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Title

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Permalink

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Journal

Alzheimer's & Dementia, 16(1)

ISSN

1552-5260

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Publication Date

2020

DOI

10.1016/j.jalz.2019.06.4947

Peer reviewed

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The Longitudinal Evaluation of Familial Frontotemporal Dementia Subjects (LEFFTDS) Protocol: Framework and Methodology

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Abstract

INTRODUCTION: It is important to establish the natural history of familial frontotemporal lobar degeneration (f-FTLD) and provide clinical and biomarker data for planning these studies, particularly in the asymptomatic phase.

METHODS: The Longitudinal Evaluation of Familial Frontotemporal Dementia Subjects protocol was designed to enroll and follow at least 300 subjects over at least three annual visits who are members of kindreds with a mutation in one of the three most common f-FTLD genes – microtubule associated protein tau, progranulin or chromosome 9 open reading frame 72.

RESULTS: We present the theoretical considerations of f-FTLD and the aims/objectives of this protocol. We also describe the design and methodology for evaluating and rating subjects, in which detailed clinical and neuropsychological assessments are performed, biofluid samples are collected and MRI scans are performed using a standard protocol.

DISCUSSION: These data and samples, which are available to interested investigators worldwide, will facilitate planning for upcoming disease-modifying therapeutic trials in f-FTLD.

Keywords

frontotemporal dementia; genetics; *MAPT*; *GRN*; *C9orf72*; tau; TDP-43

1. Introduction

Frontotemporal lobar degeneration (FTLD) is caused by two major proteinopathies– microtubule associated protein tau and TAR DNA binding protein molecular weight 43 [1, 2]. At least 20% of all FTLD presents as a dominantly inherited familial disorder (f-FTLD), usually due to mutations in the microtubule associated protein tau (*MAPT*) [3], progranulin (*GRN*) [4], or chromosome 9 open reading frame 72 (*C9orf72*) [5, 6] genes, which together account for at least 50% of f-FTLD [7–9]. Because each mutation is highly predictive of a specific proteinopathy, the study of f-FTLD mutation carriers has the unique opportunity to provide specific biochemical targets in clinical drug studies. In addition, f-FTLD is currently the only practical way to identify people in asymptomatic or very early symptomatic stages of FTD, making it the best context for testing drugs aimed at delaying symptom onset. To prepare for disease-modifying trials, it is important to establish the natural history of f-FTLD and provide clinical and biomarker data for planning these studies, particularly in the asymptomatic phase.

The rates of clinical and biomarker change in f-FTLD are complex and dynamic (Figure 1). The alterations in the molecular biology of tau, progranulin and the granulins, C9RAN proteins, etc., undoubtedly occur early in life during the presymptomatic phase. As neuronal and/or glial dysfunction evolves, changes in neuronal networks occur over an acceleration phase which can be demonstrated on neuroimaging measures, with functional MR changes likely preceding structural MR changes. Various other ancillary studies, including behavioral measures, neuropsychological measures, motor measures, etc., likely show the evolution of clinically silent to very minimally evident cognitive, behavioral or motor changes over the several year transitional period from presymptomatic to prodromal to minimally symptomatic phases of f-FTLD. MR-based and other imaging measures likely change over this transitional period also. Additional changes occur with the onset of overt symptoms and continue onward through the mild, moderate, severe and terminal phases of the symptomatic period – the latter aspects likely evolve in a decelerated manner. This hypothesized cascade of dynamic changes is analogous to what has been proposed in the evolution of Alzheimer's disease [10, 11].

While there is growing data that supports the cascade of events and findings just described [12–26], many of the findings are based on cross-sectional analyses, and little longitudinal data has been published thus far. Plus, many questions remain. How does one predict the

onset of symptoms and rate of progression? What dictates the initial seed of neuronal dysfunction and hence the constellation of early features and evolving neuronal network dysfunction and associated clinical phenomenology over time? Why do some mutation carriers develop symptoms early in life while others never develop symptoms (i.e., incomplete penetrance)? Longitudinal evaluations of a large number of individuals in families with known mutations, followed prospectively in a standardized and comprehensive manner, offer the best hope of providing insights to these and other questions while also informing investigators how to optimally design clinical trials.

We sought to address many of these questions as part of the Longitudinal Evaluation of Familial Frontotemporal Dementia Subjects or LEFFTDS protocol (UO1 AG045390). We describe herein the design and methodology of the LEFFTDS protocol. The initial baseline characteristics and analyses and other topics will be reported separately.

2. Objectives/Aims

The specific aims/objectives of the LEFFTDS protocol are:

1. To model the rates of decline in traditional measures of clinical (neuropsychological and behavioral composites) function and cortical volume on structural MRI in the *symptomatic* phase (+mFTLD-CDR>0) of f-FTLD.

2. To model the rates of decline in traditional measures of clinical (neuropsychological and behavioral composites) function and cortical volume on structural MRI in the a*symptomatic* phase (+mFTLD-CDR=0) of f-FTLD.

3. To assess the value of novel imaging and clinical measures for characterizing asymptomatic f-FTLD subjects, and identify factors predicting clinical rates of progression in each group.

4. To identify genetic and biofluid factors that modify rates of clinical and neuroimaging decline in the asymptomatic and symptomatic phases of f-FTLD.

These aims are shown schematically in e-figures 1–4.

Note that the term "asymptomatic" is preferred over "presymptomatic" in the context of these LEFFTDS aims since there is incomplete penetrance across all three major genetic groups.

3. Study Design

3.1 Overview

The overall schema for the LEFFTDS protocol is shown in Figure 2. The project is designed to enroll at least 300 subjects from families with f-FTLD into a longitudinal clinical and biomarker study. The subjects are recruited based on interest of potential participants, with the expectation that enrollment will transpire in an approximately even fashion across kindreds with mutations in three most common genes associated with f-FTLD: *MAPT* (n=100), *GRN* (n=100) and *C9orf72* (n=100). Our goal was to recruit approximately equal numbers of symptomatic mutation carriers, asymptomatic mutation carriers, and non-carriers

(i.e., familial controls). At least three annual assessments (henceforth termed "visits") for each subject are planned over this five year phase of the study. Each visit includes a clinical assessment, biofluid sampling with blood and CSF collection, and MRI; CSF collection is optional. The clinical data is entered into an electronic data capture system (via the iMedidata RAVE system, Houston, TX). The majority of the data is collected using measures in the Uniform Data Set (UDS) and Frontotemporal Lobar Degeneration (FTLD) Module of the National Alzheimer's Coordinating Center (NACC), and these data are uploaded to NACC at the University of Washington. Blood and CSF are collected and sent to the National Cell Repository for Alzheimer's Disease (NCRAD) at Indiana University. Aliquots of DNA, plasma and CSF are sent to LEFFTDS-associated laboratories for genotyping and protein quantification. Brain MRI is performed using a standardized protocol similar to the Alzheimer's Disease Neuroimaging version 3 (ADNI-3) protocol. The data is transferred to the Laboratory of Neuroimaging (LONI) at the University of Southern California, and downloaded and assessed at Mayo Clinic Rochester for quality review. All data and samples are available to internal and external investigators. *The overarching design of the LEFFTDS protocol is to address the specific aims and to provide clinical, biofluid and neuroimaging samples and data to investigators*. More details on this infrastructure and procedures are described below.

3.2   Recruitment

The subjects are recruited from subjects/kindreds already identified at the collaborating centers. In addition, referrals are solicited from other centers interested in f-FTLD, the Association for Frontotemporal Degeneration (www.theaftd.org), and the ClinicalTrials.gov websites for LEFFTDS (https://clinicaltrials.gov/show/NCT02372773) and a closely related protocol known as the Advancement in Research and Treatment for Frontotemporal Lobar Degeneration (ARTFL) (https://www.rarediseasesnetwork.org/cms/artfl/). Interested subjects and clinicians are welcome to contact any of the individuals listed on this ClinicalTrials.gov websites. A website for the LEFFTDS protocol is under development at the time of this writing.

3.3   Inclusion/exclusion criteria

Subjects are eligible for enrollment if they are members of families with a known mutation in one of the three major FTLD related genes: *MAPT*, *GRN*, and *C9orf72* and is age 18 or older, and preferably above age 30. Other inclusion criteria include: the predominant phenotype in the kindred should be cognitive/behavioral (ie, kindreds in whom bvFTD or PPA is the predominant clinical phenotype among affected relatives is favored over parkinsonism or ALS, although all phenotypes are eligible for enrollment), a reliable informant who personally speaks with or sees that subject at least weekly, subject is sufficiently fluent in English to complete all measures, willing and able to consent to the protocol and undergo yearly evaluations, willing and able to undergo neuropsychological testing (at least at the baseline visit), and no contraindication to MRI imaging. Exclusion criteria include: absence of a known mutation in *MAPT, GRN* or *C9orf72* in the subject or family, presence of a structural brain lesion (eg, tumor, cortical infarct), presence of another neurologic disorder which could impact findings (eg, multiple sclerosis), unwillingness to

return for follow-up yearly, unwillingness to undergo neuropsychological testing and MR imaging, and no reliable informant.

Individuals are not required to know or learn their own genetic status, but all are offered the option of determining the mutation carrier status via genetic testing after genetic counseling. Genetic results are confirmed by a CLIA approved lab before disclosure. Counseling and testing services are paid for by the study.

3.4 Ethics

This protocol has been reviewed and approved by all local institutional review boards.

4. Procedures

4.1 Overview

A summary of the procedures for each visit is shown in Figure 3. The procedures can be viewed as five arms – clinical, biofluid-blood, MRI, biofluid-CSF and genetic testing. Each visit includes, at a minimum, the clinical evaluation, blood draw as well as MRI scanning; the CSF arm and genetic testing arms are optional. A genetic evaluation for counseling with our without genetic testing is available for any subject who desires it.

4.2 Enrollment

Each presumed asymptomatic subject reviews and provides written consent. Each subject also identifies a reliable informant to provide collateral history – typically a spouse, sibling, parent or adult child. For symptomatic subjects, the person provides written consent if deemed to have capacity; for those who are not viewed as having capacity, the informant is the proxy who provides written consent and the participant provides written assent.

4.3 Clinical arm

All subjects undergo a detailed interview, examination and neuropsychological assessment. Each informant is also interviewed. The data, measures [27–63] and databases where the data are stored are summarized in Table 1.

Most of the subject- and informant-based questionnaires/measures are administered by a trained study coordinator who is experienced in assessing FTLD subjects. All measures are completed in-person with subjects and informants whenever possible; when this is not feasible (ie, insufficient time during the scheduled in-person visit, informant not present), then measures are completed by telephone. The standard medical/neurologic interview and examination is completed face-to-face by a clinician experienced in FTLD, which is usually the site PI. The clinician interviews the informant in person or by telephone whenever feasible. The neuropsychological battery is administered by a trained psychometrist who is experienced in assessing FTLD subjects.

Most of the data are collected using measures developed by the National Alzheimer's Coordinating Center (NACC) Uniform Data Set (UDS) Task Force, which comprise the UDS version 3.0 (UDS 3.0) [48]. While the UDS measures have been applicable to subjects

with normal cognition, mild cognitive impairment and a variety of dementia syndromes, the focus over many years was on subjects with MCI and AD dementia. In order to support FTLD research, the NIA and NINDS jointly funded the FTLD Module Task Force which led to the creation of the measures expanding the characterization of the cognitive, behavioral, language and motor features typical of FTLD spectrum disorders. More information on UDS 3.0, the FTLD Module and other aspects of NACC can be found at: https://www.alz.washington.edu/.

Both the LEFFTDS and ARTFL protocols were designed to develop methodology and infrastructure to prepare for therapeutic trials in FTLD. Some measures were therefore added to both protocols to supplement the UDS and FTLD Module – these are designated as being only in the ARTFL/LEFFTDS (A/L) database in Table 1.

4.4 Clinical ratings and diagnoses

4.4.1 Overview—The key ratings for the assessment team include the CDR® and the NACC FTLD Module scale [64] (which is a modification of the standard CDR® Dementia Staging Instrument, [65] – more details on these scales are below), neuropsychological data, the consensus clinical diagnostic assessment and the confidence rating. The measures used in the diagnostic ratings and assessment are shown in Figure 4 and Tables 2 and 3.

To broaden the utility of the Clinical Dementia Rating scale (which is now known as the CDR® Staging Instrument and will be abbreviated as CDR® hereafter), into FTLD spectrum disorders, the Behavior/Comportment/Personality and Language domains were added to the CDR® to form the 8-domain "FTLD-CDR". The older terminology "FTLD-CDR" represented the exact same group of measures now used by the updated name of "CDR® Dementia Staging Instrument PLUS National Alzheimer Coordinating Center (NACC) Frontotemporal Lobar Degeneration (FTLD Module Behavior & Language Domains (CDR® plus NACC FTLD). Since the CDR® is now trademarked, this updated abbreviation for the 8-domain ratings was proposed by the developers of CDR® and the NACC FTLD Module, and all references to this combination of measures will be abbreviated "CDR® plus NACC FTLD" henceforth in this manuscript.

A foundation of the LEFFTDS protocol is the rating of each subject as normal or not, and if not normal, how severely abnormal (questionable, mild, moderate, severe) each subject is. The CDR® scale, adapted more for FTLD spectrum cases to represent the CDR® plus NACC FTLD scale, was determined to be the initial benchmark.

The six domain CDR® has functioned very well in the Alzheimer's disease clinical spectrum. Two additional domains were added as part of the FTLD Module – behavior/comportment and language – but these ratings are viewed separately from the six domains and have not been incorporated into a FTLD-specific global score. Motor dysfunction as seen in FTD with parkinsonism, PSP, CBS and ALS is also important in the clinical and functional assessment of FTLD subjects, requiring a motor domain to be designed – this is under development at the time of this writing.

Another key aspect of FTLD characterization, particularly in the early phenoconversion transition from normal to minimally symptomatic, is to determine the drivers of change. One could hypothesize that for some syndromes (eg, bvFTD), the data from the informant's interview may be more informative than the data from the subject's interview and neurologic exam and the traditional neuropsychological data. For other syndromes (eg, PPA), the data from the subject's interview and exam as well as the language-based neuropsychological data would be most informative. To capture these scenarios in order to test hypotheses, it would be important to analyze data based on 1) interactions with and measures completed by the clinician with the *subject*, 2) interactions with and measures completed by the *informant*, and 3) the *neuropsychological assessment*. Furthermore, attempts should be made to complete these ratings as independently as is feasible. Finally, a consensus rating considering all data would be the key classification for determining the clinical status at any given visit. It would also be possible for investigators to go back and analyze data from different rating streams to earlier visits to determine which data was optimally predictive of phenoconversion.

4.4.2   CDR® plus NACC FTLD—There are two scores that are generated as part of the CDR® plus NACC FTLD scoring system – the global CDR® plus NACC FTLD score and the CDR® plus NACC FTLD Sum of the Boxes (SB). For the CDR® plus NACC FTLD SB score, the value is determined by simply adding all 8 of the domain scores.

The global CDR® plus NACC FTLD is more complex. First, it does NOT follow the standard CDR® algorithm. For example, if there are one or more scores of 0.5 in the non-memory domains of the standard CDR®, the global score may still be 0; this standard CDR® algorithm was developed to emphasize the importance of at least mild memory impairment for the global value of the standard CDR® to be >0 for those with suspected Alzheimer's disease pathology. Since the earliest manifestations of evolving FTLD are usually non-memory, the CDR® plus NACC FTLD does not require memory impairment to score >0 – any domain score >0 will result in a global score >0. The guidelines of the CDR® plus NACC FTLD global score are therefore as follows:

1. If all domains are 0, the global CDR® plus NACC FTLD score is 0.

2. If the maximum domain score is 0.5, the global CDR® plus NACC FTLD score is 0.5.

3. If the maximum domain score is above 0.5 in any domain, then the following applies:

    A. If the maximum domain score is 1 and all other domains are 0, the global CDR® plus NACC FTLD score is 0.5.

    B. If the maximum domain score is 2 or 3 and all other domains are 0, the global CDR® plus NACC FTLD score is 1.

    C. If the maximum domain score occurs only once, and there is another rating besides zero, the global CDR® plus NACC FTLD score is one level lower than the level corresponding to maximum impairment (e.g. if maximum = 2, and there is another rating besides zero, the global

> CDR® plus NACC FTLD score is 1; if maximum = 1, and there is another rating besides zero, the global CDR® plus NACC FTLD score is 0.5).

> **D.** If the maximum domain score occurs more than once (e.g. 1 in 2 domains, 2 in 2 domains), then the global CDR® plus NACC FTLD score is that maximum domain score.

4.4.3 ARTFL-LEFFTDS (A/L) FTLD-CDR classification—The A/L FTLD-CDR classification was developed in an attempt to categorize subjects for purposes of comparison similar to the manner with which the classic CDR® score has served the aging and Alzheimer's disease field for many years; the Behavior/Comportment and Language domains were added to the classic CDR® in an attempt to capture similar degrees of neurologic impairment among the phenotypic variability inherent to f-FTLD. Note that the "CDR" in this A/L FTLD-CDR classification scheme represents a more broad clinical dementia rating perspective. The criteria for this A/L FTLD-CDR classification are as follows:

A/L FTLD-CDR=0 - Asymptomatic: These subjects have a) normal cognitive, behavioral/comportment and language functioning based on the absence of subjective complaints of cognitive, behavioral, and language changes from their baseline, b) a global CDR® plus NACC FTLD score of 0, and c) cognitive/behavioral/language functioning based on a normal neurologic examination and performance on neuropsychological and behavioral measures within normal limits.

A/L FTLD-CDR=0.5 – Questionably/Minimally Symptomatic: These subjects generally have a) a questionable or mild change in cognitive, behavioral, or language functioning based on the subject and/or informant, b) a global CDR® plus NACC FTLD score of 0.5, c) a mild degree of impairment in cognitive/behavioral/language functioning based on neurologic examination and/or neuropsychological and behavioral measures, and d) does not fulfill established criteria for probable bvFTD, PPA, or another defined neurodegenerative disorder.

A/L FTLD-CDR=1 – Definitely and mildly symptomatic: These subjects generally have a) at least mild change in cognitive, behavioral, or language functioning based on the subjects and/or informant, b) a global CDR® plus NACC FTLD score of 1, and c) at least mild degree of impairment in cognitive/behavioral/language functioning based on neurologic examination and/or neuropsychological and behavioral measures, and d) does fulfill established criteria bvFTD, PPA, or another defined neurodegenerative disorder.

A/L FTLD-CDR>1 - Definitely and moderately to severely symptomatic: Subjects with moderate severity dementia (or moderate degree of neurologic impairment associated with another defined neurodegenerative disorder) plus a moderate degree of dependency on caregivers +/− devices would be classified as FTLD-CDR=2, and those with severe dementia (or severe degree of neurologic impairment associated with another defined neurodegenerative disorder) plus near complete or complete dependency on caregivers +/− devices would be classified as FTLD-CDR=3.

Atypical cases: Any subjects who do not fulfill any set of criteria as stated above are classified in the most appropriate A/L FTLD-CDR category (e.g. a subject who fulfills criteria a and b for A/L FTLD-CDR=0.5 but has a normal neurologic examination and normal neuropsychological scores will be classified as A/L FTLD-CDR=0.5 since this designation best approximates the criteria.

4.4.4   Clinicogenetic classification—The clinical classification scheme described above was designed to be paired with the genetic status of any subjects, such that the presence (+m) or absence (−m) of a mutation is followed by the clinical code (e.g., +mFTLD-CDR=0 for asymptomatic mutation carrier). This is described in more detail below.

4.4.5   ARTFL/LEFFTDS Clinical Diagnosis and Confidence Rating Form—This form (Table 3) permits the consensus committee to render primary (and secondary and tertiary, when appropriate) diagnoses – including mild features outside of the amnestic and non-amnestic categories of MCI – as well as make a confidence rating (0–100% confident) in the primary diagnosis.

<u>**MCI-behavior.:**</u> In the FTLD field, it is not uncommon for patients to have mild behavioral changes that are definitely a change from baseline, but these changes are not of sufficient severity to warrant a diagnosis of dementia, or more specifically, behavioral variant FTD. Some investigators have applied the term "mild behavioral impairment or MBI" for this phenotype, but this terminology and its interpretation are increasingly being used in the setting of Alzheimer's disease and/or Lewy body disease and not necessarily applicable to FTLD. We have therefore chosen to use the term "MCI-behavior" and purposefully use this diagnosis loosely, since there are no operational criteria for this presumed intermediate stage in the normal to bvFTD evolution.

A reasonable application of the MCI-behavior diagnosis would be in the setting of any patient who exhibits features and findings consistent with clinically possible bvFTD using the Consensus criteria (see below) [66]. In other words, the presence of one or more of the following would be fitting for MCI-behavior:

- Disinhibition: Socially inappropriate behavior; loss of manners or decorum; impulsive, rash, or careless actions

- Apathy or inertia: Loss of interest, drive, and motivation; decreased initiation of behavior

- Loss of sympathy/empathy: Diminished response to other people's needs or feelings; diminished social interest, interrelatedness, or personal warmth

- Ritualistic/compulsive behavior: Simple repetitive movements or complex compulsive or ritualistic behaviors

- Hyperorality and appetite changes: Altered food preferences, binge eating, increased consumption of alcohol or cigarettes, oral exploration or consumption of inedible objects

Importantly, particularly in familial FTD, there are circumstances in which delusions, hallucinations, and other forms of odd behavior may be part of the evolving behavioral phenotype. Therefore, the diagnosis of MCI-behavior is a loosely-defined clinical diagnosis which will be operationalized with more rigor in the future after more data is gathered and analyzed.

Accessing data.: The procedures for accessing data from the clinical arm are described in the Accessing Data and Samples section below.

4.5   Biofluid arm - Blood

The procedures involved in acquiring, processing, storing and accessing biofluid samples are described in detail on the National Cell Repository for Alzheimer's Disease (NCRAD) website (https://ncrad.iu.edu/). Briefly, each subject undergoes a blood draw in the morning after an overnight fast. The blood is obtained to collect DNA, plasma, serum (serum collection began in mid-2016), RNA and PBMC. The blood is collected in appropriate tubes and processed; the tubes designed for PBMC generation are submitted overnight express to NCRAD, and the others are submitted later as batch shipments to NCRAD.

ARTFL/LEFFTDS blood biofluid sample processing.—Several key analyses on biofluid samples are carried out internally in specialized laboratories within the ARTFL/ LEFFTDS consortium so that the specific aims can be addressed. Aliquots of blood for each subject are sent from NCRAD to UCLA (Giovanni Copolla, PhD, site PI for genomic analyses) for DNA analysis (see additional description below), and to Mayo Clinic Florida (Rosa Rademakers, PhD, site PI for genomic/proteomic analyses) for genotyping of modifier genes such as *TMEM106B*. An aliquot of plasma is also sent to Dr. Rademakers's laboratory for progranulin quantification. The results from these laboratories are then submitted securely to a separate ARTFL/LEFFTDS Genomic/Proteomic database within the RAVE system that is purposefully housed separate from the clinical data. Access to this database is password-protected and only accessible by a few key staff.

Accessing data/samples.—The procedures for accessing data from the biofluid-blood arm within the ARTFL/LEFFTDS Genomic/Proteomic database are described in the Accessing Data and Samples section below.

4.6   Biofluid arm - CSF

All participants are asked to undergo CSF collection, and this arm is optional. The procedures involved in acquiring, processing, storing and accessing CSF samples are described in detail on NCRAD website (https://ncrad.iu.edu/). Briefly, CSF is collected via standard lumbar puncture procedures in polypropylene tubes and aliquoted.

ARTFL/LEFFTDS CSF biofluid sample processing.—Several key analyses on CSF samples will be carried out internally in specialized laboratories within the ARTFL/ LEFFTDS consortium; these samples will be analyzed at periodic intervals to permit standardization across measures. Additional information is provided below. The results from

these laboratories are then submitted securely to the ARTFL/LEFFTDS Genomic/Proteomic database.

Accessing data/samples.—The procedures for accessing data from the biofluid-CSF arm within the ARTFL/LEFFTDS Genomic/Proteomic database are described in the Accessing Data and Samples section below.

4.7 MRI arm

Acquisition.—Images are acquired at all centers at 3Tesla using sequences that are harmonized across multiple vendors (i.e. GE, Siemens, and Phillips), and similar to those employed in the Alzheimer's Disease Neuroimaging Initiative – versions 2 and 3 (ADNI-2 and ADNI-3 basic) protocols (see: http://adni.loni.usc.edu/methods/documents/mri-protocols/). Scanning begins with a three-planar localizer scan and an auto-alignment scout scan which yields orthogonal orientation and AC-PC alignment followed by MRI sequences as follows. **1) T1-weighted MPRAGE** with parameters: TR/TE/TI = 2300//900 ms, flip angle of 9 degrees, a bandwidth of 240 Hz/pixel, sagittal orientation with a FOV = 256×240 mm with slices. Time is min. **2) T2-weighted FLAIR:** TR/TE/TI = 6000/390/2100 ms with a 800 ms long turbo spin echo readout train, 750 Hz/pixel bandwidth with 3mm. slice thickness. Time is 7 min. **3) Diffusion Tensor imaging (DTI):** A 2D single-shot gradient echo sequence with TR/TE = 7200/56 ms, a 232×232 base matrix, 2.0 mm slices yielding $2.0 \times 2.0 \times 2.0$ mm isotropic resolution [67, 68]. The sequence is augmented by diffusion encoding gradients and incorporates two refocusing pulses to reduce distortions from eddy-currents. Diffusion-weighting gradients will be applied along 48 directions with b=1000 mm^2/s. Time is 7:30 min. **4) Arterial Spin Labeled (ASL) perfusion imaging**: The ASL protocol consists of a 3D (FSE) pseudo-continuous ASL sequence with an interleaved stack-of-spiral readout and background suppression on GE scanners [69]. The imaging parameters used were, a labeling duration of 1450 ms, post labeling delay of 2025 ms, repetition time/echo time of 4800/10 milliseconds, refocusing flip angle 111 degrees, FOV 240 mm, acquisition matrix 512/8 samples re-gridded to a 128×128 matrix with an in-plane reconstructed resolution of 1.875×1.875 cm^2; 40 slices with slice thickness 4mm, no gap. 3 excitation averages of label and control volume pairs are acquired, as well as a proton density (PD) weighted volume using the same readout scheme, resulting in an overall scan duration of 4:30 min. **5) Intrinsic Connectivity Network functional MRI (ICN fMRI):** A T2*-weighted gradient echo–echo planar sequence with TR/TE = 3000/30 ms, flip angle 90°; FOV = 210×210 mm; matrix size: 64×64; 3.3 mm slices with 2.5×2.5 mm in-plane resolution. Subjects are instructed to keep their eyes open. Time is 10 min.

Processing.—Quality control (QC) measures are performed at Mayo Clinic Rochester, which permits analytic integrity across centers and MRI scanner manufacturers. All scan data along with QC data for each scan are uploaded to the Laboratory of Neuroimaging (LONI), Arthur Toga, PhD, site PI (website: http://www.loni.usc.edu/).

4.8 Clinical genetics arm

Each subject enrolled in LEFFTDS has a personal history or family history of a known mutation in *MAPT, GRN* or *C9orf72*. Each subject who is not already aware of their

mutation status (positive versus negative), whether asymptomatic or symptomatic, is offered the opportunity to undergo genetic counseling and genetic testing (which includes assessment of psychologic/psychiatric status to determine mental readiness and psychological fitness). In those who are deemed appropriate for genetic testing, a clinical blood sample is collected (usually via cryopreservation) and then a portion of this sample is submitted to a CLIA-approved laboratory for testing; most sites use Mayo Medical Laboratories for this purpose (https://www.mayomedicallaboratories.com/). Results of genetic testing are then provided at least three weeks later according to site-specific procedures.

The specific procedures for psychologic/psychiatric assessment, genetic counseling, genetic testing and results disclosure are according to clinical practice guidelines at each site.

4.9 Research genetic and proteomic analyses

Individuals recruited into this study are part of known *MAPT*, *GRN* or *C9ORF72* mutation families. For each family member we therefore specifically sequence the exon harboring the known *MAPT*, *GRN* or *C9ORF72* mutation observed in that family using previously published protocols[4, 5, 70]; sequencing is also performed to detect variants in the following genes: *TARDBP, PSEN1, PSEN2, APP;* For individuals from *C9ORF72* mutation families, the presence of an expanded GGGGCC hexanucleotide repeat is considered likely pathogenic if the characteristic stutter amplification pattern is present on the electropherogram [5]. For all expanded repeat carriers the approximate length of the repeat in blood is determined using Southern blot analysis as published[5]. Taqman SNP genotyping assays are further used to genotype rs5848 (*GRN*), rs1990622 (*TMEM106B*) and rs1799990 (*PRNP*) as well as the extended *MAPT* H1 and H2 haplotypes (rs1052553) and *APOE* genotypes (rs7412 and rs429358) in all individuals. Progranulin expression levels are measured in human plasma samples using the human Progranulin ELISA kit (Adipogen Inc., Seoul, Korea) using a 1:100 dilution of plasma samples and undiluted CSF samples.

Aliquots of CSF for each subject are sent from NCRAD to University of Pennsylvania (Les Shaw, PhD, site PI for CSF proteomic analyses) for quantification of AB42, total tau and phospho-tau; and to Mayo Clinic Florida (Rosa Rademakers, PhD, for progranulin quantification and to Len Petrucelli, PhD, for C9RAN translation quantification). Progranulin expression levels are measured in CSF samples using the human Progranulin ELISA kit (Adipogen Inc., Seoul, Korea) using a 1:100 dilution of plasma samples and undiluted CSF samples. C9RAN protein is quantified as previously described [71]. Samples are run in duplicate and six interplate control samples will be used to adjust for plate-to-plate variation.

4.10 Clinicogenetic characterization

Many scientific questions are anchored on the clinical plus genetic status of subjects. For example, are there differences in clinical, biofluid or imaging measures in f-FTLD between asymptomatic mutation and non-mutation carriers? What is the temporal course of change on clinical, biofluid and imaging measures of mutation carriers as they transition from the asymptomatic to the symptomatic state? Therefore, a clinicogenetic characterization system

was developed so that each subject is assigned to one of the following categories: asymptomatic non-mutation carriers (−mFTLD-CDR=0), asymptomatic mutation carriers (+mFTLD-CDR=0), and symptomatic mutation carriers (+mFTLD-CDR>0). Depending on the analysis of interest, the +mFTLD-CDR>0 group can be further subclassified as +mFTLD-CDR=0.5, +mFTLD-CDR=1, +mFTLD-CDR=2 and +mFTLD-CDR=3.

An obvious tenet to the LEFFTDS approach is ensuring confidentiality and blinding. For those subjects who undergo the clinical genetic testing arm of the protocol, while they can share the results of testing with any of the research staff with whom they come in contact, this process is not encouraged so as to promote blinding of the study staff. For those subjects who do not wish to undergo clinical genetic testing, all research staff who may interact with the subjects or their relatives *must* remain blind to the genetic test results which are performed for the purposes of the protocol. The research genetic testing is performed at UCLA, and the results for each subject based on their subject code (but not name or other identifying information) are uploaded into a secure database.

4.11 Accessing data and/or samples

The schema for accessing data and/or samples is shown in Figure 2. The clinical data (which includes neuropsychological data) can be accessed via two mechanisms – the ARTFL/LEFFTDS database management system (RAVE) or the NACC; note that the data in the ARTFL/LEFFTDS RAVE system includes more measures, and can also potentially be attached to genetic and biofluid data if desired. The process for requesting data is explained at the website: https://ucsf.co1.qualtrics.com/jfe/form/SV_e4BBGMiXV7HRTg1. The data requests are reviewed by committee and adjudicated in a timely fashion, and data is provided in a secure manner after all vetting and confidentiality measures are satisfied. Clinical data focused on UDS 3.0 and FTLD Module measures can be requested at NACC at the website: https://www.alz.washington.edu/.

Samples can be requested by accessing the NCRAD website and following all procedures as described at the website: https://ncrad.iu.edu/accessing_data.html. A minimum data set of clinical and genetic information can be attached to each sample. If more detailed clinical and/or imaging data is desired in addition to samples, then this website should also be accessed: https://ucsf.co1.qualtrics.com/jfe/form/SV_e4BBGMiXV7HRTg1. The sample request and approval processes are similar to those regarding the clinical +/− genetic data. Samples are provided to investigators in a blinded manner, in which the investigator is expected to submit all findings derived from his/her analyses for incorporation into the full ARTFL/LEFFTDS database. Additional aspects on this process are explained at these websites and associated links.

MR imaging scan data can be accessed as described on the LONI website: http://www.loni.usc.edu/. There is a quality control file associated with each scan. A minimum data set of clinical and genetic information is also attached to each scan. If more detailed clinical and/or genetic data is desired in addition to scans, then this website should also be accessed: https://ucsf.co1.qualtrics.com/jfe/form/SV_e4BBGMiXV7HRTg1. Additional aspects on this process are explained at these websites and associated links.

5. Future considerations

The methods and processes described herein will surely undergo evolution in the future. Updates will be maintained in the website (under construction). The LEFFTDS protocol is also similar in many ways to the Genetic Frontotemporal Dementia Initiative (GENFI) study in Europe and Canada, and attempts to harmonize many aspects of LEFFTDS and GENFI will continue over the years ahead.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Acknowledgements

Abbreviations

ALS	amyotrophic lateral sclerosis
ARTFL	Advancing Research and Treatment for Frontotemporal Lobar Degeneration
bvFTD	behavioral variant frontotemporal dementia
C9ORF72	gene encoding chromosome 9 open reading frame 72
CDR®	CDR® Dementia Staging Instrument
CDR® plus NACC FTLD	CDR® Dementia Staging Instrument plus NACC FTLD Behavior and Language Domains
CSF	cerebrospinal fluid
DNA	deoxyribonucleic acid
FTD	frontotemporal dementia
f-FTLD	familial frontotemporal lobar degeneration
LEFFTDS	Longitudinal Evaluation of Familial Frontotemporal Dementia Subjects
MAPT	gene encoding microtubule associated protein tau
MRI	magnetic resonance imaging
NACC	National Alzheimer's Coordinating Center
NCRAD	National Cell Repository for Alzheimer's Disease
PBMC	peripheral blood mononuclear cells
GRN	gene encoding progranulin
PPA	primary progressive aphasia

RNA	ribonucleic acid
−mFTLD-CDR=0	asymptomatic non-mutation carriers (familial controls)
+mFTLD-CDR=0	asymptomatic mutation carriers
+mFTLD-CDR>0	symptomatic mutation carriers

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Research in Context

1. Systematic review: The authors reviewed the literature using traditional (e.g., PubMed) sources and meeting abstracts and presentations.

2. Interpretation: Our methodology provides details on the recruitment scheme, evaluation and rating procedures, and processes for accessing data and samples.

3. Future directions: The manuscript proposes a framework for the considering the dynamic processes associated with familial frontotemporal lobar degeneration evolution. The data and samples collected in this protocol, which are available to interested investigators worldwide, will be used to test this framework as well as facilitate planning for upcoming disease-modifying therapeutic trials in f-FTLD.

Highlights

- It is important to establish the natural history of familial frontotemporal lobar degeneration (f-FTLD) and provide clinical and biomarker data for planning these studies, particularly in the asymptomatic phase.

- The Longitudinal Evaluation of Familial Frontotemporal Dementia Subjects (LEFFTDS) protocol was designed to enroll and follow members of kindreds with a mutation in one of the three most common f-FTLD genes – microtubule associated protein tau, progranulin or chromosome 9 open reading frame 72.

- The theoretical considerations of f-FTLD, aims/objectives of the LEFFTDS protocol, design and methodology for evaluating and rating subjects, and scheme for collecting biofluid samples and performing MRI scans are described.

- These data and samples, which are available to interested investigators worldwide, will facilitate planning for upcoming disease-modifying therapeutic trials in f-FTLD.
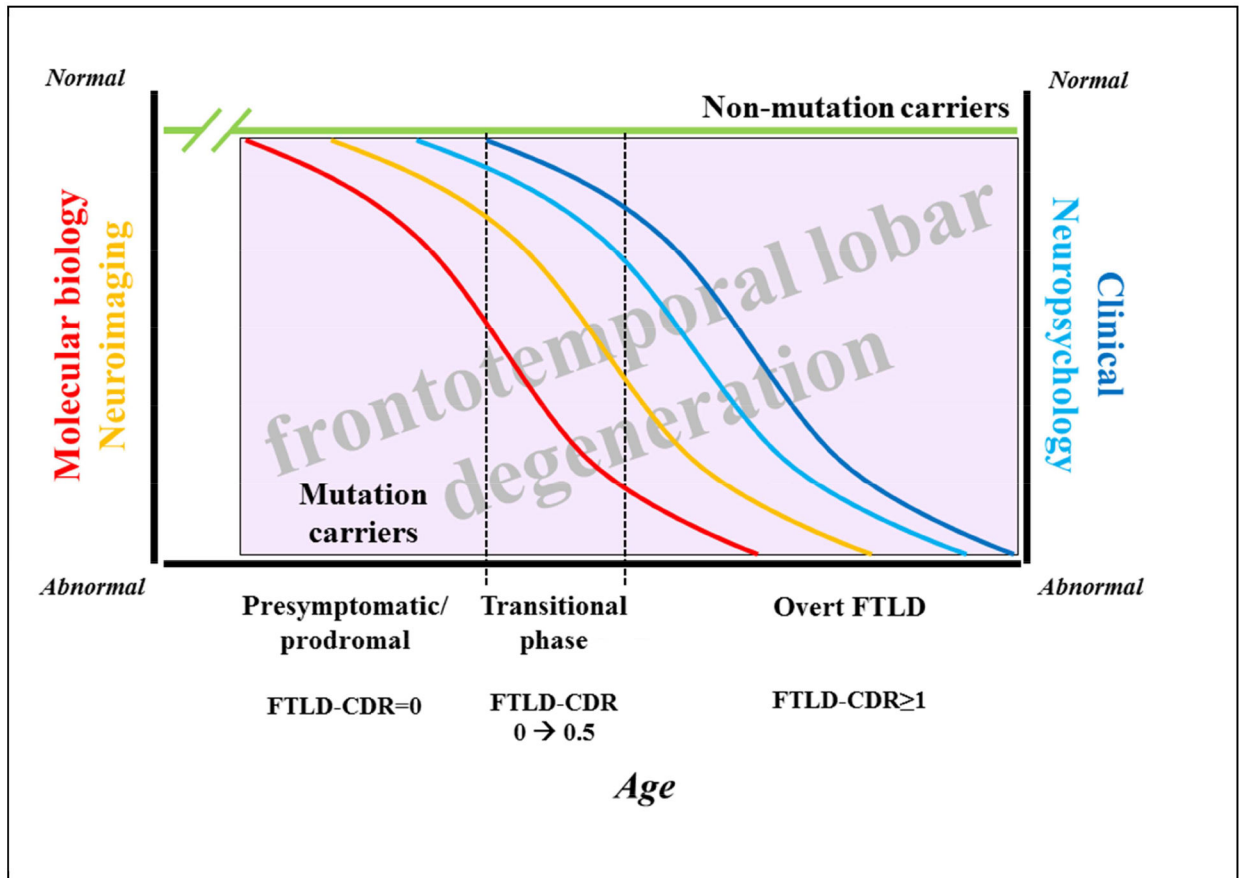
Figure 1. Schema and research approach of familial FTLD.

The alterations in the molecular biology (red curve) of tau, progranulin and the granulins, C9RAN proteins, etc., undoubtedly occur early in life during the presymptomatic phase. As neuronal and/or glial dysfunction evolves, changes in neuronal networks occur which can be demonstrated on neuroimaging measures (orange curve), with functional MR changes likely preceding structural MR changes. Other measures including neuropsychological measures (light blue curve) and clinical (including behavioral and motor measures, as shown in the dark blue curve) likely show the evolution of clinically silent (represented by an FTLD-CDR rating of 0) to very minimally evident cognitive, behavioral or motor changes over the several year transitional period from presymptomatic to prodromal to minimally symptomatic phases of f-FTLD (represented by an FTLD-CDR rating of 0.5). MR-based and other imaging measures likely change over this transitional period also. Additional changes occur with the onset of overt features (represented by an FTLD-CDR rating ≥ 1) and continue onward through the mild, moderate, severe and terminal phases of the symptomatic period. For each set of measures, there is likely a slow change phase, followed by an acceleration phase, then a deceleration phase, and then a terminal slow change phase. Those individuals who do not carry a mutation (shown as the green line) are expected to show no consistent change across these measures. This hypothesized cascade of dynamic changes is analogous to what has been proposed in the evolution of Alzheimer's disease. See text for abbreviations.
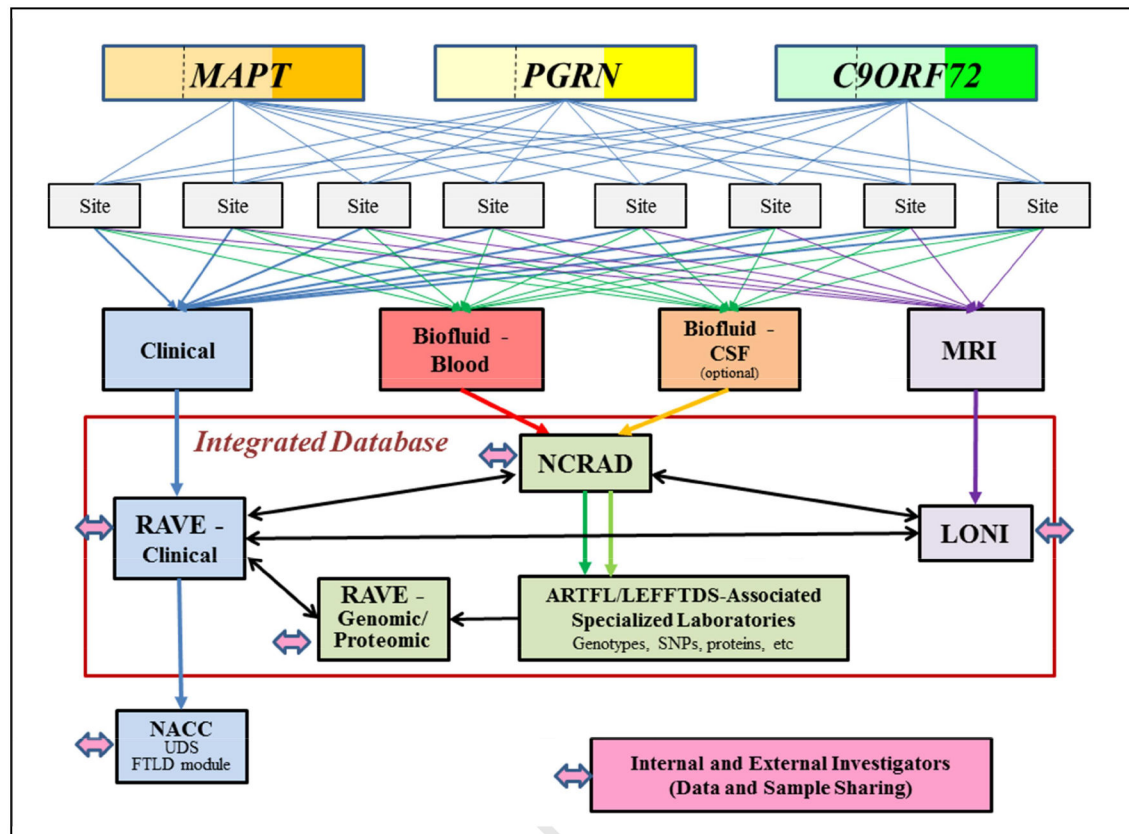
Figure 2. Protocol Schema.
Three hundred subjects (100 among kindreds with a mutation in *MAPT*, 100 among kindreds with a mutation in *PGRN*, and 100 among kindreds with the *C9orf72* mutation) are enrolled and followed at one of the eight sites. Within each gene, approximately 1/3 are symptomatic (reflected by darker shades of orange, yellow or green) whereas 2/3 are asymptomatic (reflected by lighter shades of the colors). The lighter shade areas are divided by a dashed line, which reflects one half of the asymptomatic are non-mutation carrier/ family controls while the other half are mutation carriers. Each subject can participate in four research arms – clinical, biofluid-blood, biofluid-CSF and MRI; the CSF arm is optional. Each subject can also participate in a 5th arm (not shown) in which clinical genetic counseling and testing can be performed. The clinical data is entered into an electronic data capture system (RAVE), and the majority of this data is uploaded to the NACC. Biofluid samples are submitted to NCRAD for processing and storage. See text for abbreviations.
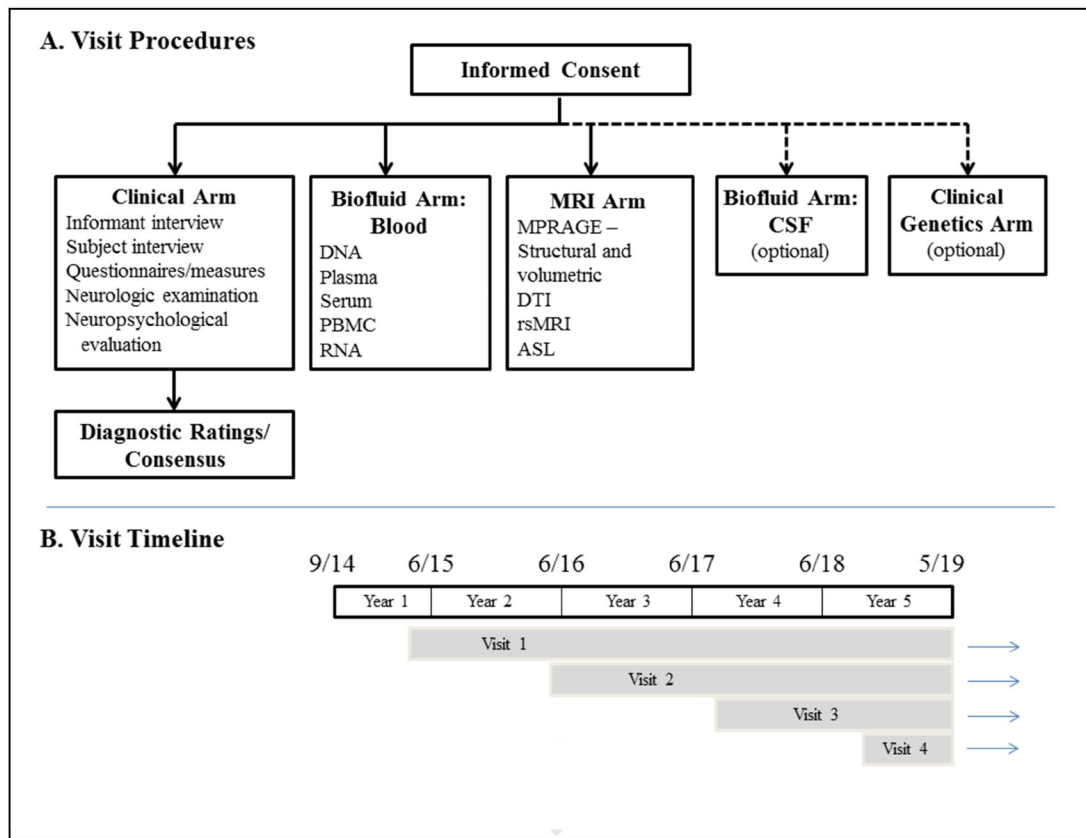
Figure 3. Study Procedures and Timeline.
See text in Section 4 for details and abbreviations.
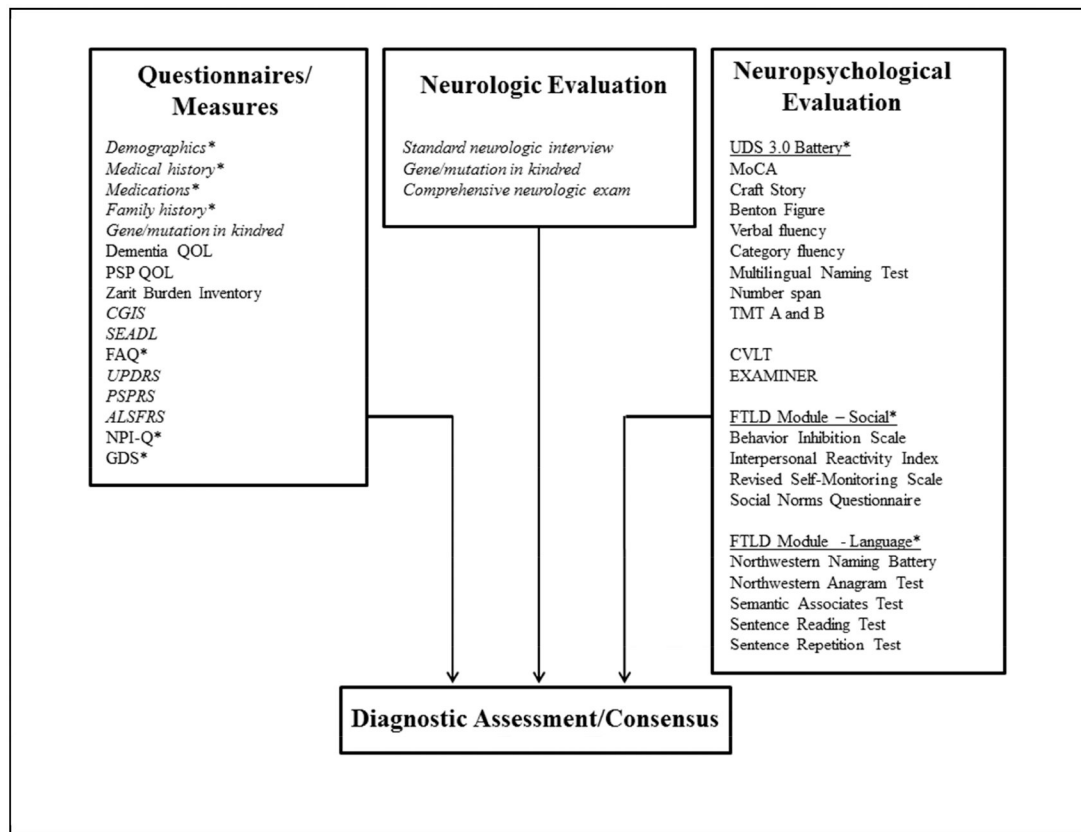
Figure 4. Diagnostic Assessment Scheme.
*measures from the NACC UDS version 3 and FTLD Module; additional references: [39, 49–63].
See text in Section 4.4 for details and abbreviations.

Table 1.

Data and Measures

Data	Measure	Database
Standard History and Physical Examination		
Demographic	A/L, UDS form	A/L, UDS
History	Clinical Global Impression [27]	A/L
Medications	A/L, UDS form	A/L, UDS
Past medical history	A/L, UDS form	A/L, UDS
Family history	A/L, UDS form	A/L, UDS
Physical examination	A/L, UDS form	A/L, UDS
Neurologic examination	Neurologic examination form	A/L
Functional/Clinical Status/Quality of Life		
Global/functional	Modified Clinical Dementia Rating Scale (mCDR) [28]	A/L, UDS
Activities of daily living	Functional Assessment Questionnaire (FAQ) [29]	A/L, UDS
	Schwab and England Activities of Daily Living (SEADL) [30]	A/L
Clinical severity/change	Clinical Global Impression - Severity and Change [27]	A/L
Quality of life	Dementia Quality of Life - subject and informant [31]	A/L
Caregiver burden	Zarit Burden Interview [32]	A/L
Cognitive/Neuropsychologic		
Global intellectual function	Montreal Cognitive Assessment (MoCA)[33]	A/L, UDS
Executive	Number Span - forward and backward [34]	A/L, UDS
	Trails A & B [35]	A/L, UDS
	*EXAMINER battery [36]	A/L, FTLD
Language	Semantic Fluency - fruits and vegetables [34]	A/L, UDS
	Verbal Fluency - Phonemic Test [34]	A/L, UDS
	Multilingual Naming Test (MINT) [37]	A/L, UDS
	*Semantic Associates (Northwestern Naming Battery)	A/L, FTLD
	*Regular and Irregular Word Reading (Hopkins Experimental Battery)	A/L, FTLD
	*Action Naming (Northwestern Naming Battery)	A/L, FTLD
	*Northwestern Anagram test	A/L, FTLD

Data	Measure	Database
	*Sentence reading (Hopkins Experimental Battery)	A/L, FTLD
	*Sentence repetition (Hopkins Experimental Battery)	A/L, FTLD
Learning and memory	Craft Story [34]	A/L, UDS
	California Verbal Learning Test [38]	A/L, FTLD
	Benson figure recall [39]	A/L, UDS
Visuospatial	Benson figure copy [39]	A/L, UDS
Behavioral measures		
Depression	Geriatric Depression Scale [40]	A/L, UDS
Neuropsychiatric	Neuropsychiatric Inventory Q [41]	A/L, UDS
Social	*Behavioral Inhibition Scale [42]	A/L, FTLD
	*Interpersonal Reactivity Index [43]	A/L, FTLD
	*Revised Self-monitoring Scale [44]	A/L, FTLD
	*Social Norms Questionnaire	A/L, FTLD
	*Social Behavior Observer Checklist	A/L, FTLD
Neurologic Disorder-Focused		
Parkinsonism	UPDRS - Motor subtest [45]	A/L
PSP	PSP Rating Scale [46]	A/L
ALS	ALS Functional Rating Scale - Revised [47]	A/L

A/L = ARTFL/LEFFTDS database in RAVE; FTLD = National Alzheimer's Coordinating Center Frontotemporal Lobar Degeneration

Module; A/L, UDS = National Alzheimer's Coordinating Center Uniform Data Set [34, 48]

*
experimental measures from the FTLD Module; additional references: [39, 49–63].

Table 2.

Rating and Diagnosis Measures

Rating/Diagnosis	Measure/Description	Database
Clinical Rating Scores		
Standard CDR - Subject	Standard 6 domain CDR with Global and Sum of the Boxes measures	A/L
FTLD domains - Subject	Supplemental Behavior/Comportment and Language domains	A/L
FTLD-CDR - Subject	Global and Sum of the Boxes measures rating based on all subject data	A/L
Standard CDR - Informant	Standard 6 domain CDR with Global and Sum of the Boxes measures	A/L
FTLD domains - Informant	Supplemental Behavior/Comportment and Language domains	A/L
FTLD-CDR - Informant	Global and Sum of the Boxes measures rating based on all informant data	A/L
Standard CDR - Neuropsych	Key domains on CDR with Global and Sum of the Boxes measures	A/L
FTLD domains - Neuropsych	Supplemental Behavior/Comportment and Language domains	A/L
UDS Neuropsych Rating	Cognitive domain and global rating based on all UDS neuropsych data	A/L
FTLD-CDR - Neuropsych	Global and Sum of the Boxes measures rating based on all neuropsych data	A/L
Consensus Clinical Dementia Rating		
Standard CDR - Consensus	Standard 6 domain CDR with Global and Sum of the Boxes measures	A/L, UDS
FTLD-CDR - Consensus	Global and Sum of the Boxes measures based on all data	A/L, UDS
Consensus Clinical Diagnosis		
Primary clinical diagnosis	Primary clinical diagnosis	A/L, UDS
Confidence rating	Confidence in the rating of the primary clinical diagnosis	A/L
Secondary clinical diagnosis	Secondary clinical diagnosis, if applicable	A/L
Tertiary clinical diagnosis	Tertiary clinical diagnosis, if applicable	A/L

A/L = ARTFL/LEFFTDS database in RAVE; UDS = National Alzheimer's Coordinating Center Uniform Data Set

References: Clinical Dementia Rating (CDR) scale, updated terminology is CDR® [65], Frontotemporal Lobar Degeneration-Clinical Dementia Rating Scale (FTLD-CDR); updated terminology is CDR® plus NACC FTLD [28]

Table 3.

Clinical Phenotypes and Confidence Rating

Clinical Phenotypes (primary, and secondary and tertiary if applicable)	
Normal neurologic functioning	
Behavioral variant frontotemporal dementia	
Primary progressive aphasia – agrammatic/nonfluent variant subtype	
Primary progressive aphasia – semantic variant subtype	
Primary progressive aphasia – logopenic variant subtype	
Corticobasal syndrome - typical or variant	
Progressive supranuclear palsy/Richardson's syndrome	
Amyotrophic lateral sclerosis	
FTD/ALS	
MCI - cognitive variants: aMCIsd, aMDmd, naMCIsd, naMCImd	
MCI - behavior	
MCI - language	
MCI - unknown	
Alzheimer's disease dementia	**Confidence in Primary Clinical Phenotype Diagnosis**
Dementia with Lewy bodies	100% (extremely confident)
Parkinson's disease	90%
Parkinson's disease with dementia	80%
Multiple system atrophy	70%
Posterior cortical atrophy	60%
Primary psychiatric disorder - Mood	50%
Primary psychiatric disorder - Thought	40%
Primary psychiatric disorder - Personality	30%
Other, specify	20%
	10%
	0% (not confident at all)