

**Centers for Disease Control and Prevention  
Agency for Toxic Substances and Disease Registry**

**Summary Report:  
Amyotrophic Lateral Sclerosis (ALS) Surveillance Annual  
Meeting**



**November 3-4, 2010  
Atlanta, Georgia**

This document has not been revised or edited to conform to agency standards. The findings and conclusions in this report are those of the meeting presenters and attendees and do not necessarily represent the views of the Agency for Toxic Substances and Disease Registry.

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**Amyotrophic Lateral Sclerosis Surveillance Annual Meeting  
November 3-4, 2010**

***NOVEMBER 3, 2010***

The Centers for Disease Control and Prevention (CDC) and Agency for Toxic Substances and Disease Registry (ATSDR) convened a meeting of experts to discuss the surveillance of Amyotrophic Lateral Sclerosis (ALS). This annual meeting was held on November 3-4, 2010, in Atlanta, Georgia, at the Marriott Century Center Hotel. The meeting participants (listed on Attachment 1) represented federal agency staff and contractors, advocacy groups, individuals with expertise in neurodegenerative disorders, particularly ALS, and a person with ALS.

***Welcome, Introductions, Opening Remarks***

Meeting facilitator Mr. Bob Kingon greeted the panel members and outlined the agenda. Dr. G. David Williamson, Director of ATSDR's Division of Health Studies (DHS), appreciated the progress the ALS Registry had made in a short time, including the launch of its Web portal in the past week. ATSDR is committed to broadcasting the registry's existence, as it offers so much more than national data. Other than providing a status update, this meeting was to celebrate the accomplishments to date and to plan future actions. The latter includes aspects of biomonitoring (e.g., who will bank specimens and oversee the bank) and how best to make the data available to researchers. Dr. Williamson expressed his great appreciation of the dedication by CDC staff and those in the field represented at this meeting, for the progress made to date to defeat this terrible disease.

## Overview, Registry Project and Goals

Presenter: Kevin Horton, DrPH, MSPH, Chief, DHS Surveillance and Registries Branch

Dr. Horton outlined ATSDR's work on ALS to date and future plans. ATSDR conducted four pilot projects from 2006-2009, in three states and an HMO consortium, to test the feasibility of capturing ALS cases from large national databases. The algorithm used produced a positive predictive value of 85%.

**ALS Registry Act**

- Enacted as Public Law 110-373 (October, 2008)
- Purposes
  - Describe incidence and prevalence of ALS
  - Describe the demographics of ALS patients
  - Examine risk factors for the disease

The October 2008 ALS Registry Act (PL 110-373) mandates the description of ALS incidence and prevalence, the demographics of ALS patients, and examination of ALS risk factors.

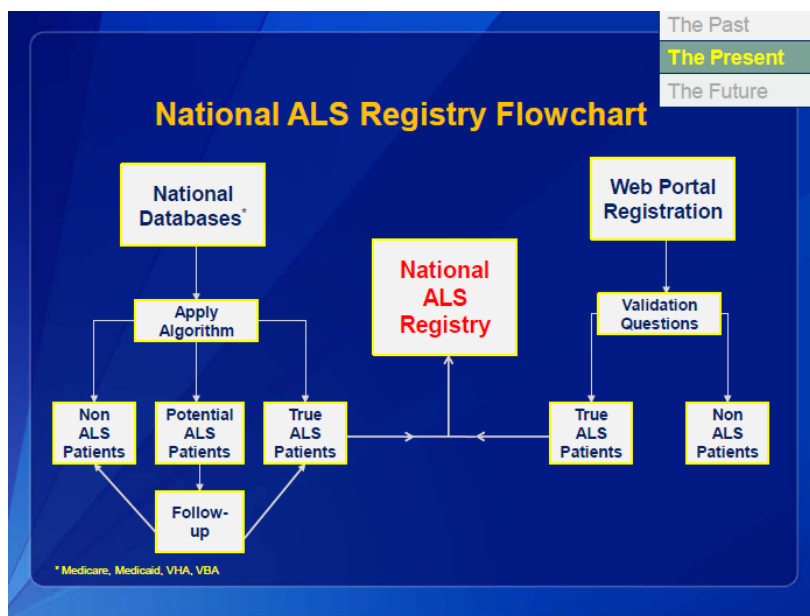
**The National ALS Registry**

- 2 pronged approach for capturing ALS cases
  - National databases\*: apply algorithm to Veteran's Benefits Administration, Veteran's Health Administration, Medicare, and Medicaid databases
  - Web portal: to capture patients not in the national databases. Portal will also contain risk factor modules
- Web portal launched on 10/19/10

\* Represents approximately 90,000,000 Americans

ATSDR uses a two-pronged approach to capture ALS cases. The national databases, the Veterans Benefits Administration and Veterans Health Administration, Medicare, and Medicaid, includes ~90 million Americans. The additional Web portal will capture ALS patients not in these national databases.

After only 12-13 days of operation, a significant number of patients have registered. The challenge is to keep the message about the registry alive and fresh to maintain momentum. A flowchart of the registry process was shared.



ATSDR’s algorithm to identify ALS patients in these databases includes, but is not limited, whether the individuals were ever diagnosed or prescribed ALS medication; their frequency of seeing a neurologist; or had the ALS ICD9 code (335.20) assigned to their case. The individual is categorized as non-ALS, potential ALS or true ALS. Potential ALS cases are reevaluated as additional data are obtained and status is updated as appropriate. The Web portal registration also requires answers to validation questions. Depending on the answers, true ALS patients are placed in the registry and non-ALS are not. Duplicate cases are avoided by checking Social Security numbers (SSN) and other data to cross-reference the national databases’ and Web portal’s information.

Other than the CDC/ATSDR websites (and e-buttons and e-cards to link to or promote the registry) and traditional materials (e.g., trifold, fact sheets, etc.), venues to advertise the registry include outreach to major media and use of social media (Flickr, Twitter, Facebook). Advocacy groups such as the MDA and ALSA have participated in Webinars and provided major help. Attendance at relevant large scientific conferences is planned, as are ads in neurology journals to target physicians, neurologists and others who see ALS patients. More input on other outreach activities will be welcomed.

The Past
The Present
<b>The Future</b>

## Upcoming Plans

- **Funding state/metro based surveillance projects**
  - 3 state Health Departments: NJ, TX, & FL
  - 4 -6 metro-based Health Departments selected by year's end
  - Data collection: 2009-2011
  - State/metro data available in 2012
  
- **Exploring the feasibility of linking DNA and brain banking**
  
- **Sharing Registry data with researchers**

Planned activities include funding state- and metro-based surveillance projects to check the completeness of this ALS registry; exploring the feasibility of banking DNA and brains/spinal cords; and sharing the registry data with qualified researchers. The goal is to share a full year of cleaned, validated, non-duplicative data, based on cancer registry models. The World Trade Center (WTC) registry involved such research facilitation. This group's input on how to share the data will be very important.

#### Discussion

The national administrative database data and portal data will be combined. A summary of the pilot projects' data will be submitted to a journal in early 2011. ATSDR will share updated information (e.g., number enrolled) as possible, but IRB and OMB regulations dictate what can be shared. The VA fines \$5,000 per name of its data released and CMS prohibits re-release of its data. The one exception is CMS's End-Stage Renal Disease Registry and CMS is willing to help ATSDR set up a similar process. And, when OMB cleared the registry Web portal, the OMB limited data release (to first ensure the representativeness of combined database data).

To keep the patient population engaged in the registry, Dr. Kasarskis urged that a bidirectional feedback loop be created, to let them know where they stand. Dr. Horton agreed. The registry will have service links (e.g., to ALS trials), and perhaps a mapping application to ALS treatment centers, etc. These will be built with advocacy groups' help.

Dr. Brooks suggested a continuously updated map of patient locations, but the OMB prohibited that. To ensure the involvement of the clinical community in research, Dr. Sowell asked if a registry mechanism could indicate the clinics where ALS patients present. Dr. Horton distinguished between this registry's public health surveillance

versus the greater level of detail of a clinical registry. That could perhaps be added at a later date. Mr. Gibson added that the registry's planned quality of life (QOL) surveys also should engage the patient community.

### **ALS Registry Demonstration**

A demonstration of the ALS Registry Portal ([www.cdc.gov/als](http://www.cdc.gov/als)) was provided by Dr. Horton and Emergent Business Analyst Mr. Greco Johnson. The introductory page was written to allow simple and easy navigation through the registry. The National ALS fact sheet and other promotional tools are posted for use by organization chapters or by physicians for their patients. The disease itself is defined through the "What Is ALS?" link; a News Functions tab is in development and will be similar to those of ALSA and the MDA. Papers and other resource materials will be added as they are released. The advocacy groups' ongoing input to the very important FAQs to be posted will be welcomed. The Resources link includes the content of the ALS Registry Act and summaries of these meetings' minutes (since 2006). Quick Links are provided to ATSDR, ALSA, MDA, NIH, and the clinical trials. Additional link suggestions will be welcomed. New technologies being used include E-cards about the registry and its URL. The "card" can be sent with a click to anyone who might be interested. There is also a "Button" which takes you directly to the ALS Registry webpage which can be downloaded to websites. CDC's Web page is coded to make it easy to incorporate it to others' websites. Links to Facebook, Twitter, and Flickr show pictures of ATSDR registry staff and their interaction with partners, to show the collaboration and seriousness of ATSDR's commitment.

ATSDR worked with ALS patients to ensure that the registry website would meet their needs, despite any disabilities. The registry information is secure, being approved by CDC's Office of the Chief of Security. It was awarded secure status by a rigorous certification/accreditation process.

Mr. Johnson demonstrated the registry process from the ALS patient's entry to the portal. In order to participate in the registry, each ALS patient must be a U.S. citizen or legal resident. They are provided the consent form information (registry background and purpose, confidentiality of patient information, risks/benefits of participating in the registry, what will be done with results, and the voluntary nature of participating). The patient enters their information for validation (ever diagnosed with ALS; clinically diagnosed; seen a neurologist and, if yes, the date) and again provides their consent before proceeding. They then can create their own patient account by providing their first and last name, gender, date of birth, and last 5 digits of their SSN. The latter is used to avoid duplication. The advocacy groups' help to reinforce patient confidence in the portal's security will be helpful.

### *Discussion*

- To reassure the patient about the registry's security, Dr. Pentz recommended the insertion of pop ups to clearly describe the need and the security beyond what

the FAQs provide. For example, a pop up explaining why the SSN is requested, and reassuring that it is secure, will encourage the patient to continue.

- Dr. Kasarskis felt the Web site may be too complex. For example, the large amount of information on the entry page could discourage the patient who just wants to register. He also wished for a better indication that the site is a research tool, not just a public portal about ALS. It is important to engage the patients first, emphasizing that this is participatory research, and appreciating their willingness to help. Patients have related their desire to participate in studies in their own environment/area that are both easy to do and meaningful. If they are first welcomed to registry, thanked for their participation, and have the registry explained, even those not computer-skilled will be more willing to go through all the information screens. Dr. Bruijn agreed. The message should be brief (i.e., “Welcome, thanks for participating in our research”); more in-depth information can be provided in later clicks.
- Dr. Brooks pointed out that someone filling this out, but lacking an email address, is prevented from going further. Mr. Gibson reported work with ALSA chapters and clinics to create a Gmail account to allow that. Mr. Johnson added that there is an 800 number they can call for help in registering. OMB prohibits direct contact of a patient, but if they contact ATSDR, they can be guided through the registration process.
  - Dr. Bruijn advised inserting a pop up box to explain what to do if they don't have an email, or to immediately provide the 800 number.
  - To address the email issue, Dr. Weisskopf suggested adding an option by which the patient allows ATSDR to contact them by phone rather than email.

Mr. Johnson continued the demonstration. On the ALS patient account page, an entry of a country other than the U.S. prevents further entries. The page provides an ATSDR contact phone number at which they can be referred to a resource. Dr. Kaye reported a CDC requirement that the patient create a user name and a password. These expire in 60 days, but ATSDR is collecting data to support a request to extend that to 6 months.

The user name and password is entered and three security questions are asked. A safeguard was incorporated to ensure only one use of the same email address to avoid redundancy. A warning pops up, asking for a new username.

- Dr. Kasarskis asked if a relative or caregiver could enter information for an ALS patient who has no computer or email address, with the patient put on the relative's email account. Dr. Kaye confirmed that, as long as the patient is present to provide their consent. There just cannot be more than one person registered per email.
- Dr. Bradley commented that the need for Internet access may introduce a systematic bias (e.g., lower SES patients' participation). He suggested providing a route for practitioners to enter the patient's data. However, Dr. Horton



responded that they may not know all of the patient's information (e.g., demographic or occupational).

- The advocacy organizations are trying to help address this, for example, by setting up laptops in their chapters for ALS patients' use. ATSDR is working closely with them. The state and metropolitan area-based surveillance projects will help determine if this is a problem by evaluating the completeness of the ALS registry.
  - Dr. Kaye acknowledged that the registry will not capture all ALS patients. But the databases and portal will provide an accurate count, after which ATSDR will determine if these are representative of the population as a whole. Any groups that ATSDR feels may be missed can then be focused upon.
- Dr. Brady asked what the VA data would provide and Dr. Kaye responded that this will provide ALS incidence and prevalence. Dr. Horton also hoped to have subsequent years of CMS data to determine the validity of the ALS case.
  - Dr. Bruijn suggested that ATSDR also contact other, smaller foundations and non-profits to post a link on their Web pages. (Dr. Horton reported that done with some small advocacy partners and welcomed all suggestions.) She also suggested, given multiple registries, that the site immediately and clearly state this one is distinct from multiple other registries and requires its own registration.

Dr. Horton credited Dr. Lorene Nelson for her collaboration in developing the registry's seven questionnaires. Their questions have been standardized for use in studies of ALS.

- Dr. Kaye stated that, except for the QOL survey, the surveys are numbered consecutively and do not have descriptive names. This was done to ensure that none are skipped because the patient thinks it does not apply to him/her.
- Dr. Bruijn suggested stating that the amount of time the survey may take. Dr. Kaye stated that text can be added at the top that the surveys take at most ~5 minutes. Dr. Horton reported that OMB does not allow extended surveys because of the burden to participants. Mr. Johnson responded that the instructions state that the patient can return later to finish the survey.

Mr. Johnson continued the demonstration. The patients provide their date of birth, age on the day of the survey, age at diagnosis by a neurologist, gender, marital status, and level of education. Dr. Horton explained that these help determine their risk factor status. One survey addresses military history, another is occupational history and demographic information. The more people who take these brief surveys, the greater the value will have to ATSDR's research and that of the larger scientific community. At the end of each survey, the person can review his/her responses and can see and questions that have been skipped. The participant has the opportunity to edit the responses before they are submitted.

- Dr. Weisskopf asked if the initial information provided while creating an account is linked to this part of this survey. If the initial information included a question about having email, that could create a subset allowing analysis of possible differences between the two, perhaps indicating a part of the population being missed.
- Dr. Bradley stated that one of the important things for researchers interested in the causes of ALS would be the difference between the demographic and other features of those with ALS compared with another population, but the registry has no control group. Is ATSDR planning to compare it to national statistics? Dr. Horton answered that public health surveillance involves no control group. That is where studies come in. We, theoretically, would give this information to researchers such as yourself to do a study and you would get a control group.

The panelists' suggestions were requested for new questionnaires, to follow these initial seven, in 2011 and 2012. For the first six surveys, the patient cannot return to change the answers once they have been submitted. But the patient will receive an email offering the opportunity to take the QOL survey a second time each year. That iterative process will allow the determination of their disease status (i.e., remaining mobility, using a feeding tube, etc.). Dr. Kaye added that this QOL survey is the self-administered version of the ALS-FRS with a few adaptations for this computerized application.

Mr. Johnson continued. Public account holders such as healthcare professionals can access educational materials for family members and others on the website. Dr. Horton emphasized that ATSDR will try to attract physicians' participation with incentives such as CME hours. This education is particularly geared to those who do not generally see ALS patients, to familiarize them with ALS signs/symptoms and how it targets the body.

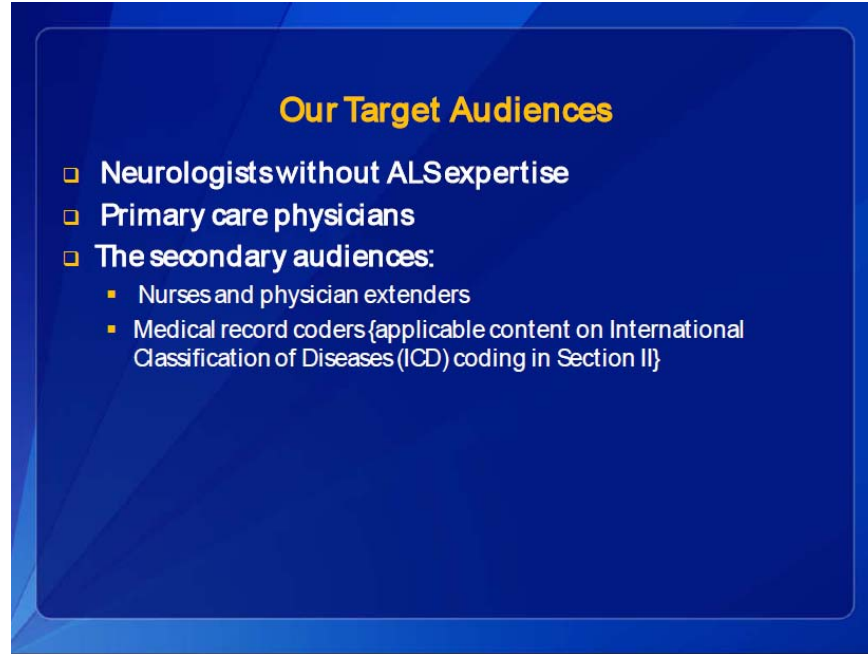
For researchers who would use the registry's materials to do projects which require funding, Dr. Bruijn suggested engaging the NIH to factor ALS in its project proposals. Dr. Gubitza stated that NIH Project Officer Dr. Annette Kirshner at NIEHS might be interested. Dr. Gubitza offered to explore the potential contacts at other NIH Institutes and Centers.

### **Development of the ALS CME Module**

*Presenters: Mr. Brian Tencza and Ms. Kim Jenkins, ATSDR Division of Toxicology and Environmental Medicine (DTEM), Environmental Medicine Education Services Branch, Education Services.*

Mr. Tencza and Ms. Jenkins outlined the development of the CME component of the ALS registry. This branch develops physician education materials on toxic substances, as well as such materials for the public. The DHS enlisted the Branch's educational expertise, content expertise from within and without ATSDR, and audience input, to develop the CME module. It was developed in five stages: analysis, design, development, implementation and evaluation.

*Analysis:*



The analysis identified the primary audience (neurologists without ALS expertise and primary care physicians) and secondary audience (nurses, physician extenders and medical record coders). Attention was paid to the target audiences' characteristics. Their baseline ALS knowledge varies and they like to control the material's pace and content and to take the course around their own schedules. Twenty-three learning objectives were developed and potential constraints identified. With that, instructional strategies were developed.

*Course Design:* The learning units of instruction were designed, as was a module prototype. Consistency in visual design was ensured and a list of illustrations and multimedia was developed.

*Course Development:* The course content relates to the 23 learning objectives, and how that is tracked was shown on a five-column chart. The sample objective was to "Explain the purpose of creating/maintaining the National ALS registry." The components addressed were the module content, online activity, the practice and feedback, and finally, the post-test of how well the objective was met. In the development process, the instructional goals/learning objectives are validated and the module content is assembled. Subject matter experts are consulted, content clearance is obtained, and the module website is developed. The content developed focused on "need to know" versus what is "nice to know" and is aligned with the 23 learning objectives.

## Content

- A clinical overview on ALS
- Current clinical practice recommendations for diagnosis, treatment, and management of patients with ALS, including communication strategies
- Information on the importance of standard diagnostic coding procedures for diagnosis of ALS patients in clinical practice
- Information on the new National ALS Registry and the importance of ALS patient self enrollment in the registry

Clinical content includes an overview of ALS; practice recommendations for ALS diagnosis, treatment and patient management, including communication strategies; the importance of standard diagnostic coding procedures; information on the ALS registry and the importance of patient self-enrollment.

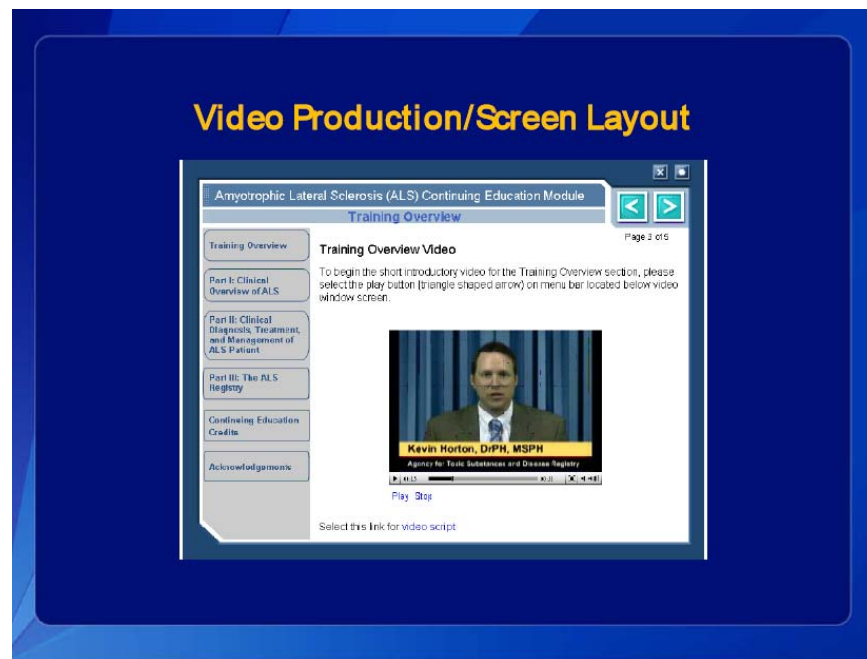
Objectives include the ability to describe ALS' differential diagnosis and the clinical assessment in ALS diagnosis, and to describe healthcare providers' communications strategies in clinical encounters with ALS patients

## Select Objectives-Registry

- Explain the purpose of creating and maintaining the National ALS Registry
- Describe the benefits of creating and maintaining the National ALS Registry
- Describe the methodology used to collect and synthesize data for inclusion in the National ALS Registry
- Discuss benefits of encouraging ALS patients to self-enroll in the National ALS Registry

Registry content addresses its purpose, benefits, methodology used to collect and synthesize data for registry inclusion; benefits of the registry and encouraging ALS patients to self-enroll.

*Materials development.* The multi-media approach used includes illustrations, pictures and other representations to enhance learning the module's content. Also developed



were video scripts and four ~one-minute introductory videos to each module, with closed captioning. A sample screen layout was shown. Every module includes the primary references used in its development.

*Implementation.* CME materials can be accessed via the registry portal, but the materials also can be accessed through the ATSDR website.<sup>1</sup> Quarterly usage reports were designed. The data gathered includes the occupations accessing it (e.g., physician, nurse) and their site of origin, and feedback rating of the module.

*Evaluation.* When the site was almost complete, a formative evaluation was done, with the content peer-reviewed by experts (neurologist, internist, nurse). The module was revised based on their comments. The instructions provided before their formative evaluation were shared. They encouraged the reviewer to “think out loud” (e.g., why something is present – or absent -- on a page; difficulty in navigation, etc.). Other than revealing some typos and suggestions to change the sequence of some screens, for example, very few changes were needed. The training was well accepted. Follow up suggestions included providing a list of tests a physician might want to run. A usability test was also done, screen by screen, to ensure it was ready to launch.

<sup>1</sup> <http://www.ATSDR.cdc.gov/emes/ALS/index.html>

The branch also produces other products, whose development are coordinated with SME's, instructional designers, educational and marketing specialists, etc. Once the product is developed, message and format consistency is ensured, and that they are based on best practices. Templates and materials' style guides ensure consistent quality and build/reflect the ATSDR brand. They provide procedural guides (procedural flow), formative evaluation and post-education evaluation materials (e.g., what was included, or not, and that would be helpful). Based on that feedback, the modules are revised to be more useful.

A list of the continuing education credits CDC is authorized to grant for physicians, nurses and health educators was shown, as were types of products produced by the branch. The latter include 28 case studies in environmental medicine and toxic substances, Grand Rounds, community presentations, patient education sheets, and a pediatric environmental health toolkit for physicians' use to guide their patients. These and others can be accessed at the ATSDR website.<sup>2</sup> Feedback on the materials will be welcomed.

### *Discussion*

- Similar to the e-button for the registry, Dr. Horton wondered if the mutual links of the ATSDR, MDA and ALSA websites should include one to the CME website, to attract the target audiences. Since there are physicians who do not have a lot of resources about ALS, another suggestion was made to consider developing something similar to the e-button or other materials to be placed on the Registry to direct physicians and persons with ALS to the national service organizations, such as ALSA and MDA, which provide support to ALS patients and their families. Brochure or flyer PDFs can be downloaded and ATSDR could issue a one-page email blast about it. ATSDR is cultivating a relationship with the American Academy of Neurology; a separate email could be sent to them. The site's capability to track the origin of its hits could be interesting in this regard.
- Ms. Kennedy urged ATSDR to seek as many endorsements as possible from the national organizations to lend credibility to this effort. Dr. Tencza commented that normally, when the AMA's CME requirements (the most rigorous) are met, others' requirements are grandfathered as well. The fact that CDC's CMEs are also free of cost is attractive.
- Dr. Horton commented that the website is less appealing in appearance than others because it had to be 508 compliant. However, a new template is in development that will make it more visually appealing and still compliant. The goal is to make the material on the page easily transferrable by cutting and pasting to other websites. ATSDR will demonstrate the site at the upcoming Orlando conferences. Ms. Kennedy suggested also attending the Allied Health

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<sup>2</sup> <http://www.ATSDR.cdc.gov/emes/index.html>

Professionals meeting there, held on a separate day. This would be a perfect group to help get the word out. She also said that, upon the MDA's advisory committee's approval of the ALS registry site content, the MDA will post a Web button or other link on its website.

- Dr. Muravov advised focused outreach to physicians who are less specialized than neurologists. They do not expect to find ALS in younger patients, who are often diagnosed later. He also noted another factor of CDC's website security is that data collected in the last 24 hours is moved every midnight to another station not Internet-connected.
- Dr. Kasarskis complimented ATSDR for the CME feature, but saw it as a small distraction from the site's primary goal of being an engine for researchers. With people already inundated by in-person and Web presentations, he urged outreach to associations such as nursing groups, etc., as more important. Dr. Horton agreed. While the DHS focus is on epidemiology, the Division of Toxicology educational group will focus on the site's content more in the future.
- Dr. Brooks related his clinic patients' report that the length of time to get into the system and complete the informed consent was a barrier. He suggested creating an online mockup of the website for nurses and caregivers to review, so they can tell patients what to expect. Dr. Horton reported ATSDR's investigation of that for the Internet and for advocacy group chapters, as well as a short (~5 minute) orientation video. Ms. Kennedy commented that this need not be on the Web; it could be a PDF.
- Dr. Weisskopf asked if the surveys could be formatted into a single survey, rather than 6 individual surveys, so that if the patient had to stop at any point the data could be saved. Drs. Horton and Kaye reported their separation for easier completion by the patient, easier data analysis of the subsets, and OMB requirements for the burden to do it. Reassembling them would require the whole OMB package to be redone. The patient can skip a module; those completed are grayed out. Once done, they cannot go back to correct an error, but they could advise the system administrator to correct it for them.
- Dr. Brooks asked if advocate support could be used to persuade OMB to change their process so that amendments to the registry could be completed in less than two years. Dr. Kaye said no, explaining the requirements of the Paperwork Reduction Act concerning the collection of research data
- In response to Dr. Brady, Dr. Horton stated that the enrollees will be able to compare themselves to others in the registry, once the first year's data is validated and posted. The patients also should know this registry's advantage of having both a numerator and denominator. That makes it unlike other websites such as "Patients Like Me," which are not population based or necessarily

representative. Again, he emphasized the need to be clear that ALS patients will have to sign up for the CDC/ATSDR registry.

- Ms. Kennedy and Mr. Wildman agreed that the value of the registry must be made clear. Posting an FAQ to do so was suggested, as there are other such websites as Patients Like Me. The FAQ should be shared with MDA, ALSA, etc. It probably should not specifically name other websites to avoid possibly offending some group.
- Dr. Muravov reported that OMB had removed a previous interactive map of the U.S. on which the number of ALS cases per state was updated. It will be reinserted in the next submission.
- Dr. Boylan asked when the first year data would be ready to post. Dr. Horton referenced the cancer registry model, where it takes approximately 2 years before the data can be released. The reason for the delay is due to the time needed to clean the data, to test it for completeness, and to check for duplicates. Since ALS is not a reportable disease, we have additional challenges to make sure the data are as complete as possible. Therefore, a realistic time frame for ALS is about 2 years to release the data. We recognize that researchers are not happy about that; however, we have to make sure the data are as complete as possible so that it does represent the true incidence and prevalence of ALS.
- Dr. Brooks asked a frequently posed question from the ALS community: can a dead patient be entered? Drs. Horton and Kaye said no and cited some of the barriers included:
  - Complete information may not be known by someone other than the patient, which can introduce bias.
  - Registries normally are longitudinal, requiring one starting point. If a person who died with ALS in the 1970s is entered, that date would be their starting point, which would leave big data gaps in the registry.
  - The IRB's requirement of the patient's consent. Dr. Muravov commented that the deceased relative may well be captured through the national databases. ATSDR will annually compare its data to that of the National Death Index to capture those cases longitudinally.
  - The validity of the diagnosis cannot be as readily verified as for a living patient. While surveillance cannot validate each of the thousands of ALS cases in the registry, the pilot project demonstrated the ability of ATSDR's algorithms to capture ~85% of cases. That validation may be repeated. (Four groups pulled medical records for all national data and sent de-identified data to ATSDR. Based on that data, the algorithm was developed.) The Web portal is similarly efficient. Dr. Kasarskis added that



the screening questions were taken almost verbatim from the VA. When validated by team of neurologist, 93-95% confidence was shown to match the medical record.

- Dr. Bradley advised ATSDR to be sure that is stated in the very first publication.

**Briefing on State and Metro Area-Based Surveillance**

*Presenter: Wendy E. Kaye, PhD, McKing Consulting Corporation, ATSDR/DHS*

Dr. Wendy Kaye outlined the purpose of the state and metro-area surveillance projects. The project data will be used to evaluate the completeness of ATSDR’s National ALS Registry. Its data will provide reliable and timely information on the incidence and prevalence of ALS and better describe the related demographic characteristics (age, race, sex, and geographic location).

## State Selection and Demographic Diversity

- States have at least 4 million population
- States selected to over represent some minority populations

Race and Ethnicity	US Total Population		Texas, Florida, New Jersey	
	%		%	
Total		<b>301,237,703</b>		<b>50,686,978</b>
White alone	74.3	223,965,009	73.1	37,040,347
Black or African American alone	12.3	37,131,771	13.2	6,688,461
American Indian and Alaska Native alone	0.8	2,419,895	0.4	190,589
Asian alone	4.4	13,164,169	3.7	1,860,507
Native Hawaiian and Other Pacific Islander alone	0.1	446,164	0.1	31,043
Some other race alone	5.8	17,538,990	7.8	3,955,077
Two or more races	2.2	6,571,705	1.8	920,954
Hispanic or Latino	15.1	45,432,158	27.0	13,672,498

From a competition of states with ≥4 million population, three states (Florida, New Jersey, and Texas) were selected to participate in ALS surveillance. CDC/ATSDR also is expanding this surveillance project to include 4-6 metro areas to over-represent some minority populations, particularly African-American and Asian American.


The CDC/ATSDR IRB approved the project this past June. New Jersey and Florida determined this to not be human subjects research and did not require a state IRB approval; Texas did, and its IRB approved. The metro areas must obtain local IRB review and approval, or they may request to defer to CDC’s IRB.

*Methods.*

*Case ascertainment:*

## Methods: Case Ascertainment




- Collecting Case Reports for all ALS patients diagnosed or treated from January 1, 2009 to December 31, 2011
  - Case Report Form will be completed by physicians and submitted to health department
    - Identification Information
    - Demographic Information
    - Diagnosis Information
- 

Case reports are being collected for all ALS patients diagnosed or treated from January 1, 2009 to December 31, 2011. The case report form, completed by physicians and submitted to the health department, will include identification, demographic, and diagnosis information. Each state or metro area is assembling a comprehensive, up to date list of practicing neurologists to contact, who are being identified by consulting neurologists. Those sub-specialties unlikely to see ALS patients (e.g. pediatric neurologists) will be deleted from the list. A mass mailing will be sent to providers in the project area, followed by phone calls to confirm if the provider sees ALS patients.

## Methods: Quality Assurance



- Assess accuracy of reporting - Up to 20% of reported cases will be reviewed by a neurologist to confirm diagnosis
    - Verification Form: signs and symptoms
    - Copy of EMG report if available
  - Assess completeness of reporting - using existing data such as death certificates and hospital billing data to identify possible cases that have not been reported
- 

The accuracy of reporting will be assessed by a neurologist's review of up to 20% of reported cases to confirm the diagnosis. The verification form will include the signs and symptoms and, if available, as a copy of the EMG report. The completeness of reporting will be assessed through existing records such as death certificates and hospital billing data, to identify unreported possible cases.

*Promotional and Outreach Activities.* ATSDR is seeking written endorsements from the ALS Association's national and local chapters, the MDA's ALS Division, state and national Neurological Society offices, and key ALS specialists. ATSDR also has attended or will attend and exhibit at neurology-related meetings and conferences.

*Data analysis:* Having a sufficient number of states to test national representation will be a valuable registry component, for example, to compare how ALS affects African-Americans versus Latinos, versus Asian-Americans. Data from the state/metro surveillance projects will be used to assess the completeness of the National ALS registry and, in particular, to check that sub-populations are not missed. Extended outreach will be done in certain areas to ensure more complete representation. Ultimately, ATSDR expects that state and metropolitan health departments will use the registry data to calculate area-specific incidence and prevalence rates.

The project timeline was shared (below). The metro areas selected to date include metro Atlanta and Detroit/Wayne county. A full listing should be available by the end of this year and all should be collecting data by fall of 2011.

## Project Timeline

2009	2010	2011	2012
<ul style="list-style-type: none"> <li>•Awarded State-Based Surveillance Contract</li> <li>•Selected States to Participate in the Project</li> </ul>	<ul style="list-style-type: none"> <li>•Prepared and submitted protocol for IRB review, CDC and state health department</li> <li>•Prepared and submitted OMB package</li> <li>•Prepared materials and began conducting outreach to stakeholders and neurologists</li> <li>•Awarded Metro Area-Based Surveillance Contract</li> <li>•Selected Metro Areas to Participate in the Project</li> </ul>	<ul style="list-style-type: none"> <li>•OMB approval expected in 1<sup>st</sup> quarter</li> <li>•State-Based Surveillance data collection begins 2<sup>nd</sup> quarter</li> <li>•Metro Area-Based Surveillance data collection begins 3<sup>rd</sup> quarter</li> </ul>	<ul style="list-style-type: none"> <li>•State-Based data collection ends and data transmitted to ATSDR by the end of 2<sup>nd</sup> quarter</li> <li>•Metro-Area Based data collection ends and data transmitted to ATSDR by the end of 3<sup>rd</sup> quarter</li> </ul>

### Discussion

- In response to Ms. Kennedy's question, Dr. Kaye said that the national registry has not yet been translated to any other language. Spanish is certainly being considered. Dr. Horton expected that data indicating effects among various groups will indicate the need for translation to reach specific groups. However, Ms. Kennedy reported that all their materials are automatically issued in English and Spanish. ATSDR could be missing people from the beginning by not having the content in Spanish. Dr. Horton thought that at least the home page could be translated to Spanish. But the modules would take longer, and have to be validated to ensure they are as clear as in English. Dr. Kaye added that the state/metro reporting is being done by physicians, so little language difficulty was expected. And, to issue the registry application/survey in another language, ATSDR essentially would have to recreate the entire site in another Web portal. So, any changes would have to be redundant across the portals, increasing the complexity of keeping it timely and accurate.
- Dr. Weisskopf asked what data will be collected. Dr. Kaye reported 14 variables reported by the physician for the state and metro areas (name, address, last 5 digits of the SSN, date of birth, date of diagnosis, etc.). These data are similar to those collected for reporting cases of infectious diseases. State and contractor staff will be available to provide any help abstracting records.
- Dr. Bruijn thought that the physician report would be good place to ask about the genetic aspects. However, Dr. Kaye responded that this data collection is only to ensure the completeness and alignment of the registry survey data. These data

will not become part of the National ALS Registry. This will help identify gaps and strengthen the national registry.

### ***Potential Enhancements To the ALS Registry***

The balance of the afternoon focused on specimen banking. After three presentations, the discussion focused on four questions posed by CDC: 1) is specimen banking justified; 2) why is it important; 3) is it value added; 4) what about sampling methods, where to store the samples; and 5) should pilot projects be done to begin with and, if so, by whom? How large should they be?

Joining the conversation by phone were Valerie Cwik, Bryan Traynor, and Peg Gallagher.

Dr. Horton asked the panel members if banking biological specimens was a sensible thing to do. ATSDR is considering that, but there is no guarantee it will be done. With the registry set up, banking would make for a top-notch registry. Feedback will be welcomed.

### **Banking Biological Specimens**

*Presenter: Nicole F. Dowling, PhD, CDC Office of Public Health Genomics*

Dr. Dowling presented the general and specific considerations related to genomic research. The latter involve banking specimens, study designs and the ethical, legal and social implications of this work. She also outlined genomic technologies, and described the related considerations.

*Approaches.* There are two possible approaches for a genome bank: designing both it and the specimen collection done for a particular type of research (e.g., involving a certain genomic SNP or marker); or collecting all specimens for use in future research. The latter may be more useful for multiple research purposes.

## Considerations

### □ Two approaches

- Design bank and specimen collection with particular research question in mind
- Collect all specimens and determine research questions down the road

### □ Specimens

- What types of specimens to bank? Serum, buccal swabs, saliva, other tissues
- Processing
- Storage
- Lab analysis
- Uniformity across registry sites

*Specimen questions* include deciding on the type of specimens to collect (i.e., in DNA or other analyses: serum, buccal swabs, saliva, whole blood, and other tissues such as from the brain). Each offers advantages and disadvantages (e.g., ease of collection but limited usefulness). There are also processing questions (who does it and how); storage issues (where; centralized or spread out); lab analysis decisions, such as who to do them (uniformly, but by one person or many) and ensuring uniformity across registry sites to allow data comparison.

## Considerations

### □ Study design

- Case-control – how to select a control population?
  - Matched from population
  - NHANES
  - Coriell (for purchase)

### □ Human subjects and ethical implications

- Blanket approval for research up front vs. re-consent for each use of samples
- Confidentiality and identifiability
- Reporting results of genetic tests
  - Individual notification vs. aggregate reporting
  - Clinical relevance of findings— now and down the road

*Genomic study design issues* may remain in the distant future, but have to be kept in mind. Case-control or nested design analyses are likely; a control population could be matched to a studied population. For example, the NHANES study samples are population-based and representative of the population and already genotyped. Coriell sells specimens and, while they are not population based, their private sector character allows greater freedom of use.

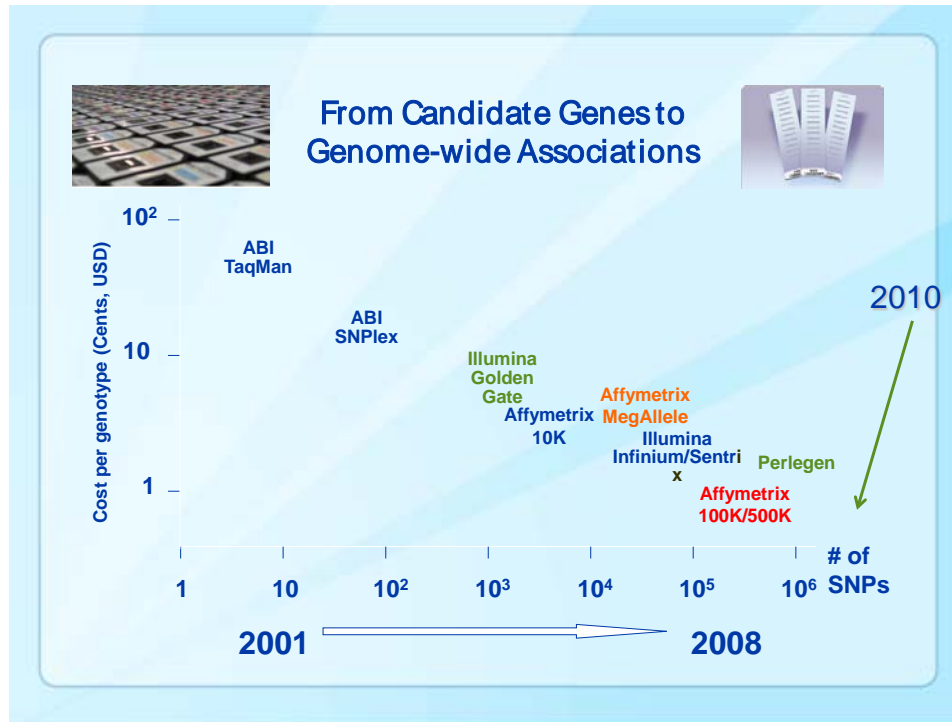
*Human subjects/ethical implications* are not insurmountable, but are challenging. Approval for banking specimens would require approval for re-consent, or an amendment to stipulate how the specimens would be used. IRBs can vary significantly in their opinion of such studies, with some providing blanket approvals and others requiring specifics. This poses clear implications to a multi-site study. Confidentiality and identifiability issues arise if the genetic results are inherently identifiable or if they are sufficient to identify any one person. Recent publications have spurred the current debate, but most agree that sufficient genetic data points would allow comparison to FBI or other genetic databases and identification of the person.

Finally, the reporting of genetic test results varies (i.e., individual or aggregate) as does the related implications of the finding's clinical relevance, at the time and in future.

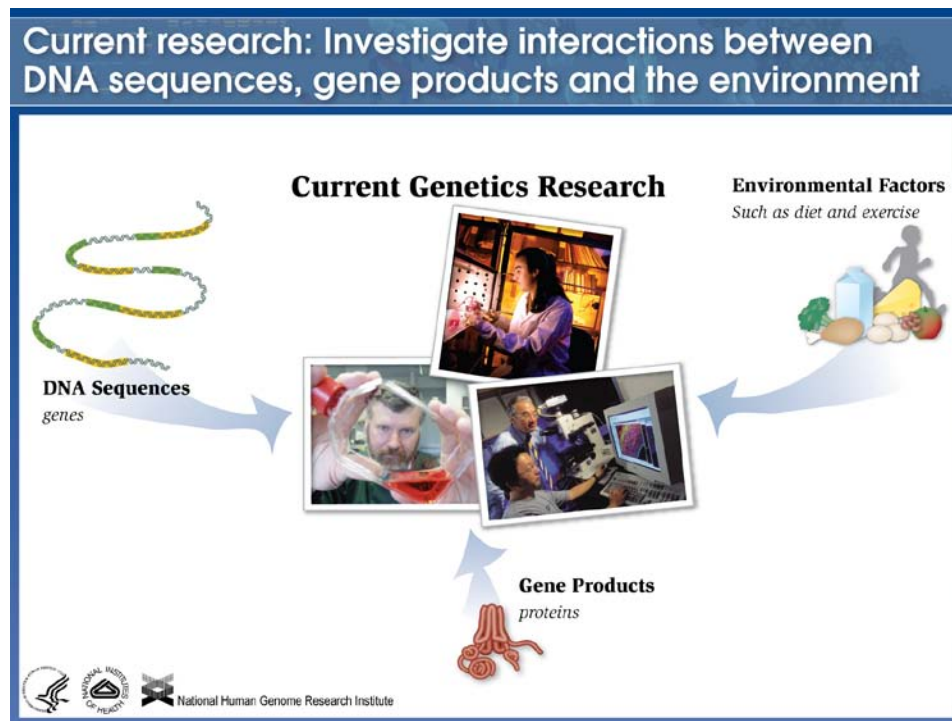
*Analyses possible with banked specimens* relate to issues of the type of specimens collected, the cost of analysis and others.

*The Candidate Gene (CG)* analysis was the state of the art until ~5 years ago. Now, new technologies allow more than one gene at a time to be examined. But the CG analysis is still useful. With enough information on the disease and the part of the genome of interest, a targeted approach most suitable to the study can be taken. As many variants as desired can be genotyped, perhaps looking at one set relative to their outcomes and interaction with other genes and environmental factors. It is likely that ultimately, candidate gene analyses will be done.

*Genome-Wide Associations (GWA)* are technological advances that greatly reduced the cost of such analyses. The plummeting cost of genotyping was charted from the original TaqMan test (2001) through the whole-genome sequences to 2008. The latest technologies allow analysis of millions or more of variants in NHANES samples for ~\$200-\$300.

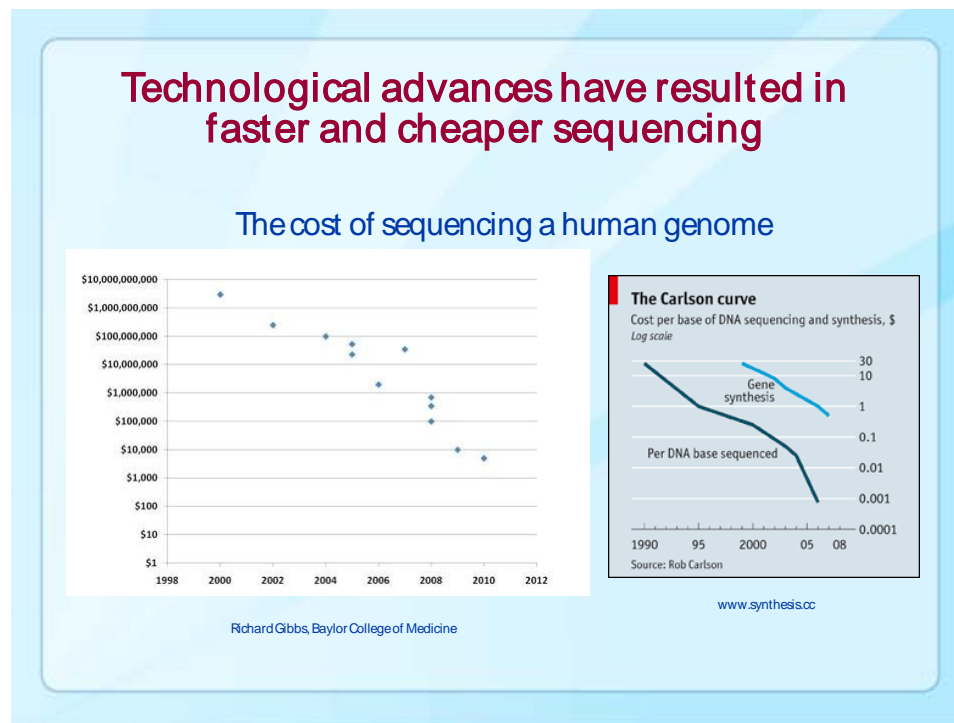


A GWA study can evaluate all 10 million variable points across the human genome at once, in a hypothesis-free, agnostic search (i.e., unlike candidate gene, no *a priori* expectation of a genome point of interest is needed). Since variation is inherited in groups, or blocks, not all 10M points must be tested. Rather, the  $\geq 1$  million tested impute information on other parts of the genome not directly tested.





GWA studies have multiplied since 1985, with the first publication on the macular degeneration gene. Current genetics research across the whole genome targets specific diseases and includes examination of DNA sequences (genes) as they relate to environmental factors like diet and exercise. However, these analyses still miss a lot. Rapid technology advances are moving from GWA platforms to others, such as biomarkers that could provide more information. The candidate gene and GWA methods of examining single nucleotide polymorphisms and other variants have moved on to sequencing. The latter is now “almost affordable” and should be considered for future studies. In the future, other “omic” technologies (e.g., transcriptomics, proteomics, metabolomics, etc.) will evolve into a more global view of human genomic and biological variation: epigenetics.



A chart illustrated how technical advances have produced faster and cheaper sequencing. The Thousand Genome Project is exploring the cost of sequencing. Such work will make these technologies more mainstream and available.

### *Impact of sequencing*

The promise of genomics has not yet been realized; it has not yet contributed greatly to improve healthcare. The common variants found to date incompletely explain complex disease genetics. It is hoped that sequencing will better capture the spectrum of variability in the human species (rarer SNPs, CNV, etc.). Those rarer variants, with a frequency of <5%), may contribute more to susceptibility and disease progression. When incorporated into new GWA platforms to allow wider study, hopefully those variants will provide a better etiological understanding.

The shift from candidate gene analysis to GWA is important because common variants alone have not been found to contribute largely to common disease susceptibility. Genomes are rather static; they focus only on DNA sequence-level changes, ignoring higher-order structures and processes. Most disease susceptibility is influenced by environmental exposures and gene-to-gene and gene-environment interactions.

Other “omics” technologies were outlined:

Transcriptomics: Study of the complete set of RNA transcripts produced in the genome (mRNA, rRNA, tRNA, nc-RNA) at any one time.

Proteomics: Large-scale study of proteins produced in a cell (expression, structure, modifications, functions).

Metabolomics: Global study of metabolites (intermediates and products of metabolism) in a cell, tissue or organism.

Epigenomics: Understanding the dynamic aspects of the genome in a more holistic manner. This evaluates the interactions between variations in the genome, DNA methylation and gene expression. This is a challenging field. A number of other parameters need to be accounted for than the static genome that was occurring in the patient when the sample was collected.

So, advances in genomics include faster, cheaper genotyping and sequencing technologies that have moved the field from genetics to genomics (the GWAS, the hoped-for \$1,000 genome). However, the fully realized potential for genomics to positively impact public health will not be realized until there is a more global view of the human genome variation and biological variation that considers environmental effects.

### **VA Biorepository Brain Bank (VABBB)**

*Presenter: Dr. Christopher Brady, Director of Scientific Operations for the VA Biorepository (VAB)*

Dr. Brady described its background, mission and processes. Its Principal Investigator, Dr. Neil Kowall, is also PI of the Boston University Alzheimer’s Disease Center. The brain bank repository itself is in Tucson, AZ.

The VA initiated a concerted research effort in ALS upon discovery of its link to Gulf War (GW) veterans (nearly double the risk<sup>3</sup>), and to military service in general. The VA’s National Registry of Veterans with ALS operated from 2003 to September, 2007. It enrolled 2050 veterans aged 23-93 years, who served in combat from World War II to the 1990-91 Gulf War. The VA’s Scientific Advisory Committee recommended establishing the VABBB under the VA Cooperative Studies Program, to collect brain and spinal cord tissue from veterans in the ALS registry. It is coordinated at the VA Boston Healthcare System by the Massachusetts Veterans Epidemiology Research and

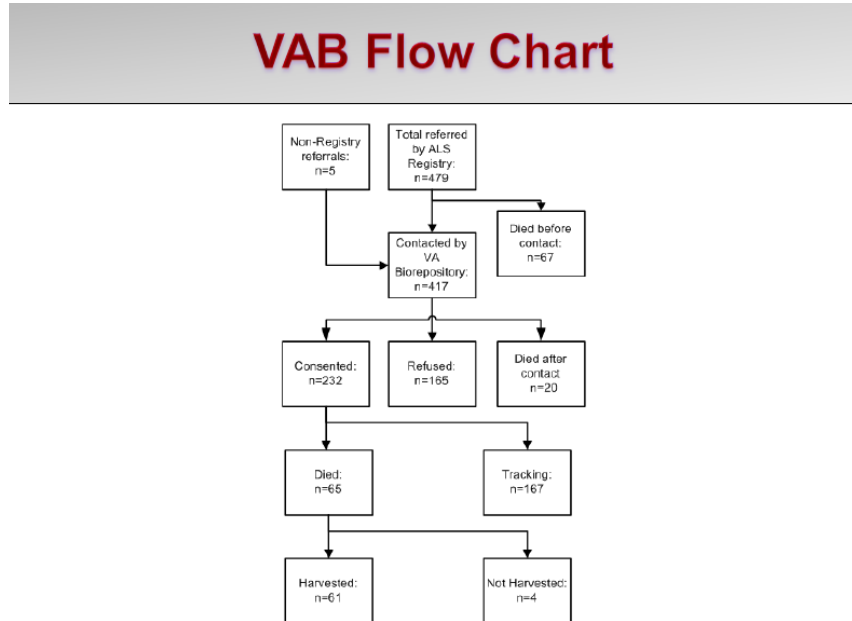
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<sup>3</sup> (Haley, 2003; Horner et al., 2003).

<sup>3</sup> Institute of Medicine, 2006

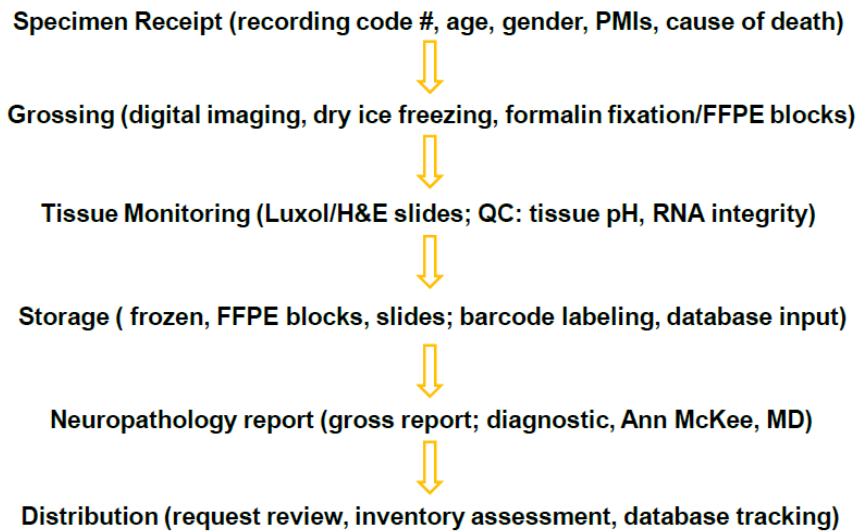
Information Center (MAVERIC). The tissue is analyzed, processed and stored at the Southern Arizona Core Tissue Laboratory (SACTL) at the Southern Arizona VA Healthcare System (SAVAHCS) in Tucson, AZ. Diagnostic neuropathological analyses are conducted by Dr. Ann McKee at the VA in Bedford, MA.

*Process.*



A flow chart illustrated the process involved. The VA contacted those in their ALS registry to explore their interest in participating. Upon their consent, which is verified by the patient and their next of kin (who must reconfirm at the patient's time of death [TOD]), their contact information is taken. They are assessed for their health and ALS severity. The latter determines the scheduled phone follow up, which increases with the disease progression.

## Tissue Processing and Storage (Tucson)



The VABBB faced a logistical problem in harvesting the cooperating veterans' brains at the TOD. If the nearest VA hospital's pathology department cannot do it, they work with others (e.g., private dieners, hospitals) on disposition at TOD. Pre-positioned shipping boxes facilitate the process. VABBB staff members are available by pager 24/7/365 for brain/spinal cord harvest and delivery to Tucson within 48 hours of death. When notified, the VAB has a 100% success rate in brain harvests. The patients and their families usually are very supportive and heavily invested in finding ALS' cause and cure.

The ALS registry provided 479 volunteer donors and five more from word of mouth. Of these 484 veterans referred to the VABBB, 232 have been enrolled (47% success rate). Of the 252 who were not enrolled, 87 died before or just after contact (i.e., unable to be consented prior to death) and 165 declined to participate. The VABBB's start-up cost was ~\$2.2 million. It is currently tracking 167 volunteers in 47 states. Once harvested, the process by which the special courier takes the sample to Tucson was described.

*Tissue distribution.* Requests to VAB by investigators (VA or non-VA) are reviewed for their scientific merit and completeness. Initial recommendations are sent to the VA R&D Central Office, which reviews and finalizes the approvals and the amounts/types of tissue to distribute. Tissue and associated clinical data released to investigators are de-identified, but other annotation data are available (e.g., age of onset, family history, etc.)

The VABBB's informed consent protocol allows broad based consent for optimal future use. The participants know that there will be ongoing data collection and recontact and that their VA medical record will be accessed for additional information. Testing is open-ended. However, the initial patient consent is null and void at TOD. The family is recontacted for consent, which is why the VA works so hard to gain the family buy-in.

The VA also is frank about the potential for disclosure, although its reputation for protecting privacy is well known.

## Brain Bank Critical Elements

- Informatics
- Subject Identification and Consenting
- Tissue Processing Expertise
- Tissue Bank Infrastructure
- Associated Clinical Data Capture
- Governance
- Distribution
- And last, but not least, substantial funding

The critical elements of the brain bank include informatics; subject identification and consenting; tissue processing expertise; tissue bank infrastructure in place (partly due to the VA medical centers, and to NIH existing infrastructure that can be tapped). A brain bank's governance and method of tissues distribution has to be considered up front. Also to be considered is the substantial cost: \$900,000/year and \$1.2 million to set it up. Even with all that, the reason for the VABBB's success is largely due to its excellent, committed staff and the support of ALS patients and their families.

### **DNA Banking for Epidemiological Studies**

*Presenter: Dr. Margaret Gallagher, CDC, National Center for Environmental Health (NCEH), Division of Laboratory Sciences (DLS)*

Dr. Gallagher is the Team Lead for the Banking and Genetics activity. By telephone, she described the sources of DNA, factors that guide the selection of specimens for genetic epidemiologic studies, and the relative merits of using buccal cells versus whole blood specimens.

## Factors that Guide the Selection of Specimens for Genetic Epidemiologic Studies

- Cost
- Convenience of collection and storage
- Quantity and quality of DNA
- Ability to accommodate future needs for genotyping and other analyses
- Participant willingness to provide specimens

DNA can be extracted from virtually any part of human body, but blood, saliva, and cheek cell scrapings (buccal) are the most common sources. The factors guiding specimen selection for genetic epidemiologic studies include: cost, convenience of collection and storage, the quantity and quality of DNA that can be gathered, the ability to accommodate future needs for genotyping and other analyses, and the participant's willingness to provide the specimen.

## Buccal Cells vs. Blood

- **Buccal specimen**
  - Low cost
  - Self collected, return by mail
  - Limited yield of DNA, lower quality, mix of bacterial and human DNA
  - Limited utility in other analyses
- **Whole blood**
  - Higher cost
  - Requires a trained phlebotomist
  - High yield of DNA, high quality, option for transformed cell lines
  - Can recover serum or plasma for other analyses
    - Toxicants (pesticides, heavy metals), infectious agents, other

Buccal cells have the advantage in that they can be self-collected and returned by mail. Their disadvantages include a limited and lower-quality DNA yield, in which human DNA

is mixed with a high percentage of bacterial DNA. This limits their utility in other analyses.

Whole blood has the disadvantage of being more costly and requiring a phlebotomist to gather the sample. But it provides a high-quality, high DNA yield that allows the option of analyzing transformed cell lines. Its serum or plasma also can be recovered for other analyses, such as for toxicants (pesticides, heavy metals), infectious agents, etc.

*Buccal cell* collection methods were outlined. The interior cheek is brushed for ~30 seconds with a cytobrush; or the participant “swishes and spits” mouthwash into a tube and returns that. In the commercial method, whole saliva is expectorated into a tube. Post processing for the cytobrush involves it to be mailed or frozen indefinitely. The mouthwash is centrifuged and the cells are stored. Saliva is stable for an extended period of time.

Collection costs rise from the simple cytobrush (\$1.10) to that of the mouthwash (\$1.70) to the Oragene saliva test (\$19.50). With associated costs, the cytobrush sample collection cost of \$8.50. The mouthwash cost was much higher, due to the need for centrifuge on arrival and the associated costs of personnel time, equipment use and supplies. (Full costs for the Oragene saliva test were not calculated.) In terms of human DNA yield, the buccal sample produced a very limited amount (1.6 ug), versus the mouthwash (17.2 ug) and 19.2 ug for the Oragene.

*Blood specimens*, a variety of specimen collection techniques can be used to obtain DNA. A 10 ml blood draw provides ~350 ug for DNA, and its buffy coat and plasma allow analysis of RNA and cell line information. Clotted blood and its sera provides DNA, while a ~2ug sample (equivalent to ~0.075 ml of blood) in a dried blood spot collected at birth allows analysis for DNA, RNA, and other analytes.

**Participation Rates for Genetic Studies**

Study	Biologic Sample	Participation Rates	Comment	Reference
NBDPS <sup>1</sup> 2008 cases	Buccal cells	60-78%	Non-Hispanic blacks and Hispanics least likely to consent, Rates varied by geographic region	NBDPS
2008 controls		47-87%		
NHANES <sup>2</sup> 1999-2000	Blood	84.8%	Female and non-Hispanic black participants least likely to consent	McQuillan et al., 2006
NHANES <sup>2</sup> 2000-2001	Blood	90.1%	Same as above	McQuillan et al., 2006

<sup>1</sup>National Birth Defects Prevention Study  
<sup>2</sup>National Health and Nutrition Examination Survey

Participation rates for three genetic studies were outlined. The National Birth Defects Prevention Study (NBDPS) was not necessarily representative, but they collected buccal cells from cytobrushes. The participation rates were 60%-78% for cases and were lower (47%-87%) for controls. The NHANES surveys typically have good participation. They take blood samples and offer a monetary incentive, but the greater driving factor for its good participation rates (84.8% and 90.1%) may be that the participants receive a lot of information on their health status. Even so, interesting differences in participation were seen. For the NBDPS, Non-Hispanic blacks and Hispanics were least likely to consent, and rates varied by geographic region. Even for NHANES, female and non-Hispanic black participants were least likely to consent.

To increase the DNA available from the sample gathered, two options were outlined. One is the Whole Genome Amplification (WGA). Similar to the polymerase chain reaction (PCR), this makes many copies from a small amount. But unlike PCR, it targets the whole genome rather than any particular region, and is done with buccal or blood specimens. While its reliability may be greater when amplifying DNA from blood specimens (e.g., as determined by comparing the genomic sequence of unamplified DNA to the amplified WGA products), there may be discrepancies when amplifying buccal cells. WGA also cannot be used in all genotyping platforms.

Another option is to use EBV transformed cell lines. The disadvantages here include high cost (from \$100 to several hundred) and, since this only is done with blood specimens, the received samples need to be quickly processed. There is also some discussion, in comparing the starting material to the DNA that emerges from transformed cell lines, of whether EBV is accurately representational.

**DNA Requirements**

Method	DNA Required(ug)	type of DNA
Pyrosequencing	0.005	gDNA or WGA
Illumina Golden Gate	0.25	gDNA or WGA
GWAS 1million SNPs	0.5-0.75	gDNA or WGA
Exome sequencing	20	gDNA (WGA not validated yet)



The DNA requirements for various methods are a consideration for the different types of studies that may be contemplated.

Pyro-sequencing is used for analysis of lower numbers of single nucleotide polymorphisms (SNP), to investigate a few targeted candidate chains or SNPs. A higher density SNP panel, such as the Illumina Golden Gate method, is used to investigate larger numbers of SNPs and slightly more DNA is required for this. As already mentioned, the GWAS may require more DNA and already has been used to process 1 million SNPs. A commercially available GWAS capable of 2.5 million SNPs is available and one for 5 million is pending. A new panel for gDNA now receiving a lot of attention is the Exome sequencing test. However, it is not yet validated for WGA and requires 20 ug of DNA. But it is an exciting technology, and the hope is that, over time, its costs will decline.

So, in deciding the method to use, the investigator needs to weigh the advantages and disadvantages of the specimen choice. Pilot studies are wise to do to indicate a study's potential participation rate and how to best process the specimens. For example, a pilot study could verify a commercial lab's capability to deliver quality results. QA incorporated into the strategy can ensure a quality product, eliminating the risk of an entire study's outcome being hampered by poor quality.

### *Discussion*

- When asked, Dr. Brady could not estimate the VA's cost per brain and spinal cord specimen, as the funding is nested in the entire budget. The work is done because ALS is a service-connected issue. They are in the process of expanding their biorepository capacity and more work for Gulf War veterans is expected. That includes enrolling new ALS cases beyond those in the ALS registry. The VA also is interested in making this a national resource, supplying tissue to private and commercial research. Almost all samples are received within 48 hours of death.
  - Dr. Bradley was impressed with the VA's achievements, stating that anyone banking should link with them. Their "extraordinary" 40-50% success rate for enrollment exceeds that even for those programs working with patients and their families. Dr. Brady credited the VA staff.
- Dr. Bruijn admired the VA's "ideal" collective infrastructure. She asked if that could be used, given additional funds, to help the tissue banking concept. Dr. Brady foresaw a strong case for tying into a pre-existing network to biobank for veterans. Doing so for non-veterans would be difficult, requiring interagency agreements, but perhaps not impossible.
- Dr. Bruijn noted the new technologies' need for human tissue, alongside little awareness of the VA resource. She asked how that could be promoted and how much is likely to actually be available. Dr. Brady reported VA's current secondary review of the initial applications to their recent RFP. The amount of tissue to be

distributed has not been decided, a point of frustration for some researchers who have waited for two or more years. But the VA will soon release some tissue and that should re-raise awareness. Given his report, Dr. Bruijn thought that any promotion of this resource would still be premature.

### *Sample Collection*

Dr. Horton stated that the sample collection process for the registry should be as easy as possible for ALS patients. However, this conversation indicated that mailing out a kit of buccal swabs, for example, would probably not be optimal. He asked for the participants' opinion, from a research perspective, of the best way to collect tissue and non-tissue samples. With the registry now in place, he asked what ATSDR should do next, and how that would be justified.

### *Discussion*

- Dr. Kasarskis responded with some background. The VA registry reviewed and collected cases several years before the DNA banking began. The latter's success was due in large part to the VA nurses visit to the patient's home to draw the blood. That was critical for a geographically dispersed veteran population, whose travel to be sampled may be hampered by impaired mobility. The veterans were stratified on the ALS disability scale with the nurse visiting the weakest first; nonetheless, some died before they could be reached. There was high interest when asked about participating; >90% agreed, and even higher agreement after the home visit.
  - The registry will not have the clinical data that the VA had with Coriell, a 1-1½ page list of common data elements in a clinical snapshot to which all agreed. Using the ALS rating scale might indicate a higher statistical chance of true ALS, but the amount of detail the registry may get is still unknown. Coriell processed 2000 specimens in ~18 months within the NIH grant infrastructure. They paid the sampling personnel ~\$25/draw and NINDS paid for the shipping. That was enough inducement for the site to do this work; without compensation specimen collection will not be sustainable in a busy clinic. Even an additional 10 more minutes with only 6 patients to see rolls into an extra hour. Given that burden, this will have to be funded as a research activity. Blood donation will work if it is convenient and if staff members are compensated for sending in the samples. Local IRB consents are also needed, involving funding and compensation factors. The easy part of all this is getting the blood sample. Getting voluntary clinical data will likely be very successful, although perhaps not as high as Coriell's.
  - Another possible approach is to do a skin biopsy for induced pluripotent stem cells (IPS). A Harvard research paper recently published in Genomics suggested a very high efficiency protocol for creating stem cells. That might provide more cost effective (CE) impact than DNA banking, and be more applicable for future long-range research.

- Finally, Dr. Kasarskis asked what environmental, geological, geo-sampling data could be matched to this DNA banking. The entrée was the gene susceptibility-environmental exposure paradigm, but little had yet been said about the environmental aspect.
- Dr. Bruijn noted that Coriell's immortalization provides a limitless supply, which Dr. Kasarskis noted IPS also will do. Given governmental restrictions, he asked if samples could just be sent to Coriell, making the registry a joint effort not possible in the past.

### *Sampling Mechanisms*

Dr. Horton asked for comments on the sample mechanisms used (e.g., buccal versus blood spot). Researchers' interest could indicate what types of samples are collected.

- Dr. Traynor, who is quite experienced in GWAS work, thought this would depend on resources, with graded possibilities. At one end is doing a full panel; collecting DNA in blood and send it to Coriell for immortalization. However, since there are insufficient time and resources to do so for every patient, the midway approach would be to use a selective process. Given the available ECHO and next generation sequencing, exploring familial implications might be more cost effective. On the other end of the spectrum, one cost-free method for CDC/ATSDR could be to provide researchers with the names/contact details of individuals who sign on the website and meet the ALS diagnosis criteria. Of course, ethical standards would be guaranteed. Medical chart data could not be shared, but perhaps patients signing up on website could give their permission for researchers' use of their data.
  - Dr. Horton responded that release of patient data is not presently possible. Dr. Kaye added OMB's requirement that the data are representative prior to release data is an issue because that kind of validation requires registry/existing administrative data combination. The concern was that the portal data would differ from the population as a whole (e.g., demographics, racial/ethnic, etc.), which would make any research with it invalid.
  - In response to Dr. Bruijn, Dr. Horton stated that ATSDR had tried to include an option on the registry for patients to certify their interest in giving a blood draw. However, waiting for that approval would have prevented the Web portal's launch. ATSDR preferred to launch it and then address the bureaucracy of tweaking or adding to it.

Dr. Horton asked again what the registry's true value would be; what unmet need it could allow to be addressed, or how it could complement others' work.

- Dr. Bruijn identified the brain/spinal cord banking component as important to fill a huge research gap for the ALS community. The VA resource is marvelous, as is

Coriell's in the ease it provides (e.g., no sample transport issues, etc). Doing that in a network would be very important.

- Dr. Gubitza asked the extent to which the registry captures familial cases. Dr. Kaye said that one module explores family history, which is the most complicated module to computerize (with information on siblings, parents, children, Parkinson's disease, Alzheimer's disease, and ALS).
- Dr. Bradley supported the tissue bank concept but thought that the lack of controls is a serious flaw. Also, a drawback to DNA/RNA banks is that they frequently lack an adequate control population. Coriell has a control population. Dr. Bruijn noted that its collection is under-represented for diversity; it is still accepting those samples.
- Dr. Traynor added that Coriell also has thousands of samples for which corresponding genotyping is available. Analyses to match those can be done based on genotype rather than demographics. New statistical methods can determine who the population is with a high degree of accuracy, to stratify between cases and controls, and to then correct for it. While there is no control for the environment, beginning with genetic factors makes that approach reasonable to use with controls.

Dr. Kasarskis reported blood samples as the VA's primary DNA banking approach; buccal smear was only done for those with poor veins. And, since the cells are not immortalized, only a finite amount of DNA was banked. In answer to Dr. Horton's question of what this registry would best be used for, he referred back to his clinic patients' consistent question – "What causes my ALS?" Reconstructing their life history helps to answer that question, as will ATSDR's research platform. People are more sophisticated now about genes, genetic susceptibility, and environmental influences — which, he recalled, also was ATSDR's original goal. This related back to selecting the environmental indices. This work will be hypothesis generating which he felt to be "perfectly fine." A strong link between the susceptibility factor of an identified gene, paired with industrial benzene, etc., would allow future population research to prove it.

Dr. Bradley said that, even without any additional elements or complete ascertainment, ATSDR still could do regional and small regional analyses. The analyses of Finnish ALS data in papers by Clive Sabel showed a surprisingly variable geographic distribution of ALS indicating regional causative factors in that very stable population.

- Dr. Nelson suggested that ATSDR consider getting spit samples on as many subjects as possible, and blood samples from those with familial ALS. This is a complex disease in which environmental factors probably act with a background of genetic susceptibility. That interaction needs to be examined. The average 20 ug of DNA in each spit sample will provide a large quantity for most current genome platforms.

## **Pilot Programs/Procedures**

Mr. Kingon asked if ATSDR should do pilot projects, such as one on DNA banking. Dr. Horton added that this would demonstrate a feasibility that merits funding. A pilot could set a certain number of samples and demonstrate their process. Dr. Kaye said that a pilot of feasibility rather than efficacy, for example, could indicate whether a little data on everyone or a lot of data on some made more sense. Both applications offer advantages and disadvantages. For example, a pilot could explore how to get a blood specimen from rural residents who do not go to specialized clinic, but without whom the registry would not be representative.

- Dr. Brooks suggested that ATSDR/CDC link a deceased individual in the registry to existing brain bank data, as a cost effective alternative to the \$900,000 the VA mentioned. Dr. Horton agreed that ATSDR is committed to non-duplication and to partnering with any relevant resources and facilities. However, Dr. Brady raised technical feasibility challenges, such as differing methods used to process the brains. Some of the centers with local brain banks are working with Alzheimer's disease centers, relying on their pathologists' standardized methods. That is one way that a pilot project could assess the feasibility of developing SOPs for all to use. There also has been some initial discussion about standardizing pathology sample collection for ALS patients.
- Dr. Bruijn added that at least four centers have agreed on procedures, so to some extent this is established in the ALS community. The main barrier to doing this, especially piggybacking on the AD centers, is the inability in all cases to procure a spinal cord sample. It is not unusual for ALSA to get phone calls offering samples that they cannot retrieve in time. The first step is to educate people to that opportunity; it would significantly add to the registry.
- Dr. Kasarskis commented that, even with the patient's and family's consent and a mechanism to participate, significant costs remain. The VA's enviable cost (\$50,000/year for shipping) to retrieve the body is unmatched in the private sector. Additionally, the declining genome sequencing costs are not matched for autopsy. A funeral home charges \$250-\$500 per person to send a body to a medical center for brain harvest, followed by the costs for DNA samples, skin biopsies, etc. Additionally, not every pathology' department considers an autopsy as part of normal clinical care, with potentially high added charges (e.g., Jeff Rodsky of Hopkins estimated \$1500 to conduct an autopsy). So, partnering with medical centers for autopsy could save some startup costs.
- Dr. Brooks observed that CDC/ATSDR's bar for success was set by the NIH-supported brain bank in New York. In 5 years, they moved out 1000 samples to investigators.
- Dr. Gallagher addressed some practical banking aspects. A backup protocol of collecting 2 tubes of blood would provide one for directly isolating DNA. And, if resources are lacking to create more live cell lines, those costs can be deferred

by isolating the buffy coat and storing it in liquid nitrogen, for immortalization at a later date. Dr. Dowling would encourage banking specimens if possible, as they offer many research possibilities, especially for etiologic studies.

- Dr. Pentz thought it an ethical mandate to do tissue analysis, given modern technology; that is the only way to make progress.
- Dr. Brooks asked of any analysis done of gene involvement in epidemic outbreaks as they relate to environmental toxins. Dr. Dowling reported that one OPHG pilot study, of host genomic factors and severe influenza in children, collected specimens in a surveillance project. OPHG has discussed environmental studies with other CDC entities, particularly involving infectious agents, but she did not know their status.
  - Dr. Brooks followed up, commenting that if ALS etiology is heterogeneous, environmental factors could relate to genome susceptibility (e.g., those exposed to cyanobacteria may have different phenome susceptibility for ALS versus an exposure to arsenic). NIEHS is studying the potentially slower course of ALS as related to a higher lead burden, which may also depend on genome structure.
  - Dr. Weisskopf responded that perhaps future case-control studies will address what are issues of disease etiology versus disease manifestations, as related to environmental toxins which can be addressed in a hypothesis generating approach. Toxicants in blood also could be studied, but sampling also poses implications to what is being explored (e.g., ensuring tubes are free of lead or trace-metals, or organics, etc.).

Dr. Weisskopf was interested in the idea of the potentially different ALS trajectories based on different sets of exposures. Dealing just with the case set and the exposures collected at the time of disease, might be more etiologic and/or of interest, relative to progression. There also may be inexpensive analyses possible, such as one at Harvard on heavy metals measured in toenails. The latter are certainly easy to collect and store, and can be mailed in for analysis. They provide material to measure metals and even cotinine for smoking exposure. Perhaps DNA could be explored.

The meeting then adjourned at 4:13 p.m.

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**NOVEMBER 4, 2010**

On the following morning, NCEH Director Dr. Chris Portier, formerly of NIEHS, attended to greet the panel. This project is important. ALS is a devastating disease, and we only know the cause in about only 3% of the cases. This registry can open the door to understanding its origins and indicate directions to explore for cures or treatments to delay its inevitable effects. ATSDR will work with as many partners as possible to advance and strengthen this exercise. Dr. Portier's 2009 paper in *Systems Biology* linked 900 chemicals to 200 different human diseases, one being ALS. In that study rather than just looking at genes, they looked at their associated pathways (e.g., single transduction or metabolic pathways). That allowed a view, beyond the pathways, of how diseases related to each other. Diseases with multiple pathways in common could be clustered together. The same approach was used to examine genomic changes induced by chemicals in cells. Interestingly, ALS and neurological disorders as a whole had an extremely tight cluster, with similar genetic and single transduction profiles. That offers some hope, but the disease clusters by themselves had little relationship to chemicals. That led the researcher to question what about this group left them independent of chemicals. There is a large research gap in this area. This registry could help the field advance if it can indicate such links to humans with genetic disease or exposed to things suspected of raising the risk of ALS.

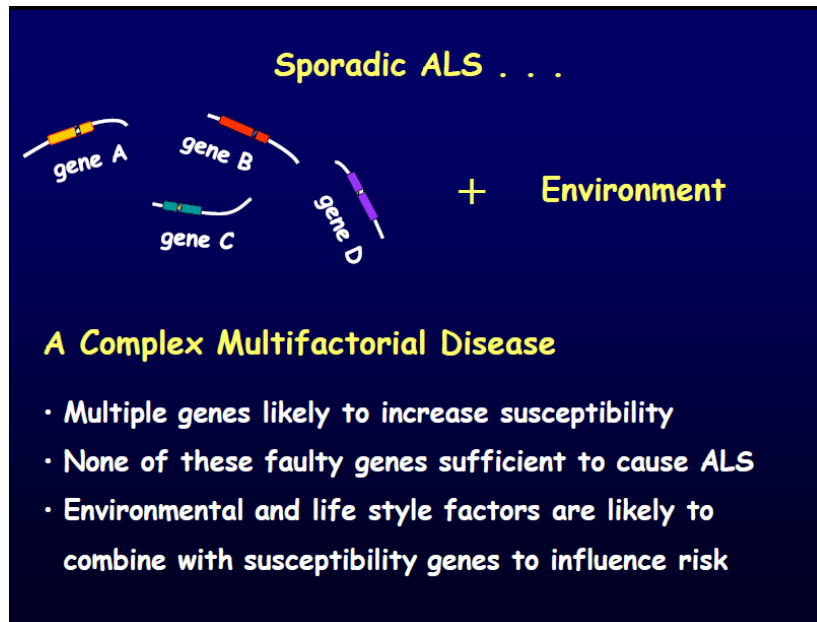
### **Potential Enhancements To the ALS Registry, Continued**

*ALS Consortium of Epidemiologic Studies (ACES)*

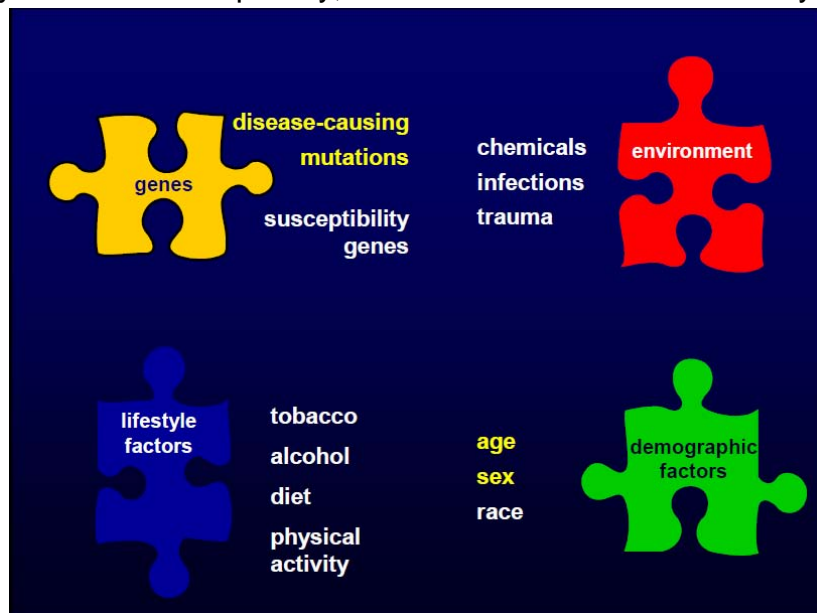
*Presenter: Lorene Nelson, PhD, Director, (ACES)*

Dr. Nelson congratulated CDC/ATSDR for their success in establishing the registry so well. She is the director, and Dr. Valerie McGuire is co-director, of the ALS Consortium of Epidemiologic Studies (ACES). ACES is based at the Stanford University School of Medicine's Division of Epidemiology. She described its origin, composition and activities, as well as future surveys that might accompany the registry.

*Risk factors for ALS* are elusive; 90-95% have no family members affected with the disease. ALS also can cluster, as seen in ALS/Parkinson's clusters in the Pacific Mariana Islands, among Persian GW veterans and others. Epidemiologic studies show incidence to be fairly uniform among countries but examination of risk factors show conflicting results. Some environmental exposures such as cigarette smoking have been associated with increased risk of ALS, but only a few risk factors have been found to definitively raise the disease risk. Among these are disease-causing mutations, age and sex; men more affected than women.



“Sporadic” ALS is the term used to describe ALS that is not caused by a known oncogenic gene. This complex multifactorial disease involves multiple genes. Their mutations likely increase susceptibility, but none of them alone are likely to cause ALS.



Among the environmental factors suspected of increasing risk are heavy metals, solvents, pesticides, infections and various physical traumas. Suspected lifestyle factors include tobacco and alcohol use, diet, and physical activity. All of these likely combine with susceptibility genes to influence risk. Along with the known demographic risks of age and sex, race also has been implicated in sporadic ALS.

Dr. Nelson asked the panel to consider if there may be protective factors to reduce risk. These could be similar to Parkinson’s protective factors against increased risk (e.g.,



smoking and higher coffee consumption, although the biological mechanism for those is not known).

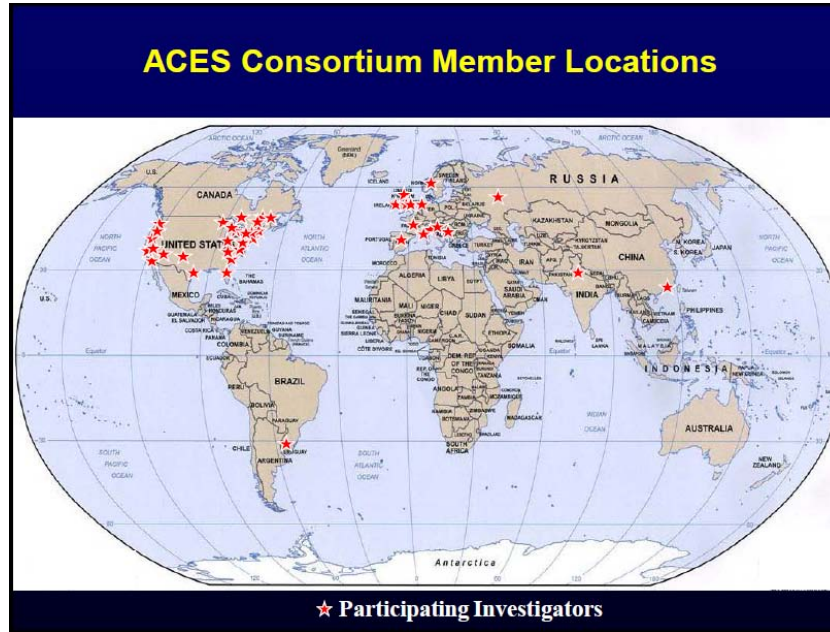
Important research questions for Sporadic ALS include:

- What are the genetic factors that increase or decrease the risk of sporadic ALS? Adding a biological sample collection function to the registry would greatly contribute to the search for genetic factors such as susceptibility genes.
- Lifestyle factors (diet, physical activity, etc.)
- Toxicant exposures that may cause selective motor neuron death in ALS patients are of interest. One study is exploring selective neuronal death from ALS in the upper spinal cord, and those neurons' specificity relative to etiological factors. Other studies explore what is unique to the motor neuron milieu that could explain the selective vulnerability of selective neurons such as the anterior horn cells.
- Medication use, whether as protection from antisteroidal inflammatory drugs or increased risk from statin medications.
- Potential protective factors that reduce the risk of developing ALS.

Challenges to risk factor study include:

- **Rarity.** This devastating but rare disease affects only 2/100,000 population annually, which makes it hard to study even in a large population. Dr. Nelson's four-year study in Washington state, among Kaiser's 3-4 million population, found <400 newly diagnosed patients. That illustrates the clear benefit of a national registry.
- **Complexity:** Many study sites will need to be combined to answer questions of gene-environment interaction.
- **Cost:** This multifactorial disease requires multidisciplinary approach.
- **Very large research scope** because ALS' unknown cause involves study of factors over a subject's lifetime.

These questions and challenges led to ACES beginning in 2005, supported to 2008 by an ALSA grant. Its broad objective is to form an interdisciplinary group of ALS researchers to conduct research on environmental and genetic factors associated with ALS, including sporadic ALS. To date, the >100 multi-disciplinary scientists involved include epidemiologists, neurologists, geneticists, toxicologists, and statisticians. The



partners' locations were mapped. The ACES website ([www://Aces.Stanford.edu](http://www://Aces.Stanford.edu)) is hosted by the Stanford School of Medicine, and mapped its membership. All are welcome to join, whether or not they are engaged in active research. ACES' initial objectives were to: 1) develop a consensus on standard data elements to collect in epidemiologic studies. Building on those, they 2) developed standardized data collection forms/instruments to assess risk factors for ALS. This was to lay the groundwork for large-scale pooling of environmental and genetic data across research sites. Given the time and the 3-4 million sample size necessary to collect enough data for statistical power, it was clear that the future combination of data would be key to identifying the subgroups at risk. The need for data standardization was a lesson learned from the difficulty in pooling the research data on Parkinson's disease, which has six times the incidence of ALS. ACES developed 3) a modular format so that investigators can tailor the instruments to suit their research questions, and 4) support a website where investigators can access information on risk factors in the literature to spur research collaboration. Finally, 5) they set up data dictionaries for all research modules' data elements.

The ACES partners developed an epidemiologic overview of the ALS literature, soon to be updated. It addresses the potential risk factors (e.g., lifestyle, skeletal trauma) for ALS and conveniently links the visitor to PubMed through Stanford's medical journal access.

### **Epidemiology Modules Already in Use, National ALS Registry**

- Sociodemographic characteristics
- Occupational history
- Military history
- Lifestyle factors: alcohol intake, smoking
- Physical activity
- Family history of neurodegenerative disease

ACES' epidemiologic modules for the national ALS registry, already in use, address: 1) sociodemographic characteristics, 2) lifetime occupational history, 3) military history (branch, war deployment), 4) lifestyle factors such as alcohol intake (ever drank, still drink; total years drank, average drinks per week/month); caffeine use and smoking (ever smoked, age started, data elements or date of last cigarette; total years smoked, average number, to allow computation of cigarette "pack years").

Of the last two modules, selecting questions for 5) physical activity was a challenge. They decided to ask about vigorous physical activity ever done, that involved heavy sweating and large increases in breathing and heart rate, in six age periods from age 15-65 years. The last module 6) addresses family history of neurodegenerative disease. That includes both parents, all biological siblings and offspring; their vital status, current age (or age at death), diagnosis and age at diagnosis by physician for ALS, Parkinson's disease, and Alzheimer's disease. The denominator is all the time spent at risk, to develop a cumulative incidence for the family members of the patients answering the questions.

### Epidemiology Modules Under Development, National ALS Registry

- Occupational toxicant exposures
- Residential history
- Residential pesticide exposures
- Hobbies involving toxicant exposure
- Trauma
  - head injury
  - fractures
  - electrical shock
- Hormonal and reproductive history (women)

Other modules proposed for development include occupational toxicant exposures; residential history (locations, dates); residential pesticide exposures; hobbies involving toxicant exposure; trauma (head trauma, fracture, electrical shock); chronic medical conditions; medications; and hormonal and reproductive history for women.

Prior to the discussion, Dr. Horton emphasized that this session was intended to help brainstorm other risk factor surveys not currently listed. The participants' review of present tools or suggestions of additional aspects will be welcome. ATSDR will work with the MDA, ALSA, and use media to ensure that people are aware that new risk factor surveys are online. Due to the level of detail necessary to answer the survey questions, physicians or even the deceased's loved ones may not be able to answer them.

#### **Discussion**

- Dr. Bruijn asked how future additional information will be imported to the registry. Dr. Kaye responded that OMB would clear the new documents. ATSDR will bundle them all together and apply to OMB and IRB to add them; then mechanize them for web access and apply for and receive security clearance which would take time. Upon registering, people can indicate their willingness to be contacted by email. New modules likely will be announced by email and media, including social media. For regular visitors, new modules will pop up in their personal queue. An auto-email about the new information will be sent to those registered and agreeing to be contacted.
- Drs. Bruijn and Gubitz suggested review of other research on OTC medication usage, such as nonsteroidal anti-inflammatory drugs (NSAIDs) and statins, and Vitamin E for Alzheimer's disease (although a negative outcome was recently published). Dr. Nelson said that ACES developed instruments for interviewer-

administered epidemiologic studies. Something similar could be done if it is decided to be a priority.

- Dr. Brady asked if pesticide exposures are covered in the current military history questions. Dr. Nelson responded no; a simple military history form is used. However, there are instruments for a full epidemiologic study that could be adopted. If it is a priority, the military survey could possibly be expanded to include pesticide exposures. Dr. Brady thought it would be a priority for 1990-91 GW veterans, along with other exposures in subsequent GW fields (e.g., exposures in Afghanistan such as jet fuel). Dr. Nelson said that such exposures could be captured either in occupational exposures or in military history.
- Dr. Brooks suggested taking a reproductive history for males (i.e., for effects on male sperm, aspects such as vasectomy) and the children of GW veterans.
- Dr. Tom Sinks, NCEH/ATSDR Deputy Director, asked if ACES was considering designing standardized questions on, for example, residence and occupational history, to provide a background referent for comparison. Dr. Nelson answered that, when choosing survey items, the highest priority is assigned to those already used in instruments such as NHANES or BRFSS, that can provide population benchmarks.
- Dr. Kasarskis commented that military history often is so general as to be unhelpful (i.e., only indicating an individual's service branch and whether they were deployed to a war zone). He asked if present military leadership had been consulted about data sources such as products used (e.g., annual purchase/delivery of pesticides or jet fuel to a base). Dr. Nelson confirmed that ACES received a NIOSH grant to further develop a retrospective methodology to collect military history and has begun collecting data. Detailed records stored in St. Louis, Missouri, hold records of military job title, assignments, dates of entry/exit, medals awarded in combat, etc. That information is being obtained for subjects participating in ALS and Parkinson study areas in Western Washington state and California. They also contacted each military branch's industrial hygiene groups for information to reconstruct potential historical exposures to service members in war zones. (For example, the Army Exposure Assessment Group has done an "exquisite job" of tracking and calculating potential soldiers' exposures in conflicts.) ACES is interested in Alzheimer's and Parkinson's, and has found that most (55%) of the men in the age group at risk for developing ALS have served in the military. A methodology is needed to study those exposures and, as developed, it can be applied to ALS.
- Dr. Weisskopf asked if a website link to allow military personnel to grant access to their military records would be helpful. He also asked if occupational exposure would be reconstructed from job history, or by targeting specific toxicants. For the former, Dr. Kaye again raised OMB barriers, and reported that a fire in the St. Louis storage depot had destroyed many records. Dr. Nelson was aware of that;

the military has tried to reconstruct them from NIOSH records. For the latter question, Dr. Kaye noted that the respondent burden has to be considered. Dr. Nelson noted that generally, the interviewer-administered study will get a lifetime occupational history and then move on to analysis by industrial hygienists who are not blinded to status. That is likely the most methodologically challenging of the items. They may have to use a less-than-gold standard such as simply asking them if they ever were exposed or in a job that might have exposed them.

More suggestions were offered:

- Dr. Brady commented that the responses to these initial enrollment questions are likely to change over time (e.g., alcohol use, physical activity, living with parents). ATSDR might consider an annual re-administer of the more dynamic baseline variables. Dr. Nelson agreed to that, for other than the subset of “immutable factors” that are unlikely to change.
  - Dr. Gibson supported this as a way to create a more dynamic history as the disease progresses.
  - Dr. Kaye felt that quarterly updates of disease progression probably could be done after the patient is in the registry for a certain period of time. The program is sufficiently flexible to allow re-entry to the patient’s queue at a scheduled time, to check either “no change”, or to fill in specific changes, such as a family history update. Upon registering, the patient can check a box allowing the registry administrator to directly communicate with the patient, although how many have done that to date was unknown. Dr. Kaye thought that at least 50% of those joining the registry were completing the surveys.
  - Ms. Kennedy re-emphasized the quarterly feedback loop as the route with which to link the QOL data back to the day of diagnosis.
- Dr. Brooks asked about the possibility of exploring factors such as foods in the diet containing glutamate. These investigations would be more hypothesis-generating; as there would be no direct control group, but there may be complementary data from historical control groups. Dr. Nelson responded that, when possible, questions are selected from national probability samples. But diet is hard to explore well in <98 questions, except perhaps for very specific aspects (e.g., estimated total kilocalorie intake and adjustments for micronutrients). But again, there is the survey time burden, as well as such confounding factors as disease progression that impedes swallowing. Dr. Weisskopf added that study findings from diet history report data are heavily affected by recent diet and have raised questions of reliability.
- Dr. Sinks commented that it would seem that one of the goals of the survey data would be to plant a seed that enables other researchers to score higher on NIH-funded research to do the more detailed work. Because there is a balance

between putting everything possible into the surveys and the burden on the patient that comes with that versus trying to encourage the use of this registry as leverage for funding very targeted, well done research on for example diet or military history or other things.

*Scope of study.* Dr. Horton appreciated this discussion. Although ATSDR certainly wants to learn all it can, he paused to consider the ALS patients, and asked if it was necessarily good to develop yet another questionnaire and 1 million data points for them. Or, should CDC/ASTDR consider being somewhat selective?

- Mr. Gibson and Dr. Brooks reported hearing the opposite. Patients are surprised that more information isn't requested.
- Dr. Bradley agreed and pointed out that patients would welcome feedback which would let them know how they are doing as compared to other patients. The feedback would also enhance the patient's desire to take part in the registry surveys. He asked if there are plans for ongoing analysis of the information that could be passed back to the patients, which could be a part of primary research. Dr. Horton indicated that this is the direction that the registry is headed in. He thought that it could possibly be included in annual reports after the first year, when the data's completeness is verified. While OMB and IRB issues prevent releasing the raw data itself, it can be shared in the aggregate.
- Dr. Williamson said that along with the initial data collection, ATSDR will consider what the detail of the registry's standard reports should be, as done for the WTC registry's now-regular reports. That reinforces the need for many people to enroll and the need to convey the registry's value to them.
- Dr. Brooks cited the epidemiologic importance of social networks (e.g., the benefit to cancer patients who have friends with cancer; the longer survival rate of those married, etc.). He asked if non-genetic relationships such as friendships could be examined. Dr. Nelson thought so, in the sociodemographic status survey.
- Dr. Bruijn described the data release of other genetic data sets, such as NCI's (i.e., the data are requested, vetted, the project is reviewed and described), and asked about the ALS process. Dr. Horton expected a standardized application process by researchers, who receive de-identified data after a review board's approval. That will be clarified before the registry's clean data are ready (~1½ -2 years).
- Ms. Kennedy appreciated the current strong enrollment but urged a greater outreach for partnerships with the clinical and research communities, so that clinicians suggest enrollment to their patients. One incentive might be to provide maps to show clinicians how their patients compare to others; another could be

to have different website tabs for clinicians and patients. That makes the site accessible to all and increases transparency.

- Dr. Horton reported discussion of posters for physician offices. CDC/ATSDR will provide as many materials as desired and that best reach patients and physicians. Attendance at relevant conferences is one way the agency is starting to engage physicians in a dialogue, along with an established connection with the American Academy of Neurologists.
- Dr. Bruijn suggested crafting a standardized message to emphasize the importance of the research to the clinicians.
- Dr. Nelson asked if this registry would have enough clinical data, even self-report, for researchers, since the registry does not contain medical records. Dr. Kasarskis acknowledged that the gold standard is to have medical records; however, the registry's filtering questions will capture a lot of the positive patients. Some validation of true cases will come from following the ALS functional rating scale changes, which have been very well validated and should reflect some deterioration over time. For example, clinical drug studies look for a number of set points of progressive deterioration at an average annual rate of 1.5, as was seen in the VA registry (not yet published) and in clinical drug studies. Of course there will also be some patients that are very slow in their progression, which may be contaminated by people who have PLS or some of the minority difficult cases.
- Dr. Brooks noted patients, such as those on the website Patients Like Me, like the ability to list their symptoms/details. He thought the first symptoms and current symptoms to be the most important data to gather.
- However, Dr. Brady reiterated the OMB's concern about the burden. However, it could be reported to OMB that this is a very engaged, highly invested/involved population, in which 47% of those contacted are willing to donate their brain/spinal cord and are willing to spend extended time (e.g., a half-hour) on the phone with researchers.
  - Ms. Kennedy warned, however, that increasing the burden also skews the population that will complete the surveys; a fine balance is needed. Mr. Dumas agreed. He suggested the registry send quarterly update requests of changes/improvements to the patients.
- Dr. Kaye asked the panel's opinion on what the upper limit of the burden might be. The reason it was modularized was to allow data entry at the convenience of the person with ALS. When the next OMB submission is due, ATSDR will recontact this meeting's participants to see if they still wish to provide input to



OMB that supports the motivated ALS population is willing to do more, that is accept more burden.

- Dr. Kasarskis suggested the agency advise new registry enrollees that in coming months, they would be asked to fill out extra modules. That would prepare them to gather their information on personal history aspects as well as allow them to be surveyed in a more paced fashion. The first survey would gather basic demographics, after which they would receive a note of thanks. Without disclosing what the next module would be, they would just be asked to gather types of information (e.g., family history). That would also improve the data quality
- However, Dr. Brooks reported that Web MD's similar test found that the respondents hated the iterations.
- Dr. Kaye stated that CDC/ATSDR will know when the patients start and finish the survey and how they complete it (all at once, in portions, etc.).
- Dr. Horton could see, from the ALS patient's perspective, the value of receiving an alert about future questions. Dr. Kasarskis indicated that the burden on the patient is part of the concern, but data quality also needs to be considered. He pointed out that if the patient is made aware of the survey subject area in advance, he/she will have the opportunity to gather information to more accurately respond. Dr. Williamson added that the patient can save their data and revisit the site to update or change information, and Dr. Muravov reminded all that upon registering, the person sees the modules available.
- Sharon Matland commented that since we do not know what the burden is and how persons with ALS are going to feel about the number of questions being asked, pending feedback, shouldn't we simply begin by seeking the information needed by researchers and see what the feedback is and then make adjustments as needed?. Ms. Kennedy responded that there are other experiences of ALS data collection, from other resources such as ALS Care, that provide information regarding the attrition and response rate so that we can learn from their experience.

There was general agreement to Dr. Bruijn's suggestion that the survey add a question about the site of onset. In fact, Dr. Nelson hoped for an entire clinical module, developed with the neurologists at this meeting. Drs. Bruijn and Kasarskis agreed, endorsing an additional link to others such as Coriell, whose clinician's survey also could be done by patients. Dr. Bruijn noted that the NIH/NIAIDS common data elements for ALS will be released in spring 2011. Those for this registry should be comparable.

Dr. Weisskopf knew that the lack of a comparison group would be an ongoing factor in collecting neurological information pertaining to risk factor incidence. However, he

expected that the disease progression and phenotypes involved could be examined just by looking at these cases alone.

### **CDC/ATSDR World Trade Center Registry**

*Presenter: G. David Williamson, PhD; ATSDR; Director, DHS*

Dr. Williamson commented that all registries differ based on the reason they were established. The World Trade Center (WTC) registry, for example, will require at least 20 years of follow-up to evaluate the expected respiratory outcomes related to 9/11 exposures. However, some process-oriented aspects can be modeled between registries. In the WTC health registry case, the biggest obstacle was gaining participant buy-in, because those impacted by the towers' collapse wanted *treatment*. The registry had to be identified as providing service that is complementary to the treatment. The ALS registry is somewhat similar; it will provide service to many for many reasons.

In some cases, it takes a long time to establish a registry. The WTC registry began in 9/11/03 – 2 years after the event; and it took another 2 years before it could begin issuing data regularly. The lessons learned by ATSDR to date inform how to continue engaging with people, getting them to continue registering and neurologists to continue to promote the registry. The WTC registry required coordination with the labor unions.

Dr. Williamson emphasized that the most important aspect is the engagement of people like those at this meeting *all*, not some, of the time, as their expertise provides the ideas for which ATSDR can then provide processes.

### **Promotion of the National ALS Registry (to patients and physicians)**

*Ms. Lisa Briseño, Health Communication Specialist, ATSDR Office of Communication*

Ms. Briseño provided an overview of the promotion process for the ALS registry. The input of the attendees to this very long-term project will be welcome.

*Activity to date:* The registry promotion plan's objectives are to inform key audiences about the registry and thereby maximize the number ALS patients joining. The agency has worked with the Rip Van Winkle Foundation to use the Lou Gehrig image throughout its communication materials. A roll-out strategic plan was developed that incorporates the communications plan to involve partners and key stakeholders, including those on Capitol Hill.

	The Past
	<b>The Present</b>
	The Future

## Registry Rollout

<p><b><u>Mechanisms</u></b></p> <ul style="list-style-type: none"> <li>❑ Press Release(s)</li> <li>❑ Social Media (Facebook, Twitter)</li> <li>❑ Advocacy Groups (ALSA, MDA)</li> <li>❑ Journal Ads (eg., Neurology)</li> <li>❑ Conferences (eg., APHA, American Academy of Neurology)</li> <li>❑ CDC/ATSDR Websites</li> </ul>	<p><b><u>Products</u></b></p> <ul style="list-style-type: none"> <li>❑ Factsheet</li> <li>❑ Trifolds</li> <li>❑ e-Button</li> <li>❑ e-Card</li> <li>❑ Videos</li> <li>❑ Webinars</li> <li>❑ Promotional giveaways</li> </ul>
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Patients are the primary but “audience” also includes family members, advocates and support groups, specialized healthcare providers, and researchers engaged with patients.

### Tactics

- The patient guide has photos, in addition to Lou Gehrig, of persons who could have ALS. The text is written so as to be easy to understand and share with many backgrounds.
- Partnerships are needed for outreach. While informal, these have been important with the ALSA and MDA. Both have been very cooperative in sharing information about the registry with their constituencies (e.g., website links to the registry portal).
- Emerging media is also used: Facebook, e-cards, Twitter, etc. One Tweet was sent to 64,000 followers.
- Media targets include the traditional media (AP, CNN) and specific media (e.g., consumer magazines targeting those aged >50, such as the AARP’s and professional publications), as well as conference attendance and issuance of letters, fact sheets, posters, etc.
- Direct outreach to patients/neurologists, researchers, etc. was illustrated in an outreach summary matrix. On this, the top row represented the audiences, and those below represented the outreach route (e.g., emerging media like the e-

card). Posters and exhibits can be modified for the specific audience. Web content can be broad to meet patients' interests (e.g., clinical trial information). An article is in development for the CDC community and its contacts throughout the media world, and another article on the registry was featured on the CDC.gov front page.

CDC staff members have met with members of the media, press releases have been issued, and direct contact has been made with some reporters following ALS stories.

### *Discussion*

- YouTube's two videos (not created or produced by ATSDR) about the usefulness of ALS registry and its importance are part of ATSDR's outreach. Dr. Brooks found these to be very important and encouraged ATSDR to emphasize them more.
- Ms. Kennedy applauded the work done to date. Both the MDA and ALSA sites have the link button for the registry, but it needs to stand out more. Since the Lou Gehrig image is often used, perhaps ATSDR should "freshen" it occasionally so it is not overlooked. Another suggestion was, like Facebook's "I Voted" upload to individuals' pages in the recent election, they could do so to indicate they had registered on the ALS registry. Ms. Briseño agreed; and asked if a physical sticker for conferences ("I told someone about the ALS registry") and for patients' use would be helpful. Mr. Dumas said yes. It gives the patient an opportunity to give back, which many wish to do, and could influence hesitant patients to register. He also encouraged outreach in clinics and referral centers, etc., to promote the registry's value (i.e., the quarterly updates, patients' opportunity to make friends with other patients, etc.).
  - To cultivate relationships with patients, for example, Mr. Wildman reported an email issued on this morning. It was written by a patient on why he registered, is involved in the registry, and encouraging others to enroll. The value of such stories was generally agreed upon, especially to involve patients before the disabling stages of the disease.

Dr. Horton reported CDC/ATSDR's consideration of hiring a public relations firm to help ATSDR get the message of the registry out to key channels and gain more attention. Responses included the following.

- Dr. Kasarskis compared this effort to the experience of some VA patient support groups. The 1600 now in the ALS registry are those primed to participate. But like their support groups, some just won't participate because it doesn't fit into their worldview. He wondered if there was a way to gain insight about those not registering despite all outreach. That was part of the reason he suggested iterative modules. As they approach this illness, patients go through phases. There is an average 9-10 months between onset and confirmatory diagnosis and, by the second opinion, many are angry with physicians. Then they mourn the

diagnosis and are disengaged. Then they get proactive until the illness progresses and they are overwhelmed by the care needed. Attention is needed to those timing intervals in engaging people. Dr. Bruijn thought the voluntary health organizations might be able to help in this.

Dr. Horton asked how to determine how people found out about the registry. An informal poll on the portal, perhaps by ALSA and MDA, was discussed (e.g., referred by a friend, ALSA, MDA, etc.). While not scientific, it would serve as more of a benchmark to inform marketing efforts.

- Dr. Bruijn suggested measuring the number of clicks on the icon.
- Ms. Matland noted that the chapters also can be involved, to inform and engage people in the registry, to survey people about their knowledge of it and whether they are enrolled.
- Dr. Horton offered ATSDR's standardized language for posting on the ALSA and MDA sites, as well as drop in newsletters.
- Other opportunities: (Dr. Weisskopf): the 2009 CDC-major league baseball partnership on TV featuring Lou Gehrig; (Dr. Horton) CDC's Office of Communication has worked with MLB and the NFL to get the ALS message out; (Mr. Wildman) all the ALS chapters have walks and other relevant promotional activities. The chapters are encouraged to bring laptops to meetings and clinics to educate the patients and promote the registry.
- Dr. Kaye commented that realistic expectations are necessary. It would be lucky to have 50% participate. The consistent 5-10% of those uninterested will probably not be convinced. Given that, Mr. Gibson wondered if a PR agency would be effective. He believed ATSDR could more effectively work with the MDA, ALSA and their chapters and clinics to get the information out. At the least, hopefully, patients would be aware of what's going on and perhaps the AP would pick up the story from the wire.
- Ms. Briseño reported discussion with ALSA and the MDA about doing formative research with ALS patients, based on their experiences and information. But that cannot be done directly with patients; the amount ATSDR can reach out to them is limited by government regulations about contacting people.
- Dr. Bruijn commented that the difficulty in making the registry a big media splash is that it is a useful tool, but not a result. So, opportunities such as with CNN on Veterans Day to discuss a study that could link veterans and health are valuable.
- Ms. Matland agreed; one size doesn't fit all. But the information needs to get out, and having people who can tell the story is a compelling vehicle. She would identify the first audience as the ALS patient and the second as the researchers,

for the end-user perspective. She also suggested posting the email received this morning from the ALS patient on the site. Ms. Briseño agreed. People with ALS want to hear from other patients.

Mr. Gibson summarized that the primary audience is the ALS patients to enroll them, using the available networks at “full throttle” for the next 6-9 months to get the word out. The more that is done, the more press; but first, the focus is on the patients.

Dr. Horton asked what percentage of ALS patients the MDA and ALSA cover and Ms. Kennedy answered at least 80%, perhaps 90%. Most patients come to them or their clinics. So again, she reiterated the need to reach out to clinicians, hospice workers, etc., to involve them in developing responsive strategies (e.g., with a website tab for clinicians and another for researchers).

Dr. Horton responded that the new website template will have buttons for clinicians and patients. With their, MDA’s and ALSA’s, high capture, it seemed that organizations rather than a PR firm were the most likely route to take. But, he asked, how could ATSDR/CDC find those not involved?

- Mr. Kingon suggested that formative research could be done by the partner organizations. Drs. Bruijn and Gubitza advocated for a feedback link beyond that on the website’s front page, to add ones for clinicians, patients and researchers.
- Dr. Bruijn observed that the NEALS and WALIS consortia are strong potential partners to advertise the registry. Outreach also could be done to people looking to participate in clinical trials.
- Dr. Muravov reported his and Mr. Dumas’ discussion about developing a video for ALS patients. Additionally, the American College of Neurology’s public relations firm is willing to provide the names and addresses of their 22,000 members in the U.S. A sidebar about the registry launch also was inserted into their Neurology Now newsletter, published this month.
  - Mr. Wildman suggested developing a checklist for the chapters and provider communities about what can easily be done for ALS patients, supported by a list of the tools to help them.
  - Currently, the ATSDR website offers PDFs of their materials, and the agency will provide as much as is wished. Perhaps an “Order Now” link for bulk orders could be placed on the website.
  - Dr. Boylan suggested linking to the state surveillance projects that work with clinicians, for help in raising awareness, especially among less Web-savvy patients, or those attending ALS centers or support groups.

- Dr. Sejvar reported that recently completed Guillain Barre surveillance linked to influenza immunization was aided by the AAN and their support groups. A subset was pursued through neurologists as well.
- Mr. Dumas noted the ALSA and MDA walks scheduled this weekend in Atlanta. The walks provide good exposure opportunities if people are present to answer questions and promote registry enrollment. Mr. Gibson agreed to the power of the walks as tools. Every chapter has an advocacy booth there and ALSA provides a walk “map to the cure” about things that can be done. Mr. Wildman said there is a toolkit for the walks, one component of which is the registry. They also provide the chapters with talking points about the registry at the walk’s kick-off.
- Ms. Kennedy suggested that CDC ask the organizations for a list of those to whom the CDC warehouse should send the ALS materials. Other than walks, they have seminars, forums, etc., where they can disseminate information.
- Mr. Kingon suggested attention to engage CDC’s larger partnerships in state/local health departments.
- Mr. Gibson added that other government partners, such as those providing early Social Security or VA benefits, etc., could be valuable in distributing information. ATSDR itself also can develop a plan for opportunities in the near future (e.g., international association meetings) to target.

Dr. Horton reported consideration of work with the AARP, which represents the age group of many of those diagnosed with ALS, to provide materials or drop in an article for their publication. Dr. Bradley reported having been at the Orlando AARP meeting, which include the Dana Foundation’s Healthy Living program, which presents to AARP annually. He offered to provide that information to Dr. Horton.

### **External Organization Activities Supporting the ALS Registry**

- Dr. Brady suggested linking those who have signed up for NIH publications on multiple topics of senior health to the registry. Dr. Gubitzi agreed to talk about that with the Office of Communications and Public Liaison at NINDS, the NIH lead Institute for ALS.
- Dr. Nelson suggested snowball sampling. Dr. Horton said that can be done with the e-card, which can be sent to 20 people. Dr. Kaye thought that some ways may be more effective to promote e-card use. It is now on the front page, but might be more effective after registration (i.e., “I’ve registered; thought you might be interested.”). Briseño agreed, adding the idea of an e-card to be sent to caregivers (e.g., “Thanks for the job you do.”)

- Dr. Horton liked the “I Voted/I Registered” idea, so long as it is consistent with IRB and OMB policies.
- Dr. Kasarskis appreciated the good suggestions made, but noted the potentially low return for the effort. Ten conventions of 10,000 people would have to be attended to find one case. The messages should be issued in such venues, but he advocated first inculcating the registry into the normal activities of the ALS centers. The priority should be on places where ALS patients are seen weekly as a normal activity, to encourage people (perhaps with a computer onsite) to visit the registry site. Those practitioners are where the “mother lode of patients who are true ALS cases”. Further, ongoing refreshment of the process has to be done with clinicians, to make promoting the registry the same routine as getting vital signs or educating about clinical trials. ALS Cares failed due to its large burden on the clinician (10-15 minutes to fill out a form, as related yesterday, with no credit on a publication, declining billing hours, etc.). But if clinicians need only to *facilitate* the patient’s entry, that could be done. A one-time splash such as might be done by a PR firm will be much less effective.
- Dr. Bradley agreed, also suggesting feedback to the referring clinician to keep the momentum going. He noted that most neurologists (95%) are members of the American Academy of Neurology (AAN). Mr. Gibson emphasized the need to partner with the AAN.
- Dr. Brooks noted that the stroke community’s success stemmed from a “Get with the Guidelines” registry as part of recertification. Also noteworthy is that those registered there do better than those who don’t.
- Mr. Wildman agreed. Part of the registry’s intent is to take the burden off the practitioners, to simply pass the news along to the patient. A checklist for neurologists was developed and for chapters particularly, to just ask “Is the patient enrolled in the registry?”
- Dr. Kasarskis noted that the ALS centers’ neurologists have a lot of authority with the patients who present there for advice and guidance, to find out their status and what will happen to them in the next 6 months. Participating in such multidisciplinary clinics has been shown in Europe to extend life by a year and a half (and importantly, all in the studies involved a registry). That success likely stems from guidance given in an organized way. Part of that guidance is to reinforce the importance of this registry to build a research infrastructure engine to address the questions patients already have. The primary care physician and first neurologist had not identified the disease; the patient comes to the center to confirm what all had been done before. That sets up the clinic’s authority to support this effort; and that is where “the bang for the buck” is.
- Ms. Kennedy stated that the MDA covers a number of diseases, all of which have at least one registry. Neurologists in their clinics see many patients and diseases.



The MDA has been promoting the Duchenne registry alongside the clinical trials. Feedback heard from neurologists indicates confusion about what registry to refer the patient to; whether it's private, who funds it, etc. One of the things that sets the ALS registry apart from all of the other registries is that it is the only ALS registry that is federally funded and whose data will be available in the future (and, Dr. Horton added, is congressionally mandated). That needs to be part of the message.

- Ms. Matland added the need to stress that registries are not cross-populated. It needs to be clear that to be part of this, an individual must register in it. Absolute clarity is also needed that its data will be de-identified before research use.
  - Dr. Sowell stated that, with a push from the ALS community as well as from researchers to allow names to be shared between groups, work can be done to obtain OMB/IRB approval. The support that both community and researchers want it is essential. Even absent that, there are intermediate mechanisms that may help, such as researchers stating specific criteria of people they want to involve. With IRB approval, they could contact those people about their interest in participating. No such mechanism to do this is currently available.
  - Drs. Gubitz and Bruijn agreed that that message needs to be issued. Researchers think this registry is being created to conduct clinical trials, so clarity about the goals is essential. Dr. Bruijn suggested putting that fact under the clinician/researcher tabs, with a feedback option.
- Mr. Wildman reported feedback to ALSA indicating that the patients want to provide more information to surveys. He suggested an open box at the end of the survey to allow that. Dr. Horton agreed that those stories are important for both the organizations and CDC/ATSDR to know. The organizations are creating that engine for the agency.
  - Mr. Gibson suggested also adding a box to indicate that the individual had a loved one who died of ALS, to defuse that issue.
  - Ms. Smith emphasized that the information should go through ATSDR, with their contractors reviewing the data to ensure that any inability to enter certain data isn't a software issue.
  - Dr. Horton stated that the organizations' feedback can be compiled and sent to Stanford for use in prioritizing the next module's contents.

Mr. Wildman asked about any potential of people without ALS to be controls, such as family members who lost a relative to ALS. Dr. Horton responded that such would depend on the study hypothesis, but this is public health surveillance. Control efforts would be in future studies, for which ATSDR could provide the numerator for the study.

## **Closing Comments**

- Mr. Dumas thanked all the participants for their interest in helping ALS patients. He was very touched by the meeting participants caring and appreciated being invited. Dr. Horton returned the thanks, as Mr. Dumas represented ATSDR's reason for doing this.
- Dr. Bradley had been involved in registries and databases in the past, but was impressed at CDC/ATSDR's very productive entrance to the field.

## **Next Steps**

Dr. Horton was happy the registry is launched, although it is not perfect, and he appreciated the feedback from meeting participants. Everything mentioned was noted, and the meeting transcript will be reviewed. The registry can be tweaked to reflect sensible suggestions. On behalf of ATSDR, he thanked the participants for their time and hoped for an ongoing dialogue; the ATSDR ALS group can be contacted at any time. ATSDR is committed to keeping the message going and developing good strategies to do so. Advice such as to not hire a PR firm, but rather to focus on MDA and ALSA to get the message out, was exactly what the agency needed to hear.

Dr. Kaye will send a copy of the meeting transcript for all to review, after which it will be finalized and posted on the website.

Mr. Gibson thanked ATSDR. He wryly commented that sometimes, working with the government is like making sausage. Now, after 5 years, a very good product has emerged. He agreed to the need to celebrate such a wonderful milestone and to work toward celebrating a cure. The next 9-12 months will be key to getting the message out and to involve people and CDC/ATSDR must not miss that opportunity. This is the time; the field is ready and ATSDR is ready. As Dr. Kasarskis had said, everyone here was critical to its success.

With no further comment but for CDC/ATSDR's reiterated thanks, the meeting then adjourned.

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