Development of a Composite Diagnostic Biomarker for Amyotrophic Lateral Sclerosis: Experimental Approach and Progress to Date

Poster #38

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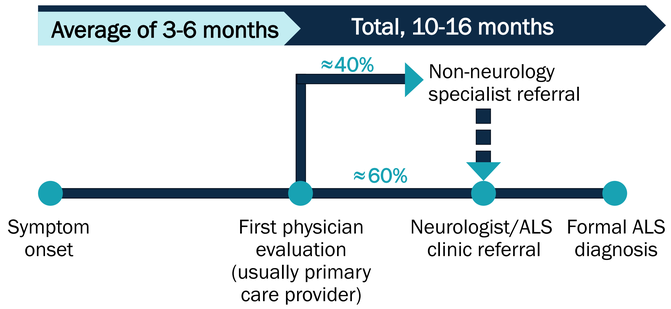
BACKGROUND

- People living with amyotrophic lateral sclerosis (PLWALS) spend approximately one-third of their disease course searching for a diagnosis[1-6]
- One of the key drivers of diagnostic delay in amyotrophic lateral sclerosis (ALS) is the lack of reliable, validated biomarkers to aid in diagnosis
  - Currently, diagnosis of ALS is largely clinical and requires demonstration of progressive motor neuron signs as well as the absence of evidence supporting alternative diagnoses[1,7]
  - Most studies report ALS diagnostic delays of 10-16 months from symptom onset[1] **(Figure 1)**

FIGURE 1. PATHWAY TO ALS DIAGNOSIS[1]



STUDY RATIONALE

- Techniques to support earlier diagnosis are critical to advance care and treatment for ALS[8-12] and mitigate the significant psychological stress that PLWALS and their families experience during a lengthy diagnostic process[2]
- Numerous published studies have identified biomarkers with potential value as ALS diagnostic screening tools[11,12]
  - Although these studies have generally been conducted in small cohorts of PLWALS, the biomarkers that they describe exhibit relatively strong sensitivity and specificity[12,13]
  - Once combined and replicated in larger, independent cohorts, the biomarkers may harbor substantial potential as part of an early ALS diagnostic approach[12,14]

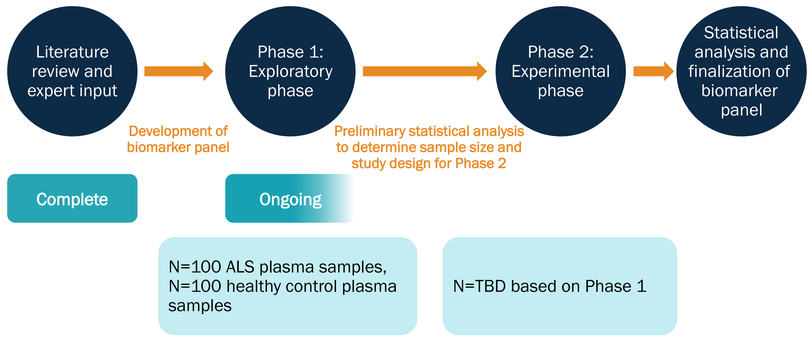
OBJECTIVES

- Verify the utility of putative ALS diagnostic biomarkers and discover new potential ALS diagnostic biomarkers in a large sample set
- Determine whether a diagnostic biomarker panel that incorporates a combination of these biomarkers may lead to improved sensitivity and specificity of diagnostic testing and facilitate early diagnosis and intervention for PLWALS

METHODS

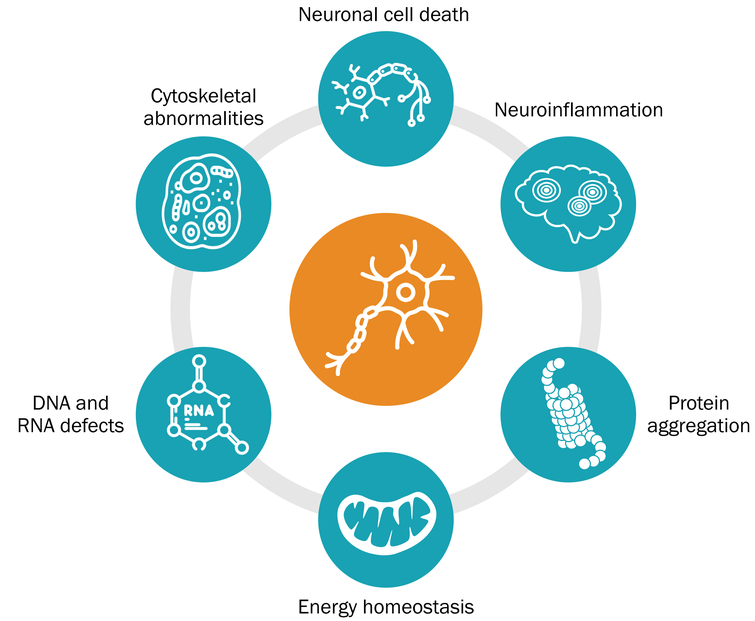
- A comprehensive review of the literature to identify putative ALS biomarkers with preliminary evidence of favorable sensitivity and specificity was performed **(Figure 2)**
- A team of ALS physicians and diagnostics experts then collectively aligned on the most promising biomarkers **(Figure 3)** in terms of published evidence as well as scalability for further investigation. Experts participating in the review were as follows:
  - Dr James Berry (Massachusetts General Hospital, NEALS Co-Chair)
  - Dr Sabrina Paganoni (Massachusetts General Hospital, NEALS Investigator and Executive Committee Member)
  - Dr Robert Bowser (Barrow Neurological Institute, NEALS Scientific Advisory Board Member)
  - Dr Sasha Bakhru (Perosphere Technologies, Founder & CEO)

FIGURE 2. EXPERIMENTAL DESIGN



TBD, to be determined.

FIGURE 3. HALLMARKS OF ALS AND NEURODEGENERATION CAPTURED AMONG STUDIED BIOMARKERS[a]



[a]Biomarkers used in this study are relevant to the above hallmarks of ALS pathogenesis, among others.

- After the selection of final analytes for testing, an exploratory study was designed to provide a preliminary sense of differential analyte levels between ALS and healthy control samples and evaluate potential composite biomarkers
- The initial sample set for testing comprised ≈100 ALS and 100 age- and sex-matched non-ALS control plasma samples from the NEALS biorepository

STUDY PROGRESS AND NEXT STEPS

- Exploratory phase testing of a potential composite biofluid biomarker for ALS diagnosis is underway
- This study will provide information about the performance of the putative biomarkers and identify new candidate biomarkers
- The results will inform the design and biomarker selection for a larger follow-up validation study

Acknowledgements

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Disclosures

- JT and EM are full-time employees of and may have stock option ownership in Amylyx Pharmaceuticals, Inc.
- JC and JK are co-CEOs of and own stock in Amylyx Pharmaceuticals, Inc.
- SB is the founder, President, and CEO of Perosphere Technologies.
- JDB has received consulting fees from Amylyx, Alexion, Biogen, MTPA, MTPHA, and has received research funding from Rapa Therapeutics, Brainstorm Cell Therapeutics, Amylyx, Biogen, MTPA, MTPHA, nQ Medical, MDA, ALS Association, ALS Finding a Cure, ALS One, and Tambourine.
- RB has received consulting fees from MT Pharma, RRD International, and Amylyx Pharmaceuticals, Inc., and has stock options in nVector, AcuraStem, and Aural Analytics.
- SP reports research grants from Amylyx, Revalesio Corporation, UCB, Biohaven, Clene, Prilenia, Seelos, Calico, Denali, Alector, Cytokinetics, Anelixis, the NIH, DoD, the ALS Association, the American Academy of Neurology, the Muscular Dystrophy Association, and consulting fees from Amylyx, Cytokinetics, Arrowhead.

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