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FALL 2020

# The ALLFTD Study

*A comprehensive multicenter cooperative study targeting FTLD*

ALLFTD is a comprehensive multicenter cooperative study targeting the spectrum of frontotemporal lobar degeneration disorders (FTLD). The study aims to advance understanding and support the development of treatments for these progressive neurodegenerative disorders.

The goal for ALLFTD is to prepare for clinical trials by improving methods for accurately diagnosing participants with FTLD and measuring disease progression. Specifically, ALLFTD investigators hope to identify **biomarkers** to track biological changes indicative of disease progression and develop ways to predict the risk of worsening symptoms.

As a research consortium comprised of 19 sites in North America, ALLFTD is the combination of previous FTLD-focused research studies: Advancing Research and Treatment in Frontotemporal Lobar Degeneration (ARTFL) and Longitudinal Evaluation of Familial Frontotemporal Dementia Subjects (LEFFTDS).

Funding for ALLFTD, provided jointly from NIH's National Institute on Aging (NIA) and National Institute of Neurological Disorders and Stroke (NINDS), is expected to be more than $63 million over five years to advance the development of treatments for FTLD.

## What is FTLD/FTD?

FTLD is an overarching term that refers to a group of neurodegenerative conditions. Neurodegeneration means that nerve cells (neurons) shrink to a point that connection between cells can no longer happen, eventually causing the nerve cell to die. Disease symptoms develop because neurons can no longer perform their intended functions. FTLD-related symptoms vary depending on what part of the nervous system and what part of the brain is disrupted by these changes.

FTLD usually affects the frontal and/or the temporal lobes of the brain causing social-emotional function, language, memory, and other cognitive functions to be impacted. Sometimes parts of the nervous system that control movement can be impacted, affecting mobility and strength. These movement disruptions can occur with or without social, emotional, or cognitive symptoms. Collectively, the various syndromes caused by

***This glossary is available to help you understand the scientific terms used in this article. Glossary terms are shown in bold the first time they appear.***

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FTLD are often referred to as frontotemporal dementia (FTD). FTLD, however, includes additional disorders not considered typical FTD, such as progressive supranuclear palsy (PSP) and corticobasal syndrome (CBS). ALLFTD is enrolling participants with all of the major FTLD syndromes. Learn more about the different FTLD syndromes here.

An estimated 30 percent of cases of FTLD are familial (f-FTLD), caused by hereditary genetic abnormalities, commonly called mutations. In these instances, several people in the same family can be diagnosed with FTLD. Genetic mutations can also occur in people who have no known family history of FTLD, and the ALLFTD study is hoping to learn more about how this happens, as well as potentially identifying additional FTLD-associated genes. Other FTLD cases in individuals without any mutations known to cause-FTLD are referred to as sporadic (s-FTLD).

## Eligibility and Protocols

This observational study seeks to evaluate symptomatic participants with sporadic (s-) and familial (f-) FTLD, and family members of f-FTLD persons without symptoms.

The study has two different types of visits:

1. A "longitudinal arm" visit, which involves a comprehensive assessment of clinical, functional, imaging, and biofluid data collection annually throughout the course of the study.
2. A "biofluid-focused arm" visit, which involves a one-time clinic visit to collect biospecimens and limited clinical data.

Participants must be 18 years or older and either have a referring FTLD diagnosis or be a member of a family with a strong history of FTLD. Disease syndromes include:


- Frontotemporal lobar degeneration (FTLD)
- Progressive supranuclear palsy (PSP)
- Corticobasal degeneration (CBD)
- Behavioral variant frontotemporal dementia (bvFTD)
- Semantic variant primary progressive aphasia (svPPA)
- Nonfluent variant primary progressive aphasia (nfvPPA)
- FTD with amyotrophic lateral sclerosis (FTD/ALS)
- Amyotrophic lateral sclerosis (ALS)
- Progressive Supranuclear Palsy (PSP) or one of its variant syndromes like pure akinesia with gait freezing.
- Any member of a family with a history that suggests f-FTLD, including:
  - Patients with symptoms of any form of FTLD and
  - People who are part of these families but have either no symptoms or questionable symptoms

In addition, each participant is required to identify a "study partner" (usually a close friend or family member) who can provide perspective on how the participant is doing.

Study participants in the Longitudinal Arm of ALLFTD receive a comprehensive evaluation annually. This annual research visit usually takes about two to three days to complete.

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The visit includes:

- Interview and examination by a physician
- Cognitive testing using traditional "pencil and paper" tests as well as computerized tests
- Interview of the study partner by a nurse or study coordinator
- Brain imaging using MRI
- Blood collection
- Lumbar puncture (often called a spinal tap), optional

Participants and their informants also fill out questionnaires about various aspects of the participant's life, including habits such as exercising, eating, occupation, and hobbies.

ALLFTD has developed remote and "virtual" visits through a subset of their clinical sites. These visits may take place by phone or video; participants may also be asked to visit in person for some procedures such as the blood draw.

Targeted enrollment is 2,100 participants. There are 19 study locations in North America: 17 in the United States and two in Canada.

## The Data

Data and biospecimens collected in this study are stored in several secure locations, established for the purposes of storing and sharing data from large cooperative studies like ALLFTD. All data and specimens have removed any information that could potentially identify participants, thereby maximizing confidentiality.

After going through the ALLFTD Data Request process, qualified and approved investigators are provided the clinical data and biospecimens required for their research project.

ALLFTD has partnered with the FTD Disorders Registry to help provide outreach and conduct remote follow-up on study participants. This will include short surveys to learn more about participants' health journey about a year after their ALLFTD research visit.

"We're excited to be a part of this pivotal study," said FTD Registry Director Dianna Wheaton, Ph.D. "One of the purposes of the FTD Disorders Registry is remote collection of data which eases the study burden on participants and staff. This will reduce the amount of time required for on-site study visits."

## History

The ALLFTD study grew out of collaborations that began in the early 2000s when significant advances in understanding the biology of neurodegenerative diseases were being made. This new cognizance in the pathology of neurodegenerative diseases led to the awareness that treatments for Alzheimer's disease would be different than treatments for FTLD. A one-year study to address these differences in neurodegenerative disease biology began at five different research centers.

Following the success of the initial FTLD-focused research study, two studies followed shortly thereafter, the Frontotemporal Lobar Degeneration Neuroimaging Initiative (FTLDNI) and the **4Repeat Tau Neuroimaging Initiative** (4RTNI). These studies gave insight into how people diagnosed with FTLD change over time.

Adding in the information gathered from the initial FTLD-focused research studies, scientists discovered genetic causes of FTLD due to mutations to the following genes:

1. Microtubule-associated protein tau (*MAPT*)
2. Progranulin (*GRN* or *PGRN*)
3. Chromosome 9 open reading frame 72 (*C9orf72*)

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Additionally, the development of improved cognitive assessments and advancements in PET and MRI scanning have supported a more sophisticated understanding of the biological complexities of FTLD.

Most recently, the ARTFL and LEFFTDS studies began in 2015 with an aim to learn more about FTLD by evaluating more individuals impacted by FTLD than previous research studies. The two studies were extremely successful and enrolled more than 1,400 persons across 17 sites in North America. ALLFTD, a merger and continuation of both of these studies, will build on the data and infrastructure of ARTFL and LEFFTDS and aims to enroll more than 2,000 participants.

## The Sophisticated Staff

It takes numerous people serving in a variety of capacities to set up, oversee, and administer this study.

ALLFTD is co-directed by Dr. Brad Boeve at Mayo Clinic in Rochester, Minnesota, and Dr. Adam Boxer and Dr. Howard Rosen, at the University of California, San Francisco (UCSF). They serve as the principal investigators (PIs). Mayo Clinic serves as the administrative and data management center.

As ALLFTD program managers, Dr. Leah Forsberg, with Mayo Clinic in Rochester, and Dr. Hilary Heuer, with UCSF, together serve as the linchpin to connect the various parts of the study so it functions as a unit. They coordinate between the study's three PIs, each site's investigators, study coordinators, and other team members, and the investigators in each of the study's cores.

Each study location has at least one site PI and a study coordinator, but most sites have a team of staff who play a large role in making the study successful at their site.

## Incorporating the Old and the New

Because ALLFTD is an extension of ARTFL and LEFFTDS, any previous ARTFL or LEFFTDS study participant will be encouraged to continue participating in research by joining ALLFTD. Site facilities, visits, and staff mostly remain the same from the previous two FTLD studies. Some sites have new staff and study coordinators who are learning about FTLD research for the first time while other sites have seasoned personnel. "All of the study coordinators are incredible, with varying degrees of experience and familiarity with FTLD, we're really lucky to have such a great group of coordinators working on this study," said Dr. Forsberg.

"Many of the ALLFTD study procedures are similar (to the ARTFL/LEFFTDS studies)," noted Dr. Heuer, "but we've added some new study elements that we're really excited about, such as new cognitive tests done on a tablet. I think that our research participants will like the new versions of these cognitive tests and the data should be very informative."

More details about FTLD and the study can be found on the ALLFTD website. Information for persons interested in participating as well as for investigators who wish to collaborate by requesting data and samples is also on the website.

**Visit the ALLFTD website**

**Read about ALLFTD on ClinicalTrials.gov**

**Read about the ALLFTD Sophisticated Staff**

**Read about the 3 Study PIs**

**See a list of the study sites, site PIs, and the study coordinators**

**View the Glossary**

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# THE ALLFTD STUDY

**Official Title:** ARTFL LEFFTDS Longitudinal Frontotemporal Degeneration (ALLFTD)

**Brief Summary:**
ARTFL LEFFTDS Longitudinal Frontotemporal Lobar Degeneration (ALLFTD) represents the formalized integration of ARTFL (U54 NS092089; funded through 2019) and LEFFTDS (U01 AG045390; funded through 2019) as a single North American research consortium to study FTLD for 2019 and beyond.

**Condition or disease:**
- Frontotemporal lobar degeneration (FTLD)
- Progressive supranuclear palsy (PSP)
- Progressive Supranuclear Palsy (PSP) Richardson's syndrome or a variant syndrome Corticobasal degeneration (CBD)
- Behavioral variant frontotemporal dementia (bvFTD)
- Semantic variant primary progressive aphasia (svPPA)
- Nonfluent variant primary progressive aphasia (nfvPPA)
- FTD with amyotrophic lateral sclerosis (FTD/ALS)
- Amyotrophic lateral sclerosis (ALS)

**Detailed Description:**
The ARTFL LEFFTDS Longitudinal Frontotemporal Dementia (ALLFTD) study aims to evaluate sporadic (s-) and familial (f-) frontotemporal lobar degeneration (FTLD) patients and asymptomatic family members of f-FTLD patients, characterizing the cohorts longitudinally and informing clinical trial design. The study has two arms: a "longitudinal arm" involving a comprehensive assessment of clinical, functional, imaging, and biofluid data collection annually, and a "biofluid-focused arm" involving limited clinical data to accompany biospecimen collection.

**Study Type:** Observational
**Estimated Enrollment:** 2,100
**Observational Model:** Cohort
**Time Perspective:** Prospective
**Actual Study Start Date:** March 1, 2020
**Estimated Primary Completion Date:** July 2024
**Estimated Study Completion Date:** July 2024

**Groups and Cohorts:**
- Longitudinal Arm: Annual clinic visits throughout the length of the study
- Biofluid-Focused Arm: Single clinic visit

**Outcome Measures:**
1. Change in Brain Volumes [Time Frame: Baseline, 1 Year, 2 Year, 3 Year, 4 Year, 5 Year]
   Compare rates of change in whole brain and regional volumes between asymptomatic f-FTLD and symptomatic f- and s-FTLD, measured using MRI.
2. Change in NIH Examiner Executive Composite Score [Time Frame: Baseline, 1 Year, 2 Year, 3 Year, 4 Year, 5 Year]
   Evaluate change in NIH Examiner Executive Composite Score in asymptomatic f-FTLD.
3. Change in Multidomain Impairment Rating (MIR) Scale [Time Frame: Baseline, 1 Year, 2 Year, 3 Year, 4 Year, 5 Year]
   Annual change in MIR score (total score 0-3), which is a new global scale for FTLD that incorporates behavioral, cognitive, and motor dysfunction in the rating.

**Secondary Outcome Measure:**
1. Plasma Neurofilament Light Chain Analysis [Time Frame: 5 years]
   Annual blood samples will be collected to detect changes in plasma neurofilament light chain concentrations.

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**Biospecimen Retention:** Samples with DNA
DNA, RNA, plasma, serum, PBMC, CSF (CSF is optional)

**Ages Eligible for Study:** 18 years and older (Adults, Older Adult)
**Sexes Eligible for Study:** All
**Accepts Healthy Volunteers:** Yes
**Sampling Method:** Non-probability sample

**Study Population:**
Participants will have a referring diagnosis of an FTLD clinical syndrome or will be a member of a family with a strong family history of an FTLD syndrome.

**Inclusion Criteria:**
Longitudinal Arm Inclusion Criteria

- Familial FTLD (f-FTLD) participants (either is acceptable):
  - members of families in whom at least one member has a known disease-associated mutation in one of the major genes that cause f-FTLD: MAPT, GRN, C9orf72 (or other rare genes)
  - an autosomal dominant family history of an FTLD syndrome (without a known gene) verified by medical record review or well-documented family history including family members with a medical history consistent with FTLD or a related disorder.
- Sporadic FTLD (s-FTLD) participants:
  - Sporadic participants should be symptomatic with no known family history nor a genetic mutation indicating f-FTLD. All sporadic participants must have an FTLD syndrome as a referring diagnosis; those determined by ALLFTD clinicians to have non-FTLD diagnoses will be excluded from longitudinal visits, but their baseline visit will be included in comparative datasets. For inclusion in the longitudinal follow-up, participants should meet research criteria for one of the following FTLD syndromes:
    - ◇ Progressive Supranuclear Palsy (PSP)
    - ◇ Semantic variant Primary Progressive Aphasia (svPPA)
    - ◇ Nonfluent variant Primary Progressive Aphasia (nfvPPA)
    - ◇ Corticobasal Degeneration (CBD)/Corticobasal Syndrome (CBS)
    - ◇ Behavioral variant Frontotemporal dementia (bvFTD)
    - ◇ Frontotemporal Dementia with Amyotrophic Lateral Sclerosis (FTD/ALS)

Biofluid-Focused Arm Inclusion Criteria

- Participants enrolled in the biofluid arm may be either f-FTLD or s-FTLD.
- All general inclusion criteria apply.
- Participants should meet research criteria (as specified above) for any FTLD syndrome or meet familial FTLD inclusion criteria.
- Because the biofluid arm participants do not undergo the same detailed clinical and functional assessments required for the longitudinal arm, participants may be included regardless of primary language, as long as an appropriately translated consent is available.

**Exclusion Criteria:**

- Known presence of a structural brain lesion (e.g. tumor, cortical infarct) that could reasonably explain symptoms in a symptomatic participant.
- Known presence of an Alzheimer's disease-causing mutation in PSEN1, PSEN2 or APP; or biomarker evidence for Alzheimer's disease as a cause of the clinical syndrome.
- A previous history of Korsakoff encephalopathy, severe alcohol dependence (within 5 years of

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onset of dementia), frequent alcohol or other substance intoxication, or other neurological disorder.
- Evidence through history or laboratory testing of uncorrected B12 deficiency (B12 < 95% of local laboratory's normal value), unregulated hypothyroidism (TSH >150% of normal), HIV positive, renal failure (creatinine > 2), liver failure (ALT or AST > two times normal), respiratory failure that requires supplemental oxygen, large confluent white matter lesions, significant systemic medical illnesses such as deteriorating cardiovascular disease.
- Current medication likely to affect CNS functions in the opinion of the site PI.
- In the site investigator's opinion, the participant cannot complete sufficient key study procedures. The participant may be enrolled into the biofluid-focused arm if they can tolerate a blood draw and short clinical exam, but must be able to complete at least 75% of study procedures for enrollment into the longitudinal arm.

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**Additional Information:**
- ALLFTD Study website
- Mayo Clinic Clinical Trials

**Funder:**
- National Institute on Aging (NIA)
- National Institute of Neurological Disorders and Stroke (NINDS)

**Locations:** https://ftdregistry.org/press/sophisticated-staff-coordinates-new-allftd-study#ALLFTD-staff

**Responsible Party:** Bradley Boeve, Principal Investigator, Mayo Clinic

**ClinicalTrials.gov Identifier:** NCT04363684
**Other Study ID Numbers:**
- 19-004543
- U19AG063911 (U.S. NIH Grant/Contract)

**Individual Participant Data (IPD) Sharing Statement:**
**Plan to Share IPD:** Yes
**Plan Description:** De-identified subject level data will be shared upon approved data request.
**Time Frame:** De-identified data will be available for at least the duration of the study.

**Access Criteria:**
Interested researchers must complete a data request through the ALLFTD website. All data requests will be reviewed by a committee for evaluation of scientific merit and feasibility. Please consult the website for additional information regarding this process (https://www.allftd.org/policies).
Approved requests will be delivered in a de-identified manner.

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