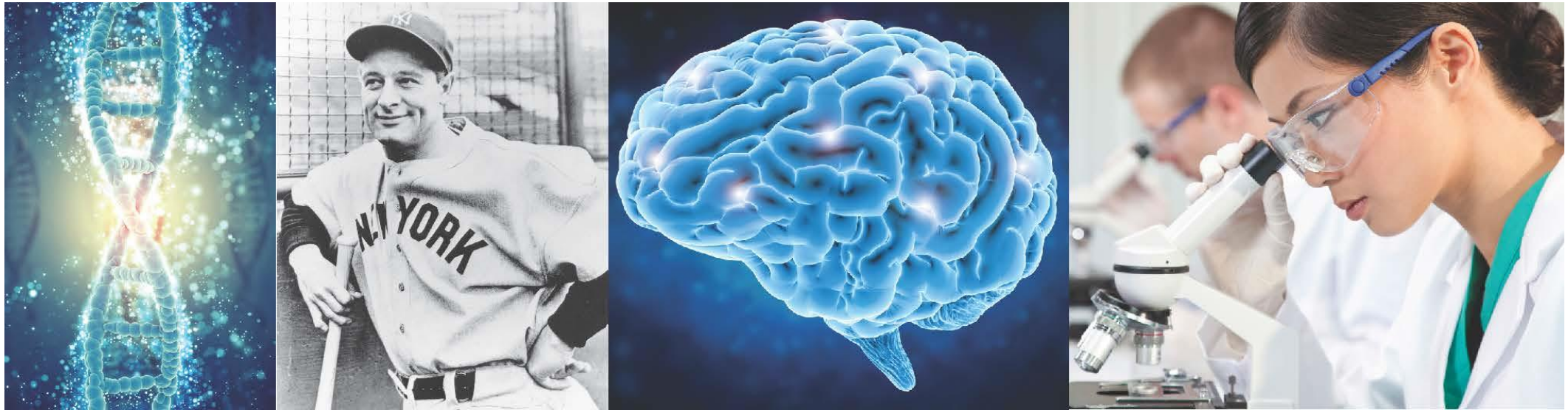
CDC PUBLIC HEALTH GRAND ROUNDS

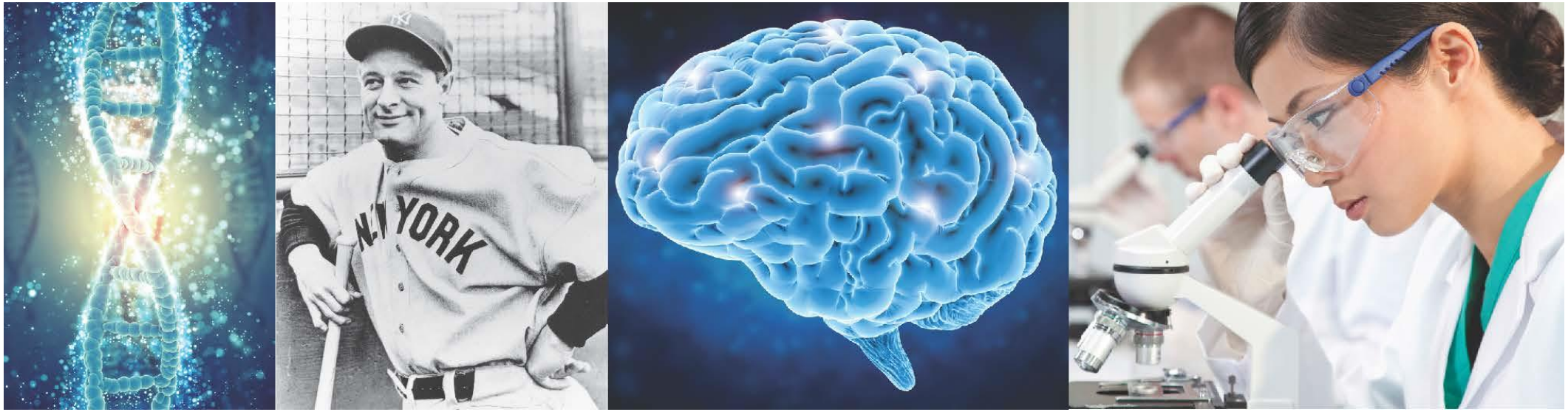
National Amyotrophic Lateral Sclerosis (ALS) Registry
Impact, Challenges, and Future Directions



April 18, 2017

U.S. Department of Health and Human Services
Centers for Disease Control and Prevention

Overview of the National ALS Registry – Past, Present, Future



Kevin Horton, DrPH, MSPH

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

What is Amyotrophic Lateral Sclerosis?

- **Amyotrophic lateral sclerosis (ALS) is a rapidly progressive, fatal neurological disease caused by the degeneration of motor neurons in the brain and spinal cord**
  - Approximately 80% of patients die within 2–5 years of diagnosis
  - 10% are familial cases; 90% are sporadic cases
  - No known cause for sporadic cases
  - No cure

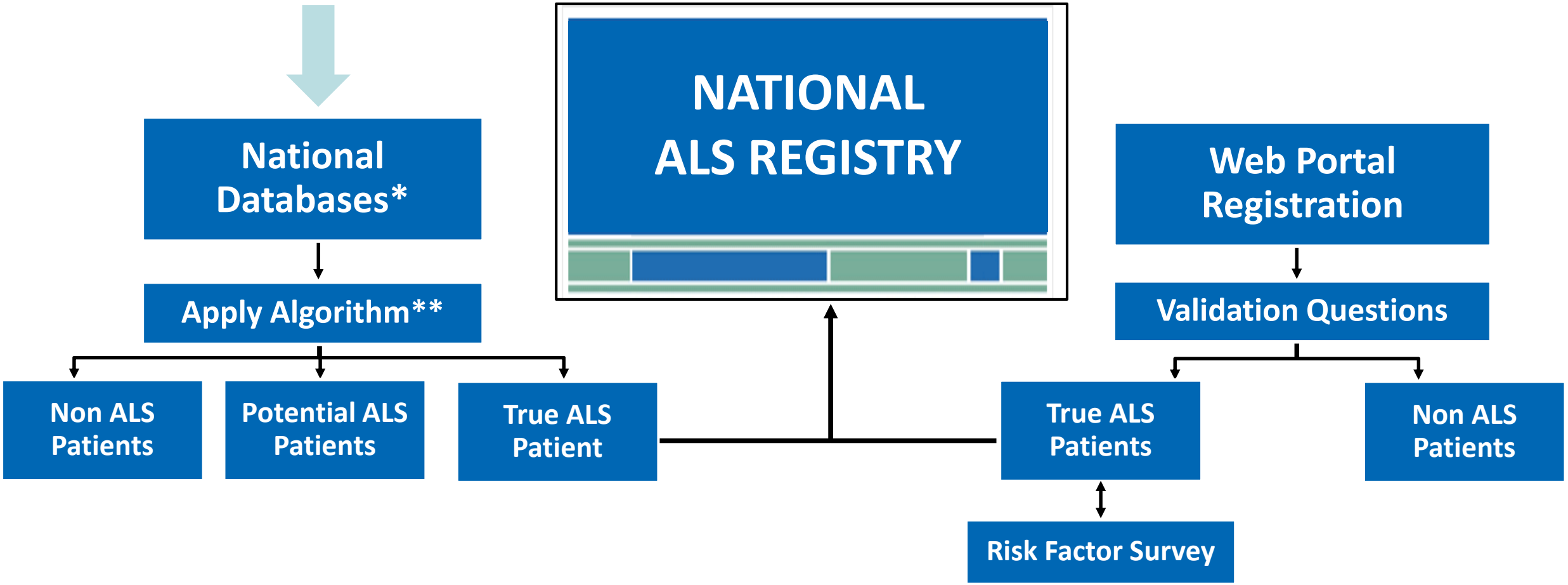
Public Health Surveillance Barriers

- **ALS is a non-notifiable disease**
- **Because of this, there is a lack of reliable incidence and prevalence estimates for the U.S. and by geographic area**

Need for a National ALS Registry

- **In October 2008, Congress passed the ALS Registry Act**
  - Directed CDC/ATSDR to create a population-based ALS registry for the U.S.
- **Registry objectives (as specified by the Act)**
  - Describe incidence and prevalence of ALS
  - Describe the demographics of ALS patients
  - Examine risk factors for the disease
- **Novel approach was needed to track ALS cases**
- **National ALS Registry was launched in October 2010**

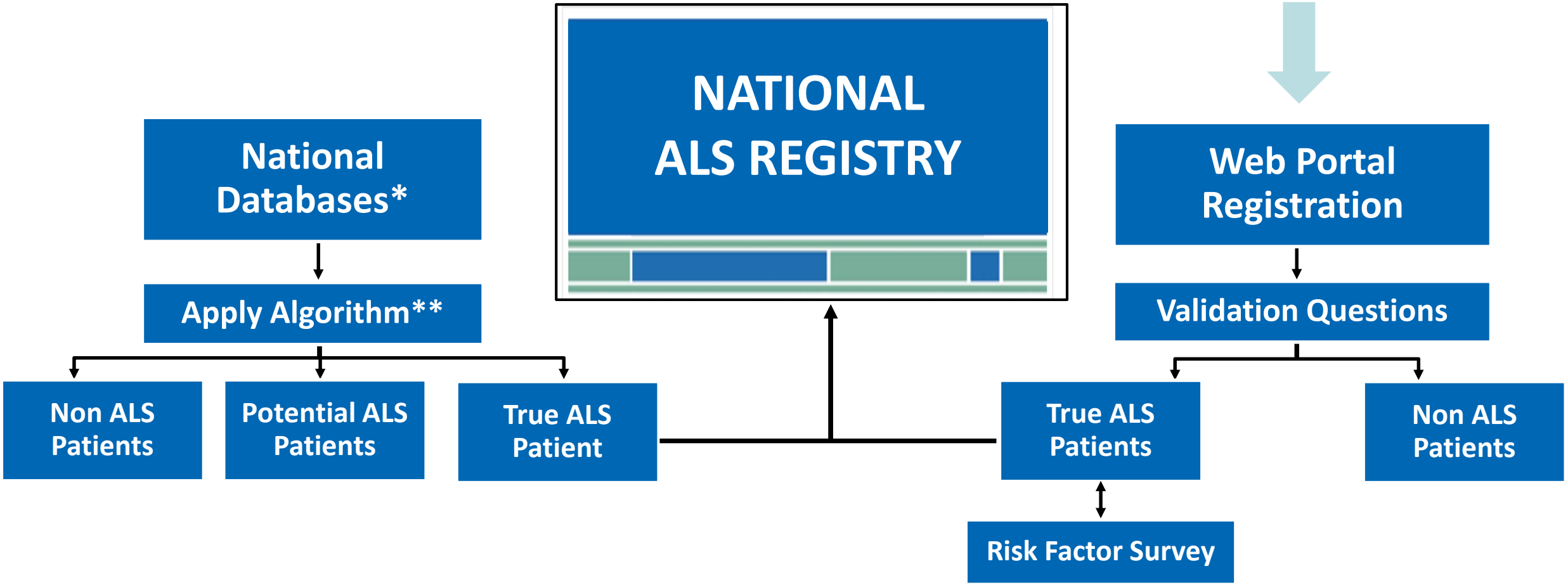
Overcoming Surveillance Challenges by Novel Methodology



* Medicare, Medicaid, Veterans Administration

** Algorithm: ICD code, frequency of neurological visits, Rx drug usage

Overcoming Surveillance Challenges by Novel Methodology



* Medicare, Medicaid, Veterans Administration

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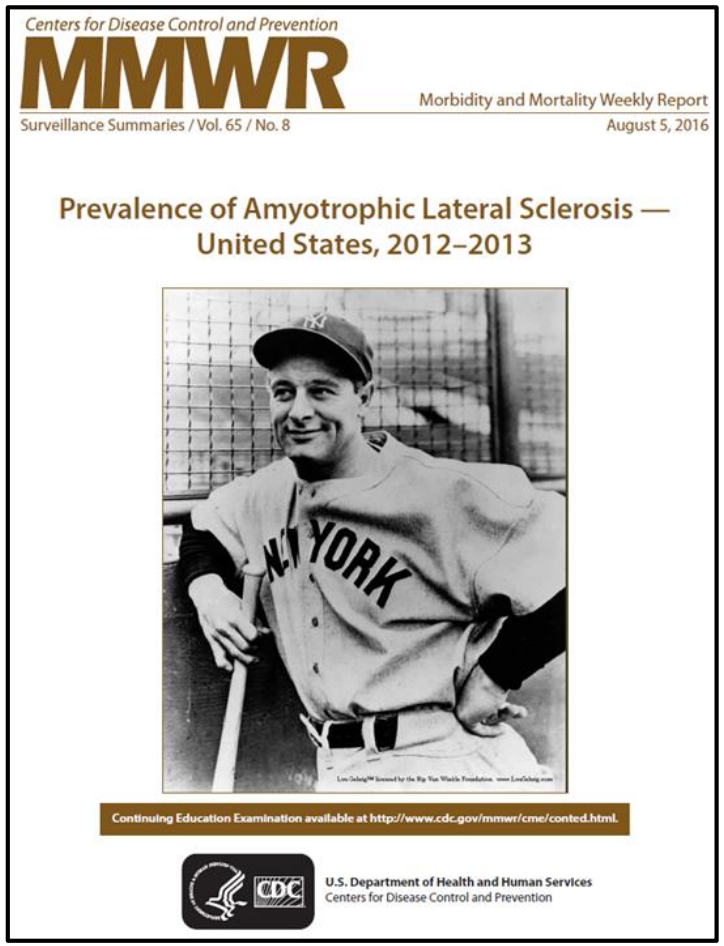
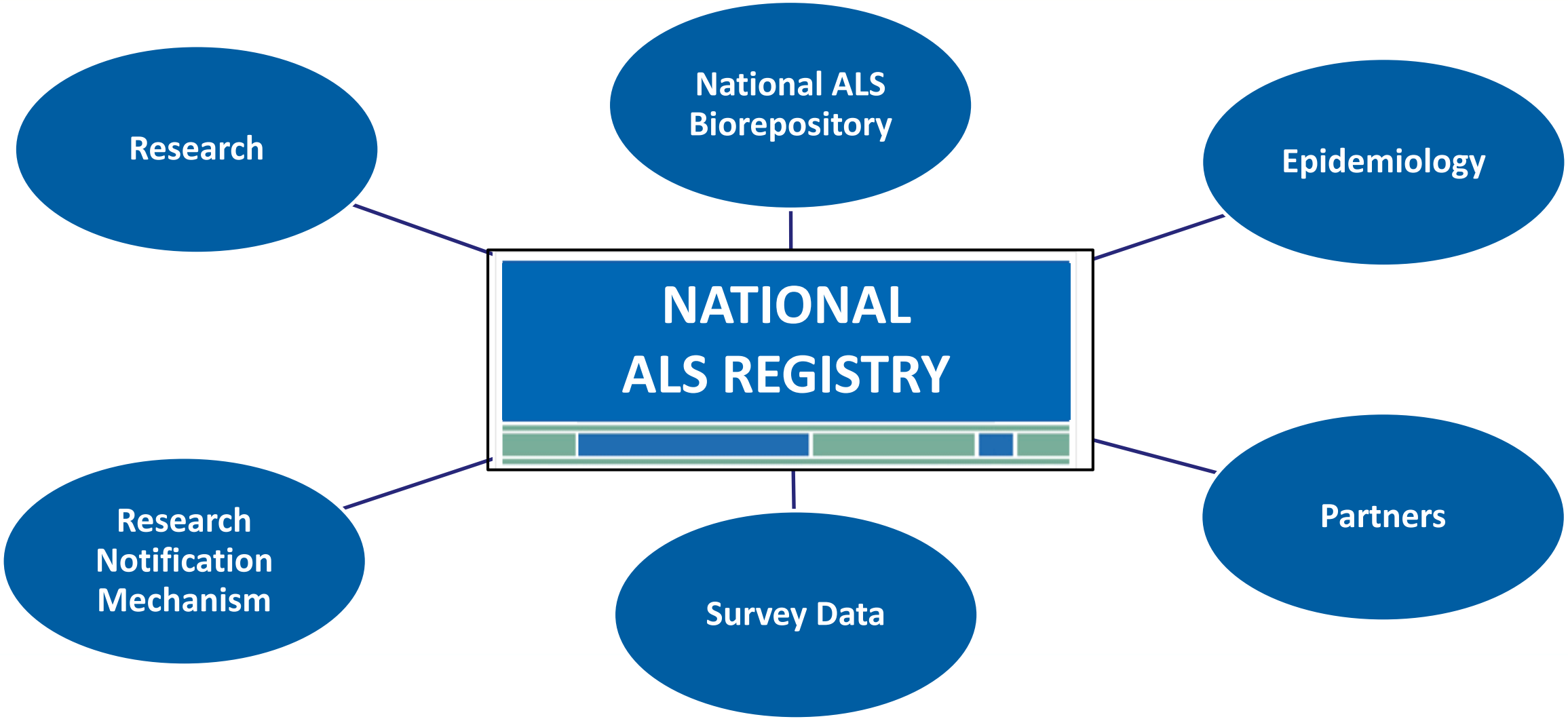
Sharing ALS Surveillance Findings

- **ATSDR publishes annual reports of our findings in *MMWR***
- **Our third report for calendar year 2014 is anticipated to be published later this year**

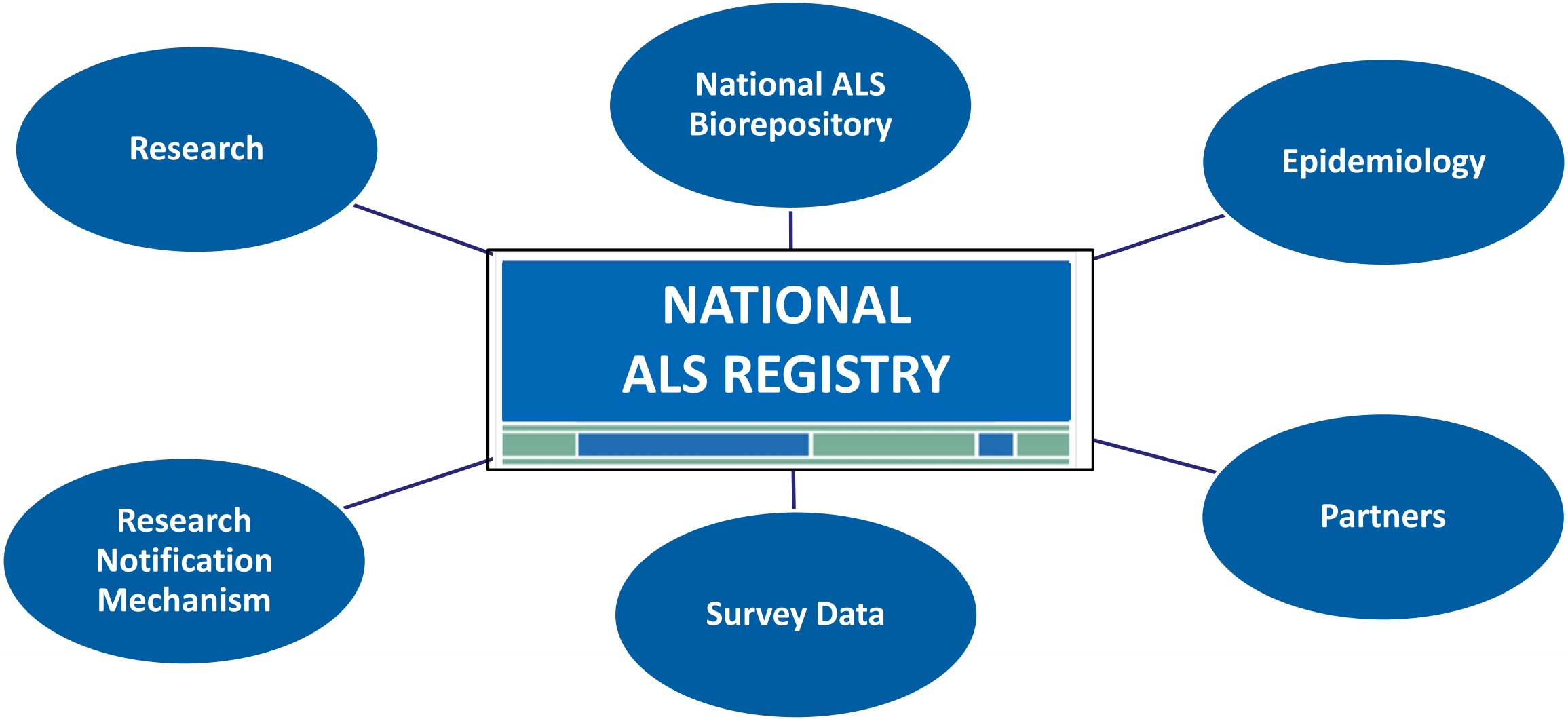


ATSDR: Agency for Toxic Substances and Disease Registry

Registry Does More than Just Count ALS Cases: Specimen Collection and Research Funding



Registry Does More than Just Count ALS Cases: Giving Patients Access to Clinical Trials



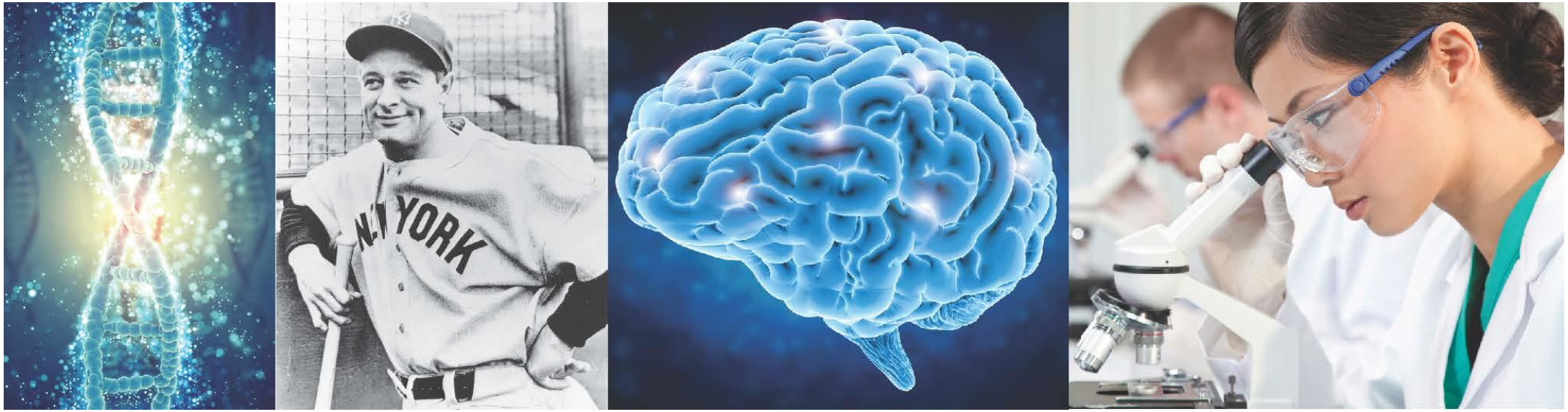
Registry Partners

- **Patients and caregivers**
- **National ALS patient organizations**
  - ALS Association
  - Muscular Dystrophy Association
  - Les Turner ALS Foundation
- **Healthcare providers**
- **Other federal agencies**
- **Research institutions (e.g., academia)**

Impact of Registry

- First and only population-based ALS registry for the U.S. that is quantifying the epidemiology of the disease
- Used as a recruitment tool for domestic and international researchers
- Awarding funds for external research
- Providing epidemiologic data and biospecimens to scientists
- Building the evidence to better describe the ALS experience in the U.S.

The Known and Unknowns about ALS



Paul Mehta, MD

Principal Investigator, National ALS Registry

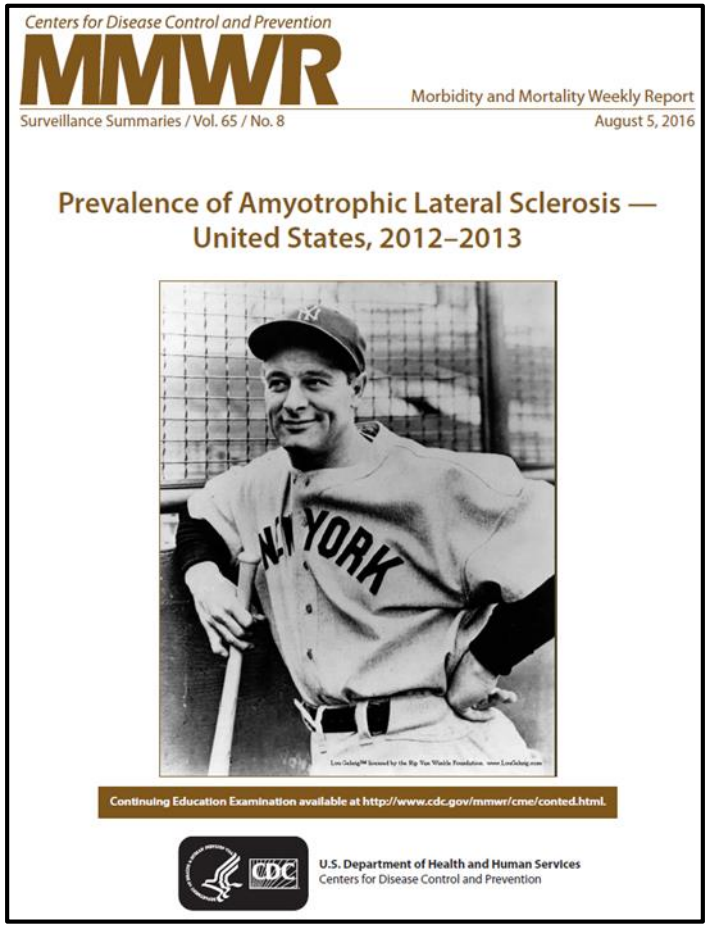
Environmental Health and Surveillance Branch

Division of Toxicology and Human Health Sciences

Agency for Toxic Substances and Disease Registry (ATSDR)

Epidemiology of ALS According to National ALS Registry

- **In 2013, 15,908 definite cases of ALS identified**
  - Prevalence rate of 5.0 cases per 100,000 persons



Mehta P, Kaye W, Bryan L, et al. *MMWR Surveillance Summary*. 2016;65:1-16.

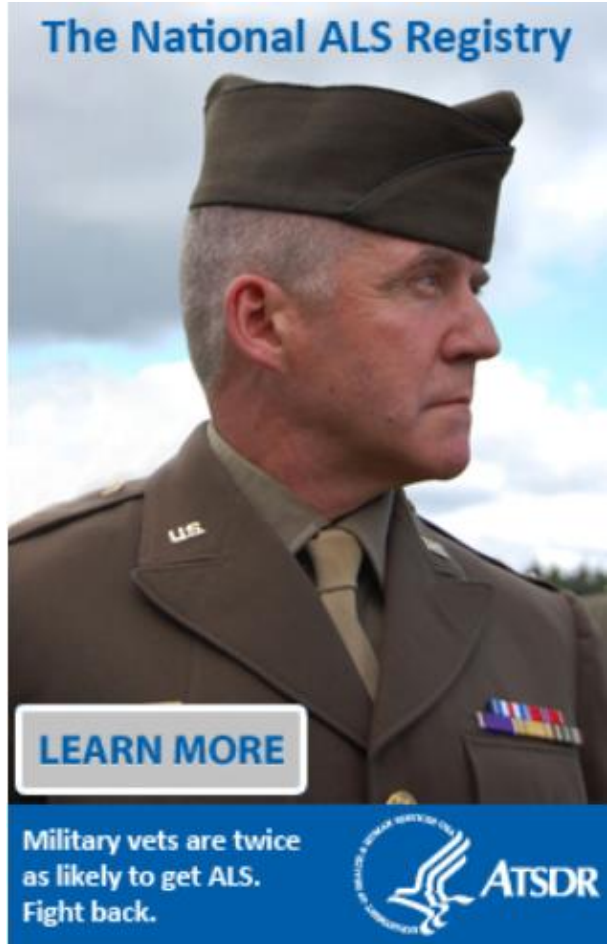
Epidemiology of ALS: Risk Factors

- **ALS is found to be more common in**
  - Whites
  - Persons aged 60–69 years
- **Lowest number of ALS patients among persons**
  - Ages 18–39 and >80 years
- **Males have a higher prevalence than females**

Mehta P, Kaye W, Bryan L, et al. *MMWR Surveillance Summary*. 2016;65:1-16.

Epidemiology of ALS: Increased Risk for Veterans

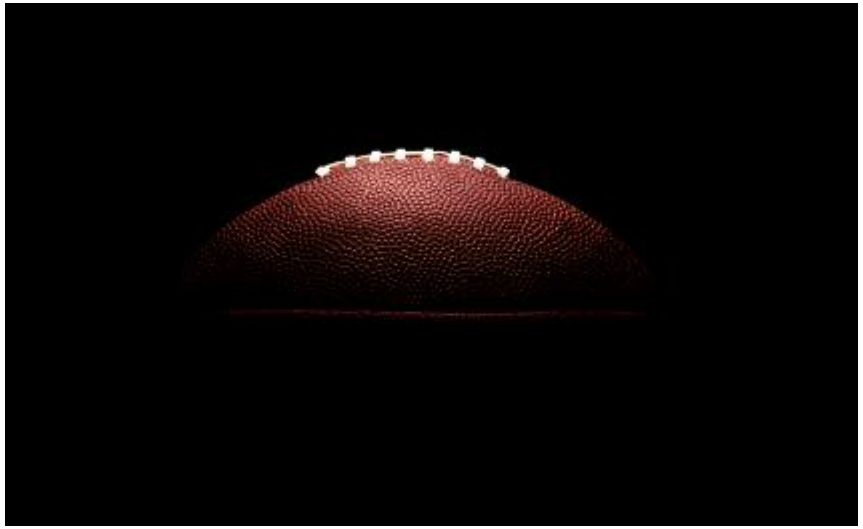
- **ALS and military service connection**
  - 50% greater risk of ALS than men who did not serve in the military
  - Military personnel deployed to the Gulf Region during the Gulf War (1990–1991) had double the risk of those not deployed to the Gulf Region
  - Possible link to environmental factors
  - More research is needed and is ongoing



Weisskopf MG, O'Reilly EJ, McCullough ML, et al. *Neurology*. 2005 Jan 11;64(1):32-7.
Horner RD, Kamins KG, Feussner JR, et al. *Neurology*, 2003 Sept; 61(6)742-749.

Epidemiology of ALS: Risk for Professional Athletes

- **ALS and football**
  - In one non-ALS registry study retired National Football League players were at four times greater risk of ALS
  - Need to confirm increased risk and better understand possible causes



Lehman E, Hein M, Baron S, et al. *Neurology*, 2012 Nov; 79(19)1970-1974.

ALS Disease Trends

- **National incidence stable**
- **Prevalence increasing slightly**
  - Patients living longer with comprehensive, multidisciplinary care
  - Registry capturing more cases, better case ascertainment
- **Additional years of data are needed to assess trends**

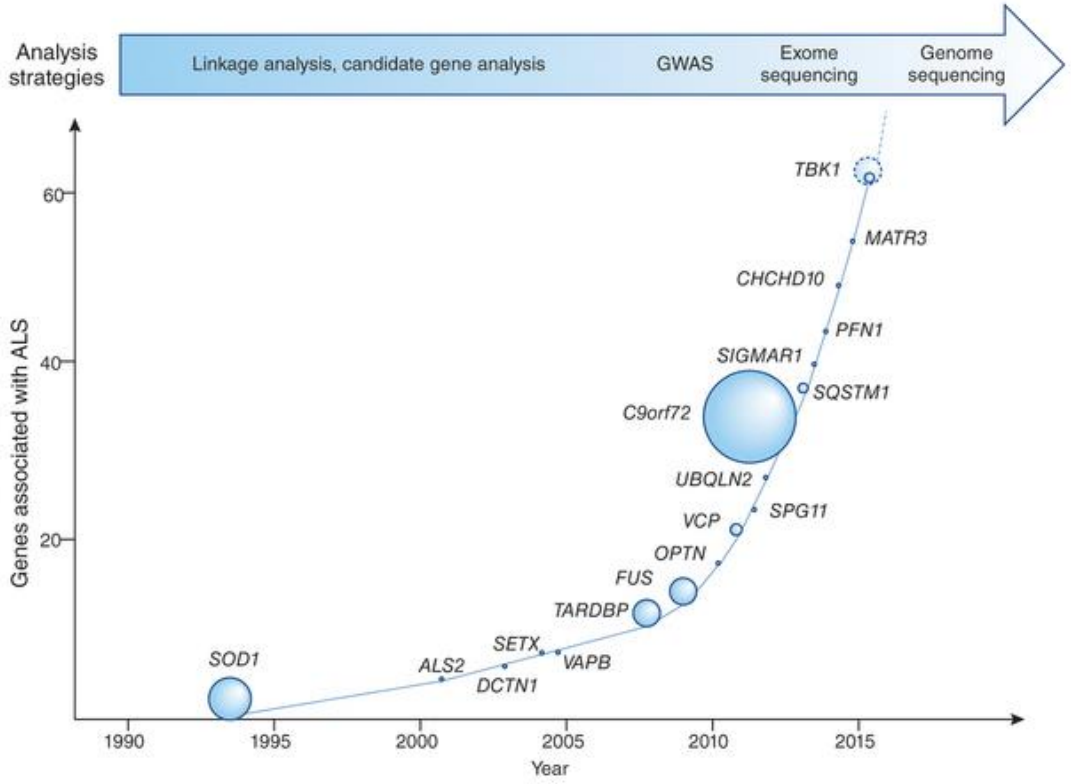
CDC, unpublished data

Causes of ALS Remain Elusive

Two type of ALS

- Sporadic (SALS): 90% of cases
  - Environmentally linked
- Familial (FALS): 10% of cases
  - Genetically linked
  - Genetic counseling available

Progress of Genetic Findings Related to ALS Etiology and Pathogenesis



Bettencourt C, Houlden H. *Nature Neuroscience*, 2015 Apr;18:611-613.
GWAS: Genome-wide association studies

ALS Registry Risk Factor Surveys

- **More than 60,000 surveys completed by more than 12,000 patients**
- **Further exploration of etiology and risk factors**
  - Demographics, environmental and occupational exposures

CDC, unpublished data

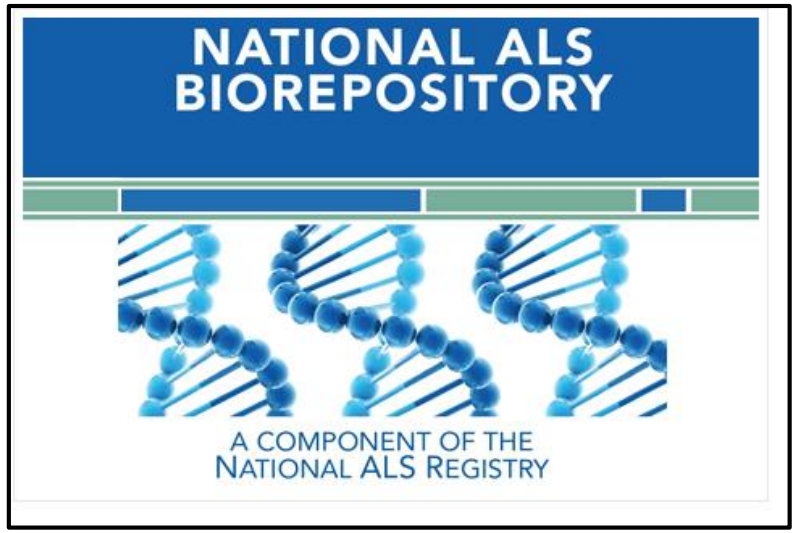
ALS Registry Risk Factor Surveys

- 17 surveys, taken by patients who enroll via the online portal
- Shed light on ALS causes and factors that may either be protective or contribute to disease onset or progression
- Topics range from demographics to smoking, alcohol, disease progression, and environmental exposures such as pesticide use
- One survey allows patients to state what might have caused their ALS
- Survey data are also available to external researchers

National ALS Biorepository

Component of the National ALS Registry

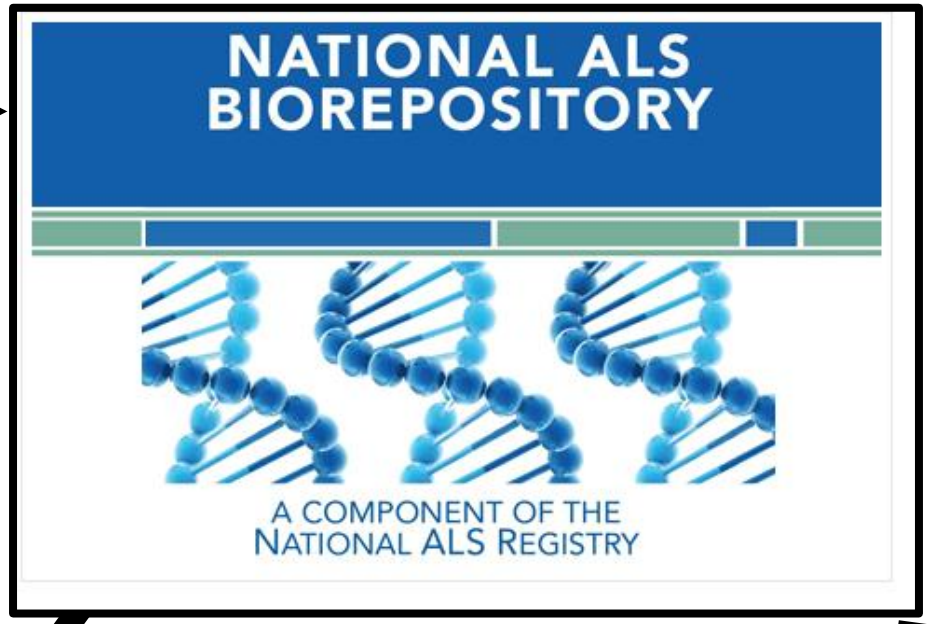
- Launched in January 2017
- Expand ALS research in biomarkers, genetics, environmental exposures
- Sample collection will be geographically representative



National ALS Biorepository

In Home Collections

- Blood
- Urine
- Saliva



Post-Mortem Collections

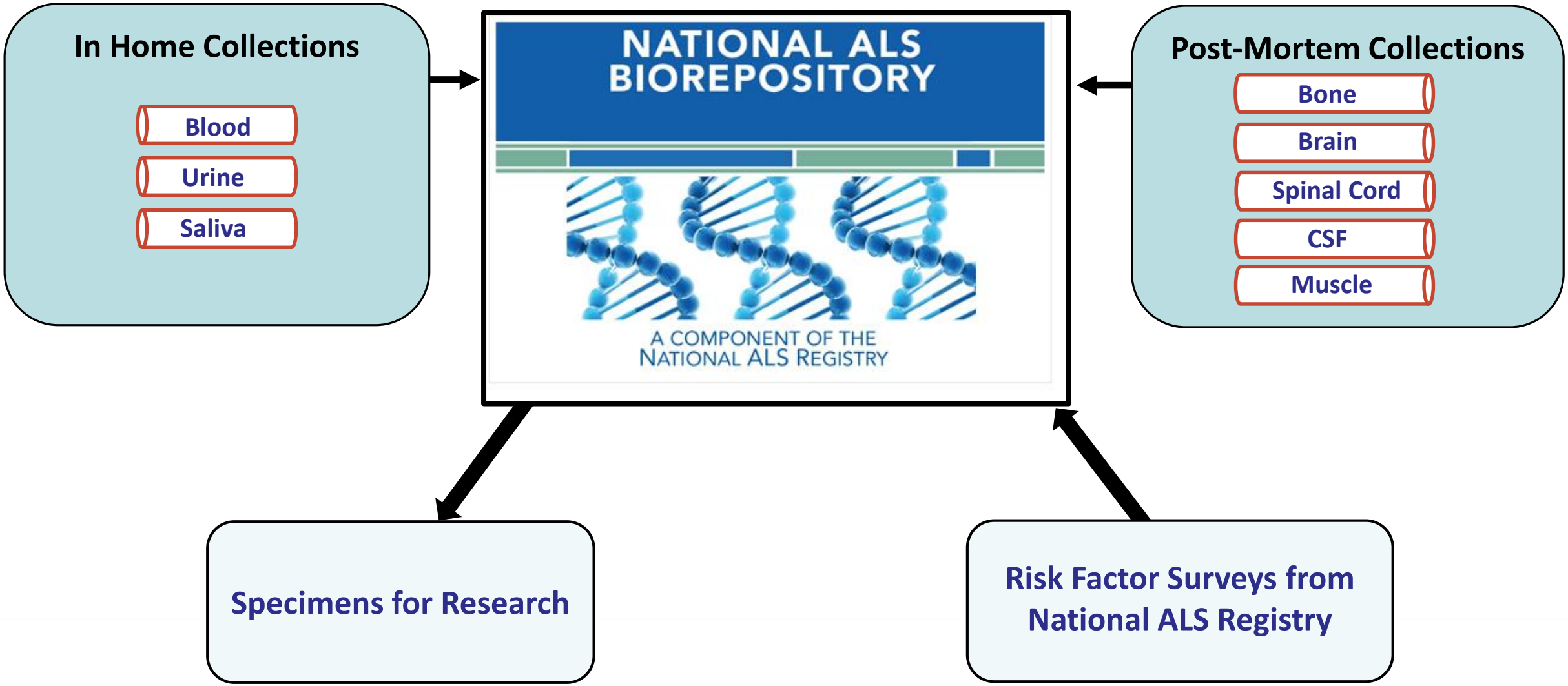
- Bone
- Brain
- Spinal Cord
- CSF
- Muscle

Specimens for Research

Risk Factor Surveys from National ALS Registry

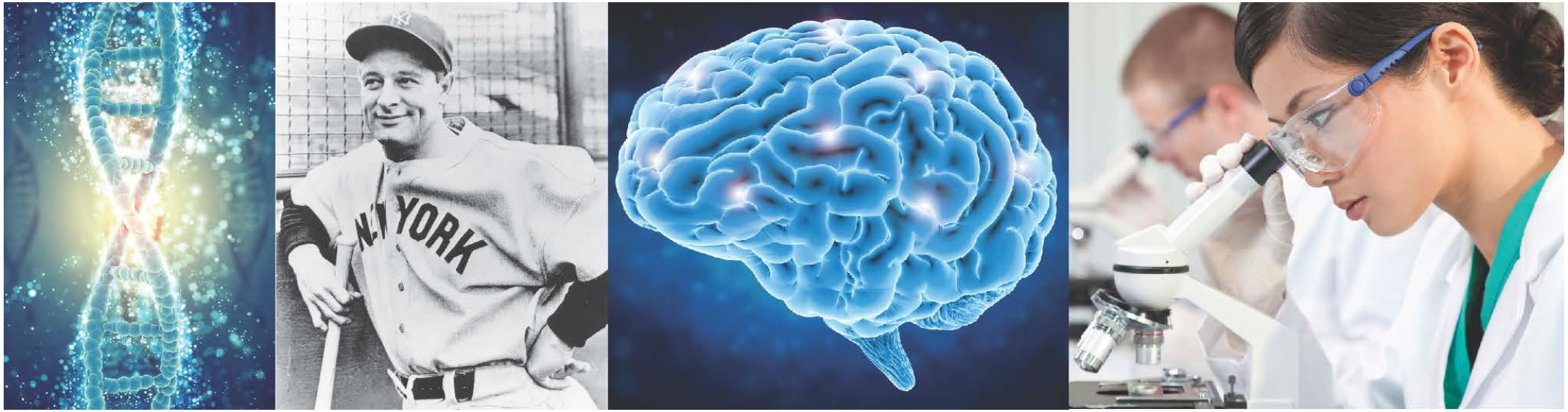
CSF: Cerebrospinal fluid

National ALS Biorepository



CSF: Cerebrospinal fluid

Challenges for Research, Drug Development, and Patient Care



Edward J. Kasarskis, MD, PhD

Professor of Neurology

Cynthia Shaw Crispen Chair for ALS Research

University of Kentucky, Lexington

U.S. Department of Health and Human Services
Centers for Disease Control and Prevention

ALS Shares Some Clinical Characteristics with Other Neurodegenerative Diseases

- **Alzheimer's disease, Parkinson's disease, and ALS are prototypical**
  - ALS presents with insidious rather than acute onset of neurological dysfunction
  - Neurological deficits are concentrated in certain realms
    - Alzheimer's disease: Cognitive and behavioral
    - Parkinson's disease: Slowed movement (bradykinesia) and tremor
    - ALS: Weakness of most voluntary skeletal muscles

- **ALS remains a clinical diagnosis**
  - No definitive imaging biomarker
  - No definitive blood or cerebrospinal fluid biomarker

Clinical Characteristics of ALS

- **Onset of weakness in one bodily region**
- **Progression and spread from one region to involve other regions**
  - 80% limb onset
  - 20% “bulbar” onset
    - Difficulty speaking or swallowing
- **Relatively preserved function of some muscles and other neurologic functions**
  - Sensation
  - Sphincter control (i.e., bladder and bowel)
  - Eye movement
  - Awareness, cognition, and memory

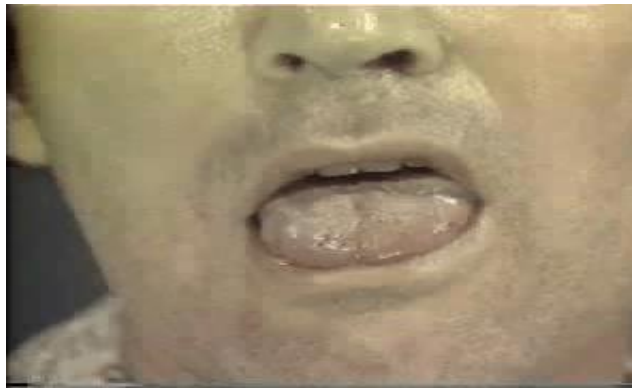
Clinical Outcomes of ALS

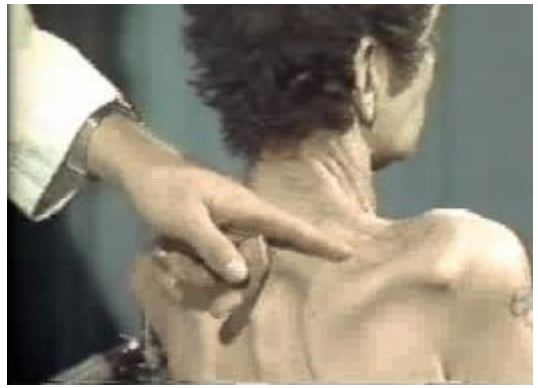
- **Uniformly fatal, typically due to respiratory failure**
- **Little effective treatment**
  - Riluzole slows rate of progression and extends survival by at least 2–3 months

- **Most ALS cases are sporadic without a family history of ALS**
- **However, 10% of cases are familial**
  - More than 20 genes have been identified as causing familial ALS (fALS)
  - Typically, fALS patients have onset at a younger age

Miller RG, Jackson CE, Kasarskis EJ, et al. *Neurology*. 2009 Oct 13;73(15):1218-26.
Miller RG, Jackson CE, Kasarskis EJ, et al. *Neurology*. 2009 Oct 13;73(15):1227-33.
Miller RG, Mitchell JD, and Moore DH. *Cochrane Database Syst Rev*. 2012 Mar 14;(3):CD001447.

What Does “Weakness” Look Like in ALS?

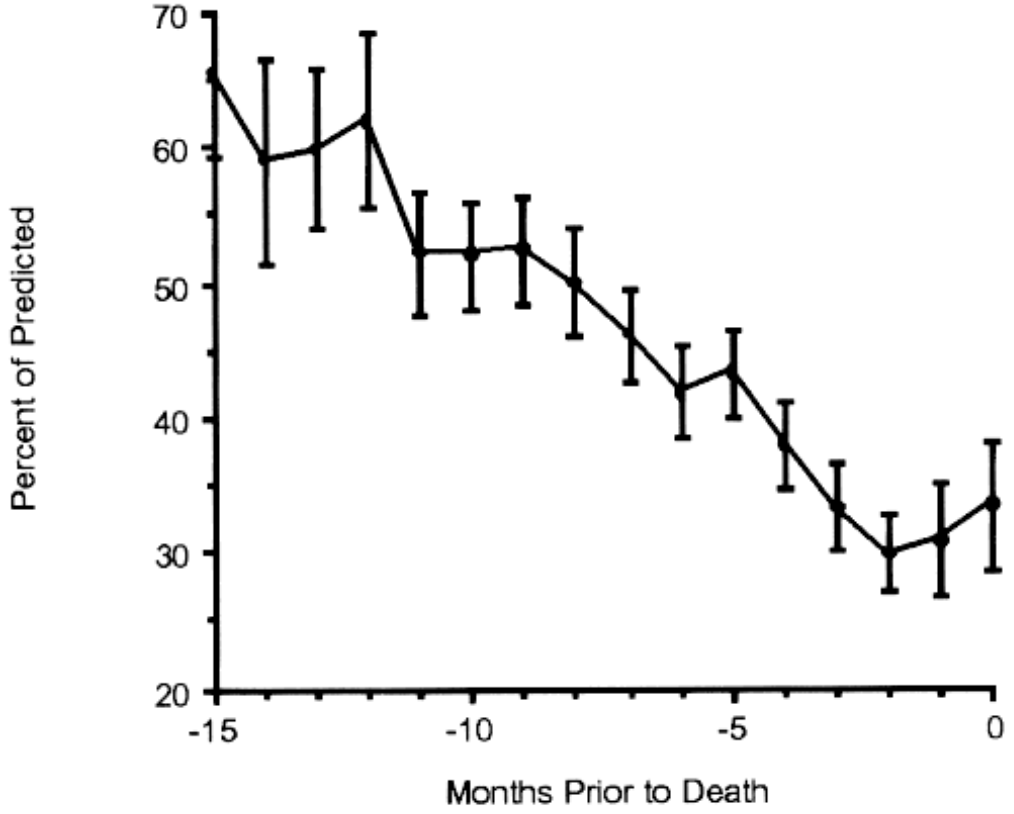




- Images shown with permission

Weakness in ALS is Progressive

%FVC at Study Entry and 9-month Survival Probability

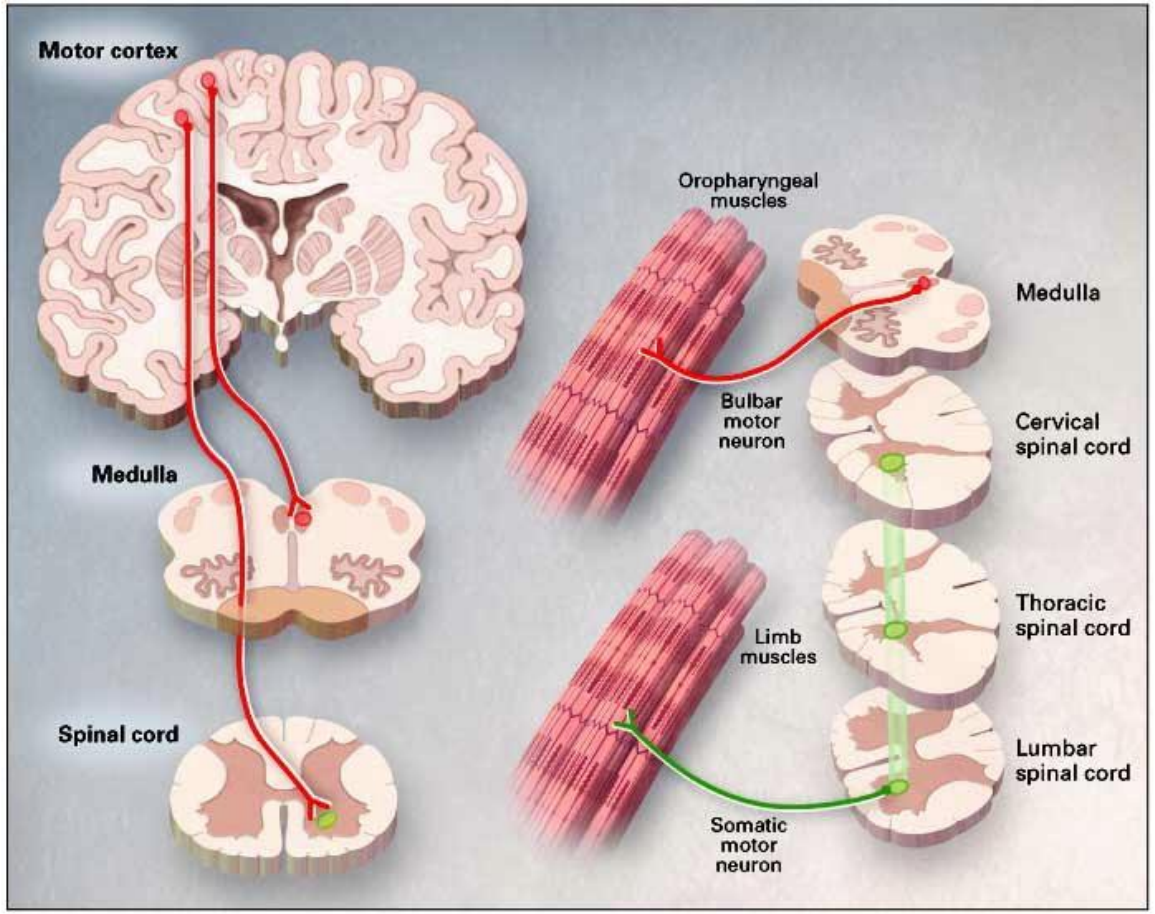


%FVC: Percent forced vital capacity

Stambler N, Charatan M, Cedarbaum JM. *Neurology*. 1998 Jan;50(1):66-72.

Degeneration and Death of Cortical and Spinal Motor Neurons is Source of Progressive Weakness in ALS

Preferential Upper and Lower Motor Neuron Loss



Rowland LP, Shneider NA. *N Engl J Med*. 2001 May 31;344(22):1688-700.

How Do We Diagnose ALS?
Challenges for Case Ascertainment in Epidemiology

- **ALS remains a clinical diagnosis**
  - Coexistence of upper and lower motor neuron signs in a single bodily region
    - Upper motor neuron findings include overactive tendon reflexes, clonus, Hoffman and Babinski signs
    - Lower motor neuron findings include muscle atrophy, weakness, and fasciculation (i.e., muscle twitching)
  - Verify normal functioning of other neurological systems, (e.g., sensation)

- **To some degree, ALS is a diagnosis of exclusion**

Diagnosis of Exclusion:
Diagnosis reached by a process of elimination, if presence cannot be established from history, examination or testing

How Do We Diagnose ALS?
Challenges for Case Ascertainment in Epidemiology

- **Diagnostic testing is essential to rule out so-called "ALS mimics"**
  - These include multiple sclerosis, Parkinson's disease, Alzheimer's disease, and many others
- **Testing may include**
  - MRI of brain and spinal cord—structural causes of progressive weakness
  - EMG/NCV—evaluate for disease of muscle and/or nerve
  - Laboratory studies—endocrine, metabolic, immunologic, etc.
- **All patients must have a second opinion from another neurologist**

MRI: Magnetic resonance imaging
EMG: Electromyogram
NCV: Nerve conduction velocity testing

So, How Good Are Neurologists at Diagnosing ALS?

- **Actually, not bad at all**
  - Clinical diagnosis has 95% sensitivity compared to autopsy
- **Diagnostic standards**
  - Basic clinical principles: UMN/LMN findings
  - El Escorial criteria (1990; Arlie House, 1998)
  - Awagi criteria (2008)
- **Recent Scottish study**
  - 1,226 registry cases
  - 44 came to autopsy
    - 100% confirmation of ALS or motor neuron disease diagnosis

UMN: Upper motor neuron
LMN: Lower motor neuron

Kurian KM, Forbes RB, Colville S , et al. *J Neurol Neurosurg Psychiatry.* 2009 Jan;80(1):84-7.

Advances in Clinical ALS Research Makes Epidemiology Possible

- **Despite these challenges, we are able to diagnose ALS or motor neuron disease with a fair degree of certainty**
  - This makes epidemiologic research possible
- **We have tools to measure progression of ALS**
  - These aid clinical drug development

Monitoring Progression of ALS

- **ALSFRS-R rating scale of function**
  - Self-report by patient, or even just the caregiver
  - Can be administered over the phone or on computer
- **Tests of pulmonary (ventilatory) function**
  - Percent forced vital capacity (%FVC)
  - Maximum inspiratory pressure (MIP)
  - Sniff nasal pressure (SNP)
- **Survival**
  - Without assisted ventilation

A spirometer measures lung function and is used to monitor changes in a person with ALS's functional abilities

ALSFRS-R: ALS Functional Rating Scale (revised)

Monitoring Progression of ALS

- **Functional measurements**
  - Gait speed
  - Timed up-and-go
  - Perdue pegboard
- **Quantitative muscle testing**
  - Manual muscle testing
  - Measures of isometric muscle power

Perdue pegboard

Barriers to Progress

- **By the time people become clinically impaired, the majority of vulnerable neurons have already degenerated and died**
  - Estimates are perhaps 50%–70% of motor neurons are gone
- **Large numbers of patients are required for clinical studies**
  - Trials are labor-intensive and therefore costly; millions of dollars
- **Barriers to progress for ALS patients and their families**
  - Time: activities of daily living take longer, time away from work for family caregivers
  - Distance to tertiary care medical centers
  - Out-of-pocket expenses

Reasons for Optimism

- The ALS research community is expanding
- The ALS research community is creative, passionate, and committed
- The National ALS Registry stands as a prime example
- My prediction: ALS causes will be found and treatments will be developed

Living with ALS: A Patient's Story

Ed Tessaro, BA

Person Living with ALS (PALS)

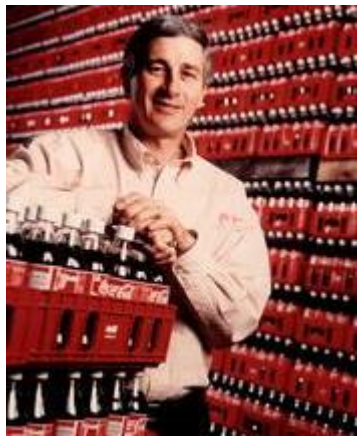
U.S. Department of Health and Human Services
Centers for Disease Control and Prevention

Making Connections to Make A Difference

- **The ongoing struggle to encourage newly diagnosed patients to come forward, register, and take charge of their condition**

Edward Rapp
Caterpillar

Daniel Doctoroff
Bloomberg News



Steve Ennis
Coca-Cola

Pete Frates
Ice Bucket Challenge

Bruce Thompson
Gold Key Resorts

Suzanne Malveau
CNN

Not All Costs Are Financial

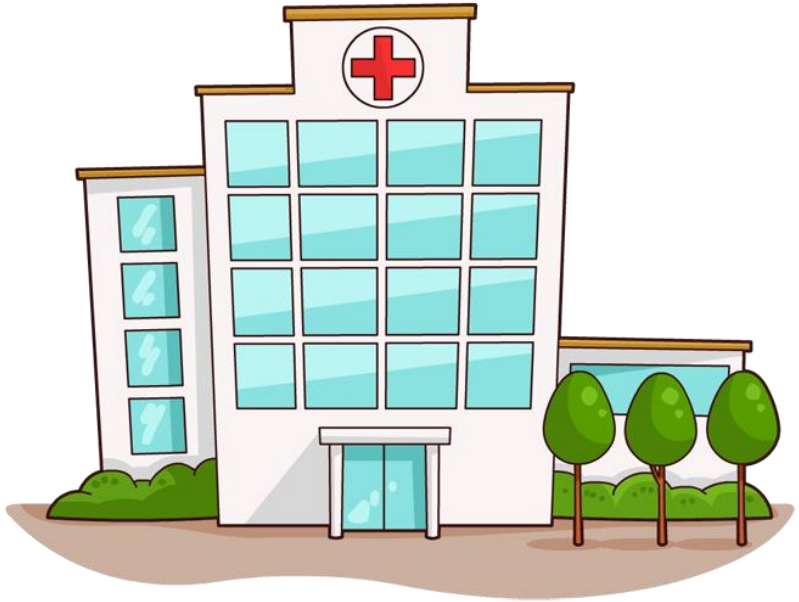
- **Cost of living with ALS, fear of consequences, and the consequences of that fear**

Average Costs for the 20-month Diagnosis Seeking Period	
Professional fees for Physicians and therapists	$16,460
Testing/procedure expenses including all out-patient care & services	$10,556
Inpatient hospitalization	$6,250
Travel expenses	$2,675
Treatments including enteral nutritional & supplies	$2,096
Other equipment & supplies	$1,814
Medications	$1,148
Medical records copies & shipping	$396
Caregiver salary	$255
Total Costs	$41,650

Obermann M, Lyon M. *Amyotroph Lateral Scler Frontotemporal Degener*. 2015 Mar;16(1-2):54-7.

Increasing Openness of the Medical Community Would Help

- **Openness of medical community, researchers, and investigators toward new patients and their families**



Need to Lower Barriers for PALS and Increase Support

- **The daunting patient process to determine eligibility for clinical trials, and to receive timely information**

PALS: Person Living with ALS

Finding Affirmation for PALS and their Families

- **There is a great need to counsel patients in an affirmative way—to accept reality of the disease and turn it into their life-force**
  - Purposeful
  - Selfless
  - Self-determined
  - Empowered
  - Courageous

PALS: Person Living with ALS

Practical and Relevant Resources

The Inherent Injustice and Necessity of Double-blind Trials

- **ALS plateaus and reversals info—deserves more discussion**

ClinicalTrials.gov

A service of the U.S. National Institutes of Health

Expanding Access

- Right-to-try legislation
- Compassionate use
- Expanded access

Ted Harada
in memoriam

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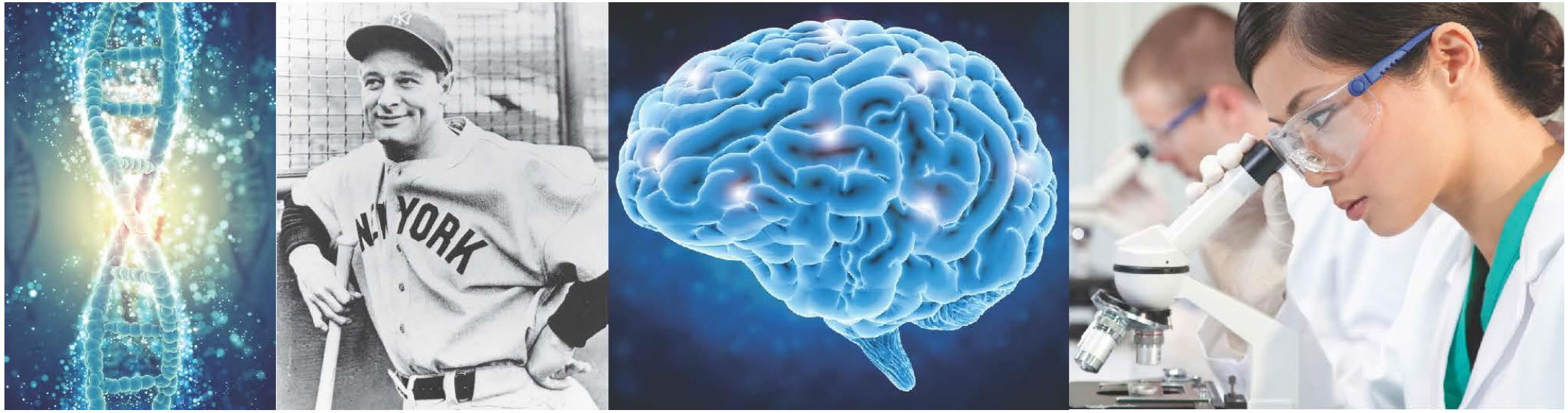

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