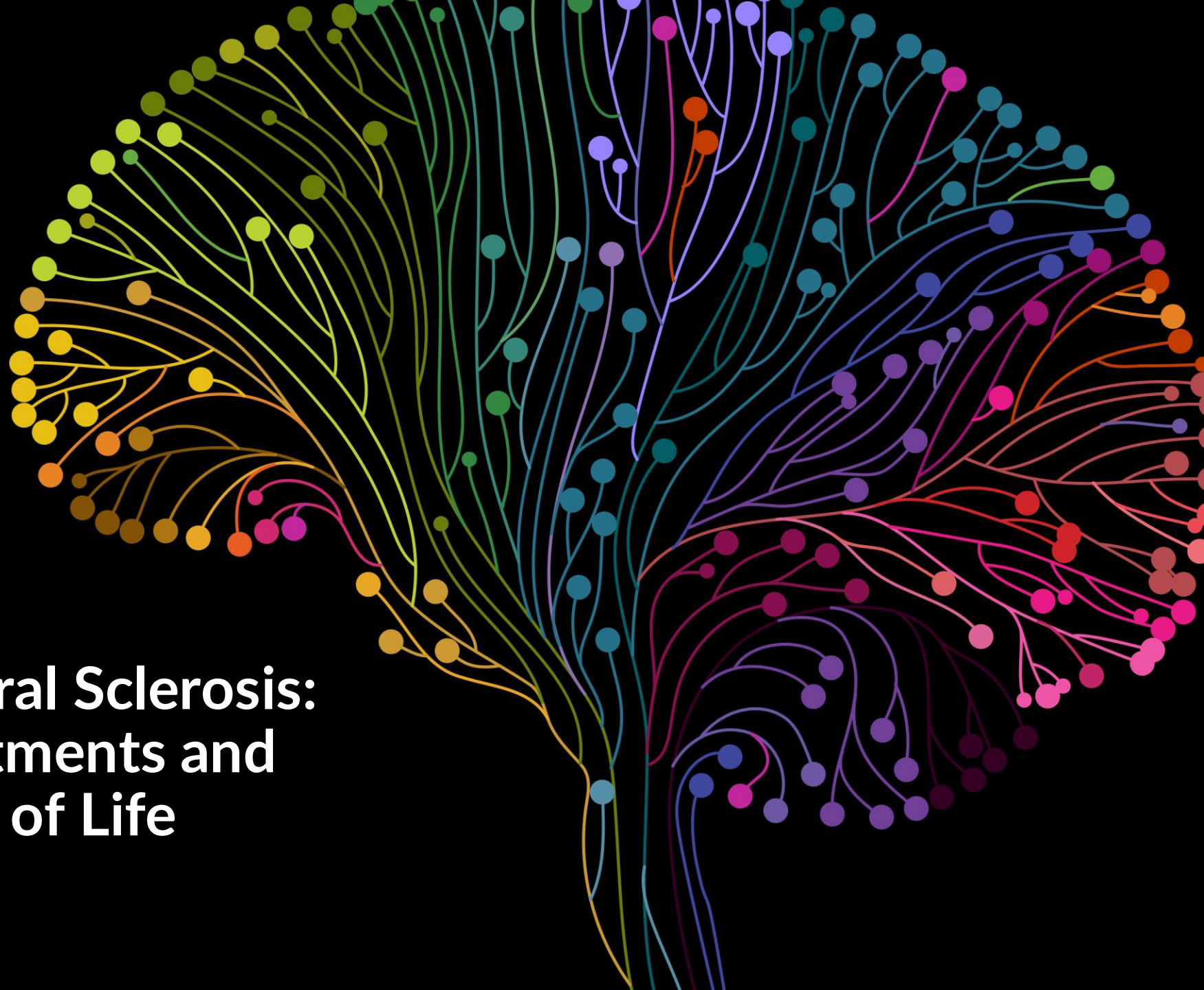


March 23, 2023

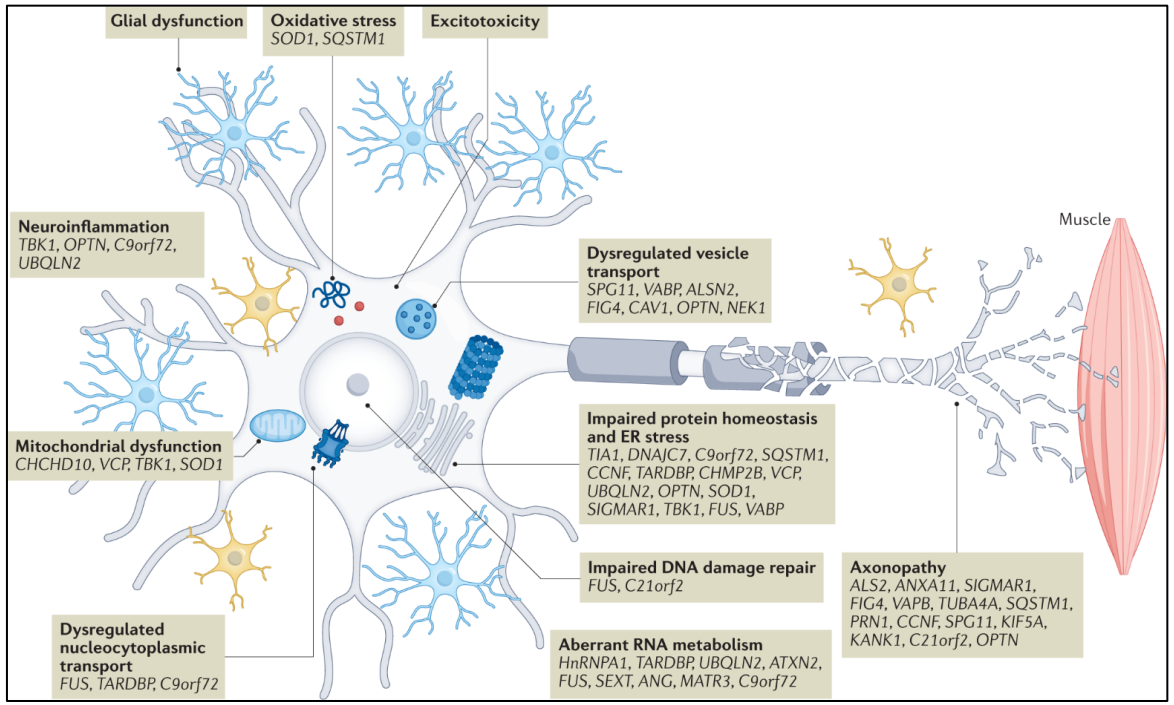
Amyotrophic Lateral Sclerosis: Accelerating Treatments and Improving Quality of Life

NIH National Institute of Neurological Disorders and Stroke

Challenges in ALS

- ALS causes rapid, progressive motor weakness, typically leading to death 3-5 years from time of diagnosis.
- ~33,000 Americans currently are living with ALS, and the estimated lifetime ALS risk is 1/400.
- Although four drugs have been approved for ALS, none are cures. The four available slow or ameliorate some symptoms of ALS.
- No interventions are known to prevent ALS in people at high risk for the disease.
- The rapidly degenerative nature of the disease places an enormous physical, financial, and emotional burden on people living with ALS and the people that care for them.

ALS pathophysiology, genetic causes and risk factors



Mead *et al*. *Nat Rev Drug Discov* (2022).

Lots of unknowns but some promising advances give hope for more effective therapies in the future.

Nat Med. 2022 January ; 28(1): 117–124. doi:10.1038/s41591-021-01557-6.

SUPPRESSION OF MUTANT C9ORF72 EXPRESSION BY A POTENT MIXED BACKBONE ANTISENSE OLIGONUCLEOTIDE

Hélène Tran[1,‡], Michael P. Moazami[2,‡], Huiya Yang[1], Diane McKenna-Yasek[1], Catherine L. Douthwright[1], Courtney Pinto[1], Jake Metterville[1], Minwook Shin[2], Nitasha Sanil[3], Craig Dooley[3], Ajit Puri[4], Alexandra Weiss[1], Nicholas Wightman[1], Heather Gray-Edwards[4], Miklos Marosfoi[4], Robert M. King[4,5], Thomas Kenderdine[6], Daniele Fabris[6], Robert Bowser[7], Jonathan K. Watts[2,*], Robert H. Brown Jr[1,*]

Antisense oligonucleotide silencing of FUS expression as a therapeutic approach in amyotrophic lateral sclerosis

Vladislav A. Korobeynikov[1,2,6], Alexander K. Lyashchenko[1,2,6], Beatriz Blanco-Redondo[1,5,6], Paymaan Jafar-Nejad[3] and Neil A. Shneider[1,4]

ORIGINAL ARTICLE

Trial of Antisense Oligonucleotide Tofersen for *SOD1* ALS

T.M. Miller, M.E. Cudkowicz, A. Genge, P.J. Shaw, G. Sobue, R.C. Bucelli, A. Chiò, P. Van Damme, A.C. Ludolph, J.D. Glass, J.A. Andrews, S. Babu, M. Benatar, C.J. McDermott, T. Cochrane, S. Chary, S. Chew, H. Zhu, F. Wu, I. Nestorov, D. Graham, P. Sun, M. McNeill, L. Fanning, T.A. Ferguson, and S. Fradette, for the VALOR and OLE Working Group*

Mis-spliced transcripts generate de novo proteins in TDP-43-related ALS/FTD. Seddighi S et al. https://doi.org/10.1101/2023.01.23.525149

A fluid biomarker reveals loss of TDP-43 splicing repression in pre-symptomatic ALS

Katherine E. Irwin[1,2], Pei Jasin[1], Kerstin E. Braunstein[1], Irika Sinha[1,2], Kyra D. Bowden[1,2], Abhay Moghekar[3], Esther S. Oh[1,4,5], Denitza Raitcheva[6], Dan Bartlett[6], James D. Berry[7], Bryan Traynor[8,9], Jonathan P. Ling[1], and Philip C. Wong[1,2]*

RESEARCH ARTICLE SUMMARY

NEURODEGENERATION

Mechanism of *STMN2* cryptic splice-polyadenylation and its correction for TDP-43 proteinopathies

Michael W. Baughn†, Ze'ev Melamed*†, Jone López-Erauskin, Melinda S. Beccari, Karen Ling, Aamir Zuberi, Maximilliano Presa, Elena Gonzalo-Gil, Roy Maimon, Sonia Vazquez-Sanchez, Som Chaturvedi, Mariana Bravo-Hernández, Vanessa Taupin, Stephen Moore, Jonathan W. Artates, Eitan Acks, I. Sandra Ndayambaje, Ana R. Agra de Almeida Quadros, Paayman Jafar-nejad, Frank Rigo, C. Frank Bennett, Cathleen Lutz, Clotilde Lagier-Tourenne*, Don W. Cleveland*

NIH National Institute of Neurological Disorders and Stroke

NIH ALS Strategic P;anning

ALS Strategic Research Priorities developed with input from ALS community, scientists, clinicians

Public Request for Information

- NS-22-056 received over 300 responses
- Responses given to steering committee & working groups and posted publicly

5 Working Groups Develop Draft Priorities*

- Basic Science
- Translational
- Clinical
- Quality of Life
- Partnerships and Collaboration

*3 priorities each

Public Workshop to Discuss Priorities

- October 26-27, 2022 (virtual)
- Draft priorities posted online
- Opportunities for discussion and public comment

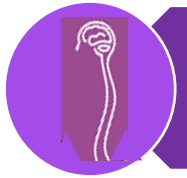
Public Comment Period

- Revised priorities posted online for ~30 days for formal, written public comment
- Responses given to working groups for further consideration

NINDS Advisory Council

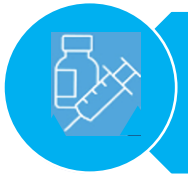
- Advisory Council: Consider priorities and vote
- Feb 2023 onwards: NIH and other ALS stakeholders: Begin implementation

Strategic Planning Working Groups



Accelerating Research on the Biology behind ALS

From Research to Therapy



Optimizing ALS Clinical Research

Optimizing ALS Quality of Life

Improving Collaborative Partnerships

The Strategic Planners.

Steering Committee
Robert Brown, Jr.
Rita Sattler
Aaron Gitler
Layne Oliff
Ellyn Phillips

Accelerating Research on the Biology Behind ALS
Clotilde Lagier-Tourenne (Co-Chair)
Ammar Al-Chalabi (Co-Chair)
Sami Barmada
Sali Farhan
Myriam Heiman
Piera Pasinelli
Leonard Petrucelli
Hemali Phatnani
Cooper Penner
Michael Ward

Translating Fundamental Research into Potential ALS Therapies
Neil Shneider (Co-Chair)
Stacie Weninger (Co-Chair)
Frank Bennett
Thomas Gaj
Joe Lewcock
Stefan McDonough
Nadia Sethi
James Wilson
Henrik Zetterberg

Optimizing ALS Clinical Research
Merit Cudkowicz (Co-Chair)
Tim Miller (Co-Chair)
Alberto Ascherio
Robert Bowser
Christina Fournier
Stephen Goutman
Chiadi Onyike
Gwen Petersen
Melanie Quintana, PhD
Jeremy Shefner

Optimizing the Quality of Life of People Living with ALS and Caregivers
Terry Heiman-Patterson (Co-Chair)
Jean Swidler (Co-Chair)
Jinsy Andrews
Chelsey Carter
Melanie Fried-Oken
Steve Kowalski
Emily Plowman
Zachary Simmons

Identifying Opportunities for Collaborations and Partnerships
Lisa Gold (Co-Chair)
Dan Doctoroff (Co-Chair)
Andrea Pauls Backman
Allison Bulat
Kuldip Dave
Sharon Hesterlee
Ed Rapp
John Ravits
Jeff Rothstein
Neta Zach
Robyn Bent (*ex officio*, FDA)

NIH (*ex officio*)
NINDS:
Christine Torborg (Designated Federal Official)
Amelie Gubitz
Emily Caporello
Robin Conwit
Codrin Lungu
Jane Hettinger
Samantha White
Carlo Quintanilla
Rebekah Corlew
Partner IC's:
Emily Carifi
Jonathan Hollander
Cristina Kapustij
Enrique Michelotti
Van Nguyen
Lisa Opanashuk
Lana Shekim
Coryse St. Hillaire-Clarke
Tiina Urv

FDA (*ex officio*)
Michelle Adams
Teresa Buracchio
Michelle Campbell
Billy Dunn
Elizabeth Hillebrenner
Diane Maloney
Michelle Tarver
Bryan Wilson
Celia Witten

CDC (*ex officio*)
Paul Mehta

Department of Defense ALS Research Program (*ex officio*)
Kristy Lidie

People affected by ALS & stakeholders through RFI responses and workshop participation

Build on NIH Strategic Priorities for ALS

ALS Strategic Research Priorities developed with input from ALS community, scientists, clinicians

- Unlock **sporadic** ALS- causes, basic biology, mechanisms of disease, therapeutic targets.
- Understand clinical **heterogeneity** and the molecular mechanisms that contribute to it

- Optimize the design and performance of **trials at all stages of the disease**, including pre-symptomatic gene carriers
- Enhance and expand **biosample and data infrastructure**
- Foster **collaborations** among all stakeholders—people with lived experience, academic, industry, government, philanthropic organizations

- Improve understanding of how ALS symptoms affect **daily living** of people with ALS and their caregivers
- Identify interventions to promote **maximal function and daily participation**
- Identify evidence-based **best practices and resources** for care

Implementing ACT for ALS

On December 23, 2021, President Biden signed into law the Accelerating Access to Critical Therapies (ACT) for ALS Act.

Grants for Research Utilizing Data from Expanded Access (Section 2)

- Scientific research utilizing data from expanded access to investigational drugs/biologics for ALS for people not otherwise eligible for clinical trials
- ALS phase 3 clinical trial sites sponsored by a small business
- **RFA-NS-23-012**: Amyotrophic Lateral Sclerosis (ALS) Intermediate Patient Population Expanded Access Applications due May 1

HHS Public-Private Partnership for Rare Neurodegenerative Diseases (Section 3)

- Critical Path for Rare Neurodegenerative Diseases
- Accelerating Medicines Partnership for ALS

FDA Action Plan for Rare Neurodegenerative Diseases, including ALS (Section 4)

- Released June 23, 2022

FDA Rare Neurodegenerative Diseases Grant Program (Section 5)

- **RFA-FD-23-028:** Natural History and Biomarker Studies of Rare Neurodegenerative Diseases Applications due May 4
- **RFA-FD-23-03:** Systematic Review of Clinical Outcome Assessments for Communication Brain-Computer Interface Devices in ALS Applications due May 24

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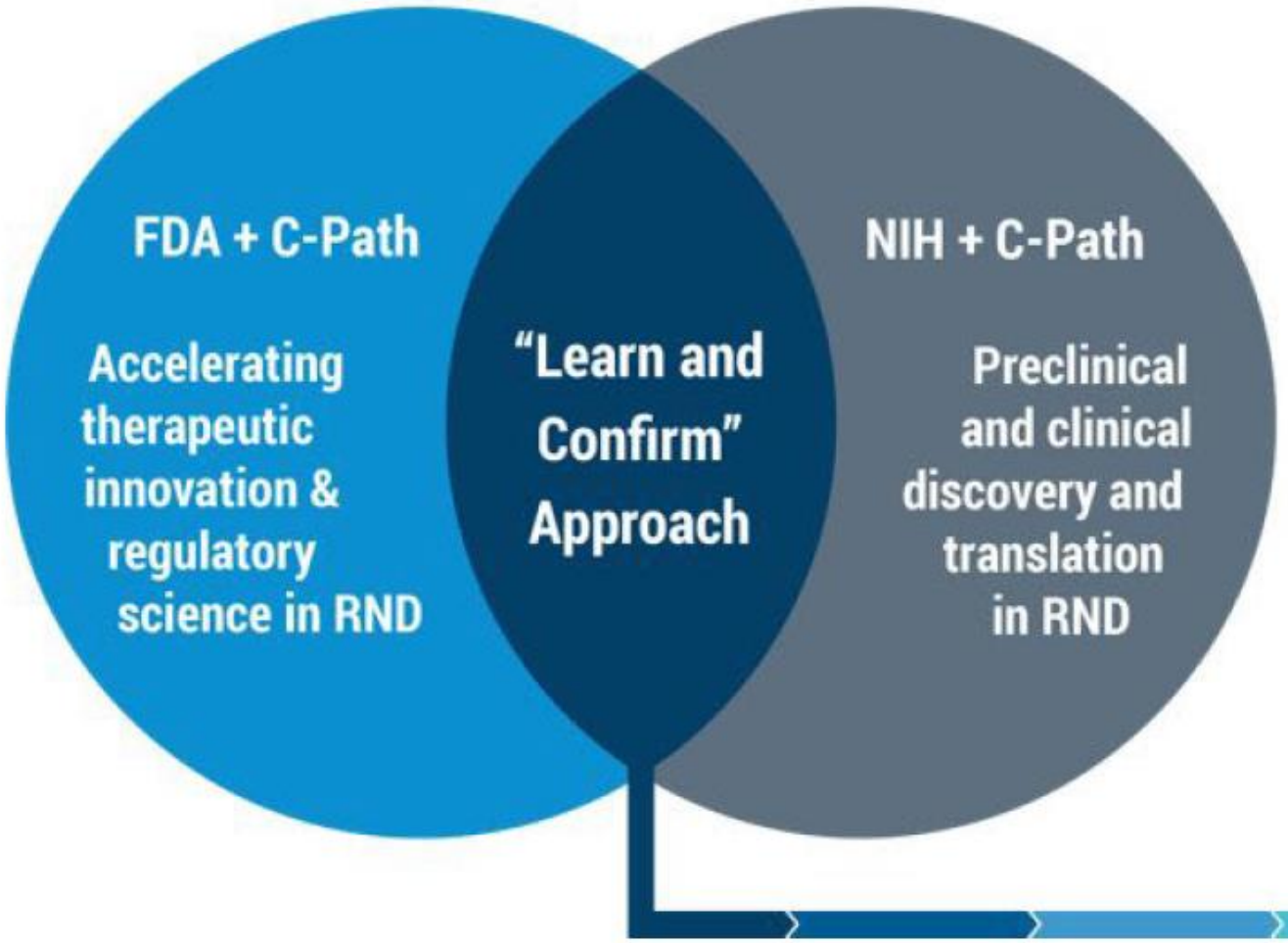
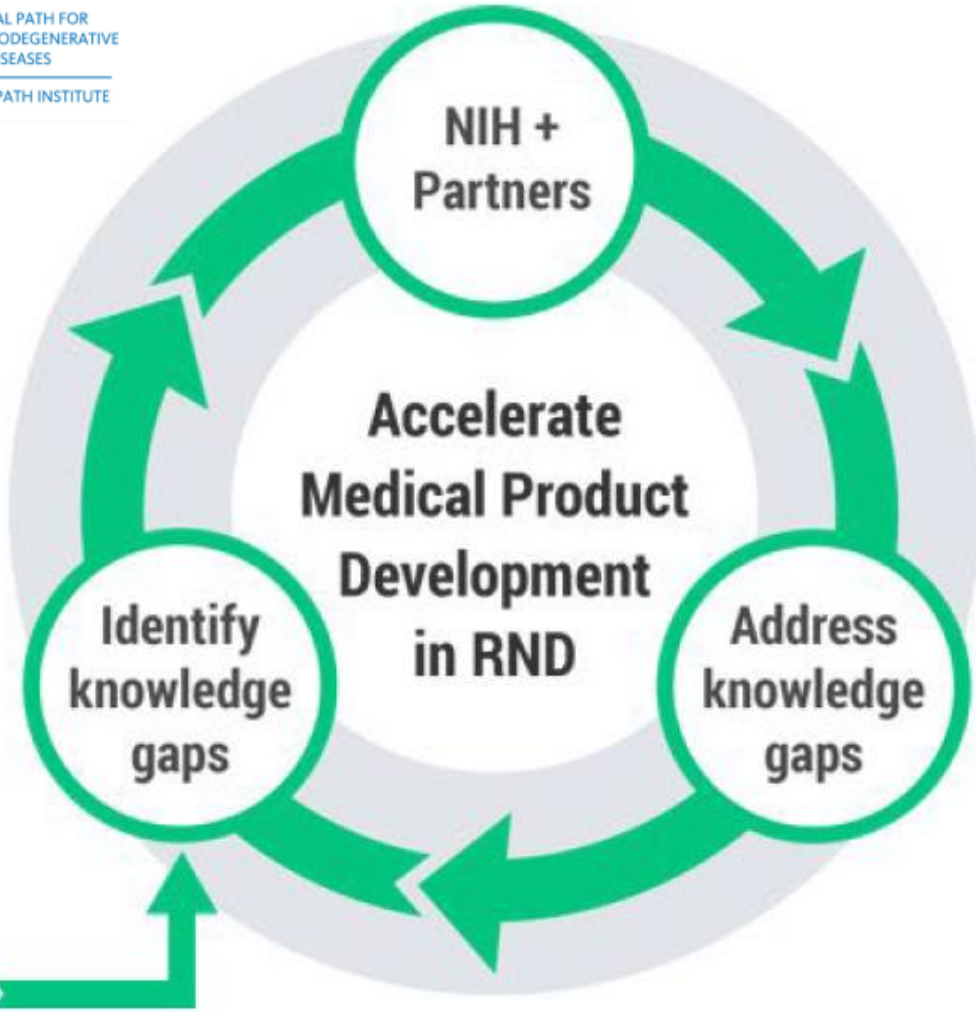
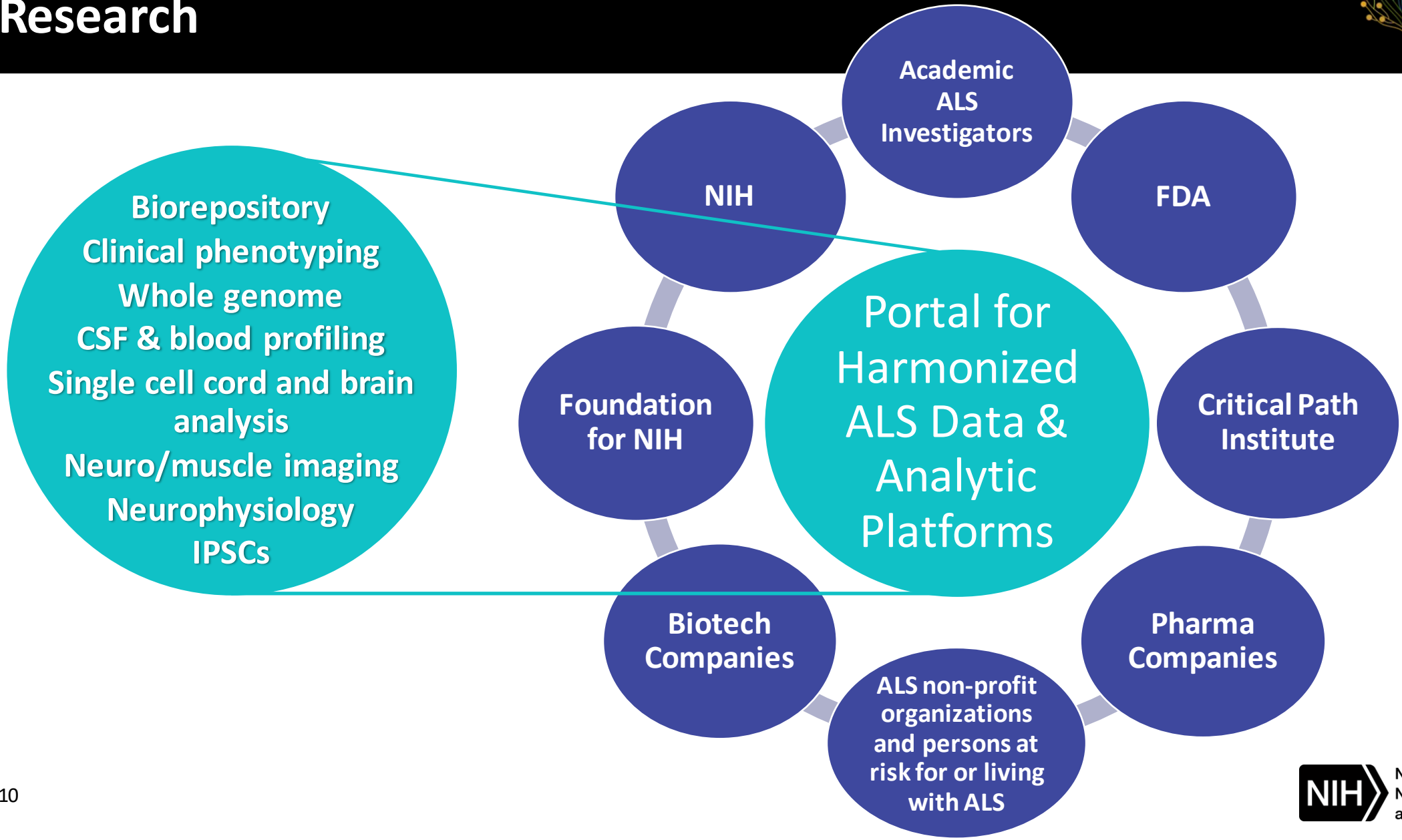
NIH-FDA Public Private Partnership (PPP) for Rare Neurodegenerative Diseases



CP-RND
CRITICAL PATH FOR RARE NEURODEGENERATIVE DISEASES
CRITICAL PATH INSTITUTE

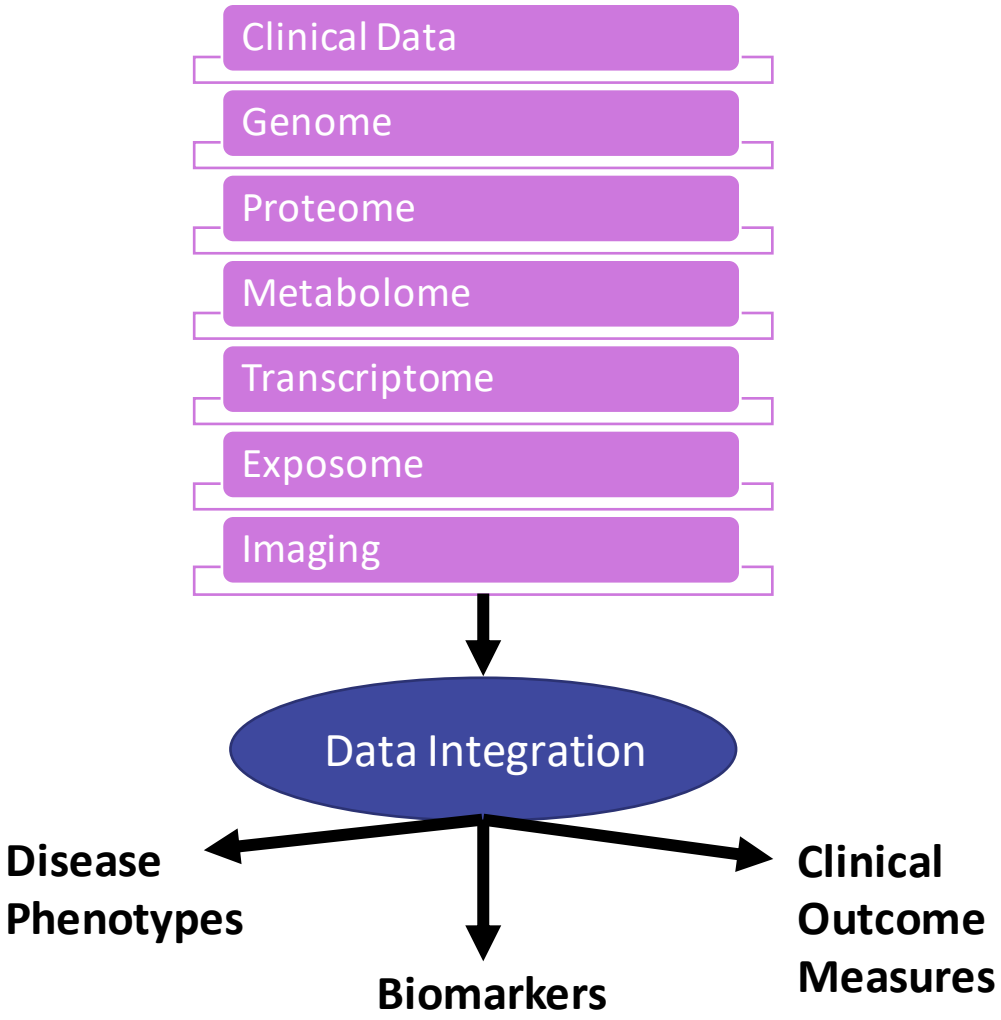


Expansion of the Public Private Partnership for ALS Research



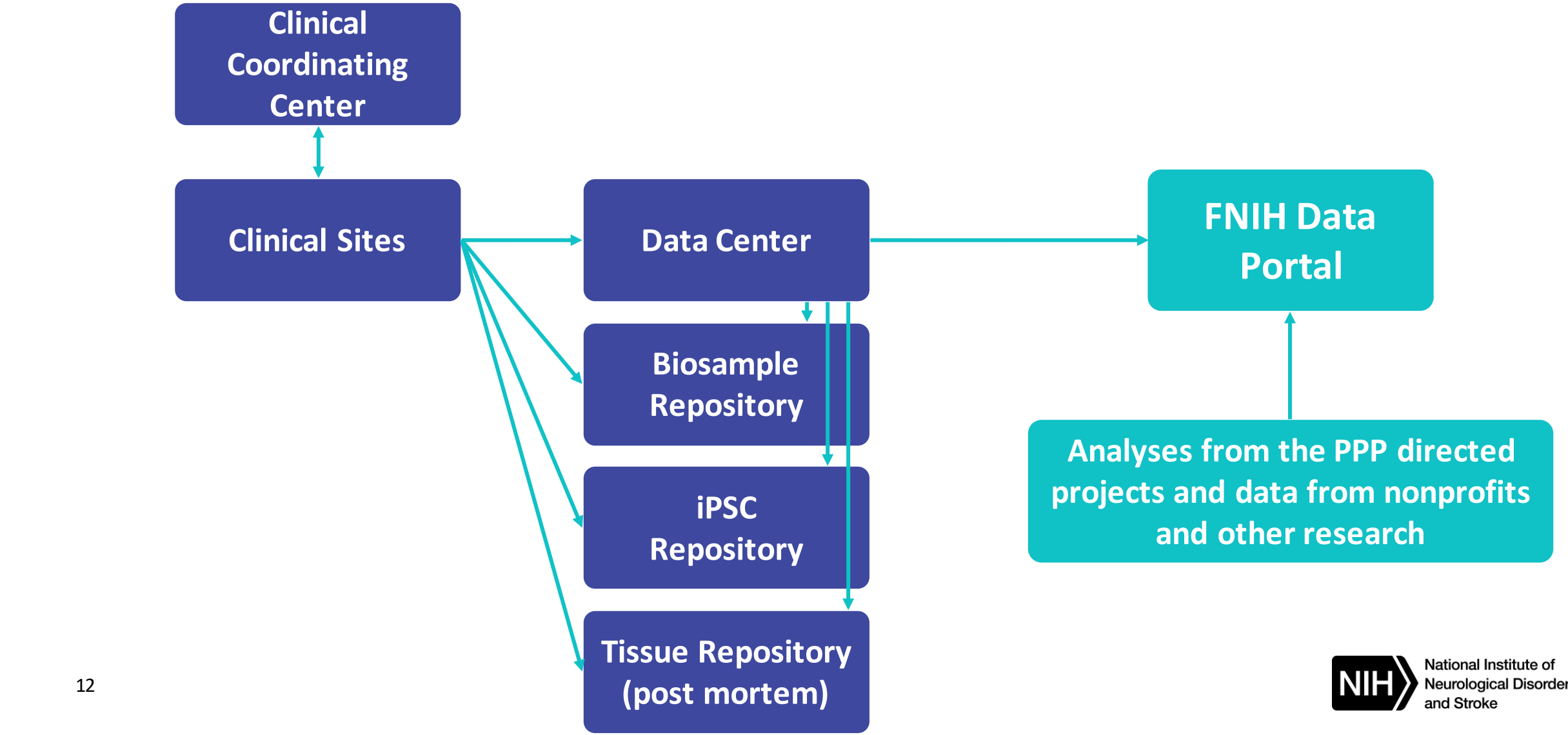
Objectives of an Expanded Public Private Partnership for ALS

1. Harmonize and connect clinical data
2. Establish a large-scale repository for ALS and encourage investigator analyses of these samples
3. Create a repository of research tools, protocols and resources
4. Integrate clinical data with biologic measures to identify biomarkers of the pathology of ALS for diagnosis and progression of disease



National Institute of Neurological Disorders and Stroke

Data Flow to Accelerate Development of Effective Treatment of ALS



National Institute of Neurological Disorders and Stroke

Congress directed NIH to commission a NASEM study on ALS Research, Care, and Services

The Committee includes $1,000,000 to commission a study by NASEM to **identify and recommend actions for the public, private, and nonprofit sectors** to undertake to make ALS a **livable disease within a decade**. Given the significant adverse physical, financial, psychological impact this progressive neurodegenerative disease has on the individuals and families affected by it, a comprehensive assessment of what is necessary to address its effects is warranted. The study should include, but not be limited to:

- how to develop more effective and meaningful **treatments and a cure**;
- interventions to **reduce and prevent the progression and complications** of ALS;
- the type and range of **care and services people and families with ALS need** and how to ensure they receive comprehensive, quality care;
- what **care, services, and preventive measures people at-risk of ALS need**; and
- how to **improve the quality of life, health, and well-being** of affected individuals and families.

The Committee directs NIH to submit this study to the Committee no later than October 2024 and requests an update on the status of this study in the fiscal year 2023 Congressional Budget Justification.

Gather input from people with lived experience and a wide range of experts

People affected by ALS must play a central role

- People living with ALS, caregivers, and people at risk for developing ALS on the committee
- Public Engagement Consultant to ensure the committee engages a diverse group of individuals
  - could include approaches such as crowdsourcing patient-centered input and focus groups
- Public workshop with opportunity for public comment
- Diversity is crucial as they will have different needs, challenges, and perspectives!
  - race, gender, age, geographic location, culture, socioeconomic status

Other expertise on the committee

- the science of ALS;
- therapeutic research, development, and regulation;
- health care, services, and supports (e.g., medicine, physical therapy, occupational therapy, respiratory therapy, nutrition, speech-language pathology);
- delivery, access, and payment for care, services, and supports.

NIH is implementing the Strategic Priorities

New ALS Initiatives

- **Notice of Special Interest (NOT-NS-23-062): Advancing Research for ALS**
  - Data Harmonization, Curation, and Analysis
  - Development of Biomarkers and Biomarker Signatures to Optimize Clinical Trials and Clinical Care Decisions
  - Early-Stage Therapy Development for ALS
  - Small Business Funding Opportunities
- **HHS Public-Private Partnership for Rare Neurodegenerative Diseases**
  - Critical Path for Rare Neurodegenerative Diseases with FDA, NIH and other partners
  - Foundation for the National Institutes of Health (FNIH) ALS initiative with NIH and other partners

Important questions that will facilitate implementing research priorities

- Develop better instruments to assess QOL so as to define and measure clinically meaningful benefit of any treatment/treatment program.
- Impact of expanded access on QOL of those with ALS
- Effectiveness of assistive devices
- Are there things that could improve the drug approval process? Gets into clinically meaningful benefit.
  - How do you factor in the side effects/burden/admin/cost/transportation. (e.g. Stem cell transplants. Are the potential harms worth the risk to patients. That goes under adverse events of admin)

Strategic planning process revealed needs and issues that are not NIH's strong suit

How can public, private, and nonprofit sectors work together to meet these challenging needs?

- Reduce the emotional burden on people with ALS and caregivers
  - Respite care to combat burnout, emotional/mental health services for persons with ALS and families
- Implement innovative models to deliver care more effectively at home
  - Persons experienced in ALS care; i.e., ventilator and tube feeding issues, prevention of pressure sores and aspiration.
- Coverage for essential aspects of ALS care
  - Home health care should not be dependent on ability to pay (note that people diagnosed with ALS are Medicare-eligible)
  - Motorized assist devices for transfer; tracking lift system
  - Construction of wheelchair ramps into the home and other modifications to make homes conducive to optimal function.
  - Transportation once unable to ambulate
  - Back up ventilator device in case of failure of the primary device
  - Eye-tracking enabled devices
  - Particularly for people in rural or underserved areas, and improve ALS-specific knowledge of a wide range of health care providers, including neurologists, nurses, palliative care specialists
- Comprehensive resource guide to direct people to services such as voice banking, advocacy groups, clinical trial registrations, and comprehensive scientific information in plain language
- How to develop and operationalize quality end-of-life care; increase access to long term care facilities with proper expertise

Thank You!

Walter J. Koroshetz, M.D.

Director

National Institute of Neurological Disorders and Stroke

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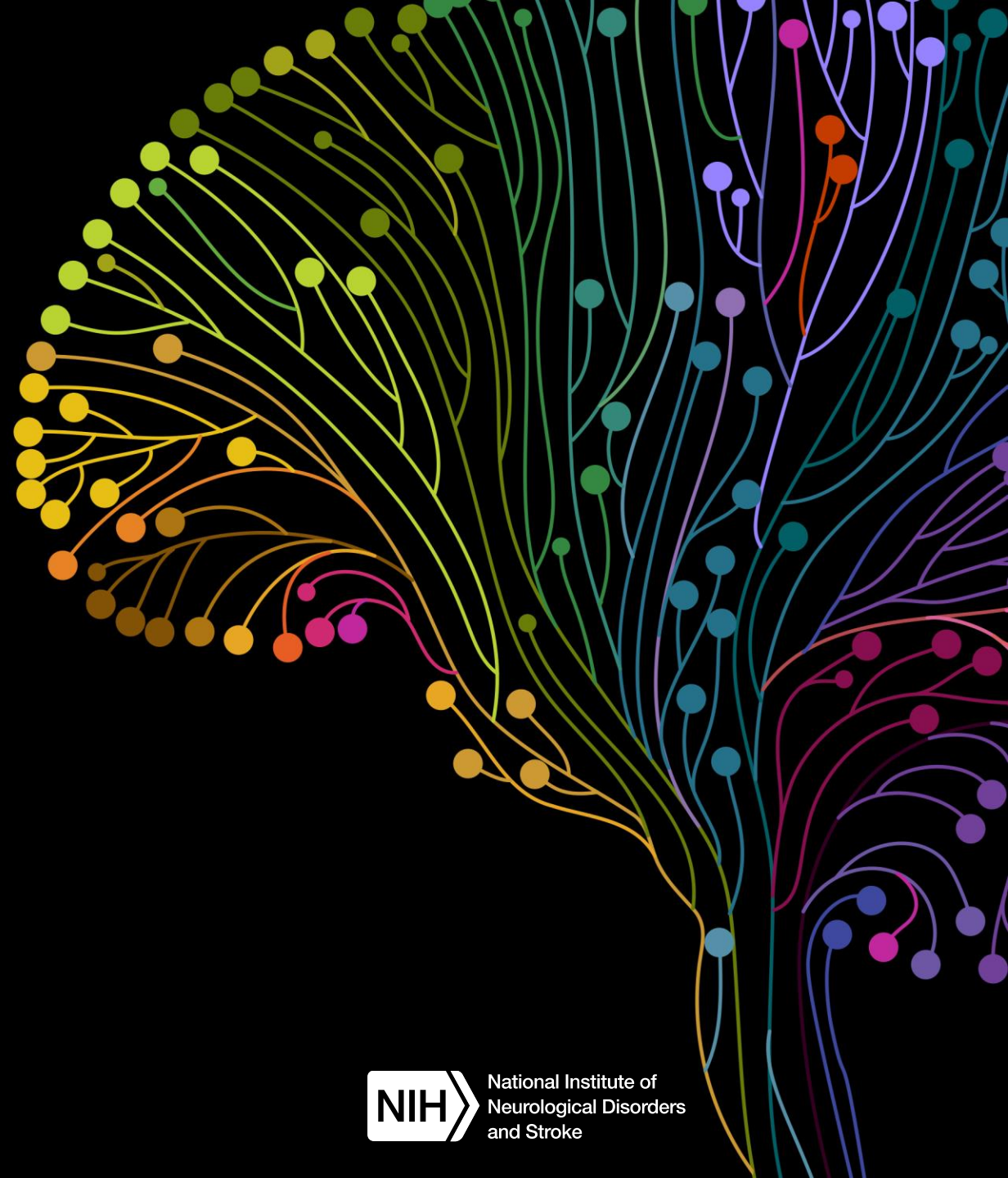
Website: http://www.ninds.nih.gov/

Follow me @NINDSdirector



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