware as well that there has been a call for a review of the 510(k) process at FDA. People had complained that it was ineffective for many reasons. Either it was too stringent or it was not stringent enough or that it was being used incorrectly, and so on. FDA is conducting an internal review. IOM is conducting a review at the request of FDA, independently of FDA. We expect recommendations for any changes needed this summer.

Interestingly, many of the issues that people had complained about in the office that regulates *in vitro* diagnostics we already did it the way that may be recommended, so I would not expect major changes for in-vitro diagnostic devices. But until we see the report and the recommendations, we won't really know.

(Slide)

Now this is the biggy. We are announcing today that FDA intends to implement oversight of laboratory developed tests. The Federal Register Notice is -- that is the docket number. The advance display will be available at 8:45, in about a half hour. We are going to start by holding a public meeting on July 19th and 20th here in Bethesda or Rockville, I can't remember which.

Our intent is to establish risk-based oversight framework for all tests, not just commercially distributed tests. Our general expectations at this time are that we will require a registration and listing period in order to figure out who is out there, that we will do a risk-based phase-in, looking at the highest risk first, that we will take all precautions to avoid disruption to access to tests that are currently on the market, and that we will probably provide a low bar or no bar for certain tests, such as for rare diseases and so on, where we are not sure that additional oversight beyond CLIA will really be beneficial.

(Slide)

The meeting format, again, is open to the public but you do have to register. We are allowing the public to make five-minute presentations. We are requesting them to be subject matter presentations, not complaints about "this is not legal" or something like that. What we are working for is

actually help from the public on putting the correct framework in place.

To do that we are going to have four different sessions that are addressing four different issues. The patient needs for one and clinician needs as well. So we are going to have how this affects patients and clinicians. How it affects laboratory. We are going to have a separate session on direct-to-consumer testing and then we are going to have a session on educational issues, how FDA can help educate labs and help labs get started on this process.

We will also have panels in each of these four sessions to discuss the issues that will be laid out on a website that will, I guess, go live today or tomorrow because today is just the advance notice. The docket will not actually be open till tomorrow. The panel can propose approaches and so on.

(Slide)

Our intent is, indeed, to implement oversight of laboratory-developed tests, but we are very cognizant of the need to work with the stakeholders to construct the framework. We have been discussing a little bit with NIH on this.

We are also very cognizant of the need to minimize disruption to the current paradigm of medical care. We want to provide as much access to FDA and education as possible to labs on how to do this, how the whole system works, and so on.

We are certainly looking forward to ongoing public engagement as this story unfolds. You should not expect a draconian wall to go up where today you are not regulated and tomorrow you are. This will be a gradual process. So it should be interesting.

Well that was pretty quick.

(Laughter)

DR. MANSFIELD: I started early. So I will stop there and I can actually take questions if you want now, Steve, because I am going to be leaving.

DR. TEUTSCH: That is terrific. This is really exciting. Obviously, these are issues that have been of extraordinary interest to this committee and --

DR. MANSFIELD: Well the Secretary actually -- we did have a meeting with the Secretary where she said SACGHS has recommended this for years.

Questions and Answers Session

DR. TEUTSCH: We really do appreciate your thoughts on all of this. So let's open it up for questions. I was going to say let's start with the senior person on our oversight report. Andrea?

DR. FERREIRA-GONZALEZ: Thank you so much for the overview presentation. When you say that you are going to regulate LDT you are talking about all LDT, not just genomics?

DR. MANSFIELD: The framework will encompass all

LDTs. The level of regulation will be scaled to the risk of the test and other factors such as rare disease testing and so on.

DR. FERREIRA-GONZALEZ: Now as you start regulating LDTs are you going to put that information on your website accessible to individuals that you have actually -- this registry will have to be up there?

DR. MANSFIELD: I actually do not know any of the mechanisms at this point. We have not predetermined really anything except that it will be risk based and we will work with the public to build the right framework.

DR. FERREIRA-GONZALEZ: I am just concerned between the registry at the NIH and your work here that it might be, you know, duplications.

DR. MANSFIELD: It is highly probable that we will try to work with that registry to avoid duplication, but again we have no predetermined details.

DR. FERREIRA-GONZALEZ: One more question please. When you have the Walgreen and Pathway test, you said the test was not an LDT. Can you explain that?

DR. MANSFIELD: A laboratory-developed test is a test that is developed and offered by a laboratory. They were using arrays that they purchased from someone else and a whole system that they purchased from someone else, including the instructions for use that came with that system and all the

reagents. They were merely providing those results with an interpretation and we do not consider that to be laboratory developed.

DR. TEUTSCH: Jim.

DR. EVANS: I was just wondering, risk based, is that risk of an inaccurate result due to complexity? Is it risk based on clinical stakes?

DR. MANSFIELD: Yes. This is going to be a very important one for us to cover carefully. Our risk assessment is based on the possible harm to the patient based on an undetected incorrect result.

DR. WILLIAMS: Going to the array meeting that you are having, I was just curious in terms of the FDA's thoughts. Obviously we have been doing whole genomic assessment of cytogenetics for 60 years, and there has not been any enthusiasm at least up to the present time for standard cytogenetics to be under this type of regulation. Could you talk a little bit about what the FDA perceives is the difference between the arrays and what has been done in standard cytogenetics that raised it to the level of saying we think this is something that needs now to have some oversight?

DR. MANSFIELD: Well for one thing, we have had about five different companies approach us with an intent to file, so we need to be able to give them answers.

In addition, the normal cytogenetics -- mostly

people could use ASRs, develop their own tests with their own knowledge. Karyotyping in general is something where we regulate the -- as well as for FISH testing and so on -- regulate the bits and pieces, but it is primarily a judgment that the laboratory person makes by looking at something using regulated pieces, whereas the array copy number actually uses somebody else's system that spits out a result that is not a result of judgment.

Somebody needs to use judgment after that, but we have always regulated the parts that go into this testing and that is what we are intending to do at this point when companies come in. We are not going out and saying well, I mean, oversight is all --- but otherwise we are not going out and saying this is a special problem. Everybody gather now and we are going to regulate everything. So it was based on people coming to us.

DR. BILLINGS: Liz, how is this going to interact and interplay with the CLIA oversight of laboratories?

DR. MANSFIELD: So CLIA as I think everyone on this committee probably has tried to forget the long conversation around the oversight. CLIA regulates lab and lab activities and has a certain set of requirements that are part of the CLIA regulations. FDA regulates things, products, pieces, bits and pieces.

If you run a lab, you will know that FDA cleared and

approved tests are also somewhat regulated by CLIA in what the laboratory has to do with them. It will probably be something like that, however, laboratories will be considered the manufacturers now and the difference is that -- one of the big differences is that the quality systems are largely overlapping but CLIA does not require design controls which we do and we are going to publish a guidance that tells you where CLIA and FDA quality systems correspond and we will be providing lots of help on getting people up to speed on this. We know basically what level labs are now and we will take that into account.

DR. BILLINGS: I think that is a real serious concern. I mean, the FDA controlled labs, and there are a couple, are a completely different kettle of fish than the average clinical laboratory.

DR. MANSFIELD: Yes, right.

DR. BILLINGS: So that is going to be a large cultural transition --

DR. MANSFIELD: Yes, it will.

DR. BILLINGS: -- with an enormous amount of expense involved.

DR. MANSFIELD: Well we are aware of the big transition. We actually think the quality systems are one of our best regulatory tools because it tells you to do whatever you need to do to make sure that your test is designed

properly, manufactured properly, and stays the same over time. So it is very nondirective, it is very flexible, in that you can implement how you need it to be in order to fit your situation.

DR. TEUTSCH: Liz, can you give us some sense of what we can anticipate on the oversight of LDTs in terms of the process and timeframe until you have the guidance or framework in place or the regs in place?

DR. MANSFIELD: I think that is still to be determined. The expectation is, I guess, that we will make calls for certain tests over time. We do not expect this to happen very fast because it is actually hard to figure out what to do in the first place and we have to give people time to get, you know, their ducks in a row. So probably calls over time for the highest risk and then descending to the level where we think we can cut it off.

We are probably actually going to have to make some changes as well to the kind of tests that we regulate as commercially distributed because, you know, there is a resource dependency here and there are certainly a lot of tests that we regulate now that may not benefit from our oversight anymore because they are old technology, old tests, low risk. AdvaMed has actually given proposals on some that we could possibly exempt.

DR. FERREIRA-GONZALEZ: I just want to follow up to

what Paul brought up on the quality system because some of the laboratory-developed tests or some tests that actually have not very high volume are very important for patient management and these need to be still available for patient care.

There are certain laboratories that, you know, might have extremely high quality, but not necessarily fit the quality system within the FDA.

DR. MANSFIELD: Right.

DR. FERREIRA-GONZALEZ: So that is a very high concern that I have that some of the testing that there will never be an IVD because commercially it is not feasible for a company to develop, but it still has a huge clinical impact and patient access.

DR. MANSFIELD: I point you to here -- it is our intent to avoid disruption at best and certain tests, rare disease, low volume --

DR. FERREIRA-GONZALEZ: I am talking about even infectious disease, not just regular diseases. You can have some infectious disease like herpes for CSF specimen where volume is not so high that actually are critical for patient care. This could completely disrupt --

DR. MANSFIELD: We are not intending to that so those will be the kinds of comments that we need to hear at this public meeting. So I invite you all to register and if you would like to make a presentation --

DR. FERREIRA-GONZALEZ: This goes beyond the genomics and, you know, the infectious disease, and everything that -- another kettle. I mean very different fishes.

DR. MANSFIELD: Right. This is the kind of commentary we are looking for like what tests are really sensitive if they were to disappear from the market or something like that.

DR. TEUTSCH: Any other comments? Liz, this is great. Thanks. There was a lot in what you presented today in terms of looking forward for some of the oversight, not only of laboratory to develop tests, but our concerns about DTCs and some of the issues that were raised. It is good to see Kevin in the back of room because he was so much involved with the Pharmacogenomic report on the co-development of tests. So thanks so much to you and all your colleagues for moving these agendas forward.

DR. MANSFIELD: Right. My pleasure. Yes, I look forward to seeing a lot of input from the individuals here on the process.

DR. TEUTSCH: We will report updates from you as all of this moves forward and the details emerge.

DR. MANSFIELD: Okay. Well, look for the FR notice to go on advance display in about 15 minutes. It will have all the information in it.

DR. TEUTSCH: That’s great. And for those of you

who have not noticed, there is, I think, a copy of one of the letters that went to one of the manufacturers of the DTC test within the folder --

DR. MANSFIELD: Yes.

DR. TEUTSCH: -- so you can see what --

DR. MANSFIELD: They were all pretty similar --

DR. TEUTSCH: They were similar. Right.

DR. MANSFIELD: -- similar questions. Thank you.

DR. TEUTSCH: Terrific. Thanks so much Liz. That was great.

(Applause)

Genomic Data Sharing

Issues and Next Steps Related to Genomic Data Sharing

DR. TEUTSCH: So next is a session on genomic data sharing and Charmaine has been moving this agenda forward and is going to summarize some of the central issues in genomic data sharing followed by the committee discussion to determine how we proceed. It is good to see you again. Welcome Kevin in the back of the room who, as part of our planning process put this on the agenda.

Findings from the Literature and Stakeholder Consultations

by Charmaine Royal, PhD.

DR. ROYAL: I tried to move it. I am trying to move this agenda forward. I am hoping that our session today will be a productive one in terms of where we go from here. I am

going to talk about some of the things that we have been doing since our last meeting and some of our thoughts about where we should go and looking forward to your perspective on that.

(Slide)

So I am going to revisit our issue statement which has been the same since our last couple of meetings in that genomic data sharing has increased over time, is increasing, and is a valuable tool for advancing research. But this sharing can result in a lot of questions and concerns about issues related to consent and privacy and discrimination, and some other issues that we are going to talk about. Of course, the issue statement is what brings us here in terms of thinking that this is an important topic for us to address.

(Slide)

So what have we done so far? In 2008 genomic data sharing was identified as an important topic for SACGHS.

In 2009, ASPE contracted with the Lewin Group to develop a report on this and this report is expected to guide our deliberations. Now, the Lewin Group has completed their preliminary lit review and their final report should be available in the fall.

In the interim we have gone ahead with doing some fact finding in terms of the committee itself and our work will overlap, I am sure, with their's. When their report comes to us, we will see where the overlap is and where there

might be differences in terms of how we approach the issue.

Last October, we formed a steering group to begin to look at these issues. In February, we had a number of people come to talk to us about different models of genomic data sharing and the sense is that there is an information overload. Hopefully, we have culled some of that and we will able to pull some things out that we are going to focus on.

(Slide)

So the group, the steering group thus far comprises the current members Sheila and Dave, ad hoc members Kevin, Sylvia, and Julio. Kevin is here. Good to see you Kevin. Julio and Sylvia have been really instrumental in helping us think through some of this.

Our *ex officios*, Michael, Doug, Laura and Michele. Symma has been the staff lead and with Symma, Kathy and Sara, I really can't thank them enough for their efforts and their work in the fact-finding and in moving us forward.

(Slide)

So our goals today. We are going to go through some of what we found and identify what the central issues are and what we think they might be for SACGHS. We are going to talk about those and the policy implications. Of course, the policy implications are where we might come in in terms of what we recommend and what we decide to do. Then our next step, what do we do? Do we continue to pursue this and how?

(Slide)

So the fact-finding activities that we have engaged in comprise a literature review. For the most part, it is focused on the blurring of that line between research and clinical practice. People participating, people being involved in clinical care and samples collected from them being used for research. The blurring of that line.

The line is also blurred in terms of samples used in research, data generated through research that feeds back into the clinical setting. So it is really a circle in terms of how this information gets moved around.

So the blurring has been a major issue, I think, from the onset of this discussion and raising issues of literacy and provider and researcher attitudes.

And of course, the blurring of the line between research and clinical practice is just one aspect of genomic data sharing, one that probably many are not looking at. I mean, of course, a big aspect of genomic data sharing is sharing just between researchers, so the blurring of that line in clinical care and research is one, but researchers share samples with research and share data with researchers. So that is really the big picture in terms of sharing.

In addition to the lit review, we have conducted some consultations with program directors from two different types of genomic medicine programs or programs where data is

shared from a government model and a consumer disease registry. We also talked with three secondary data users and we also interviewed an ethics researcher.

(Slide)

So our literature review, in terms of looking at the implications of the blurring, the lit review revealed a number of topics or issues under that topic really. The timing and nature of informed consent, when do we give consent? How many times do we need to give consent in the process? For clinical care and then for subsequent research projects or is it just one consent that we need, a broad consent?

Articulation of risks and benefits, some of which we may not know at the time of the generation of the data or the collection of the samples.

And then the communication between the provider and the patient and the ability of the provider. We talked a lot yesterday about the limited knowledge of providers and genetics and that also comes into play here in terms of genomic data and the interpretation of that data and communication of the risk to participants and to patients.

The whole issue of incidental findings and return of research results. Who returns those findings? Is it the clinician? Is it the researcher? And of course, the whole issue of how that is done.

And allocation of resources and in many cases, time

constraints. Physicians often don't have time to do all of it. In many cases it is the project coordinator or the nurse that provides this information and the resources to communicate the information. Additional staff that might be needed to move these agendas forward.

The issues of privacy and security keep coming up, not just in genomic data sharing. I think it comes up in just about everything. A lot of other groups are looking at privacy and security. One of the questions that our literature review raised is the reasonable expectation. Do we promise anonymity? Do we promise that we will be able to keep things private and secure? I think most of us recognize that we really can't promise that. So what are the expectations? What is reasonable to tell participants and patients in terms of what we will be able to do in securing their data?

The issue of group harms. This is one that comes up not just here and the issue of health disparity is public health actually it is. The whole issue of public health has, I know, been a major issue for SACGHS. Questions about whether it needs to be a separate topic that SACGHS addresses, I think, in my mind is probably no longer a question in that it cuts across just about every topic that we will address.

So I think we talk about whole genome sequencing and the issues that health disparities and public health activities raises there. So really it is something -- and the

issues related to groups and identity and protection of groups and group rights. I think it cuts across just about every topic that we may touch on as a committee.

(Slide)

So I am just going to talk about some of the things that we found in terms of our fact finding. In our consultations with the two programs directors, you know, the government model and the patient consumer controlled model, we learned that there are mechanisms in the consumer controls and the government also to provide for patient input into the policies and the program goals and authorization of data.

When asked about returning of results and how that is done, both persons we consulted with talked about it being done through websites and newsletters and patient education conferences, and providing aggregate summaries of findings.

We asked about successes and risks and problems. The greatest challenge that was voiced was that of data breech, the perception of the potential for data breech. There are successes that both programs talked about, the numerous studies and publications that had been generated from the data. We asked about data on environmental exposures, how that is handled and the response was that it is included in genomic datasets. Family history is not. We asked about the ability to link EHRs with this data and that for both programs is currently under development.

(Slide)

In talking with secondary data users they talked a lot about the potential value in using this information, but then they also talked about the lack of guidance in terms of how it is done and who is responsible for communicating incidental findings.

We asked about the challenges that secondary data users experience. Some talked about the application process, how difficult it was to get through to get those samples or the data. And preparing of the datasets for their use and some challenges there.

We asked about the biggest barriers to data sharing and again they talked about the lack of standards. They talked about the lack of standards concerning phenotypic data and then the lack of incentives for making data easier for secondary research use.

(Slide)

We talked with a bioethics researcher, Dr. Amy McGuire, who has really been one of the few that have been looking at participant perspective on genomics data sharing and some of her previous research found that patients have a desire for information and control about their data sharing, about the sharing of their genetic and genomic data.

Her current study which was done between 2008 and 2009 looks at six GWAS studies that were conducted ongoing at

Baylor and participants in those studies. This study, in terms of looking at participant perspective involved 229 people from those studies. They did a randomized trial of three models of consent.

Traditional informed consent which just asked people to consent for a research project period, with no options for sharing. Binary informed consent included the traditional informed consent asking people to participate in research but giving them just two options in terms of full sharing, full release of their data or no release. Then the tiered informed consent gave them three options. The traditional consent consenting to the research project but also full release, restricted release, and no release.

(Slide)

The research and her project has generated some really interesting findings and Dr. McGuire has graciously allowed us to present this unpublished data. She is working on submitting it for publication so it is unpublished data. She found that there is a gap between what people understood about study goals and the samples and what was actually told to them or what actually is the case.

I just have -- I had to bring it so I could just remember the numbers. But what she found is that 40 percent of the participants did not know they were participating in research. 28 percent never heard of genetic studies. Now I

am talking about people who are in GWAS studies at Baylor. 28 percent never heard of genetic studies. 16 percent did not know they had already given DNA to their doctor. 26 percent did not know their DNA was stored as part of any study. 26 percent -- get this -- 26 percent did not remember signing an informed consent, signing a consent form.

Very interesting findings and I am sure we will hear more about this later when Amy publishes this work.

So the whole question about what people really understand from that informed consent process -- and that is not new to any of us I think in terms of what people were told and what they come away with, what they believe they were told. I think there are other studies that have shown the disparities and the differences there, in many other situations, not just genetics but in research in general.

So that really raises an issue about communication. You know, the communication may be fine but it is more peoples' understanding or what they remember. I don't know how we are going to address some of those issues.

The study also found that the traditional -- and I think this is actually a no-brainer -- traditional and binary consent did not provide as much information as the tiered consent model.

She also found that participants gave equal importance to privacy protection and advancing scientific

research. So I think in general, many people would have thought that people would give higher value to privacy, but in this case people are as interested in advancing scientific research as they are in protecting their privacy which really creates a very delicate balance in terms of how we even think about privacy.

The majority of participants feel it is important to be involved in the sharing decisions. 65 percent want to see all of the data sharing options.

(Slide)

From this research some of the recommendations that Amy has -- some of her preliminary recommendations, are, you know, that we may want to think about, really think about a paradigm shift in terms of how we think about privacy and being more concerned about trust and respect than we are about this whole issue of privacy which we can't guarantee anyway.

Then one of the other things that she suggested, and she and I have talked about this too in terms of a stratified or tiered consent process. Not just a stratified or tiered consent form that they use here, but a tiered consent process meaning one that occurs over time.

So people participate in the study, but the consent process and peoples' understanding of the study is evaluated at different points in the study and when new studies come about, we would evaluate whether we need to do another

consent. So that it is a process, as we talk about very often, but in most cases, it is not treated as a process. It is just treated as a one-time thing, but this whole thing of a process and ongoing process in terms of consent.

(Slide)

So from our fact-finding between those consultations and the lit review, we identified three major areas that we might focus on, three major areas that keep coming up in the literature. One is the implications of the blurring of the lines, the blurring of the line between research and clinical practice. How do we deal with the issues that research raises and its connection to clinical practice? How do participants and patients understand those connections there?

Second, the potential for group harms and the whole issue of groups harms. As we all know, groups are defined in all kinds of ways and I think at one earlier stage we talked about vulnerable groups and that could be expanded to specific disease groups, we could be talking about prisoners, we could talk about children, we could talk about some many groups.

In much of our work, we really tended to focus on "racial ethnic cultural diverse group" and that is a question we can talk about a little more later, whether we want to expand this whole definition of group. Much of the literature that we found in terms of this potential harms have dealt with cultural ethnic groups.

And the whole question of privacy and what might be the reasonable expectations. What role could SACGHS have in informing that decision? I think there is a general sense that privacy -- what we can do in terms of security and privacy is limited and how do we deal with communicating those limitations and doing the best we can to protect and secure people's data while moving research forward.

(Slide)

So in terms of the blurring, some of the major issues are the informed consent process and the adequacy of that consent. In clinical settings, but also doing public health activities, screenings and newborn screenings, general population screenings that might occur where data samples are collected, data is generated and used for genomic research and shared.

The provision for return of results. Return of results is a major issue now in genetics and genomics and who is responsible for communicating that? The doctor? The researcher? And how is that done?

And then the education that is needed to providers. Some of our earlier work, our educational reports for one, we can build on in terms of how we address and to what extent we deal with education as it is covered already in one of our earlier reports.

(Slide)

Even in group harms, some of the issues relevant to group harms have been dealt with in the report on a prospective cohort study and we may want to go back to look at some of those and see where we may pull things out and emphasize certain things as we think about group harms. So some of this we have already done some work in some of these areas and we just need to expand it.

So informed consent the way we think about it currently in general doesn't address the issues of group harms. In many cases, that happens only if there is a particular group that is involved in a study and how do we tailor consent forms so that they might be inclusive in terms of potential harms to identified groups.

Community engagement has been talked about a lot and written about a lot and implemented a lot as a means of addressing some of the issues related to group harms. I know of one study that is actually looking at -- and I don't think I have seen a publication from it yet, but actually looking at the effectiveness of community engagement. What it accomplishes and how useful is it? I think in general many of us think it is a good thing, it is a useful thing. I have done it here in the U.S. and in a couple of African countries and it is useful. It is helpful in terms of how people understand the research and in researchers connecting with participants.

But we also need to revisit that in terms of how that process might be changed, might be improved, and are there other approaches that we might use to address this issue. In general, the general sense is that guidance is needed to help us in thinking about how we appropriately involve “communityism.”

I am going to try to hurry on so we will have enough time for discussion.

(Slide)

Some of the central issues -- so I talked about the general issues. These are just some examples of cases involving group harms. Most of these cases, I think, don’t even have to with genomic data. Some have to do with genetic data. Some have to do with samples as opposed to data which for me is also an issue that we may want to talk about later. Our topic has been genomic data sharing, but we also know that samples are shared for genomics research and whether that is a part of what we are talking about or whether it is really just the actual data.

So I think many of us are familiar with the Havasupai case which is really recently settled. John Martin at Arizona State University in 1989 was approached by the Havasupai to do -- he has worked with them since the 1960s, I think. He was trusted by the community and they approached him about doing research related to diabetes which was of

concern to the group.

He started that work which he later collaborated with Therese Markow who started doing work on schizophrenia. Subsequently over the years, I think, between 1993 and 2004 or something like that the data, these samples were shared with researchers, other researchers at ASU doing research on schizophrenia, inbreeding, migration which raised a lot of issues.

In April of this year, the case was settled and that case has been ongoing. It was filed I think maybe six or seven years ago. It has been ongoing and it was recently settled and the Havasupai received $700,000 out of their original request for $45 million. Was it $45 million or $75 million; 45, I think, million? They got $700,000 out of that case.

That case has raised a lot of issues in terms of sharing of data, of samples and groups and the impact on different groups.

The second there, this is a paper by Rebecca Tsosie in 2007 where she talked about this notion of cultural harm and the fact that when we collect data and samples from groups and something goes awry, it is not just the participants and -- I would argue it is not just for Native Americans, I think whenever we think about an indentified group -- it is not just that group that is involved in the study, but the whole tribe,

the whole group as a whole.

She talked about the notion of cultural harm and that values and culture needs to be factored in to decision making about how groups are engaged in genetic research. Native American tribes she talked about specifically. It is more than just, you know, a study that related to some particular goal of a researcher. The value of those materials to the tribe transcends the physical harm that we might think about.

Research in Mexico with different tribes and Seguin talked about that and about the genomic medicine program in Mexico developing guidelines about involving groups in Mexico in genomic and research in general.

The paper there about the tribe is about the Nuu-Chah-Nulth tribe in British Columbia that, I think over 25 years ago, provided samples to researchers to look at rheumatoid arthritis which has been a major issue with them. Over the last 25 years those samples have been shared widely with researchers in Canada and elsewhere.

Since then, the National Institutes of Health Research in Canada has developed some guidelines about involving indigenous groups in health research which includes genomic research.

The last case there, really has to do with a case I am sure many are familiar with in terms of researchers at

Harvard getting samples from about 200 thousand farmers in Central China for genomic research with Millennium looking at pharmacogenomic work and not having appropriate informed consent, shredding of evidence, and all kinds of inappropriate behavior by the researchers.

But as I said before, many of these cases do not deal specifically with genomic data sharing or genomic research in general. But the involvement of groups in genetics and genomic research are some of the things that we may talk about. We may not have -- we don't have a lot of examples in terms of problems with these groups being involved with genomic research just because many have not been involved in genomic research to date.

I think as we do more in terms of genomic research and whole genome sequencing and more groups become involved, hopefully more diverse groups become involved in this research, then we are likely to see an increase in that.

(Slide)

The issue of privacy and security and someone talked about the tension between uncertainty and trusting versus trying to protect your privacy and not trusting that it is going to be able to be protected. The informed consent in data sharing is difficult. It is different from, as we know, a typical informed consent because the bigger concern is about inappropriate use of data.

Some would argue what is the problem there in terms of inappropriate use of data. In many cases it depends on who the subject is and what is actually done with that data.

(Slide)

So in framing our discussion that we are going to have hopefully in a few minutes, some of the questions that are raised about the blurring of that line between research and clinical practice, how do we design informed consent with information that participants want most or participants feel that they need to make an informed decision about the sharing of their data?

How do we design informed consent that have meaning for them? Is one-time consent adequate? Are there times when We need to think about waiving consent and that discussion has been an ongoing one. How broad should a consent be? Who is the best person to obtain participant's consent for genomic clinical studies? How should incidental findings and secondary data be reported?

(Slide)

For group harms, what steps can be taken to prevent group harms? One of the questions that has been raised is what has been lost? What is lost when researchers don't identify groups?

There has been a lot of literature in the past -- well not a lot, but some literature in the past that talked

about not naming groups as a means of protecting them from exploitation and from identification. There was some pushback on that in terms of what we would not gain by naming groups and being able to identify what group we need to look at particular outcomes in.

So that is an issue that still keeps coming up in terms of -- I don't think it is as big of an issue now because I think in many people's minds it is of value to identify and to name. We just need to figure out how to do it and how to do it well so that group harm is minimized.

Are their best practices for raising awareness among researchers about the potential influence of diverse values? The whole issue of best practices, as I mentioned, the Canadian Institutes of Health or their corollary to our NIH has come up with guidelines for involving indigenous groups in health research and genomic research. Mexico has done it. Other places have done it. Is it time for us to do something like that in terms of the U.S.? How do we approach research with groups.

Whose responsibility is it to think about addressing group harms? Is it the group? Is it the researcher? Is it the clinician? Are there additional concerns that we need to think about?

(Slide)

Privacy again. The consent forms and how we talk

about privacy and how we will be able to protect and secure people's data is something that we need to address.

Do existing policies have provisions for notifying breeches of security? We talk a lot about privacy and the need to protect data. There haven't been, I don't think, a lot of documentation of breeches that have occurred so in some people's mind, a lot of this is hypothetical and is prospective in terms of potential breeches. But how do we document and have we been documenting actual breeches?

Should privacy be deemphasized? Going back to Amy McGuire's work in terms of how people even think about privacy versus the need to advance research.

(Slide)

So our next step. Should we continue to pursue this? I probably should ask and try to get a yes/no answer to this question. Should SACGHS continue to pursue this and if so what should our focus be? There we have the three topics that we identified, the blurring, group harms, privacy.

Another issue that keeps coming up a lot is the international issue. We found that a lot in terms of the group harms, but we know that international issues in terms of genomic data sharing transcend group harms.

There are questions about whether there needs to be regulations or whether it is even possible to reconcile regulations across the globe, across different countries in

terms of data being shared between researchers in different countries? How do we think about the international issues related to genomic data sharing?

Are there issues that we have not touched on that people think we should?

I am going to stop there and then we will move on.

Questions and Answers Session

DR. TEUTSCH: Thanks Charmaine for sharpening up our thinking a lot on this. We really appreciate it. So those are the questions we need to answer today to decide how to move forward. I wonder if -- Kevin I don't know if you have seen all these slides in this form before, but you raised the original issue. Do you have some general thoughts about are these the right questions? And are they framed as well as they might be? Come to the microphone, would you?

DR. FITZGERALD: I think Charmaine has done an excellent job of focusing in on some of the things we were trying to get at and I think one of the things we the committee has to wrestle with is SACGHS, the organization or the structure that needs to be driving this or if it has to go somewhere else. Because, I think, as we discussed, there are a lot of people looking at this from a variety of angles. One of the questions is does this fit with the initiative of SACGHS to pursue or somewhere else within HHS? I think it definitely has to be within HHS somewhere though. Yes, I

think the questions are exactly on target.

DR. TEUTSCH: Great. Okay. Marc and then Jim and then Gwen. Do you have your hand up?

MS. DARIEN: No.

DR. TEUTSCH: Marc and Jim.

(Simultaneous Conversations)

(Laughter)

DR. WILLIAMS: Just to follow on what Kevin said, I mean the two questions that I have in terms of following through here are, you know, there are a lot of people that are working a lot of different aspects of this. So in some sense I think we have to say where are the potential gaps where there are not people working on some of these issues that could potentially be targeted. And if we can identify some of those gaps, then the second question is, are these gaps that could be addressed by the Secretary in a charge. I think that, you know, it would be hard for me to weigh in on this without, you know, a pretty good sense of those two issues.

DR. TEUTSCH: I think that is what we need to figure out today. Where are those important gaps that we can meaningfully fill. Jim?

DR. EVANS: Right. The idea of addressing the broad front of genomic data sharing in all its manifestations seems quixotic and impossible. That is my view. I think, however, there are perhaps discreet subsets, sub-questions that this

committee may be very well positioned to weigh in on in an informed way.

That was a great presentation and you covered a lot of ground. The things that I think we might be able to address in some tangible productive manner, getting again to what -- I don't see Sheila -- getting to what Sheila reminds us of frequently which is real recommendations to the Secretary that she can do something with.

The two things that seem to me where we may be well positioned would be tangible aspects of informed consent. Right? Some of these questions about broad consent, about ongoing consent. The second is the return of results. Because that gets into the whole clinical issue that I think we have some expertise in.

But I think that getting into things like group harms, et cetera, may be so nebulous that we at best might come up with extraordinarily unproductive broad platitudes. I would be really interested in what Charmaine thinks. You have been very careful to kind of present everything in a really nice way and present frame out issues very nicely. But you are the person on the committee who has been deeply immersed in this. Right? So I would love to know what you think about whether we can contribute something, whether we should, and if so should we pick a subset.

DR. TEUTSCH: Thank you Jim.

DR. EVANS: You are welcome.

(Simultaneous conversations)

(Laughter)

DR. ROYAL: I must say, and this may have been obvious and it may not have been, that I have struggled some with where were we need to go with this since it was dumped on me by Kevin.

(Laughter)

DR. EVANS: Don’t pull any punches.

(Laughter)

DR. ROYAL: So I have been trying to find my way as well in terms of where we go because, as you said Jim and I think Marc as well, there are so many issues and others are addressing some of them. I think in particular with the informed consent issue. Personally, I think that the area of group harms is, and that may be because that is one of my personal interests in terms of how we deal with groups in genomic and genetic research. I don’t think that that is an issue that is being addressed at a high enough level where it makes a difference. So I think there may be a place for us to do something there.

But informed consent and privacy are both two areas I struggle with a lot more than I do group harms. For me, groups harms is a given in terms of an area that needs some attention. I am not sure what yet in terms of where we go

with it.

But the issue of the blurring of the line is one that has been on the table since this came up with SACGHS. That I think, as opposed to genomic data sharing broadly among researchers -- the blurring of the line between clinical care and practice -- I agree with Kevin, he raises some issues that may not be at the fore in terms of how the informed consent issues are being dealt with. I think we could probably take some things out there to look at in terms of how we engage patients in research and how their data is shared. I talked about the data being shared from the clinic to the research and back to the clinic and how we even look at that model.

So those for me are probably the two areas. Some aspect of the blurring. And I am not quite sure if it is the informed consent aspect of it, but that too is a major aspect, but that and the group harms issue for me.

DR. CAROME: Just to make the committee aware of some of the activities, I think I have mentioned this before. The Secretary's Advisory Committee Human Research Protections or SACHRP has spent well over a year now exploring issues related to research involving biospecimens which is a little broader. But research using biospecimens for genomic genetic research certainly is a subset of the type of things they are looking at within that topic.

One of the big things they are focusing on is the

adequacy of informed consent. When is informed consent for future unspecified research sufficient for when the future research is finally designed? When someone consents to research for a specific use like research involving genetics of diabetes, under what circumstances could you then share the specimens with other researchers who will use it for a different purpose? And do that without informed consent or with waiver of informed consent, when is that appropriate, if ever?

In that context, our office realizes a great need for further guidance on research involving biospecimens and a big topic of that guidance can be many of these issues related to informed consent. We are looking forward to the guidance or advice we expect to receive from SACHRP.

So those are just some of the things that are ongoing and that you should be aware of. They really are focusing on the informed consent issue in great detail, but not necessarily this specific, but in sort of more global terms researching biospecimens.

DR. TEUTSCH: So Mike can you help us then identify what you see as specific gaps or issues that may be very specific to the genomics arena/genetics arena that aren't going to be addressed here so that we can get maybe a little better sense of what we should be addressing that is likely to be meaningful?

DR. CAROME: I think the group harms issue is one that they have not spent much, if any time on. Although at the SACHRP meeting in July they actually are going to have a session involving the University of Arizona research involving the genetic studies involving members of Havasupai tribe. Actually invited to that are the principle investigator, members of the tribe, some commentators and I think maybe representatives from the University. So whether they might turn their attention to the group harms issue is unclear to me, but that type of planned panel certainly could open the door to that. But they haven't explored a lot.

That is certainly one area where this group may have more expertise to address within the genomic setting and group harms.

DR. TEUTSCH: Rochelle and then Barbara.

MS. DREYFUSS: It was interesting to me to hear this concept of group harms and social harms because in my world all of the same cases are taught and it is called rights, not harms.

(Laughter)

MS. DREYFUSS: There is a huge amount of work going on on the question of who owns their genes and who owns the information in it, and that case is litigated a little bit on that theory as well, and part of the money with that kind of recognition of a property right. So, you know, I think there

is just a huge amount of work going on on this.

As you say, the international issues are very much at the forefront. So the convention on biological diversity has provisions on who owns rights to genes and things like that, usually applied to plants, but people are trying to apply it to people.

The World Intellectual Property Organization has been working on a series of protocols along the lines of what you are saying. The United States has been a little bit back in thinking about these issues and intersecting with the international groups. Canada has done a lot more than we have.

So that is an area where, you know, I think there is a lot of room for our government to be doing something whether HHS, I don't know, but I think for people who do genetic research, this notion of re-conceptualizing things as the rights of people to control their genes is something that is very important. So I second what you say about group harms, although I call it group rights.

Then just one other thing on terminology, when lawyers say reasonable expectations of privacy, they are very cynical about that because the Supreme Court uses that phrase to say you have no rights of privacy. So if we do something on that, I would suggest we change the phrase because it sounds like how are we going to deprive people of any interest

in their privacy rather than how are we going to think about what kinds of privacy rights they ought to have, or privacy expectations they ought to have.

DR. ROYAL: I appreciate your comments Rochelle. I mean I have gone back and forth with this group harms thing and thinking that that is not really the term. It is a place holder. I think something, group rights, ownership, that those issues are what we think about.

DR. DREYFUSS: The knowledge in the international literature.

DR. TEUTSCH: Barbara?

DR. McGRATH: Charmaine, this is great. I could -- you guys did a lot of work in a short period of time and I just know that you did struggle sort of the boundaries on this because it could be huge or it could be smaller. But I think I am sort of seconding what a number of people are saying. It seems to me informed consent is covered by a lot of people and the whole notion of the process of informed consent is definitely where we should be looking. Lots of people are looking at that. It is not so specific to genomics I don't think.

But the two areas that I think would be really useful are if we could come up with models to report to the Secretary. So I am kind of interested in whether the Consumer Disease Registry is doing things differently because they

start from a different etiology. So I wondered whether we have anything to learn from that as well as look into international.

To me the two issues are return of research results and group breaks. I think the return of research results is kind of -- it does cross over to non-genetic, non-genomic research, but it is really coming to a fore in here where you have got people reading about research on social networking and on the internet and getting -- knowing their family has a condition and calling the researcher directly who is not a clinician nor has the communication skills for giving those kinds of important results back.

So I think that is a interesting area to look at and if there are any models about how could that be done because it is just going to escalate.

The other one is the group rights or group harms issue. I really liked your approach where your comment that we have traditionally put it into the category of racial and ethnic minorities as sort of vulnerable populations, but I like the idea of expanding it to disease groups and other sorts of groups that we do not traditionally think of as vulnerable but around notions of identity.

DR. TEUTSCH: Paul?

DR. BILLINGS: So I want to speak in favor of the topic of blurring between the clinical and research uses and I

want to draw upon a comment that Paul made yesterday about the social networks driving more and more people to have extensive knowledge about their genomes in a kind of non-medical or social setting and those becoming very valuable for research discovery and allele frequency and all sorts of things.

So having good processes for resolving the blur if you like it would seem to me would be very important. It may take to some extent outside of medical offices, but may impact research results in medical offices.

DR. TEUTSCH: Gwen and Marc and then Paul. I know you have been dealing with a lot of these issues in terms of groups and rights and things like that so I assume you have some comments to share too. Gwen?

MS. DARIEN: So just to build on what Barbara said, I think that that is a really interesting place to start which is -- a place to look, not start. A place to look is what groups have been doing in terms of the registries that they have been starting because the impetus for starting these was to control the destiny of their samples and what they were given.

One of the groups is the Inflammatory Breast Cancer Research Foundation which actually has an alliance with Duke Cancer Center. They have aligned with other groups so it is something to look at. There is also the tissue bank at Indiana University, so there are a bunch of groups that

started so that they could say who owned their genes and who owned their samples. So I mean, we can talk about it and I can give you some ideas of people I know to talk to.

DR. TEUTSCH: Marc?

DR. WILLIAMS: So it seems like we are in a bit of an analogous situation to some of the issues that we were talking about, I think, in February around newborn screening and the idea that we have -- I have now heard that there are two Secretary's Advisory Committees that are sort of working around the same types of issues, so I wonder if it would be practical to again try and coordinate between what Michael has told us about what is going on at SACHRP, if I am pronouncing that correctly, and what we are doing. I think if there is coordination there that that could potentially result in a more effective communication to the Secretary about areas of interest and I would like to see us pursue that.

DR. TEUTSCH: Of course, we can involve Mike's office directly. We can get -- if we form a taskforce, we can definitely ask for them to, you know, have some membership from their organizations.

I don't want to call you out inappropriately here, but I know this is what you deal with a lot.

DR. WISE: Thank you. I am struggling with the issue of what is our strategic contribution. We have heard quite a bit this morning the words, "a lot of people are

working on this," which is usually a signal for us to be cautious. However, it is also perhaps in this case, as in other times for this committee, a signal that indeed we do have a potential role in that often I have been impressed that some of the greatest contributions this committee has made have actually been contributions of coherence in a field where a lot work is being done, but there is no conceptual clarity as to what the challenges to this department really are.

There are technical issues, there are legal issues, there are political issues, and frankly, there are justice issues broadly conceived in operation here. It may be that the fact that so much work is being done is actually a very good reason for this committee to take a step back to frame the field in terms of policy for the department and identify particularly funding priorities that may be required to make sense of a field that is fairly chaotic.

DR. TEUTSCH: Iliana?

MS. PETERS: I just wanted to bring to -- I am sure most of you are already aware, but I heard breech and privacy a couple of times in your presentation and HHS Office for Civil Rights in August of last year did issue an interim final rule that was the first sort of national framework for notification in the case of breech.

It does only apply to HIPAA-covered entities and their business associates. FTC also wrote one of their own

rules in conjunction with us that applies to certain other entities. We do post -- we are required by HITECH to post a certain level of these breeches on our website. They are available on the OCR website.

So in terms of thinking about breech and privacy and information about breeches and whether or not all of these entities would be covered by these rules is another question. But we have been doing quite a lot of work in this area.

DR. TEUTSCH: Mike.

DR. CAROME: So just to give you an idea of sort of SACHRP timeline for some of the work. They have been working on the issues of consent and biospecimens for over a year now and they are sort of entering the final stages of preparing what is going to be their major work product from that. The way they approach this, they develop a series of questions and answers, real life questions about use of biospecimens and how you would get informed consent and could you waive it. For those questions they formulated what they think should be the answers and they intend to probably finalize that work product at their meeting in July and then it would be forwarded to the Secretary and then back to us with the hope that we would use that as the framework for developing our guidance on this topic.

They may finish, at least, their first work product on this product at the July meeting. Now they have a

subcommittee on harmonization that they recently formed which is looking broadly about harmonization of regulations and policies across HHS on multiple issues, but one of them might also be issues related to how you apply the regulations to research involving biospecimens. So that subcommittee may lead to other work products in this area which are in their mason stages. But their first work product is likely to be finalized in July.

DR. TEUTSCH: That is very helpful. So we will clearly have the benefit of seeing that and not falling over. That committee would be helpful. What I think I am hearing is that there is a lot of interest that we have some general issues Paul raised about framing. That there is a lot of interest sort of in the group-related issues, whether we call them rights, harms. We need the right vocabulary. But they are clearly a set of issues here and genomics is probably particularly relevant since that relates, I think, I should say more broadly than some other types of specimens might in terms of the group issues.

Then on the sort of blurring between clinical and research, while there are some issues here, probably informed consent is not the place we want to be, but in some of the how information gets communicated back and forth are areas where we might have a specific niche.

I did not hear anybody speaking very directly sort

of to the international data sharing issues, but that might be another place if that -- a gap -- unless you see that -- Mike do you see that as an area that -- a space that is being filled?

DR. CAROME: They are looking at international but very, very broadly across human subject research in general, not specifically research in genomics or biospecimens. At least at this point they haven't.

DR. TEUTSCH: Okay. Let me -- it sort of reminds me -- so as part of your process are you looking at return of results to research subjects?

DR. CAROME: We have not. The subcommittee SACHRP has not focused on that a great deal. They did have one panel session on incidental findings and reporting that but they did not spend -- they have not taken that anywhere. It is not clear that they will.

DR. TEUTSCH: Yes. I mean clearly we talked about yesterday there is a lot of potential for challenges with sharing information that may or may not be useful or actionable. Marc?

DR. WILLIAMS: So you mentioned the international. One reason I did not bring that up was because I was not sure about, if you will, jurisdiction. Under what circumstances would the Secretary be able to engage around issues of international --

DR. TEUTSCH: She can have -- she can be in groups on harmonization of standards and things like that. I mean, very much like we talked about with -- and you will be talking about with, you know, coding and phenotyping and things like. I think these are international things that HHS weighs directly into.

MS. WALCOFF: I was just going to reaffirm that. Yes, there is a lot of interaction and direct involvement internationally on issues related to anything within the scope of HHS so it is a --- bailiwick.

DR. TEUTSCH: So it sounds like there is sufficient interest. So the answer to the first question was probably yes, we should continue to pursue this topic. Does anybody want to suggest that we not do that?

(No response)

DR. TEUTSCH: Hearing none. I don't know if that is enough guidance based on what I just said in terms of allowing you to move forward? Are you good?

DR. EVANS: I don't -- do you actually have -- that is what I worry about. I mean, do you have any kind of concrete charge?

DR. TEUTSCH: Well we need to form a charge. We have a taskforce and we will probably need to come back with a specific charge, but I think we do need to, you know -- yes we will need to form a taskforce so we can talk about that. Do

you want to share it? Did you draft a charge Charmaine? Do you want share that with us?

DR. ROYAL: Yes. ---

DR. TEUTSCH: --- All right.

DR. ROYAL: We do have a draft charge which relates broadly to the topic that I covered. And following our discussion now, I think we can refine it a bit in terms of taking some things out and still not sure what the boundaries are going to be. And it might be for the taskforce to decide that once we get together.

I think we are going to -- right now Sheila and Dave, and I am sorry David is not here, but they are the ones, the current members on SACGHS who are members of the taskforce as our *ex officio* Kevin and then our agency folks. So I would imagine that we would probably need some other bodies on the taskforce if anybody else is interested in helping us think through where we go from here. I don't know. Steve?

DR. TEUTSCH: I think just looking quickly at this for a second, not just before. It sounds like on the first -- I am just looking at the bullet points right now. The primary focus of the first bullet would probably be reframed to be more on some of the return of results? The group harms and disparities would be a primary focus? I am hearing that the privacy and understanding would probably be off the list?

Actual risks in genomic data sharing versus

perceived risks for potential harm? I am not sure, but I sort of suspect that Mike's group is already dealing with. Then we would have the last two being potential things depending on whether we, after a little exploration, find that there is a real role for us on international data sharing issues that we could advise the Secretary on. Then I am not sure what to do with the phenotypic information.

DR. EVANS: Am I missing return of results? Did we say not to?

DR. TEUTSCH: I thought we would talk a little bit -- that would be a topic. I heard -- Mike sort of said that that was not a primary focus of his --

DR. CAROME: Right. Nor have they focused, you know, actual risk of genomic data sharing. That is certainly not a topic they have explored in the specific at all. Just to note that.

DR. TEUTSCH: So it is something that we could consider. But we would scope down that first bullet significantly.

(No response)

DR. TEUTSCH: I am not sure if silence is reading, silence is agreement, or silence is "holy smokes." Kevin, come sit here. Paul is done. You can sit here.

DR. FITZGERALD: I don't know.

DR. TEUTSCH: Yes, I know. It is dangerous.

DR. FITZGERALD: There we go. I am just curious because if I remember correctly, the charge initially was for us to find topics to pursue as something that SACGHS could, you know, make a significant contribution, as Paul was saying. Why, since you -- it seems to me you have identified a couple of different targets. Why would they both have to fall under the same taskforce?

One of the things that comes up in the blurring of the lines between research and clinical practice also seems connected to some of the discussions we have had on comparative effectiveness research. If I am not mistaken, two people, two members of this panel co-authored a very extensive paper last summer on scientific foundations for personal genomics and I do believe the first author on that was Muin.

(Laughter)

DR. FITZGERALD: And you were on that too. But I mean, if you look at the very recommendations you made in that paper and you follow them out, they are going to lead to that blurring of the line between research and clinical activity.

So you might actually have two tasks here to pursue, the one that is more focused on the blurring of the line and the other that comes more under what Charmaine was talking about, group benefit, harm, rights, risks, those kinds of things.

I don't know. I mean, it is a different way to

parse it. But it might help clarify some of the confusion because then you are not trying to stuff too much under one thing. Which really means you have to start another taskforce and you and Muin have to head it up Steve.

DR. TEUTSCH: Yes. And we also have to remember what the heck we wrote.

(Laughter)

DR. FITZGERALD: Paul gets credit for that. Right.

DR. TEUTSCH: Yes. Muin?

DR. KHOURY: You know, as I look at this and listen to this discussion, I think we are still unfocused. We live in a blur. I think the discussion yesterday, for example about whole genome sequences blurs the line between research and practice. We have had discussion that night over dinner about, you know, what do you do with information that is still in the research domain but, you know, what information would you return back to people.

I think we should take out this blurring of the line discussion about the thresholds between clinical practice and evidentiary issues away from this genomic data sharing and focus only on the research aspects of this. Otherwise, it gets too blurry.

You know, I am not suggesting a course of action here but tend to think or suggest to the group that unless you have a very focused mission the result will be a blur.

DR. FROSST: So I think the idea of focusing in on one specific thing, I think, gives the committee power to say something that really will resonate. The other way that I would think about potentially breaking out this list of topics is the idea of return of results in a separate but slightly more broad way in the way that it fits in with our discussion yesterday on return of results in genomic data in general. Looking at it from a research and a clinical perspective and then focusing this taskforce in on, I think as Muin says, sort of group harms and the international flavor.

DR. TEUTSCH: Muin, you are shaking your head.

DR. KHOURY: This is an example of a blurred discussion here. I think we are probably not saying the same thing, but I mean, I think the -- I need to think about this.

DR. ROYAL: I am going to go back to square one and ask a question of the group because it seems -- this has been our third session on this topic, I think and we are still blurred as Muin said.

I really am going back to the first question there on that slide. Whether we should -- because there is so much overlap with other things that we are already doing and overlap with things that others are already doing. Do we really feel that there is a place for us to say something about genomic data sharing or is it something that we will address in whole genome sequencing? And we will address in,

you know, comparative effectiveness. And we will address in other things that we are doing. Do we really need to single it out as an area of focus? And I want an answer.

DR. FROSST: Maybe a reminder of the other taskforces that are ongoing so that we can look at this potential question in the list of ongoing taskforces?

DR. FROSST: I can't remember.

DR. TEUTSCH: As you said Charmaine, we have now been down this road several times without getting sharpened focus. I do think we need to figure out where there is a place for us here and maybe it is what Paul said. Maybe there is a lot going on and we just need some umbrella framing of all of this to get it right to genomics. Barbara were you going to say something?

DR. McGRATH: Yes, I was just briefly. I think one place that this group -- that this potential taskforce is different than the others is the perspective of the consumer or the patient or the participant.

A lot of the other ways of looking at return of research results, some of those are a little more technical aspects of information and things, but if this group took the perspective of the participants, that is a different blend than the other ones are doing and that might be a small enough and unique enough and actionable sort of approach.

DR. ROYAL: That is a good point Barbara because the

participants could be the individuals as well as the group, right? If they make it a participant's focus? That is a good point.

DR. EVANS: I guess I have the same trouble that you are articulating and what, you know, -- I see you trying to chair this nebulous beast, and it is frustrating.

I am actually skeptical that we are going to have something at the end of the day tangible to say. I think it is very worthwhile to go through the list of these points and say okay, you know, is informed consent being worked on? If it is being worked, are we really going to be able to add something to it?

Return of research results is a very important issue, but again, is it being addressed? Those are things, I think, one could come up with tangible recommendations for, but I am not sure that it is needed because of other work.

The thing I have trouble with with group harms and all is not any lack of importance, but it, and maybe this is just my own naiveté about the field, but I am having trouble envisioning tangible kinds of products from that.

So all I would say is we should go down the bullets, we should answer yes or no whether it makes sense for us to weigh in based on those two things. The prospect of tangible results would just be redundant and decide whether we move on because, you know, this vague charge that you have had for so

long has to be very frustrating and I think you need a very concrete charge.

MS. DARIEN: I actually agree with Barbara. I think that could be a potentially really interesting thing to come with group rights. Taking Rochelle's term and going from the point of view of the participants. But I think maybe one of the reasons why there is so much trouble in determining this is that we do not know where the redundancies are.

That is the next thing to look at is where are the things that are on this potential draft charge, where are they being done in other places, and how do they overlap? So concretely, we do not really know and that is one of the things that I think Phyllis was asking. I think, you know, it is very difficult to say whether we are being redundant if we do not know exactly where the redundancies potentially lay.

DR. TEUTSCH: In fairness, the staff and Charmaine have been going through that. I mean, it may be a matter of depth, but certainly they have looked at that. Rochelle?

MS. DREYFUSS: I think if we did the group harms one, the thing that we could bring to this is the question on the other side, not only the impact to the group, but also the importance of the genetic research. So a lot of the people that are working on what people call traditional knowledge or, you know, indigenous rights, those kinds of issues, are looking at it only from the point of view of what is the

impact on the group.

I think we could bring a much more balanced look at it because we -- not me but you guys -- know a lot about how this information is going to be used. What the potential is of it and you do not see a lot of that, at least in the legal literature. So that will be a more controversial study if we look at both sides because people will disagree. But I think it is quite different from, at least the things that I see in the legal literature on this question of who owns the genes.

MS. DARIEN: I think that is an excellent point and I actually think that you will see when you look at some of the advocacy groups that are working on it, that many of them are research advocates. So their whole point of view is to make sure that the research happens. So they --

MS. DREYFUSS: They are not talking to each other.

MS. DARIEN: No, they are not talking to each other. There are some people that are talking but there are a few groups that are aggregating together, so I think that could be really interesting.

MS. BACH: I just wanted to add about the idea of group harms and risk. One thing I think that could be contributed that would be fairly tangible would, at least to be able to say where in the process and who should oversee that. Because right now, it is not clear to me that IRB's are really charged with that.

I mean, you may even -- the data is aggregated into the biorepository and then IRB oversee that's. Then IRB may oversee the release of the data. But let's say the data is de-identified, it could certainly deal with a group, but an IRB is going to have no real look at whether a large body of de-identified data is going to harm a particular group or not because it is either exempt or not even human subjects research.

So I think, at the very least, we could say who and where in the process this should be overseen and, perhaps, suggest some ideas about how one would look at it ethically in order to approve a project. That would be something fairly tangible that could be added.

DR. TEUTSCH: So we are getting a little more concrete. I am hearing looking at the participant's side. I am hearing looking at the balance of benefits and harms so we get both sides of all of this.

DR. EVANS: And I will retract my criticism of the nebulousness of the group harms stuff since Rochelle. That is a great comment. I mean, that is a really interesting way of framing it.

DR. TEUTSCH: Then there are some of the institutional issues regarding oversight of who is looking out for these group's benefits and harms which is really different than how we have looked at it before. Just primarily at the

individual level.

DR. ROYAL: Rochelle's point also gets to the broader public health indications of this also in terms of genomics research.

DR. TEUTSCH: So that is a fairly discrete thing. This would bring it down to what we generally call the group-related issues and rights and ownership. It seems to me that if we use that as the starting point for this that there can still be a bit more exploration about whether there is an important gap in the others, and I am not sure there are, like in the international issues, that could be explored but wouldn't be part of the immediate charge. Is that where you all would like to see this go?

(Nodding of heads)

DR. TEUTSCH: Jim is affirmative. Are there people who think that is either too narrow or we are missing some real opportunities that we need to make sure are part of this?

DR. McGRATH: So return of results, is that off now?

DR. TEUTSCH: That would not be included in this. I mean, we can go back and revisit that.

DR. EVANS: I thought what you said was you were still going to look for gaps. So, in other words, I would advocate if nobody is looking at return of results in some kind of formal way, I think that is an exceedingly important issue.

DR. TEUTSCH: Yes, but it is not part of the direct charge right now, other than on an exploratory basis.

DR. EVANS: Right, right, right.

DR. ENG: Well if you follow through with Rochelle's framing, there will be a little touch on the return of results there, obviously because what is a group benefit? But then the other thing that is an issue, and you might know this, apparently the NCI is going to look into return of results in regard to cancer biorepository. But remember, cancer biorepository tests somatic data, as well as germ line. Apparently I am sharing one of these sessions. This was incredibly good Charmaine.

But that is one of the specific things that are troubling them and I suspect this is sort of a high level look. And I suspect that if everyone blesses it, it may go into a formal taskforce, so stay tuned.

DR. TEUTSCH: Just to be clear, when we talk about return of results, I thought we were talking about return of results to individuals of general things, as opposed to the results of the research in general which --

DR. ENG: Yes. Correct.

DR. TEUTSCH: -- which I think would be part of -- All of these groups would learn something about their --

DR. ENG: Right and the research individuals have sort of grappled with that.

DR. TEUTSCH: So if people are good with that, we need to form a taskforce. Among the draftees, of course, are Charmaine, because no good deed goes unpunished in this group. You are willing to continue the leadership role? And we need -- Mike, you have been part of it. I think the taskforce that we have probably should continue unless people want to move off of it.

You know, Mike, if you think there are others from your group who could help with making sure that we stay coordinated and knowledgeable, maybe you can work with Sarah on who those individuals might be? Then we need other volunteers from this. Rochelle, Gwen. Great. That is the kind of input we need. Barbara. Others? Charmaine are there are other issues that we need to cover?

DR. ROYAL: No. I just wanted to be clear Steve. Part of our work, part of the work of the taskforce would be looking to see where these gaps are. Would that be part of our -- and I guess another discussion, and I don't know exactly for the taskforce what our produce would be, whether it is a letter or a full blown report, but that is probably something we would talk about later.

DR. TEUTSCH: I think you can bring a recommendation back to us as to what this looks like, but what I am hearing is these group-related issues will be the primary focus and then you can explore a number of these others, and we talked

about them, the international, the return of results, and see if there is really a need where we can add some significant value, make some recommendations that are likely to be meaningful, and if so, they can be added to the charge. But then bring that back to us.

Whether this is a letter or larger report really depends on what you find as you get into it a little bit further and how much of that is sort of, yes, that is what we know and we can begin to move ahead or whether we need to do more research.

Is that all right?

(No response)

DR. TEUTSCH: Cool. Thank you very much. That is terrific. So we are a few minutes ahead, but we also have a few extra things that we have to do. I would suggest we go ahead and take our break now and come back at five after. Then we have public comments. Before we get to that, I wonder, Marc are you going to be able to share with us some of the issues you brought up yesterday about what we would we get back to the Secretary?

DR. WILLIAMS: Yes.

DR. TEUTSCH: Okay. So we will do that as soon as we get back from the break. Are there any -- we have not heard that anybody wishes to make public comments. Are there individuals? Okay. That is good.

(Whereupon a brief recess was taken.)

DR. TEUTSCH: We will regroup. We will get started again.

(Simultaneous conversations.)

DR. TEUTSCH: As we get started, what we would like to do is to revisit the issues that Marc raised yesterday in terms of the ARRA money that has been available for the comparative effectiveness research and what we took as a desire to get back with some recommendations for how those resources can be well utilized this fiscal year with some specific recommendations.

So Marc, you had some ideas that you wanted to share with us with the idea that we would craft this into a letter that we would get to the Secretary on a very rapid time frame.

So Marc, take it away.

Update on Phenotypical Data

by Marc Williams, Ph. D.

DR. WILLIAMS: So the first thing to say is that the letter that I was reading from yesterday that is behind tab ten was dated the end of March and so there is a certain presumption here that we have not been able to absolutely confirm, which is that there are still some funds that are under the Secretary's control that have not been designated or for which announcements have not been written. So that is the

assumption that we are working under. That assumption may, in fact, not be accurate.

What I wanted to do is, Steve sort of asked me to talk a little bit about the issues of phenotyping and I wanted to give a little bit more context to that. Again, I am not sure if all of you had read the paper that was behind tab six or not, but let me just make a brief case about the need for phenotyping.

(Slide)

So phenotyping is any observable characteristic or trait of an organism. That would include morphology, development, biochemical, physiological properties, behavior, products of behavior.

Phenotypes result from the expression of an organism's genes as well as the influence of environmental factors and interactions between those two. I, of course, went to the definitive source on definitions, which is Wikipedia, so you may have some quibbles with that, but I think it is a fairly reasonable definition.

(Slide)

So Dr. Angrist in his article says there is really a big elephant in the room. That we are highly skilled at aggregating genomic data, but we have a deficiency of detailed phenotypic data which ultimately leads to inadequacy of relevant clinical information to associate with the genomic

data.

Incorrect phenotyping requires more samples to achieve statistical power. Now this is more from the perspective of genome-wide association studies, but I think this also has applications in terms of some of the things we heard yesterday in the afternoon session about doing sort of ground-up systems biology.

Dr. Angrist's contentions are the commitment to better phenotyping make scientific and financial sense because we are not going to be wasting money trying to do genomic studies with poor phenotypes. And that it is a fundamental reason for some of the disappointing progress in clinical implementation of what is really amazing science.

(Slide)

But phenotyping is hard and I think we saw that briefly in that little document about how do we do the phenotype of cigarette smoking and the environmental exposure. We do collect lots of data routinely in health encounters. We collect lots of information around physical characteristics, our height, our weight, our BMI, our blood pressure, et cetera. We have laboratory studies. We have x-ray studies.

But the problems that we have are that these are not collected in standard fashion. Most of them are text-based and even those that are represented electronically such as laboratory data are frequently collected in different systems

that do not talk to one another, the interoperability problem. So there are barriers to aggregation of data.

Unfortunately, we have a heavy reliance on diagnostic codes that are clearly not up to the tasks. When we talk about things like All-Payer databases and that, we are relying on things like ICD-9 codes. As a clinical geneticist, basically every genetic syndrome has the same ICD-9 code which is multiple congenital anomalies not otherwise specified. It is a little bit useless to try to do any sort of studies if that is the only code you can pull on.

(Slide)

There have been some other approaches. There are some consumer-focused approaches such as PatientsLikeMe where they created the database to collect rich phenotypic data. It is limited in the sense that it is self-reported data so there is not any sort of adjudication taking place.

It's focused around communities with a shared expressed disease as opposed to general populations. But it has been shown to have an important role and at least provides the evidence of feasibility.

We have heard about dbGaP, a database of genotypes and phenotypes in a number of presentations here. That is a collection of de-identified phenotypic data. The limitations here are that the information is study specific. The data collection is not ongoing for submitted cases, so there is not

ongoing collection of phenotypes that change over time, and because of the de-identification, there is really no way to go back and enrich phenotypes to answer questions that may have been raised by the initial research.

We heard briefly yesterday about GENEVA and then also the eMERGE which I did not put on the slide here, which are also looking at ways to aggregate phenotypic data using different models.

(Slide)

There are some project specifics issues like the UK Biobank, the Marshfield Personalized Medicine Project, and others that are committed to prospective phenotype collection. These are all done under re-contact consent so they can continually upgrade and improve the phenotypes. They are beginning to develop standardization of information collected, although the information is still not readily consumable across all informatics platforms.

There is disorder-specific phenotyping. There is an emerging effort in the world of inborn errors in metabolism that I think Rod has eluded to in some of his presentations to this group about actually being able to collect phenotypic information around inborn errors that can lead to better care.

If you want an example of how not collecting good phenotype data impairs patient care, I would point you towards phenylketonuria. If you ask any metabolic specialist what is

the ideal phenylalanine level to treat a patient with phenylketonuria to, they cannot answer the question. We have only been treating phenylketonuria for 50 years. We should be able to answer the question about what is the target phenylalanine level, but we can't.

One of the reasons is we are not collecting the data. You know, again, the data there -- you know you are looking at neurocognitive outcomes and so that is hard phenotype to collect, but if we don't invest in trying to collect it, we are not going to get anywhere.

There has been some work in some dysmorphic conditions, Velo-Cardio-Facial syndrome, Williams syndrome where there have been very intense phenotyping that has lead to some extraordinarily interesting discoveries.

(Slide)

So I think there is a potential for how the ARRA funds that are under the Secretary's discretion could be used in this space. Highlighting the issue would not be a bad use of funds, but I think funding opportunities -- that should be convene, not convey, although I suppose part of convening is conveying, but that is parsing -- to develop a long-term phenotyping strategy using, you know, defining what would be a minimal dataset? How do we standardize collection and representation?

Again, this is not work that has to be redone and

redone and redone. If you have one project that says we are going to define standardized collection of phenotype around blood pressure, then once that is accepted you could then use that in any other project that wanted to do work around blood pressure.

There would be issues relating to how do we store and access this information. What are the ELSI issues relating to collection of phenotype? Are there sensitive phenotypic issues such as mental illness or other data that would have to be treated differently? What are the roles of the various DHHS agencies in collection and maintenance and evaluation of dbGaP?

(Slide)

We could also find opportunities that are related to currently funded projects. We have disease-related projects and among all those projects that have been funded by the various groups, we could do an analysis of gaps in phenotype collection. What aspects of phenotype are not being collected that would be important?

There could be project-specific standardization of phenotypic data collection. There is also a lot related to infrastructure. The informatics capability to collect, store, and retrieve phenotype data, guidelines for phenotype collection for future projects, funding for training for dedicated “phenotypers,” and GENEVA.

Freimer in *Nature Genetics* in 2003 suggested we need a human phenome project. That may be a bit much to consider, even with the funds at the Secretary's disposal. There may be others that I wasn't able to come up with in the half an hour that it took me to put this together.

(Slide)

So we are going to be discussing the letter that is in front of you to the Secretary regarding unannounced ARRA funding that could be applied to this problem. Obviously, we are going to have much more time at the October meeting to discuss it, but as we talked about yesterday, there is a certain time criticality if we are going to have any direction on ARRA funds.

It may be that the group decides, hey, you know what, that train has left the station. We are just going to look at opportunities going forward and I can certainly understand if the committee does not really feel that this is germane or interesting that we would not carry that forward at all.

So hopefully that clarifies to some degree the issues that were raised yesterday about what are we talking about in terms of this phenotype gap. Maybe before we discuss the letter, I could entertain questions related to this specific topic. Phyllis?

Questions and Answers

DR. FROSST: Thanks Marc and thanks for a very concise and engaging summary of such a broad ranging issue. You pointed to a couple of programs that being run out of the NHGRI Office of Population Genomics.

There is a third one that I think you might find really interesting. It is called PHENX and it is all about consensus measures for standards of phenotypes and exposures. What it really does is it gets together groups of experts on a particular area and comes up with a series of measures that can be -- originally it was designed to apply for GWAS studies, but could really be applied to anything. So there is a core of sort of a nexus of how you might do this that is already in place. But you know --

DR. WILLIAMS: Do you need money?

DR. FROSST: How can you possibly ask. Yes. We think it is a great place where additional researchers could really expand the scope of this project.

DR. WILLIAMS: Okay. So I think that would meet the ARRA definition of “shovel-ready.”

DR. FROSST: Yes. I mean, they are “shovel-ready.”

DR. WILLIAMS: Any other questions? David?

DR. DALE: I will just comment, Marc. I think this is really important and I think there is a great likelihood we are going to have lots of information about sequencing and so

on of samples where we do not know anything about the person. Trying to create a platform and strategies and also deal with the ethical issues around connecting clinical and genetic data is a top priority issue if this area is going to go forward.

DR. WILLIAMS: So Steve, let me turn it back to you since you had some significant questions about this. I mean, does this clarify from your perspective the role that we may play in this?

DR. TEUTSCH: Yes, in terms of advising the Secretary. I mean, it seems to me there are a couple of things. One is the immediate ARRA issue and what can be done with that and what falls within the scope. Some of this probably we cannot answer today. But what I think what you are talking about is there are a number of issues here that bear attention and the ARRA money may potentially be able to be useful, but even if it can't, these are still issues that we think need to be addressed whether it is through, you know, some of the other activities of HHS or otherwise.

So I think you have clarified the phenotyping issue. But now we need to talk about the letter which I think all of you have in front of you. It is fairly sweeping in some ways. There are parts in here where I say, "Whoa. I am not sure we can decide in five minutes." But the -- we should talk -- so I think it is sort of how do we frame the letter, which I would probably do a little bit differently in terms of saying

these are issues many of which may be appropriate for ARRA and then she needs to explore that.

Then to see if we are comfortable with the three main bullet points that you have there. I don't know if you want to walk us -- unless there is more discussion on the phenotyping issue which is just one of the bullet points.

We should probably give people a minute to read this.

DR. WILLIAMS: Right. I think that would be appropriate.

DR. TEUTSCH: Do you want to walk us through this?

DR. WILLIAMS: Yes.

DR. TEUTSCH: So let me give everybody just a minute to read it.

(Committee reading draft letter to Secretary Sebelius.)

DR. TEUTSCH: Before you start walking us through this, I think we will put this in the context that we do hope to take up the whole issue of comparative effectiveness in October so this is not our only shot at this.

DR. WILLIAMS: Right.

DR. TEUTSCH: So this is the sort of short term stuff that we really want to the Secretary now. So there is immediate potential. A lot of this looks sort of like long-term infrastructure building.

DR. WILLIAMS: Which is under the purview of particularly the FCCCER recommendations for ARRA funding. So the intent there was to get people off the ground and support long term infrastructure building.

DR. TEUTSCH: Exactly. Exactly and that is fair enough. But the ARRA money is, of course, just short term money, but then there needs to be longer term support which hopefully the FCCCER and the advisory committee that is being formulated can maintain.

DR. WILLIAMS: And also, for the people that are responding to those grants, they also have to, you know, provide information relating to sustainability. So there is onus on the people that are responding to the RFAs to talk about how are you going to keep this going beyond just this infusion of funds.

DR. TEUTSCH: All right. So realizing that we are not going to have the opportunity to really wordsmith right now, but we just need to make sure we have the right concepts here and what we want to go forward with. So why don't you walk us through each of the bullet points?

DR. WILLIAMS: Right. So the first bullet point really relates to a center, a research center focused on comparative effectiveness related to genetic and genomic information, et cetera. One of the things that this center would be tasked to do would be to address the issue of

defining evidentiary standards for utilities, something that kind of keeps coming back in a number of different contexts. We heard it this morning in the FDA comments and we heard about it a lot yesterday.

And then also developing the ability to disseminate these findings to appropriate audiences and stakeholders. This is consistent with what the FCCCER recommended related to strategic framework, building human and scientific capital for CER and we have previously recommended creation of an entity in the report on oversight of genetic testing.

DR. TEUTSCH: So let me just start by asking a couple of things. One thing you did not mention was the sentence that reads, “The center would collect the genomic data of populations that are underrepresented in genomic databases, work that would enhance the applicability of genomic technology.” That is a fairly sweeping statement.

DR. WILLIAMS: Right and I must admit that, you know, this has gone through several iterations including the ones just in the last ten minutes or so. I am not sure that I would suggest in the short term -- I don’t think that it could be done in a year to basically have collection. I think that it would be more addressing, you know, issues relating to collection of data from underrepresented. I would see it as more studying the issue than actually collecting the samples. I think that is an important clarification.

DR. TEUTSCH: I would also go beyond that. I think it relates to the discussion we just had regarding genomic data sharing. Maybe it is something that would be better deferred to that.

DR. WILLIAMS: I think that would be fine.

DR. TEUTSCH: The other is it talks about building the human and scientific capital?

DR. WILLIAMS: Fine, but then that is about workforce development. Which is what ARRA is about. So any request for ARRA funds must explicitly talk about what is the investment in human capital along with the sustainability. So this is language that is directly extracted from the documents that are guiding the disbursement of ARRA funds.

DR. TEUTSCH: Right. It is about jobs. This is really about sort of developing training and that sort of thing. At least as I read it.

DR. WILLIAMS: Well, I would agree that the term “capital” is not adequately explicit. I would read that -- I am just saying this is the language that is actually in the documents. We just purloined it and included it.

DR. TEUTSCH: So we need some wordsmithing.

DR. WILLIAMS: It doesn’t necessarily need wordsmithing. If that is the language that was put out in the proposals. We could choose to use that.

DR. TEUTSCH: Yes. So Sheila?

MS. WALCOFF: I just wanted to follow up on how this would relate to the new patient centered outcomes research institute that was established in health reform that will have a separate standing methodology committee to come up with national standards for comparative effectiveness.

I am wondering if this might be something that could be created, you know, maybe a standing subcommittee, a methodologies committee, or an advisory group under the framework that has been set up for that because it does seem to be pulling all of the standards and evidentiary discussions within the framework of CORI.

DR. WILLIAMS: Maybe one way to deal with that is since this is targeted specifically to funds that are available through ARRA and you are talking about a different funding source, is that we could add a sentence to say part of the group's task in the year of funding is to look at the feasibility of adding this as a standing subcommittee to the Patient Center for Outcomes Research funded under the health reform act. Would that be reasonable?

MS. WALCOFF: Yes, I think that is closer. It is just when I see create a new research center and they are creating a, you know, research center right now. I think that that is going to cause people to say why would be create two research centers. Sort of how they are going to fit together, I think, is going to be important to this.

DR. WILLIAMS: We could probably word -- if that is acceptable, we could probably, you know, indicate that in the sentence.

DR. TEUTSCH: By the same token, we have the centers that are similar to this that are doing this for cancer. Right?

DR. WILLIAMS: Correct.

DR. TEUTSCH: So as I read this, this is now centers that would deal with genomics more generally. Right?

DR. WILLIAMS: Yes.

DR. TEUTSCH: In addition to the ones that NCI has been sponsoring. But I agree with you Sheila that somehow we need to put the context that although we may be talking about some one-time finding, that there is this part of a larger --

MS. WALCOFF: Right. Because the CORI is so new, I don't want people to look at this and say, "Oh, they are already doing that. That is part of the CORI."

DR. TEUTSCH: Sam did you have your hand up?

DR. NUSSBAUM: It is really building on this dialogue. Do we know whether any ARRA funding has been used to create centers? Because when you look at the sustainability of the CORI, I understand it is going to be a $2 per head tax on many Americans so once you are creating major new centers and that is pretty expensive.

So it may just be a nonstarter to focus on a center.

However, that said, I think there really is a need for this. So how could that become a broader recommendation of our group and where should this be housed? Should it be part of PCRI or other centers? So that is where -- I am just asking. Do we know whether ARRA funding has been used for this yet?

DR. WILLIAMS: Yes. ARRA funding has definitely been used to create centers. CancerGen is one example in the genomics realm, but there are a number of other centers that have been created through the use of those funds. Again with the implication that you had to say how are you going to sustain this beyond the initial startup funding.

DR. TEUTSCH: Is there a general sense as to whether -- clearly there needs to be some wordsmithing. Probably delete the collection word. But, is there a general sense that if we go forward with a letter at all that that this is an appropriate kind of thing with the broader context that Shiela and Sam are talking about?

(No response)

DR. TEUTSCH: I am seeing some nods and no shakes, so why don't you go on to the second bullet.

DR. WILLIAMS: Okay. So the second bullet relates to informatics infrastructure which again was a specific target of the recommendations of the FCCCER document. We have communicated in a number of different venues to the Secretary the concern that we have about the current informatics

infrastructure being able to accommodate genetic and genomic information.

This bullet articulates again those concerns and talks about actually looking at building on the work that had been done by the American Health Information Committee to Personalize Healthcare workgroup which really articulated a lot of these issues and offered some recommendations going forward.

So this would be funding that would allow continued evaluation with recommendations to the offices under the Secretary, such as the Office of the National Coordinator of Health IT, the certification, et cetera, et cetera, that this is what we think is needed to really adequately support genetic and genomic collection and to address the disconnect where both the IOM report and the FCCCER report indicates that it is going to be critically important to examine subpopulations, including subpopulations defined by genetics and genomics, whereas currently we do not have the ability to collect that information in standard healthcare processes.

DR. TEUTSCH: Comments?

DR. NUSSBAUM: I think it is an important consideration and support it, but just have again, a question. To my understanding, the National Quality Forum has been asked to look at sort of measurement performance and what elements would be in a meaningful use medical record, as are the regs

that are going to be finalized soon. So I am just trying to understand where the intersection of this is with those two initiatives.

DR. WILLIAMS: I think that is an interesting question. The reality is right at the present time there is no intersection because there is no one either, despite our comments to meaningful use and certainly not at the Quality Forum having just reviewed everything that is there. There is no reference whatsoever to the genetics and genomics.

So the disconnect that I see -- that I would be looking for -- this bullet to bridge is the idea that, as you state, there is a bunch of things going on relating to electronic health records and outcome measures and comparative effectiveness research that are completely ignoring the importance that we think that these genetic and genomic markers are going to bring to the table. The idea of this would be to say, you know, how do we bridge that gap? How do we fix that problem?

DR. NUSSBAUM: And I think for that explanation it makes it even more important to probably be not wordsmithing, but a little bit bolder in saying with all this work going on, no one is really specifically looking at something that is critical.

DR. WILLIAMS: Yes and the reason I specifically referenced the AHIC on this was because they were charged --

the Personalized Healthcare Workgroup was specifically charged to address this issue and did a tremendous amount of work in two years under the leadership of John Glasser who is now in ONC. That work is essentially just lying sallow.

DR. NUSSBAUM: As is other AHIC work. I mean is AHIC continuing?

DR. WILLIAMS: No, I think AHIC is sunsetted.

(Simultaneous conversations)

DR. WILLIAMS: There were ten different workgroups under there, but I chose to focus on this one just because it is relevant to the work of our committee.

DR. TEUTSCH: So it sounds like a little more context here as to how it fits in broadly would be helpful.

DR. WILLIAMS: But otherwise this is very consistent with what we have already said. There is no -- I don't hear any policy change here.

DR. TEUTSCH: So why don't you walk us through the third one.

DR. WILLIAMS: Okay. The third one relates to what I just presented about phenotyping. I was talking about using funding to convene, but I think that based on what Phyllis has presented I think we could also potentially make recommendations to provide additional funding to existing efforts which would include things like GENEVA, PHENX, Emerge, and those types of things. You know, groups that are

currently constituted to try to address these issues. Again, emphasizing why it is important to do this and why this would be a good use of funds to really move the field forward. I think that could be a pretty concise recommendation with a very targeted focus of funding.

DR. TEUTSCH: Comments? This is the one that is really new.

DR. WILLIAMS: Correct. The one thing I might, as I just look at this one more time, the other thing that I think now I would move out of the second bullet which is where I referenced the IOM top 100 CER studies. So we have that list that the top 100 that the IOM put forward for funding and many of those studies have, in fact, been funded. In our analysis of those projects which we presented to the group back in February, we identified certain of those projects that seemed to have more relevance to the idea of genomics and personalized medicine.

What I am thinking is that if we move that to bullet three and say, you know, analysis of those specific projects with attention to whether or not the phenotyping associated is actually adequate, and specific enough to move this forward would be a reasonable investment of some funds as well.

I don't know if that is within the purview. I assume there is some sort of an ongoing review of the projects where there could be midcourse corrections as needed. So I

would propose just moving that down and adding that to the third bullet. Does that make sense?

DR. TEUTSCH: That just provides a concrete example of why it would be useful. Right?

DR. WILLIAMS: Yes. And we could actually take that previous document that we presented here where we say here are the ones that seem to have direct relevance. Here are the ones that have at least reasonable relevance to genetics and genomics and use those as the exemplars where we think here are the ones that probably could use some analysis of the adequacy of the phenotyping.

DR. DALE: Steve, if the Secretary says this great, who would get the money?

DR. WILLIAMS: I think what would have to happen would be there would have to be funding announcements that would be developed around each of these that would then be put out for applications and then whoever, you know, whatever applications went through the review process and were awarded, then they would have the responsibility to actually do this.

DR. TEUTSCH: But that is the nub of the problem. I mean the ARRA money has got to be obligated by September 30. There is no opportunity to putting out new funding announcements.

DR. WILLIAMS: Well according to the latest information we have is that there are still nearly $100

million of the Secretary's money that has not been announced.

DR. TEUTSCH: Right. But presumably, and I am not privy to knowing what is happening to all of that.

DR. WILLIAMS: We have not been able to confirm that. So, again, as I prefaced the announcements, I think this discussion -- it may be that the window of opportunity for the ARRA funds has already closed in which case we would not forward this.

DR. TEUTSCH: It seems to me there are two things that you can do. One is, I don't know what is in the funding opportunities. I assume they are already out and they have some applications that are either in or on the way. And these would be to encourage them to fund this type of work that might already being submitted.

Or we take it outside the context of ARRA and say that these are things that need to be done. If they are not under ARRA, that they be done under whatever future auspices there area because there is going to be comparative effectiveness.

DR. WILLIAMS: Yes. My suggestion is that, you know -- I know that Sarah and Darren had been working within the office to determine whether or not there still is the opportunity to-- you are shaking your head no. Do we now know for sure that there are no opportunities there?

MS. CARR: We know definitely that the money has to

be spent allocated by 30th. I did not think, like Steve, that there would be time to do an actual new funding announcement because people, you know, you have to get it out there.

So I was always assuming that there were applications that had come in that we were saying, with any remaining funds, here are the priorities that we think you should target. But it sounds like --

DR. WILLIAMS: What I am saying is that I don't think we know if all of the announcements have actually been written so that is why I thought we were taking a little bit of time today to say that if, in fact, there are still some opportunities to put out funding announcements, here is what the Secretary's Advisory Committee would recommend that we do.

And that was not something that we were able to answer yesterday. What I would say is if they say no, we have written them all. Everything is out, then what this document becomes is the starting place for the bigger discussion in October about how we look at other funding opportunities. But this was really to take advantage of the fact that there might be something available within ARRA that could be got out the door quickly and that is why we were taking time.

DR. TEUTSCH: So we need to couch it somewhat in that term. Dave, did you have other -- but this has been over the question, whether it is worth writing something to her right now about this, given probably our inability to

influence the funding opportunity announcement because that probably is not likely. But whether there are things coming in that we would think should be, if there are things coming in on these topics, that they should be given priority?

DR. WILLIAMS: There could be some prioritization.

DR. TEUTSCH: Prioritization or at least to help set the agenda going forward. I think that is sort of the context with which this needs to be written. Staff can explore whether, by some miracle, that they could still get a funding announcement out this year. But based on my understanding of civics, and watching the government in action, it is almost impossible.

DR. WILLIAMS: My observation of watching the government in action is that there are deadlines and there are deadlines. Almost every deadline relating to the Secretary's discretionary money had been long past before the things were actually happening, so --

DR. TEUTSCH: But we can explore that. We can find that out.

So I guess there are two questions. One, if we were to write to the secretary, are these the right things to write about? And if these are the right things to write about, given the fact that this committee will probably not have a chance to do much review of them, maybe we could identify one or two people to go over it because we would need to get this

out really fast if it is going to have any impact this fiscal year. Do we actually want to send something? I will entertain either. Are these the right things to say?

DR. WILLIAMS: Maybe asking are these not the right things to say?

DR. TEUTSCH: Are these not the right things to say? Do you want to just do a -- how many people on a quick basis think that we should actually try and write to the Secretary about this issue. Take that first. Should. How many people think that we actually should?

(Show of hands)

DR. TEUTSCH: How many people think we should not?

(No response)

DR. TEUTSCH: So if we are going to do so, then do we have -- would anybody -- do you want to take them one at a time and say whether these are the right things? Or take them in the aggregate? What would you like?

DR. WILLIAMS: I am going to take them in the aggregate.

DR. TEUTSCH: Okay. Let's take them in the aggregate. How many people think -- who knows whether there are other things. These three things should be part of what we communicate to her. I am seeing about six hands and some ambivalence.

How many people think these are not the right

things?

(No response)

DR. TEUTSCH: Those are mostly abstentions in that case I guess. Are there other things that you all would like to see put in that letter and if so, what are they? Okay. Janice.

MS. BACH: I just have one comment on that first bullet. I would be interested in lieu of recommending creating a new research center whether we could explore the potential for integrating the genomics component within other existing centers. I don't know how fully that has been explored.

DR. WILLIAMS: Well, I think it is fair to say that we have had no exploration of anything. What we are trying to do is say here are some potential ways that you could chose to use these funds and creation of a center is consistent with what has been done with other ARRA funds. I think it would be intrinsic in creation of a center that there would have to then be collaboration with other centers. But the sense that I have had from what we have sent to the Secretary before, is that the integration, if you will, of genetics and genomics into other centers always seems to get short shrift. That it never really rises up to the point where we can seem to have an impact. That is why we thought it might be the best way to go.

DR. TEUTSCH: Other thoughts?

(No response)

DR. TEUTSCH: Seeing none, I would say we are going to have to work a little bit on the general framing via ARRA and other opportunities and priorities so that it gets the right context because we don't really know what flexibility there will be. But these are important things that we think need to be done with these or other funds.

And then we will tailor these bullet points. I think it would be helpful if we could, because this will be on short turn-around so you all probably will not see it again, but it will be helpful if we have at least a couple of people in addition to Marc and myself who work with staff to get this crafted.

DR. WILLIAMS: I would semi-volunteer David and Sam.

DR. TEUTSCH: David and Sam? That would be great. Anybody else that feels you want to be part of that? Dr. Khoury. Okay.

DR. WILLIAMS: Do I have veto power?

DR. TEUTSCH: No, no, no.

DR. WILLIAMS: I just don't want to see nofig (sic) represented in all this letter.

DR. TEUTSCH: So we will go forward with that and I think it will be fast tracked. We will need to get it out probably within a week or so.

DR. WILLIAMS: Well thanks everybody. This may be a record of sorts for this committee. And we will find out if that is a good thing.

DR. TEUTSCH: So let me ask one last time, are there any public comments? I am unaware of any.

(No response)

Carrier Screening

Issues and Concerns Related to Carrier Screening

DR. TEUTSCH: So hearing no public comments, we will move forward to a topic that we began addressing at our last meeting and we will have the pleasure of hearing again from Rod Howell and his colleague. As you now, Rod chairs the Secretary's Advisory Committee on Heritable Diseases in Newborns and Children, our erstwhile sib.

As you recall in February, Rod said that his committee would be interested in forming a joint taskforce to address issues related to carrier screening. They have had some discussions of this. Whether a taskforce or some other kind of activity is going to be the most appropriate way to move this agenda forward is really what we want to talk about.

So we have asked Rod to come back and talk about what emerged from his committee so we can have a discussion of how we would like to proceed. So Rod, welcome and I gather Sara Copeland is going to be presenting with you. Welcome again.

An Option for Addressing Issues Related to Carrier Screening

by R. Rodney Howell, M.D.

DR. HOWELL: Thank you very much Steve. As you recall, the last time I was here we were hurrying away because the empiric and pending show storm which was the largest of the century and I think we may all die of a heat wave today. So that is an interesting thing.

But I appreciate the opportunity of coming back today. As you remember, I mentioned before that we have been identifying carriers in newborn screening for decades and specifically when we screen for sickle cell disease which has been on the panel for a very long time, we routinely identify carriers. That information is then handled in a variety of ways.

As we have recently added cystic fibrosis, we now routinely identify carriers of cystic fibrosis. So our work in newborn screening has naturally moved us into the area of carrier detection and so forth. Our committee has been working on this a lot and Sara Copeland has been working with a workgroup on carrier screening.

The reason we had spoken to you before is that we thought that there may well be some issues that are of interest to this committee and you might be interested in participating in one of the workgroups. So I will ask Sara Copeland who is the Deputy Director of the Genetic Services

Branch at HRSA to tell you what the committee has been up to. Sara?

Carrier Screening

by Sara Copeland, M.D.

DR. COPELAND: Thank you. It is my pleasure to be presenting to you today. To say that I already have a workgroup formed is kind of ambitious. I would say that we have talked about having a workgroup form. So today's main reason to speak with you is to get your input, get your insight, and help us address how we might go forward with this topic and addressing it.

I want to preface my talk by saying I am here representing the Secretary's Advisory Committee for Heritable Disorders. What they said was something to go forward with. I also want to say that a lot of these slides are taken from previous meetings and so they are not my own original work. I am not trying to take credit for them. They are referenced in the bottom in the notes.

(Slide)

So the objectives today are to review some of the issues related to the carrier screening. Review what we already know, the current status of this carrier project, where we are at, outline a proposed plan of action and get some insight from your committee on a possible joint taskforce or possible other options.

(Slide)

What do we mean by carrier screening? Traditionally this has been detection of asymptomatic people who carry one mutation of an autosomal recessive disorder. We are starting to question whether or not the carriers are truly asymptomatic, but traditionally that is who we are dealing with.

We are looking at not necessarily detection of effected offspring but detecting the risk for having an infected offspring. Carrier screening at this point can be deliberate where we are actually looking for carriers such as some of the prenatal testing for cystic fibrosis, or incidental such as what we find on hemoglobinopathy screening and trait detection.

(Slide)

Some of the examples would be cystic fibrosis screening, sickle cell, Gaucher in Ashkenazi Jewish population, limb girdle muscular dystrophy 2B, Fukuyama muscular dystrophy, et cetera. These are some groups of disorders that have very common founder mutations.

Or we could even look at disorders that are actually autosomal dominant but have very decreased penetrance with high mutation rates. So looking at things like Duchenne muscular dystrophy, neurofibromatosis, or tuberous sclerosis in looking at carrier status there.

(Slide)

Some considerations for carrier screening is that the disorder should impair the health of the affected offspring. It should not be a benign condition. There should be a high frequency of carriers in screened population in order for it to be useful. You should have technical and clinically valid screening methods. They have to be efficacious and there has to be some options of ways to deal with this information. Consent needs to be informed and voluntary and protected.

Here is the big one. Knowledge of benefits and harms is transmitted to the screenee both pre- and post-testing. That is very difficult to do as we all know for any kind of genetic counseling and education

Privacy as we discussed today is very important and needs to be protected. Stigmatization of the carrier by the community is minimized. As we have also mentioned, there is a dearth of genetic professionals out there so, professional resources are another issue.

(Slide)

Perspectives to consider when looking at carrier screening are the public health impact. Are we decreasing the impact of disease on society? Look at the impact on clinical specialties and primary care practices, the burden to the subspecialists as well as to the primary care physicians. How

current screening programs impact carrier screening and how carrier screening would impact current screening programs? Looking at some of the incidental findings we have as part of newborn screening and then also looking at family and individual perspectives, the stakeholder perspective.

(Slide)

So I went through this and I am thinking, who, what why, when, and how. So who do we screen? Do we screen the whole population like we do with newborn screening or do we do high risk population screening, such as Ashkenazi Jewish population or the Old Order Amish populations in Pennsylvania?

Do we do targeted screenings with indications from history? If you know that someone is of a descent that has a founder mutation in a certain gene? Look at the cystic fibrosis as a great example for Caucasians. The carrier frequency is high, so if you know that both sides of the family are from Caucasian background, do you do it then? How do you screen it? Do you do the traditional family history? If there is no family history, then you don't do the screening. Or do you do genetic testing? Can you do it on a blood spot? Or do you maybe look for impacts of decreased protein efficiency in biochemical markers?

(Slide)

When do you do the screening? Do you do it at the newborn timeframe? Do you do it in the childhood timeframe at

the time of other mandatory testing (lead, hemoglobin levels at 12 months of age), at 18 years of age such as they do in Israel in some communities? They do a cheek swab for all seniors in high school. This is technically the age of consent, not necessarily informed consent, but consent.

Prior to, when they are planning a pregnancy or when they are already pregnant?

(Slide)

What is the purpose of the screening? Is it to inform reproductive choices or could it be possible that we are doing carrier screening that may have impact on the health of the parent as well as the infant, such as the urea cycle disorder OTC in female carriers?

(Simultaneous conversations)

DR. COPELAND: --- carriers who end up with acute

(Simultaneous conversations)

DR. COPELAND: --- with acute --- of pregnancy. SC trait and some of the sudden deaths, or Fabry and FX in x-linked conditions, and when there are no other interventions that can avoid the problem, so detection is important prior to onset of symptoms? Or are there other reasons?

We need to weigh the pros and cons of the other reasons as well.

(Slide)

It has come to light with the issue of sickle cell

trait in the recent NCAA rulings that rescreening has become an issue. These, for the most part, athletes at college age have all been screened for hemoglobinopathies and their trait has been determined at some point in time, but it may not have followed them through. So who do we do this on? How do we ensure that it stays with them? Who is responsible for this counseling both at the time of detection as well as when they get older? When should the counseling be done and who should be targeted for re-screening?

(Slide)

Direct-to-consumer testing, I think this might be a very dead horse for this group today. We have talked about it a lot. As you know, there are commercial panels being offered to consumers, but we are concerned as are you, about who is making sure that the testing is done per professional guidelines and that the counseling is done and is adequate. And then keeping the information for reproductive choices.

(Slide)

So if you look in the literature, there have been some previous experiences discussing population-wide carrier screening. Cystic fibrosis prenatal screening, California did a study. In that study, less than 50 percent of OBs even offered the screening to the parents. Of that, 17 percent of couples were offered it. So only 50 percent would even suggest it.

As we introduced cystic fibrosis on newborn screening, this has improved markedly, but it is still not whole population. The panel to screen is also growing and this is going to be an impact throughout all of these disorders because ethnic background makes it very important that you chose the right panel. And there is always the concern about discrepancy between prenatal and newborn screening results. This also brings up the bane of all autosomal recessive disorders, non-paternity and who the dad is and whether or not we can even use the carrier screening effectively.

(Slide)

The Ashkenazi Jewish population has probably the best history in preconceptional screening. They started in 1973 for Tay Sachs with an enzyme methodology and moved to DNA in 1990. As of 2008, they had a recommended panel of nine disorders, but could offer up to 16 disorders because of known founder mutations.

(Slide)

We have had some very negative experiences as well. For sickle cell disease, in the 1970s the Air Force developed a policy for trait carriers and there were some problems with the urea provision. There has also been the stigma related to being a carrier. There is NCAA policy.

And then there has been the negative impact on

detecting carriers that was written up in four journals that addressed the issues of stigmatization, reduced maternal bonding and discrimination, all related to being trait carriers.

(Slide)

There have been three recent, since 2006, big meetings discussing this issue. In 2006, the first one at the bottom was held in the Bronx for Moving Population Genetics from Theory to Practice. In 2008, there was a meeting in Rockville to discuss Population-Based Carrier Screening for Single Gene Disorders. And at the NIH in 2009, there was a Carrier Testing for Spinal Muscular Atrophy Meeting.

(Slide)

So some of the conclusions: The Rockville meeting in 2008, some of the high priorities for what to screen for, when to screen, and getting the criteria developed, is that you need to know the carrier frequency. You need to know the disease burden and the cost as well as rationale for screening. What is it going to impact? How is it going to change what you do?

(Slide)

And then balancing the screening interests of individuals, communities, and societies. The first order, and what we have found with our sickle cell disease projects is you need to engage the communities. The community-based

organizations are huge in this kind of decision making.

You also need to identify the correct gatekeeper. But there are other options. Maybe we could look at other screening models where maybe we just bypassed individual interests such as with seatbelts or helmet laws and just say this is a mandatory screen.

Or maybe we make it standard of care, not necessarily mandated, but everybody should get the cholesterol blood pressure check, et cetera.

(Slide)

Then do we target certain subpopulations and if so, on what basis? So we need to know when we are targeting these issues. Are we targeting subpopulations prior to screening or after screening in order to interpret the results? The community-based organizations, again, are incredibly important. But then there is the problem of identifying the correct community. Ethnicity self-identity are based on scientific markers and subpopulations should be targeted only if population characteristics justify the approach.

(Slide)

How is informed consent defined and obtained? Models for multiple complex tests applied to the general population. So for informed consent, we need to be able to accurately describe what a carrier is and not variant of uncertain significance.

We also need to be able to educate people on levels of uncertainty about the test. The more tests we add the more complex this issue becomes.

(Slide)

So how do we measure the success of carrier screening programs and developing an evidence base? This is another big issue that we have discussed a lot here today. So maybe we could do pre- and post-test education surveys? Assessment of opt-in/opt-out rates, cost per net health benefit measures or qualitative measures of “choice” in carriers and what they determine to do with this information.

(Slide)

In 2006 the meeting in the Bronx determined that they needed standardization of criteria for who to be tested. The need to understand the burden and natural history of each condition which came up again yesterday in the whole genome sequencing. The fundamental questions about the performance of the test and how follow-up results should be considered. Then we need to make sure we can actually read the lab results.

(Slide)

There was consideration at that time in light of the success of the CF carrier screening that this could be applied to spinal muscular atrophy carrier screening in the future. Some considerations for other subpopulations that are known to

have serious genetic conditions with founder mutation effects. So maybe candidates for ethnic specific mutation panels.

They concluded that models for earlier preconception or childhood screening should be undertaken and funded.

(Slide)

They suggested to improve care including providing newborn screening test results for hemoglobinopathy carrier status and that the trait results become part of the health record.

Looking at the mandatory nature of newborn screening can put certain populations at a disadvantage and customized counseling is very important.

There is case law that has set a precedent for antidiscrimination in terms of -- and we also have GINA, but there are some areas that are not clear cut such as the duty to disclose. So if we know that they are a carrier, whether or not we have to disclose this is still to be determined. And we need to get input from professionals and community members.

(Slide)

The NIH meeting this last fall in 2009 on Spinal Muscular Atrophy came up with the recommendation that panethnic carrier screening for SMA is technically feasible and studies for implementing this program raised wider issues to look at the scope and specifics of carrier screening in

general.

The consensus was to effectively address the broader issues, a federal process such as that begun by the SACHDNC will be needed to balance stakeholder interests, values and ethical considerations. So we need an evidence-based or some kind of model for determination.

They recommended that we work with you to pursue carrier screening issues more broadly. Screening should be spelled correctly, but it is not.

(Slide)

So in summary, some work has been done previously by others. Some populations have been very successful with carrier screening. There is no model for population-based carrier screening at this point in time. There are many issues and probably no right answers. Deciding what conditions to be screened and when is difficult at best.

(Slide)

So the plan for this workgroup, I have already taken care of the May presentation. This is the June presentation to discuss with you all. Then next steps if you agree, would be to discuss the options of doing a workgroup, looking at the proposed purview, possible activities, and how best to go about this.

One thing I did want to tell or mention was that I do not see us or any taskforces coming up with a suggested

panel for disorders to be screened, but more guidelines on ways to evaluate the role of carrier screening.

So I am done and I want to take notes on any questions.

Questions and Answers Session

DR. TEUTSCH: So what is the actual recommendation of your committee that be done now?

DR. COPELAND: The recommendations from our committee were that we go forward with forming a workgroup and taskforce in order to further develop carrier screening.

DR. TEUTSCH: Rod? I don't know was Rod here yesterday?

DR. HOWELL: Yes.

DR. TEUTSCH: But Sara was not. So we had actually a very interesting discussion --

DR. COPELAND: I was here for ---

DR. TEUTSCH: -- related to the whole genome sequencing which really talked about what do we need before we do screening in a general population and the need for real outcomes data. So part of the design -- I am not quite sure where we are, but I would be very interested in people's sense of what the evidence base is that needs to be -- is it the fear that whether there is enough here to warrant going forward and if so, what that might look like in terms of what we might really add?

DR. WILLIAMS: Can I get one point of clarification first? What was the upshot, and maybe you said this and I just missed it, but was there a proposal to develop a taskforce from the other Secretary's Committee? So that you have agreed that we are going to form a taskforce?

DR. COPELAND: If we can do it in conjunction with your advisory committee. That was the -- it was to be done in conjunction with this committee.

DR. HOWELL: But we are going to have a workgroup of our committee. And the question is would you all -- Would this group like to participate as a joint effort? Because we clearly are going to go ahead and do some additional work on carrier screening.

DR. WILLIAMS: Right. That was just a clarification. So you are going to do some additional work on it and you think it would be good for us to participate. So really the decision is not do we or do we not, it is do we participate or do we not.

DR. HOWELL: Yes. And then it was felt that it would be helpful to have this committee. Let me elaborate on one thing that Sara mentioned briefly. That is the issue that has come up recently in carrier screening for sickle cell disease. You all might well be aware of that. But to our surprise actually, the NCAA made a recommendation that all level I athletes in the United States be screened for the

carrier state of sickle cell disease. Our committee immediately worked on that because we have been identifying those and we work with a variety of constituent groups and actually ended up sending a letter that was sent this week to the Secretary basically saying that we don't think this is an appropriate thing to do because there is considerable evidence that if you appropriately handle carriers for sickle cell disease and other people alike, you abolish the increased risk that seen as sickle cell disease as far as athletic problems and so forth.

So the bottom line is that we are going to have a workgroup and we are going to work on sickle cell disease. We would invite this group -- other carrier diseases -- but we would invite this group to participate if you would find that reasonable in working together.

DR. EVANS: Steve, could you repeat what you said about your question about evidence?

DR. TEUTSCH: Well, I looked very much at what is here and I think it is a continual challenge with all of these rare disorders to show that there is a real outcome difference, that there is evidence if you will. I think it is an evidentiary question before we start recommending these sorts of things.

DR. EVANS: I am not so sure. I think it is apples and oranges. Correct me if I am wrong, but I mean carrier

screening has a whole different set of utilities associated with it. I am just going to go ahead and say it here, but abortion is a major reason people do carrier screening. And therefore, if that is an option to couples who have positive carrier screening, you now suddenly are removed from all the necessity for showing that clinical utility and knowing about it, et cetera, et cetera. Do you see what I am saying?

I think it is a whole different question and frankly a much easier one. Carrier screening can be of considerable use to couples in guiding their reproductive choices. It is independent of that whole wrath of evidence issues that we have to grapple with in diagnostics.

DR. TEUTSCH: I still think you have to figure out what the outcome is and decide whether the screening actually contributes to helping better outcomes from the patient's perspective. You can argue what the outcome should be.

DR. EVANS: Well yes. But we know what the outcome is.

(Simultaneous conversation)

DR. TEUTSCH: -- do they participate?

DR. EVANS: We know what the outcome is for most carrier screening, I would argue, and that is reproductive decision making. Therefore, I think that the evidence bar is actually much, much lower for carrier screening. Does that make any sense to you guys who know more about carrier

screening than I do?

DR. COPELAND: I was here yesterday for the whole genome sequencing discussion, et cetera. The main difference I can see between this and genome-wide sequencing is that it is for known disorders. And depending on how it is done, if it is done as targeted founder mutation, then you know the impact of that significant mutation. If it is sequencing for all possible mutations then you run into some more problems.

But there is definitely some good evidence for outcomes in effected individuals and then what the parents choose to do. There has been some good research among the Ashkenazi Jewish population, as well as in Taiwan and some of the Eastern Asian countries on beta thal screening and their choices for reproductive decision making with the known carrier frequency and known carrier status for beta thal.

DR. FROSST: I would draw an analogy in this case to the work that Rod's committee has done in the past around newborn screening where what was really lacking was a method to discern what should be on the panel. It was process that the committee put in place in a realm where there was no decision making and no clear way to go forward, public health being very much a state issue.

So we were very involved in the SMA meeting and what comes out is a very similar feel in many ways. That there is data that comes out and research that comes out on the results

of individual carrier screening programs, but no comprehensive method in which to make decisions about which conditions should be screened for in terms of carrier screening.

There is really kind of a gap if you will. The methodology for figuring out kind of where to go may or may not be the same as what is done for newborn screening, but after having sort of become more involved in this issue than I had anticipated, I would be -- there seems to be a need and it did seem like a very good fit and a very worthwhile endeavor.

DR. EVANS: I think it is an extremely worthwhile endeavor. I think we should be involved in it. I think it is really important. I just want to highlight, I think, there are big differences between this and the other things we have been grappling with.

I mean, you know, doing carrier screening for SMA has very different implications than whether diagnosing SMA as a newborn is worthwhile and I would argue that the decisions are much easier in the realm of carrier screening if one accepts a certain -- well that gets into values. But from an evidence base, it is easier.

DR. COPELAND: What is interesting to me is the Ashkenazi Jewish population because they are very much -- they are not proponents of abortion. They have come up -- and I think it was Adam actually, who told me this -- they do the panel and your results come back as “good match” or “bad

match."

DR. EVANS: Absolutely, but I think that is an utterly unrealistic model to apply to the general population. And I think that if you look at at least the thalassemia data that I am aware of, you see a very different use for that information. You know, that use for that information is the law of the land and is, you know, acceptable by most in our society.

DR. KANIS: I just want to clarify. That was actually an Islamic inbred Bedouin population in Israel. It was a match-making --

DR. COPELAND: Actually there is one in New York a well.

DR. TEUTSCH: Dr. Khoury?

DR. KHOURY: Okay so to answer the question whether or not this committee should be involved or help the other committee deal with this, the answer is yes. I mean, I second Jim. Although I do not share Jim's sweeping generalization that this is easier than the other stuff we have been dealing with. Actually, this is much more complicated because of the values issues and the outcomes and what you measure. And we are all carriers for one or more autosomal recessive disease. Where do you draw the line? You know, this is big. This is much more complicated. It is easier for me to think --

DR. EVANS: Okay. Let's say it is very different.

DR. KHOURY: Yes. Very different. It is easier to think about evidence for health outcomes in preventing morbidity and mortality in the person being tested, but when you explode this to everybody in the population who we know are carriers for one or more rare genetic disease, so in aggregate this is big. This is all of us.

DR. EVANS: I stand corrected.

DR. KHOURY: Where do you draw the line? I think we need to engage the other committee with a very fruitful discussion along the lines that you have put out there, including sort of the discussion about outcomes and values. You know, the whole discussion of whole genome sequencing is going to make that a reality whether we like it or not. It is going to happen. So I think we better be involved rather than not being involved.

DR. FROSST: I think on this issue it comes down to, lest I follow on what you say and misinterpret what you say, I am going to just add that from what I have understood in terms of carrier screening, what is wanted is a choice, being given the option. Unlike newborn screening which is very much public health program and done on, you know, kind of babies largely en masse, being given the option of deciding whether you want carrier screening or not is one of the mechanisms for how to input.

DR. TEUTSCH: Barbara?

DR. McGRATH: I would think this would be one of the committee's, like all of them would benefit, but really from consumer input. Members of the disability rights community as well as patient and family advocacy groups would really have an important role.

DR. HOWELL: Our committee has very active consumer input.

DR. COPELAND: And if you guys do decide, I am looking for volunteers for the workgroup.

DR. HOWELL: I think Steve will probably have to work out to see who will do that.

DR. TEUTSCH: Charmaine?

DR. ROYAL: I was just going to endorse what Muin said. I have been part of the sickle cell discussions. NHLBI had a meeting a couple of weeks ago on sickle cell trait. It is very interesting how very little know about sickle cell trait. I mean, we have thought about it as being benign.

The NCAA ruling certainly raises issues about that in terms of athletics but the need for research into what sickle cell trait brings in terms of some of the medical and clinical implications of people with trait that we really don't know a whole lot of information about.

So I think the issue of "trait" is a complex issue and there is not enough knowledge about what "trait" actually means. There are people who are talking about whether sickle

cell trait should be in some cases defined as a disease. Certainly that is taking it a bit far, but some people with trait do have symptoms very similar to people with sickle cell disease. So it is an interesting question I think.

DR. TEUTSCH: Well that is very different from what Jim is talking about which is mostly clear informed reproductive choices. You are talking about clinical significance of the traits themselves.

DR. HOWELL: I will provide Steve with a copy of the letter we sent to the Secretary and you might want to send it to the committee, about sickle cell disease and the carrier screening for sickle cell. It was sent earlier this week.

DR. COPELAND: The work we have done with the trait workgroup is kind of the current all around which we are looking to build this carrier screening group and that implications in that group do discuss the pros and cons of screening, when it should be done, should you be rescreened, how to make sure that your status remains with you so that it does address many of these other issues apart from just the health impact.

DR. DALE: I will just raise the question in talking about carriers, you are usually talking about recessive disorders right? But there is this whole range of mosaicism and dominant disorders where the disease is inherited but you do not necessarily detect it. Are you interested in those

more subtle areas of genetics?

DR. COPELAND: Personally yes. But I think that would be beyond the purview of this workgroup at this point in time.

DR. HOWELL: Let me point out that if you do a carrier screening program let's say for Gaucher disease, let's use that, you will detect persons who are affected with the disease who do not yet manifest the condition. That is also an issue that you will be dealing with. In other words, when you would do a carrier screen, you will pick up a carrier, but the person might well be affected. It is an extremely interesting area. The more you think about it, you find all these little interesting subsets.

DR. TEUTSCH: So we have an invitation in front of us. Clearly -- yes. Let's RSVP. I am hearing general interest that there is enough meat here that we should have some engagement. So maybe the focal point of our discussion should be what that engagement should be. And I think realizing what is on our plate and what our priority list was, we could take this on and still say we will -- you know be equal partners. We can also have members participate, bring it back, inform or other variants of that.

DR. WILLIAMS: It seems to me that it does not make a tremendous amount of sense to try and do a two-headed leadership of this. Clearly this is something that the other

committee is going to be taking on whether or not we participate.

It seems more appropriate that we do participate and select some representatives from our group to participate as part of this group with reporting back, but not that we somehow try and create a co-leadership type of -- we may have to adjudicate how the final product will be moved forward and whether both committees would have input on it. I would think that that would be desirable, but I don't know that we necessarily have to work out all the details today.

DR. TEUTSCH: That is right and that is consistent with how we have worked with other groups in the past. Jim?

DR. EVANS: I just was going to say why don't we ask specifically how would you like us to be? I mean, what would be most useful?

DR. HOWELL: It would be helpful to have a group from this committee since I sense a considerable interest in it, a group of persons who would be interested in participating in an ongoing workgroup. So I think that Steve and you should decide who that would be and we will work on that and then we can coordinate how that will come together and how that will actually function.

DR. TEUTSCH: I have got to say, I like the idea that Marc sort of endorsed. That we identify a small group of people who would work with you under the leadership of your

committee and, you know, as all of this evolves, can bring back the nature of the work and we can, you know, make recommendations, other kinds of things that might be appropriate for us to review as we see what emerges. Muin?

DR. HOWELL: Phyllis was very articulate in summing up some of the issues that came out of the SMA meeting about gaps that really have not been systematically looked at and I think it can be very helpful.

DR. TEUTSCH: Was that the report of a workgroup or was that an NIH kind of position on all of this?

DR. FROSST: No it is very much the result of a multi-stakeholder workgroup that we held. We are actually just about to submit our publication on it. So stay tuned. And it was a great meeting. A lot of people who had a lot of differ opinions sort of weighed in and then the question was wow, it would be a shame to have to do this for every condition that comes up for being included in a screening panel.

DR. TEUTSCH: Including research needs again.

DR. KHOURY: So this is a general comment and Rod maybe the one to comment on it. I know we have two advisory committees with two different mandates. You know, this one is more genetic health and society and the other one is more focused on heritable diseases of newborns and children.

But increasingly, and we have a few examples like

residual newborn bloodspots and other areas, I think that, you know, with the evolving of the technology the two committees will have a lot of joint endeavors and maybe similar things to look at. Sometimes the interest may originate from one committee or the other, but invariably we are going to have to find ourselves in a situation where we are increasingly working with the other group and vice versa.

So I think we can explore this as a model for how to go about doing this. I don't like the two-headed beast leadership model. Depending on where the issue originates, maybe that committee can lead the effort and then you could have representatives from the other committee. But I think it is unavoidable that the two committees will increasingly converge over time in their efforts and what they look at.

DR. HOWELL: I think Muin is absolutely correct. For example, one of the things that is already being discussed in the newborn screening community is genome biosequencing. I am sure that doesn't surprise you. Obviously, that is an area that we would certainly need leadership from this group.

DR. TEUTSCH: And that is certainly reasonable to talk about which group might be the leader depending on what the topic is. So let me ask a question since I clearly sense that people want to be engaged in all of this. Is the model where we identify some committee members to work with Rod's advisory committee on a workgroup, taskforce, whatever is

finally constructed based on this, the model that we would like to go forward with?

DR. TEUTSCH: More Muin?

DR. KHOURY: Just one minor clarification. So if that happens and some of us work with other committees, you know, what comes next? So you bring back the results of the discussion. I mean, do we have to weigh in? Do we have to bless what the other group says or what? Are we just passive observers? Will this be a joint effort? I know this other group will be the lead in this, but we have to kind of walk this a couple of steps down the road in terms of what will be outcomes and will it come to this whole group for a vote as to what the final report would look like?

DR. TEUTSCH: I think it depends on what finally emerges. I mean obviously Rod's committee can make recommendations independently. If they are asking for joint recommendations that come back here, then we would need to vet those and vote on those.

DR. HOWELL: Certainly the persons from this committee should be active participants. They certainly should not be observers. That would not be what we would be thinking about, but obviously if it were a joint recommendation then it would obviously have to be approved by both committees.

DR. TEUTSCH: But in the meanwhile, I think our

representatives would be working, as Rod says, closely and actively, and as issues arise that need to be brought back either on a, you know, an interim basis or finally, those are things that can be done. You know, I think what we are seeing, even with the residual dry bloodspots which we will get to next, they have been soliciting comments directly from us, which we very much appreciate. But we are in an advisory capacity to them, not in an approval capacity. So I think all of that needs to be worked out as we go forward, depending on the nature of the recommendations.

DR. HOWELL: To go back to Phyllis' comments again. She will probably throw me out if I keep talking about them, but this SMA conference was extremely interesting and very rich as far as text. We had one group, we had one foundation that was established exclusively to support carrier screening for SMA. We had another large foundation that did not support that at all.

So in the final analysis, this docket note that she and Jonathan have been working on at great length was reviewed and if you agreed with it, you signed on. If you didn't, you didn't. So that has been going on for quite a long time. But I think it has been a very successful effort.

DR. FROSST: Yes. There is stuff they did not teach you in grad school.

(Laughter)

DR. TEUTSCH: All right. The sense as to whether what we have outlined here is a reasonable way to go forward? And if so, let's identify the individuals who would like to perform that function on that taskforce or workgroup.

DR. EVANS: Can I ask what it would entail? I mean I assume it wouldn't mean going to the meetings in person.

DR. TEUTSCH: Rod, I don't know how much you know about how our taskforces work, but they do meet offline, by phone and, I guess, occasionally in person. We would expect whoever -- so that is how we work. But you might want to explain how you all go about your business.

DR. HOWELL: I could visualize there might be a time when the group might want to get together, but I don't visualize repeated meetings and so forth. Our group, our committee, like yours, always meets in the Metropolitan DC area. But I would visualize, and again, Sara who is as you already know, this group would be convening and getting things to work.

DR. TEUTSCH: But the taskforce members don't necessarily come to your overall committee meetings. Right?

DR. HOWELL: They do not, although they are always welcome.

DR. TEUTSCH: Sure. They are open meetings like ours so the people are welcome. I know this is probably not fair, but do you have a rough timeline for how you see this

proceeding?

DR. HOWELL: Eww.

(Laughter)

DR. TEUTSCH: Well starting. It sounds like you have already begun.

DR. HOWELL: I would visualize that we would really try to get the group convened really relatively soon. This is a tough time of the year and I think it would just have to be a practical issue that we would get started as soon as practical.

DR. TEUTSCH: So then are we talking about a sort of a year, two years? Do you have any --?

DR. HOWELL: It is hard to say.

DR. TEUTSCH: I mean, it is the question that I always get asked and I cannot answer. Is it going to be a letter, a report, recommendations, you know, major research endeavor? I guess all that is to be worked out.

DR. HOWELL: Yes.

(Laughter)

DR. TEUTSCH: That is usually what I say too, yes. All right, so understanding those parameters and some of that is to be solidified, who is interested in working on that as a, we will call it a liaison right now, but presumably will be part of the workgroup or taskforce as they get formed? I see Adam, Charmaine, Jim. Okay Janice if we need more. But I

think that is a great group because we have people who bring a different perspective.

DR. HOWELL: And Phyllis just raised her hand.

DR. TEUTSCH: Phyllis just raised her hand. Good.

DR. FROSST: You are in so much trouble Rod. My goodness.

(Laughter)

DR. TEUTSCH: Be careful what you ask for, you may get it. Okay. Well that is great. So I think we have a way to move forward. We have clearly a lot of issues here that need to be flushed out and we will follow with interest how this goes and look forward to getting some interim reports. So we will hold some of these folk's feet to the fire to make sure they report back to us on progress.

I think we actually have a little time. Rod, do you want to get started on the residual dried drop bloodspot? I don't know where we are. Is lunch ready Allison? Do they have the lunch out there yet?

We had a break and you are all okay with that?

DR. FROSST: I would say unfortunately that there are people who follow online or who show up for specific sessions. And I know that committee business is committee business and in that case --

DR. TEUTSCH: We can start, be we are still going to wait until 12:45 because I know we are going to lose people on

the other end. It is not set up yet?

All right. Tell you what, why don't we go ahead at least with -- Adam, are you prepared? Rod do you want to introduce the session and we will ask Adam to do that and then we will continue after lunch with --

Retention and Use of Residual Dried Bloodspot Specimens

After Newborn Screening

DR. HOWELL: We are very pleased to have this committee's input on the dried bloodspot issue and Adam is going to address the IOM meeting on the subject. He is going to start off.

DR. TEUTSCH: Janice, do you want to say a few words because I know you have been busy preparing some responses which people have in front of them. So why don't you introduce this.

MS. BACH: Okay. Actually, I was just going to introduce the overall session. Thank you, Steve.

At the February meeting, our committee decided to form a steering group to comment on the Secretary's Advisory Committee on Heritable Disorders in Newborns and Children's draft briefing paper on retention and use of residual dried bloodspot specimens.

You have that full paper under tab nine. The report is now out for public comment and before I go over the steering group comments and recommendations regarding the

briefing paper, we wanted to introduce our first two speakers who are going to provide us with the background on issues facing the states and the nation regarding residual dried bloodspot specimens.

So Dr. Adam Berger is Project Director of the Board on Health Sciences Policy, Institute of Medicine and he is going to tell us about a recent IOM workshop that explored the challenges and opportunities in using newborn screening samples for translational research.

Then we will hear, after that from Dr. R. Rodney Howell who, as you know, is Chair of the Secretary's Advisory Committee on Heritable Disorders on Newborns and Children, and, as has already been alluded to in February, he provided us with an overview of the draft briefing paper and today will give us an update on the current revised version.

Okay. Dr. Berger.

Challenges and Opportunities in Using

Newborn Screening Samples for Translational Research

by Adam Berger, Ph.D.

DR. BERGER: Thank you very much for inviting me here today. My name is Adam Berger. I am actually the Project Director for the Roundtable on Translating Genomic-Based Research for Health from the Institute of Medicine, as Janice just alluded to.

What I am here to talk to you about today is a

recent workshop we put on specifically on challenges and opportunities of using newborn screening samples for translational research.

Since I was asked to switch positions today, I scrambled last night and put together a little bit of background for you.

(Slide)

Newborn Screening Programs are actually state mandated and run public health services which identify children who are born with serious or life-threatening disorders, as you are well aware. The goal of the program is to detect and provide treatment for children who typically appear normal at birth, but have an inherent disorder which will lead to disability of death without intervention.

Currently, over four million infants a year are screened using what is, as of last month, now a recommended uniform panel of 30 separate disorders. So congratulations to Rod and the SACHDNC for getting that updated, though specific testing in this regard is actually determined on a state by state basis. Screening is performed on blood samples and here you can actually see an infant's heel prick going on. The collection sample is for dried bloodspots being collected in this case.

In order to assure the specimens can be reevaluated, based on initial screening results, excess blood sample is

actually collected. Now since the collection is state mandated, they are managed by legislation. It is not -- informed consent is not routinely obtained. Legal challenges, notably two highly publicized lawsuits which have come up in Minnesota and Texas, and I believe Rod will allude to these later on in the afternoon, have really recently shed light on the utilization of these samples for alternative purposes, other than that which the donors are made aware.

Although in this case, the Minnesota case was summarily dismissed, the ruling in Texas resulted in 5.5 million dried bloodspots being destroyed. The lawsuits such as these highlight some of the concerns surrounding newborn screening, autonomy, confidentiality, privacy, informed consent, consent to future use of samples originally taken for a different purpose. As newborn screening expands, it will only become more significant.

With this in mind, the Institute of Medicine put together this workshop on the challenges and opportunities in using these samples for translational research, as I just said. What we did was we ensured that the workshop would be done synergistically with the SACHDNC by speaking to Rod and Michele specifically about this. We designed it to coincide with the public comment period for that report that Rod will talk about this afternoon.

(Slide)

So the workshop goals were to ensure that various stakeholders were identified and their views and interests were heard. In this case, we wanted to promote an open and honest discussion where everyone could basically come together and potentially find a common ground.

Now just a quick disclaimer in this case, the presented information that we are going through and the remainder of the talk comes from the statements and opinions of those participating in the workshop itself and should not be construed as reflecting any kind of group consensus from the Roundtable or the IOM.

(Slide)

So the focal questions of the actual workshop were what are the benefits of making newborn screening samples available for research? How do we protect the privacy and rights of the individuals if we allow samples to be used for such? How do we make it basically the norm so the research can progress without actually compromising the main function of the newborn screening program itself?

(Slide)

So we designed the workshop to sort of go back through and look at the status of the states in terms of the policies they have on the books as well as the rationale for storing, the opportunities that could be gained by using these samples for research, as well as the challenges and the value

versus the cost to the program itself.

(Slide)

So as I said, we really looked at the state practices and policies and I know Rod will go into that in a little more detail.

(Slide)

As of May 2010, what we found was that basically 18 states have legislation that could easily be identified if you go through the state laws. Their policies vary based on storage and retention, access, allowance of secondary uses, and even whether parental education materials are provided.

Now the individual states are storing these samples not only for use in newborn screening but also for secondary uses as well. Really the rationale for storing is that currently you can analyze 162 different analytes, development of new tests. They can be used for public health surveillance. They reflect fetal exposures. They are also a source of DNA. They can be used for retrospective studies, even unexpected uses and discovery.

(Slide)

I think the real question is why are they being stored? I think Ken Pass but it best, they are irreplaceable and they sure beat daily wet diapers by the hundreds.

(Slide)

So with this rationale for storage in mind, what

were the research opportunities? We really looked at this from a continuum from service to research, really looking at examination of research for public health benefit that ultimately can feed back to further a uniform (sic) screening process.

In addition, we looked at the broader research implications as well as that of looking at dataset linkage.

(Slide)

So what we found is that there are a number of several uses and I am going to pick one out to explore a little bit more in detail. But to give you an idea of what came out during the actual talks, there is an epidemiological/ public health benefit. Specifically we discussed disease prevalence or susceptibility. In this case, HIV seroprevalence was brought up as a specific example. Global health, research in developing countries, case control studies, birth cohort studies, and even longitudinal studies to be used with these samples.

Another major impetus for using them for research is expanding the screening process itself. Here was saw things such as pilot screening which helped SCID to the panel and we see similar testing going on for Krabbe disease.

Data linkage I wanted to go ahead and pull out a little bit and I wanted to thank David Hunt yesterday for setting this up with his talk on HITECH because it really is

looking at a program that is trying to create a virtual health profile which would integrate much of the siloed databases that are out there. And it is being done in a way that would help provide protection for privacy as well as take into account legal, regulatory and technology issues.

(Slide)

So if we take a look at this and this is -- I guess it did not like any of the words apparently from this screen. But if we look at this from different aspects, it is basically taking all these different parts where we have immunization and child health, we have the national level, we have the local levels from the city feeding it to the state health departments, we have RHIOs out here. Managed care clinics, physicians offices, as well as hospitals, nursing homes, and whatnot, all feeding in to what will eventually become, at least it is hoped it will become a patient centric database.

(Slide)

The whole purpose of this is to move away from the current application which is going on. In this case, having each of these as individual databases which are only readable from one station into something that is much more workable and accessible by individuals.

And so all this feeds into a view where you would have restricted access and privacy restrictions in place to ensure that the data is accessed properly.

(Slide)

Now the benefits of this that were highlighted were that they would allow better coordination of care and treatment, as well as having meaningful health information exchange between clinicians and the public health departments. One of the other benefits is that you could create a standardization for the data and diagnostic criteria that would be involved.

One of the other benefits of this is that it is basically moveable within the state. This is just a model of something that came up which, you know, potentially could be useful in looking at other locales or even on the national level.

(Slide)

With all these potential benefits, it is still necessary to weigh the value that this provides with the cost to the actual system itself. I think Alan Fleischmann* put it best when he said the samples are actually collected for newborn screening purposes and all other uses are secondary to that.

(Slide)

So we really looked at the challenges and the value that this would add and specifically looking at the core mission of newborn screening. How do you retain that? We looked at parental concerns and expectations were brought up,

informed consent and responsible stewardship of samples, legal issues that were involved and, as I said, the value versus the cost.

And so essentially what came out of this, I think from the discussion, was what is somewhat of a way forward? What are the issues that need to be resolved in order to allow research to proceed while still maintaining and protecting the valuable service that is newborn screening.

(Slide)

And so there were clear issues that the participants indicated needed to be resolved. And, as we heard Bin Chen briefly discuss this yesterday, education was one of the primary ones that we heard. Funding was another issue and consent, transparency and trust, stewardship and accountability as well policies, laws and regulations.

So if we explore these a little bit more in terms of what we have actually developed, much of the discussion centered on how there was a general lack of a public knowledge about the newborn screening program itself, let alone the alternative uses for samples for dried bloodspot samples.

(Slide)

In this case what was espoused was the idea of saying there needed to be some type of public outreach to inform and more of a constant outreach to keep informing about newborn screening, as well as the other use.

In addition to this, we heard there was a call for informing even about the public health infrastructure including the databases that are collected and the information that is stored in these systems. They seem to be fairly related.

In addition to patient education, it is also necessary to educate providers of -- the providers themselves. Then something else that was somewhat novel in the workshop with letting parents know the risk of destroying samples, that if you opt to destroy samples today, they will not be available for your family our your child 18 years from now if they are needed.

Now all this comes down to the question, and this was also brought up quite well was where is the financial resource going to come from to provide this education and the answer at that point in the workshop was that they are currently not available.

(Slide)

This leads right into one of the second points that I think came out well in the workshop which was funding. This is also actually from a different context, but in this case it is something from the state program perspective and how there is actually a lack of the needed resources to further the program. Currently they have a minimal amount of funding that would allow them to complete their mission and that there is

actually concern that there would not be enough staff or funding to respond to new added regulations that would be put on.

It turns out many states are looking at destroying samples due to financial constraints and this is leading to basically an inability to store samples long term. So this is also something that was discussed.

(Slide)

Now as we heard from Charmaine Royal this morning about patients not fully understanding the consent process with information that was presented during that time or even remembering that they went through the consent process. This was also an issue that was brought up in the IOM workshop, specifically from a number of different viewpoints. One of them was that there was concern from the public health perspective that if there was mandated language being adopted that it would actually hamper the ability of the programs to function.

Another issue with consent, and we heard this also from Charmaine's nice talk this morning, was different ways of obtaining consent and how do we make it more adaptive and manageable by the consentee. We heard from a number of participants that there are ways being developed to make what they are calling "dynamic handshakes" in which case the consentee would be able to change consent depending on

information that they developed over time, so making it a more adaptive consent process.

Lastly, there was also concern in trying to apply a single standard across projects that they may not be applicable to all and therefore there should be somewhat of a project-specific approval, consent and review process in this case.

(Slide)

Transparency and trust was also a major issue brought up by the participants. Specifically, this centered around allowing access to their own data, allowing patients to be able to go in and see what is being produced from this. Integrating participants into the process itself, into the decision making processes and helping it build the trust in this case that would be needed to ensure the participants that their resources are being used properly and in accordance with their wishes.

Lastly one of the ideas that was espoused was building relationships proactively rather than in response to an adverse event.

(Slide)

This leads somewhat into stewardship because part of the building of that trust is involving the community in the decision-making process. A number of times this was developed with the idea of having participants have input in the

oversight of their own samples. Looking at the composition of the oversight committees themselves and the IRB committees that go ahead and review the research proposals that come through, and making them more reflective of the communities from which the samples are obtained.

There was also a question about ownership and I will leave some of the legal wrangling to those who are better suited in the audience, but the question about ownership was brought up and what constitutes fair use. I think the analogy that was brought up during the workshop was I may own my keys or I may own my car, but I don't have the right to throw those keys at somebody or try to run somebody over with my car. Just because I own something doesn't mean I can use it in any way I feel. So I think that was also a point that was fairly made. So I think that also needed to be defined.

There is also once again the project-specific approval in terms of the stewardship and accountability going through the IRB approval process, making them specific for projects.

Accountability was also one of the things that was espoused at the workshop and this is really crafting data and sample access agreements which hold the signer accountable for inappropriate handling of information, making there be some type of repercussions for failing to uphold the agreement that they originally contracted with.

Also with ongoing follow up, how samples were used, who has had access to the samples and why, as well as the outcome of the project itself, relating some of this information back to either participants or to proper authorities so that there can be continued follow up on the project itself once it has been approved.

(Slide)

Then lastly, is something that was really focused on during the workshop was how do you prioritize the different use of samples? These are finite resources and they cannot be used up on just anything, so how do you prioritize research when one, you don't know what the research is going to come up with and two, you don't know what the future will hold for development of new tests or new possibilities.

There is also the prioritization of leaving some of this finite resource intact for the process of newborn screening or allowing the patient to be able to go back and access their sample later on in life if needed.

(Slide)

Then lastly as I mentioned, with policies, laws and regulations, there are questions about the adequacy of HIPAA in regards to this, as well as the question around the idea of developing policies around law enforcement, as well as return of results and we heard some of that today with return of results already.

(Slide)

So with that I would just like to thank you very much. I would be happy to take any questions if anyone has any.

Questions and Answers Session

DR. TEUTSCH: I think probably is worthwhile at to ask some direct questions for Adam. We will have a chance for more discussion later but this is probably worth doing.

DR. CAROME: On your slide under consent, your first bullet point was the mandated language of consent may hamper program function. Could you explain a little bit more what that means?

DR. BERGER: Yes. Essentially what they -- some of the public health, well some of the participants from the audience had basically questions whether or not if there was going to be mandated language being sent down from legislation. If they would actually mandate a specific type of language, it may hamper their ability to function within their current programming.

It was really a question of -- it really would be question of what the language actually said and there was some concern on the public health department side that if there was a mandate for a specific language, that it would be inhibitory.

DR. CAROME: Are you talking about just consent to

do the newborn screening or consent for secondary research uses?

DR. BERGER: In this case, it would be consent for secondary purposes.

DR. TEUTSCH: Paul and then David.

DR. WISE: Thank you. This is very articulate, diplomatic, and balanced. We could take some lessons.

(Laughter)

DR. WISE: My question is where were the real controversies in this process and which of these bullets makes you least happy about the way that you are, in a sense, forced to convey what came out of the group's deliberations?

DR. BERGER: Let me put a disclaimer at the moment, since I am representing the IOM and we are -- the Roundtable actually acts under non-FACA so I will change my hat to my own personal view, if that is okay, just to make sure I lay that out that it is not actually consensus coming out from the IOM. This will be my own personal mandate.

So in terms of what I think are some of the most important sides of this, trust was a major issue. And I think this is really what it came down to. We heard from quite a number of people. Twila Brace actually got up and spoke at this workshop during some of the open discussion times. Coming from Minnesota and relating to the Bearder cases versus Minnesota, which was summarily dismissed.

Then in relation to that, it was really a question of how the public health department had really kind of knocked down the trust from her point of view, so far down that they really don't trust even going back to the public health department to try to work with them.

So I think from my own point of view, I think building trust is probably the most important issue with addressing newborn screening and the use of samples. Trust in this case is going to have to go into making sure people understand what it is they are getting in to.

We heard from Kelly Edwards who said that coming from the University of Washington that in this case Washington is collecting their consent and then going back and re-consenting for use if they use them for research down the line.

So it is really getting around to the question of how do you make people trust in the process itself enough to say okay we can't guarantee that there is security and there is adequacy of security for your information, it is just an impossibility to guarantee, but if you trust us enough, we have done a very good job so far and if you keep trusting us, we will continue doing that job.

I think some of the viewpoints that were put out during the workshop were surprise that people really put up so much information freely on their own on things like facebook

and the internet, yet when it comes to stuff like this, they are very apt to say no, we are not going to go ahead and do this.

So there are some of those surprises going on and I think trust is probably the one that I think is probably the biggest stumbling block to get past.

And whether this is related to the whole public service announcement, I think if you follow some of the news stories that are still going on in Texas as well as over in England now, there is still, I think, a lot of negative press. I think negative press is, you know, not free but it is free to get negative press. It is hard to get positive press without funds.

So how do you make some type of a public service announcement that is going to continually inform the public that there is this great system out there, newborn screening, that is going on and if you allow us to use these samples for other purposes we will be able to have a better impact on public health later on.

DR. TEUTSCH: David.

DR. DALE: I was going to, in a sense, extend Paul's question about the roundtable. Who was around the table or who was not there in terms of what sort of a consensus does this represent?

DR. BERGER: As I said, going back, putting on my

hat again as a representative of the IOM. The roundtable basically brings together people from academia, government, industry, public, around a table to basically discuss issues around, in this case, translating genomic-based research for health. Because we were actually formed, we operate under non-FACA rules. We actually can't make a consensus recommendation out of the roundtable.

What we can do is highlight issues and bring in people to discuss these important topics and those people when they participate are able to make their own recommendations. That is actually what I was reflecting in today's talk, what people in the workshop actually went ahead and sometimes recommended or not.

As I said, talking from the IOM perspective of where I am, I don't like to even use the word recommendations just for that purpose, but speakers from the workshop are able to get up and make recommendations, as they did at this workshop as well.

I tried to reflect that somewhat in the latter half of the talk, namely the issues that came up, consent, funding, education, policies, stewardship and accountability, and trust and transparency. Those are really where the consensus comes out if by the participants in the workshop.

DR. TEUTSCH: Other comments? All right. Why don't we break here and only take three-quarters of an hour for

lunch. That will bring us to about 12:45 p.m.

(Whereupon logistical matters around lunch were discussed.)

DR. TEUTSCH: So Adam, thank you very much.

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

(12:46 p.m.)

DR. TEUTSCH: So we are going to continue with the discussion that Adam began this morning on the draft report on The Retention and Use of Residual Dried Bloodspots and Janice has been facilitating our comments in response to those recommendations. I will turn it over to her to give everyone an update.

Committee Report on the Retention and Use of Residual Dried Bloodspot Specimens

MS. BACH: Thank you Steve. First we wanted to go ahead and hear from Dr. Howell.

Overview of the SACGHS Draft Briefing Paper

by R. Rodney Howell, M.D.

DR. HOWELL: I will try to be mercifully brief. Our committee has been working on the retention and use of residual dried bloodspots for some time. I would like to go through a few comments that can set the stage for this whole thing.

(Slide)

The committee which I chair we have discussed a good bit today is a legislatively mandated committee. It was originally mandated under Healthy Children in 2000 and it was then reinstituted under Newborn Screening Saves Lives Act of 2008. I will spend a little bit of time on that because some

of the things about the law that established the committee, the new law that was signed into law in 2008, brought up some of the issues that we are going to discuss. It fundamentally amends the public health act to assist the newborn screening program, to establish grant programs, and reauthorize a variety of programs.

(Slide)

There are a variety of very interesting things. The bill requires the Secretary of HHS to ensure the quality of the laboratory, to develop a national contingency plan for newborn screening. It gives the NIH oversight responsibility for newborn screening specifically, and names the research program with the NIH the Hunter Kelly Newborn Screening Program after one of the major advocates for newborn screening.

(Slide)

It basically reauthorized the committee that I mentioned and established an interagency coordinating committee, et cetera, et cetera.

(Slide)

Now this bill, interestingly enough, that reauthorized the committee and it was signed as Newborn Screening Saves Lives Act of 2008, was originally drafted by Senator Hillary Clinton when she was obviously in the Senate. As she left the Senate, the bill that was actually introduced

and passed into law was under the leadership of Senator Dodd.

The bill had, interestingly enough, extremely wide bipartisan support, almost unheard of, but it did, and it was passed by unanimous consent by both the house and the senate and it was just at the end of that bill. It went to the White House just in the last few months of President Bush.

Interestingly enough, within this bill there is a good bit of discussion about newborn screening, spots, et cetera, et cetera. One of the comments that was issued at that time is quoted here:

> "President Bush last week signed into law a bill which will see the federal government begin to screen the DNA of all newborn babies in the U.S. within six months, a move critics described as the first step towards the establishment of a national DNA database."

That sort of commentary has been behind many of the issues that have come up about dried bloodspots.

(Slide)

There have been a handful of folks, particularly in Minnesota and they spent a good bit of time in Texas, that have been focused on the potential harm that might come from the dried bloodspots.

An extremely widely publicized case was settled by the Texas Department of Health Services and the Texas A&M

Health Science Center. They settled a lawsuit that was brought by a couple of families in Texas who contended that DNA was stored on their babies without their information indefinitely for undisclosed future uses.

The suit charged that the storage and future research was a violation of the Fourth Amendment right against unlawful search and seizure. Under the agreement that the state developed in settling this lawsuit, they destroyed 5.3 million DNA samples, dried bloodspots, that were stored within Texas.

(Slide)

Now that was a controversial lawsuit, et cetera, and when the lawsuit was settled, Dr. Nancy Dickey who is President of Texas A&M University issued the following statement:

> "The Texas A&M Health Science Center is glad that we have reached an agreement to settle lawsuit. We are saddened, however, that a superb database has been lost. This database could have continued to shed light on the causes of congenital birth defects and potentially led to preventive measures saving thousands of infants and their families the distress these defects cause."

Now, I simply give that background to point out that

this has been a fairly visible question in recent months and in the past year and there are polar opposites in some of the comments that have come about the dried bloodspots.

(Slide)

Now the status of the residual dried bloodspot storage in the United States is shown on this slide. As you can see, you can see some states save the samples for just a little while, a month, six weeks, three months, et cetera. And there is a long, long line and then you get over to the right of the slide and you will see that there are a group of states on the right of the slide that keep the samples for a long time and a considerable number that at the current time keeps them indefinitely.

Now I might point out that the folks on the right is where most of the babies are, so at the current time 54 percent of the newborn population is stored for more than 18 years because as you will notice, if you read along the bottom, the big states are over on the right by and large. 46 percent have them stored for less than three years.

(Slide)

Over the recent years, there have been a variety of articles and guidelines that have been published. One that was published by a group from the newborn screening community in 1996 published guidelines for the retention, storage and use of residual dried bloodspots.

(Slide)

More recently, another paper was published that has policies and controversies about storing dried bloodspots.

(Slide)

One of the best known repositories in the world is that that is in Denmark. Many of you are aware of that. But the Danish Biobank was officially established in 1993, although it has samples that go back into the 1980s. It has been under the leadership of Dr. Bent Pedersen who is shown here at the Statens Serum Institute in Copenhagen. They have millions of samples that go back for a very long time.

That bank operates with very strict criteria that actually are part of the law in Denmark.

(Slide)

The American Academy of Pediatrics task force issued a policy statement about dried bloodspots in 2000. They recommended that you develop policies for unlinked or linked residual samples, organize collaborative efforts to develop standards for storage, and consider creating a population-based specimen resource.

(Slide)

The APHL also issued policies about residual dried bloodspots.

(Slide)

As did the American College of Medical Genetics in

2009. The ACMG statement has one interesting comment and that is that if a parent lives in a state that discards a sample, those parents should have an opportunity of retaining that spot indefinitely for reasons that the family may have and so forth.

So for those who are interested, we have a great deal of information about how the residual dried bloodspots have been used in the various and sundry states.

(Slide)

Now the advisory committee has recognized that developing some guidelines about storage of dried bloodspots is very important. We have gone through the following process. The staff of the committee prepared a draft outline. Our committee approved the outline, and recommended working groups as you can see to validate current storage lines, literature review, draft recommendations.

We then had a draft that was approved and we had informal comments. By informal comments, it was really circulated among some of the federal agencies and various public health organizations, et cetera for comments.

(Slide)

We had three webinars on this particular area. It was designed, obviously to provide newborn screening stakeholder communities with information about the subject and also have input into the "White Paper," a draft of which you

have before you.

We had three major participants. We had the Genetic Alliance, we had the Regional Collaborative for Genetic Services which is an organization under HRSA that networks the state newborn screening laboratories, and we have the Association of Public Health Laboratories. There were substantial participants, in all up to 220 with the APHL.

(Slide)

The comments that we requested were in three types. We had technical questions, educational and policy.

(Slide)

The technical questions that we wanted input on, what is the temperature of the biobank? What sorts of things should you be aiming for? What should be done with unsatisfactory specimens? A small portion of all the samples that come in are unsatisfactory. The other question is prenatal providers, educational material, et cetera.

(Slide)

The public education is that, and we had comments that said will you discuss the possibility that more parents will opt-out due to fear of research on their child's DNA? One of the things in examining informed consent for storage of the dried bloodspots, one of the things you certainly don't want to have happen is for families to opt-out of newborn screening. There is in all states the opportunity to opt out,

but really no informed family would opt out of newborn screening for such critical things as MCAD, PKU, et cetera.

Do you have support from prenatal providers about improving educational material? Educational material is a consistent issue that comes up. According to the recommendations, the states need to be more proactive in prenatal NBS education. It would be helpful if we would make similar recommendations to professional organizations.

(Slide)

The policy is that any of the states that don't keep bloodspots, are they thinking of changing their policies for longer times? Some of them -- there are many reasons states don't keep their samples. Adam talked about economic, but the other thing is that it also gets you out of legal arguments about the spots and so some states would rather just not deal there. Are you aware of any state that uses a Scientific Advisory Committee in addition to the IRB? Would you comment about the added cost that comes from requiring the expanded collection staff and the retention of dried bloodspots?

(Slide)

Now the other questions that came in. Do these policies address the issues pertaining to de-identification of stored samples? What type of policy and recommendations can you speculate are needed if DNA sequencing of the entire newborn genome is incorporated in the screening panel in the

future? We have already mentioned that briefly.

Is there potential for a recommendation regarding what researchers can do regarding anonymous findings that might be of interest to the newborn?

(Slide)

The committee in the document that you have before you has a series of recommendations that I will go through. The first recommendation is that all newborn screening programs should have a policy in place that has been reviewed by the state attorney general or other appropriate legal authority addressing the disposition of dried blood specimens remaining after newborn screening.

Policymakers should consider that value of the specimen as a promising resource for research, the importance of protecting the privacy and confidentiality, and the necessity of ensuring the public's trust.

In discussing the whole issue of dried bloodspots with the public, the recurring issue is the fact that so many people don't know the spots have been stored and later discover that something had been done. I might point out, very few things have been done on dried bloodspots that we would consider research without permission. We can go there if you would like to, but some folks would consider, for example, if you are trying to develop a new test using an anonymized sample in the laboratory, that that would be

research. We would consider that laboratory QA.

(Slide)

Recommendation two is that all state screening programs should have a policy in place that has been reviewed by the state attorney general or other appropriate legal authority that specifies who may access and use dried blood specimens once they arrive at the state-designated laboratory, including further access after newborn screening tests are completed.

(Slide)

The third is that all state programs should develop a well-defined strategy to educate healthcare professionals who provide patients with pre- and postnatal care about newborn screening and the potential use of residual dried bloodspot specimens for research.

(Slide)

All state newborn screening programs should work proactively to ensure that all families of newborns are educated about newborn screening as a part of prenatal and postnatal care. It is quite amazing how many families do not know that their baby has had newborn screening done. They will go home from the hospital with a band-aid on the heel or other appendage, but are really unsure of why it is there, in spite of the fact that it many cases they have been told and so forth, but there are so many things happening in the

hospital at the time of the delivery of the baby that that just goes right over the head of most of the listeners.

(Slide)

If the residual specimens are to be available for any purpose other than the legally required newborn screening process for which they were obtained, an indication of the parent's awareness and willingness to participate should exist in compliance with federal research requirements if applicable.

(Slide)

Recommendation number six is that the Secretary should provide administrative support and funding to the advisory committee to facilitate a national dialogue among federal and state stakeholders about policies for retention and use of the blood sample, including model consent and dissent processes.

Develop national guidance for consent or dissent for the secondary use of specimens and mechanisms to ensure privacy and confidentiality.

Collect and analyze national data on the utility on any additional consent or dissent processes implemented relative to potential research uses of bloodspots.

(Slide)

The final recommendation was to provide administrative support and funding to HRSA to award grants to

states to develop model educational programs for the general public on the importance of newborn screening and to create educational materials directed to healthcare professionals and consumers with facts about the potential uses of residual newborn screening programs related to these issues.

(Slide)

The final recommendation was that the federal government is encouraged to provide administrative support to develop national data on the utility of any consent or dissent processes implemented relative to potential research uses of residual NBS specimens and educational material with facts about potential uses for both consumers and prenatal healthcare providers.

(Slide)

The next steps -- the document that is before you has been posted in the Federal Register requesting public comment. There have been a goodly number of comments that have come in, but that process will be completed by June 30, 2010. Those comments will be reviewed and the briefing paper revised accordingly. Obviously, we are anticipating the document that this group is preparing, at least I understand is preparing, and then we are planning to revise our report and review it at our September meeting of this year. We will plan to send then final recommendations to the Secretary of HHS soon thereafter.

Thank you very much.

DR. TEUTSCH: Are there specific comments or questions directed to Rod before we have Janice go over what we purpose to respond?

(No response)

DR. TEUTSCH: Rod thank you and --

DR. HOWELL: Thank you.

DR. TEUTSCH: All right. Janice, go ahead please.

SACGHS Comments on ACHDNC Draft Briefing Paper

by Janice Bach, M.S.

MS. BACH: Okay. I think Kathy is going to get the slides on.

(Slide)

So we appreciated the opportunity to review and comment on this SACHDNC briefing paper.

(Slide)

I would like to acknowledge and thank our steering group which consisted of several of our members as well as *ex officios*. Of course, I would also like to thank the staff, Kathy Camp who I believe was the lead on this. She worked very hard with me. Cathy Fomous and Sarah Carr.

(Slide)

Our goals right now are to review our steering group comments on the briefing paper, discuss the recommendations regarding the paper, and come to a consensus on comments that

we would like to submit to our sister committee.

(Slide)

Yes. The summary of the comments that we are proposing to submit were distributed this morning and should be on your table. Everybody -- it is just a one page. It is a one-page act. It starts with SACGHS Comments on the Draft Briefing Paper. It looks like this. It was placed at your space this morning. If anybody needs a copy, let me know.

(Reviewing the Draft SACGHS paper)

(Slide)

MS. BACH: So in general, our steering group felt that the paper does comprehensively address the issues and concerns that are related to retention and use of dried bloodspots and it certainly recognizes that newborn screening programs are administered by states and yet still called for development of national guidance.

The paper at this point does not put forward any specific models or policy options, however, they could facilitate adoption of state policies.

(Slide)

We also felt that the paper may in some ways give not enough attention to state costs of supporting the ongoing oversight involved in potential secondary uses of dried bloodspots. These could be related to program administration, advisory board coordination, the honest broker systems,

counseling associated with potential return of results, research results, or even all the processes involved in de-identifying the samples for research distribution on larger scales.

And it does not necessarily address the recent concerns about destruction of residual dried bloodspots by some states.

(Slide)

Another point that we noticed was that while the paper does appear to call for establishment of a voluntary national repository, it really did not rise to the level of one of their seven final recommendations. So we thought there was insufficient discussion of the need for and value of such a repository as well as how it would be developed and what the oversight for that would be. These were just some of the elements that we thought we would want to know in more completely discussing a national repository.

Are we talking about data alone, or specimens, or both? What mechanisms would be used to submit the data and specimens to a national repository? Who would provide the stewardship? Who would have access to the repository, as well as how would decisions be made about potential secondary uses of specimens in that national repository?

(Slide)

The recommendations of our steering group were that

our committee endorsed the draft paper but with the following comments. That in developing national guidance and model policies for retention and secondary use of dried bloodspots for research purposes, that such organizations as the National Conference of State Legislatures, Association of Public Health Laboratories, and Association of State and Territorial Health Officials be included in the dialogue as stakeholders as they maybe influential and helpful in helping states formulate their policies.

Also to consider providing some examples of actual model legislation that states could use. Also to facilitate state adoption of the retention and use of dried bloodspots, to add a recommendation that funding be provided to support states as they implement the new policies.

(Slide)

Also to consider elaborating on the call for that national repository and clarify if it is intended to be a formal recommendation coming out of the committee.

Also we wondered about, in light of the movement toward development of the national guidance, should there be a recommendation calling on the Secretary to, at least at this point, discourage states from making premature changes that might actually shorten their retention policies or lead to disposal of specimens before the issues have been fully discussed.

(Slide)

So these are some of the questions that we would like to discuss this afternoon. Some of you may certainly have others that we would want to consider, but one of the things would be does the briefing paper sufficiently address the issues and concerns, for example, given the finite nature of the dried bloodspots, should the paper give specific guidance on how research allocation decisions should be made?

Should the paper address the availability of resources to cover costs that would be incurred by states to implement any future guidance concerning retention and use of dried bloodspots? We had mentioned what some of those costs potentially could be.

(Slide)

Should SACGHS actually encourage SACDHNC to express stronger support for the value of research uses of dried bloodspots? Should we encourage SACDHNC to go further in this paper by actually providing models or policy options for retention and research uses that states could adopt? The paper states that states should have policies, but it does not quite say what the policies should actually be.

Also in the interest of promoting greater harmony across states, should we consider recommending that states defer developing their policies until national guidance has been issued? We felt that in some ways, the recommendations

may be somewhat out of sequence because they are calling for states to develop policies, but then talking about a national policy so you could have all the state policies already in the works and everyone inventing their wheels before the national guidance policy is actually available.

I think that was it for the potential questions that our steering group came up with, but we would be interested in hearing from other committee members.

Questions and Answers Session

DR. TEUTSCH: So, open for discussion. No comments?

DR. EVANS: What a rare occurrence.

DR. TEUTSCH: What a rare occurrence is right. I appreciate Janice's work in bringing folks together to talk about all this and get some consensus. I mean, my general sense is too that to the extent that we can actually provide stronger guidance like model laws that states could use would be pretty helpful and strengthen this report to facilitate some greater harmonization as adoption across all the states.

Any other thoughts on these issues? Jim. I am glad.

DR. EVANS: My answer would be yes to the second too. I don't really know. I don't have a good enough feeling to address the --

DR. TEUTSCH: Yes, you were on the -- I think it was on the last slide. There.

Does anybody want to speak to the issue of what more needs to be said on the area of research?

DR. WILLIAMS: I was going to speak to the first one, the endorsement one. I read the report and I was really very impressed with the briefing paper and I did not identify any issues that would interfere with my wanting to endorse that.

DR. TEUTSCH: Endorse the recommendations from?

DR. WILLIAMS: Endorse the paper, the draft paper.

DR. TEUTSCH: As is or with the comments that Janice has presented.

DR. WILLIAMS: I guess I don't feel strongly that any of those comments would necessarily need to be -- you know, again, it gets to the issue that we were talking about previously which is does the process -- I mean we could certainly, I suppose make recommendations back, but ultimately this is their paper. They could choose to --

DR. TEUTSCH: Oh sure. These are actually just part of the public comment period, but they were kind enough directly solicit them from us and so, I think if I heard Rod right, they would like input from us to the extent that we have constructive suggestions.

DR. HOWELL: And the committee, I think, has a variety of other comments that have come on the paper and so forth, so I think this is certainly not the final thing, but I

would think it is basically final. I mean, I don't think there will be cataclysmic changes and so forth.

A lot of the things that you have brought up have been discussed at great length. For example, maintaining the storage facilities at the state level is a very big deal. I don't know how many of you have actually had direct experience with that, but if you look at California which has an exemplary system and so forth, it requires an enormous amount of space and material, and the ability to access it.

For example, when an investigator would like -- most states will make totally anonymized samples available for test development and things of that nature. But when you do that, if you come to the state and you say, "I would like 100 thousand samples" and so forth, that is a very expensive thing for the state to do.

Texas got into really serious problems in this area because they had someone that came and said, "We would like to have these anonymized samples." They said, "Yes, we would be pleased to work with you on that, but we cannot take money from you as a state entity." So the person wanting the sample ended up providing some support to the laboratory in forms of equipment which, of course, hit the newspaper immediately as Texas was selling spots.

So it is a very complicated circumstance and so forth and they were not selling spots, but it does have a real

cost tied to it and so forth.

I might also point out that for those of you who don't know this, and that is that Texas when they were required under their court settlement to destroy the samples it caused them $600 thousand to destroy the samples because, you know, you just can't take 5 million samples and put them in the dumpster. You have to have all sorts of carefully mandated things because they are biologic samples and to be sure that they were done. So all aspects of this has costs built into it, et cetera.

I might point out, I have had an opportunity to look at some how these samples are used and I will be brief on this. But if you go through a 20-year experience of states who keep very detailed records about any sample that leaves and so forth. The vast majority have come from a couple of areas. One to develop a new test, for example, if you are bringing a new lysosomal enzyme, you need to standardize the test.

The other consistent things are from families and the families have requested them over many, many years because they have a child who died and they suddenly realize that that child might have had an inborn error of metabolism, the most common form of MCAD deficiency. So families routinely go back and request the samples and that is the kind of requests that you get.

DR. TEUTSCH: Andrea?

DR. FERREIRA-GONZALEZ: I think I would recommend that we keep the stronger recommendation to keep the blood for future research. I think these are invaluable tools and I think we can foresee other uses in the future.

I think also it is very important to keep in mind the cost of keeping those bloodspots that are actually usable twenty years after they have been collected. But there also has to be some information associated with these bloodspots that have to be provided to the investigators because sometimes just having the bloodspot alone does not help you much. So there may be even more costs associated to make it really usable for other research uses.

DR. TEUTSCH: Do we have to be more specific about what that additional information is? Or content?

DR. WILLIAMS: That is where those phenotypic dollars come in that we talked about earlier today.

DR. TEUTSCH: Marc?

DR. WILLIAMS: I would still come back and recommend that we endorse the draft as is. The sense I have from listening to the discussion is that, you know, there has been a lot of debate about where to fall on this retention issue. It is clearly a major issue. It is clear that we could, you know, be more prescriptive about how to do things or recommend that there be more attention paid to it. But I think there is

also a balance of where can we reasonably be right now.

It sounds to me like the group is really thoughtfully considered that and is comfortable with what the current draft says. So from my perspective at least, I would be comfortable leaving that language as is.

DR. TEUTSCH: So just to be clear, you are suggesting that we just send a simple statement. This is a great report. We are supportive. End of paragraph.

DR. WILLIAMS: That is what I -- that is my feeling.

DR. TEUTSCH: As opposed to saying --

DR. WILLIAMS: We like it but do this, do this, do this. Yes.

DR. TEUTSCH: What you are saying is that most of these are sort of gilding the lily.

DR. WILLIAMS: Well, I mean, I understand the arguments for it. I guess it is just that I am a little bit more sensitive to the process issues of being, you know, the recipient of this, you know, to say are we adding substantively to the discussion that has already taken place and if we feel comfortable that the process has really struggled with these issues and have come down that this is where we need to be for right now, recognizing that there is more work to do, I am comfortable with that because I trust the people who are involved in the process. But again, I am just speaking for me.

DR. TEUTSCH: I think what I heard from Rod is other public commentors have had similar kinds of comments as we assembled and it would probably be useful if we would be reinforcing some of those and that would be useful to you. Is that fair Rod?

DR. HOWELL: I do not know the nature of all the comments but I think that it would not strike me as being an issue to say that this group thinks this is a fine document and endorse it, but I think you ought to consider these things that we discussed. So I think that would be well received.

DR. EVANS: You know, I think back on some of the reports that we have done. I mean the comments are extraordinarily helpful and they really inform. So if there are issues that we think are worth saying, you know, this is a great report, we have amplified this or we would mention that. They can take it or leave it and I don't think it undermines. I don't think it would be perceived as undermining.

DR. TEUTSCH: No. I agree with Jim. I mean, clearly they can take or leave whatever comments they get from anybody. But to the extent that we want to offer them, they are available.

DR. WILLIAMS: So if we are going to parse this document then I say that the last paragraph on the first page where we say "in light of the stated goal to lay the foundation for development of national guidance, it is not

clear why recommendations one and two call for states to develop policies concerning retention and use." Then it would be more efficient for the Secretary's Advisory Committee to first issue or facilitate the development of national guidelines.

I guess I don't -- I think if there are policy issues that are currently deficient at the state level, I don't see why we should ask them to wait for whatever this process is going to develop, assuming the process will, in fact, develop some guidance.

I guess I don't -- I am not supportive of that last paragraph on the first page.

DR. TEUTSCH: So I think what you are putting your finger on is a couple of things. One is if there is enough information, go forth. The other, I think, does deal with the harmonization issue. One of the issue we face in this country is a federal system with all its attractiveness of having local control over these issues, but we also have substantial heterogeneity on a number of issues where had there been some real common guidance we could have at least some model legislation that they could tweak. Obviously, rarely it gets adopted in the whole cloth, but do we think there is an advantage to having that kind of a model out there so that we would begin to move towards a more consistent system across the country.

DR. WILLIAMS: I don't disagree with the statement that it would be good to have a model out there. The issue relates to the recommendation that, you know, I read it saying states should hold off on doing anything relating to policy development until we come up with this because it assumes that it is going to come out in a timely fashion and that, in fact, we will produce a document.

Of course, earlier on, I want to say we recognize that it is the state's rights to do whatever they want to do, but there may be states based on the Minnesota and the Texas issues that are already moving in that direction. So in some ways, I am trying not to put them in an uncomfortable position of waiting for something that may be a while in coming.

DR. TEUTSCH: So maybe the point is to just be silent on that issue of whether they should wait or not, but indicate that we --

(Simultaneous conversations)

DR. TEUTSCH: -- model legislation --

DR. WILLIAMS: -- indicate that we are doing it. The intent is to develop guidance, but, you know, again, they are going to do what they are going to do.

DR. TEUTSCH: Maybe they want to -- I mean, I can see states saying, you know, I don't want to do anything. I would like there to be -- this would give them cover, you know.

MS. BACH: I could just add, I mean, I agree with you Marc on the one hand but, I think, part of what our thinking on that was that you could have states that would go ahead and engage in their whole policy development process, get it all completed and then in a year or two, maybe being optimistic, but if some national guidelines came down, they might be reluctant to actually revisit what they had -- the process they had just completed to actually change their policies or legislation to be more harmonious with the national guidelines. So that was the concern there.

DR. WILLIAMS: Although again, I think the notification piece in the prior paragraph. I mean, I really don't need to wrestle to the death on this because, as you have already sensed, I really have really unstrong feelings about this.

But the prior paragraph states that the issue -- there will be a convening function which presumably would happen quite rapidly where you would have national and state stakeholders that would be convening around these issues. So the states would have the opportunity to be fully cognizant of what is happening and use that information. It just seems to me a little bit intrusive. I might say hold off.

DR. TEUTSCH: Rochelle.

MS. DREYFUSS: I have to agree with Marc, having been around the block on a few of these issues about

environmental regulations and enforcement to foreign judgments, a whole bunch of areas. States just go crazy when you tell them to hold off. You know, it is just viewed as a real affront to state's rights. Actually the way states do things sometimes has its advantages. They think of things that other people don't. You know, you get bottom-up harmonization which sometimes is an easier sell than top-down harmonization. So I would agree about removing that paragraph.

DR. DALE: I will suggest an intermediate position. If you just look at the phrasing of that, I would propose that we recommend that the other committee, I can't pronounce that word, recommend development of national guidance on retention and then as states lacking policies develop those policies with reference to national guidelines. Take out this first "in light of" business.

But we would be declarative that we recommend that the government develop guidelines and that states that don't have a common policy proceed in that direction. It is an intermediate course. It does not speak to telling them not to do anything. It just says what somebody should do.

DR. TEUTSCH: You are okay with that? I see Marc is sort of neutral. That is fine. Other thoughts on what we need to do with this document?

(No response)

DR. TEUTSCH: Does someone want to move that we approve it with the change as David suggested?

DR. DALE: I think we could be a little more declarative at the first statement that we appreciate the effort and endorse the report with the following suggestions for any revisions, something like that. We appreciate the opportunity to comment, but I think we could be a little stronger in terms of an endorsement of the report as was suggested.

DR. TEUTSCH: Put it up in the first sentence?

DR. DALE: In the first sentence, yes.

DR. WILLIAMS: So looking at the very last paragraph which is about the voluntary national repository and I guess the recommendation that we would be sending back to the other committee is to perhaps further consider whether a voluntary national repository should be a recommendation that will go to the Secretary.

Again, it seems to me that that may be -- that even that recommendation for consideration goes maybe a bit far. Again, I am just thinking about the rights issues and how that would work. It seems just a -- I liked it in the context of the overall discussion in the body, but not as a recommendation because clearly the other things are much more timely and important to deal with than trying to sort out how a voluntary national repository would work. That just seems

like work down the road.

DR. TEUTSCH: Rod do you want to talk a little bit about why the committee did not make any recommendation like that?

DR. HOWELL: I think the committee is extremely sensitive to the state's individual rights and so forth and I might point out in recommending that we work with ASTHO and so forth. Most of those groups are actually members of our working group. ASTHO and APHL and so forth. So we will tend not to be terribly prescriptive when it tells about what we think a state should do.

We might have model procedures, but we are not likely to say California, we think you should do that. I would assume that that is the reason that is worded that way.

MS. BACH: I just wanted to clarify. Really what we were trying to do in pointing that out is we felt that there just wasn't enough discussion and description in the body for us to really even know like what was envisioned by that national repository and we were not trying to say one way or the other whether we endorse the idea or not, but just would they want to clarify what even the thoughts were behind it.

DR. WILLIAMS: So if that is really the intent, then I would suggest that we remove the sentence that says the Secretary's Advisory Committee should consider whether the idea of a national RDBSS repository should rise to the level

of the recommendation. Really our recommendation is to provide more clarity on this issue. Is that a fair statement?

DR. TEUTSCH: Paul?

DR. WISE: Well responding to my comment earlier about being bland, neutral and diplomatic, I am concerned that we are being too bland and diplomatic here and not really responding or taking advantage of our ability to be a little more proactive that their committee can be and trying to emphasize the importance of the briefing paper in the real world right now.

In other words, trying to elevate the issue that, not in these words, but that basically that states can create great mischief by not carefully recognizing that work is being done across the country on these issues and that this paper should be viewed as a very important resource for guiding the deliberation of these issues within each state.

In other words, to really try to elevate the importance of this briefing paper given what has been going and some measure the lack of informed dialogue in some of the state conversations. And then go into the specifics that we talked about. But that the preface here should call attention to the fact that this is a very active conversation and that this briefing paper begins a much more informed conversation than what has really been going on at a national level or at a state level previously.

DR. TEUTSCH: So let me see if I can put a couple of those pieces together. Given what you said about the importance of visibility and the fact that, you know, people need to be cognizant of this. It seems to me that some of the other things that we are recommending, much clearer policy recommendations, model laws, whatever they are, would it help to strengthen the report and give them even more guidance and make it, if you will, more actionable? And we can tie these pieces together in a way that, if you will, gives this paper more clout.

DR. WISE: That would be my suggestion. I think we have an opportunity here as the advisory committee looking in a sense at a broader range of issues to elevate this report and not merely endorse it, but endorse it with the strong emphasis that this needs to be taken very seriously and that this should be viewed as caution for some of the states.

The states are not only -- this is from my perspective, what I hear -- not only looking for input and guidance, but looking for cover. Anything that would elevate what is in fact a highly informed diplomatic briefing paper, I think we should do that, given that we can do it better than they can given it's their report. I just think we ought to be strong about how we endorse this and elevate its presence, if everybody agrees.

DR. TEUTSCH: I see some nods. Is that -- better

than usual. Yes, I know. After lunch.

DR. EVANS: I agree with Paul. I don't think we should bend over backwards. I don't think it is even being diplomatic to not say what we think strongly. I think it is being helpful.

DR. WILLIAMS: So I am sorry. I am dealing with a bit of a nonsequitur moment here. Since I kind of proposed taking a sentence out and I was not sure if Paul's comments would seem to be much more general towards the whole document.

So just for my clarity, was there a sense that we should -- that the recommendation -- that the suggestion that I made to remove the sentence about the repository, the voluntary repository be removed or was that part of the point you were making that we should include that along with some other things?

DR. WISE: No, I was completely ignoring your point.

(Laughter)

DR. WILLIAMS: Okay, great. Thank you. Okay. You and my wife.

(Laughter)

DR. WILLIAMS: I guess I would still like to make sure that we have the sense of the whole committee about the very specific --

DR. TEUTSCH: So let me see if I can -- I have not been taking great notes here. But what I am hearing is the

introduction needs to be strengthened in terms of an endorsement, as David suggested.

I am hearing that endorsement be strengthened if you will, as Paul said, and the need to take all of this quite seriously. That is all in this introductory paragraph.

The other suggestion I heard was in the last paragraph on the first page to remove this thing about states should hold off. That was what you suggested Marc, we sort of delete that part. Then the last thing was that on the voluntary national repository that these are a bunch of considerations that we think you should flesh out, but we are not really making a recommendation one way or the other. That is what I have heard so far.

DR. EVANS: Could you say -- I am just throwing this out there because I also don't, you know, I wouldn't fall on my sword about any of this, but could you say something to the effect that the ultimate document will be a great resource to states and could help them craft their policy.

In other words, try to maybe a little more indirectly without raising the issues that Rochelle has brought up, that we do not want to tick them off. But we do want to point out, I mean, it seems awfully wasteful to have all these different states going at this when there will be some guidance with a well-thought out plan, you know.

DR. TEUTSCH: I think what you just said Jim --

well, Sarah is asking me how we are going to send this? Are we sending this to the Secretary or are we sending it directly to Rod? I am not sure I have the answer to that in terms of providing the strongest statement about what we want.

DR. WILLIAMS: I thought the point of this was to participate in the public comment process.

MS. CARR: I think that as an advisory committee, we have done this before but I have sort of had second thoughts about it. I think we are an advisory committee to our secretary. Our sister advisory committee has asked for input, so I would rather do it as a letter from Steve to Dr. Howell or with regard to what Paul Wise was saying, is writing from us directly to the Secretary with a "cc," for example, to the chair of that committee. Might that elevate, strengthen and help them?

DR. TEUTSCH: Send it to Rod with a copy to --

MS. CARR: That could be it, or that way.

DR. WISE: Could you put it on our website as well?

MS. CARR: Yes.

MS. BACH: Before we conclude this discussion, I just wanted to go back and make sure that we are all okay with the statement that we have in the paragraph at the top of page two about due to the unique value of these specimens for future research, SACGHS suggests adding a recommendation that the Secretary should exhort states to defer making policy

decisions in light of the policy deliberations. I am not sure. Are people still in agreement with that or do we need to rephrase that?

DR. EVANS: Or maybe be cognizant, you know, rephrase it -- be cognizant of, you know, presumably forthcoming recommendations?

DR. KANIS: I think that the chance to be strong is when something that is irretrievable, so I would lean toward the not to be cognizant, maybe not exhort, encourage. I think being too bland here is not the right way to go in something that is irretrievable. I would push for being strong.

DR. TEUTSCH: Okay. Let me try again. I think we have had a number of comments and we will send this forward to Rod. But the process from here after approval from this group, we will probably go ahead and incorporate what we think we have heard and then send it out to all of you for a very fast turnaround. Make sure we are capturing some of the nuances one more time before we actually transmit it. Anything else before I ask for a vote to make sure that we are, you know?

(No response)

DR. TEUTSCH: All right. So all in favor of the recommendations as more or less amended in the process, you will have one more chance to see this. Signify by raising your hand.

(Show of hands)

DR. TEUTSCH: Any opposed? Abstentions?

(No response)

DR. TEUTSCH: Did you count that fast enough? I am sorry. Where is the abstention? It was unanimous.

DR. WILLIAMS: So in honor of this Dr. Evans has a comment.

DR. EVANS: I don't know if it works. Marc wants me to play the vuvuzela. We will try it.

(Pause)

Closing Remarks

by Steve Teutsch, M.D., M.P.H.

DR. TEUTSCH: Let me recap a little bit what we have heard. I think we have had a productive meeting and hopefully. Kathy can you move this forward? All right, let's talk about what has happened.

(Slide)

I think one thing we should be really gratified by over the course of the last two days we have actually heard that some of the things that we have been dealing with over the last two years are actually beginning to make a difference. To me, that is what we are here for.

We heard about the registry for genetic tests. It was a key recommendation that came out of our oversight report. We heard from FDA that they have taken action on a

number of things, including some of the issues regarding direct-to-consumer testing and oversight of laboratory-developed tests which have been really important discussion points and I think for which we have made recommendations that they have taken to heart so that is terrific.

We also heard from CLIAC that they have considered some of the recommendations that we have made in updating their guidance. So I think we can look across all that and say "well, maybe what we do around here goes further than the basement of the hotel." So that is good.

We did hear a number of updates clearly from NIH, from CLIAC. We had a long, and I think really informative discussion on whole genome sequencing and out of that emerged a task force which Charis and Paul will be co-chairing. We appointed a number of members. Your names are up there. Janice, Jim, Andrea, Muin, Charmaine, and Gwen. If that is not right, and Sam. If you are omitted or co-mitted in error, you can let us know.

We will look to move that whole agenda forward in October and the committee will hopefully identify some areas that we can begin to focus on.

We had a good discussion this morning on genomic data sharing, including forming a task force. I think Charmaine -- there you are in the back. So hopefully, we got a little bit of clarity on focus. Thank you for leading us

through all of that. Again, that task force includes Mike Carome, David Dale, Gwenn, Rochelle, and Barbara.

The focus will be primarily on the group-related issues, group rights, group harms and we will explore other gaps in the policy.

The steering group, Sarah reminds me, that in addition to the people whose names appeared up there, we will co-op the people from the steering group who in addition to them, and I can't crosswalk it back, it includes Sheila, Kevin, Sylvia, Julio, Mike Amos, Doug Olsen, Laura Rodriguez, and Michele Puryear. So that will be a large group and we will look forward to hearing back from them in October.

(Slide)

On comparative effectiveness, I looks like I was conned into a workgroup. The comparative effectiveness research workgroup was formed under Marc with David, Muin, and Sam.

DR. WILLIAMS: Can I clarify that? This is just the letter?

DR. TEUTSCH: Yes. This is the letter. I am sorry. I am trying to read as I go along since I have not seen these slides before. But it is good to see the second bullet there which is about completing the letter regarding the use of ARRA funds and other things we think need to move forward regardless of the applicability of that funding mechanism.

We heard about carrier screening and the committee agreed to work with the Advisory Committee on Hereditary Diseases of Newborns and Children and formed a workgroup including Jim, Phyllis, Adam, Charmaine, and Janice. They will be working closely together as that gets more detailed and focused and we will stay abreast of what goes on there.

(Slide)

A couple of other things that happened over the course of the meeting which some of you were not aware of. I certainly have been learning as we go along. One is I mentioned in the beginning we had submitted a prospective article to the *New England Journal*. We learned this morning that they have not only received it, which is only a week or so ago, ten days ago, two weeks ago? It was not long. But today we received a notice that what I would call are asking for revision and submission. Mostly they are looking for some editorial kind of changes.

So we are looking forward to getting that back and getting, I guess, a very nice step in recognizing that there will be some increased visibility for our work and the importance of the issues that we have been addressing. So that is great.

Rod, I think, I appreciate that you provided us with some of the information we needed on this because we were trying to get some clarity here just around lunchtime. But I

understand that the AMA House of Delegates passed resolution on gene patents this week. I believe those bullet points, Rod just to be clear, those are the bullet points from the resolution that they opposed patents on human genes and their naturally occurring mutations, that they opposed future issuance and enforcement of patents on human genes, and support legislation requiring the existing patents to be broadly licensed.

DR. EVANS: Actually no. They specifically echo our recommendations. Support legislation that would exempt from claims of infringement those who use patented genes for medical diagnosis.

DR. TEUTSCH: So you have the actual written law. But I think it would, as it emerges it clearly is in sync with the part that you were just reading Jim. It is clearly in sync with our report from earlier this year.

(Slide)

So I think a lot has been done. A lot has been accomplished and we are making progress. We will be reconvening in October on the 5th here in Washington somewhere. We will be hearing from the Genetics Education and Training group. We should have the results of our public comments and an updated set of recommendations for us to consider.

Look forward to sessions on whole genome sequencing, comparative effectiveness research which is a carryover from

our prior meeting, and genomic data sharing. As we talked about, things in GINA are just now unfolding in terms of the regs so hopefully we will be able to get our agency colleagues together to give us more details.

Sarah was suggesting that we will hopefully have some information not only on what the rules and regs are, but what difference it makes in terms of the implementation on various individuals and groups.

So a productive meeting. Thanks to everyone. It is always an enormous amount of work on many people's parts to pull all this together and to get us to the point to have the kind of discussions that we can have around the table. So many thanks to our incredible staff and to all of you who worked so hard on all of this.

(Applause)

DR. TEUTSCH: Safe travels and stay out of blizzards.

(Whereupon the meeting adjourned at 1:53 pm)