premodiALS

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IDENTIFICATION OF A DISEASE SIGNATURE FOR PRE-SYMPTOMATIC AND EARLY ALS

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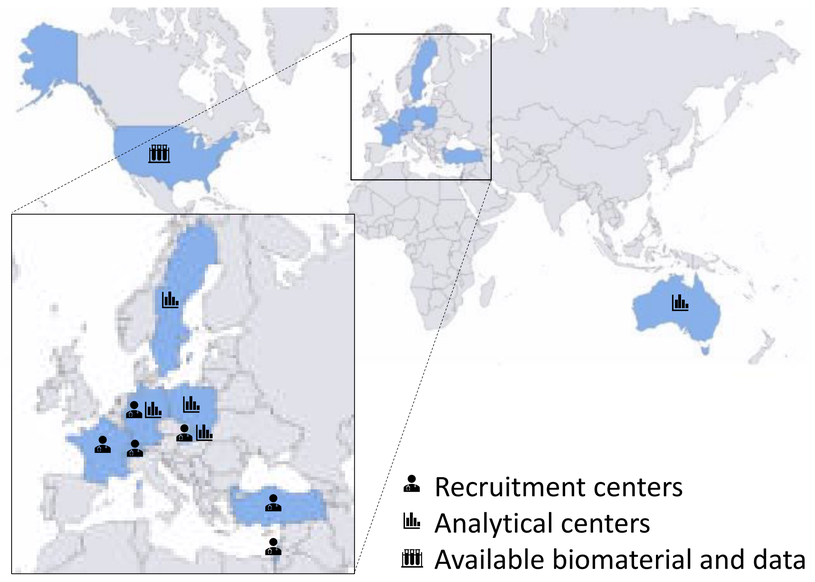
Introduction and study aims

Amyotrophic lateral sclerosis (ALS) is the most common motoneuron disease (MND) affecting the upper and lower motor neurons, with death resulting mainly from respiratory failure three to five years after symptom onset. Additional overlapping symptoms, such as cognitive and behavioral changes, or even frontotemporal dementia, may occur in ALS patients [1]. Even in industrialized countries with advanced medical service, it takes on average 12 months after the first symptoms **(early ALS)** to be diagnosed with ALS [2]. Because of the rapid and fatal progression of ALS, a timely diagnosis is crucial to start therapy early and allow for inclusion in clinical trials.

Although several **ALS biomarkers** have been proposed, including neurofilaments in serum and cerebrospinal fluid (CSF) [3] and soluble sp75ECD in urine [4], a multi-modal signature might be more sensitive to detect early ALS or even pre-symptomatic disease.

About 10-15% of ALS patients have a genetic cause [1]. The term **'pre-symptomatic' ALS** is used to describe people with a genetic family history of ALS, but who have no symptoms or other manifestations of disease at the time of testing [5]. Pre-symptomatic ALS have a high likelihood of developing ALS in the future and offer a unique opportunity to study the pre-symptomatic state of ALS.

In our study, among ALS patients with genetic mutation, genetic testing of their family members help us identify subjects, who carry the mutation, but have not yet developed symptoms of the disease, so-called **"pre-symptomatic gene mutation carriers" (PGMC)**. We aim to **identify a panel of ALS biomarkers** that differentiates PGMC and early ALS from controls and **disease mimics** (patients with other disorders that can mimic ALS) [6].



References:

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[2] Paganoni et al., (2014). Diagnostic timelines and delays in diagnosing amyotrophic lateral sclerosis (ALS). Amyotroph Lateral Scler Frontotemporal Degener.
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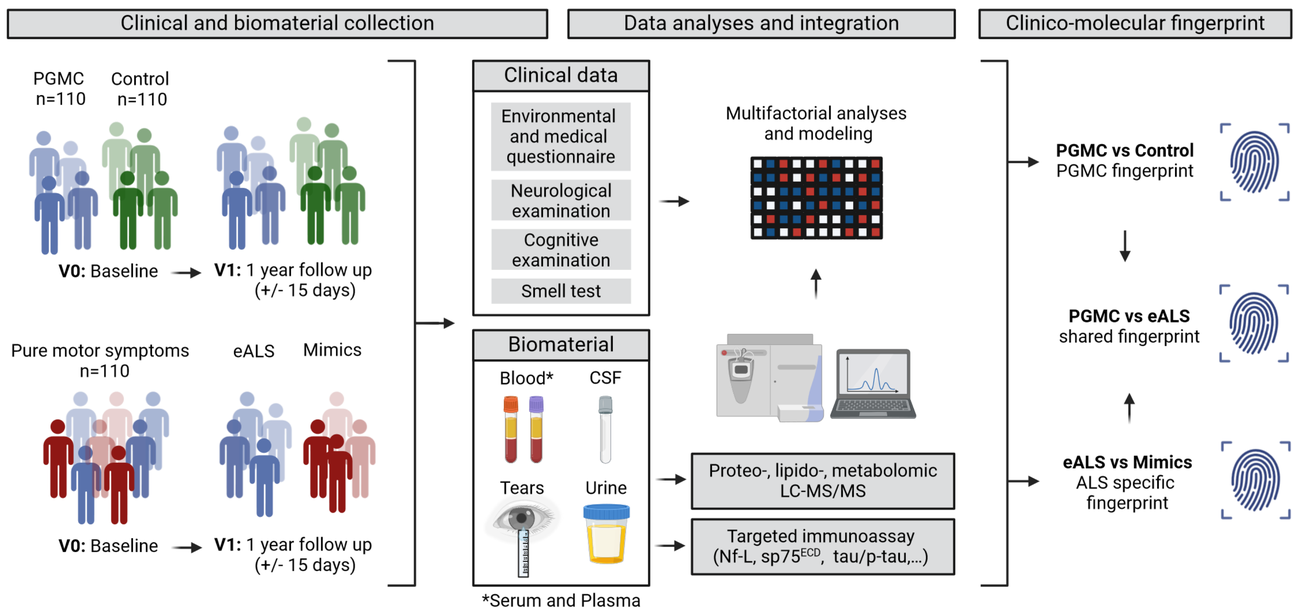
Methods



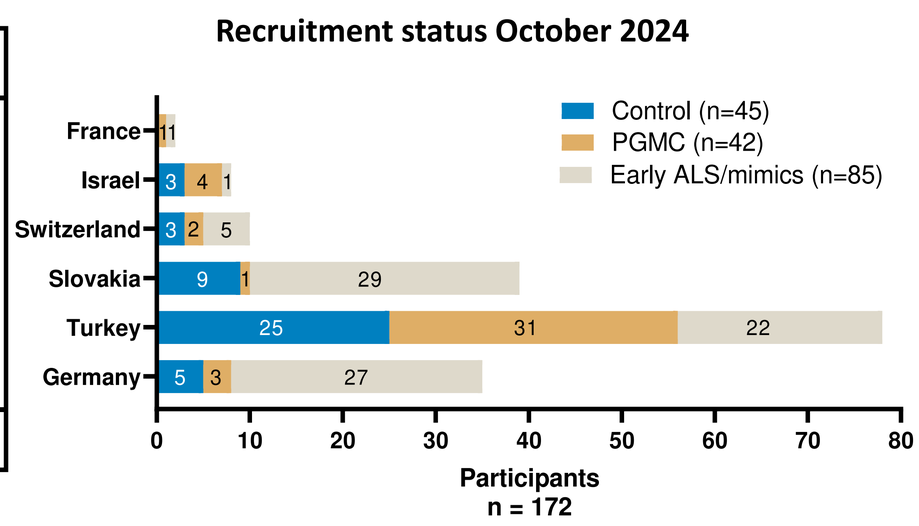
For this study, researchers from 10 different countries join forces:
Germany, France, Switzerland, Turkey, Slovakia, Israel, Sweden, Poland, Australia and USA.

PGMC, **controls subjects** and patients with **early ALS** or **ALS mimics** (n=110 per group) are currently recruited and assessed longitudinally at **two visits** with a one-year interval (**baseline visit V0** and **follow-up visit V1**). Assessments include a medical and environmental history questionnaire, a neurological examination, a brief smell test examination (B-SIT), a cognitive screening (ECAS) and the collection of biological samples (serum, plasma, urine, tear fluid, and CSF). Proteomic, metabolomic and lipidomic profiles will be analyzed by mass spectrometry and targeted immunoassays. Data will be processed by standardized protocols and consecutively integrated to identify **clinical and molecular fingerprints of PGMC and early ALS**.

Outcomes of the project?

The premodiALS recruitment started in Q1/2023. As of end October 2024, a total of 172 participants were recruited, including **45 controls, 42 PGMC and 85 early ALS/mimics** individuals. Recruitment is still ongoing. Parts of the **biomaterial collected is available** for yet undetermined **collaborative projects** and future analyses not specified in the initial study protocol. The premodiALS project has been presented at several international conferences as well as during patients' days, on the TV and other media of the country members.

Total	
V0	V1
2	
8	1
10	3
39	13
78	50
35	17
172	84



Significance and Impact

The **identification of a panel of pre-symptomatic biomarkers** would enable 1) The identification of individuals at risk of developing ALS before manifest motor symptoms, and 2) confirm ALS diagnosis when the presence of motor symptom are not sufficient. An early detection of the disease would result in a timelier diagnosis offering the opportunities of earlier intervention, earlier inclusion in clinical trials and will facilitate the development of disease-modifying treatments for ALS.

Next steps and future chalanges

A **manuscript detailing the premodiALS protocol** is prepared for submission aiming to promote collaboration and encourage harmonization of protocols across presymptomatic ALS studies. Plasma, serum and CSF samples from the baseline visit (V0) from **110 participants are currently being analyzed** via the multiplex NULISA targeted immunoassay. We aim to **extend the premodiALS study by an additional three years** to 1) extend the recruitment period to include as many participants as originally planned, or even more, and 2) add additional follow-up visits (V2, V3, and V4), each visit separated by one year and ensure a more detailed longitudinal follow-up of the disease evolution.