

**Department of Health and Human Services
Centers for Disease Control and Prevention
Agency for Toxic Substances and Disease Registry**

**ATSDR's Annual National Amyotrophic
Lateral Sclerosis (ALS) Registry Surveillance Meeting**



**August 3 - 4, 2016
Meeting Transcript**

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2016 Annual ALS Surveillance Meeting Transcript

Welcome

Bob Kingon, Facilitator

My name is Bob Kingon.

I'm your facilitator, and this is about my sixth or seventh meeting facilitating this conference. It's always enjoyable. A couple things I need to go over with you in terms of housekeeping. You've probably all seen this before, which are my rules for how we conduct ourselves. You can't see this all the way from the back, but basically it's one person talking at a time, no side bars. We're going to debate and have good discussion. No arguments.

Cell phones should be on vibrate, and this is a picture. You can't see it, but it's a dead horse. So if I'm up here going like that, then that means we've been beating a dead horse and need to move on. Here's an eye over a ball. We need to keep our eye on the ball and remember why we're here and I put a bottom line, which is a bottom line meaning that we are here being supported to participate and move this project along.

Some of the data that's being presented this morning will be released tomorrow, and we request that you not tweet or otherwise communicate these results until tomorrow. Local folks who are parking, be sure and get the slip from the desk out here so that you get the lowest rate when you check out of the motor lobby.

Wi-Fi is not available in this room, but is available down the hallway in the lobby. Also, Wi-Fi is available in your room, and if you check out tomorrow and there's a charge for it there should not be, so bring that to their attention. As the meetings are in progress, if you would use the third door, down where Tom is, to go in and out using this door, we'd appreciate it.

Also, one of the very important things is that this meeting is being transcribed and the transcribers try and identify each speaker. Once in a while you'll see in the report that there's an unknown with a nice comment. Well you don't want to be unknown. You want to click on your speaker, identify yourself and then proceed with your comments or questions.

I believe that's it, so let's get started.

I'd like to first introduce Jimmy Stevens who is the Director of the Division of Toxicology and Human Health Services at ATSDR.

Jimmy.

Opening Remarks

Jimmy Stephens, Ph.D.

Director, Division of Toxicology and Human Health Sciences
Agency for Toxic Substances and Disease Registry

All right, well thank you. Welcome everybody.

It's my delight to be able to welcome you all to this meeting. I will say also it's a great delight for myself because this is my first meeting. I took over as the Director of the Division of Toxicology and Human Health Sciences at ATSDR a little over a year ago, and this is the first meeting I've been able to make, so this is very exciting for me.

I really appreciate all of you attending the ATSDR's ALS meeting, having clinicians, researchers, and especially persons with ALS together is really very important for us. It allows us to get feedback from all of you. And I do want to highlight that we welcome all feedback and we really actively solicit it. We love hearing it if the feedback is good and we're doing good things. If it's not good or if there's things we can do better, then that's feedback we very much need. So I want to make sure that we have plenty of opportunities throughout this meeting for you to tell us what's on your mind and things that we can do better.

I can't emphasize enough the success of the National ALS Registry depends on this kind of effective collaboration from as many ALS stakeholders as we can hear from. We think the ALS registry is a groundbreaking effort, and we're very excited about the progress and the ability of the ALS Registry to help scientists as they work towards a cure for ALS. I just wanted to highlight a few things that we think are both progress in terms of from the ALS Registry and also let you know about some of the partners that we're looking forward to hearing from during this meeting.

So, as was mentioned, we are going to be publishing the second report on ALS prevalence tomorrow, but today you will get the prerelease presentation. We're very excited about launching the National ALS Biorepository. That's going to be launched this fall. You'll be hearing more about it this morning. And once it's operational, we're going to have the largest sampling of ALS blood and tissue samples in the United States. And with these samples, we're going to be able to pair the risk factor data. We're really looking forward to and very excited about the possibilities this is going to give us to provide a basis and a framework for what we think is going to be a whole host of research projects based on the Biorepository.

During this meeting we're looking forward to updates from our funded researchers across the country and internationally. We're also working on internal research papers that you'll hear about, including ALS morality, disease progression, survival models, and risk factors. And, again, we would really love to get your input and feedback on these topics as we present them.

You're going to hear from our communication partners that will provide updates on the National Awareness Campaign and outreach, and I'm also really excited to report that regarding the Registry's research notification system, we've had just extraordinarily good progress with this. We've got over 95% of people opting in to receive notifications about the ALS research that they may be eligible for. So once again, an opportunity for us to really leverage the ALS Registry for multiple purposes.

You're going to be hearing more about these new initiatives and others, and as well as our progress on the Registry in the next day-and-a-half. So we turn to you as the leading experts on

ALS to help us shape the Registry. Again, don't be shy. Let us know what you think and give us any feedback, both during the meeting, at breaks, or separately.

So, again, welcome to Atlanta, and we're looking forward to having a very productive meeting.

Thank you.

Introductions

Bob Kingon, Facilitator

Thank you, Jimmy.

Before Kevin gives us an overview, I'd like to go around the room. Everybody tell us who you are and who you're with. And, Pam, I want to start with you.

Good morning. My name is Pamela Litvak. I'm an epidemiologist at the Mailman School of Public Health at Columbia University.

Hi. My name is Lorene Nelson. I'm an epidemiologist, also from the Stanford University School of Medicine.

I'm Marc Weisskopf also here in the epidemiology corner. I'm a neuroepidemiologist from the Harvard School of Public Health.

I'm Wendy Kaye. I'm an epidemiologist from McKing Consulting, and I work on the Registry as well as on the Biorepository.

I'm Amelie Gubitzi. I'm a program director for ALS research at the National Institutes of Health.

Pat Wildman, ALS Association.

Kristin Stephenson, Muscular Dystrophy Association.

Calaneet Balas, the ALS Association.

Marianna Bledsoe, biorepository consultant to McKing Consulting.

Amanda Haidet-Phillips, scientific program officer for ALS research at the Muscular Dystrophy Association.

Ed Tessaro, ALS patient since 2009, with Dr. Jonathan Glass at the Emory ALS clinic.

Sarah Kulke, I'm a Senior Medical Director at Cytokinetics.

I'm Bill O'Shields. I'm a person with ALS here in Atlanta, diagnosed January of last year.

I'm Allen Alderman, and I'm a person with ALS. I was diagnosed in September of 2001.

Nicole Yarab, ALS Association.

Hi. I'm Lauren Webb, the National Director for Clinical Services for the Muscular Dystrophy Association.

Ed Kasarskis, neurologist, University of Kentucky at Lexington.

Benjamin Brooks, Carolina's Neuromuscular/ALS MDA Care Center, Charlotte, North Carolina.

I'm Michael Benatar. I'm a neurologist at the University of Miami.

Hiroshi Mitsumoto. I'm a neurologist at Columbia University.

Walter Bradley, neurologist and ALS physician at the University of Miami.

I'm Stephen Goutman. I'm a neurologist at the University of Michigan.

Lucie Bruijn, Chief Scientist at the ALS Association.

I'm Orla Hardiman. I'm a neurologist at The National Center for ALS Research and the Trinity College, Dublin, Ireland.

I'm Paul Mehta. I'm the Principal Investigator of the National ALS Registry.

Kevin Horton, Chief of the Environmental Health Surveillance Branch at ATSDR.

And Jimmy you've met me.

And I'm Bob Kingon, retired CDC person with a 30-year career, and glad to be here.

Also, we have a number of people in the back. Any of you who have the opportunity and you want to speak, just move up to one of the tables and grab a mic, and we'd be glad to hear from you.

Kevin Horton is going to present next. He's the Chief of the Environmental Health Surveillance Branch within the Division of Toxicology and Human Health Sciences.

Overview of the National ALS Registry

D. Kevin Horton, DrPH, MSPH

Chief, Environmental Health Surveillance Branch
Division of Toxicology and Human Health Sciences
Agency for Toxic Substances and Disease Registry

Good morning. Thank you all for coming. Again, it's good to see many of the familiar faces that we see year in and year out. And for those of you who are new here, welcome, and especially to our PALS, we really appreciate you coming. I know it's not the easiest thing to get here, but we do value your input greatly, and essentially we're here for you all.

Welcome to Atlanta.

So what I want to do this morning is give an overview of the Registry, and we actually have an exciting agenda today. You're going to be hearing about our results from our second report. This report has been a long time in the works and I think, as many of you know, we published our first report in 2014, and this is the follow-up report, and it's going to cover two years 2012 and 2013, whereas as our first report covered 2011 and part of 2010. So Paul is going to cover the details of that.

Again, as was mentioned, this is going to be published tomorrow in CDC's MMWR. Some of the support groups – ALSA, MDA, and Les Turner, you could be getting some questions, but we can make sure that you understand what we're saying here in terms of the results, and if you get any questions, we can work with you all.

So, for those of you who don't know, we are ATSDR, and we are actually part of The Centers for Disease Control and Prevention (CDC). We are the part that handles a lot of the environmental health issues, especially the issues that deal with toxic exposures and environmental exposures. We are located here, probably about five miles from here, and we are co-located with CDC.

So, again, I apologize. I know that some of you, or many of you, have seen these slides before, but, again, since we have a mixed audience today, I think it's important that we realize and we fully understand how we got here. So the ALS Registry Act was passed in October of 2008. A lot the credit goes to people in this room, especially the support organizations such as the ALS Association and the Muscular Dystrophy Association. If it weren't for groups like this there would not be a Registry. So a lot of credit goes to those groups, and particularly their stakeholders such as patients and caregivers.

So essentially what the Act says, it directs CDC ATSDR to create and maintain a population-based ALS Registry. We conducted some pilot testing or pilot studies in 2008, and really completed them in 2010, and the purpose of these pilot studies is to help us basically test out case finding methods for ALS. So I think some of you or many of you know that ALS is not a notifiable disease. In other words, if a person is diagnosed, CDC, or the federal government, we don't know about those cases. Most of the notifiable diseases in the U.S. are infectious diseases, so Ebola, SARS, things like that are notifiable, and that's how we're able to keep track of, you know, certain conditions.

But ALS, and, frankly, thousands of non-communicable diseases, are non-notifiable, so it makes it very challenging for us to keep track of how many cases of X, Y, and Z are going on around the country. But for ALS, because the ALS Registry Act was passed, it didn't make the condition a notifiable disease, but it did set into motion a path that we can take to create appropriate case finding methods, and I'll discuss that in a few minutes.

The registry was launched in October 2010, about two years after the ALS Registry Act was passed. If you go to our website you can actually read the Act. But it really outlines three specific things. You can see here, the first thing is really to help us describe how common is this disease in the U.S. And so obviously we're interested in the incidence and prevalence of the disease. We want to know who gets the disease. You know, why does it strike Caucasian males more than, you know, African Americans. So really trying to figure out who has the disease. And probably the most important part of the whole Registry is to help find out or tease out what are the risk factors for this disease. You know, why do some people get it? Is it occupational? Is it some kind of chemical exposure? Is it oxidative stress? What really leads to a person getting this disease? And as I mentioned, because it's not a notifiable condition, we had to come up with some novel, unique ways for us to track cases in the U.S.

And so we do take a two-pronged approach at capturing cases. On the left-hand side you can see here, we use large national databases, such as Medicare and Medicaid and the Veterans Administration datasets to identify the bulk of the ALS cases that are in the registry. And we created an algorithm during the pilot testing that I mentioned that, when you apply this algorithm to the national databases, it helps us tease out who has ALS versus those who don't. And some of the things that go into the algorithm are, one of the big things is the ICD code, which is kind of a billing or diagnostic code. Each disease and condition has an ICD code. But we know that, just through our pilot testing and other previous studies in the literature, we cannot rely on ICD codes alone, because there's a lot of miscoding that goes on. We can capture probably a bulk of the cases using ICD codes, but we can't capture them all.

Other things that go into this algorithm are prescription drug usage. So, for example, people who take Rilutek or Riluzole, if you're taking this drug, there's probably a good chance that you have ALS, otherwise you wouldn't be taking it. It's a very expensive drug, and it's really the only FDA-approved drug on the market to treat ALS. It prolongs life, on average, about two to three months, but still, it's very telling if we can see this in the dataset that a person is on Riluzole. We also look at other things like frequency of visits to neurologists or to ALS clinics. That's a pretty telltale sign if someone's going frequently versus kind of a one and done thing.

So, most of the cases that we have in the Registry come from the national database approach. Now for our PALS, the national database approach is done behind the scene, so our PALS don't need to do anything. It's where -- the right-hand side I think is where people know us the most, and we're trying to get new PALS and existing PALS to come to our web portal and enroll.

And this is just basically a series of validation questions that a patient answers, has a physician ever told you, you have ALS? If so, when were you diagnosed? And depending on the way a person answers, they're either considered a case or they're not. And we do know there's going to be duplication. People are going to show up on the web-based side and people are going to show

up on the National Database side. So we cross reference based on a couple of unique variables, and we shake out duplicates to make sure that we capture a person only one time, because we know that some people are going to show up on both sides.

The Web portal side is critically important because, number one, it's timelier than us getting -- finding out cases from the National Database side. Some of these databases like Medicaid, it takes years for us to get the data. Medicare is a little timelier. The VA is even more timely. So for that reason, we really want people to come and enroll in our web portal, because it's essentially real time.

The other really important thing about the web portal approach is -- and I'll show you the risk factor surveys in a few minutes. But it gives the patient the opportunity to really tell us about their disease in terms of, you know, what was their occupation, were they in the military, things like residential history. It really gives us a feel for that person, versus just capturing their medical history through the National Database approach.

So this is one of the takeaways that you'll hear from us today. One of the big challenges for the registry is ongoing promotion. We know that PALS are diagnosed every day, and how do we get in front of newly diagnosed PALS? How do we get in front of existing PALS who don't know about the registry? And it's critical that everyone in this room and beyond this room become a mouthpiece for the Registry. So you heard there's a lot of neurologists in this room. We rely on neurologists to inform their patients of the Registry.

I think many patients probably trust their neurologist a great deal, and they put a lot of faith in what you say, so if they hear it directly from you that the registry is a worthwhile endeavor, hopefully that will lead a patient to come and enroll in the registry. So that's it in a nutshell. That's the novel case finding approach that we're using for ALS.

So I mentioned that we have the ability for patients to take risk factor surveys to tell us more about their disease, and you can see here right now we're up to 17 different risk factor modules. It covers everything from occupational history to family history of ALS, hobbies with toxic exposures, and you can read through here, trauma history. And since basically we launched the registry back in October 2010, we have almost 60,000 completed surveys. And this is a good number. The response rate is actually really good. Approximately 55 to 60% of people who enroll in the Registry complete these surveys. And for a federal survey, that's a pretty good response rate.

But we know we can do better, and another takeaway is it's great for people to come and enroll in the Registry, but if they can take that second step, not only enroll but go on and take these surveys, obviously the more data we have the higher likelihood that we can potentially find maybe a common thread or some kind of risk factor for the disease.

And so we are in the process now of analyzing the data. We've already included some of the data in our first MMWR. We had another paper recently published three or four months ago, and we're actually analyzing more of the data right now. So we hope later this year we'll have a couple papers in publication, or at least submitted to a journal. But this is an ongoing process.

So let me just take a minute to show you where we are today. So, you know, many of you in this room have been with us since day one, and you've seen the progress that we've made, and I realize that for some people, especially if you're a patient, maybe we haven't made enough progress, or made progress as quickly as people like. But understand that this is a huge endeavor, you know, trying to capture cases of a non-notifiable disease in a country the size of the U.S., it takes time.

But I'm happy to say that we have turned the corner. We're starting to amass a lot of data now, and I tried to capture it in a table. You can see that we have different metrics that we're using with the Registry. Obviously we had our first report issued in 2014. Tomorrow will be our second report, and that gives detailed prevalence estimates. We also capture prevalence through our state and metro efforts. That actually ended a year or so ago. But we have detailed prevalence estimates from three states and eight large metropolitan areas of the country. I'll talk a little bit more about that in a few minutes.

We do have incidence data that we also captured through our state and metro efforts. The problem with incidence data on a national approach is we can capture when a person was diagnosed with ALS on the web portal side, but it's not always documented in the national database approach when that person was diagnosed with ALS. Obviously we need a diagnosis date to be able to document incidence. So right now what we have is highly detailed incidence level on state and metro effort. We're capturing demographics obviously through a number of different ways. Risk factors, I mentioned. And we've also gotten mortality data from CDC's National Center for Health Statistics. We're doing a couple papers right now with the mortality data, and, actually, you'll see, either today or tomorrow, we'll give a presentation on some of the findings that we see from the mortality data.

And I just wanted to show -- you can see in the footnote here -- that the first four metrics really support the goals of the National ALS Registry, so looking at incidence, and prevalence and demographics and risk factors. So we are, as much as possible, following the letter or the spirit of the law of the National ALS Registry Act.

So what have we done so far? So we've actually done quite a few things. We've got two annual reports, or, as of tomorrow, we'll have two annual reports. We've published a number of different peer-reviewed publications and abstracts. There are more in progress right now. And if you look at the data categories, it covers a number of different things, and this is only just the start, but they obviously include incidence and prevalence metrics and demographics and risk factors. But we're also looking at things such as survival analyses, looking at how the Registry can be used for recruitment purposes. We've had a paper or two that documents that.

We're doing specific geographic analyses, looking at how ALS cases are distributed in a geographic area, whether that's in rural or metropolitan areas. We're actually looking at how the cases distribute on a national level right now, and we're going to try to generate some heat maps. We've got some papers looking at case ascertainment methods. And, again, this is just the start. There are many more topics that we're going to be looking at. And I would encourage any of you who are interested in any of these findings to go to the Registry website.

We have a Publications page, and you can click on any of these articles. We have gone, you know, the extra step and purchased open access to all the articles that have been published that pertain to the Registry or use Registry data. That's the least we can do. We don't want patients or stakeholders to have to find it in PubMed and then pay for access to the article. So any article that we publish we try to purchase right away and make it available for stakeholders to read and review.

So, just quickly, some select national ALS Registry results. Again, I just compiled some that I thought were more relevant. The first one, the prevalence rate, again, this is going to be outdated as of tomorrow. But our first finding in the MMWR, we found over 12,000 prevalent cases of ALS for a prevalence rate of 3.9 or, basically, 4 per 100,000. Our incidence rates are really in line with what's in the literature based on our state and metro surveillance incidence rates of 1.5 cases per 100,000 population.

Our findings back up, again, what's found in the literature; that we see PALS are more likely to be white, male, non-Hispanic, and in the older age brackets. Median age at diagnosis, 64 years. We validate that males develop the disease more than females. We're also looking at -- remember I mentioned demographics, how does this disease affect different subpopulations. So we're at least seeing that whites have twice the incidence rates of blacks and Asians. And similarly, non-Hispanic have twice the rates of Hispanics. Now, again, we really need to start digging into this. Is there some kind of biological mechanism that's causing this? Is this a case finding artifact? Again, this is what registries do. It allows you to dig into the data and start looking at different aspects.

Four percent of the people in one of our studies had a family member with ALS, and I think, as many of you know, that it's thought that about 5 to 10% of the cases of ALS are genetic. So this fits in with that assumption, or fits in with what's stated in the literature. Again, we're doing more analyses on that. If you look at some of the risk factor modules that we analyze, we saw that about 25% of the people in the web portal approach were veterans. And this is higher than what is in the national population -- about 9% of people in the U.S. are veterans. So, again, this is all descriptive statistics, but it fits with the findings that show that veterans are twice as likely to have or develop ALS, or if you have military experience.

Jobs, we're looking at occupational series. We see that the highest percentage of people in the web portal were in the teacher, professor, or educator roles, followed by physician, nurse, dental, or health-care worker. Half the survey respondents smoke or ever smoked in their lifetime, versus 41% of those in the U.S. population. We also saw that median survival time post-diagnosis in California was about two-and-a-half years, and those diagnosed in California and New Jersey at a later age have shorter survival time versus those diagnosed at a young age.

And just a couple more, SES, socioeconomic status and race were associated with ALS incidence in New Jersey. In Florida, over 4% of the cases had dementia. Median mean age at symptom onset was 61.9 years in California. ALS was specified as the cause of death for 94% of incidence cases in New Jersey. The other percentage, I can't remember exactly what they were, but you're

going to hear from Ted Larson later on that mortality data is not always reliable either. So if you have ALS and you die of ALS, it may not always be coded as ALS.

Median survival time was shorter among females versus males, whites versus blacks and Asians, and non-Hispanics versus Hispanics. And, again, this is not comprehensive findings, these are just select findings that we put together. And we encourage anyone to go and read the factsheets and the articles that we've published thus far.

So shifting gearing here. The Registry, yes, we are all about metrics, you know, capturing cases for incidence and prevalence. We're also using the Registry for other purposes as well. And you'll be hearing later on today about specifically what are some of the ways that we're using the registry in detail. But I'll just briefly mention that we've opened up the registry for recruitment purposes. You'll be hearing from Sarah later about how her company used the Registry to recruit for clinical trials.

We're also funding research to help us look at the etiology and the risk factors for the disease. You'll hear a couple researchers that we've funded give an update on some of their findings. And you'll also hear in great detail about the Biorepository that Jimmy mentioned earlier that we're very excited about, and we're capturing things that really will fill a gap in the ALS science community.

So, just briefly, the Research Notification System, you know, I think if you talk to any of our PALS out there, people want to be involved with clinical trials or studies. You know, they want to find out why did I get this disease, and so, as I mentioned, we opened up the Registry for recruitment purposes. And over 95% of the people in the Registry have indicated, yes, they want to be notified about clinical trials or epi studies that they're eligible for. And so, to date, we've had over 20 institutions domestically and abroad use the Registry to recruit for research. And we'll have a discussion on how that's being used in detail later on today.

Extramural research funding, again, we do intramural research, but we can't do it all. We're a small group, and so for that reason we have to fund external research. And, really, we want to know more about the etiology and the causes and the risk factors for this disease. And so, to date, we've funded 13 studies, and we want to continue funding, but, again, with the way this election cycle is shaping up, we can't guarantee what's going to happen. But, if the past is any indication, we'll continue to stay on this trajectory of getting money from congress, and we'll make money available for researchers. If some more money becomes available, we will work with our support organizations to get the word out. We'll tweet, use CDC social media to let people know.

And, again, these are the 13 studies that have been funded thus far. Yesterday we had a pre-meeting that we brought in all of our researchers for them to give us an update on where they're at with their studies. We heard some really fantastic presentations. And, again, you'll hear a little bit about some of these studies later on. All this information is on our website, so if you're interested in the studies that we're funding extramurally, go to our website. You can click on the study. There's a brief description of what it is they're doing in the study, their aims. And, again, any time publications are made from these studies, we will secure open access and put the study

findings on our website. And we'll also run social media when these new publications are available.

The National ALS Biorepository, I'm not going to go into a whole lot of detail, because McKing will go into great detail about what they're doing and how this is going to work. But we know that having not only epi data but biosamples is very important for research. And so we just completed a four-year feasibility study back in September. Is it feasible for the National ALS Registry to implement a National ALS Biorepository? And so the bottom line is, yes, it's feasible and warranted, and we're moving forward with the Biorepository.

But through the pilot, we were able to collect about 330 -- biospecimens from 330 people. This included blood, hair, nails, saliva, and urine. We're even doing postmortem collections as well. I believe we're up to 19 postmortem collections now, and that's collecting brain, bone, spinal cord, CSF muscle, and as I mentioned, we're going to be launching this fall. Right now we're just waiting for OMB approval. The Office of Management and Budget in Washington, D.C. has to give approval for not only this but many government projects and studies, and so we expect this fall we will get approval.

Once we get approval then we will be able to officially start the Biorepository. But right now we do have samples available for researchers to use, and so any of the researchers in the room that are interested, we can talk to us offline. In this picture here is the actual facility that's storing the pre-mortem samples. It's in Rockville, Maryland. We actually, a month or two ago, made a site visit and toured it, and so, not only can we tell you about it but we were there to see and witness it and how they operate. So we have a good working relationship with this company.

And then lastly, I just want to mention this is another critical endeavor that we're launching right now. So we're collecting a lot of stuff; right? We're collecting a lot of epi data, risk factor data. Now we'll be collecting a lot of biospecimen data. So what we want to do and what we're in the process of doing right now is creating an integrated data/biospecimen platform. And this platform, it's going to be an online platform. Researchers can go to our Registry website, and they can actually request epi data. You know, maybe someone's interested in having data from the military risk factor module. Maybe they're just interested in getting good specimens. Or maybe they're interested in pairing the biospecimens with the data. So what we're doing right now is creating this online platform where a researcher can come in and indicate what it is that they want. They would upload a standard application that would cover things like what's the study goals and the aims. We'd want to see the protocol, make sure that they have IRB approval and other information. And this is actually similar to the way that we have it set up now for the recruitment process in which some of you are familiar.

If you want to use the registry right now for recruitment purposes you can go to our website and fill out the standardized forms, upload it, and it comes to us where we evaluate. And so this is going to be the same principle for this new integrated data/biospecimen platform. Again, we have a very big package at OMB right now, and so this is one of the things that we're seeking approval for. So we're hoping by this fall that we'll get final approval and we'll be able to launch this platform to make it easy and more efficient for researchers to come in and request whatever it is that they're interested in.

So, in summary, again, this is the first registry of its kind on the national level in the U.S. We're doing everything that we can to follow the letter of the law and the congressional mandate, looking at the metrics that they specified in the bill. We're using the Registry for recruitment purposes, helping companies and researchers populate their studies, funding extramural research. Again, talk about the Biorepository, this is a new exciting endeavor, and then this new platform that I mentioned, we really think it's going to be a big help to researchers around the country, and around the world, who want access to National ALS Registry data.

I believe you've seen this slide before. Again, this is not an all-encompassing slide, but it gets at the spirit of what we're trying to say. We're not in this alone. We're all in this together, whether you're a neurologist or you're a researcher or you're an epidemiologist or family member, we all have to work together to make sure that our PALS out there know about the Registry, they know how to go and enroll in the Registry, and so we really, kind of rely on one another to make this happen. And so the more that we can educate PALS about the registry I think the better and the stronger that this project is going to be.

And with that, I will take questions. Again, if you have detailed questions about the Biorepository or things like that, you can ask it here, but, we're going to have subsequent sessions on some of these things in detail. So any questions?

Ed.

Ed Kasarskis, University of Kentucky and VA Medical Centers

Kevin, I guess I say this every year, but I think we all have to thank you for your leadership on this, because people who don't know the history of the headwinds that you've faced to try to get this done don't really appreciate the magnitude of the effort. And so that's my annual thanks or behalf of everybody.

But the question I have -- and this, I think, perhaps feeds into PR with individuals, meaning mostly patients -- is you've never mentioned what your budget is for this thing, because it all looks magical, like it happens. But what is the annual budget to run the Registry as you have it currently?

I would say we spend about a third of our budget really doing internal things like paying salaries, purchasing data, analyzing data completeness, conference travel, CDC overhead, etc. The other two-thirds is being pushed out the door in terms of promotion contracts, external epidemiological studies, and the Biorepository. But I will say that for the last year, our budget was about six million to get a lot of the stuff done. Now it has increased since then, and you'll see, especially from the ALS Association, if you subscribe to their mailings, you know, they're always helping, along with the Muscular Dystrophy Association -- to go to congress to emphasize the importance of the Registry. For example, this year \$10 million was requested. But after appropriations and CDC overhead, we're more down toward the 6-7-million-dollar mark. But regardless of what funding amount we ultimately receive, we're grateful.

And, again, we try to use the money wisely in a lot of different ways, not only for research but for registry promotion as well. We can't just do it ourselves. We can't necessarily rely on docs, because not all docs or neurologists know about the Registry, as you'll hear from some of our presenters. So, it does take a lot of work, and we can't do it without people in this room, especially the support groups.

So I don't know if that answers your question. But the good thing is the budget has been fairly robust, and it's continued to go up in the trajectory format over the last couple years; whereas, if you look at other CDC programs and budgets, their budgets are either flat lined or they're going down. So we've been very happy with the support that we're getting from our partners and congress.

Orla Hardiman, Trinity College, Dublin, Ireland

Thanks very much, Kevin. Just like to thank you for having the foresight to provide funding for a project that has relevance to the U.S. But is not actually going to be conducted within the U.S. It's going to be conducted, as you know, in South America. And also as the person I think our ALS Register is the longest running continuous register for ALS in the world.

Right.

I think that you've outlined all the significant benefits, and I don't think they can be underestimated how valuable having a very complete dataset of people with ALS in a defined geographic area is important.

One quick question about the familial ALS, because this is obviously something of a hot potato, as to how do we define familial ALS. So, within the registry, we struggle with this in Ireland and also in Europe, as to what sort of definition we should use. In our register in Ireland we define familial ALS, for registry purposes, as one -- first-degree relative, another first-degree relative, and it's 5%. But if you extend it out to somebody in the family with either ALS and FTD that's known to the family or that we can link families, it's actually 20%. So it depends on how you define it.

Kevin Horton, ATSDR

So we actually define ours as first-degree relative as well.

Wendy Kaye, McKing Consulting

It's parents, siblings, and children. So it's only first degree.

First degree eligibility.

Yes, only first degree.

So that's pretty good. So that's only 5% in ours, and that's over 20 years. That it's pretty good, yeah.

And, you know, again, when we started this, we looked at the inventory of registries around the world. Obviously the Irish Registry is one of the ones we really looked at, because you're right, you guys are one of the longest running registries.

Sorry. The longest running.

Right.

Okay.

If I could just quickly add, this is Paul Mehta here. So historically we made the push to funding the grants that you guys were awarded. There was pushback internally from our Grants Department about, you know, not funding this internationally. And I made the argument that ALS does not stop at the borders of the U.S. It's international, and we must learn from our partners overseas, such as the Irish Registry as well. And so we're certainly happy to have you guys on board as an international border, and we can certainly learn from you, and vice versa.

Orla Hardiman, Trinity College, Dublin, Ireland

Could I just comment? The study that you're funding is actually a collaboration with our European study. It's actually using the same methodology as we've used to do the same study across three different registries in Europe. Actually, five different registries in three different countries. So it will be a very, hopefully, very successful project, but it will certainly give us a lot of information.

Right.

I agree.

Do we have time for one more?

One more question.

Hiroshi.

Hiroshi Mitsumoto, Columbia University

So I'd like to thank you to Ed and, really, some of you are still new and, really, several years ago the first time, based on ALS Association's tremendous effort to make this national registry, and Kevin presented one of annual meeting of ANA, and at the news meeting, there were about 50 people there, mostly, of course, neurologists, with tremendous skepticism and criticism and comments. So, really, I think we are now taking for granted for this National ALS Registry. But I think as Kevin and his team, preference and progress, we have gone a long way to come to this level. So, really, I think I congratulate you and your team. Thank you have much.

Thanks.

I've been at this long enough, you've got to have thick skin. You know, not everyone is going to agree with you in terms of what you're doing, how you spend your money, what methods you use. Not only for ALS but for any government project, there's going to be skeptics out there. But to have the support of neurologists and patients who can really see the value of something like

this makes all the difference in the world. And you're right, we have made a lot of progress, but it's not me, it's everyone, and it's patients. If the patients didn't participate, we wouldn't be here.

Okay, Ben, one last comment.

Benjamin Brooks, University of North Carolina

I just want to make one important comment is the relevant financial efficiency that you're using. Essentially the CDC gives .1 ice bucket unit annually to do this, and you are able to achieve this with .07 ice bucket units, so I think that should be in the record for sure.

Thank you. And so we'll be here all day. If you want to ask questions, in the public forum or offline, feel free to do that.

Thank you.

All right, our next speaker is Paul Mehta, National ALS Registry Principal Investigator.

Annual Report on Registry Results

Paul Mehta, MD

National ALS Registry Principle Investigator

Environmental Health Surveillance Branch, DTHHS

Agency for Toxic Substances and Disease Registry

Thank you.

Hopefully you can hear me okay.

So I'm going to be giving you an overview of the 2012/2013 national prevalence estimates, just very quickly, the data are currently embargoed, and so we will release it tomorrow, like Kevin mentioned.

And so we wanted to make sure -- we actually had to go to the MMWR, the journal where we'll be publishing these particular findings and to get the permission to present this information, and they were fine with it. But if you could refrain from sharing this information outside this room until it is released that would be great.

A quick outline of the presentation.

I'll be giving you a background of the report, which is coming out tomorrow, as well as findings from the report 2012/2013 estimates, as well as 2010/2011 revised prevalence as well, and as well as a theory for increased prevalence estimates, why we feel the prevalence has increased, limitations, as well as take-home messages and conclusions, and next steps. And finally, a Q&A session as well.

So, just very quickly, before I start, I just want to mention, this is a very, very -- you know, there's been some pushback, hey, why can't we get these reports out on a yearly basis.

I mean, it's a very, very, very difficult and challenging process. We work with all of our partners, all the various databases out there, Medicare, Medicaid to a certain extent, VA, and getting in all the data, getting it cleaned up, getting it validated, getting it cleared.

So we actually put this into clearance, I believe, like, around March, and so it goes into internal clearance at CDC, where it goes through our division, leadership, and then it goes to the OD, which is our division leadership just above the Office of Director in our own division, and then it goes to CDC, then it goes beyond CDC to finally land on the steps of MMWR, who themselves will go ahead and, you know, look over the report and make revisions and so forth. And we sent this to them, like I mentioned, February/March timeframe.

And so we were hoping to have it published sooner, but with the impending Zika epidemic, there's been some challenges of getting it to the actual schedule. But I can tell you this was not planned. This certainly was one of those things that having it -- you know, present it at the meeting today is certainly opportune.

So just a quick background.

So we chose our MMWR because it is free. There's no subscription required. We work with these guys very closely, and so more importantly, they also focus on surveillance trends, and so this is really important to us, because this is a surveillance summary report after all. And it also allows us to estimate a timeline for publication, so we were told about mid-July that August 4th would be the publication date, and so this allows us to kind of go ahead and prepare and let the partners know and so forth. So I think it's very important for us to work with MMWR in the future, only because it allows us to have more flexibility.

I briefly touched upon why the delay. Like I mentioned, I mean this is a long process. It's not just something that we can just do very quickly to go ahead and put these reports out. Validation takes time, and more importantly, clearance takes time, so.

So these are the findings from the second report. Just to quickly clarify, it covers calendar years from January 1, 2012, through December 31st, 2013. And 2012 and 2013, we found 14,713 cases in 2012, and 15,908 in 2013, which is the registry, so this is portal, as well as national databases as well. And the prevalence has increased. In 2012 it was 4.7 cases per hundred thousand, and in 2013 it's 5.0 cases per hundred thousand. So as you can see, it has increased from initially, which was four back in 2010/2011.

ALS continues to be more common in whites, males and persons between the ages of 16 and 69. The lowest number of ALS cases occur in those between ages 18 and 39 and those greater than 80 years old. Males had a higher prevalence than females across all the data sources.

Continuing on the findings, so we also revised the actual estimate for 2010/2011. I'll tell you why we did that shortly. So that went ahead and increased the prevalence rate from 3.9 to 4.3 or 13,292 cases, which is a slight increase from 12,187. But the findings were unchanged. So the sex and age groups also remained the same. And the increase of the cases came from the national databases alone and not from the portal end. And more importantly, these findings are consistent with other registries out there, as well as other studies as well.

This histogram right here shows the actual prevalence rates by age groups, and as you can see, 18 to 39 for 2012/2013 has the lowest, and it gradually increases as the age advances. And so between the ages of 60 and 69, that's where it starts jumping up, and then 70 to 79 is where it increases, and it gradually decreases as patients pass away.

Prevalence rates by sex for 2012, males were 5.9 and females were 3.5 for 100,000. This was a ratio of 1.6 to 1. And for 2013, males were 6.4, and females were 3.7, with a ratio of 1.7 to 1. So there was an uptick in 2013, and the totals, as you can see, were 4.7 and 5.0.

Going to the actual prevalence rates by race, so whites, like we mentioned before, they do have the highest prevalence estimates of ALS. And for this one, whites were 5.0 per 100,000, while blacks were 2.4. So whites were pretty much double. And in 2013 it was 5.3 versus 2.4 per 100,000.

So the theory behind the increased prevalence is multifold. So, first of all, there was a revision in the algorithm itself, which led to better case ascertainment, so capturing of the cases that is. The original criteria for the algorithms was looking at an encounter code for ALS, as well as one or greater years of either having a prescription for ALS or death certificate for ALS as a cause of death.

The updated criteria included the addition of more elements. So persons who had any of the two to three elements; for example, a prescription for Riluzole, death certificate, or death certificate and encounter code, or prescription for Riluzole, as well as encounter for ALS. And this revision allowed us to have a better case ascertainment, and this also, in a way, helps us to also capture Medicare Advantage data as well, which is also important, since we don't directly get that data now.

And in addition, we also included the national death index as well, looking at the vital status to determine if these patients were actually possible cases on a definite for any less or not possible. Those who were determined to be possible cases were aside to be looked at later. And this updated algorithm was applied for 2010/2011, as well as '12 and '13.

Looking at -- and as well as our theory for the increased prevalence is increased public awareness. Since the Registry was launched in October 2010, there's been a gradual increase in awareness, and this is made possible by the efforts of the ALS Association, MDA, Les Turner, and other groups as well. We've also leveraged social media channels too, so Facebook and Twitter has been very, very important. And so whenever we tweet something, we ask our partners to also reciprocate retweet as well. And this has also led to increased web portal enrollment in '12 and '13, leading the patients converting into actual registrants themselves.

The ice bucket challenge was tremendously helpful. You know, our enrollment and web traffic increased by 8% and 45% respectively. So the IBC certainly helped to raise awareness for ALS multifold, and that, by itself, we feel certainly led to increased individuals coming to the website and converting into registrants.

The limitations, so with like any report, you're going to have limitations. Like Kevin mentioned, ALS still not a notifiable disease. It's not reported to state health departments. It's not an infectious disease. For example, HIV, STIs, those are all infectious diseases and reported to the state health department, resulting in a much better accurateness of incidence, as well as prevalence for these diseases. Because we do not receive this reported information, we have developed an algorithm using these various databases, as well as the portal, to do an estimate of prevalence. So without being notifiable, it's a challenge, but we certainly feel that we have been successful in capturing these cases without having this notifiable card in our pocket.

Another thing is duplicate records could exist, but they're unlikely to affect the overall conclusions, as well as Kevin mentioned we can't calculate incidence at this time. Incidence is possible on the portal end. It is self-reported. But with the national databases, it's not there. And more importantly, you know, the registry is maturing. We are gradually doing a better job ascertaining cases, capturing cases, working with partners and so forth. And this is certainly leading to a better understanding of ALS. But as well as you mature further, we feel the prevalence at this time may increase, or may not increase. We're not just sure.

And some of the take-home messages I do want to say is, this does not mean that the number of ALS cases is increasing in the U.S. That's one of the important take-home messages. We feel we're doing a better job of capturing these cases, and so possibly in the second report we can determine more of a trend if we feel a trend is up ticking and so forth. And like I mentioned, this is also consistent with other studies out there, whites, males, and those between the ages of 60 and 69 tend to have the highest prevalence of ALS. Males, for whatever reason, are diagnosed higher than females, and ALS affects whites more than blacks. And like I mentioned about the maturity, we are maturing. We are doing a much better job of capturing cases.

Next steps, we'll be working on a third report. We're in the process of getting all these data sources from Medicare, VHA internally, and once this happens, probably in the fall of this year, we are hopefully looking for a publication sometime next summer. More importantly, we also have additional resources on board with the Registry. So we have some more epidemiologists, some more stats people as well to help us out, to go ahead and crunch the data, to go ahead and look at it and so forth, and that's very, very important. So with these additional resources we're bringing in more experts to help us out to go ahead and get these reports out sooner.

Another thing we want to do is look at ALS geographically nationally perhaps, and so I think that's very important. But there are some IRB/OMB limitations. For example, we cannot report ALS lower than the state level. Because it is a rare disease, we can't say, in a specific county in Georgia, there are two or three cases. It just doesn't work that way, because there are prohibitions about releasing data and possibly inadvertently identifying a patient. So we're under strict IRB orders not to do any sort of release of data below the state level.

And the questions to be asked, certainly in future reports, is there an increase in the ALS prevalence rate? We're not sure if our 2014, like I mentioned, that data is still becoming in-house, and are there any changes regarding the sex, race, or age groups? I believe that the data will probably remain the same.

We're also going to be including Medicare hospice data, which is exciting, because this has information on Medicare Advantage, which is part of the Medicare with the HMOs use. So, for example, the State of California uses HMOs much more heavily than other states, and so hopefully we can get a better case ascertainment from these particular states, as well as by leveraging Medicare hospice data.

For 2015, it's somewhat of a challenge. As many of you are aware, ICD-10 came into effect on October 1st. Well since it came into effect, there's no specific code for ALS. We've been working with CDC and other partners out there to request an update to ICD-10 to have a specific code for ALS, and that makes it somewhat difficult to estimate prevalence if there's no sort of specific code. I mean we're going to have a big umbrella of all the MNDs. And more importantly, this may require us to revisit the algorithm we currently have and make any necessary changes to it.

We're also going to be comparing our state and metro surveillance data with the data in the Registry, and this will allow us to have a much more accurate look at completeness of the registry, and as well as determining which minority groups are missing. We do know the portal, which is the website, does skew to a much more Caucasian population, and, therefore, we want to reach out to the minority communities, the Hispanics, the Asians, and the African Americans and so forth.

We're hoping for a winter 2017 publication date. This is currently in progress with our team to have this out hopefully in January/February of next year. Another important thing is capture/recapture methodology. Lorene Nelson will be giving you a presentation tomorrow on that, and that will allow us to estimate the number of possible missing cases in the Registry.

So the first report they're currently looking at 2010/2011, which I believe will be presented tomorrow, if I'm not mistaken, and then subsequent reports for 2012 and 2013 will also be looked at, and this will probably have a publication date of spring or summer of next year. But capture/recapture will, like I mentioned, allow us to give an estimate of the missing number of cases. So it's one of those things where we know, like with any surveillance system, you cannot capture all cases. It's virtually impossible to do that. So, therefore, with the capture/recapture methodology we could have an estimate regarding the amounts or the numbers we're actually possibly missing.

That's it in a nutshell, and I want to acknowledge the Registry staff, as well as the other folks at CDC who make this possible. So I'm here for questions.

Michael?

Michael Benatar, University of Miami

Thanks, Paul.

I wonder, are you able to break things out a little bit by cases that are being identified through the portal versus those through national databases? I'm wondering about sort of the bias of access to the portal that may be introduced? I'm thinking about the racial differences that you note and whether there's anything to learn from sort of looking individually at the subsets coming from the

two sources. I realize there's overlap but the national datasets, I'm guessing, maybe have less potential for bias.

Yeah, the national datasets, we get about, I'd say, 75 to 80% of the cases from the national databases and 20% from the portal. And with the portal, because it's access to the internet, there are socioeconomics, SES also plays into a factor awareness, getting online and so forth. So we do know it does skew a little bit to a much more Caucasian population and a population that has access to the internet itself. With Medicare and Medicaid, VHA, that's much more homogenous. Wendy, is that correct? I mean, we're picking up a lot more as in terms that cases are coming from there with the algorithm. But we know there is a bias in the portal, but probably not as much with the databases.

Wendy Kaye, McKing Consulting

The other issue with the portal is we're able to pick up people who are younger. I mean, I think we're skewing that way as well. So the people that you would expect to be missing from something like Medicare for example, so, yes, they do tend to be whiter, and probably more educated, because they have access to computers. But they are also somebody -- people that we couldn't pick up any other way, because they're not using those benefits. Even though they would be eligible for Medicare benefits with ALS, there seems to be some kind of lag, I think, before they get in.

And that's where awareness comes in so importantly. Like what Kevin mentioned earlier, you know, the boots on the ground are the partners out there, are the neurologists, or the ALS Association, MDA, Les Turner, and so forth, to raise awareness. To let people know about the Registry is very, very important. To have them, you know, enroll and take surveys. You know, we can only do so much, as in terms of like, giving them information, doing infographics, brochures and so much. But, really, with your efforts, that's really important to go ahead and raise awareness and draw that particular cohort, which is missing, into the portal end.

Pam, do you have a question?

Pam Factor-Litvak, Columbia University

So when I was just glancing at the data that you presented, it seemed to me that the largest increases over the time period were in whites, in males, and in younger age groups. And so that may open up some other hypotheses perhaps as to why there seems to be an increase over the time period.

Sure.

Marc, state your name, please.

Mark Weisskopf, Harvard

So just thinking about it now, it strikes me that another way to sort of look at this is kind of potentially missing cases, is actually to take the people who respond to the portal that are captured in your other databases and determine who in your other databases those web people

are missing; right, and then you can sort of use that to figure out for that 20% that don't show up in your databases how many people they're missing sure. And you can up at that point.

Steven.

Steven Goutman, University of Michigan

One of my questions about -- great very interesting data. One of my questions about prevalence is do you have the ability to see if people are living longer with this disease with the -- it sounds like some of the reasons why you think the prevalence is increasing is because of better case ascertainment.

We are looking at ALS survival, but that's coming from the portal end, not from the national databases, per se. So we are in the process of looking at that as well, to see if we can report on that and do some sort of measure on that as well.

My other questions is, in terms of case ascertainment, when I sign death certificates, sometimes I get a little bit of pushback for listing ALS as the diagnosis. I pushback and include it. But potentially if others who are non-ALS physicians are signing death certificates and they get pushback from the County Health Department and they say, you know, ALS is not a cause of death, then there may be a possibility there that you miss capturing some of these cases.

Sure.

And I think Wendy looked at about 20,000 death certificates she mentioned before, and I think a percentage of them actually were misclassified.

So can you say that again?

I'm sorry.

Sometimes when I sign a death certificate the Health Department will say, "ALS is not a cause of death," and, "Please remove it from your diagnosis list. And I push back and say, "No, this is the cause of death.

But for those of us who --

Do they not want you to put it as the primary cause and they want you to put down as contributory cause?

That's sometimes the issue.

Right.

But I wonder sometimes, though, for people who don't understand the significance of listing this as a diagnosis may just take it off entirely and say respiratory failure, and then you miss out on case ascertainment using the algorithm that was presented, especially with the updates at ICD-10.

Wendy Kaye, McKing Consulting

Well two things; one, you can't get in with just a death certificate, so, yes, that might prevent us from providing a few people. But there are six ways to get into the algorithm, and death certificate is considered only as a sub-part of one of them. The second thing is, is that as Paul mentioned, I read 21,000 death certificates and 21% are not ALS. 17 to 18% were supranuclear palsy.

Sorry, within G12.2, which is supposedly neuron disease, 17 to 18% were supranuclear palsy, which really should be in the Parkinson disease category and not in that one. The other ones were probably motor neuron disease but not ALS or not well specified, or not quite sure what they were. But, you know, I read the multiple causes death categories, and if ALS was in any of the fields I put it in with ALS. So I think you're right, we're probably missing a few. But we also gain a few, because when we read the -- I'll give you an example.

I got one from Georgia for the state project and I said, "I don't think this is ALS. And I read the codes, and it said -- it was supposed to be also has blah, blah, blah, and the person had typoed, and the clerk had typed -- coded it for ALS, and I called the desk registrar who I know and I said, "Could you take a look at this. I really don't think this is ALS. They had heart disease and a stroke and all these other -- and I think it's just a typo." And she just started laughing. "You know, yeah, you're right, it is a typo, but I'm not allowed to change it. I have to call the doctor and get them to fix this." So that's, like, my one anecdote of, yeah, they are only as good as -- and some of them I couldn't read because in some states they're still letting you all write on the death certificates.

Orla Hardiman, Trinity College, Dublin, Ireland

Dublin again.

One of the things that we see -- On our registers is something called "Diagnostic Creep". We've just been looking at the long-standing registers writing review. You see a creep in the diagnosis from the mid '90s through -- because our increased recognition of FTD. So people who are coming to our clinics now with FTD motor system degeneration, we were classifying them as ALS FTD. Whereas in the past we wouldn't have captured them. So we've seen an increase in prevalence of ALS in Ireland, which is partly related to and proven in ascertainment over the first ten years. And so, part of it has to be with really subtle changes in diagnostic criteria, so I don't know if that's something that's going to be an issue in the American registry, but certainly over longstanding registries you see this sort of creep that's changing and diagnostic criteria and inclusion of clinical phenotypes that we might not have necessarily have seen in the past that now come to us.

Walter Bradley, University of Miami

You mentioned about the problem of the ICD-10 not having a specific code, and I worked with the WHO, back in the early 1990s in fact, and we published what is called the ICD-10 "Neurological Expansion", or "Neurological Adaptation." That book is published and has sub-codes for all neurological conditions, which were not in the original ICD-10. I don't think that's achieved very great significance in terms of perhaps only academic departments having used it.

I'm sure that it's not going to be of any great value to you because it isn't being used. On the other hand, if you are going and trying to see if you can increase the specificity of the ICD-10, there's the basis for you for doing so.

Paul Mehta, National ALS Registry

Yeah, we had a justification that we sent over to -- actually, there's a working group at CDC which works with WHO to make this happen. So we were working with them, gave them justification why making that change should take place. Hopefully they'll take our recommendations, and October 1st of this year, there will be an update on that. But perhaps you've got some pull with WHO to go ahead and give them a call, Wally for us.

Walter Bradley, University of Miami

Well I'm not sure I have any pull, but it's a published book, and, therefore, it's openly available. Sure.

Right.

But the G12.2 expansion includes final muscular atrophy within the ALS category is what the issue is.

Have you looked at the --

Yes, I've seen the [inaudible].

Yes. I've seen the one that the U.S. is going to use.

No, have you looked at the original application. I don't mean reference to it.

I haven't seen that one. But the one the U.S. is going to use includes spinal muscular atrophy within the ALS category.

And we have proposed that they take that out and they move it into the motor neuron disease not otherwise specified, or the general category, and take it out of G12.21.

Walter Bradley, University of Miami

Well the wonderful thing about producing the ICD-10 Neurological Adaptation is that those of us who are obsessive, we were able to do sub-fractionate all the way down, so there are individual codes in there for spinal muscular atrophy, infantile onset, adult onset, ALS, PLS, SMA, and so forth.

Right. But that's not the one the U.S. adopted.

Well, but I think you're in a position to be able to push it.

Bryan.

Bryan Traynor

This is a big issue. I mean, Walter contributed greatly to the ICD-9 and all of those things. Tory Beggy is on the committee for ICD-11. Professor El Shalabi, Professor Hardiman, and others have come together, trying to put out a paper on classification, because this is very important.

Absolutely.

Particularly Dr. Hardiman's issue with respect to the emergence of FTD. Your presentation of 4% with dementia may change over time if, indeed, we are going to see what's happening in Europe happen in the United States as well.

Alicia Fraser, Massachusetts ALS Registry

And I just wanted to follow up on the ICD-10 issue and ask if part of your request for updating it has to do with are you just trying to update that sub-code or have you also run -- so we've run into an issue of even using that sub-code that data are often not reported out that far in medical databases vital records statistics. So even if the code exists and if they update the specificity of it, it's really not available in most of the databases that we use. Have you encountered that as well?

We're not using 15 yet. But my understanding is, is that the expansion was required as of October 1.

Of last year?

Of last year. Yeah. But it was not required prior to that time.

So 2014 should be fine, it's just when 2015 comes into place, and I think January 1st, 30th of September we'll be fine, but it's just October 1st when that new code comes in, that's when we can capture the cases.

Lorene Nelson, Stanford University

I wanted to follow up on the Medicare Advantage as a new feature in the 2012/2013. Can you determine how much of the bump you got from that?

Wendy, how much of a bump was that?

Wendy Kaye, McKing Consulting

Well first let me clarify. We haven't -- Medicare advantage is the HMO option, and so those do not have claims data. In other words, it's just like any other HMO, Medicare pays your fee for Kaiser or Geisinger wherever you are, and they don't provide individual encounters. And the algorithm requires encounters. And some Medicare Advantage also include prescriptions, so those people would be out. But if they're taking regular Part D and they have a death certificate potentially, we would be able to find them.

We don't know that they have Part D -- they have taken Medicare Advantage or not.

But that is sort -- I guess that those are why we have people who we have no claims data on, but we have prescription data and we have a death certificate that it's most likely that's because they've taken an HMO option.

The advantage, as Paul mentioned, in adding the hospice data is that, for whatever reason, which I don't understand sometimes why CMS does it, but they have put all hospice encounters into one file, regardless of whether you are fee for service or HMO, and that includes whether you're in a facility or getting home health care or respite care. And so that will be a place to find an encounter with a medical person that we didn't have before. So that may also help find some people who are taking the HMO option that we know we're missing, and we've always sort of known we're missing, but if they don't self-register, there's no way to find them.

We have time for a couple more questions.

Andrea Pauls-Backman, Les Turner ALS Foundation

I have a comment regarding given the ALS Registry on your finding more incidence or higher incidence, my question to Paul is, in those cases, and you may [inaudible], but in those cases that are [inaudible], also with ALS, are they capturing them, and if not [inaudible].

So we capture ALS first. I mean regarding FTD, if that's in there, I mean it's like a secondary thing. But ALS we're capturing first in terms of the top, and then FTD would also be a part of that diagnosis as well.

So we don't do FTD first then ALS. It's ALS first, then FTD.

Wendy Kaye, McKing Consulting

I mean, as long as they have a code in there for ALS. Or they report that a doctor told them they had ALS then we'll find them, but we're not combining them.

The problem is other scoring diagnostic criteria, because other scoring criteria were defined before we recognized the link between ALS and FTD. So we have this problem in our registry as well, and we have a suspense list as well, where people come in and they have frontal dementia and risk reflexes. So they wouldn't -- from a neurological point, they're an abnormal exam but they don't fulfill the criteria for ALS, so we have a -- we have decided to put those into a suspended list, and then over time, as those patients progress, because we see them regularly, they migrate over to the ALS registry. But it's a very difficult one, because many of those patients will be familiar, so they'll have another family member who had classical ALS, some with cognitive impairment and some without.

So when we revise the other score criteria to include the presentation with cognitive impairment, I think this problem will resolve. But by definition, at present, you can't include them if they don't have signs of ALS. But they're the same disease, that's the problem.

We have time for one more. Mark.

Mark Weisskopf, Harvard

So I think we've discussed this issue a little bit, so we going to have to go on at length if this is a repeat. My first question is with this HMO issue, is it known for certain that someone was -- If they were in the HMO were not be captured by the other databases here? So if they were in the HMO, would they not be captured?

They will not be in Medicare. They will not be in that file. They could be in the VA file, though, because they could have VA benefits. But they won't be in the Medicare file.

The reason I just raised that is that there are many places, including us at Harvard, that are working with these new you know a lot of the HMOs are partnering with academic institutions to use their databases to do exactly this kind of thing.

I can't remember where we were in the discussions with HMOs to provide data, but we're talking to Optum/UnitedHealthcare -- places like this that we can purchase their data. We've also discussed it internally as well with the Blue Cross Blue Shields, the Uniteds, and so forth, the private pay health care out there as well. And it's kind of cumbersome because they don't have to do this if we ask them. We even thought about looking at the back end, possibly looking at let's say at [Vicks Server], some of the other back-end systems as well. But I think that portion is probably what we're missing out there -- is the people, individuals, who are going through their normal health care companies, insurance companies, right now. And they're not going into Medicare or they're not going into VA. And that's certainly a segment we are missing.

Wendy Kaye, McKing Consulting

But the issue is that, by law, those groups cannot give us identifiers. So we can't cross-reference them across the Registry. We could do an estimate in those, separately. But we can't add people to the Registry based on those data because we can't get identifiers.

And that was the point of my first question because if you know they're not in your other databases, then you could just count the ones in the HMOs.

Yeah, but we don't know exactly.

All right, it's time to move on. Paul, thank you very much.

You're welcome.

Our next speaker is Alicia Fraser from Massachusetts Department of Health. And she's going to share the report from their Registry.

Massachusetts ALS Registry Report

Alicia J. Fraser, MPH, DSc
Assistant Director, Environmental Epidemiology Program
Bureau of Environmental Health
Massachusetts Department of Public Health

Hi, I just want to thank ATSDR for inviting us here. It's really a pleasure to be here, and we're really excited this year that we finally have enough data and resources available to release a report, and I did bring copies of that data brief. But I'm also going to share with you some additional analysis that we've done that, like Paul mentioned for his data, haven't been published.

So those additional tables in the slides -- if you wouldn't mind keeping those to yourselves in the next year or so until they come out. Before I get started, I'm going to give you a little history of our Registry. I'm not sure how familiar you are with the history. And I always like to add a little comic relief, so this is what I got when I googled "history" and "cats." I like cats so just keep you guys awake here.

So, as a State Department of Public Health, we routinely get inquiries from the public regarding concerns of either potential environmental hazards in their area that may be affecting health or perceptions of disease clusters. And often these are about cancer, the most frequent one. But we pride ourselves historically as being very responsive to these issues.

And back in the '80s, there was a community in Southeastern Massachusetts called Middleborough, where communities were really concerned about a number of hazardous waste sites, and the perception that some autoimmune and neurological diseases may be elevated in the area. So at that time, there was very little surveillance data available on ALS, nothing available in Massachusetts. And actually, a researcher from Harvard did a mortality study and found that there were elevated rates of mortality associated with ALS but it was inconclusive.

So, jumping ahead here, that was in the 1980s. And then about a decade later, in the late '90s, the community concern over that time period in part because there was no data available patients, families, ALS advocacy organizations really lobbied the legislature until in 2003 an amendment was passed establishing a statewide Registry.

And around the same time, kind of in a separate effort, Massachusetts applied for and received a research grant from ATSDR in order to develop methodologies for surveillance for ALS. There were, I believe, four other states that also were granted those projects. And so we used that money to go back to Southeastern Massachusetts, develop methods for surveillance, and do a much bigger study.

At that time, we looked at cases between 1998 and 2003; and interestingly, we did not find a single case in Middleborough during that time period. So if there had previously been any kind of elevation that was associated with an environmental exposure, it must have been something that occurred earlier. We also did not find an elevated prevalence overall in the area. The prevalence that was found was 2.4 cases per 100,000, which is similar to what is reported elsewhere. But the main thing that came out of this effort was the development of our methods that we're still using now for the Registry.

And then because of the legislative mandate for the Registry, we were given some State money to do planning. And so we did a feasibility study. We did a couple of additional pilot studies

trying to determine what methods would be needed to allow physicians and neurologists to feasibly report cases on an annual routine basis, as opposed to just a single time for the study. And we did focus groups with families, physicians -- both general neurologists as well as ALS specialists.

A few important things came out of that. One is that our original abstract form was 20 pages long, and now it's 2 pages long. We had big ambitions of collecting all kinds of risk information, case histories, and residential histories. It just wasn't feasible to do. Another thing was that we decided to have an ALS Advisory Committee, which is supposed to meet annually. We're hoping to meet again in the coming years. And the importance of using the vital records in order to not only identify cases, but also follow up patients after they've been in the Registry. And using as broad a criteria as possible for initial capture because we also do physician verification, so we want to have a broad capture at first.

This is just a timeline here to show you after 2003 when the Registry was established, in 2004 they actually made it a reportable disease as well, which helps a lot. The feasibility study was in 2005, and then over the next couple of years were those other pilot projects.

And then finally, in 2008, we actually implemented our State Registry, although we didn't receive State funding again until 2013. And I actually came on board as the Director of the Registry in 2014. And we've just been playing catch up, really, trying to get cases from all of those previous years when we didn't have resources for staffing.

So like I said, we are really excited to be almost caught up. We're actually going to start collecting 2015 cases later this year. And we will see about those ICD-10 issues.

Overall, our purpose is what you'd expect: to determine the prevalence and incidence of ALS throughout Massachusetts; to investigate geographic patterns, as well as temporal trends; but also to explore the impact of environmental factors on rates of disease. Our Registry is housed in the Bureau of Environmental Health, and so that is a key focus of our project. And then, finally, to develop and maintain a population-based database that can be accessible to researchers.

Our data sources are divided into primary and secondary sources. Our primary sources are neurologists, which are identified through the Medical Licensure Board. And we send solicitation requests annually to all neurologists in the state. We also separately send requests to all hospitals, as well as separate requests to Special Eds, Neurology and ALS clinics because sometimes they have separate medical record databases.

And then our secondary sources: vital statistics for death records, hospices and nursing homes, and ALS advocacy organizations, those latter two of which were more important in the early years of the Registry, particularly the hospices and nursing homes, when those patients we might not have captured otherwise because they may at that point not be routinely seeing physicians outside of that facility.

The cases by source this blue, the 43%, this is over the five-year period of 2005 to 2011 those are cases that came only from a neurologist hospital or ALS clinic. Fifty four percent of our cases

were reported at least once by both a hospital or a neurologist and one of those secondary sources. And only 3% were from a secondary source, and we saw that taper off over the years. So at this point, we're not actively seeking cases from hospices, nursing homes, or ALS advocacy organizations.

In terms of collection and verification, like I mentioned, it's every year. It's based on the ICD code. We have a nurse abstractor that is trained to extract all the relevant information. The first step is just whether they live in Massachusetts or not. We actually get a lot of out-of-state patients, I think because there are so many teaching hospitals in Boston. Patients come in for a diagnosis, but they don't live here; so they're ineligible. So we rule them out.

The nurse checks whether there's enough information to possibly diagnose ALS, and then we send it out to our consulting neurologists who use the El Escorial criteria to score the diagnosis from definite down to possible. There is definite, possible, indefinite, and suspected. All the possible and suspected, we continue to follow up for three additional years. And after that time, if we have not received enough information to conclusively say that it's ALS, then we stop following those patients.

Over the five-year period, we had 3,200 individual reports, which were actually just 2,300 unique names since some names were reported from multiple locations. Of those, there were only 1,800 that were Massachusetts residents; 1,500 that had enough information or were not clearly something else. Some of the time, the nurse can determine, oh, this is MS; this is clearly not ALS. And we don't send those out.

So we had 1,500 cases that we sent out for verification, and 1,100 of those were verified as ALS over the five-year period. So it's definitely a refinement down, and we definitely feel that the physician verification is an important step at this point. Although one of my goals for the next few years is to try to compare a nurse's diagnosis with a physician's if we were to, for example, not have funding forever, which is always a possibility.

And finally, our results on prevalence and incidence. This upper line is the age-adjusted annual prevalence of ALS in Massachusetts. It ranged from 5.1 to 5.9; the average was 5.6. And the incidence ranged from 2.0 to 2.5, with an average of 2.2. You will notice a slight upward trend in the incidence. These look like yes, the top bar, the prevalence. We think that this is possibly due to just incomplete capture during the early years of the Registry because we haven't seen any increase in incidence over that time period. But as the years go on, we can evaluate that; but it seems very likely that they were cases that we missed in the early years.

We also evaluated incidence and prevalence at the county and the community level. I'm not showing the community-level data because there were really not enough cases to even evaluate that, but we were mandated by the Legislature to do that. At this point, the county level data, there is still so much variability it's really hard to tell whether there are any geographic trends, although at this point we're not seeing any. This county, which is the one with the highest bar, I will point out is one of the islands. Very few people live there, so it's probably not a true elevation.

Incidence by age of onset looks very similar to Paul's graph here that he showed earlier. The peak age here of incidence is 70 to 79. And here I have it broken down by age at onset among males and females. The green bar is the female; those are the bars on the left. I'm not sure if you can see this clearly. We have an average age at onset of weakness of 65 in females and 61 in males. And then age at diagnosis, a year later for both of those groups. And then age at death ranging from four years after diagnosis for females and five years for males.

This is total cases by sex, just so that you can see the ratio. For incidence, we found a ratio of 1.2 cases of males per female; and the prevalence was 1.3. And comparing this to other reports, obviously, this is not a comprehensive list. Sorry, I don't have Ireland in here.

And this is the old measure for the National Registry, so I didn't know about your new data. We found it interesting that our prevalence was a little bit higher than the national measure, but it looks like your prevalence is coming up over the years; so that's very interesting. And also notice that the ratio of males to females is a little bit higher, and even higher now in the more recent data that was presented. So we're really interested in whether there is actually a difference in that ratio in Massachusetts or whether it's something to do with the difference in our collection strategies.

But overall, our results are really similar to what's seen in international estimates. I'm just giving here I picked Yugoslavia and Faroe Islands because they're kind of at the extremes of the range. And two of the CDC pilot registries that I have up here, LA County and New Jersey, I found interesting because the incidence, 1.2 and 1.7, is a little bit lower than what we're seeing. And the prevalence as well, 4.4, is a little bit lower. As far as the male/female ratio, these are kind of hovering more around the 1.2, although I'll note that California also looked at San Francisco Bay County; and they're male to female ratio was more like 1.4. So it seems clear that more males are getting this disease, but it's not clear to me exactly what that ratio is.

Some of the challenges that we face, that I'm sure that you are facing here as well, is trying to evaluate this at a smaller geographic scale, which is one of the primary missions of our Registry in Massachusetts. It's just a rare disease, and we don't have enough cases yet to really be able to do that. Patient migration is an important issue besides the ineligible cases. We're not sure necessarily on the number of patients that actually migrate to Massachusetts for care. And so in terms of looking at environmental exposure and associations, we would probably have a hard time doing that without doing a full-blown study using IRB and going back to patients to get case histories and residential histories. It's not going to stop us from trying though.

And we have had trouble getting patient data from the VA in the past because of their privacy regulations, and they are not required to report to us through our State. Just because we have a rule in Massachusetts that says that all physicians have to report to us, the Federal facilities are not beholden to that. I believe that's starting to shift. The VA clinic, the biggest one in Massachusetts actually, nearest Boston has recently started a specialized ALS clinic in the past few years. And we are starting to develop a good relationship with them. So I think that data are going to be easier to get in the future.

Case definition issues I know that's been mentioned here both with ICD-10, just in terms of collecting but also defining the disease and comparing rates across different studies. How are we

all defining it? Where are we cutting it off? For us, we're including every case down to possible and suspected; but we can always separate that data out and report it differently. And resources are always an issue.

Future goals as I mentioned, in general we would like to be able to use this data to better understand the causes of ALS. We'd like to be a resource for outside researchers and feel like we're at a point where we can actually start to provide that. So any of you who are interested in talking with us about collaborating or writing a proposal for IRB to use the patients in Massachusetts for studies to try to better understand the causes of ALS, or even for treatment studies, we would love to do more outreach and networking towards that goal. We would love to collaborate with the National Registry if there's anything we can do. I know that's been mentioned before. It's always been challenging with privacy issues. But if there's something we can do to try to compare, for example, cases that we're finding through our sort of more comprehensive and verified analysis to look at like the male/female ratio or something like that, we would love to do that.

And then we don't currently get National Death Index data. So patients that move out of state, we only know about their deaths by obituaries that we find. And then lastly, we do want to publish these results in more detailed analyses in the next year.

We have time for just one or two questions.

Kevin?

Kevin Horton, ATSDR

Very interesting data, thank you for coming down; we appreciate it. Just a couple of things so how are you guys evaluating the overall completeness of the Registry, and what's your reporting enforcement? Now that it's a reportable disease in Massachusetts, are there penalties for doctors or groups for not reporting; and, if so, have you actually challenged some of these people?

We have very few doctors that actually refuse to report; I only know of one since the Registry began that has actually refused to report. We get a fax from one physician every year that says, "I don't have any cases; but if I did, I wouldn't tell you about them." So that's a second person.

But this past year, we did have somebody who had a case and didn't want to report it. Actually, the patient was reported from a separate hospital; and we were trying to get past records to verify the diagnosis, and this doctor didn't want to share those records. And so that was the first time it had come up. We can file a report to the Board of Registration and Medicine, which controls their licenses. Technically, it is a licensure issue. We chose not to do that in this case, and we were able to work it out. But what I would like to do, and what hasn't been done we're actually hiring another epidemiologist this summer, which I'm really excited about. What I'd like to do is go back to some more historical data and actually look at the response rate across the state from year to year.

But from our physician consultants that I've spoken with, we feel really good about the completeness of our data, especially now in the later years of the Registry, because most patients

seek second opinions for one thing. And almost all patients go to one of the main hospitals or specialists in order to get that second opinion. So we get most of our patients from like just a few places.

Orla, you have a question?

Orla Hardiman, Trinity College, Dublin, Ireland

Yes, in your prevalence rates, the European prevalence rate is 6 to 8 per 100,000, not 2 to 3. So the incidence rates in the European registries are 2 to 3 per 100,000; and the prevalence rates are 6 to 8.

Are you saying that I flipped those on my slide? I think your slide the 2 to 3 per 100,000 would be incidence; the 6 to 8 per 100,000 would be prevalence.

Yes, sorry, I might have just flipped those.

Okay, one last question Ben?

Benjamin Brooks, University of North Carolina

Your prevalence creep could be an age creep; it could be a diagnostic creep or a survival creep. Have you looked at this, and is the Registry able to sort those out?

Yes, we do have the data to be able to at least sort out the survival creep for sure, also the age creep if you're suggesting people are younger patients. Yeah, so we could look at that as well. And the diagnostic creep is harder to evaluate.

If you cut it off at definite or probable, how does it look compared to your total?

So you think if more patients are being diagnosed, you're suggesting that there's a broader diagnosis that may be happening?

You were saying you're doing possible, probable?

We are doing that, yes. But I don't know that we could evaluate whether more patients are just being identified as having ALS than diagnosed in general.

Alicia, thank you very much; and let's hope Massachusetts keeps the funding up.

Thank you.

Just a reminder that you can tell if your microphone is on; it's got a green light.

Let's take a break. We're five minutes behind time, so let's move our return to 10:45. And if you can, keep your conversations in the room; it's easier to get everybody back in their seats.

Thank you.

[Break]

All right we're almost there. All right, let's get to our seats, please. I'd like to remind all of you, you were given a release form. And because we're being taped today and also I think there's going to be a picture later on at the end of the session, so it's a release to allow us to do that. So please turn those in at lunchtime if you can, if you haven't already. I'd like to start out after the break with Wendy Kaye, who is the Senior Scientist with McKing Corporation, who has been involved in many aspects of the study and, most recently, the Biorepository.

National ALS Biorepository

Wendy E. Kaye, Ph.D.

Senior Scientist

McKing Consulting Corporation

I'm going to give you an overview of the National ALS Biorepository. I'm going to start with the pilot study that ended in September of 2015, what we've been doing since then, and the plan to go forward once OMB clearance has been obtained. I am going to be a tag team today with Marianna Bledsoe, who is going to talk about some work we did to determine specimen demand and what people might want going forward.

So, let me first start with the pilot study. We thought about what do people want to do with specimens from a biorepository? For example, correlate biomarkers with epidemiological data that we have in the National ALS Registry. It enrolls a national representative population-based sample of participants, so it's not selected by geographic area, exposure, or by specific clinical characteristics, and it would increase the number of specimens that are available for research. The pilot study was basically the way to pilot methods for collecting and banking these biological specimens from participants in the National ALS Registry. The main criteria for being in the pilot study is that you had to be in the Registry.

We had a number of expert panel meetings over the years. In March of 2012, we had a meeting where many of you in this room were there, and people had input into the protocol. At other meetings there has been input ongoing about issues related to governance of the specimens, how to release specimens to researchers, and other things. What we came to at the end of that meeting related to the protocol was that we were to collect specimens from 300 participants and specimens should be collected twice, approximately six months apart. I'm saying approximately because doing that exactly is very difficult.

We would collect some of the specimens metals free and we would add a specimen processing form to facilitate the collection of some necessary information for sample processing. This would include things like when the person had something to drink, when the person last had caffeine, and medications.

What we ended up with was five tubes of blood. We have one that has red blood cells, plasma. We have whole blood that was collected metals free; that's the second one. We had one for serum. We collected two PAXgene tubes for RNA. We collected urine, hair and nail clippings.

We did collect saliva on people who were unable to give blood.

So I have some pictures of our kits. The kits were created by the lab, and they were shipped directly to the patient's home. The phlebotomist came to the house and collected all the specimens in the homes and then took them directly to Fed Ex and shipped them back to the lab.

We also have a subgroup of people who participated by providing postmortem tissue that included brain, spinal cord, CSF, bone, muscle and skin samples.

Again, here is a picture of the kit, although this is the main kit, we do have the skin going to a different laboratory in a smaller box; and the bone and muscle also going to a third lab.

Just to show you a map, this is a distribution of the participants in the in-home, the 300 people. In the end, we ended up with 330. We had so many people who were unable to do their second collection mostly because of illness that we got permission from the IRB to increase our sample size so that we could have more paired specimens in case people wanted them.

This map shows the distribution of collections across the United States. We do have one person in every state, and you can see we have clustering in some areas. People were selected to be proportional to population density, so that there are more people in California than in Montana. We tried to distribute them as best as we could in both rural and urban areas. Again, we had one person in each state; and we were interested in where people were. And as you can see, around 50% lived 50 or more miles from a referral center. And 27% lived 100 miles or more from a referral center.

This is the age distribution. We have slightly more males than females, but you can see from the age distribution that it looks pretty much like the age distribution of ALS in general.

The lab processed the specimens as soon as they arrived at the lab. The first tube that we talked about is the one that they used for plasma, and it was aliquoted into 0.5 ml and frozen; serum, the same thing; metal free were 1.8 ml. We extracted the DNA from the buffy coats and made 2 microgram aliquots; and the RNA is also being extracted.

For the urine, we have one special aliquot that has a special preservative in it, so it can be used for mercury analyses and the rest are made into 1.8 ml aliquots.

For the postmortem collection, you can see these are the people who participated. We had 30 people, and we did not try in any way to worry about them being geographically represented because of the small numbers but I think we did get a good distribution across the country. It turns out that everybody who participated in postmortem collection also did the in-home collection, so we have both sets of specimens. It was not a requirement; you can be in one or both, your choice, but everybody chose to be in both.

You can see that the age distribution, we had equal numbers of men and women sign up for postmortem; so that, I think, explains a little bit of the age distribution. We've had 19 participants who have donated postmortem so far; 2 patients withdrew and did not donate for a variety of

reasons. We have most specimens on everyone except for skin, and that's because it was added to the protocol later and some people passed before they had consented to that part leaving us fewer of those.

The brain and spinal cord, we do both fixed and frozen segments. CSF is spun down and frozen in aliquots. Bone and muscle are currently being stored in formalin, but that's about to change. And the skin went directly to a lab, where they extracted and expanded fibroblasts; and all of those have been frozen out in one-million-cell aliquots.

Just for those who might be interested, I'm not expecting to read all this but this is the elaborate processing that's being done for the postmortem sections, brain and spinal cord. We have both fixed and frozen.

I should give a plug here to Boston University, who is doing all this processing. They're also doing all the processing for the VA, so these specimens are being processed in exactly the same way as all the VA specimens so that comparisons can be made across all of them.

I will also point out, so far, of those 19 we have processed 18 of the specimens and all of them are confirmed as definite ALS. They had some other comorbidities but they were all confirmed.

At the end of the pilot study, there were some recommendations about what you would want to do differently if ATSDR wanted to make this part of the National ALS Registry and what could you do to make it easier. One of the recommendations was to make learning about donating specimens part of the enrollment process within the National ALS Registry because for the pilot, it was just a cold call like any other study, and in that process, collecting some additional contact information would be necessary because right now the Registry only has e-mail address. We could ask them to get mailing address and phone number to facilitate getting to them more quickly and enrolling them in the biorepository.

It was suggested that we continue to do the specimen collection in the home. We had a number of people who would not have been able to get to a facility. We had a couple of cases where phlebotomists drove for hours to collect specimens because they were in a very rural area.

There was some recommendation to collect specimens from 400 to 500 people per year. And a recommendation that we only do a specimen collection one time and potentially increase the amount of blood collected at that one time. We lost so many people and there's so much maintenance to keeping track of people and going back to them that you could have more people for less than trying to keep track of people and going back.

It was recommended that postmortem collections be continued, and we continue quarterly contacts we were doing with them to see how they were doing and see if they were still interested in participating. It's something similar to what the VA is doing, but they're doing it as part of clinic visits; and we incorporated this into phone calls and e-mail chats.

It was recommended we continue collecting blood and urine. All the DNA and RNA has been extracted from the pilot specimens, but it was not part of the routine processing so it was recommended that we make it part of the processing so that as soon as they came in, that would

be done. There is some thought about stopping the metal-free collection and then just adding it as people need it. It does complicate the collections considerably because of needing a lot of specially tested materials.

Stop hair and nail collection until we see if somebody uses it. Again, it's not that expensive to collect; but there are what I call "opportunity costs." You still have to inventory it; you have to keep track of it; it takes up space, and if it's not going to be used, then make sure we use up what we have and then add it back in again.

Continue collecting the saliva and then consider whether or not we could add additional saliva collection for a subsample of the people we weren't getting bloods on because we could just mail them the saliva kits. Recommendations for postmortem collection didn't change very much and we are still collecting the brain, spinal cord and CSF. About the bone and muscle, decide if it's useful and people want it before collecting it and then, again, same thing with the fibroblasts.

And then for the operations, now that the Biorepository was going to be part of the National ALS Registry, it needed to be amended into the overall protocol and become part of that from the IRB perspective. Originally, the pilot project was done as a separate protocol and was under a commercial IRB and not under the CDC IRB.

We had to amend the OMB package – we'll talk a little bit more about that in the third part of the presentation – to include the biorepository. And then update the National ALS Registry website with information for researchers to be able to get specimens. We recommended keeping the specimens in a private laboratory rather than moving them back to CDC. Currently, they're in multiple labs. We could not have moved back the tissue specimens anyway because they can't store brain, spinal cord, and those types of tissues. We have to integrate distribution of specimens into the Biorepository operations so that there's a process for applying for specimens, maintaining the inventory, retrieving and shipping all of those, and then obtaining approval to be able to charge a small amount for retrieval and shipping, and custom sectioning of the postmortem tissue.

ATSDR decided after the meeting and with some recommendations that they would include the biorepository as part of the Registry. We'll continue storing the specimens at the different laboratories. The new contract that we are working on has some expanded responsibilities; in addition to recruiting the participants, collecting, storing and processing specimens, we will be assisting with researcher requests for specimens. We have some lab consultants who will be reviewing researcher requests and helping work through some of the fine details before they go to the Scientific Review Committee and who will be responsible for assessing specimen demand to see what kinds of things are coming up, what kinds of things people need, to make sure the repository is getting those kind of specimens into the biorepository.

With that, I'm going to turn this over to Marianna Bledsoe, who is a consultant with us as well as having worked on the VA biorepository, and she did an assessment of the specimen demand.

National ALS Biorepository

Marianna Bledsoe, MA
Biorepository Consultant
McKing Consulting Corporation

Good morning. Thank you, Wendy, for that nice overview of the pilot study so far. What I'm going to talk to you about in the next 20 minutes or so is our strategies for assessing specimen demand and ensuring effective utilization of the National ALS Biorepository. I'm going to tell you about some analyses that we did and the findings of those analyses.

Let me just take a few moments to talk about why assessing demand is so important. There is a lot of activity in the biorepository world right now. A lot of people, institutions, and researchers are jumping on the "let's build a biobank" bandwagon without really thinking about the purpose of the collection and what they're going to do with the samples.

Unlike the ballfield in the movie *Field of Dreams* that Ray Kinsella built, if you build it, they won't necessarily come. There has been some experience that demonstrates this. There was a company several years ago that started some relationships with some major academic centers to collect samples. They collected specimens during the course of routine care, but they also collected everything that came in the door. They very quickly found out that they had to change the business model because they collected samples that nobody wanted. The company is since no longer in existence.

Collecting specimens that are not in demand is not only an obvious waste of resources, but it also does not show respect for the participants who donated their samples. Participants want and expect their specimens will be used for research.

Assessing demand is also important for ensuring the repository is fit for purpose. In other words, the samples that you collect should meet the researchers' needs. They're prepared in such a way that they can meet their needs. Obviously, you want to satisfy your customers of the biorepository.

Specimen underutilization has been shown not only to be a practical issue, but has also been identified as an important ethical issue. It is an ethical imperative to use specimens for research that are scientifically and ethically sound. We have a responsibility to our specimen donors, who want and expect their samples to be used for research. The biorepositories have to be able to demonstrate use to justify continued support; but most importantly, we cannot make scientific and medical advances from biorepositories if the specimens are not being well-utilized.

How do you ensure effective specimen utilization? Well, the first factor is that the biorepository must be designed to meet an identified scientific need. There also has to be effective biorepository design – whether your biorepository is designed as a traditional biobank that collects and stores samples with extensive clinical data, or whether you set up a prospective procurement system in which specimens are collected real time to meet researchers' identified scientific need, or some combination of both.

Another very important factor is market research to determine what the needs of the scientists are. To that extent, there is an importance to identify what the most pressing issues are in the field, and what kinds of samples are needed to meet those needs. What is the demand for the samples by the scientific community?

There should also be an assessment that is frequent and ongoing because the science changes so rapidly, thus the needs may change very rapidly as well.

It is also important to determine what other resources exist. Are the samples available from other sources? What do they collect? How frequently have they been provided? What are researchers requesting that these resources cannot fill? Where are the gaps that a new biorepository could help fill?

Active marketing is extremely important. This should be done not only at the implementation of a biorepository, but it should be often and ongoing. Wendy is going to tell you a little bit about this later in this presentation.

Access policies in the process should be conducive to broad sharing. The requirements for access should not be so onerous that researchers are afraid to request access or can't get specimens because the requirements are so stringent.

We used a number of approaches to analyze the demands for specimens from persons with ALS. First of all, we did a historical evaluation of use of specimens from persons with ALS from a review of the literature. We also reviewed the literature to identify some of the important issues that needed to be addressed in ALS research. We also reviewed currently-funded research to identify what kinds of specimen people were using in their grants, and then we interviewed a number of experts in the field. We interviewed both researchers and staff at biorepositories and distribute samples.

These are the results of our first analysis. We looked at the literature to look at the historical use of specimens from persons with ALS by specimen type. We did a PubMed search looking for ALS and these various sample types within the last five years, and we also restricted it to "human" as a search term.

This analysis turned out about 180 papers, and those abstracts were reviewed for relevance. The most frequent specimen types – as you can see by this graph – that were identified in these papers were DNA, followed by CSF and then blood. About 29% of the papers used some sort of postmortem tissue. Among the postmortem tissues, spinal cord was most prevalent, followed by brain.

You'll notice here that hair, bone marrow, saliva and urine were only very infrequently reported. We also then reviewed the literature to identify pressing research areas in ALS. We used PubMed to identify review papers in English published in the last five years that focused on ALS and mentioned human samples.

Commonly identified research areas included the identification of biomarkers for a wide range of purposes, including disease risk in the pre-symptomatic phase, early diagnosis, biomarkers to reliably subclassify the disease into disease that would be slowly progressing versus taking a longer time to progress, disease progression, prognostic markers to help stratify patients who may be enrolling in trials, including panels of biomarkers and biomarkers to assess drug advocacy.

With regard to specific specimen types, a lot of work has been done in CSF and blood. A number of promising biomarkers were identified. These include some of these biomarkers shown on this slide.

It was also noted that many of these studies used only a limited number of samples and limited choice of controls. They needed further study and validation to see if the results can be more broadly applied.

Urine and muscle were identified as having some promise. Additionally, postmortem tissue needed to be collected to characterize new candidate biomarkers and correlate them to ALS pathology.

Many of the review papers emphasized the need to use standardized collection and storage procedures so that results of the studies could be compared to validate the biomarkers. Some animal models were identified as being important to validate candidate pathways derived from human motor neurons generated from iPSCs.

We also looked at funded ALS grants. There are two databases. "NIH RePORTER" includes data on grants funded by the NIH. "Federal RePORTER" includes data on grants funded by a number of agencies including NIH, VA, DoD, CDC and others. We reviewed that database to look for ALS grants by specimen types. We identified from that review about 80 projects that actually mentioned the use of some sort of ALS specimens. From that analysis, you'll see that brain was most frequently reported, followed by blood serum, plasma, iPSCs, DNA and spinal cord, CFS, skin fibroblasts and muscle. You'll also see that RNA urine, saliva, nerve and feces were reported only infrequently and that there were no reports of hair, nails and bone.

Then we interviewed some experts. We interviewed a broad range of researchers and consortium leaders, funding agency staff, and advocacy group representatives, some of whom are in the meeting today. We spent time on the phone with these individuals. We spent around 30 minutes on average per call. We talked about what the most pressing needs were in ALS research and what kinds of samples were needed to support those studies.

During those discussions, there were some common themes that emerged. I'm not going to go through all of the comments that we received because we got a lot of very useful information that we've documented and will have available to help guide the future operation of the repository, but I'll just mention a few. Some identified the obvious strengths of the National ALS Biorepository, such as the fact that we have extensive epidemiological data and very broad geographic representation. We also will have access to specimens and data from non-Caucasians.

You heard from this morning's previous presentations about the differences between Caucasians and non-Caucasians. Hopefully this will help to address some of those questions.

We will also have blood specimens associated with a pathology report from the postmortem collections. They also identified ways that the National ALS Biorepository would be particularly useful, for example by supplementing whole genome sequencing studies. This was a common theme from many of the experts – that we need large numbers of samples for these kinds of studies, as well as environmental studies to look at occupational and other environmental exposures, including gene environment interactions.

Some of the specimens that were identified as being most needed in these discussions were postmortem tissue and particularly brain, spinal cord and CSF. It turns out from a survey that the VA did, these were the most commonly needed postmortem tissues. They also need high-quality, fresh-frozen, and formalin fixed material with biofluids from the same patients. A need was noted for high-quality plasma, particularly plasma that is spun and frozen within an hour of the blood draw, and for other kinds of high-quality preparations of plasma. Fibroblasts and iPSCs were identified as a need.

Although many groups are deriving iPSC cell lines, it's not clear how widely available cell lines are, although NINDS has a number of cell lines available from their collection. One frequently identified need was specimens from patients with known mutations including c9ORF. This is a type of specimen that some of the repositories got requests for but had trouble filling. The need was noted for large numbers of cases of specimens for whole genome sequencing studies and RNA sequencing as well.

In regard to environmental studies, they noted the need for specimens, including blood collected in metal free tubes. There were some specimens that were identified as being potentially useful, but there were concerns expressed about how widely they would be utilized. One of these is urine, although there have been some promising studies of markers in urine. There were concerns about urine being collected and stored and that they would not be utilized. Hair and nails was another type of specimen that was identified as being potentially useful, but also some concerns about whether or not they would have widespread utility.

There are a number of specimens that were identified as being potentially useful that are not currently being collected. These included good control samples – especially those from unaffected family members – and then for environmental studies, samples before exposures. Samples before disease diagnosis were also mentioned as a need. I think that concludes our analyses.

I just wanted to mention a couple of limitations of our analysis. These included the fact that we didn't have enough time to really do a full-fledged survey of the research community because of the time constraints involved with getting OMB approval. We did, however, build in questions into the annual report that users of the replier repository will need to complete to try to assess their needs moving forward.

Finally, I should note that assessing specimen demand is inherently difficult to predict because of the fact that science changes so rapidly. What might be needed today might not be needed tomorrow because of changes in the science and technology.

I'd like to thank all of the experts who participated in our interviews, and some of you are in the audience today.

ATSDR awarded a contract to work on the National ALS Biorepository, which is what we're doing. The responsibilities have been somewhat expanded at the National ALS Biorepository, as we've mentioned before. It's not just being responsible for recruiting and collecting the specimens. There's also some processing involved with the specimen because we'll now be extracting the RNA and the DNA as the specimens come in.

ATSDR has also talked to us about doing some other tests, sending some things out to different labs to get some other analyses done immediately. Those will all be part of the Biorepository. Bryan Traynor at NIH will be doing genomic work on all of the specimens that are in the Biorepository going forward, and those will become part of the Biorepository as well. We're assisting with researcher applications and doing some processing on that in addition to everything else.

So what have we decided to do? There have been a lot of discussions about which specimen to include, and there has been a little bit of change to the process. As we mentioned, we are dropping the collection of hair and nails for now, until we see what the demand is. We will be extracting the DNA and the RNA as the specimens arrive. We had some discussions about whether or not to drop bone and muscle from post mortem until we see what the demand is. We have had two researchers contact us about possibility of getting specimens out of the Biorepository, and we are working with them now. We're not quite sure what specimen they want. That's one of the issues with the application. The second one actually wants muscle specimens.

As I have mentioned, this is now part of the National ALS Registry and it had to be included into the OMB package for data collection. For those of you who are not aware, any kind of Federal data collection has to have IRB review for ethical considerations and OMB review for burden to participant. Within this new package, it's a very lengthy procedure with a 60-day public comment period and then another 30-day public comment period and then OMB review. I'm happy to report, we are through all of the public comments periods and we are on schedule. The Registry OMB clearance expires September 30th of this year, and we have to have clearance again by then in order to continue collecting data in the Registry.

Some things that have been added include some things that have been recommended from participants, such as additional e-mail addresses so that if they wanted a family member to get an e-mail on their behalf, consent to have one or more GUIDs calculated, and attached to their record, and collecting the variables needed to do that. In addition to a consent to receive more information about the Biorepository, there's a very lengthy consent form. This is just "I'd be interested in hearing about it," and providing information. There are also forms for researchers to complete if they want to get specimens or data and a small annual report form.

As you heard from Marianna, we're also responsible for keeping up on specimen demand. We're responsible for marketing the Biorepository, so we're talking about advertising the availability of the specimens by attending some meetings and creating exhibits. We have some materials in the works such as fliers and trifold.

We've talked to some groups about co-marketing the Biorepository including NEALS, NIH and others. We can co-advertise with the Registry. These are other places researchers could get specimens or you could get specimens from them so that people can combine specimens across biorepositories.

As we said, we're working on these requests and we have two that have been submitted. The process works like this: It will come in on the platform once it is up. We are taking requests now. We just don't have the formal application process up and running until OMB clearance, but we work with the researchers to get in a protocol. We make sure that the protocol has all of the information necessary. We have people, like Marianna, looking at them to make sure that the number of specimens requested seems reasonable and that the tests are reasonable. The request will go back to Paul, who is responsible for the scientific review of the applications. Once the researcher has been approved, they'll come back to us, and we will work with the different laboratories to pull the specimens and get them to the researchers and coordinate the annual review process.

I want to thank the other people in the Biorepository: Laurie Wagner, who is sitting back there, who is the coordinator, and Ariel Weiss, the research assistant. We'll also be hiring another person when we start collecting again, which we hope will be this fall or early winter.

The only other thing is to say that right now, we are approved by the IRB. We asked OMB for permission to collect specimens in 325 people per year for in-home collection and approximately 40 people for postmortem collection total, not per year. We did this as a total for the project because it is hard to calculate postmortem collections per year. We will be only collecting specimens one time.

ATSDR is also looking into possibly adding a control group and collecting a small number of control specimens as well. That will have to wait until OMB clearance has been obtained because it will require an amendment to OMB to add more people, which will increase the burden.

Yes?

Lucie Bruijn, ALS Association

You'd mentioned that investigators can get access now, right away, already. What is the contact for that because I have a few requests?

Wendy Kaye, McKing Consulting

I can give you the phone number. Just call the Biorepository. The information is on our website.

If you can send it to me, I'll send you the number. We can't ask them to fill in the form because it doesn't have the official approval, but we can tell you what you need to send us and step you through the process. Like I said, we have two we're working with now.

Yes, Michael?

Michael Benatar, University of Miami

Wendy, thanks for that. I have a couple of questions and comments. I think that we can't underscore enough the importance of thinking about what will the specimens be used for as you think about collection. So I would venture that I'm sure there's a tremendous need for plasma or serum collected at a single time point from people in whom we have very little limited phenotypic data. I'm not sure what that adds. I would also say that I worry from a DNA and genetic perspective that we have passed the point of collecting DNA samples from people from whom, again, we know almost nothing about their phenotypic presentation, longitudinal cause, and prognosis. What we're doing is we're just sort of able to look at that. We have this richness of genotypic data from a whole genome, and phenotypically, we know you have ALS. For the RNA, I would ask if we've done due diligence to note the samples that come in the mail.

Have we tracked the temperature as those are being shipped back? Have we looked at the quality of the RNA to know when that's extracted, is it yielding RNA in sufficient quality to permit the sorts of studies that we'd want to be done? Lastly, from the tissue perspective, I would ask if you've considered as opposed to and this may be the horse has left the barn or whatever the expression is. NIH has a significant infrastructure through a network of neuro biobanks around the country to collect and process postmortem tissue. I'm wondering if you could comment on why we didn't tap into or utilize that existing resource rather than sort of build this from scratch. I guess I have sort of a number of questions about how you've elected to proceed, if you could comment on those.

Wendy Kaye, McKing Consulting

I'm going to go backwards because I can remember them that way. We do have temperature loggers in all of the kits, so we do have temperature data on all of it. We do know that basically, the temperature on all of them was acceptable, except for a few in -- it was either the summer of 2013 or the summer of 2014, where there was a heat wave in Arizona and we fried a few specimens. They got stuck on trucks and didn't make it back to the lab. We do have that data that can go along with the specimens.

The reason that the RNA has been extracted now from the PAXgene tubes is because the lab recommended that based on data that they were seeing, the company specification that they are good for five years was not really -- in their way of thinking, was not accurate. They started to see degradation within X period of time. That's why we pulled everything out of the tubes right away. They have not checked it for quality.

Michael Benatar, University of Miami

And when you extract RNA, do you remove globin at the same time?

Do I what?

Do you remove globin at the same time when you extract RNA, because that's what dominates the RNA species collected from blood?

Wendy Kaye, McKing Consulting

I don't know. I can't tell you that. I'd have to check with the lab. Regarding the postmortem collection, are you asking why we're processing that through BU rather than through NIH? With ATSDR, the decision was to do it the same way that the VA was doing it and have those same neuro-pathologists reviewing those specimens in order to be able to pull specimens across those two sources.

Amelie Gubitza, NIH

Just to that comment, certainly NIH now has a central neuro biobank. It's funded by several institutes. NIH is actually the lead, and certainly ALS would not be a major focus with them and NINDS is also participating.

I think it's probably too late now, but we could still have a conversation. There are certainly bandwidth issues, and I think BU had already a lot of expertise with collecting ALS brains and spinal cord. The NIH neuro biobank is relatively new. They probably wouldn't have that track record. The question has always been, who provides the funds for the banking of the ALS brains and spinal cords? I think leveraging the expertise of BU probably was a good way forward. We certainly could have a conversation with the lead of the NIH repository sort of an information exchange to see if there are future opportunities. They don't have a track record with the collection of ALS samples, but I know you're very interested in that resource.

Michael Benatar, University of Miami

Maybe Lucie can speak to this, but I think Target ALS has spent a huge amount of time and effort thinking about best practices for collection, processing, cutting, aliquoting. I hope that you've taken input from that group of investigators who, I think, have worked hard at this and have gone about it a little differently. I don't know Lucy whether you can add to that?

Lucie Bruijn, ALS Association

Certainly, I echo the concern that there are going to be lots of these biorepositories; and I think that's where the discussion and reviewing was very useful. I think certainly each of them will have a component of value because obviously here, there's maybe a lot of other big data groups are also collecting environmental data based on data that Lorene put together through ASIS. There will be a lot of similarities. I know with the Target ALS Biobank, it's again bandwidth. I think that they probably at the moment haven't got the funds to do beyond what they've committed to. We're actually adding on the biofluids component to that collection. I really hope as a community, and it certainly is the interest of the Association, it's just a matter of timing and getting it done is that we have a clearinghouse where all of this is. One of the things that I think is useful about this particular biobank versus what others are building is that I don't think there are any groups through Answer ALS and through GTEC that, I stand corrected, are going to homes. It does lend to involvement maybe in areas we wouldn't be thinking of.

I do think your comment about the fact that this is a one-time collection is an important one because many of the biobanks that we are now helping support have driven the concept of being longitudinal, have driven the idea of phenotyping because you really are passionately trying to figure out the heterogeneity of disease- difficult with the one-time. Again, I think it's like any of these endeavors; they have limitations. We just have to be realistic about it, see their value, and be sure we're all talking together.

Amelie Gubitzi, NIH

In terms of sort of making information centrally available, NINDS has the iPSC consortium repository, which is now being housed at Rutgers University.

Target ALS is also housing their iPSC lines at Rutgers University. We now have linked the two databases; they're cross-searchable, so it's a one stop place for researchers to go to see the iPSC lines. I think it probably would then be useful then, once your collection is ready, to add a link to the CDC lines, to that website, so that researchers become aware of that resource and to sort of cross advertise.

Lucie Bruijn, ALS Association

I would add again, we also had hoped we'd have one central place; but we have supported the iPSC Core at Cedars-Sinai. Again, I think everyone has their value. The more we connect the dots, the better because really we need a lot of resources.

I think your first question, which I probably didn't answer was if the expertise from Target ALS used? I do think so. Bob Bowser has been very engaged in the team. Lyle Ostrow has also been engaged. At some point, there has been cross connectivity. I think one of the things I did want to bring up and – in fact, Michael and I were talking a little bit about it – there is a sense, whether it's a real or not a real sense, that some industries feel that they don't have easy access to samples. I know that creators worked very hard with MTAs around it, and we are working with teams. The question to you is, what is it going to be in terms of industry access?

Wendy Kaye, McKing Consulting

It's not any different.

Lucie Bruijn, ALS Association

Is it easy access?

Wendy Kaye, McKing Consulting

They would have to fill out the same application as everybody else and have it go through the review. On the back end, once they've been approved, there are some additional pieces of paper that have to be signed, like an MTA. Those can be done at the same time that the lab is pulling the specimens. We're anticipating that the approval, once you get the specimens, should be a month or less.

Lucie Bruijn, ALS Association

The MTA will have no limitations in terms of reach through because that's where the industry has had some issue.

Wendy Kaye, McKing Consulting

Our consent form clearly states that specimens may be used for commercial products and that the individuals providing those specimens have no claim in those specimens. We were very careful to put that onto the consent form.

One last comment.

Paul Mehta, National ALS Registry

It's also our hope to have industry come to the Biorepository and request samples as well. It's not just for research institutions universe and so forth, it's for industry as well.

And last comment?

Benjamin Brooks, University of North Carolina

Well, I think one of the most important points here already has been proven by you – is that you're collecting samples far away from academic centers. So if NIH-funded academic centers are getting a certain set, this has to be a parallel set. Having a central clearinghouse, as Dr. Bruijn suggested, is a very good point.

Thank you, Andy.

Next on our agenda, Paul again to talk about research notification mechanisms, an update on this.

Research Notification Mechanism Update

Paul Mehta, MD

Environmental Health and Surveillance Branch, DTHHS

Agency for Toxic Substances and Disease Registry

I'm going to go ahead and give you an update on the mechanism. During our talks at conferences or symposiums, we call this "connecting PALS with researchers." I think this is really important to say because this is how we in the Registry can go ahead and connect the patients with clinical trials and studies and so forth.

Just very quickly, a brief overview. With the notification system is a patient recruitment tool for industry, as well as researchers, to go ahead and reach out to patients via the Registry. We all know recruitment can be very difficult, and so we feel this system right here can go ahead and make it much easier to go ahead and access a large cohort of patients.

Kevin mentioned this earlier, but 95% of PALS who register will go ahead and opt into receiving notifications, which is really, really good. Once these notifications come in, whether it's domestic or international, they are reviewed by our team.

This is just a quick overview of exactly how it works. A patient enrolls in the Registry will go ahead and consent to receive emails from us. A lot of the researchers submit an application to us. It's reviewed for completeness and so forth. It goes to an external committee for review. Once the committee reviews it and approves it, we'll go ahead and notify the researcher it's been approved. We'll go ahead and send out an e-mail to the PALS, depending upon the criteria that they've actually requested.

The benefits of the system we feel are multifold. First of all, in terms of www.clinicaltrials.gov is one of the places where there are tons of trials, whether it's ALS or so forth. It's a very cumbersome website. We feel our website, in terms of helping out/reaching out to PALS is very important. We connect with PALS and reach out to industry and researchers to go ahead and use this mechanism. It is extremely important.

So far, we've actually sent over 80,000 e-mails to patients since inception. Keep in mind, this is not 80,000 PALS, but e-mails that have been sent out repetitively to possibly the same PAL as well. There has been a year-by-year increase in notifications sent.

For the recruitment of PALS by researchers, we feel a national effort certainly is best. If an application comes in and they want to go ahead and reach out nationally, over 5,000 PALS are going to receive an e-mail from us to go ahead and reach out to the researcher. The materials for recruitment and so forth will be attached in the e-mail itself, and they will go ahead and reach out to the researcher. We will never, at any time, disclose the names of the patients or send the researcher their e-mail addresses. In terms of the study itself, like I mentioned, a national approach, especially for a clinical trial nationally, coast to coast will yield a tremendous amount of interest from PALS.

This is the criteria for recruitment right here. A researcher can go ahead and request a specific age range, as well as a time period since diagnosis, sex and geography as well. Whether they want to go ahead and focus on a national effort or a regional effort or a state effort, they can go ahead and submit those criteria to us.

Benefits, like I mentioned, to PALS are timely and tailored opportunities for research participation. This is one of those systems which was engineered to go ahead and get the word out to PALS about opportunities for clinical trials and some studies.

For researchers, it speeds up recruitment time, it can increase the sample size, achieves diversity in geography, as well as it efficiently identifies PALS who meet their criteria, whether it's just males between the ages of 40 and 60, and so forth. It's also a free service. We are here for the researchers to go ahead and help them connect with PALS.

We are really looking forward to working with biotech and pharma, and we actually have worked with Cytokinetics as well as Biogen. Sarah will be presenting after me regarding their experience working with the notification mechanism. We feel for biotech and pharma, this certainly has multiple benefits. Instead of creating your own sort of cohort for patients, we are here to go ahead and help you. We have a large recruitment pool, and we can do a targeted recruitment. Whether you want just California, like I mentioned, or wherever, we can certainly go ahead and work with you. As we all know, patients are certainly hungry. They're looking

for clinical trials and studies. We are there to go ahead and make that connection between patients and researchers.

I do want to mention that recently, we have worked with these two drug companies, but we want to go ahead and get the message out to other companies as well, who could possibly also use this mechanism as well. Working with neurologists out there who actually are on the front lines is certainly important. Many of the researchers at this table actually do use this mechanism already for their own studies.

The feedback from researchers has been overall very positive. The recruitment for studies has ranged from less than 5% to almost 80%. All the researchers have recommended using the mechanism for their studies. There has been some feedback regarding sending out more than one e-mail reminder to a patient. However, there are some limitations, we can't do that because of IRB. So once an e-mail goes out to a PAL, that PAL most likely will not see the same e-mail again. Actually, they will not see the same notification of that particular study again. However, researchers can go ahead and request another notification.

For example, if we did a notification in January and they want another notification, let's say in March or in June, we can go ahead and submit a new notification for those who have enrolled from January through March or April. We can go ahead and do notifications again, but just for newly enrolled patients.

This right here shows the actual trend and the notifications that have been sent to PALS. As you can see, in 2013 when we started, we were a little over 6,000; in 2014, we went to about 27,000; last year, we were over 40,000. This year, we're starting off a little be slow; but we're at 10,000 right now; but certainly, there's been a huge interest in using this mechanism.

This right here is a list of the participants. The ones in red are clinical trials, and many of you are sitting in this room. So far, we have 23. I want to go ahead and call out the last two ones for Cytokinetics as well as Biogen.

Certainly, like I mentioned, we are excited about partnering with biotech and pharma to go ahead and have them leverage this useful tool. We also have information for PALS as well, in terms of connecting PALS/researchers. This information is really for neurologists, as well as researchers, to go ahead and let them know about this particular tool. This brochure is available to download, and we can even send out pre-brochures as well. Once the Biorepository comes on line, hopefully in the fall of this year we'll have a similar system of requesting applications.

I believe, Lucy, you mentioned we've got some individuals who want to go ahead and use it. We can have them in the back end before we're up and running talk directly to Wendy's team and make that happen. Once you get full approval, full launch, they can go to our website. They can go ahead and submit an application to us with all the requisites IRB approval and so forth and we'll go ahead and review it, and we'll go ahead and submit it to our Review Committee for approval. This probably will be a little bit longer approval time compared to the notification system, only because there are more moving parts. It's got to go to, for example,

Marianna Bledsoe to make sure what they're doing or what they're asking for is in our inventory or not. So we have a little bit more moving parts with this particular system.

More importantly, we have all those surveys that you saw that Kevin presented this morning. Those surveys in the biorepository will be merged together. Currently, we have 325 individuals in the pilot study. As individuals start enrolling in the biorepository, their risk factor surveys will be merged together. We'll have a tremendous amount of information on the patient's tissue as well as their military history, their occupational history, and so forth. I think that by itself makes it very unique for this particular tool, where we have epi data merged with actual tissue itself.

There has also been a huge request. I got a call just a couple of days ago from somebody requesting Registry data as well. Currently, we're in the process of having a researcher dataset available for request. Once this is available, probably timeframe late 2016/2017, it will be available for dissemination. This will also be a very similar process for report for an application, where somebody comes in to request this data.

We are currently in the process of looking at 1 through 7 to go ahead and get those surveys cleaned up. We are also working on Surveys 8 through 17 as well. This also requires a tremendous amount of effort, staffing – it's very time-intensive – validation, and so forth. These are some of the challenges ahead.

Right now we mentioned the OMB process is ongoing. We submitted information to OMB. Hopefully, it will be a clean process. There won't be too much pushback from OMB regarding getting the necessary approvals. All these systems, whether it's having a researcher come to our website, submit their application, requires OMB approval. So it's pretty time and labor-intensive.

There will also be a new portal to go ahead and have this information. SA researcher could go to our website and say they're requesting notification for an epi study or a clinical trial, or they want to go ahead and request data, or they want to go ahead and request tissue. There will be like a trifold of options to go ahead and choose from, from our website itself.

Last point right here. I do want to mention the fact that we are looking for reviewers for the Research Committee. I mentioned this last year. We are looking for folks with backgrounds as stats, laboratorians, to go ahead and review these applications as they come in. We already have a pool of individuals, but we're always looking for new individuals, whether it's post docs, fellows or so forth, who want to go ahead and participate in this Committee for those data request notifications for clinical trials, epi studies, or the biorepository itself. We're always looking for individuals. If you know anybody, please let them know. They can contact me, we can have them submit their information, and have them come on the Committee itself.

That's pretty much it. Questions?

Pat?

Pat Wildman, ALS Association

Could you talk a little bit more about public access? I know you focused really on researcher access, but could you talk about public access today?

We're also looking to go ahead and have a public use dataset as well. An individual, for example, could come on our website and look at prevalence if they wanted to. For example, with public access, I mentioned in my earlier talk, we're looking to go ahead and have data more or less at the state or above. So possibly in the future, they can go in there and look at that dataset to see if they want to have a look at prevalence, let's say, for the Northwest or the Southeast or something like that. But right now, the push is to go ahead and work on the researcher dataset first and then do the public-only dataset.

Pat Wildman, ALS Association

Do you have timing?

Paul Mehta, National ALS Registry

Probably sometime in 2017, I'd say, for the public dataset.

Yes, Andrea?

Andrea Pauls-Backman, Les Turner ALS Foundation

Paul, how are you populating the researcher database?

Paul Mehta, National ALS Registry

You mean as in terms of the Committee itself?

Andrea Pauls-Backman, Les Turner ALS Foundation

No, with respect to you're sending out e-mails to all of these researchers. How is that group being determined? Are you relying on volunteers to log on?

Paul Mehta, National ALS Registry

No, so once an individual comes to the portal end. The researcher or the PAL? The researcher, right?

Andrea Pauls-Backman, Les Turner ALS Foundation

Researchers.

Paul Mehta, National ALS Registry

Well, it's really almost by word of mouth. In terms of where there is really we go to conferences and symposiums and let them know about these particular tools we have.

We'll be also updating our website booth as well, to go ahead and have it much more pronounced on the booth to let them know they can use this tool. We have brochures and handouts to let them know word of mouth and so forth. We are working with yourself, MDA, and the ALS Association to go ahead and let pharma know there are tools available. Like I said, we can only do so much on our end; but we rely upon you guys to go ahead and work and let people know. If it's a researcher sitting at Northwestern, or if it's a researchers sitting wherever to go ahead and use this particular tool.

Andrea Pauls-Backman, Les Turner ALS Foundation

My suggestion, again, would be if you're able to get access to research grants that are currently being funded in ALS, get a face on those individuals and then that can be pushed out rather than waiting on volunteers.

Paul Mehta, National ALS Registry

What I also do is for example if there's a webinar, like a NEALS webinar, I'll go ahead and e-mail the researcher and let them know, hey, we have a system available for you. I did that just last week for a study as well as Sabrina's study, to let them know, hey, this particular study is available if you wish to recruit from it. So we do reach out via e-mail, letting them know and so forth. But really, like I said, once someone has used it, they realize the benefits of it. It's just a matter of having more individuals use it. Like I mentioned, we have 23 so far, and we're looking to go ahead and expand that as well.

Yes, Ed?

Ed Tessaro, Patient Advocate

Paul, would you clarify on your benefits for biotech and pharma, about 10 slides ago, that last one needed help from neurologists, researchers, ALS organizations to get the message out to pharma. What does that mean; how do we do that?

Let me just back up by saying this. I was privileged to be part of Hiroshi's Airlie House big event that you were at back in March, where a hundred scientists and more came to grips. But at the end of that meeting, the team was very specific about the language. If we agree something is a good idea, is it a mandatory thing? Who is going to do it? In other words, there were no good ideas left out there. Somebody owned it when they walked away from Airlie House. As a business guy, I thought that was a brilliant way to approach research or any other big objective that's difficult. So that's the background for my question. How do we get everybody in the room, how do you do it? What obligation does a researcher, scientist, MDA, ALSA have?

Paul Mehta, ATSDR

Just to go back to the Airlie House, there is text and language that we gave to Hiroshi to go ahead and include in the document as well to go ahead and give information about this particular tool. More importantly, the FDA guidance document that Pat's working on, that also has a passage in there I think about a page-and-a-half regarding the Registry and using this particular tool. I believe FDA is very interested in registries as a whole to go ahead and leverage them for these particular studies. That information actually is in the FDA Guidance Document that ALS Association, MDA and so forth have been working on. We are leveraging that way with pharma as well.

Now, I mean, obviously, we can only do so much. We have esteemed researchers here who know about this system and have used this system. I think it's for us to work with you guys to let them know about it.

Unfortunately, we can't snap our fingers and make everybody use it. There's no mandate to use it,

but we are here to work with you, to work with pharma to let them use it and work with the neurologists if they have any questions about it.

If there's a future clinical trial they'll be working on, they can go ahead and utilize our system. We do whatever we can as much as we can to go ahead and get the message out. Whether it's via FDA or whether it's via the Airlie House as well where we were present, we try to leverage all channels.

Another question?

Michael Benatar, University of Miami

Yeah, I just wanted to say from the user perspective, we've used this twice. You've sent out e-mails, and they've been incredibly helpful. I should know this, but I've forgotten; but it's a technical point, and perhaps you can remind us Paul. I'm thinking that in IRB approvals, people need to mention the National Registry as a recruitment tool so that they have IRB approval in their study to be able to ask you to do this. Can you remind of that? I should know.

Paul Mehta, National ALS Registry

The IRB approval would come from the actual institution itself; it would not come from CDC. So as long as they can mention in the information they'll be using the Registry as a recruitment tool.

Michael Benatar, University of Miami

Right, that's the key thing; it's not just that they have IRB approval for the study, but that they're planning to use the National Registry as a recruitment tool. So it's key to get that out to people as they're submitting their IRBs. It's not just recruiting in clinic or fliers or websites, but using this tool.

Paul Mehta, National ALS Registry

Also to add to that, recently the clinical trial for Cytokinetics had multiple sites. We didn't require the IRB for 100 sites; it just wouldn't make sense. We required just one IRB approval, which went to the Committee as, hey, this is their IRB approval. Please note, this is a multicity clinical trial. It would not make sense for us to get 50 IRB letters to submit to the Research Committee itself. More importantly, if the FDA went ahead and blessed it if it's good for the FDA, it should be also good enough for us; that's my take as well. So we're not going to make it very onerous. To say, hey, you've got 100 sites, I want 100 letters from you. That really would not make very much sense.

Lauren?

Lauren Webb, MDA

I just want to make a comment. We just released our new policy guidelines for the National Clinic for MDA. In that, we included information about share information about the ALS Registry, which was a requirement now for sites to become an MDA ALS designated site. I think that's going to drive home the legitimacy and the questions around this accountability issue, that this is a new process for us. I think that that's really important. In terms of a comment,

with some of the challenges ahead, I would really recommend that you connect with genetic counselors as being part of the Review Committee because they are oftentimes the study coordinators. They're often the ones that are doing some of the biobanking. They're running these types of studies, and they have intimate knowledge of the varying different degrees that takes place in the lab. I think you should look at that.

Also, I would really recommend having an experienced clinical research professional that's at a site level to be able to help inform. I think that that's the other part of building clinical trial readiness is inclusion of these people who are really at the front lines and recruiting and talking. They're the ones that are filling out the IRB applications. We go, oh, yeah, let's include this as part of the process as we're putting together their packages. So that's just a comment.

Paul Mehta, National ALS Registry

Yeah, we've actually had discussions with Wendy's team just exactly for that reason right there. We are reaching out to these various groups, whether it's Microbiologist, ASM or whether it's different ones as well. We certainly want to go ahead and make sure we have a robust team to go ahead and review these applications once they start coming in. So you're right; we've actually looked into that, and we'll be contacting these particular groups to reaching out to them and simply saying, hey, if you have individuals interested, please let us know.

Bob Kingon, Moderator

All right, that leads us to our next speaker, who is going to share with us experiences with Cytokinetics and their use of the system – Sarah Kulke, Senior Medical Director.

Clinical Trials Recruitment through the Registry

Sarah Kulke, MD
Senior Medical Director
Cytokinetics, Inc.

Good afternoon or good morning. I'm the last one before lunch, so I won't take too much time.

I'm very pleased to be able to share our experience. I think we have a bit of a different take. We're going to touch on some of the comments, Michael, that you just asked about because industry is a different beast than academics. So I hope I'm able to highlight some of those and that you feel free to ask lots of questions because I think the more we understand the worlds that we each operate in, the better we'll be able to collaborate and make things move forward.

I'm a full-time employee with Cytokinetics. I want to tell you about our experience using this tool to recruit for our large Phase III study, known as VITALITY-ALS, which actually does stand for something, although we will all forget in short time. It's Ventilatory Investigation of Tirasemtiv and Assessment of Longitudinal Indices after Treatment for a Year in ALS. It is, as was mentioned, a large study; it's across many countries with 80 treatment centers.

In doing this study, it was recommended by a couple of our investigators to use the Registry. That was a new idea, and new ideas in industry are met with lots of questions. So it wasn't something that was immediately sort of grasped onto and run with. There was a lot of back and forth. I just want to say the Registry team was so helpful. It was e-mail after e-mail, unfortunately, question after question; and they didn't all come in at once. And they were just very, very patient; so we appreciated that.

We operate in a highly-regulated situation. We have very firm rules that are the guardrails for our industry; and we're very cognizant of those, and we adhere to them. So we had to be very careful of a couple of things. You can see some of the things that we have to worry about or just we have to pay attention to. We have to be sure we're aligned with the Code of Federal Regulations. One of the big ones there is we can't have an e-mail go out nationally that could, in any way, shape or form, be misconstrued as preapproval promotion. So we had to be certain that there was nothing that could be considered that way. Absolutely, we will do nothing that could look that way.

We also have to make sure we're following good clinical practice. And one of those pieces has to do with IRB approval. Michael is correct that it isn't so much that the Registry has to know our study is IRB approved. Any recruitment material that goes out to patients has to be approved by the IRB, which means that any e-mail that we use to recruit has to be approved by each of our IRBs. But there's one workaround; and the one workaround for that, the one hall pass we're given, is www.ClinicalTrials.gov posting. So you're allowed to post on www.ClinicalTrials.gov. It's expected, and you don't have to have IRB approval. So as you'll see, when we actually did the e-mail, all we did was send a link to clinicaltrials.gov. There was absolutely no information in the e-mail other than there's a study. I'll go through it because we had to actually get the e-mail preapproved through our company before it could even go out. This the degree to which they were willing to work with us, in that they shared the e-mail.

We took it through our internal processes for approval, and then it went out. The application materials are very straightforward. It's online. Yet, again, each of the materials requested raised some questions. You fill out a form; you provide a cover letter; you provide the CV of the principal investigator, the study protocol, the recruitment letter you want sent out, and the confirmation of IRB approval and information on materials. Those are all very straightforward. When you have a study with 80 different sites, who do you list as the PI, right? We weren't going to list 80. What we decided to do and I think this is something to think about for other companies is we used the medical monitor at Cytokinetics, who is soon going to be at Columbia University. It's an amazing, amazing catch.

We used her as the PI, and we chose to use an example of an IRB approval which was for one of our not institutional-specific IRBs but I forget, what do you call the other ones? You guys know what I mean; the IRB that's not institutional, like the Western IRB. Then we could not send our protocol. The protocol for any clinical trial that's done by a pharmaceutical company is highly confidential. It's like a patent; it's a very confidential thing that's only given under strict confidentiality approval, et cetera. We weren't able to just send that to the Registry.

We also had to be certain that we were not going to, that no one within Cytokinetics would know the names of any of the patients or participants and be very careful of the HIPAA requirements. So there were a lot of places where we needed our hand held and needed to be assured that we weren't going to get into any sticky situations. Again, the Registry was incredibly helpful. As I mentioned, we had to see the e-mail, and we had to get it approved. You can see that the only information here is just a link to the ClinicalTrials.gov posting.

Now, I agree with Michael. We're looking at doing another ALS study with a new compound, and I will recommend that in the protocol and in the IRB forms that we mention we're going to use the Registry and even have a sample letter because we would need that. That would give us even more comfort with the system. To know that beforehand we were able to submit it to the IRBs would be even better. So agree with you.

What that tells you is that industry needs to know before Phase II. They need to understand that this is an opportunity. Whenever anyone knows – for instance, one of our partners is Astellas Pharmaceuticals – they're going to now be starting work in ALS. It would be very important for the Registry and for you folks to reach out to Astellas and create that relationship so they'd know they can use this and incorporate it early in their processes.

Overall, from the time I took it on as a project that I was going to make this happen I think it took me six weeks. The Registry got back to me within 24 hours with every e-mail, but it took about six weeks for me to internally get all of the approvals and get everyone on board and be willing to do this.

The e-mail was sent in mid-April. I monitor our medical information requests, so I was able to see an immediate increase; it was about tenfold from one day to the next day. I knew exactly when the e-mail went out because of what happened at medical information. Over the following week, there was a fourfold increase, so there was definitely a nice blip there. Again, it would have been nice to have been able to repeat that a month later because not everyone reads the first e-mail they get, et cetera. So I think that was a good point that you raised.

In conclusion, it was an excellent service, a really outstanding partnership and just very responsive, the Registry staff; and I would highly recommend it. Again, working in a way to do multiple e-mails would be helpful. And that's it.

I'd love to open it up to questions. It was a very interesting path; I'm very, very happy I did it. I'm very glad I now know how to do it and would encourage other companies to do so.

Paul Mehta, National ALS Registry

If I could just quickly add, Sarah, it was very nice working with your team. You guys made things very, very easy for us I mean, responding to our e-mails and questions and so forth. That e-mail was also approved by the CDC IRB as well, so we also had an approval process there as well.

Typically for the recruitment of a trial or a study, there will be a PDF document which is attached. For this particular one, we couldn't give them a PDF. We had to give them just text; and that text had to be approved, like Sarah mentioned, on their end and our end as well. The protocol came not into question, but into the conversation in talking to Sarah. I'm like, look, your protocol is proprietary. There is probably information on mechanism of action of the drug and so forth. We don't want that; that's probably something that is probably locked up in your safe at Cytokinetics or wherever. So I did not want to have that protocol be disseminated to the Committee, even though there's non-disclosure information in there, because if some other company got that god knows we did not even want to take that chance, especially with that protocol. I made it very clear to the Committee, this is a special application coming your way. Therefore, it has these items right there for review. The committee reviewed it; there wasn't a problem there. But like I mentioned, we certainly are flexible with pharma to go ahead and get these notifications out to PALS.

Question.

Lucie Bruijn, ALS Association

So knowing that it was actually quite complicated, not everyone might have had the same appetite for going through on the company end; and obviously, maybe Biogen had a different experience. Is it going to be helpful, perhaps, if there is some kind of a primer or a guide already upfront for industry being eager to participate. There's lessons learned from this which maybe can be useful to make sure that other companies are more enticed into the use of it.

Yeah, that's a really good question. We could maybe even tweak our websites and maybe have a segment or a portion for pharma in there and let them know to please contact us directly. Hate to have someone come in there and say, oh, this is too onerous; we're not going to do it and just leave, but there is information on there. Any questions, please let us know, obviously. Certainly you think about having maybe a page or something for pharma where we could maybe have much more information. Like you're saying, hey, we don't want your protocol because your protocol is proprietary. So maybe we can revisit that and have some sort of, like I mentioned, a section on the website just for pharma it's a great idea.

I'd be really happy to share tips, like the tips I would suggest to someone else. Even I would be happy to discuss it. You're welcome to share my contact information with somebody else who might be in my position, and I can help them walking through it.

Yes, Michael?

Michael Benatar, University of Miami

I wanted to ask if you could comment on the extent to which you were able to tailor who the e-mail was distributed to, to the inclusion criteria. Because I know one of the things we often struggle with is patients who have an interest in a particular study who are not eligible. So I wonder whether you could just say a word about that because I know there are things in the Registry. I know that you can specify about disease duration, but I think you know where I'm going, so if you could comment on that.

On the form, you are able to do age; so we were able to put ages and time from diagnosis, which that's, I think, the trickiest one. Then they had to go to the link, and they had to see what the eligibility criteria are. Those are pretty clearly laid out on clinicaltrials.gov. It's possible that many people received the e-mail and then went to ClinicalTrials.gov and saw that they probably were not eligible.

If we had the e-mail, we could have listed inclusion/exclusion criteria; gotten IRB approval from all 80 IRBs from all 80 sites. Actually, we wouldn't have done the European ones; it would have just been the U.S. ones, but then we could have done that. So this situation did require more legwork on the recipient's side.

Just to follow up and maybe I don't know if that's what maybe you meant can the Registry identify so that it only goes out to some of them, or is that then a danger of missing people? Because some of the frustration in the community is getting this and getting excited, and then going and saying, oh, but I'm not able to register for it. Can you prescreen, so that you only send it out to people that will be eligible?

It would depend upon the actual criteria itself. When you say prescreening, ones who have been diagnosed, let's say within 12 months or 14 months; and that's what we did.

I think yours was two years.

Yeah, two years. We actually tweaked our system so it has to go to our IT guys. They do a data dump, and they go ahead and get the actual e-mails. We tell them, these are the particular criteria. It's a national recruitment; however, the data diagnosis must be within 24 months. We can go ahead and do that; we can go ahead and tweak it to that specificity as well.

Okay, reminder to state your name first Ed?

Ed Tessaro, Patient Advocate

Sarah, just a general question. It's industry-based. Are the long-term prospects for our kind of research better or worse as companies get bigger? News this week that Biogen may be bought by Merck, et cetera, those types of big getting bigger. Does that serve our research, or does it make it more difficult? I know it's a tough question, and I don't want to put you on the spot; but 10 years out, is that a good thing when big pharma gets bigger or is it not?

That is a very, very good question. I would say, as with all portfolios, diversity is the optimal way to go. Little companies are nimble and hungry, and big companies aren't so much. On the other hand, big companies have a lot of something that little companies don't have which is money. So you really want both; you want to support the grassroots academic work that gets in license to the little hungry companies, and you also want your large, well-funded company doing the big, very, very expensive clinical trials.

It was very good news that one of our partners, a very large Japanese company, Astellas is interested in ALS and is interested in both Tirasemtiv in Japan and is interested in a follow-on next-generation compound that we're taking into the clinic. So that is really good news. We

know how to do these trials. We have some very, very good people in-house; but we're only 100 people at Cytokinetics. Having both the small and the big is a really good place to go. Again, a lot of the most basic work comes out of academics. Then little companies tend to in-license it, sometimes bit companies; and then those are brought forward. That's the traditional model.

Cytokinetics actually has a lot of R&D, so we brought our things in from our own research and development. In general, that's how most things work. That's why you need all branches of science and research to be healthy. You need your academics healthy, and that's made possible in the United States by the NIH. You need your small companies to be healthy with venture capital. You need your big pharma to fund the big, very expensive, very, very risky trials. So don't bash big pharma because big pharma takes very, very large risks with many hundreds of millions of dollars. And so I think you need it all, how was that?

That's good; I think that's a good point to end on.

That's great. So let's break; we're only five minutes late, so let's break for lunch. I think we'll return at 1:45 p.m. The people who had lunch yesterday are there any recommendations for the crowd today?

[Lunch break]

Our first speaker this afternoon is Ted Larson, Epidemiologist with ATSDR. Ted is going to address some mortality data analysis for us. Thanks, Ted.

Mortality Data Analysis

Ted Larson, MS

Epidemiologist

Environmental Health Surveillance Branch, DTHHS

Agency for Toxic Substances and Disease Registry

Today I'm talking about preliminary analyses that relate to ALS mortality and disease progression that ATSDR is working on. I have no disclosures to report.

The three analyses that I want to talk about are calculation of ALS mortality rates, excluding deaths from other motor neuron diseases. The second analysis is fitting a survival model using data from active participants in the ALS Registry. The third is fitting a multistate model for disease progression in ALS registrants.

The first analysis, again, it's calculating national rates of ALS mortality. By way of background, we talked about this, this morning some. In the International Classification of Diseases, 10th Revision, which was implemented in 1999, there is no distinct code for ALS; instead, you must use a broader disease category for motor neuron diseases, coded G12.2. This includes ALS and other diseases. So the issue is if you use G12.2 to define ALS in mortality studies, you may end up with inflated mortality rates. Our goal for this analysis was to determine mortality rates for

ALS in the United States for the period 2011 through 2013, again using ICD Code G12.2 but excluding deaths from causes other than ALS.

The methods that we used were we obtained death records from CDC for the period 2011 through 2013 coded MND, or motor neuron diseases. Records without ALS listed in the multiple cause of death field were excluded. I have to give a shout-out to my associate, Wendy Kaye, she not only conceived this analysis but went through the data record by record to do that partitioning. Once that was done, ALS death rates were calculated using age adjustment to the 2000 U.S. standard population by the direct method.

Starting here, I'll present some of the results from that analysis. About 21% of the G12.2 deaths were actually not ALS; the majority of those were super nuclear palsy. In total, 18,036 ALS deaths occurred during this period. Among those decedents, 91% were white; and 56% were male.

Here are some rate results in this table. Not surprisingly perhaps, the rates from this analysis are about 20% lower than those from another analysis where the partitioning of ALS from other M&D was not done. For all deaths, the rate was 1.7 per 100,000; males, 2.1, females, 1.4. Among the race groups: whites, 1.8; blacks, 1.0; and other races. 0.7.

This figure shows the relationship between the calculated rates in age category. You'll notice at younger ages, the rates are very similar; they begin to diverge as age increases. The top curve is for whites; the second lowest is for blacks; and the bottom curve is for other races. And you'll notice that they all peak at approximately the 70-year-old to 84-year-old age categories.

There are some refinements that we plan on doing to this analysis. We'd like to add one more year of data; so we requested that additional year from the National Center for Health Statistics, and NCH has approved it. In addition, we requested mortality data by state also; and the intent is here that we can add a geographic component to the analysis. That will be, again, for the period 2011 through 2014 now.

Moving on to the second analysis, this is fitting a survival model for ALS registrants. The goal for this analysis was to see if patient covariates, such as age and sex, affect survival among active participants in the National ALS Registry for the time period 2010 through 2013.

Here are the methods that we used. We used the National Death Index to determine vital status of registrants for the pertinent period. Registrants not determined to be deceased at the end of that period were censored. We then fit a cost proportional hazards model, using the interval since registration as a time variable. The covariates we considered for the model were sex, age diagnosis, race, military service, body mass index category, smoking history, and familial ALS. Among 3,719 registrants included in the model, 28% were deceased by the end of follow up.

This table has characteristics of the model registrants. This is similar to what Paul presented this morning. Males made up 60% of this cohort, 96% were white; 32% had normal BMI, 36% were

overweight, 27% were obese; 21% served in the military; and the mean age at diagnosis was 57.7, with a standard deviation of 11.8 years.

This table contains some initial results from the analysis. We interpreted BMI if a registrant was overweight or obese, they had 80% of the hazard of death compared with registrants with a normal BMI. Conversely, registrants who reported military service had a 30% increase in their hazard of death compared to people that did not serve in the military. Other studies have found similar results; that is, there was improved survival among obese ALS patients and reduced survival among military veterans.

We found two variable interactions that were statistically significant. Those were sex with race and age diagnosis with sex. In general, hazard ratios increased with age diagnosis; but because of these interactions, one needs to consider age jointly with race and sex.

In this table there are various scenarios that display the relationship between these three variables. In the top row, we're comparing white females to males at age diagnosis of 73; and the hazard ratio is 1.3, indicating a 30% increase in hazard of death for white females. In the bottom four rows, we're looking at comparison between black females and black males. So at the same age at diagnosis as the scenario in the first row, if you go down to the bottom row comparing black females to black males at age 73 when diagnosed, the hazard ratio is 5.1, indicating a strong association between being black and female and old and hazard of death. I think this is a very interesting finding. This is a preliminary analysis at this point, and I'm wondering if this is some kind of artifact of the data, maybe some participation bias. If you look at the ratio of white males to white females, it's 1.5 to 1.0; but if you look at the ratio of black males to black females, it's 1.0 to 1.0. It may also indicate an access to care issue.

We're still in the process of refining the survival model; it's actually based on a preliminary dataset. I don't think the data will change much; but it may change a little bit, so we need to finish cleaning the underlying data. Also, there are other variables that maybe should be considered for consideration as covariates in the model, such as history of vigorous physical activity. There were variables that I was interested in exploring.

I was in some haste to fitting this model, but I'd be interested to go back. For variables that had a lot of missing data, there are modern imputation techniques for filling in those missing data elements; so I'd like to consider doing that also.

Moving on to the third analysis, this is fitting a multistate model for ALS disease progression. I'm a relative newcomer to the topic area of ALS; but I learned in working on the data over the last year, there is something called the Revised ALS Functional Rating Score, ALSFRS-R. This is probably a review for most of you in the room. It's a survey for monitoring the progression of disability in ALS patients. It consists of 12 questions with responses rate from 4, representing no disability, to zero for those with most disability. A summary score is calculated summing the 12 disability questions, and so you end up with a single number representing a patient's health, with a range of 48 in the patients with the best health to zero with those of the worst.

It turns out that National ALS Registry administers the 12 disability questions at registration, and registrants are invited to take the survey every six months thereafter. Thus, these data are longitudinal and have great potential, I think, for research. The goal for this analysis is to evaluate whether patient covariates produce declines in ALSFRS-R.

I was sitting in the back of the room this morning. I was thinking maybe it wasn't such a good idea to put up this scatter plot; there are a lot of small points on it. This is a scatter plot on the y axis that's ALSFRS, from zero to 48; and the x axis is days since ALS diagnosis. The blue line represents a non-linear regression through the data.

Some features to point out at very close to the date of ALS diagnosis, the tendency is for the ALSFRS to be about 37; and it drops in a linear fashion out to about 600 days, where it is about ALSFRS of about 25. Then thereafter, the slope of the curve is much more gentle. In total, this suggests that there is larger declines in ALS patients' health very close to the ALS diagnosis.

This is another scatter plot showing the annual change in ALSFRS score in points per year; so that's the y axis. The x axis is days since ALS diagnosis. The data start at about six months; that's when a person would have had their second FRS score recorded.

Some features of this scatter plot, and some of you may not be able to see it from the back of the room, but the points above the zero line represent patients that had an improvement with their ALSFRS score with time. Every data point below the zero lines represents declines in the ALSFRS. Again, the blue line is a non-linear regression through the data.

The regression line says there's a tendency at six months after the ALS diagnosis for the FRS to have a decline of 12 points. If you follow the regression line out to about 600 days, it's still showing declines but they're smaller. They're declining at a rate of about six points per year. Again, this suggests that the rate of change for declines in ALSFRS is greater closer to diagnosis.

There's a relatively new statistical modeling technique called a Markov Multistate Model, and it's been described as a useful way of describing a process in which an individual moves through a series of states in a continuous time and for, example, progression between disease states. Given that we have longitudinal ALSFRS data, it seems like this multistate modeling may have great application to registry data.

What I've done is proposed various disease states, and these are based on tertiles of the available ALSFRS scores. I called the first one good health ALSFRS score of 48 to 36, moderate health from 35 to 25, and then bad health below 26, and then the fourth category is death.

This figure shows in a picture what the model looks like. Patient may move between any of the three health states and from any health state to death. This is to accommodate the people who had apparent improvements in the ALSFRS score with time.

The research questions that I'm hoping can be answered from this model include: Do patient covariates change the probability of changing states, and can the model be used to predict who

will be a fast progressor? A fast progressor might be defined as someone who moves from a good health state directly into death, for example. This is very much a work in progress.

Some refinements in the multistate model would be finding the health states for the model. I'm really betting the farm on ALSFRS and wondering, do the proposed states have real-world or clinical relevance. I'm hoping I can get some thoughts from people in the room on that. In addition, I've not begun to think of the covariates of this. They'll probably be very similar to those used in the survivor model.

I've presented three analyses that are underway at ATSDR using both national and Registry data. In conclusion, estimation of national ALS mortality rates, with the exclusion of other motor neuron diseases, is important to provide more precise rate estimates. The National ALS Registry is a rich database that is hopefully beginning to shed light on questions related to patient mortality and disease progression.

I thank you all for your time and would welcome any comments?

Yes, sir?

Could you go back to your slide showing ALSFRS-R and how it changes over time? I have a few questions, the first is: How do you get an ALSFRS at the time of diagnosis? I'm assuming people are not registering at that time. I'm wondering where that information comes from.

Are you talking about the scatter plot?

Yes.

There is a lot of data close to diagnosis. So people are really registering at the time that they're receiving diagnosis?

It's at the time of registration, not necessarily diagnosis.

Let's be those are two different things.

Right, the ALSFRS that is in the Registry is based on when they register, not at diagnosis.

Right, that's a key point in thinking about the trajectories of ALSFRS; they're totally different.

That's actually a really key point for all of these analyses because when you start counting time, you don't want to start at time of registration because people could have registered two weeks after diagnosis or six months after diagnosis; and that's a big difference. Ideally, you would want to do something, I would think or at least from my view, to sort of standardize the time, perhaps the time at system onset or reported symptom onset. That's a little bit better in terms of starting to count time here because otherwise you see that wide, wide variation at your time zero on the scatter plot where some people have ALSFRS scores close to zero and others have perfect scores. That's likely a reflection of how long it's been since they had symptoms.

But to that point, might there be some survival bias? Because people may not have the opportunity to register. There's always survival bias because people are going to die before they even get to register.

Exactly. So that's a limitation of the analysis, but that is something you can identify -- so they're very fast progressors, let's say. The least you could do is for these people who are registered to your source population as people who have registered, not people with the disease. That's a really big difference. Among the source population of people who have registered, you're counting time from diagnosis.

Also related to that point actual, that kind of a pattern, even if we take the timing issue out for a moment, is also something you would expect if the people who are progressing worse don't continue because they die. So we don't know that it actually is slower later; it's just that the only people who are still around later are the ones that may have been progressing slowly at the beginning. So we need to take into account that aspect of survival.

More importantly, once you start looking at time from symptom onset to time to death or the rate of progression, really what you want to do I think is to identify patterns of progressors, what makes people who progress fast and slow. So you want to do some pattern analysis on this data rather than putting everything into a model and saying, okay, sure, here it is.

Great point.

Yes, ma'am?

Orla Hardiman, Trinity College, Dublin, Ireland

I agree with all of the other points. We've done some modeling of ALS on our Register as well. There are a couple of problems. First of all, we assume linearity, which it mostly is but we don't know at the beginning. It's certainly not at the end, and it'll bottom out with ALSFRS scores lower down. But the big problem is ALSFRS, as you probably know, is built of subscores; and the subscores don't necessarily all decline at the same time. So if you pulled out the subscores, the scores look a little bit different.

The other problem is that the day before the person got the symptoms so our patients, we say when did your symptoms start? They say, "July 2014." You assume that in June 2014, their ALSFRS score was 48, but of course that's an assumption that we make that's not actually correct either. There are lots of problems in doing that analysis. If you track it back and assume linearity, actually the ALSFRS is not 48; it goes back, and we don't know where that endpoint goes.

I think your model is logical, but I think it's not correct because you can't say that good health is an ALSFRS of 40 to 48 if you just have a subset of the ALSFRS which is zero and you're dead. If you couldn't swallow at all and you couldn't breathe, you could die with an ALSFRS score of 45. So that's a problem as well that the slopes are not necessarily the subscores. ALSFRS doesn't give us a burden of disease really. Although the slope is valuable, it's not particularly predictive.

Further, it might be that the different patterns of ALS decline over time actually predict mortality differently. You might decline rapidly at the beginning and then level off, or you may not decline very much at the beginning and then rapidly decline thereafter. Those patterns are going to be incredibly important. I actually suspect, Orla, that the patterns of the subscales are going to be more important than just the overall patterns. James Rooney has just done this modeling; it's under review at the moment, and that's exactly right.

In looking at the slope, you can actually predict whether it's bulbar or spinal onset. That's absolutely right, yes. Let me just say one more thing about missing data also because that's going to be a really important issue in using the Registry data because not everybody answers every question.

There are a lot of assumptions that go under, imputing regardless of the fancy statistical method that's used for imputing data, there are a lot of statistical assumptions that need to be addressed or at least realized as limitations so missing at random, missing at complete random, and there's a whole bunch of them. You really have to be cognizant when you start doing the imputations that those assumptions are holding.

Sir?

Ed Tessaro, Patient Advocate

My question was what was the tendency of missingness, and were there certainly variables that you noticed were missing time and time again? My second point is thinking about your Markov model.

Rich Bedlack recently published an article in Neurology using the Proact dataset, which is sort of a prospective clinical trial database that has some biases inherent within it looking at what they called ALS plateaus and reversals. It may be something worth looking at while framing a Markov model. I don't know if the general belief is that there are these things, at least in the current state of treatment, to move up in that state of the model. When I've thought about the plateaus and reversals article, I sometimes wonder if it is related to some inherent biases and using a clinical trial database that has very narrow inclusion criteria. I don't know if any of the epidemiologists in the room have thoughts on using the Markov model?

I've thought about it, actually, for our data. But I don't know in ALS whether first of all, I think that some of the improvements that might be seen, and I tried to draw a line on my slide, there are very few people who actually improved over time. I suspect that that improvement might be due to some measurement error in the actual instrument. I don't think they're really transitioning to better functioning at all; I think that's just a limit noise in the instrument.

Really, the transitions in the Markov model you'd have to really have clearly-defined cut points for transitions. I'm not a clinician, and so maybe some of the clinicians can speak to this; I'm not sure if you can actually define these cut points in ALSFRS because it's my understanding just from reading literature that this is a rather sort of continuous kind of variable. If you put it together with FEC, I mean, that's also kind of continuous. I'm not sure if N=Markov models are I don't want to use the word appropriate, but for lack of a better word, I will say appropriate here.

So the two staging systems that have been generated, one by a more (inaudible) the King system, which actually has holes in it as well, and also the (inaudible) in Italy. They both actually go from Stage 1 to Stage 2 to Stage 3, and then the King's jumps to Stage 4; but that's not linear. You can kind of say that there are categorical cutoffs because if you go to Stage 1 to Stage 2, it changes your survival probability. They're very simple; they're based on going from one limb to another. We're just doing a validation study with Amar and Sharon Abrams in Edinburgh, and it's not as clean as clean as it looks in the original papers surprise, surprise.

One last comment or question Wendy and then Ben, that's it.

Wendy Kaye, McKing Consulting

I'm just curious with the hazard ration models with the blacks, how many people were actually there in that model because I wonder if some of the issue isn't for the whites, you've got thousands of people, but for African American you have much less.

If you look at the confidence intervals, they're quite wide; and then if you look at the numbers, 93 people in the black category. That may be what the issue is with the hazard ratios rather than anything else.

Ben?

Ben Brooks, University of North Carolina

Exactly how did you short out PSP from ALS, your first point?

Wendy?

Wendy Kaye, McKing Consulting

The death certificates. The National Center for Health Statistics sent me the actual file with all the text rather than the codes, so I read them.

So you had the medical record?

I didn't have the medical record; this was off the death certificate.

Oh, the death certificate.

So if the death certificate said "super nuclear palsy," I kicked it. There were all kinds of lateral sclerosis, all kinds of weird spellings.

How did PSP get into a 12.2?

Because that's where they put it in the revision. If you look at the paper by Jim Sejvar where his first paper they cut of the mortality analysis at 99 and clearly stated about two additional codes that they moved into G12.2, one of which was super nuclear palsy, that made it so that they couldn't analyze the data.

All right, thank you very much, Ted.

Most of the rest of the afternoon, we're going to be talking about Registry promotion and outreach; and to kick it off is Tom Hicks, Public Consultant with the Carter Center assigned to the ALS project.

ATSDR Registry Promotion and Outreach

Tom Hicks
Public Health Advisor
Carter Consulting, Inc.

Good afternoon. I'm Tom Hicks; and, as Bob just indicated, I'm a consultant with Carter Consulting. I work directly with the Registry program at ATSDR.

We are going to shift gears here a little bit. You've been listening to more scientific-related presentations for most of the day, and now we're going to shift into more marketing and promotion of the Registry. I'll be presenting the efforts of ATSDR in promoting the Registry.

First of all, I'll start off with the ATSDR's marketing strategies. Then I'll begin to cover the types of promotional media being used, including digital and traditional more of the print media and then move into some metrics to try and describe the level of interest in the Registry. Basically I'll talk a little bit about some recommendations from last year's meeting and then introduce some new communication partners.

Regarding strategy, we're continuing to use the traditional and digital media traditional, again, being looking at primarily print media, such as pamphlets, fact sheets, posters and our exhibits that we take to various conferences. We're also continuing to engage persons and organizations who interact with PALS in order to reach the largest number of potential Registry participants.

We're continuing to work with our internal and external partners. Our internal partners are primarily with ATSDR is our Office of Communication. We work with them a lot to get our social media posted and to put together articles for publishing on our websites. As far as external partners, those are our long-standing partners with the ALS Association, with MDA and with Les Turner ALS Foundation. These organizations are working on serving directly persons with ALS, and so they are critical for us as far as reaching directly to the patients through their local clinics and local offices. Last but not least, we work with neurologists, researchers and caregivers, as they also work directly with the patients.

Regarding digital media promotion, we've routinely put articles on online magazines and newsletters. We post ads in partner publications a good example, currently MDA is running our Get the Facts infographic ad in their Quest magazine. We also publish CDC feature articles on the CDC website. We do this generally twice a year, once would be at the anniversary in October of the Registry; and then, again, we'll do a feature article in May for ALS Awareness Month.

At the same time we're running these feature articles, we'll also post ATSDR blogs. These blogs really promote the Registry by highlighting the accomplishments in the various programs and other systems that we have in place. They also link back to the feature articles; so if a reader is more interested, they will go straight to the feature article. We also have a link on the blogs that will take them directly to the Registry.

We also promote the Registry through journal articles and through reports which describe the findings of the Registry. We also are very dependent on our social media. We use social media, of course, to get the word out about the Registry, either events that we'll be attending and presenting at, other things such as announcements regarding activities that we're doing. Lastly, we are depending more and more on infographics and other graphics to get the word out.

This is a good example of using the article with the newsletter. This is Les Turner ALS Foundation's newsletter, and they have followers of about 77,000 with this newsletter. This particular newsletter was highlighting last year's ALS Registry meeting. Not only is it focusing on the meeting, but it also focuses on the progress that the Registry has done through such things as connecting PALS with clinical trials. Also funding, the Registry funded ALS research and collecting biospecimens.

This is a good example of our CDC feature article. This particular article was published in October of 2015; it's our Registry anniversary article. It describes the Registry's goals and its accomplishments. We also use these articles to encourage PALS to go online, to register and complete the respective surveys.

This is the second article that we published last year, and this is on ALS Awareness Month in May; and it was also published on the CDC website. Again, it describes ALS and the Registry, the findings of the Registry and our programs; and it encourages PALS to register and take the respective surveys.

We also use social media quite a bit; primarily we use Twitter and Facebook basically to spread the word about ALS and the Registry. Also we build awareness about the importance of being counted by joining the Registry, PALS' role in finding the causes of ALS by completing the risk factor surveys, and reporting Registry findings and other Registry initiatives, such as the biorepository, funded research, research funded by the Registry, connecting PALS with researchers and also the state and metro ALS Surveillance project.

This is a good example of combining the Facebook message with the digital media. This message was concerning ALS Awareness Month and, again, encouraging PALS to go online to help us find the causes, to complete risk factor surveys. With this, we're combining the digital media with the Facebook message, which having the digital media there is extremely helpful in pulling attention to the message. This digital media, this graphic that you see, was produced by one of our new partners, Brunet-Garcia.

You'll be hearing more from them in the next presentation. Here's one of our most recently created new infographic; this is the one that is explaining connecting persons with ALS with researchers. You can see that it's bright; it's colorful, making it quite attention-getting. It also

explains the connecting persons with ALS with researchers through three easy steps: one, enrolling in the National ALS Registry; two, choose to be notified about studies that you're eligible for; and, three, start receiving notification e-mails.

Moving on to the more traditional media, these are three of our print fact sheets. The first one is descriptive of ALS and of the Registry. The middle one is a Quick Start Guide, which basically explains the steps of registering to someone who is going online for the first time on the Registry. The third one is targeting providers with our continuing education module. These are all available online on the Registry, easily ordered through there.

These are, again, print items three of our brochures. The Patient Guide, again, explaining the Registry; Connecting Persons with ALS with the Registry, a pamphlet explaining how that works; and then a Provider Guide. Also, all these are available online on the Registry.

Moving on a little bit to the metrics, this table presents the Registry printed materials and the amount that are distributed by organization. The organizations of course included are the ALS Association, MDA, Les Turner and also the clinics and physicians and other providers. As you can see, as of June 30, 2016, there are well over 73,000 products distributed. This histogram presents the number of people that viewed the Registry over the last years, 2011 to 2015. As you can see, from 2011 through 2014, we had steadily increasing views. However, as of 2015, we see a pretty significant drop in the number of people viewing the Registry.

I really can't tell you why that it is; we're uncertain as to the reason. We suspect that the 2014 increase had at least partially if not considerably attributed to the Ice Bucket Challenge, which went viral in the summer of 2014. However you look at it, I think that this tells us is that what we really need to be doing is focusing and increasing our efforts to increase the awareness of the Registry as we go forward.

Also, let me just add that in ways of increasing those efforts, we are bringing on new partners; and you'll be hearing from them in the very next presentation. Before I finish, I'd also like to go back and talk a little bit about the recommendations from last year's meeting. For those of you who were here, you probably recall that we talked considerably about the amount of new programs that the Registry is doing, new initiatives that were taken on and how that's furthering the Registry. But at the same time, it was pointed out in that meeting that although we're moving the Registry forward considerably, there are a lot of people in the ALS community who are unaware of these kinds of programs, these activities. Because of that, these recommendations were offered.

One, clarify and manage the expectations of what the Registry will do. Develop articles for partner newsletters to highlight the accomplishments of the Registry. Improve branding of the Registry by developing a more inviting appearance. Translate ads into other languages, such as Spanish. Increase the use of infographics and other graphics to focus on the importance of PALS' role. I'm happy to report that all of these recommendations are being implemented.

I'm also happy to report that we are bringing on new partners. You'll be hearing from Brunet-Garcia Advertising. Brunet-Garcia actually isn't quite new; they've been with us for about a year. The other new partner is Global Prairie.

Let me end there and open it up to any questions that you might have. Okay, well, if there aren't any questions, then you'll hear from Brunet-Garcia and from Global Prairie.

Thank you.

ATSDR Registry Promotion and Outreach

Anna Jaffee

Account Brand Strategist

Brunet-Garcia Advertising, Inc.

Thank you so much, Tom, for the introduction.

I have a couple of slides here that will just touch on a couple of things that Tom just covered in his as well. I am from Brunet-Garcia; my name is Anna Jaffee. We have been working with ATSDR for about a year now. We started working with them in March of 2015, not negative three months so that's a mistake, sorry about that. But we have been working with them for about a year. When we attended the meeting last year, we had just started our contract. So very excited to still be on board with them and looking forward to what's ahead.

One of the first things we did was we had a strategic session with the ATSDR folks to kind of uncover what our communication objectives were. As Tom has covered and as it has been known through some of the other presentations, we feel like our No. 1 challenge is lack of awareness. Our communication objectives are to raise awareness of the Registry among PALS and their families and caregivers. Target, inform and educate PALS of the latest happenings and updates from the National ALS Registry.

I know it was mentioned last year that there wasn't a lot of communication in what's being one, so that was one of our goals. Then to, of course, increase self-registered PALS in the Registry and encourage the completion of risk factor surveys.

The big part of our contract last year was to complete this communications outreach plan. So some of the deliverables that we had and some other pieces of research going into that was to do audit of all the exiting materials, some that Tom Hefferson did last year, and see what was out there currently. As I mentioned, we did have a strategic marketing session with the ATSDR to identify what our challenges were and objectives for the next year.

We've been attending partner conference calls with ALSA, MDA and Les Turner. Of course, we attended last year meeting; we reviewed the notes from the meeting the year before; conducted a 90-day media scan and report; and then just did some additional research of what was out there in the ALS community currently.

Some of the highlights of accomplishments from last year and working with the team, we did create a tagline, which was "ALS Research Counts on You." As it has been mentioned, I know, in Kevin's presentation, we really wanted to move away from the thought that the ALS Registry

was just counting patients. We kind of wanted to use that term and flip it on its side and give it kind of a new meaning and make it a little bit more valuable in what the ALS Registry does so using that word in kind of a different sense. So we came up with this tagline, and then we also developed a messaging platform which outlined kind of the foundation for everything that we would be developing.

We kind of split that into themes and supporting messages, and I have a couple of examples here. As I said, we just used that to set the stage for all of the content that we would develop moving forward. Then we worked very closely with Tom and the team to develop a whole database of content that we could pull and use for our marketing materials. It included Registry talking points and benefits, social media copy, Registry research, update for the notification system, and funding opportunities, Registry meeting highlights from last year, and the some information about the biorepository as well. Of course all that had to be cleared, but wanted to give ourselves a really nice foundation for developing the materials.

We also worked with the team to develop a feature article. We had interviewed Dr. Bradley, and we were able to help facilitate the article for the May ALS Awareness Month feature. Then, of course, the look of our presentation is this branded look of the Registry.

We presented a couple of concepts, and we narrowed it down to this very iconic and colorful look that still kind of has a scientific feel. All of the materials that you've seen, the new materials that Tom has presented, really kind of capture this look.

As you saw in the last presentation, these are just a couple of the materials that we did create last year. Then the digital ads, this is where I'll turn it over to Global Prairie because they were crucial in distributing these materials that we had created. We've been working closely with them, and it's been a pleasure.

I'll toss it over to Kaylie and Erin.

ATSDR Registry Promotion and Outreach

Kaylie Wallace and Erin Bunyard
Account Digital Strategists
Global Prairie

Kaylie Wallace, Global Prairie

Thanks, Anna.

For those of you we haven't met, my name is Kaylie Wallace; and this is my colleague, Erin Bunyard. We work at Global Prairie, it's a global marketing firm that's dedicated to cultivating a healthier world through our work and also through our participation as a Benefit Corporation. Before we get started on this section, you might notice that we don't have slides printed out. That's in honor of being the digital portion, but also because we have a lot of animation throughout this presentation. So if you aren't awake now, now is the time to tune in.

Yes, we joined this team a little more recently; and we've been working with Brunet-Garcia, as well as the ATSDR team, to get these digital ads out there so that people are actually seeing them.

Our goal is to develop a digital media campaign that supports the Registry objectives. You might be wondering, “why digital?” We know we're doing a lot with print, why add on digital as well? Digital typically has a better rate of getting people to act. It's more effective to get people to take the action we want them to. And with the short timeline and limited budget, we knew that this was probably the best way to reach the people we wanted.

Our strategy was multifaceted, and don't get confused if you're looking up and seeing a lot of words that you don't understand right now because we're going to talk about all of them. What we did is we worked with an audience buying and social partner as well as a direct site buy. We wanted our placements to be seen across platforms, so we put these ads on phones, laptops, tablets and desktops. We also worked to have a paid search component, and we worked to size the ads differently so that they could fit the space that we were buying for. So you're going see our ads appearing as small squares, as large rectangles - it kind of depends on where you're looking. And we'll go through that for the rest of the presentation.

This is a slide that we go over every single month with our team. It grounds us in our objectives, who we're trying to reach, what these ads are trying to do. Obviously, our objective is to increase the amount of PALS that are in the Registry. Our target audience is those PALS, but also their family, their friends, their caretakers, their doctors - people that might see these ads and then encourage them to go join the Registry.

This campaign officially launched May 6th and is ongoing. Right now, we're slated to go through September; and we're hoping that we'll extend that through the rest of the year. The data that you're seeing today though is just the first two months of the campaign. We're showing you what happened between May 6th and July 6th. It is, again, still ongoing; but this data has already been analyzed, and we wanted to show you what we accomplished at the very inception of it.

We ended up going with three tactics; we went with social, paid search, and site direct. When we say social, we're referring to Facebook. Paid search means Google search. And then site direct means WebMD. And obviously, a lot of strategy and thought went into why we chose these places, which we'll talk about later in the presentation.

And before we dive into the metrics and the success to date, we did want to answer a few questions right off the bat about terms you're going to see and hear throughout this presentation. So here's our digital glossary to get you started. When we say “impressions”, we mean the number of eyes that have seen our ads. That's the number of times a digital ad was shown to someone. The click-through rate is when you have your clicks divided by your impressions - how many people actually took the action after they saw your ad. Cost Per Click - that's a certain type of paid media buy, and that's when we only have to pay if someone actually clicks our ad. We'll talk about that when we get to paid search.

And then we have two other terms that are really important to this campaign: conversion and awareness. Conversion is a metric that measures how many people actually did what we wanted them to do, which is sign up for the Registry. Awareness, on the other hand, that's all about creating buzz. People are recognizing our campaign; they're seeing our ads; they know what our message is.

So you might think to yourself that awareness eventually could lead to a conversion, it is just harder to track. So that is what we call the "halo effect". Someone who saw our ad this week might go back in two weeks and then sign up for the Registry. And although we can't directly say it was because they saw our ad, we can assume that that might cause a hike in registrations. So we tried to tie it up in a sentence before we go into our result. What we wanted to do was get our ads in front of people that we know to be interested. So they click, go to the Registry site, fill out the survey and help us accomplish our goal to get closer to finding a cure for ALS.

So now what everyone is here for. Erin is going to present the results that we're seeing to date. Thank you.

Erin Bunyard, Global Prairie

All right.

So a little more detail on how and why we chose these three platforms. First let's start with Facebook. And this is paid Facebook, which is different than what Tom was talking about which we consider to be organic social media. Organic social media is when you sign up for a media account on behalf of yourself or a branded organization, and you're posting, and it doesn't cost you anything.

We also engage Facebook to do paid social, which is paying to place advertisements within Facebook's infrastructure. So we utilize what is called Facebook Exchange, or FBX. We reach users who have demonstrated behaviors that indicate that they have a particular interest. So, for example, we looked at people who Facebook knew had engaged with the ALS Association's Facebook page. If they liked the ALS Association, if they had liked or commented on one of their posts, then Facebook actually tracks that. A little crazy, yes, they know everything that you're doing. And they allow advertisers to actually target to people who have shown that they are specifically interested in a certain type of content or a cause or a product.

Sorry, I was just going to show you - .

(Inaudible/showing video)

So this is just showing the interaction where you might see the ad on a particular Facebook page, you click on it, it takes you directly to the Registry where you can register.

Our second tactic was Google page search, also known as Pay-Per-Click or PPC. This captures users when they're seeking more information about ALS or the Registry. Basically you're paying for your website to show up first for chosen key words on Google. So, for example, if you typed into the Google bar "ALS research" or "ALS treatment", the Registry is going to rise to the top of the results. And even in your own Google searching, if you've ever seen this small kind of

yellow square next to the top two results that say Ad, that means a brand or an organization has paid for that listing rather than just showing up there organically.

All right. And then last we partnered to do a direct buy with WebMD. Site Direct is placing your ads directly on someone else's website that's related to your business. We chose WebMD because it is considered the number one health and wellness platform on the web for over 65 million unique monthly users, so 65 million individuals are accessing WebMD on a monthly basis. We placed the ad contextually on pages within WebMD that are related to brain and nervous system and also the caregiver topics. Also, if you remember when Paul was talking about how the Registry under registers in certain geographic areas of the country as well as having some particular demographics that are underrepresented, we were able to request WebMD to what we call heavy up, or to skew the impressions to those states that are underrepresented currently, to try to level out those lower performing states to date.

So what we're seeing so far, and, again, this is the first two months of data. We monitor this campaign on a weekly basis. The other thing that we have working for us is that this offer allows auto optimization. So, for example, on Google, if there are certain keywords that are outperforming others, then the Google algorithm and the vetting structure will help us auto optimize to those terms.

The great thing about digital is you're essentially using a database to monitor the results 24/7, and it can also help to make sure that your campaign improves over time. On a monthly basis, we get together with Paul and Tom and the team and we actually review the performance to date, and then if we have specific optimizations where we want to kind of override the database or make more drastic changes to the campaign, we can do so.

We can identify if there's low-performing tactics or things especially that maybe aren't as cost efficient as we would like them to be, and we can alter them or remove them from the campaign. So, for example, recently we noticed that there was a particular size of ad that was performing better than any of the other sizes, so we said, okay, well obviously, if that size is doing better, then we want as much of that size as we can possibly get. So we maxed out the inventory for the size that was the most popular, and therefore raised our results.

We also did a small test with another health-related website called Healthline early in the campaign. It was lower performing. We weren't getting as many of those impressions or eyeballs on our campaign as we would have liked. We really weren't getting as many clicks. So after monitoring that for a few weeks and deciding it wasn't the best for us, we actually removed our money, left Healthline, and put that money back into Facebook and Google which were performing better.

So let's talk about our top performer, so the Facebook Exchange performance. And, again, we were targeting on Facebook two ways. One is that interest targeting, which we talked about. If you liked a related type of page. And the other is retargeting, meaning you visited the CDC website and so we can retarget you in the Facebook environment. So our interest targeting is our strongest performer. And the ad that's performing the best is, again, the one that you've seen before, the yellow "ALS Research Counts on You".

To date on Facebook we've had six million impressions. And one thing to note is that impressions are not unique to one person. We actually want you to see the message more than one time. It's referred to as frequency. And we realize that especially in the digital space there's a lot of clutter, and everyone is multitasking, so the sweet spot that we really want to hit is usually around seven to ten times that you see a particular message. We don't want to go much over that because then you will have what we call "burnout", which means you've seen it so many times that your eye doesn't even really register it any more. But if we do it too few times, then the message may not have resonated with you. So those impressions are not six million unique individuals, but it is six million ads that have been served.

The number of clicks that we've driven to the website from Facebook alone is over 9,000, which means our click-through rate is .15%. I know it sounds like a really small number, but across the display advertising industry, what we see on average is .08% as a click-through rate. So we're actually almost double what we would say is industry average.

We have 21 conversions from Facebook to date. And, again, conversions means that, in our case, they completed the registering process, and that's a conversion rate of .22%. So comparing that to paid search, paid search is a little bit different because on Google you actually only pay for it when someone clicks. Which is amazing, because if you see that ad, and you read it, and it registers with you, but you don't actually click on it right away, we didn't actually pay for that. You get free awareness on Google.

Our total impressions in Google are 214,888. So it's significantly lower than Facebook, but the thing to remember about Google is you only see the ad if you search for something that was related to what our message is. So we're showing far fewer total ads, but you'll see that the click-through rate here is nearly 4%. So in those terms, you're showing fewer people, but they already raised their hand and said "I am interested in your content". So the likelihood that they are going to click (and then therefore convert) is much higher.

We have 8,000 clicks to date from paid search. Our cost per click is a little under \$3.00, and again, across industry average that we see that we just use as a benchmark is as high as \$7.00, so this is also a very efficient tactic in terms of how we're utilizing budgets. And we've had 18 Registry completions from paid search specifically to date.

We have three categories of key words, so those are related to either the ALS brand, the CDC brand, or Lou Gehrig's disease. And our top performing key words to date are there on the bottom: National ALS Registry, ALS research, ALS registry, ALS causes and symptoms, ALS treatments, ALS Research Foundation, and news.

And then lastly WebMD. So WebMD is primarily an awareness tactic and not a conversion tactic. So we've focused on a little bit different part of the marketing funnel. We are trying to cast a broader net, understanding that it probably won't drive as many direct conversions, but we're really trying to make sure that people are aware of the Registry, they can recall it, and they can pass it on with word of mouth. Our impressions to date on Web MD are 1.2 million, so we've driven 1,200 clicks to the website, which is a CTR of .09%. We're also hoping that by driving this awareness of the Registry, we're lifting the overall awareness, again which we refer

to as the “halo effect”, meaning while it may have not contributed conversions to date, that that awareness will translate into future conversions down the road.

We are running three different creative variations, the three different colors of ads that Anna showed you at the end of their presentation. And so far, again, the yellow “ALS Research Counts on You” ad has been the strongest performer.

So just to kind of wrap up these total numbers. We have almost 8.3 million impressions to date. Over 18,000 clicks on our ads. The CTR of .22% average. Thirty-nine successful registrations in the first two months.

We have Facebook accounting for 54% of those conversions, followed by Google at 46%. Those registrations are also coming from 22 different states. And 32% of those states are considered “low performers”. Just a quick visual to highlight those states that we’ve driven registrations from in the first two months.

And then really to roll up the data and also symbolize the halo effect, these are the total ALS portal registrations for the year compared to 2015. So this is not the registrations that are solely attributed to the media campaign alone. These are the total registrations that could have come from a number of different sources. And we were really pleased to see that you can see in June, which was the first full month that the campaign was live, that we did beat out 2015 in terms of the total number of registrations. And while we cannot show the raw data today, what I can say is that June is a nearly 12% increase, 2016 over 2015. And we are just hoping and really excited to see that trend continue through the end of the year.

So looking ahead, we continue to monitor, we continue to optimize, report monthly through September. We’re also continuing to adjust the copy on the ads themselves, the text, test different messages and make sure that our CTR and call to action is as strong as it can be, we’re driving as much traffic to the site as possible.

And then we’re also working with Tom and Paul to explore a potential extension of the campaign through December and possibly onwards.

Thank you for your time. Thank you for having us. We’re very honored and proud to be a part of all of your efforts and to contribute to this.

So we’d like to open it up to any questions.

So first I have to thank you for the education about click-through rates, they’re terms I’ve heard before but never understood. Just so that we have a sense of sort of your expectations coming into this, what were you hoping would be the conversion rate? Just sort of wondering. The numbers seem small, and I don’t know whether that’s because it’s sort of early days, but was this an expectation or an anticipation or a hope up front as to what these would be, what they would look like, how they would grow over time, just to give us perspective.

Sure. I will say that I didn’t actually have one. And part of that is because the conversion itself, while it is related to the media campaign, also has a really strong correlation to the website

performance. We can drive people to the website, but once they're there, nothing about the media campaign can actually make them complete that form. And one of the things that I was initially concerned could hinder the performance of the campaign is that the site isn't mobile yet and I know it's in progress to be mobile optimized. And it's a really long form.

Now in the U.S. stats range between about 60 to 70% of people access the internet from a mobile device. And so to have a really long and somewhat cumbersome form on your mobile device, people will abandon and not complete. So we did have a barrier. So considering those, the fact that June, we were higher than May, so I really used that first month as a benchmark and said, okay, can we get 12 registrations a month? And then June outperformed May, and that we're up to 39. So what we hope to see is that through optimization throughout the campaign, if we're growing month over month, then we consider that success.

Ed?

Ed Tessaro, Patient Advocate

This might be out of left field, but have you guys built into any of your thinking a tie in to something that already has a great bit of ALS momentum? My example is the documentary Gleason which opened on July 29 in some cities, and opens this week in Atlanta. It's going to have a 60-day run by all accounts. It's had a Sundance honor that tends to launch these kinds of things. I don't know what the dollars are on trying that tie in. This is all very solid, but I'm not impressed with the numbers. Should you be looking for something bigger? Something that already has movement, already has juice, and try to tie into that?

Absolutely. I think that's a great idea to explore. And especially with the digital tie in. You know, a lot of the mass marketing when you start getting into TV and things you really need million-dollar budgets to play in that space.

A million, to play in what space? I'm sorry.

In like the TV, and to do TV advertising, you know, around like a premiere. Those can take a pretty big budget sponsorships. Sponsorships can also take really large budgets. So we definitely focused on tactics that we felt like were the most cost effective for a fairly limited budget. But there's no reason not to explore an opportunity for a tie in like that.

One last question,

Ed Tessaro, Patient Advocate

No, wait, I'm not, I want to follow up.

Oh, excuse me. I'm sorry.

She may not know what Gleason is. You may not know what Gleason is, is that fair?

That is fair.

Okay, well let's start there. This is a New Orleans Saints, 34-year-old guy who was diagnosed at that unbelievable age, and his life has been an inspirational story, to say the least. And it's been documented beautifully, if you look at the ratings of this documentary. And it's not a big budget film. This is not a Marvel comic. But it's a documentary that has probably the most targeted audience you could imagine. Who's going to go see a story about ALS except a lot of people with an interest, either friend, family? So I don't think you're talking about million dollar budgets trying to attach yourself to a documentary.

Now I don't know what the number is so I'm speaking from ignorance, but that's why I asked did you have it in your thinking of trying to involve yourself with something that already is on the move. This is going to have On Demand presence, more than, you know, in the next couple months. It could run to the holiday, actually. And if I were getting those numbers, I'd be wanting some new ideas in the mix, which is why I asked if you...

So Ed, this is Paul Mehta.

Paul Mehta, National ALS Registry

I think you've got some really good, valid points right there as in terms of looking at Gleason and so forth and other sorts of things kind of coming out. And this was kind of like a pilot project for us as in terms of looking at Facebook, looking at social media to see kind of what the feelers were out there. So, I mean, for the Registry folks, this was kind of new to us, therefore we brought in the experts here. But I think you've got some really valid points regarding looking at Gleason and possibly having some sort of, you know, we can place an ad there or something like that. That's what I mean. We can certainly go ahead and look at that.

But, I mean, I think, you know at this point we're just focusing on social media per se as opposed to just like going into whether it's Gleason, or whether it's, you know, the previous ALS movies which came out last year. Two movies, first released last year. Academy Award winners. And we can certainly go ahead and look at that on our next call to see if Global Prairie perhaps even talk to the Gleason group and say, hey, can we put some information, a web button, you know, ALS Research Counts On You, on your website, can we, you know, perhaps give you incentive to pay you or something like that. It's not like anybody is competing with you. You're absolutely right. You've got a very, very valid point there. But no, and since it's really important, we can certainly go ahead and talk to Global Prairie and Brunet- Garcia and see if we can leverage that sort of thing. And, you're right. The Gleason movie is certainly phenomenal... I've read about it. They applauded for five minutes at Sundance. That doesn't happen. Peter King had a very good moving article on it from SI, and I read it. It was supposed to be a very, very good movie.

And I just want to add one thing, that we developed a whole communication strategy plan last year. Digital was just one aspect of that. We do think it's a very effective asset because we're asking people to register online, so we're getting people where they are. But we did have recommendations as well, and we're actually revising the communications plan this year based on what we found. There's a lot of non-digital strategies. We even looked at like celebrities that were personally affected by ALS. Julianna Margulies... I'm not sure if I'm saying her name...the woman from... Julianna Margulies. Yeah, Margulies. She was personally affected.

So we looked at different channels of, you know, potentially in our next contract, reaching out to celebrities or people that might have an interest and to do things for free. So that is definitely in Brunet-Garcia's sights and efforts. But this was kind of, as Paul said, the first piece of the development of that strategy.

Okay, one last point.

Pam Factor-Litvak, Columbia University

So, actually two little points. One is that I just tried it on my phone. I Googled ALS, and it didn't pop up with just ALS. I had to Google ALS research to do that. So you may want to move it just to ALS so it comes up with ALS and not having to type in the research word. So that might actually give you more hits because people, for example, who have just been diagnosed may not think to type in the research, just ALS to find out more, and that might give a better bang for the buck.

The second one, maybe, is more for Tom because he said he put articles on the CDC newsletter, which is great, and people like me, I go to the CDC newsletter. But people in the general public I think tend to think of the CDC as something that is as an organization that deals with Ebola, or Zika, or any infectious type of disease. So you may want to rethink where you put the articles. CDC might not be the exact right place.

Actually I brought that up as well. We had that conversation with Global Prairie, too, Pam. Same thing what you're mentioning, too. I said, CDC, people may not realize CDC does ALS and therefore we're going to be tweaking some things going forward, but you're right, I had the same thought process as well.

I'm like CDC, you may not think about it as ALS per se, as opposed to Ebola or something else. Paul, the websites of the ALS clinics are free advertising. And no one has reached out to us. So, for example, I have a Registry icon on our website, but it's not been updated. And it would be interesting to see if there is a campaign and what is the click-through rate on our websites. And I'm sure, I don't know if the ALS Association has pulled in, or the MDA Association, or NEALS, but certainly on our clinic website where I suspect a lot of the patients look at, and we approach patients in multiple ways. So we bring an iPad to their room to register when they come to clinic, and we have this on our website. But we're generating probably no meaningful statistics for the Registry.

So those particular web buttons, they will be on the websites of ALSA, MDA, and Les Turner. We've asked them to go ahead and provide specifics where they want to put them. It's got to go through the IRB approval process, but we actually will be updating those web buttons and having them be available to download, for example, on your clinic, for your web developers to put on there as well.

All right, so... (Inaudible.)

No, we'll certainly, like I said, having your input is just valuable. We'll do that.

Okay, we're moving on to our next presentation.

Alicia Fraser, Massachusetts ALS Registry

Paul, just so you know, we also have a button... sorry, Alicia, Massachusetts. We also have a button on our website, but were you saying that you need approval to do that? Because we didn't talk to you about that.

No, it's only approval for, as in terms of official partnerships we're actually giving funds to. That's where there is the approval process with IRB. But, for example, NEALS has their web button, and you certainly, hopefully, mentioned have a web button as well. There's no approval required for you. It would only be for groups which we actually provide funding to, as in an official partnership.

Okay, our next presentations are from the Les Turner ALS Foundation. And the speakers are Andrea Pauls-Backman and Judy Richman.

Registry Promotion and Outreach

Andrea Pauls-Backman
Executive Director
Les Turner ALS Foundation

All right. Well, it's always challenging being the groups to go right before the afternoon break. So we're going to try to keep this moving along, and we'll let you know the work that we do and how we are promoting the National ALS Registry. My name is Andrea Pauls-Backman. I'm the Executive Director of the Les Turner ALS Foundation. Judy Richman is our Director of Patient Services.

So I'm going to start here with a brief overview. Most of you obviously are familiar with the work that Les Turner has done. For those of you who aren't, I just want to spend a couple of minutes talking about the work we do because that does feed into how we approach the registration process for the Registry.

So, frankly, nearly 40 years ago it began in somebody's living room. The Les Turner ALS Foundation has grown to be one of the oldest independent ALS organizations, actually at this point in the world. Although we operate locally within the Chicagoland area, we have a national and an international reach as one of the founding members of the International ALS/MND Alliance.

Just a brief overview at what we've done since we began. These numbers are through the end of 2015. And, again, remember, this is all within the Chicagoland area. Our mission, much like many of the other advocacy organizations, is scientific research, it is providing care, both through our clinic and our home and community team, as well as increasing awareness and education of ALS.

So what do we fund and how do we do it? Eighty-eight cents of every dollar that we spent last year was directly funding programs, which, if you follow this sort of thing, is a very high number. Most organizations are somewhere in the low to mid 70 cents. Seventy percent of our money went toward the Les Turner ALS Research and Patient Center, which is an institute within Northwestern Medicine. We are part of the Translational Neurology Institute, and that encompasses both our three research labs as well as our multidisciplinary clinic.

Fifteen percent of our money went toward our patient family services. This also directly impacts the work that we do with the Registry because this encompasses Judy's team, and she is going to explain that in more detail in a moment here.

Three percent of our funds last year went toward education and awareness.

For a quick overview on our laboratories, our first laboratory started in 1979. We now are employing 33 ALS research scientists in three distinct laboratories, each of which have a unique focus within ALS. Those include Dr. Teepu Siddique, Dr. Hande Ozdinler, and Dr. Evangelos Kiskinis.

Judy, if you can take it here for a moment.

Registry Promotion and Outreach

Judy Richman, RN, BSN
Director of Patient Services
Les Turner ALS Foundation

Thank you.

As Andrea said, part of our mission is to provide our patients and families with exceptional care and support. So the Lois Insolia ALS Clinic was established in 1986 and is one of the oldest and largest multidisciplinary clinics. We have a total of 26 clinicians. That includes five neurologists, two pulmonologists, nurses, speech language pathologists, dietician, genetic counselor, and a research coordinator. And this whole team of people see our patients every Wednesday and Thursday afternoon.

We have a genetic counselor to work with our familial ALS patients. We also have a tissue donation program where people donate brain and spinal cord tissue. And then we have been active in doing clinical trials throughout the years. We are currently involved in the Tirasemtiv study.

Selfishly and proudly I'd like to say that our pride and joy is our Patient Services Program, as the Director of Patient Services. In 1989, the Foundation established what is called the Home and Community Services Team. It was the first of its kind in the nation and has served as a model for other organizations to follow.

We are a hands-on agency. We have five nurses and two social workers who work in conjunction with the doctors at the clinic. They go into the patient's home and provide disease education and disease management. We make recommendations for safety and equipment. Just basically letting patients know that they are not alone in fighting this disease.

We started out with one nurse, and as I said, we now have five nurses and two social workers. And the other thing that is nice to know about this is that we do this in the convenience of their home and there is no charge for our patients at all for any of the services that we provide.

Other services that the Foundation and the Home Team provide for our patients is home visits. We have a lending closet for items of things that are not covered by insurance, so basically the low-ticket items.

And a lot of the things we also have are communication devices, which by no means are little ticket items, but we do have communication devices. We have three different grant programs to offer to our patients, one of which is the equipment grant. This grant helps to cover the cost of things that are not covered by insurance. We also have a respite grant to help offset the cost of caregivers. And then we have a transportation grant to help get our patients to and from our clinic.

We conduct four different support groups plus we attend a support group that is put on by the Heinz VA Center in Chicago.

And then, definitely, we are there to help promote and support the National ALS Registry. Another part of our mission is education and awareness. So, again as the Home Team, we are out doing patient education in the homes.

In clinics we put on professional in-services with hospices, nursing homes, home care agencies. We've even gone to workplaces to give people education about ALS, what they can do to modify the workplace to accommodate patients so that they can work as long as possible. And in addition we have a resource guide that is in the process of being updated and on our website. And then every year we hold an annual educational meeting for patients and their caregivers.
Andrea?

Registry Promotion and Outreach

Andrea Pauls Backman
Executive Director
Les Turner ALS Foundation

Thank you.

In addition to that, as part of the Les Turner ALS Research and Patient Center at Northwestern, we host an annual research symposium on ALS and neuro repair. This year will be the sixth annual symposium. Last year we had about 200 people, I think slightly over 200 people, attend.

And we bring in a national speaker regarding ALS, and it is a full day's worth of poster presentations as well as clinical information that's been attended by researchers, clinicians, patients, as well as others interested in the disease.

The other thing we have done for the month of May in the last couple of years has been called the Freeze ALS Campaign. And now that Brunet-Garcia has been nice enough to let us all know what impressions mean, with this number you can actually put this into context. The campaign that we did this last May had a reach of 360,000 impressions. And that was done not only via social media, but also done via cards that were handed out to over 75,000 people. This is just an example of some of the work that was done at the research symposium, at which we are, of course, focusing on the Registry as well.

Some of our specific promotional efforts really are across the gamut. So not only are we looking at social media, and you saw some of the presentation here, we also take a different tact. We actually, because a significant number of people with ALS are not necessarily tied in electronically, maybe not even as much as the rest of the population, they're not reachable that way. So our methods actually address that ability to reach them. As a result, we've got print newsletters. Tom Hicks showed one of the copies of our print newsletters, which go out, and you'll see an example of that here. We are promoting the Registry through our e-news and through our website in a dedicated page.

Judy discussed our home and clinic visits. Frankly, if you look at home and clinic visits and support groups, and in each of those situations, those are one-on-one or person-to-person presentations about the Registry, we had 2,000 touch points last year alone. So although social media is terrific and we think it's another avenue, we believe that actual one-on-one or person-to-person impact can do an awful lot in terms of promoting the Registry, and we do work on that.

This is a copy of the ALS National Registry page that is on our website. We launched a new website earlier this year. It's now easier to navigate, and we've updated the dedicated Registry page.

We have our Home and Community Team, which attends several exhibits, exhibitions throughout the year. We also sponsor, as Judy, mentioned, an annual education meeting for PALS and their families.

This is some of the promotion work we've done via our print newsletter and this is some of the promotion we've done via social media.

And what I'm not showing here is that we also do an e-newsletter which goes out to about 42,000 recipients each month.

And Judy, if you can talk about the last prong in our enrollment program.
Thank you.

In addition to everything that Andrea explained to you about how we're promoting the National Registry, we also have the privilege of having a dedicated National ALS Registry Associate. Danny went to our patient's home. So, say what happened is someone at the clinic, or through

one of the Home Team visits, identified a patient who indicated that he/she wanted to do the Registry, but was unable to figure out how to do this, who may have said “I’m just not computer savvy”. We had the luxury of sending Danny to the patient’s home to actually work with them to enroll them in the Registry. And besides doing one-on-one registering with them in the enrollment process, he was also available for phone and email support.

This program began in middle of 2015, basically last year, and basically tripled the amount of PALS that were enrolled in the Registry. Danny has now left us and is working for the CDC. In fact I think he started Monday. However, we are hoping to be able to hire another associate soon who this will be a part time person who will really then continue to support enrollment.

Even though all of our efforts are certainly there to get enrollment going, we certainly have heard, as I’m sure all of you in this room, that there are some enrollment concerns. I know we’re going to be addressing this more tomorrow afternoon or tomorrow morning, so I’m not going to go into a lot of it. But things that we have heard from our PALS in the home is that the initial enrollment is very time consuming. The frequency of the password change is frustrating. It limits their participation. At times some of our PALS have been kicked out and can’t figure out how to get back in. Tom was very helpful a couple months ago in helping me get someone back on. But for a lot of our patients, obviously this is more than frustrating. They tell us the number of modules is overwhelming. And I think regardless of how much teaching we’re doing, that the benefit to PALS is still not well understood. However, it is our hope, as I said, in hiring another Associate, by the work of the Home Team, clinic staff, to continue to promote the Registry and to boost up enrollment.

Thank you.

Any questions for us?

Remind me how many people, how many PALS do you all represent?

At any point in time?

Five to six hundred.

Okay. So it’s a sizable chunk.

Yes, it’s very, very big, including six counties in the Chicagoland area.

Okay. Very nice.

We actually describe the Registry at each clinic visit to the new patient, and we found that we could roughly get, I think the thing we presented before was 56% would do it. And then if we had our nurses sit with them, maybe another 15%.

You sort of glossed over; you tripled. What I want to know is how many you actually have in the Registry, per se, percentage wise.

I mean I find it very difficult to get to a certain group. You know, either the older age group.

We saw that the Registry said there was more ALS in doctors, healthcare workers, that is not true. Those are the people who are invested in going to the Registry. I think the issue is how do we overcome this? What is our conversion rate? What should it be? It is not .2%. At our place it's 50% or higher if the nurse sits on them. How can we get it up to 99%?

I guess I need to ask a question because we really don't know what the penetration rate is. We don't know how many people have registered in a particular area. So I'm curious how you get your 56%, how do you know that? Is that self-reported?

Self-reported.

Okay.

I think, you know, before Danny came on, we have representatives from the Foundation at clinic. Unfortunately, as you know, with a large multidisciplinary clinic, time is of the essence. So our representatives, our, you know, two members of my Home Team, are in and out. Everybody is getting the Registry information and talking about it, but we don't have the luxury of sitting there and registering them.

So, I think going forward my goal is when hiring this new associate, we're obviously going to be tracking these numbers even better than we are now. We do have numbers that are self-reported, and so Danny's efforts did make it so that we were able to track this a little bit better. Certainly I don't believe we have a 50% capture rate. But it is a process. And certainly also if all the patients sitting there telling you, yeah, this is a great idea, I'm going to register, and then, boom! They don't bother.

And that is the other issue. So, we're starting to track how many times we discussed it with the patient and then actual follow through. Next year I'm hoping to have really good numbers.

Yeah, I just want to follow up with that, that's our experience as well. I mean the challenge has been really one of resources and boots on the ground so to speak. We can provide a lot of information, but what we've found is that you have to continue to provide the assistance, and direct assistance of physically assisting someone in enrolling. So it's a big challenge, and therefore we are looking at a lot of different strategies to get success.

And the other challenge, too, is getting the data back. Because, we know what we're doing and who we're talking to, but we don't necessarily know, unless we actually physically assisted someone in enrolling, we don't necessarily know if they've actually done it, if we didn't do that direct assistance. So that is one of the other challenges. And we'll speak to this a little more during our presentation, that the lack of data is a significant challenge in knowing what the outcome is, knowing whether the conversion actually took place.

So maybe this is a question that invites comment from the Registry people. The discussion about the assistance, physical assistance, of a human, does the Registry have a call center where you can maybe walk somebody through the registration process on the same screen, as an example?

Paul Mehta, National ALS Registry

We actually do have a toll free number that PALS can call, or their caregivers, for any sort of questions and assistance in the process of getting registered, so that is available. These are questions which are very valid as in terms of having these folks coming and registering is very, very important. There was something that was mentioned earlier called Concierge; not a nurse but a concierge. Having someone who is dedicated to helping PALS learn about the Registry, getting informed, and actually, completing the steps. But the premise behind that is having the resources, as well as, keeping in mind that we can't coerce anybody to register. This is a voluntary system. So we do have our limitations there. But, you know, we do have a toll free number, so we do have individuals available to answer questions.

Bob Kingon, Carter Consulting

Remember to state your name. There's another question down here.

Patrick Wildman, ALS Association

This is a broader question in this presentation, but it sort of speaks to the general theme we've been discussing, and I guess it's more of a question. Paul, are you able to track where these conversions come from, so that you can feed back to individual clinics, the ALS Association, to be able to say if you've been doing this, then you can say that seems to be working. Or if you're promoting the Registry by talking to people versus sitting with them with an iPad. Is there a way to reflect back to us in the community seeing patients so that we know how good a job we're doing and then we can kind of modify our strategies accordingly?

Paul Mehta, National ALS Registry

So we actually do that. Tom on a monthly basis reaches out to MDA and ALSA and gives them a list of underperforming states. We don't give the actual hard numbers, but we do give information regarding those states that are under performing, in order to prioritize those areas that may benefit from additional outreach. That information is disseminated to the partner groups regarding performance of states. But I guess I'm wondering at a more granular level. If you get down to the level of individual clinics, for example.

Paul Mehta, National ALS Registry

We have some pilot projects that we're actually working on which we did with the state of Georgia where we worked with the chapter in Georgia and gave them information at a regional level. So we'd work up the state in various segments and simply said, hey, Southeast Georgia, there should be, in terms of the estimate, it should be actually higher, or so forth. So we actually did that on a pilot project for Georgia. And Ted Harada of the Georgia ALS Association Chapter was also involved as well, and that was successful. But that does require a lot of resources to do that.

Wendy, if you want to chime in.

So, given that it would be approved that we have added a question to the registration page that asks how you learned about the Registry. It won't go down to the clinic level, but it will say whether they got there from ALSA, from MDA, from their doctor, you know, it will give some indication as to maybe which strategies are driving people to the Registry.

I guess I'm going to be really naïve in my understanding of click-throughs and these sorts of things, but can you not tell where the link comes from in the sense of just obtaining that off of a Google analytics report or something that sits on the website to tell you where the information is coming from so it's low resource intensive? Maybe that is naïve, I apologize to the web savvy people.

We'll let Kaylie respond, but they are doing it for the digital ad campaign because they've got cookies attached to them so we know where those came from. But I think it's harder to do if you're not coming from one of those ads.

So, we should be putting those ads on our website?

If you put those ads on your website and you had a particular cookie that was attached to your ad, then we would know when your person hit the Registry website.

Another question.

Yes, there are tracking codes that you can put on ads. The website itself has to support that type of technology, so it isn't just the ad itself. The website has to be enabled. And then you essentially put the same or corresponding code. We put it on the website, like the thank you page, the confirmation once you've completed the process. So it acts as a beacon, and when someone actually gets to the thank you page and completed the process, it sends a signal back to the media supporting Tweet that said someone that came from one of your ads completed the process, and that is how we calculate the conversions.

So it's a type of technology that can be utilized on I would say most online media sources. But that is where when you get into anything that is offline or public relations or traditional, you just have to make assumptions around the impact of those people. Or rely on something like a form field where someone self-reports where they come from.

But in the digital space we can use some code to help answer those questions.

Bob Kingon, Carter Consulting

We're behind now about 15 minutes, and we're going to be continuing this general discussion so there will be opportunities to weigh in generally. So let's take a break and come back here at ten minutes to four.

Registry Promotion and Outreach

Kristin Stephenson

Vice President, Policy & Advocacy

Muscular Dystrophy Association (MDA)

MDA embraces Care, Cure and Champion. In the Care category, MDA supports care centers around the country that provide medical care to individuals living with diseases under our umbrella, and ALS has some specific ALS-focused care centers that MDA is proud to be a

supporter of. Then there are some other general neuromuscular disease care centers, of which ALS patients also participate in.

Under the Cure bucket, we fund ALS research and then also provide support services and support groups, including some equipment services and some other types of support for individuals and family members of those living with ALS.

Under Champion, we are engaged in public policy and advocacy efforts. One of those things that we're engaged in, obviously, is helping see that support is maintained for the National ALS Registry and then also raising awareness about the Registry. In terms of MDA's engagement in ALS research, we're currently funding 37 research grants. In the last five years, MDA supported 151 grants with a total commitment of \$44.8 million. Since 1950, MDA has invested more than \$153 million into ALS research. So some of the ways that we promote the National ALS Registry are through our coordination, obviously, with MDA care centers, and through our national and regional conferences.

I'll just say that for now and go into that a little bit further along in the presentation. We share information about the National ALS Registry in print and online publications. There have been a couple of folks who have spoken earlier today who talked about the importance of being able to reach people in print media but also in the digital media. Those aren't always the same people. They don't always absorb information the same way. So we communicate about the Registry through both of those mediums.

We have a permanent link on the MDA website to the ATSDR, to the Registry website. Essentially, that's button that we've heard talked about a couple of times today. We also put information out about the National ALS Registry on our social media channels, Facebook and Twitter.

We talk about the National ALS Registry when we have special events where it's appropriate, where we would be reaching people who would be receptive to that message. These include educational seminars and support groups

As opposed to having Facebook and Twitter individually, those have been combined into two social media entries. We also collaborate. We work with other organizations and work with other like-minded stakeholders who really want to see Registry numbers increase.

This is just a map that demonstrates our care center network around the U.S. These hearts indicate where there is a specific ALS-focused care center. I had mentioned national and regional conferences a moment ago, and we were very fortunate that we had a special presentation at our clinical conference this spring in Washington, D.C. Just to give you kind of a sense of who the recipients of that information were, our clinical conference had more than 450 registrants this year. Many of those individuals are neurologists or physicians. Ancillary care providers also participated. In the breakfast session where we were discussing registries and the power of registries and the National ALS Registry specifically, there were over 100 attendees.

There are also regional and local promotion opportunities. MDA conducts what are called Muscle Summits. Those are essentially regional conferences for patients and families. These conferences happen all around the country, different times of the year, and are opportunities for MDA to be handing out and sharing some of our print information about the National ALS Registry.

We also have Muscle Walks. These are essentially large, well-attended walks where MDA has the opportunity to get the National ALS Registry in front of folks by setting up our table. We have a table with have a little display and table tent that gets set up.

Then also, of course, we discuss the Registry in support groups. Some of the specific things that we are currently doing in our process, in terms of working directly with MDA staff around the country and then also with some of the stakeholders that we have some direct engagement with including providers, is we've put together a Lunch and Learn for MDA staff which is basically to make sure that all of our staff understand about the Registry and what our role is and what their role is in helping promote the Registry.

We are in the process of doing individual outreach and education engagements with the MDA-supported care centers. We've just begun this process and are kind of prioritizing what are considered the lower enrolled or what have been referred to as kind of underperforming states first, just to make sure that we're having kind of this one-on-one type discussion about what is the Registry and why is it important.

One of the things that Andrea brought up earlier was this idea of really having conversations about the Registry. I think that she raised a really good point which is having conversations about the Registry, while obviously we can't have conversations with every single person about the Registry, just from a feasibility standpoint.

When we have as many conversations as we can to kind of supplement the print materials and supplement the social media, it's really impactful because it gives people an opportunity. We see this also with providers and with our staff, to really ask questions about it, and to get more information about it, and then, you know, we can tell from their cues what is really resonating with them, you know, what is it that they're finding interesting, that they would be interested in learning more about. I think it really helps us also convey the value of the Registry. I think that is one of the challenges that was brought up before, I believe by Andrea as well, really helping people understand why they would want to take the time to enroll.

There is a lot of value for people living with ALS to participate in the Registry. I think a lot of the challenge is just helping them understand what that value is. We're also going to be putting together a webinar that would be accessible to the public on the National ALS Registry. It would be available on the MDA website and social media channels. That is something that we will need to do in conjunction with ATSDR, obviously, but something that we look forward to working on going forward.

So let me hand it over to Pat Wildman with the ALS Association. If you wouldn't mind, we'll both be up here at the end talking about what we've been doing together, and we can get to questions after that.

Registry Promotion and Outreach

Patrick Wildman

Director, Public Policy

Amyotrophic Lateral Sclerosis Association (ALSA)

Thank you, Kristin. Thank you to Kevin and Paul and the rest of the folks at ATSDR and CDC for all of your efforts to really make a difference on this, and we have come quite a long way since we started. Thanks, of course, to everyone else in the room for everything that you're doing, not just on the Registry, but really for the cause.

I want to talk a little bit about what the Association has been doing. I'm not going to get into really nitty-gritty of everything that we do, but just give you a sample of some of the things that we're doing to raise awareness, to facilitate enrollment in the Registry, and also what we're doing to get out to different stakeholders.

Obviously we want to get out to people with ALS and their families and their caregivers, but also others who may come in contact with people with ALS, whether it be clinicians or others within the community. Our outreach beyond just patients and families is not just geared to helping to get the word out and helping to drive enrollment. It's also geared to get more participation from the clinical community, from industry to utilize the Registry as a resource, whether it's advancing research, or advancing drug development. I'll speak to a little bit about that in my presentation.

First, just an example of some of the things that we're doing for our chapters and for people with ALS. We do have a very comprehensive toolkit that includes a variety of resources, from fact sheets to guides. Things that really are all turnkey, that help chapters reduce the amount of time that they have to help enroll people, help get the word out. It gets back to that resource thing that we mentioned earlier, that resources within a chapter are limited. So we want to try to make it as easy as possible for them to get out to the field, to get the word out, and to assist enrollment. This toolkit is really one way to do that.

Another thing, we have, you know, monthly newsletters. We have a lot of other communications that go out, and we have experimented with Google and Facebook ads and I thought that data was very interesting. We had done something similar before you guys did your project that showed some similar results in terms of click throughs and things like that and conversions. But another thing I wanted to point out is we do provide tablets and hot spots to all of our chapters. This gets to a point that I think was made earlier is because we do have a population, we know this through a variety of different sources, we do have a population that doesn't necessarily have computer access, doesn't necessarily have internet access, and doesn't necessarily like to use computers just because of the demographics, with the age of the population.

That was something that was identified when we first began working on the Registry and through our listening tour. That found that roughly 40% to 50% of people did not have access to a computer. So we have tablets and hot spots to really get out into the field, to bring the Registry to patients, to facilitate enrollment, and really to grow and expand participation in the Registry.

This just a map of our centers. You can't really see it from there. It's actually our chapters. We have 39 chapters across the country. We serve the entire nation, so we are certainly getting nationwide coverage. We also provide a lot of information to centers and clinics. We have 110 affiliated centers and clinics, so that is another way that we're getting the word out to the community. We're also going to a number of different conferences at which, whether it's clinicians or industry, attend. You know, the usual ones you can think of, AAN, NEALS, and a number of other ones.

One I wanted to speak to you specifically because, Ed, it gets to a point that you mentioned earlier, is the BIO International Convention. This is a convention held each year. It's the pharma and biotech industry. It's a huge convention. It's global. We've been able to participate over the years, having a booth at the convention and opportunities to present and speak.

This year in addition to the booth we had two presentations. Lucy gave a presentation. I participated in two panel discussions. A lot of it was really getting word about the Registry to industry and the value of the Registry. Sarah spoke to cyber kinetics experience. We want to grow. We want to get more in industry involved including industry that may not yet be in ALS.

I think Paul mentioned we have an element of it at the FDA guidance that we're working on that discusses the Registry, that talks about the value of the Registry, how it can be used for drug development. It's particularly noteworthy right now when I'm talking about industry because there is a big focus out there, both Capitol Hill and Congress and in industry and FDA, to really engage patients and have patient input in regulatory decision making, in drug development, how to design trials, a lot of different things.

We think that the Registry has a very potential powerful use for these purposes, whether it's as a source of patient data, for patient preference studies, for benefit-risk studies, things that can help inform drug development. We are really actively engaging industry because we think that, you know, the Registry has a lot more to offer than, and this has grown. We think that there is even more that we can do to advance the value of the Registry.

Then of course we do direct patient outreach. This is our picture from our conference this year, our big policy conference. We had upwards of 900 people attend over the course of the three-day conference. Nearly 130 people with ALS. ATSDR had a booth handing out information, answering questions. There was a lot of active outreach there. I had to throw a pic of Rick Bedlack in there with a patient with even more color than Rick.

We have our conference outreach. We do a lot of symposiums and events locally working with our chapters, working with MDA which we'll share a little bit later, really to get the word out and provide in-person assistance with the Registry. We bring out tablets and our hot spots there

so people can enroll during these events, ask questions, and really try and also really help to have them be ambassadors. We educate them about the Registry so they can tell their friends, their colleagues. They can tell their peers. We really do this outreach. It's not helter skelter. We're not just throwing darts at the wall. We're really targeting this to under enrolled states, states where we know that we need to have more penetration. So that is really where the strategy comes from.

Another thing that we do is training. Really trying to train our chapters on how to raise awareness of the Registry, how to help facilitate enrollment in the Registry. We have checklists that we provide to our chapters so they can just follow the checks how to enroll, how to raise awareness. There's other touch points that we have throughout with our chapters, whether it's webinars, whether it's other sessions that we're having that the Association is hosting for our network where we're training our chapters about the Registry and how they can help grow enrollment.

We also have a partnership with minor league baseball. The unique thing about this is minor league baseball, you know, they're not in these large media markets. They're in more rural areas, areas where we may not have great penetration because there may not be a clinic or a center locally. These are areas that we think that we're missing patients. Minor league baseball has over 40 million attendees to games each year, so it is a rich source of the public. We've had 19 Strike-Out ALS events at games this year. Fifteen more are scheduled. Baseball really has been a very good partner.

These are a couple of things that gets to kind of what Chris was talking about a little bit, and what's come up at other times. Our messages. You know, when we first began this, you know, a lot of the view out in the public was that this was all about incidence and prevalence, and it was just about the numbers. We've really, really been trying to get away from that. That is very important, but we want to get away from it a bit so the people see the breadth of everything that the Registry is doing, the value. Why is it important for someone to enroll. We stress the research notification tool and the value of that. The risk factor module, answering the question, why me? The value of the Biorepository launching later this year and how important that is. Also what research is being funded by the Registry. What research is being made possible by the Registry, and other data that is coming out from the Registry that is increasing our knowledge of the disease. These are messages that too often are not out there enough, and we've really made a concerted effort to try to get these messages out there, and repeat it and repeat it and repeat it so that people are not only aware of it, but they're also sharing with others, because that, I think, is something that we've had a challenge with as a community of getting these messages across.

Some of the needs and next steps. We're going to be redoing some of our toolkit information to update it, to refresh it. We're also going to be doing more trainings, continue our trainings with our chapters and really incorporating more of that priority messaging that I mentioned.

I do want to get to some of the challenges. Really, the single biggest challenge that we have is two things. One, it's being able to target. It's being where, you know, where are places that we need to go out? We know not enough is being done. We do get information from ATSDR about under enrolled states, but that is blanket information. It's, you know, in California, for example. We don't know if it's under enrollment in northern California or southern California. It's also,

it's very general. It's under enrolled. What exactly does that mean? So getting that type of information, where people are enrolled in the Registry, will help us drive where we want to target our outreach. Whether it is northern California. Whether it's rural sections of the state. It will help inform our success.

Right now, if we have an event in a certain state, we do speak with Kevin and Paul to see if there is a spike in enrollment, and we do see that. But we'd like to see that more on a nationwide basis because we can also track and monitor the activities of our chapters, so that we can see what successes we're having. We recognize that there are, IRB limitations to what exactly can be shared with us in terms of getting into the exact numbers. The heat map that Paul had mentioned before would be extremely valuable to us. Like I've said, it would really help us target. It has certainly other values in terms of service and how we can get services to people, but it really will help us target Registry outreach. If we can get these things on a monthly basis, on a national basis as well, it will help inform whether our strategies and our tactics are having success. So I think that is probably the most critical thing.

I'll give an example. We can talk about the resource and intensity of this effort. The Georgia pilot that ATSDR conducted with our chapter overlaid Registry data with our chapter's patient data so that they could see the differences, where the chapter has patients, where the Registry had enrollment, and they could target their outreach. They went out to those areas, they had extreme success.

Georgia was on the under rolled list, and then it got off the under enrolled list. They had challenges, then they had a staff person leave, and the state went right back on the under enrolled list, meaning that you need the boots on the ground. You need someone to help it's not just a matter of getting information out there, it's being active, being aggressive, and continuing it. That is probably the single biggest challenge is making sure that we're continuing this outreach on a very active basis with staff and volunteers.

We've looked into a number of different ways to try to address that. Really identifying volunteers is a key to it. Someone who's passionate about the Registry, whether that is a person with ALS, whether that is a family member, whether that's a caregiver, you know, someone who's passionate about it who has some time to go out and share the story. Get out into the field. Get into support groups. Get into the clinic. Get into the homes. Get online. Follow up.

A big part of it is following up. We do know as people come in, as they are diagnosed with the disease, they come to a chapter, the Registry is one of the things that the chapter talks to them about. We need to make sure that that follow up is conducted. Yes, they receive the information, but did they enroll? If they enrolled, did they complete all the surveys? It's that type of follow up is what we need. It's staff intensive. It's labor intensive. But it's something we're committed as an organization to overcoming and to really, you know, strengthening the Registry as a very valuable tool for our fight against the disease.

With that I wanted to move into a little bit more about what the Association and MDA have done together.

Kristin, you want to come up?

So there is a number of events that we've done, and we're just going to give a sample of a few. This just really highlights the collaborative effort that this is. And then the importance... something that sprung out of this discussion last year at this meeting where we committed to working together on a number of different events.

I think one of the things that Pat said is really important here, it's having someone who can really kind of get people locally excited about learning more about the Registry and about getting involved, and we're very lucky to have one of those folks with us here who worked very much with us in Utah in terms of making sure we had a successful activity there, and that is Alan Alderman. Thanks for being here with us. He really helped get the ALS community excited about coming to hear our organizations talk about the Registry, and really tried to have an in-depth conversation about the Registry. We weren't just kind of doing a presentation, we were having a discussion. It was a good, robust, long, you know, hour-and-a-half-plus conversation that we had at a support group one evening in Salt Lake City. It was really great. It gave people a chance to ask really good questions. It gave people a chance to really think through what the Registry is. It gave us an opportunity to really gauge what the interest is in different aspects of the Registry for individuals who are living with ALS in terms of helping kind of motivate people to want to participate in the Registry.

The way this activity unfolded was there was a support group one evening and then an ALS-focused clinic day the next day. Our organizations went together to both of those venues and just talked about the Registry and offered to help people sign up, essentially, and we did just that. There were some people who actually enrolled that evening and the next day as a result of the conversation, and then others who took the information forward and hopefully enrolled later. Again, we don't know exactly other than the people we saw or helped, we don't know exactly who enrolled, but it was a great outreach activity.

I'm going to hand it back over to Pat to talk a little bit about another one of the activities we worked on.

We worked with ATSDR to host a meeting on the Hill, a briefing, to really update Congressional staff, members of Congress about the Registry and where the dollars that they are appropriating, where it's going and the impact that it's having. It was a very good event, and I think as we've seen, funding for the Registry has increased over time and precisely because it is doing things.

When we first worked on the Registry to get the ALS Registry Act passed, one of the concerns coming from the Hill was that they didn't want to create a database that just collected information and it wasn't being used. I think what we're seeing is that it is being used, that it's producing things, that it's going beyond the original intent, that there is more to it that is going to advance research. This was just an opportunity to work collaboratively to really educate the Hill on how they're, and what they have funded, how those dollars are being used and that the community is supporting it.

I'm going to let Kristen talk about one more collaborative event. I'll just touch on this one briefly. We put together a kind of similar-type kind of pattern of activities as in Salt Lake City outreach, and Utah and Mississippi are both identified as states where enrollment is less than would be expected, and so that's one of the reasons that these were two of the states where we put together this kind of activity. We had, again, kind of a date pattern where there was a support group the evening before a care center day. We went and dedicated the whole support group the evening before was dedicated to talking about the Registry and taking about what it is, and why it's important, and what it's doing, and how it's moving the ball forward, and how it's putting together a robust data set to really support the whole drug development process. At the care center the following day, we talked to individual patients as they were coming in to let them know about the Registry and let them know why it might be important to them or something that they would want to participate in. I think that what our activities that we've done together have shown us over this past year are that different outreach approaches work in different ways, and there isn't really a one-size-fits all.

We are going to continue to work on identifying ways that we can work together and try to figure out what the most effective ways. We've got some good experiences to help us at this point identify what things seem to work better than others. We look forward to also working with all the other organizations that are supporting and wanting to promote the National ALS Registry in this room and outside of this room. We look forward to following up with you on that as it moves forward.

One other thing, too, about the collaboration is that it we work at the national level pretty well together. At the local level, that's not always the case. These type of events helps bring our local chapters and affiliates together in support of a common effort. It's really improving relationships there, which I think will be good in the long term not only for this project, but for the care of ALS patients.

Any questions?

Wally?

Walter Bradley, University of Miami

As somebody who has a long, historical view of all of the interactions between your two associations, this is really warming my heart. We heard that a lot. I was involved in 1968 in MDA clinics. In 1970 I started and was facilitator for the union of the East and the West Coast ALS Associations that formed ALSA. I watched, unfortunately, some long-term problems between the two organizations. It's wonderful to hear that, in fact, the Registry is acting as a unifying force to get you to be able to work together. This is tremendous, and I really am delighted to hear it.

Thank you.

Michael.

Michael Benatar, University of Miami

I have a general question for both of you but perhaps for the broader group, and I think this came up briefly in one presentation earlier but we haven't heard a lot about it. Are there any plans to reach out to the Spanish-speaking population to make the Registry accessible for, I guess, another large demographic in the U.S.?

Actually there is. We already have a Spanish website which is translated into Spanish. It's a Home Page as well as all the surveys, too. That will be posted once we have approval from OMB and hopefully sometime this fall. That's, we've been working on that. Actually it's all ready to go, we have to just go ahead and pull the trigger per se, but yeah, we are aware of that. There will be a Spanish landing page and information about the Registry. It will not be the entire full Registry per se, just the landing page, information on ALS and so forth, as well as the surveys in Spanish.

And so the ability to consent, sign up, all of that will be done?

Absolutely.

Wonderful. Thank you.

All right.

Well thank you very much. That was a great presentation. Our next presentation is Heather Jordan, Program Coordinator with McKing.

Registry Promotion and Outreach

Promotion of the National ALS Registration in Non-Referral Centers Update

Heather M. Jordan, MPH, CPH, MCHES

Program Coordinator

McKing Consulting Corporation

All right. While I get my presentation page up and running, how about we do a 7th inning stretch. Everybody up. Take me out to the ball game... You don't want to do Take Me Out to the Ballgame?

So we've heard a lot today about different ways and different approaches to get the word out about the Registry. I'm going to take a little bit different approach and talk about patient provider channels. By way of background my name is Heather Jordan. I was one of the original ALS Surveillance Specialists that came on board in 2010 to conduct the state and metro area surveillance projects. And my colleague Lindsay Rechtman came on board as well. And I also want to acknowledge Wendy Kaye. She's very involved in our project.

Also, by way of background for those of you who were here last year, Lindsay Rechtman did a really good job explaining the reasons why we decided to do this project and present this project to ATSDR.

For those of you who are new, what we found in New Jersey and Florida ALS surveillance was that one in five cases were reported from doctors who were not at referral centers. And we found that those cases were more likely to be older and non-white. So we thought this would be an area where we might want to reach out and do some promotion to talk to those doctors about the Registry.

So this is a repeat slide from last year, but for those of you who were not here last year, the objectives of our project were to implement an educational and promotional outreach campaign to these doctors and these non-referral sites in order to inform them about the Registry, to encourage them to talk with their patients about the Registry, and to try to increase self-enrollment in the Registry.

For this project we used Registry materials that were already in circulation, so those that were available last year. And we also are going to try to examine the effectiveness of our campaign by reviewing persons with ALS self-enrollment rates as well as CME enrollment and completion rates as well.

Last year Lindsay talked about our project design, but I will just go over it briefly. We chose six states. New Jersey and Florida are easy to explain why, it was because we were already in those two states for ALS surveillance. So we wanted to parlay the relationships we had with the doctors in those states that were at non-referral centers.

We also have New York and Virginia in our Group Two. And then we have Ohio and Washington in Group Three. And Group Four is the comparison, so all the other states in the country, 44 states.

Just to clarify, when we did surveillance, we found that there were 480 neurology practices in Florida and 280 in New Jersey. These are non-referral center sites. So we know there are a lot of doctors out there in these states that are potentially seeing ALS patients.

The components of our project included an initial phone call to Groups One and Two. This is like what we did in ALS surveillance. We wanted to phone the doctors to see if they do currently diagnose ALS patients, if they would diagnose patients, or if they would not ever diagnose ALS patients. We did this for Groups One and Two.

We sent a mailing to neurologists in Groups One, Two and Three. We did a follow-up call, one week post-mailing to Groups One and Two to see if they received the mailing, and then we encouraged them to promote the Registry to their patients. We also do a three-month follow-up call to the doctors in Groups One and Two as well. And during that phone call we ask additional questions about if they've seen ALS patients in the last three months and if they used the material that we provided to them.

For Group One we also conducted train-the-trainer sessions. They were brief, 30-minute talks to doctors and staff about the Registry. And we showed them the Registry website. And we encouraged them to help their patients self-enroll in the Registry.

In Group One we also conducted key informant interviews, and the purpose of those interviews was to gain more information, more insight from these non-referral center doctors about the Registry. And we also tested three of the current materials, the Infographic, the provider guide, and the website screen grabs, with the doctors to get some feedback from the doctors about these materials.

And then for all of the states we're going to be analyzing the data.

So here are our outcomes. The primary outcome is to increase provider knowledge and access to materials. Our project metrics are to look at the number of calls and faxes, look at the Registry materials that were mailed and faxed, and the numbers of TTTs and KIIs that were completed.

Our secondary outcome is to increase provider patient communication, and that's using our follow-up three phone call data, looking at the number of providers that used Registry materials and the number of neurologists that aided PALS in self-enrolling.

And the tertiary outcome is to, like I said before, look at enrollment rates, pre and post our intervention, to see if we think we had an effect with enrollment rates.

Some of these tables have a lot of information in them, so I'll point out some of the really key information for you. And just to back up for a second, I have numbers. So for Groups One, Two, and Three, we had 4,100 doctors on our lists. And for Groups One and Two, it was about 3,300 doctors. So kind of keep those numbers in mind as we keep going through these next tables.

Making phone calls to doctors is not easy. As you can see here on the top row, we made over 4,600 phone calls to doctors in Groups One and Two to try to figure out their status. And, again, that is yes, they currently diagnose and treat, they would diagnose or treat, or no they don't. So we show you the average phone calls per provider. And we did have some doctors that were harder to reach, so we sent out faxes to some of those doctors saying, hey, doctor, we're trying to get in touch with you. Do you diagnose or treat ALS patients, please call us back. So you can see in our states we also had to do some faxes and then additional follow-up phone calls as well.

All right, this is my busy, busy table. For those of you that have seen ALS surveillance, you know this is kind of a similar table. So we started with this gigantic list of doctors that we purchased from MMS. They have the American Medical Association list that we can gain that information from. Lindsay and I painstakingly went through every single record on the list trying to look up additional contact information, like phone numbers, and so this is why we were left with almost 4,100 doctors on the whole list.

We then went through the list and we scratched off doctors that we knew were currently at referral centers, so you all wouldn't have received our mailing, sorry. We also looked up doctors who are medical residents and deleted them from the list. And we scratched off others that might have died or that were practicing out of state.

So the eligible provider list line right here are the doctors that we made phone calls to for Groups One and Two, or for Group Three, right here, the 348 and the 272, those doctors received the mailing.

Of the doctors in Groups One and Two, we identified, I'll show you Florida. We identified 232 yes doctors, they said they do currently see ALS patients. And of them we asked how many patients per year, and we categorized them. So we had mostly small practices so those are doctors that see four or less patients per year. That's right here on this line. And then we have some medium-sized doctors as well in medium-sized practices. We have no large or extra-large practices in this project, which we expected because we had excluded the referral centers from our project.

We also had a good substantial chunk of doctors who were "Woulds", so they didn't currently have any ALS patients they were seeing but they said they would see them if they presented. And then we have a nice sized chunk of doctors here that are "Nos", that would not ever diagnose or treat ALS patients.

The doctors that are bolded up there are the ones that were eligible to receive our mailing. When you add up all of those numbers, it comes up to something like over 1,500 doctors that we were going to send mailings out to.

All right, so here you go. Here are the mailings that we sent. We had a couple of doctors in New York and Virginia who said please don't send me any material, I don't want to hear about this at all. There were seven of them.

You can see up here in bold, 1,561 pieces of mail went out the door to these doctors. In this mailing, here's an example of the mailing. It's right here in this nice little folder. We had a cover letter. We had an ATSDR endorsement letter. We had the provider guide. We had the CME flyer. We included the Infographic.

And then for the small-size practices, they received three copies of the patient guide. And for the medium-sized practices, they received seven copies of the patient guide. So when you add up all the materials we mailed out, it was over 16,000 pieces of Registry material that went out to the doctors in these six states.

We did have some Return to Sender mailing. You can see here, for Groups One and Two, the numbers are pretty small. That is because when we made our status calls to those doctors we asked them to confirm their mailing address, and we made a lot of changes to mailing address information based on the feedback on the phone.

You can see for Group Three, we had a few more Return to Senders, and that's because we didn't make a phone call. That was just internet searching and other things we were doing to try to fine tune our mailing list before we sent them out the door. We did re-send some, and we did have to do a mailing a second time. We had Return to Sender a second time. And we also faxed materials, I'll get to this in a minute, but what we ended up doing was during our one-week

follow-up calls, we had a lot of doctors say, I never got your packet, I don't remember seeing this come through, for various reasons. So if they said that, we then faxed them the materials. It was about an 11-page fax, so you can see in Florida alone I sent out another 108 faxes of materials. I haven't done the math to figure out how many pieces that means, but you have to add that to the 16,000 that we mailed out.

So here are our follow-up call results. For round one, these are the one-week follow-up calls. Group Three, you can see they didn't get any follow-up calls, but we wanted to show you they're there, we know they're there. You can see we had to make a few more phone calls and follow-up one calls.

It was a little harder to get the information that we were looking for. The person that answers the phone can be a gatekeeper, can be tough to get answers from, and they often didn't want to tell me if they received the mailing. I might get sent back to the person in the back room, the office manager, someone else might have to tell me if they received this in the mail. So you can see the number of phone calls we made here was greater than the number of status calls we had to make, and our averages do come up a little bit. We also had to send some faxes because people were really tough to get on the phone. So you can see that line right here. So to complete that follow-up call one, we did send out some faxes.

Then for follow-up phone call two, which are currently in process, New York is still hanging out there, we're still doing some of those follow-up calls so we don't have that data yet. You can see, though, for follow-up call two, we have to make a lot more phone calls. We're asking a bit more information, like have you seen ALS patients in the last three months. Again, the person answering the phone doesn't want to answer these questions. It takes a little longer to find the right person on the phone, like the doctor, who would be willing to answer the questions that we're asking, especially if you've seen an ALS patient in the last three months, did you hand that patient one of the provider guides we gave you in the mail. So it takes a little longer to get that information.

These phone calls are tedious at best, but the information we get is very useful once we do get it from the doctors. And, again, here we had to send out a bunch of faxes, especially in Florida, to try to get the doctors to answer the questions we had for our three-month follow-up call.

Train-the-trainer presentations, what can I say about them. We had a process of selecting the doctors that would receive the train-the-trainer presentations. For New Jersey, we split the state into three regions. And for Florida, we split the state into five regions. And then we sampled the doctors.

We went one by one down our list trying to get the doctors to allow us to come into their offices to give them our talk. You can see here that we had, you know, quite a few refusals for various reasons. We know the doctors are busy, they might not really want to talk with me, they don't see the value in it, whatever the reason is, they didn't allow us in the office. But I'm happy to report we did complete 32 trainings.

We did 11 in New Jersey and we did 21 in Florida, so we hit our target. And we had almost 60 participants in those trainings.

So the doctors were always present, and then they would bring staff members in as well. I had one practice in Tallahassee who brought in five staff members. They were all of the nurses that would ever come in contact with an ALS patient. The doctor wanted those nurses to learn about the Registry so the nurses could help the patients if they had questions about the Registry. Overall, the train the trainers were a little bit difficult when we were trying to get in the door, but once we got there, the doctors and nurses were very receptive and happy to learn about the information. And they also requested we send them additional information about the Registry. So that's the takeaway message from that right there.

Key informant interviews.

This one was also a little bit tricky because we were asking the doctors to give us at least a half hour or more of their time through an interview process. You can see here we had a larger number of refusals. We had 63 doctors in both of the states who said I'm sorry, I just don't have time, I'm not interested, I can't help you. Which is unfortunate, but, you know, we expected that was going to happen. We did complete nine interviews. The interviews ranged from about 20 to 45 minutes. We asked lots of questions. If they currently diagnosed ALS patients, tell me about a time you would maybe tell your patients about the Registry, walk me through the conversation you would have with your patients. And like I said before, we had them take a look at some of the Registry materials.

So Lindsay and I were doing these interviews, we were looking at themes, and once we got to about interview number four, we realized that the themes we were collecting from these doctors were very similar. By the time we got to interview number eight, all of the themes were similar, and then the ninth interview kind of confirmed what we were finding from these doctors, the things they did know and didn't know about the Registry, and the things that they liked and didn't like about the Registry materials. So at that point we said, we think we've reached saturation, we're not getting a whole lot of return on investment for doing interviews, and so we decided that nine was enough interviews to get the data we were looking for.

And you can see here, I did show you the status of the doctor. Most of them, seven of them, currently diagnose or treat ALS patients, and two of them would diagnose or treat if a patient presented to them.

So, what are the next steps in our project?

Like I mentioned before, we still need to finish the New York follow-up phone call twos. Those are scheduled to be completed this summer. We are also going to be looking at the CME enrollment data to see if any of our doctors in our states completed the CME module. We did hand that out in the packet so we're hoping that we'll see a bump in CME enrollment. We're going to look at Registry self-enrollment data. And we're also going to look at our project metrics and see what's going on there. We're going to continue analyzing our key informant interview data. We have started loading those things into Atlas.ti and coding them. And I don't know if any of you do qualitative research, but it takes quite a while to code and come up with your themes, so we're working on that now.

And our goal is to prepare a manuscript for peer review in the next few months to get the word out about what we've done. And I think that's it.

Does anybody have any questions?

Then let me start. I take seniority here. As you probably know, the CDC has funded a project in Ohio for trying to do a complete ascertainment and population controlled study. Are we able to partner with you in that because that's one of the key issues? We, in fact, planned to center our collection of patients from the centers that deal with it. But, the doctors who deal with ALS that are outside those centers, we really have no way of being able to, or we have a way, but it's, like you found, it's a time-intensive project. Since you've got those individuals, those doctors in Ohio, can we partner with you in order to be able to get that for a mailing list?

I think that's an interesting question because, you know, as we're all sitting here around the table, I'm thinking what are the questions I have for Brunet-Garcia, and what are the questions you might have for me, and I think this is the opportunity we have to talk with Paul and talk with others around the room and think about how can we partner in the future? And get information back and forth. I don't know if I can give you that information. I'll look into it for you, and I'd be happy to do what I can with the team to help you if possible.

So I don't know if you touched on this in the information that you sent people or when you did interviews, but it seems to me like it may have been a missed opportunity in the sense that if we have, for example, in Florida, 20% of patients who are not benefitting from the care of a multidisciplinary center, I sure hope that you gave those people information about the closest referral center so that they could get the quality of care the multidisciplinary clinic team can provide. Because if not that would have been a real pity.

I know you're right. And I think there are a lot of opportunities that might be missed when we do work like this, so backing up very, very far, when we did ALS surveillance, we were under strict guidelines to not talk about the Registry at all. So when we went out and captured those case reports from neurologists, we couldn't say, oh, by the way, there's this Registry for you to tell your patients about.

So when we moved forward, Lindsay and I were aware of that, so when we went out especially and we talked directly during our train the trainer sessions and the key informant interview sessions, doctors don't always know what resources are available, so we were able to say, well, please go to the Registry website because they have the ALS clinic locator on the Registry website page. And we provided them lots of information to send back to their patients. Because you're right, I do think there's a potential lost opportunity there.

I will also say that some of the doctors I interviewed who are not at these large academic centers said that many of their patients, especially their Spanish speaking patients, won't go to a multidisciplinary center anyway. So they're staying with their home neurologist. So those are the doctors I think we really need to make sure that are always informed about the Registry because they are seeing this group of patients that I don't think are being seen at the academic centers.

Yes, I'll just say that certainly in Miami we're very hospitable to Spanish-speaking folks.

Absolutely. And so, that should not be an issue.

I don't think its Miami, I think it was a little further north from Miami where I had that issue. Kind of right in the center of the state, up a little beyond Tampa, maybe. I'm not exactly sure.

Yes?

Orla Hardiman, Trinity College, Dublin, Ireland

This a wonderful example of shoe leather epidemiology well presented. There's another class of providers that you may want to think about, and those are the not-for-profit nurse and other healthcare providers who give educational training to the families of people. And there is one in Ohio, probably more than one in Ohio, and we're working with them on a longitudinal study of intervention of NIV and this type of thing.

The issue is as you get out there, it's sort of like what you find in real life. There are more examples of things going on than you think of. And so this whole idea of, I think it is going to be higher than 20% who don't go to a clinic. I don't know if that's only true in Florida, but in Scotland it's 40%. In other countries it's much higher. And in our own area we're finding that there's usually one visit and then about 45% of the patients don't come back because they have medical problems and things like that. So I think this whole idea that the CDC, ATSDR Registry will serve this population is going to be an important selling point at the congressional level.

Okay, any other comments or questions?

Excuse me.

Alicia Fraser, Massachusetts ALS Registry

I was just wondering, I really appreciated seeing this. I wasn't here last year, and this particular presentation wasn't reported back to me. And at least the initial survey that you did, the status survey, is something that I think might be really useful for us to try to evaluate the completeness of reporting in our state. And I was wondering if you had any estimate, if you don't off the top of your head I understand, of the staff resources and time that it took to just do that initial piece?

That is an excellent question because you know that it will take a lot of time just to take your mailing list that you put together and clean it up and get it ready. And depending on where you get that mailing list from, sometimes they don't have phone numbers. So you actually have to go in, like for New York State, for example, there is a "Find A Doctor" website through the New York Department of Health. So we had to go painstakingly through one by one for each doctor trying to find their phone number. And then making the phone calls, they are labor intensive. We don't have the costs associated with that yet, but it is something we did talk about as a team of trying to do a sort of cost benefit analysis of the time it would take to create the mailing list, to then make the phone calls, to figure out where the Yeses and the Woulds, who would benefit from receiving this mailing, or do we just do what we did in Ohio and Washington where we just sent the mailing out to every single neurologist and paid for postage for every single doctor.

So I think we have plans to maybe try to look into that and do a little bit of the number crunching that would be necessary to help folks out like you to see what would be best.

Thanks.

Does that make sense?

Yeah, thank you. I'll touch base with you after this. And get your information.

Sure.

I just want to ask a quick question.

So you're saying these non-referral centers, these offices, none of the neurologists that you spoke with even heard of the National ALS Registry? Is that the general sense?

So yes and no. Because remember we, so here's the rub. We sent a mailing out to all of these doctors. We hoped they had received this in the mail. Then Lindsay and I called them and asked them can we come in and do a training, can we come in and do an interview? And when we got into their offices, the majority of them said they had never heard of the Registry and they never got the mailing. Even though we confirmed with their offices that they got the mailing. So we know this might have gotten pitched in the trash or something.

For our interviews, I think eight out of nine of the doctors had never heard of the Registry, had never advised a patient to self-enroll, but once we were done doing the talk and went through the website, each individual screen, they thought that this was a manageable process for their patients and they were on board with telling their patients about it. So, no, they didn't know about the Registry, but once they learned about it, they were on board.

So the translation is these doctors don't even know about it, obviously the patients, the PALS, don't know about it.

At least from that channel, from the provider-patient communication channel. It's not happening there. The doctors aren't telling their patients if the doctors don't know it exists to begin with.

So I think this is a great example of gaps that we, you know, that we really need to face and come up with plans on how do we really target these physicians who in turn are the mouthpiece for the Registry.

Right.

And speak to their patients.

And do it in a way that's going to work for each individual doctor because we had doctors say we want it over email. Some doctors said we'd like a mailing. Some doctors said they wanted to see the poster come in a tube because it would look different from all the other junk mail they

get. But what's the cost associated with putting a poster in a tube and sending out to 4,100 doctors? I'm not sure it's worth it.

Our only saving grace is hopefully some of these patients are being captured through the national approach, whether through Medicare, Medicaid, who knows.

Yes, Sarah Kulke.

Sarah Kulke, Cytokinetics

So, I have seen pretty good evidence from a couple of different sources that, Ben Brooks, your numbers are right on. About 40% of ALS patients across the United States are not seen at ALS centers. Now that becomes a very important number to pharmaceutical companies. And I spend a lot of time thinking about how to reach that 40%. One way that I've identified is Medscape. Medscape knows which neurologists that do CME with them have ever diagnosed an ALS patient. So if you were going to do a Medscape program, you would be able to reach those should they want to do CME, you'd be able to reach them directly. But it's a really big problem. It's something that I'm interested in solving if anyone else has any ideas.

Along those lines, and I don't know, Ben or others over there, with the ANA or neurology, I mean do they not have, so the question is how do you reach these neurologists? I mean, I imagine a lot of them don't necessarily go to most of those meetings because they're more research oriented, but wouldn't there be, you know, even email lists or lists of these people to capture that way?

Yeah, there is a group of neurologists who do not belong to the AAN, you know, and the AAN is trying to bring those people in as well. And there are local neurology societies in the state, and some of the doctors just go to that meeting and they don't go to the national meeting. There are regional ones as well. And so there is a way to get to that neurology group, but the group you may have to get to may be beyond neurology. You know, that's the issue.

Ed Kasarskis, Patient Advocate

So, Mark Weisskopf, I know you could purchase a mailing list of neurologists that are in the American Academy of Neurology. So that's a good number of them. One of the presentations, maybe it was yours, I think it's a fallacy to imagine that everybody, every physician, is in the AMA, because I am not despite requests over and over and over again to join. But I don't know the percentage of neurologists or physicians that are members of the AMA. So just because you've got a list from them, don't make the assumptions that you've got them all, because you don't.

Yeah. I mean I think for what we did on our project is we started with that list that we had purchased from the AMA, and then Lindsay and I went through our four states, New Jersey, Florida, New York, and Virginia, went back to the state medical licensure boards and went through each record within to cross compare.

So I can tell you how many people were on the AMA list, how many people were licensed, and where the crossover is. And it was painful to do that, but it was an important exercise for us to kind of understand how many doctors are missing from those mailing lists that we purchased.

And then to go back to what you commented on, there is a way to purchase email addresses. We don't know if they're good email addresses. I'm not sure if we can drill down to just neurologists on that AMA list, either, we'd have to look into that. But it is another thing to look into because is an email that we send out in a blast format like that enough to get enough neurologists the information to get their patients educated? I'm not sure. But it is another channel for us to look at. I know we're focused on the neurologists.

Lauren Webb, MDA

But something to consider as we think about how to target and to let families know about this Registry is to consider, especially at the places that are the non-referral sites, think about social work. In the very intense populations, they're providing their care, they're setting them up with disability, they're going through that whole process, and I think that that could be a really powerful piece of the equation, and I would love to be a part of that and help. Because we know people are not attending multidisciplinary clinics, and so that leads us to a second question, well why? What are the patients' experiences of care? What are they saying? What are their obstacles? So those are some of the things.

But I think that if that's something that folks in the room are interested in collaborating. Just let me get through the MDA new care center application process, but we really want to start looking at that very closely.

Good idea.

Heather, thank you very much.

I just want to say, one of the things that we're doing with or that we're planning on doing with the 2013 data is to map it out, obviously down to the smallest resolution that we're allowed to, overlay the multidisciplinary clinics, and let's see where you have a bulk of these patients and calculate distance, closest distance to these referral centers. I think probably a lot of them are in rural areas, and it may be a two, three, and four-hour drive to the next closest referral center. I mean, I would think that would be one of the logistical hindrances of a patient going to a multidisciplinary clinic.

Ed and I still think that the best way to do this is to offer free DNA testing. It would be .1 ice bucket units per year. And that, if I remember, is your whole budget. So I think it's time for Ed Tessaro to go to Washington and double your budget.

If you recall last year, those of you who were here, we ended up at the end of the session coming up with a number of recommendations to be put into place over the coming year. And Tom addressed some of those in his presentation. And Paul is going to address some of the other recommendations that came up and what's been done this past year.

Paul Mehta, National ALS Registry

So, yeah, before I start I have four quick slides, so I know it's getting at the end of the day. But I do want to mention something really, really important. This past March we submitted an application to CDC for CDC Grand Rounds for ALS, and we were accepted. And this is an

amazing opportunity for us to have a huge audience for CDC Grand Rounds. And this will be something that will be happening next April 18th. And so what the format would be would be myself and Kevin speaking. Kevin giving an overview of the Registry, myself the epidemiology. And then we'll have a neurologist coming in and giving the provider perspective. And we identified our good friend Rick Bedlack to be that neurologist. And we'll also be reaching out to some PALS as well to see if they're interested in participating. And it will be all done here in Atlanta. But this is a huge endeavor because, I mean, we feel this is it will be live tweeted, and I think they were saying the audience could be in the thousands, so this is certainly a really important opportunity for us to get the message out on the Registry next April 18th. So at CDC Grand Rounds.

These are some four slides I have regarding the recommendations. And so myself, Tom and the team, we met with the partner groups, Les Turner, MDA, as well as ALSA, to kind of go over recommendations from last year. And a lot of them were regarding, for example, like looking at the outreach for these particular areas right here. And so we identified these particular states where we wanted to do this targeted outreach that we discussed earlier. Very similar to what we did with Georgia. And so we'll be in the process of over the next few months bringing on more staff to help make this happen. We also wanted to have Illinois in there even though it's not an under enrolled state, but because the Les Turner ALS Foundation is there, we wanted to have Illinois also on that list as well.

Regarding increasing number of PALS taking surveys. Wendy mentioned earlier that we're going through the OMB process, obviously, but we also added an alternate email address as well. So what ends up happening is we send out reminders to PALS about taking surveys. Sometimes they can get bounced back and so forth. And so we want to have an alternative email, so, for example, to a caregiver in the event the person with ALS cannot see the actual email itself regarding a reminder to go ahead and take surveys. And that will be implemented, once OMB approval is in place.

Another item was improving that National ALS Registry website. So our web team is in the process of making the Registry web site into a responsive design. Global Prairie mentioned the fact that right now it's not responsive, if you go to the website on your mobile phone, it's very small and therefore hard to read. But it's going to be adapted to your cell phone, your tablet, and so forth, so it will be responsive so you can see the actual pages in a much more user-friendly way. And there will be also be a redesign of the website as well. Right now it's kind of busy, a lot of URLs and text in there. We want to streamline it, have a place for just researchers, information for patients, and so forth. And also, like I mentioned before, we'll be also adding a Spanish version of the website, too.

Regarding branding, so Brunet-Garcia is on board, so that was one of the recommendations that we had from last year which we implemented this year by having Brunet-Garcia come on board. Let's see.

Also the Infographics were briefly touched upon, and so we'll be developing some new ones for the biorepository coming up, which probably will be geared towards patients, as well as perhaps

towards providers, too. We're not sure yet if there will be one or the other or combined. As well as having an Infographic on the prevalence report, which will be coming out tomorrow as well. All the ones that were previously shown today, they're already mentioned here regarding the notification system as well as progress to participation.

Lastly, the GUID that was also one of the recommendations. That will be implemented, and we had a discussion this morning on that, and so we'll be implementing that, the NIH as well as the one for neuroguid which is through NI.

Lastly, I just do want to mention the fact that we certainly do want persons with ALS on the research committee. Steve Reznick was here last year, and he passed away a few weeks back. And Steve was a very, very, I mean very helpful, valuable member of the committee. I'd send him an email, an application, and he would, you know, very, very quickly give me a reply back or have a question or so forth, and so he was really, really valued. And so Steve passed away, and so we're certainly looking for persons with ALS with a scientific background or a STEM background, mathematics, engineering, so forth, to go ahead and review applications for us. So if you know of any PALS, please let us know. We'll be happy to have persons with ALS on the research committee. That's pretty much it.

Questions?

Great.

Bob Kingon, Carter Consulting

All right. It's 5:00. Is there anything anybody feels compelled to say that they haven't had a chance to say yet today? All right. You'll see on the session tomorrow, in the last hour we're going to talk again about recommendations and ideas that you may have for ATSDR and others in terms of moving forward. So reflect on what you've heard today, and build that into your thoughts that you can bring forward to tomorrow's session. So thank you all very much, and enjoy your evening, and we'll see you at 8:30.