DOI: 10.1016/j.jalz.2019.06.4947

SPECIAL ISSUE

Alzheimer's & Dementia®
THE JOURNAL OF THE ALZHEIMER'S ASSOCIATION

The longitudinal evaluation of familial frontotemporal dementia subjects protocol: Framework and methodology

Bradley Boeve[1] | Jessica Bove[2] | Patrick Brannelly[3] | Danielle Brushaber[1] | Giovanni Coppola[4] | Rielly Dever[5] | Christina Dheel[1] | Bradford Dickerson[6] | Susan Dickinson[7] | Kelley Faber[8] | Julie Fields[1] | Jamie Fong[5] | Tatiana Foroud[8] | Leah Forsberg[1] | Ralitza Gavrilova[1] | Debra Gearhart[1] | Nupur Ghoshal[9] | Jennifer Goldman[10] | Jonathan Graff-Radford[1] | Neill Graff-Radford[11] | Murray Grossman[2] | Dana Haley[11] | Hilary Heuer[5] | Ging-Yuek Robin Hsiung[12] | Edward Huey[10] | David Irwin[2] | David Jones[1] | Lynne Jones[9] | Kejal Kantarci[1] | Anna Karydas[5] | David Knopman[1] | John Kornak[5] | Ruth Kraft[1] | Joel Kramer[5] | Walter Kremers[1] | Walter Kukull[13] | Maria Lapid[1] | Diane Lucente[6] | Ian Mackenzie[12] | Masood Manoochehri[10] | Scott McGinnis[6] | Bruce Miller[5] | Rodney Pearlman[14] | Len Petrucelli[11] | Madeline Potter[8] | Rosa Rademakers[11] | Eliana Marisa Ramos[4] | Kate Rankin[5] | Katya Rascovsky[2] | Pheth Sengdy[12] | Les Shaw[2] | Jeremy Syrjanen[1] | Nadine Tatton[7] | Joanne Taylor[5] | Arthur Toga[15] | John Trojanowski[2] | Sandra Weintraub[16] | Bonnie Wong[6] | Zbigniew Wszolek[11] | Adam Boxer[5] | Howard Rosen[5] | on Behalf of the LEFFTDS Consortium

[1]Mayo Clinic, Rochester, MN, USA

[2]University of Pennsylvania, Philadelphia, PA, USA

[3]Tau Consortium, Rainwater Charitable Foundation, Fort Worth, TX, USA

[4]UCLA, Los Angeles, CA, USA

[5]UCSF, San Francisco, CA, USA

[6]Harvard University/MGH, Boston, MA, USA

[7]Association for Frontotemporal Degeneration, Radnor, PA, USA

[8]National Cell Repository for Alzheimer's Disease and Related Dementias (NCRAD), Indiana University, Indianapolis, IN, USA

[9]Washington University, St. Louis, MO, USA

[10]Columbia University, New York, NY, USA

[11]Mayo Clinic, Jacksonville, FL, USA

[12]University of British Columbia, Vancouver, British Columbia, Canada

[13]National Alzheimer Coordinating Center (NACC), University of Washington, Seattle, WA, USA

[14]Bluefield Project, San Francisco, CA, USA

[15]Laboratory of Neuroimaging (LONI), USC, Los Angeles, CA, USA

[16]Northwestern University, Chicago, IL, USA

Correspondence
Bradley Boeve, Tel.: +1-507-538-1038;
Fax: +1-507-538-6012.

Funding information
National Institutes of Health, Grant/Award Number: U01 AG045390

Correcton statement
Correction added on January 6, 2020, after first online publication: The author name was corrected to read "Eliana Marisa Ramos."

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 for more than 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 magnetic resonance imaging 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
C9orf72, Frontotemporal dementia, Genetics, *GRN*, *MAPT*, Tau, TDP-43

1 | INTRODUCTION

Frontotemporal lobar degeneration (FTLD) is caused by two major proteinopathies—microtubule-associated protein tau (MAPT) and TAR DNA binding protein molecular weight 43.[1,2] At least 20% of all FTLD presents as a dominantly inherited familial frontotemporal lobar degeneration (f-FTLD), usually because of mutations in the *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 frontotemporal dementia (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 (Fig. 1). The alterations in the molecular biology of tau, progranulin and the granulins, C9RAN proteins, and so forth, 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 magnetic resonance imaging (MRI) changes likely preceding structural MRI changes. Various other ancillary studies, including behavioral measures, neuropsychological measures, motor measures, and so forth, likely show the evolution of clinically silent to very minimally evident cognitive, behavioral, or motor changes over the several years of transitional period from presymptomatic to prodromal to minimally symptomatic phases of f-FTLD. MRI-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]

Although there are growing data that support the cascade of events and findings just described,[12–26] many of the findings are based on cross-sectional analyses, and few longitudinal data have been published thus far. Also 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 whereas 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.

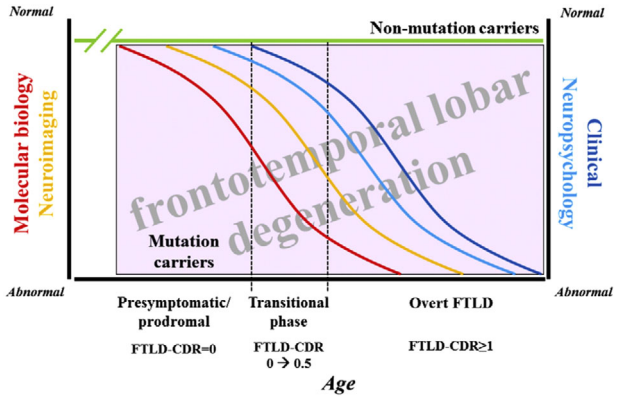

FIGURE 1 Schema and research approach of familial FTLD. The alterations in the molecular biology (red curve) of tau, progranulin and the granulins, C9RAN proteins, and so forth, undoubtedly occur early in life during the presymptomatic phase. As neuronal and/or glial dysfunction evolves, changes in neuronal 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 years of 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. Abbreviations: CDR, Clinical Dementia Rating; FTLD, frontotemporal lobar degeneration; MR, magnetic resonance

We sought to address many of these questions as part of the Longitudinal Evaluation of Familial Frontotemporal Dementia Subjects (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 as follows:

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 (symptomatic mutation carriers, +mFTLD-CDR > 0 [CDR, Clinical Dementia Rating]) of f-FTLD.

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 article proposes a framework for 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 and facilitate planning for upcoming disease-modifying therapeutic trials in familial frontotemporal lobar degeneration.

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 *asymptomatic* phase (asymptomatic mutation carriers, +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 Supplementary Figs. 1-4.

Note that the term "asymptomatic" is preferred over "presymptomatic" in the context of these LEFFTDS aims because 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 Fig. 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 the 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 noncarriers (i.e., familial control subjects). At least three annual assessments (henceforth termed "visits") for each subject are planned for a period of more than this 5-year phase of the study. Each visit includes

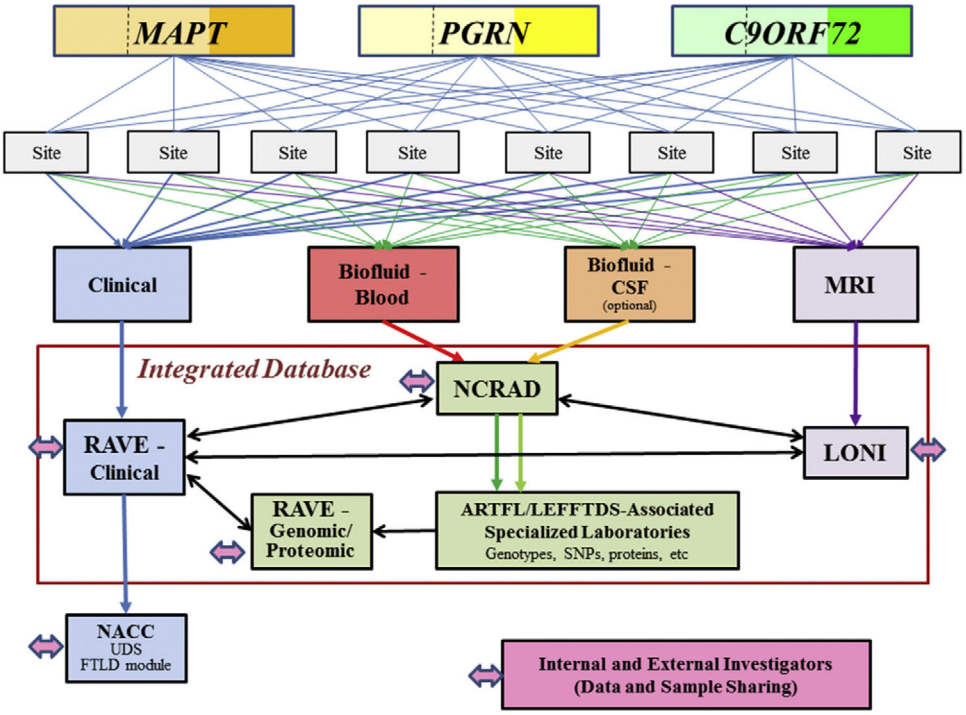

FIGURE 2 Protocol schema. Three hundred subjects (100 among kindreds with a mutation in *MAPT*, 100 among kindreds with a mutation in *PGRN*, and 100 among kindreds with the *C9orf72* mutation) are enrolled and followed at one of the eight sites. Within each gene, approximately 1/3 are symptomatic (reflected 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 nonmutation carrier/family control subjects whereas 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 fifth arm (not shown) in which clinical genetic counseling and testing can be performed. The clinical data are entered into an electronic data capture system (RAVE), and most of these data are uploaded to the NACC. Biofluid samples are submitted to NCRAD for processing and storage. Abbreviations: ARTFL, Advancement in Research and Treatment for Frontotemporal Lobar Degeneration; CSF, cerebrospinal fluid; FTLD, frontotemporal lobar degeneration; LEFFTDS, Longitudinal Evaluation of Familial Frontotemporal Dementia Subjects; LONI, Laboratory of Neuroimaging; MRI, magnetic resonance imaging; NACC, National Alzheimer's Coordinating Center; NCRAD, National Cell Repository for Alzheimer's Disease; UDS, Uniform Data Set

a clinical assessment, biofluid sampling with blood and cerebrospinal fluid (CSF) collection, and MRI; CSF collection is optional. The clinical data are entered into an electronic data capture system (via the iMedidata RAVE system, Houston, TX). Most of these data are collected using measures in the Uniform Data Set (UDS) and 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 Initiative version 3 (ADNI-3) protocol. The data are 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 subsequently.

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 web sites 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 web site. A web site 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 of age 18 or older, and preferably at age

>30 years. Other inclusion criteria include the predominant phenotype in the kindred should be cognitive/behavioral (i.e., kindreds in whom behavioral variant frontotemporal dementia (bvFTD) or primary progressive aphasia (PPA) is the predominant clinical phenotype among affected relatives and is favored over parkinsonism or amyotrophic lateral sclerosis, 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. Exclusion criteria include the absence of a known mutation in *MAPT*, *GRN*, or *C9orf72* in the subject or family, the presence of a structural brain lesion (e.g., tumor, cortical infarct), the presence of another neurologic disorder, which could impact findings (e.g., multiple sclerosis), unwillingness to return for follow-up yearly, unwillingness to undergo neuropsychological testing and MRI, 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 Clinical Laboratory Improvement Amendments–approved laboratory 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 Fig. 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, and MRI scanning; the CSF arm and genetic testing arms are optional. A genetic evaluation for counseling with or 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.

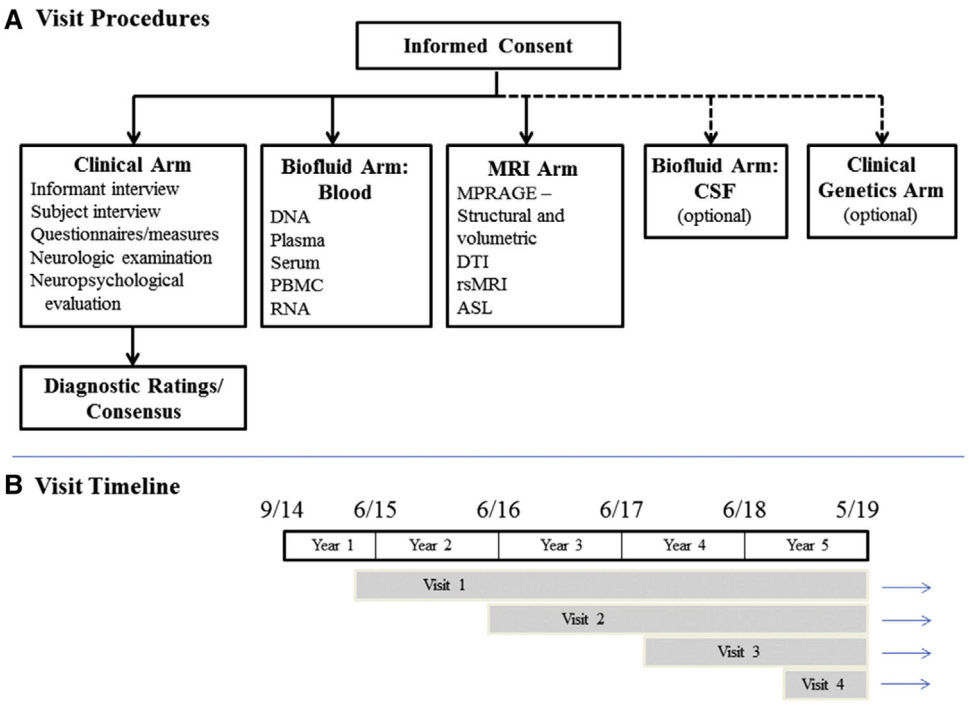

FIGURE 3 Study procedures (A) and timeline (B). See text in Section 4 for details. Abbreviations: ASL, arterial spin labeled; CSF, cerebrospinal fluid; DTI, diffusion tensor imaging; MRI, magnetic resonance imaging; PBMC, peripheral blood mononuclear cells; rsMRI, resting state MRI

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[28]	A/L, UDS
Activities of daily living	Functional Assessment Questionnaire[29]	A/L, UDS
	Schwab and England Activities of Daily Living[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/neuropsychological		
Global intellectual function	Montreal Cognitive Assessment[33]	A/L, UDS
Executive	Number Span—forward and backward[34]	A/L, UDS
	Trails A and B[35]	A/L, UDS
	XAMINER 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[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
	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

Abbreviations: A/L, ARTFL/LEFFTDS database in RAVE; ALS, amyotrophic lateral sclerosis; ARTFL, Advancement in Research and Treatment for Frontotemporal Lobar Degeneration; FTLD, Frontotemporal Lobar Degeneration Module; LEFFTDS, Longitudinal Evaluation of Familial Frontotemporal Dementia Subjects; PSP, progressive supranuclear palsy; UDS, Uniform Data Set.[34,48]

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

Most of the subject-based 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 (i.e., 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 Principal Investigator (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 NACC UDS Task Force, which comprise the UDS version 3.0 (UDS 3.0).[48] Although the UDS measures have been applicable to subjects with normal cognition, mild cognitive impairment (MCI), and a variety of dementia syndromes, the focus over many years was on subjects with MCI and Alzheimer's disease (AD) dementia. 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[28] (which is a modification of the standard CDR Dementia Staging Instrument[64]—more details on these scales are given subsequently), neuropsychological data, the consensus clinical diagnostic assessment, and the confidence rating. The measures used in the diagnostic ratings and assessments are shown in Fig. 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 eight-domain "FTLD-CDR." The older terminology FTLD-CDR represented the exact same group of measures now used

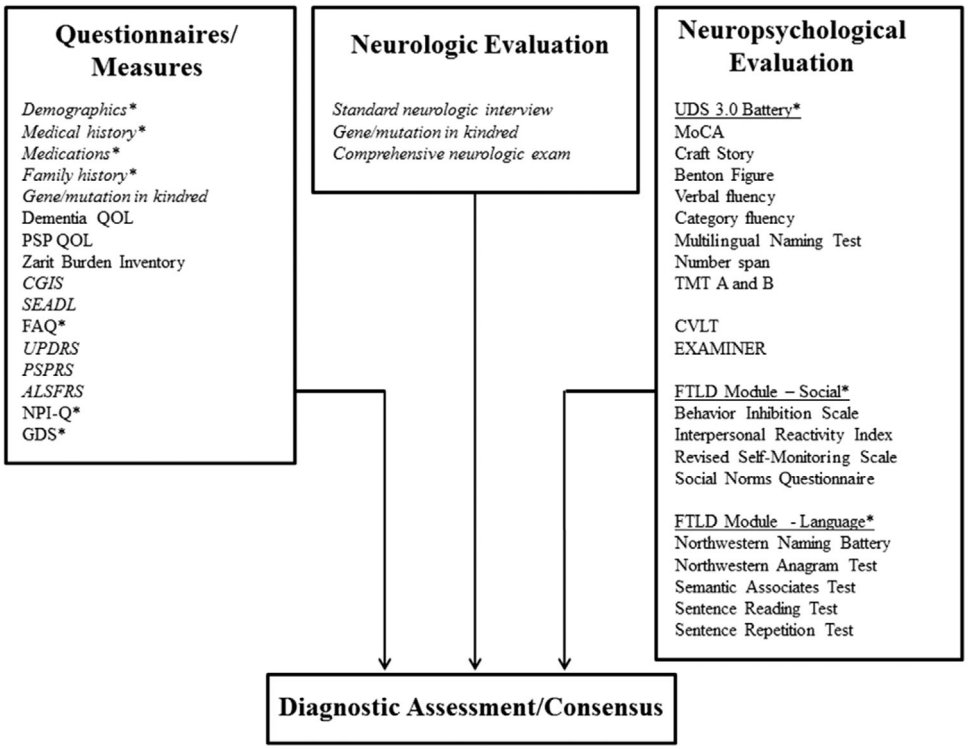

FIGURE 4 Diagnostic assessment scheme. *Measures from the NACC UDS version 3 and FTLD Module; additional references: [39,49–63]. See text in Section 4.4 for details. Abbreviations: ALSFRS, Amyotrophic Lateral Sclerosis Functional Rating Scale; CGIS, Clinician's Global Impression of Severity; CVLT, California Verbal Learning Test; FAQ, Functional Assessment Questionnaire; FTLD, frontotemporal lobar degeneration; GDS, Geriatric Depression Scale; MoCA, Montreal Cognitive Assessment; NACC, National Alzheimer's Coordinating Center; NPI-Q, Neuropsychiatric Inventory-Questionnnaire; PSPRS, Progressive Supranuclear Palsy Rating Scale; QOL, Quality of Life; SEADL, Schwab and England Activities of Daily Living; TMT, Trail Making Test; UDS, Uniform Data Set; UPDRS, Unified Parkinson's Disease Rating Scale

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—Neuropsychological	Key domains on CDR with global and sum of the boxes measures	A/L
FTLD domains—Neuropsychological	Supplemental Behavior/Comportment and Language domains	A/L
UDS Neuropsychological Rating	Cognitive domain and global rating based on all UDS neuropsychological data	A/L
FTLD-CDR—Neuropsychological	Global and sum of the boxes measures rating based on all neuropsychological 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

NOTE. CDR scale, updated terminology is CDR Staging Instrument;[64] FTLD-CDR scale, updated terminology is CDR plus NACC FTLD.[28]
Abbreviations: A/L, ARTFL/LEFFTDS database in RAVE; ARTFL, Advancement in Research and Treatment for Frontotemporal Lobar Degeneration; CDR, Clinical Dementia Rating; FTLD, frontotemporal lobar degeneration; LEFFTDS, Longitudinal Evaluation of Familial Frontotemporal Dementia Subjects; NACC, National Alzheimer's Coordinating Center; UDS, Uniform Data Set.

by the updated name of "CDR Dementia Staging Instrument plus NACC FTLD Module Behavior and Language domains (CDR plus NACC FTLD). Because the CDR is now trademarked, this updated abbreviation for the eight-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 article.

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 AD 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 an FTLD-specific global score. Motor dysfunction as seen in FTD with parkinsonism, progressive supranuclear palsy, corticobasal syndrome, and amyotrophic lateral sclerosis 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 (e.g., bvFTD), the data from the informant's interview may be more informative than the data from the subject's interview and neurologic examination and the traditional neuropsychological data. For other syndromes (e.g., PPA), the data from the subject's interview and examination as well as the language-based neuropsychological data would be most informative. To capture these scenarios 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 were 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. For the CDR plus NACC FTLD sum of the boxes score, the value is determined by simply adding all eight of the domain scores.

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
Dementia with Lewy bodies
Parkinson's disease
Parkinson's disease with dementia
Multiple system atrophy
Posterior cortical atrophy
Primary psychiatric disorder—mood
Primary psychiatric disorder—thought
Primary psychiatric disorder—personality
Other, specify
Confidence in Primary Clinical Phenotype Diagnosis
100% (extremely confident)
90%
80%
70%
60%
50%
40%
30%
20%
10%
0% (not confident at all)

Abbreviations: ALS, amyotrophic lateral sclerosis; FTD, frontotemporal dementia; MCI, mild cognitive impairment.

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 nonmemory 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 AD pathology. Because the earliest manifestations of evolving FTLD are usually nonmemory, 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 >0.5 in any domain, then the following applies:
   - If the maximum domain score is 1 and all other domains are 0, the global CDR plus NACC FTLD score is 0.5.
   - If the maximum domain score is 2 or 3 and all other domains are 0, the global CDR plus NACC FTLD score is 1.
   - 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).
   - If the maximum domain score occurs more than once (e.g., one in two domains, two in two domains), then the global CDR plus NACC FTLD score is that maximum domain score.

4.4.3 | 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 AD 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 (1) normal cognitive, behavioral/comportment and language functioning based on the absence of subjective complaints of cognitive, behavioral, and language changes from their baseline, (2) a global CDR plus NACC FTLD score of 0, and (3) 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 (1) a questionable or mild change in cognitive, behavioral, or language functioning based on the subject and/or informant, (2) a global CDR plus NACC FTLD score of 0.5, (3) a mild degree of impairment in cognitive/behavioral/language functioning based on neurologic examination and/or neuropsychological and behavioral measures, and (4) 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 (1) at least mild change in cognitive, behavioral, or language functioning based on the subjects and/or informant, (2) a global

CDR plus NACC FTLD score of 1, and (3) at least mild degree of impairment in cognitive/behavioral/language functioning based on neurologic examination and/or neuropsychological and behavioral measures, and (4) *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 caregiver +/− 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 caregiver +/− devices would be classified as FTLD-CDR = 3.

Atypical cases: Any subjects who do not fulfill any set of criteria as stated previously are classified in the most appropriate A/L FTLD-CDR category (e.g., a subject who fulfills criteria (1) and (2) 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 because this designation best approximates the criteria.

4.4.4 | Clinicogenetic classification

The clinical classification scheme described previously 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 subsequently in more detail.

4.4.5 | A/L 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 the amnestic and nonamnestic categories of MCI—and make a confidence rating (0%–100% confident) in the primary diagnosis.

MCI behavior

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 AD 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, because 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 subsequently).[65] 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 are gathered and analyzed.

Accessing data

The procedures for accessing data from the clinical arm are described in Section 4.11.

4.5 | Biofluid arm—blood

The procedures involved in acquiring, processing, storing, and accessing biofluid samples are described in detail on the NCRAD web site (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 peripheral blood mononuclear cells. The blood is collected in appropriate tubes and processed; the tubes designed for peripheral blood mononuclear cell generation are submitted by overnight express to NCRAD, and the others are submitted later as batch shipments to NCRAD.

4.5.1 | A/L blood biofluid sample processing

Several key analyses on biofluid samples are carried out internally in specialized laboratories within the A/L consortium so that the specific aims can be addressed. Aliquots of blood for each subject are sent from NCRAD to University of California at Los Angeles (G.C., PhD, site PI for genomic analyses) for DNA analysis (see additional description subsequently), and to Mayo Clinic Florida (R.R., 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 A/L 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.

4.5.2 | Accessing data/samples

The procedures for accessing data from the biofluid-blood arm within the A/L Genomic/Proteomic database are described in Section 4.11.

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 web site (https://ncrad.iu.edu/). Briefly, CSF is collected via standard lumbar puncture procedures in polypropylene tubes and aliquoted.

4.6.1 | A/L CSF biofluid sample processing

Several key analyses on CSF samples will be carried out internally in specialized laboratories within the A/L consortium; these samples will be analyzed at periodic intervals to permit standardization across measures. Additional information is provided subsequently. The results from these laboratories are then submitted securely to the A/L Genomic/Proteomic database.

4.6.2 | Accessing data/samples

The procedures for accessing data from the biofluid-CSF arm within the A/L Genomic/Proteomic database are described in Section 4.11.

4.7 | MRI arm

4.7.1 | Acquisition

Images are acquired at all centers at 3 T using sequences that are harmonized across multiple vendors (i.e., GE, Siemens, and Phillips), and similar to those employed in the 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 autoalignment scout scan, which yields orthogonal orientation and anterior commissure–posterior commissure alignment followed by MRI sequences as follows. (1) T1-weighted magnetization prepared rapid acquisition gradient echo with parameters: repetition time (TR)/echo time (TE)/inversion time (TI) = 2300//900 milliseconds, flip angle of 9°, a bandwidth of 240 Hz/pixel, sagittal orientation with a field of view = 256 × 240 mm with slices. Time is minutes. (2) T2-weighted fluid-attenuated inversion recovery: TR/TE/TI = 6000/390/2100 milliseconds with a 800 milliseconds long turbo spin echo readout train, 750 Hz/pixel bandwidth with 3 mm slice thickness. Time is 7 minutes. (3) Diffusion tensor imaging: a two-dimensional single-shot gradient echo sequence with TR/TE = 7200/56 milliseconds, a 232 × 232 base matrix, 2.0 mm slices yielding 2.0 × 2.0 × 2.0 mm isotropic resolution.[66,67] 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/second. Time is 7:30 minutes. (4) Arterial spin labeled (ASL) perfusion imaging: the ASL protocol consists of a three-dimensional fast spin echo pseudo-continuous ASL sequence with an interleaved stack-of-spiral readout and background suppression on GE scanners.[68] The imaging parameters used were a labeling duration of 1450 milliseconds, postlabeling delay of 2025 milliseconds, repetition time/echo time of 4800/10 milliseconds, refocusing flip angle 111°, field of view 240 mm, acquisition matrix 512/8 samples regridded to a 128 × 128 matrix with an in-plane reconstructed resolution of 1.875 × 1.875 cm^2; 40 slices with slice thickness 4 mm, no gap. Three excitation averages of label and control volume pairs are acquired, as well as a proton density–weighted volume using the same readout scheme, resulting in an overall scan duration of 4:30 minutes. (5) Intrinsic connectivity network functional MRI: A T2*-weighted gradient echo–echo planar sequence with TR/TE = 3000/30 milliseconds, flip angle 90°; field of view = 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 minutes.

4.7.2 | 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 LONI, A.T., PhD, site PI (web site: 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 vs. negative), whether asymptomatic or symptomatic, is offered the opportunity to undergo genetic counseling and genetic testing (which includes assessment of psychological/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 Clinical Laboratory Improvement Amendments–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 3 weeks later according to site-specific procedures.

The specific procedures for psychological/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;[4,5,69] 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 single nucleotide polymorphisms 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 apolipoprotein E (*APOE*) genotypes (rs7412 and rs429358) in all individuals. Progranulin expression levels are measured in human plasma samples using the human Progranulin enzyme-linked immunosorbent assay 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 (L.S., PhD, site PI for CSF proteomic analyses) for quantification of amyloid β (Aβ42), total tau, and phospho-tau, and to Mayo Clinic Florida (R.R., PhD, for progranulin quantification and to L.P., PhD, for C9RAN translation quantification). Progranulin expression levels are measured in CSF samples using the human Progranulin enzyme-linked immunosorbent assay kit (Adipogen Inc) using a 1:100 dilution of plasma samples and undiluted CSF samples. C9RAN protein is quantified as previously described.[70] 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 and genetic status of subjects. For example, are there differences in clinical, biofluid, or imaging measures in f-FTLD between asymptomatic mutation and nonmutation 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 nonmutation 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, when 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 University of California, Los Angeles, 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 Fig. 2. The clinical data (which includes neuropsychological data) can be accessed via two mechanisms—the A/L database management system (RAVE) or the NACC; note that the data in the A/L RAVE system include more measures and can also potentially be attached to genetic and biofluid data if desired. The process for requesting data is explained at the web site https://ucsf.co1.qualtrics.com/jfe/form/SV_e4BBGMiXV7HRTg1. The data requests are reviewed by committee and adjudicated in a timely fashion, and data are 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 web site https://www.alz.washington.edu/.

Samples can be requested by accessing the NCRAD web site and following all procedures as described at the web site 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 are desired in addition to samples, then the following web site 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 A/L database. Additional aspects on this process are explained at these web sites and associated links.

MRI scan data can be accessed as described on the LONI web site: http://www.loni.usc.edu/. There is a QC 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 are desired in addition to scans, then the following web site should also be accessed: https://ucsf.co1.qualtrics.com/jfe/form/SV_e4BBGMiXV7HRTg1. Additional aspects on this process are explained at these web sites 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 web site (under construction). The LEFFTDS protocol is also similar in many ways to the Genetic Frontotemporal Dementia Initiative study in Europe and Canada, and attempts to harmonize many aspects of LEFFTDS and Genetic Frontotemporal Dementia Initiative will continue for the years ahead.

ACKNOWLEDGMENTS

We extend our appreciation to Drs John Hsiao and Dallas Anderson from the National Institute on Aging, Drs Marg Sutherland and Codrin Lungu from the National Institute of Neurological Disorders and Stroke, the staff of all centers, and particularly to our patients and their families for their participation in this protocol.

Funding: This work is supported by the National Institutes of Health [grants U01 AG045390, U54 NS092089, U24 AG021886, and U01 AG016976].

DISCLOSURES

B. Boeve has served as an investigator for clinical trials sponsored by GE Healthcare and Axovant. He receives royalties from the publication of a book entitled *Behavioral Neurology of Dementia* (Cambridge Medicine, 2009, 2017). He serves on the Scientific Advisory Board of the Tau Consortium. He receives research support from the NIH, the Mayo Clinic Dorothy and Harry T. Mangurian Jr Lewy Body Dementia Program, and the Little Family Foundation. H. Rosen has received research support from Biogen Pharmaceuticals, has consulting agreements with Wave Neuroscience and Ionis Pharmaceuticals, and receives research support from the NIH. L. Forsberg receives research support from the NIH. A. Boxer receives research support from the NIH, the Tau Research Consortium, the Association for Frontotemporal Degeneration, the Bluefield Project to Cure Frontotemporal Dementia, Corticobasal Degeneration Solutions, the Alzheimer's Drug Discovery Foundation, and the Alzheimer's Association. He has served as a consultant for Aeton, Abbvie, Alector, Amgen, Arkuda, Ionis, Iperian, Janssen, Merck, Novartis, Samumed, Toyama, and UCB, and received research support from Avid, Biogen, BMS, C2N, Cortice, Eli Lilly, Forum, Genentech, Janssen, Novartis, Pfizer, Roche, and TauRx. P. Brannelly is employed at the Rainwater Charitable Foundation. H. Heuer, G. Coppola, B. Dickerson, K. Faber, J. Fields, T. Foroud, R. Gavrilova, E. Huey, J. Graff-Radford, K. Rankin, K. Rascovsky, L. Shaw, S. Weintraub B. Wong, J. Kramer, W. Kukull, D. Lucente, B. Miller, L. Petrucelli, and M. Potter receive research support from the NIH. S. Dickinson is on staff at the Association for Frontotemporal Degeneration and a member of the National Institute for Neurological Disorders and Stroke Advisory Council. N. Ghoshal has participated or is currently participating in clinical trials of antidementia drugs sponsored by the following companies: Bristol Myers Squibb, Eli Lilly / Avid Radiopharmaceuticals, Janssen Immunotherapy, Novartis, Pfizer, Wyeth, SNIFF (The Study of Nasal Insulin to Fight Forgetfulness) study, and A4 (The Anti-Amyloid Treatment in Asymptomatic Alzheimer's Disease) trial. She receives research support from the Tau Consortium and the Association for Frontotemporal Dementia and is funded by the NIH. J.S. Goldman is serving as a consultant to the Novartis Alzheimer's Prevention Advisory Board. She receives research support from the NIH, HDSA, New York State Department of Health (RFA # 1510130358). N. Graff-Radford receives royalties from UpToDate, has participated in multicenter therapy studies sponsored by Biogen, TauRx, AbbVie, Novartis, and Lilly. He receives research support from the NIH. M. Grossman receives grant support from the NIH, Avid, and Piramal; participates in clinical trials sponsored by Biogen, TauRx, and Alector; serves as a consultant to Bracco and UCB; and serves on the Editorial Board of *Neurology*. G.-Y. Hsiung has served as an investigator for clinical trials sponsored by AstraZeneca, Eli Lilly, and Roche / Genentech. He receives research support from the Canadian Institutes of Health Research and the Alzheimer Society of British Columbia. D. Irwin receives support from the NIH, Brightfocus Foundation, and Penn Institute on Aging. D. Jones receives research support from the NIH and the Minnesota Partnership for Biotechnology and Medical Genomics. K. Kantarci served on the Data Safety Monitoring Board for Takeda Global Research & Development Center, Inc; data monitoring boards of Pfizer and Janssen Alzheimer Immunotherapy; research support from the Avid Radiopharmaceuticals, Eli Lilly, the Alzheimer's Drug Discovery Foundation, and the NIH. D. Knopman serves on the DSMB of the DIAN-TU study, is a site PI for clinical trials sponsored by Biogen, Lilly, and the University of Southern California, and is funded by the NIH. J. Kornak has provided expert witness testimony for Teva Pharmaceuticals in *Forest Laboratories Inc et al. v. Teva Pharmaceuticals USA, Inc*, Case Nos. 1:14-cv-0121 and 1:14-cv-0686 (D. Del. filed Jan 31, 2014 and May 30, 2014) regarding the drug Memantine; for Apotex/HEC/Ezra in *Novartis AG et al. v. Apotex Inc*, No. 1:15-cv-975 (D. Del. filed Oct 26, 2015), regarding the drug Fingolimod. He has also given testimony on behalf of Puma Biotechnology in *Hsingching Hsu et al., v. Puma Biotechnology, Inc, et al.* 2018 regarding the drug Neratinib. He receives research support from the NIH. W. Kremers receives research funding from AstraZeneca, Biogen, Roche, DOD, and the NIH. C. Lungu has received honoraria for editorial work from Elsevier, Inc. I. Mackenzie receives research funding from the Canadian Institutes of Health Research. S. McGinnis has served as an investigator for clinical trials sponsored by AbbVie, Allon Therapeutics, Biogen, Bristol-Myers Squibb, C2N Diagnostics, Eisai Inc, Eli Lilly and Co, Genentech, Janssen Pharmaceuticals, Medivation, Merck, Navidea Biopharmaceuticals, Novartis, Pfizer, and TauRx Therapeutics. He receives research support from the NIH. R. Pearlman is employed by the Bluefield Project. R. Rademakers receives research funding from the NIH and the Bluefield Project to Cure Frontotemporal Dementia. N. Tatton is employed by the Association for Frontotemporal Degeneration. A. Toga receives research support from the NIH and the Alzheimer's Association. J. Trojanowski may accrue revenue in the future on patents submitted by the University of Pennsylvania wherein he is coinventor and has received revenue from the sale of Avid to Eli Lily as coinventor on Aβ amyloid imaging–related patents submitted by the University of Pennsylvania. He receives research support from the NIH and several nonprofits. Z. Wszolek is supported by the NIH, Mayo Clinic

Center for Regenerative Medicine, the gift from Carl Edward Bolch, Jr, and Susan Bass Bolch, The Sol Goldman Charitable Trust, and G. Donald and Jodi P. Heeringa. He has also received grant funding support from Allergan, Inc (educational grant), and Abbvie (medication trials). J. Bove, D. Brushaber, C. Dheel, R. Dever, D. Gearhart J. Fong, D. Haley, L. Jones, A. Karydas, R. Kraft, M. Lapid, M. Manoochehri, E. Ramos, P. Sengdy, J. Syrjanen, and J. Taylor have nothing to disclose.

REFERENCES

1. Bang J, Spina S, Miller B. Frontotemporal dementia. *Lancet*. 2015;386:1672-1682.
2. Rademakers R, Neumann M, Mackenzie IR. Advances in understanding the molecular basis of frontotemporal dementia. *Nat Rev Neurol*. 2012;8:423-434.
3. Hutton M. Missense and splice site mutations in tau associated with FTDP-17: multiple pathogenic mechanisms. *Neurology*. 56(suppl 4): 2001; S21-S25.
4. Baker M, Mackenzie I, Pickering-Brown S, Gass J, Rademakers R, Lindholm C, et al. Mutations in progranulin cause tau-negative frontotemporal dementia linked to chromosome 17. *Nature*. 2006;442:916-919.
5. DeJesus-Hernandez M, Mackenzie IR, Boeve BF, Boxer AL, Baker M, Rutherford NJ, et al. Expanded GGGGCC hexanucleotide repeat in noncoding region of C9ORF72 causes chromosome 9p-linked FTD and ALS. *Neuron*. 2011;72:245-256.
6. Renton AE, Majounie E, Waite A, Simon-Sanchez J, Rollinson S, Gibbs JR, et al. A hexanucleotide repeat expansion in C9ORF72 is the cause of chromosome 9p21-linked ALS-FTD. *Neuron*. 2011;72:257-268.
7. Rohrer JD, Guerreiro R, Vandrovcova J, Uphill J, Reiman D, Beck J, et al. The heritability and genetics of frontotemporal lobar degeneration. *Neurology*. 2009;73:1451-1456.
8. van Swieten J, Spillantini MG. Hereditary frontotemporal dementia caused by Tau gene mutations. *Brain Pathol*. 2007;17:63-73.
9. van Swieten JC, Heutink P. Mutations in progranulin (GRN) within the spectrum of clinical and pathological phenotypes of frontotemporal dementia. *Lancet Neurol*. 2008;7:965-974.
10. Jack CJ, Knopman D, Jagust W, Shaw L, Aisen P, Weiner M, et al. Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade. *Lancet Neurol*. 2010;9:119-128.
11. JackJr. C, Knopman D, Jagust W, Petersen R, Weiner M, Aisen P, et al. Tracking pathophysiological processes in Alzheimer's disease: an updated hypothetical model of dynamic biomarkers. *Lancet Neurol*. 2013;12:207-216.
12. Knopman DS, Boeve BS, Caselli RJ, Graff-Radford NR, Kramer JH, Mendez MF, et al. Longitudinal tracking of FTLD: toward developing clinical trial methodology. *Alzheimer Dis Assoc Disord*. 2007;21:S58-S63.
13. Knopman DS, Jack Jr. CR, Kramer JH, Boeve BF, Caselli RJ, Graff-Radford NR, et al. Brain and ventricular volumetric changes in frontotemporal lobar degeneration over 1 year. *Neurology*. 2009;72:1843-1849.
14. Whitwell J, Weigand S, Boeve B, Senjem M, DeJesus-Hernandez M, Baker M, et al. Neuroanatomical signature of C9ORF72: a comparison to MAPT, progranulin and sporadic FTD (IN9-2.004). *Neurology*. 2012;78: IN9-2.004.
15. Whitwell JL, Avula R, Senjem ML, Kantarci K, Weigand SD, Samikoglu A, et al. Gray and white matter water diffusion in the syndromic variants of frontotemporal dementia. *Neurology*. 2010;74:1279-1287.
16. Whitwell JL, Boeve BF, Weigand SD, Senjem ML, Gunter JL, Baker MC, et al. Brain atrophy over time in genetic and sporadic frontotemporal dementia: a study of 198 serial magnetic resonance images. *Eur J Neurol*. 2015;22:745-752.
17. Rosen HJ, Gorno-Tempini ML, Goldman WP, Perry RJ, Schuff N, Weiner M, et al. Patterns of brain atrophy in frontotemporal dementia and semantic dementia. *Neurology*. 2002;58:198-208.
18. Rosen HJ, Kramer JH, Gorno-Tempini ML, Schuff N, Weiner M, Miller BL. Patterns of cerebral atrophy in primary progressive aphasia. *Am J Geriatr Psychiatry*. 2002;10:89-97.
19. Rohrer JD, Ahsan RL, Isaacs AM, Nielsen JE, Ostergaard L, Scahill R, et al. Presymptomatic generalized brain atrophy in frontotemporal dementia caused by CHMP2B mutation. *Dement Geriatr Cogn Disord*. 2009;27:182-186.
20. Rohrer JD, Nicholas JM, Cash DM, van Swieten J, Dopper E, Jiskoot L, et al. Presymptomatic cognitive and neuroanatomical changes in genetic frontotemporal dementia in the Genetic Frontotemporal dementia Initiative (GENFI) study: a cross-sectional analysis. *Lancet Neurol*. 2015;14:253-262.
21. Rohrer JD, Warren JD. Phenotypic signatures of genetic frontotemporal dementia. *Curr Opin Neurol*. 2011;24:542-549.
22. Rohrer JD, Warren JD, Barnes J, Mead S, Beck J, Pepple T, et al. Mapping the progression of progranulin-associated frontotemporal lobar degeneration. *Nat Clin Pract Neurol*. 2008;4:455-460.
23. Rohrer JD, Warren JD, Fox NC, Rossor MN. Presymptomatic studies in genetic frontotemporal dementia. *Rev Neurol (Paris)*. 2013;169:820-824.
24. Borroni B, Alberici A, Cercignani M, Premi E, Serra L, Cerini C, et al. Granulin mutation drives brain damage and reorganization from preclinical to symptomatic FTLD. *Neurobiol Aging*. 2012;33:2506–2520.
25. Borroni B, Alberici A, Premi E, Archetti S, Garibotto V, Agosti C, et al. Brain magnetic resonance imaging structural changes in a pedigree of asymptomatic progranulin mutation carriers. *Rejuvenation Res*. 2008;11:585-595.
26. Borroni B, Benussi A, Premi E, Alberici A, Marcello E, Gardoni F, et al. Biological, neuroimaging, and neurophysiological markers in frontotemporal dementia: three faces of the same coin. *J Alzheimers Dis*. 2018;62:1113-1123.
27. Schneider LS, Olin JT, Doody RS, Clark CM, Morris JC, Reisberg B, et al. Validity and reliability of the Alzheimer's disease cooperative study-clinical global impression of change. The Alzheimer's Disease Cooperative Study. *Alzheimer Dis Assoc Disord*. 11(suppl 2): 1997; S22-S32.
28. Knopman D, Weintraub S, Pankratz V. Language and behavior domains enhance the value of the clinical dementia rating scale. *Alzheimers Dement*. 2011;7:293-299.
29. Pfeffer RI, Kurosaki TT, Harrah Jr. JM, Chance CH, Filos S. Measurement of functional activities in older adults in the community. *J Gerontol*. 1982;37:323-329.
30. Schwab R, England A. Projection Technique for Evaluating Surgery in Parkinson's Disease. 1969; ES Livingston: Edinburgh, Scotland Schwab R, England A. Projecton technique for evaluating surgery in Parkinson's disease. Edinburgh, Scotland: ES Livingston; 1969.
31. Smith SC, Lamping DL, Banerjee S, Harwood R, Foley B, Smith P, et al. Measurement of health-related quality of life for people with dementia: development of a new instrument (DEMQOL) and an evaluation of current methodology. *Health Technol Assess*. 2005;9:1-93.
32. Zarit SH, Reever KE, Bach-Peterson J. Relatives of the impaired elderly: correlates of feelings of burden. *Gerontologist*. 1980;20:649-655.
33. Nasreddine ZS, Phillips NA, Bedirian V, Charbonneau S, Whitehead V, Collin I, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. *J Am Geriatr Soc*. 2005;53:695-699.
34. Weintraub S, Besser L, Dodge HH, Teylan M, Ferris S, Goldstein FC, et al. Version 3 of the Alzheimer disease centers' neuropsychological test battery in the Uniform Data Set (UDS). *Alzheimer Dis Assoc Disord*. 2018;32:10-17.
35. Reitan R. Validity of the Trail-Making Test as an indication of organic brain damage. *Percept Mot Skills*. 1958;8:271-276.
36. Kramer J, Mungas D, Possin K, Rankin K, Boxer A, Rosen H, et al. NIH EXAMINER: conceptualization and development of an executive function battery. *J Int Neuropsychol Soc*. 2014;20:11-19.

37. Ivanova I, Salmon DP, Gollan TH. The multilingual naming test in Alzheimer's disease: clues to the origin of naming impairments. *J Int Neuropsychol Soc*. 2013;19:272-283.
38. Woods SP, Delis DC, Scott JC, Kramer JH, Holdnack JA. The California Verbal Learning Test—second edition: test-retest reliability, practice effects, and reliable change indices for the standard and alternate forms. *Arch Clin Neuropsychol*. 2006;21:413-420.
39. Kramer JH, Jurik J, Sha SJ, Rankin KP, Rosen HJ, Johnson JK, et al. Distinctive neuropsychological patterns in frontotemporal dementia, semantic dementia, and Alzheimer disease. *Cogn Behav Neurol*. 2003;16:211-218.
40. Sheikh J, Yesavage J. Geriatric Depression Scale (GDS): recent evidence and development of a shorter versionT Brink. Clinical Gerontology: a Guide to Assessment and Intervention. 1986; Haworth Press Inc: Binghamton, NY; 165-173.
41. Kaufer DI, Cummings JL, Ketchel P, Smith V, MacMillan A, Shelley T, et al. Validation of the NPI-Q, a brief clinical form of the Neuropsychiatric Inventory. *J Neuropsychiatry Clin Neurosci*. 2000;12:233-239.
42. Carver CS, Pozo-Kaderman C, Harris SD, Noriega V, Scheier MF, Robinson DS, et al. Optimism versus pessimism predicts the quality of women's adjustment to early stage breast cancer. *Cancer*. 1994;73:1213-1220.
43. Davis MC, Matthews KA. Do gender-relevant characteristics determine cardiovascular reactivity? Match versus mismatch of traits and situation. *J Pers Soc Psychol*. 1996;71:527-535.
44. Lennox RD, Wolfe RN. Revision of the self-monitoring scale. *J Pers Soc Psychol*. 1984;46:1349-1364.
45. Fahn S, Elton RCommittee MotUDUnified Parkinson's Disease Rating ScaleS Fahn, C Marsden, D Calne, M Goldstein. Recent Developments in Parkinson's Disease. 1987; MacMillan: Florham Park, NJ; 153-163.
46. Golbe LI, Ohman-Strickland PA. A clinical rating scale for progressive supranuclear palsy. *Brain*. 2007;130:1552-1565.
47. Cedarbaum JM, Stambler N, Malta E, Fuller C, Hilt D, Thurmond B, et al. The ALSFRS-R: a revised ALS functional rating scale that incorporates assessments of respiratory function. BDNF ALS Study Group (phase III). *J Neurol Sci*. 1999;169:13-21.
48. Weintraub S, Salmon D, Mercaldo N, Ferris S, Graff-Radford NR, Chui H, et al. The Alzheimer's Disease Centers' Uniform Data Set (UDS): the neuropsychologic test battery. *Alzheimer Dis Assoc Disord*. 2009;23:91-101.
49. Boxer AL, Rankin KP, Miller BL, Schuff N, Weiner M, Gorno-Tempini ML, et al. Cinguloparietal atrophy distinguishes Alzheimer disease from semantic dementia. *Arch Neurol*. 2003;60:949-956.
50. Rankin KP, Rosen HJ, Kramer JH, Schauer GF, Weiner MW, Schuff N, et al. Right and left medial orbitofrontal volumes show an opposite relationship to agreeableness in FTD. *Dement Geriatr Cogn Disord*. 2004;17:328-332.
51. Kramer JH, Yaffe K, Lengenfelder J, Delis DC. Age and gender interactions on verbal memory performance. *J Int Neuropsychol Soc*. 2003;9:97-102.
52. Rankin KP, Baldwin E, Pace-Savitsky C, Kramer JH, Miller BL. Self awareness and personality change in dementia. *J Neurol Neurosurg Psychiatry*. 2005;76:632-639.
53. Rankin KP, Kramer JH, Miller BL. Patterns of cognitive and emotional empathy in frontotemporal lobar degeneration. *Cogn Behav Neurol*. 2005;18:28-36.
54. Rankin KP, Salazar A, Gorno-Tempini ML, Sollberger M, Wilson SM, Pavlic D, et al. Detecting sarcasm from paralinguistic cues: anatomic and cognitive correlates in neurodegenerative disease. *Neuroimage*. 2009;47:2005-2015.
55. Rankin KP, Santos-Modesitt W, Kramer JH, Pavlic D, Beckman V, Miller BL. Spontaneous social behaviors discriminate behavioral dementias from psychiatric disorders and other dementias. *J Clin Psychiatry*. 2008;69:60-73.
56. Rankin KP, Gorno-Tempini ML, Allison SC, Stanley CM, Glenn S, Weiner MW, et al. Structural anatomy of empathy in neurodegenerative disease. *Brain*. 2006;129:2945-2956.
57. Weintraub S, Mesulam MM, Wieneke C, Rademaker A, Rogalski EJ, Thompson CK. The northwestern anagram test: measuring sentence production in primary progressive aphasia. *Am J Alzheimers Dis Other Demen*. 2009;24:408-416.
58. Rogalski E, Cobia D, Harrison TM, Wieneke C, Weintraub S, Mesulam MM. Progression of language decline and cortical atrophy in subtypes of primary progressive aphasia. *Neurology*. 2011;76:1804–1810.
59. Rogalski E, Cobia D, Harrison TM, Wieneke C, Thompson CK, Weintraub S, et al. Anatomy of language impairments in primary progressive aphasia. *J Neurosci*. 2011;31:3344-3350.
60. Sepelyak K, Crinion J, Molitoris J, Epstein-Peterson Z, Bann M, Davis C, et al. Patterns of breakdown in spelling in primary progressive aphasia. *Cortex*. 2011;47:342-352.
61. Crinion J, Holland AL, Copland DA, Thompson CK, Hillis AE. Neuroimaging in aphasia treatment research: quantifying brain lesions after stroke. *Neuroimage*. 2013;73:208-214.
62. Tsapkini K, Hillis AE. Spelling intervention in post-stroke aphasia and primary progressive aphasia. *Behav Neurol*. 2013;26:55-56.
63. Faria AV, Crinion J, Tsapkini K, Newhart M, Davis C, Cooley S, et al. Patterns of dysgraphia in primary progressive aphasia compared to post-stroke aphasia. *Behav Neurol*. 2013;26:21-34.
64. Morris JC. The Clinical Dementia Rating (CDR): current version and scoring rules. *Neurology*. 1993;43:2412-2414.
65. Rascovsky K, Hodges JR, Knopman D, Mendez MF, Kramer JH, Neuhaus J, et al. Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia. *Brain*. 2011;134:2456-2477.
66. Chang H, Fitzpatrick JM. A technique for accurate magnetic resonance imaging in the presence of field inhomogeneities. *IEEE Trans Med Imaging*. 1992;11:319-329.
67. Andersson JL, Skare S, Ashburner J. How to correct susceptibility distortions in spin-echo echo-planar images: application to diffusion tensor imaging. *Neuroimage*. 2003;20:870-888.
68. Dai W, Garcia D, de Bazelaire C, Alsop DC. Continuous flow-driven inversion for arterial spin labeling using pulsed radio frequency and gradient fields. *Magn Reson Med*. 2008;60:1488-1497.
69. Hutton M, Lendon CL, Rizzu P, Baker M, Froelich S, Houlden H, et al. Association of missense and 5'-splice-site mutations in tau with the inherited dementia FTDP-17. *Nature*. 1998;393:702–705.
70. Gendron TF, van Blitterswijk M, Bieniek KF, Daughrity LM, Jiang J, Rush BK, et al. Cerebellar c9RAN proteins associate with clinical and neuropathological characteristics of C9ORF72 repeat expansion carriers. *Acta Neuropathol*. 2015;130:559-573.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

How to cite this article: Boeve B, Bove J, Brannelly P, et al. The longitudinal evaluation of familial frontotemporal dementia subjects protocol: Framework and methodology. *Alzheimer's Dement*. 2020;16:22–36. https://doi.org/10.1016/j.jalz.2019.06.4947