The new NACC FTLD Module

David Knopman for the FTD Workgroups, especially: Sandy Weintraub, Marsel Mesulam, Joel Kramer, Kate Rankin, Murray Grossman, Argye Hillis

Thanks to NACC: Bud Kukull, Elizabeth Robichaud, Maggie Dean et al

Thanks to AFTD, NIA and NINDS

14-Dec-2011 ....revised 29-Jan-2012
Why NACC?

- ~30 NIA funded ADCs were collecting data on subjects each in their own way
  - Limited opportunities for collaboration and use of large datasets
- In 2005, the Uniform Data Set (UDS) introduced
  - Standard evaluations across centers including clinical and neuropsychological testing
    - Very successful but very Alzheimer-centric
- UDS v2 in 2008 added 8-domain CDR
Distribution of Diagnoses in NACC UDS V2 Sept 09

- Cerebrovascular Disease
- Lewy Body Disease
- Dementia due to Alzheimer’s disease
- bvFTD
- PPA
Why FTLD in NACC?

- In younger patients almost as common as AD
- Recognition & diagnosis of clinical syndromes of FTLDs requires expertise
- Evaluation of FTLDs is sufficiently different from AD that standard UDS is suboptimal
- Advances in genetics & biochemistry make FTLDs feasible target for therapy
- As a slightly newer area of investigation, now is the time to standardize evaluations across centers
FTLD Collaboration

• Instigated by Tony Phelps at NIA in conjunction with Walter Koroshetz at NINDS
• Data forms and database designed by Bud Kukull, Duane Beekly and Elizabeth Robichaud
• Core Leaders
  – Clinical: Knopman, Mendez, Grossman, Mesulam
  – Neuropsychology: Miller, Kramer, Weintraub, Hillis, Grafman, Rankin
  – Genetics: Boeve, Rademakers, Mayeux, Geschwind, Shellenberg, Bird
  – Imaging: Rosen, Dickerson, Josephs, Gee, Foster

NACC UNIFORM DATA SET (UDS) – FTD MODULE
So how will the FTLD module work?

- Voluntary participation by ADC’s
- To be completed in conjunction with standard UDS in patients with syndromes of bvFTD, PPA’s (and selected control normals, AD cases)
- Module use needs to be anticipated because extra time required for neuropsych and informant interview
Purpose of FTLD Module

• To capture salient information about the FTLD syndromes not currently available in AD-oriented current UDS
  – No changes in current UDS “allowed”
• To have the FTLD module mesh with the current UDS
• To foster collaborative, multicenter research in the FTLD’s
History of FTD

• Recognized pathologically by Pick in 19th century (1892)
• Clinical syndrome equated with Pick’s disease
• Syndrome of FTD not associated with Pick-body disease recognized for a long time, but ignored
• Brun and Gustafson (Lund Sweden) & Neary and Mann (Manchester UK) recognized importance of syndrome of FTD; Mesulam reported PPA in 1982
• FTLD recognized as more than Pick’s disease
• bvFTD & PPA have same pathological basis
• First diagnostic criteria 1994 “Lund Manchester”
• Modern immunohistochemical analyses demonstrated broader prevalence of frontotemporal lobar degenerations
Frontotemporal (Lobar) Degenerations

• Pathological - a group of disorders with one of several neurodegenerative pathologies showing predilection for frontal & anterior temporal lobes

• Clinical – Three types:
  – Behavioral-dysexecutive disorder (bvFTD)
  – Language disorders (nf/av- sv- lv- PPA)
  – ALS, Corticobasal or PSP syndromes;

• Major genetic subtypes: MAPT, GRN, C9ORF72, sporadic, rare mutations

• Focal atrophy: frontal, anterior temporal, insular, asymmetric
Matrix of FTLD

Clinical syndromes
bvFTD - PPA
PSP CBS ALS

Anatomic locus
Frontal Ant. Temporal
Insula Caudate Thalamus

Histologic Type
Tau TDP43

Genetic basis
MAPT
GRN
C9ORF72
Sporadic
Rarer genes
Cognitive syndromes of frontotemporal degenerations*

*not including ALS, PSP-like and CBD-like presentations
Age Distribution in FTLD Multicenter study

<table>
<thead>
<tr>
<th>Age brackets</th>
<th>N of subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;50</td>
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<tr>
<td>50-59</td>
<td></td>
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<tr>
<td>60-69</td>
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<tr>
<td>&gt;70</td>
<td></td>
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</tbody>
</table>

- bvFTD
- NF/G PPA
- Sem PPA
- Log PAA
Diagnostic criteria for bvFTD: International Consensus Criteria

1. Shows progressive deterioration of behavior or cognition by observation and history

2. Possible bvFTD: 3 of the following must be present
   A. Early behavioral disinhibition
   B. Early apathy or inertia
   C. Early loss of sympathy or empathy
   D. Early perseverative, stereotyped or compulsive/ritualistic behaviors
   E. Hyperorality and dietary changes
   F. Executive/generative deficits on neuropsychological testing

3. Probable bvFTD: meets possible bvFTD criteria and
   A. Exhibits significant functional decline
   B. Exhibits imaging changes in frontal or anterior temporal lobes

Rascovksy et al Brain online Aug 2, 2011
Diagnostic criteria for PPA: from Gorno-Tempini 2011, based on Mesulam

The root diagnostic criteria:
1. Most prominent feature: difficulty with language
2. Aphasia should be most prominent deficit at symptom onset and for initial phases of disease
3. All causes other than neurodegenerative disease are excluded
Principal Syndromes of Primary Progressive Aphasias

- **Nonfluent/agrammatic**
  - Labored, agrammatic, effortful, telegraphic

- **Semantic**
  - Loss of knowledge of word and object meaning

- **Logopenic**
  - Anomic, telegraphic speech

From Gorno-Tempini 2004
Progressive Supranuclear Palsy

• First described in 1964 by Steele, Richardson, Olszewski
• Neurofibrillary tangle pathology = tauopathy
• Originally characterized by tetrad of supranuclear gaze palsy, axial rigidity, dementia, parkinsonism
• Current definition: vertical supranuclear palsy and prominent postural instability
• Was one of the disorders that gave rise to notion of “subcortical dementia”
• Cognitive features are within spectrum of bv-FTD
Corticobasal Degeneration

• A syndrome of asymmetric rigidity and limb apraxia first described in 1967/68
  – May have cortical sensory loss, alien limb, focal myoclonus, limb dystonia

• First described syndromically with path correlate of swollen chromatolytic neurons

• Later shown to be a tauopathy (early 1990’s)

• However, syndrome turned out to be more heterogeneous pathologically
  – Tauopathy
  – Alzheimer pathology
  – TDP43 proteinopathy
Amyotrophic Lateral Sclerosis

- Long recognized neurological disorder with famous victims
- Diagnosed on basis of upper and lower motor neuron degeneration (exclusions important!)
- Only in past decade has the associated cognitive disorder been recognized
- Pathological overlap with non-tauopathy FTLDs
- Discovery that TDP43 immunostaining was universal in ALS highlighted overlap with FTLD
- Recent discoveries of mutations in TDP43 and C9ORF72 in both ALS and FTD
Age Distribution in FTDC of autopsy-proved FTLD

Courtesy of K Rascovisky
Age Distribution in FTLD Multicenter study

Percent of subjects

Syndromes

Knopman Brain 2008
Overlap of FTLD Syndromes

Kertesz Brain 2005
Overlap of FTLD Syndromes

Kertesz Brain 2005
Neuropathological subtypes
frontotemporal degenerations*

- Tauopathy
- TDP43opathy
- Other
FTLD and Neuropathology

• What is available in current UDS that is relevant to FTLD
  – Core parts of UDS neuropath readily accommodate FTLD except…
  – No items for TDP-43 subtyping
  – No FUS items

• But, it doesn’t make sense to have a new module that is FTLD specific for neuropath as this material should be in standard UDS, and therefore will have to await new version
FTLD Genetics

- **MAPT** - chr 17q21.1 (6% familial cases)
  - 72 unique mutations to date
  - Tauopathy causing bvFTD or nf/ag PPA
- **GRN** - chr 17q21.32 (7% familial cases)
  - 149 unique mutations to date
  - TDP-43 inclusions causing bvFTD or PPAs
- **C9ORF72** - chr 9p21 (11% familial cases)
  - Massive hexanucleotide repeat
  - Most common genetic cause of FTLD & ALS
- **Rare mutations**: *FUS, TAR-DP43, CHMP2B*
## Differences between Genetic Subtypes

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>MAPT</th>
<th>GRN</th>
<th>C9ORF72</th>
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<tbody>
<tr>
<td>bvFTD phenotype</td>
<td>++++</td>
<td>++++</td>
<td>++++</td>
</tr>
<tr>
<td>ALS phenotype</td>
<td>+</td>
<td>+</td>
<td>++++</td>
</tr>
<tr>
<td>PPA phenotype</td>
<td>++</td>
<td>++</td>
<td>-</td>
</tr>
<tr>
<td>Frontal atrophy</td>
<td>++</td>
<td>++</td>
<td>+++</td>
</tr>
<tr>
<td>Temporal atrophy</td>
<td>+++</td>
<td>++</td>
<td>+</td>
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From Boeve, Brain in press
The New Nosology of FTLD Pathology


NIFID = neuronal intermediate filament inclusion disease; aFTLD-U = atypical FTLD with ubiquitin inclusions; BIBD = basophilic inclusion body disease; FTLD with fused in sarcoma (FUS) mutation; FTLD with charged multivesicular body protein 2B (CHMP2B) mutation.
Imaging in FTLDs

• Majority of patients have focal frontal or anterior temporal atrophy that is identifiable by visual inspection
• Atrophy often asymmetric
• Some patients lack focal atrophy
  – Tends to be those associated with motor neuron disease
Challenges in the diagnosis of bvFTD

- **Sensitivity** of new criteria excellent esp. in persons <70 yo
- **Specificity** probably “pretty good”
  - Depends on rigor of criteria
  - Also depends on experience of clinician
- **Challenges**
  - “Phenocopy” cases that show little progression
  - AD dementia and Lewy body dementia cases with lots of behavior changes
Challenges in the diagnosis of PPAs

- Diagnosis of expressive speech deficits is still somewhat of an art
  - ...Not detecting that it is there, but rather the subtype
- AD pathology can account for aphasic presentation (logopenic speech)
- Amyloid imaging in PPA (Leyton, Brain 2011):
  - Nonfluent/agrammatic variant - 2 / 8 +ive amyloid
  - Semantic variant - 1 / 9 +ive amyloid
  - Logopenic variant - 12/13 +ive amyloid
Epidemiology of FTLD

- More difficult to study because of low prevalence
- Active surveillance methods not practical
- Methods for case detection:
  - Surveillance of regional neurology referral centers
  - Medical record review of regional medical practices
- Passive surveillance may be less accurate than active case detection
Prevalence of FTLD vs PSP

FTLD: Netherlands  UK-C  UK-L  Italy  PSP: UK

Age range

* bvFTD only

Prevalence /100,000

0  5  10  15  20  25  30

45-64  45-64  45-64  45-64  55+
Comparison of FTLD & AD Incidence

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<tr>
<th></th>
<th>US</th>
<th>UK</th>
<th>Spain</th>
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<tbody>
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<td>FTLD</td>
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<tr>
<td>AD</td>
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</tbody>
</table>

Logarithmic Incidence /100,000

- FTLD
- AD

Age groups:
- 50-59
- 60-69
- 45-64
FTLD Epidemiology Summary

- Prevalence of FTLD ~20 per 100,000 aged 45-64
  - 12,000 to 18,000 cases in US aged 45-64
  - Total 20,000 to 30,000 including younger & older age ranges

- Sum of all FTLD syndromes ≈ PSP*
- 200 fold LESS than Alzheimer’s over AD’s age range
- 10 fold GREATER than Creutzfeldt-Jakob

*Nath, Brain 124:1438, 2001, estimated prevalence of PSP=25.6 per 100K in 55+ age group
Elements of the FTLD Module
FTLD related items in current UDS

- Augmented (8-domain) CDR
- Neuropsychiatric inventory
- UPDRS
- Diagnostic choices for
  - bvFTD
  - Nonfluent variant PPA
  - Semantic variant PPA
  - Logopenic variant PPA
  - Progressive Supranuclear Palsy
  - Corticobasal Syndrome
What is missing in UDS for FTLDs

• All detail on basis for diagnoses on:
  – Aphasias
  – Specific behaviors typically abnormal in bVFTD
  – Aspects of motor exam not covered by our current UPDRS

• Adequate genetic information
• Behavioral questionnaires specific for bvFTD
• Aphasia examination
FTLD Clinical Module

• In the new FTLD module
  – Augmented neurological examination
  – Specific features in aphasia assessment for PPAs
  – Specific features for making diagnosis of bvFTD
  – Neuropsychological battery
  – Improved genetic info form
  – More Imaging information
### bvFTD Gateway Question

**Gateway Question for behavior variant Frontotemporal Dementia (bvFTD)**

| 14. Does patient have acquired, clinically important alterations in behavior, personality, or comportment consistent with bvFTD of a neurodegenerative type? | 0 No. Skip to Q23  
1 Yes. Proceed to Q15  
9 Not evaluated. Skip to Q23. |

bvFTD Gateway Question: Q14 asks the clinician whether there are prominent changes in behavior, personality or comportant that would justify a more detailed description of those abnormalities that is obtained with questions Q15 to Q20. Q14 does not constitute a diagnosis but is only a means for determining whether the clinician completes the detailed assessment of behaviors or skips it.
Root diagnosis of PPA: Q12 is the one that records the root diagnosis of PPA. It is based on the 3 features described in Mesulam 2003. By convention, an initial diagnosis of PPA - one made at the first contact for the current neurological disease – should only be made if it is the dominant or first diagnosis.
### Supplementary Neurologic Examination

**SECTION A**

<table>
<thead>
<tr>
<th>Question</th>
<th>0</th>
<th>1</th>
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<th>3</th>
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<tbody>
<tr>
<td>A1. Does the subject have limb or torso fasciculations consistent with a</td>
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<tr>
<td>diagnosis of spinal muscular atrophy (SMA) or amyotrophic lateral</td>
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<tr>
<td>sclerosis (ALS)?</td>
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<td>A2. Does the subject have limb weakness and/or hyperreflexia consistent</td>
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<td>with a diagnosis of primary lateral sclerosis (PLS) or ALS?</td>
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<td>A3. Does the subject have bulbar weakness and/or fasciculations</td>
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<td>consistent with a diagnosis of ALS?</td>
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<tr>
<td>A4. Does the subject have eye movement abnormalities consistent with a</td>
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<tr>
<td>diagnosis of progressive supranuclear palsy (PSP)?</td>
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<tr>
<td>A5. Does the subject have dystonia or rigidity consistent with a diagnosis</td>
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<tr>
<td>of corticobasal degeneration (CBD)?</td>
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<tr>
<td>A6. Is there ideomotor apraxia* consistent with a diagnosis of CBD?</td>
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<td>8</td>
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<tr>
<td>A7. Is the alien limb phenomenon* present consistent with a diagnosis of</td>
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<tr>
<td>CBD?</td>
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<tr>
<td>A8. Is there myoclonus* consistent with a diagnosis of CBD?</td>
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<tr>
<td>A9. Is there a cortical sensory deficit consistent with a diagnosis of</td>
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<td>8</td>
</tr>
<tr>
<td>CBD?</td>
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</tbody>
</table>

**Motor neuron disease**

**Eye mvmt Disorder**

**Cortico-basal syndrome**
• What is available in current UDS that is relevant to FTLD
  – Asks only about “dementia yes/no”
• What is needed for FTLD
  – Specific dementia diagnoses and method of ascertainment of dx (eg autopsy, family report, record review, etc)
• Note: information on mutation status not recorded in new module
Genetics Module: more general than current A3

Form A3F: Family History: Affected Family Members

NOTE: This form is to be completed by a clinician with experience in evaluating patients with frontotemporal lobar degeneration. For additional clarification and examples, see FTD Coding Guidebook for Initial Visit Packet, Form A3F.

Any neurological diagnosis

<table>
<thead>
<tr>
<th>AFFECTED FAMILY MEMBERS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Are there affected family members? (See box above for definition of &quot;affected.&quot;)</td>
</tr>
<tr>
<td>If the answer is &quot;No&quot; or &quot;Unknown,&quot; please skip the rest of this form.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>AFFECTED PARENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Neurological problem*</td>
</tr>
<tr>
<td>b. Primary DX**</td>
</tr>
<tr>
<td>c. Method***</td>
</tr>
<tr>
<td>d. Age of onset</td>
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</tbody>
</table>

Method of Dx needed
### Genetics Module: more general than current A3

#### Identification of mutation

<table>
<thead>
<tr>
<th>Affected Family Members</th>
<th>0 No</th>
<th>1 Yes</th>
<th>9 Unknown</th>
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</thead>
<tbody>
<tr>
<td>1a. Are there affected family members? (See box above for definition of “affected.”) If the answer is “No” or “Unknown,” please skip rest of this form.</td>
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</tr>
<tr>
<td>1b. In this family, is there a known mutation in a gene associated with FTLD? If the answer is “No” or “Unknown,” please skip to Question 2.</td>
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<tr>
<td>1c. What is the predominant mutation?</td>
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<tr>
<td>1d. Is there evidence for this mutation in the form of commercial lab test documentation?</td>
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<tr>
<td>1e. Is there evidence for this mutation in the form of research lab test documentation?</td>
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<tr>
<td>1f. Is there evidence for this mutation in the form of family report?</td>
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<tr>
<td>1g. Is there other evidence for this mutation?</td>
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</table>
FTLD Neuropsychological Module

• What is available in current UDS that is relevant to FTLD
  – Category Fluency
  – Digit Span
  – Boston Naming
  – Trailmaking
FTLD Neuropsychological Module

What is missing in current UDS

– Executive functioning
– Language testing
  • Sentence repetition
  • Grammatical knowledge
  • Semantic fluency
  • Surface dyslexia
– Social cognition
FTLD Neuropsychological Module

- A mix of cognitive tests and informant questionnaires
- Meant to be used along with standard UDS neuropsych battery
FTLD Neuropsychological Module - Cognitive Tests

- Visual memory – Benson figure
- Letter fluency test
- Word reading (regular/irregular)
- Semantic word-picture matching
- Semantic associates test
- Northwestern Anagram test, a test of grammatic knowledge
- Noun and verb naming
- Sentence repetition and reading
FTLD Neuropsychological Module – Interviews and Questionnaires

• Behavioral Inhibition Scale (Inf)
• Interpersonal Reactivity index (Inf)
• Revised Self Monitoring Scale (Inf)
• Social Behavior Observer checklist (Ex)
• Social Norms Questionnaire (S)
FTLD Imaging Module

• What is available in current UDS that is relevant to FTLD
  – Whether imaging has been performed
  – Whether there is evidence for cerebrovascular disease

• What is needed for FTLD
  – More detail on imaging abnormalities in MR, FDG-PET
<table>
<thead>
<tr>
<th>Question</th>
<th>Options</th>
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<tbody>
<tr>
<td>1. Is a structural MRI scan, obtained as part of the current evaluation or a previous evaluation, available for data sharing? (REPORT MOST RECENT)</td>
<td>0: No, 1: Yes, 9: Unknown</td>
</tr>
<tr>
<td>1a. Date of scan (MM/DD/YYYY):</td>
<td><em><strong>/</strong></em>/_____</td>
</tr>
<tr>
<td>NOTE: A value of 99 (unknown) is permissible for day only.</td>
<td></td>
</tr>
<tr>
<td>1b. Is it in DICOM format or other electronic format?</td>
<td>0: No, 1: Yes (specify format), 9: Unknown</td>
</tr>
<tr>
<td>1c. Was ADNI protocol used?</td>
<td>0: No, 1: Yes, ADNI version: ________________</td>
</tr>
<tr>
<td>1d. Scan manufacturer:</td>
<td>1: GE, 2: Siemens, 3: Philips, 4: Other: ____________________</td>
</tr>
<tr>
<td>Model: ________________</td>
<td></td>
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<tr>
<td>1e. Field strength:</td>
<td>1: 1.5T, 2: 3T, 3: 7T, 4: Other: ____________________</td>
</tr>
<tr>
<td></td>
<td>9: Unknown</td>
</tr>
<tr>
<td>1f. Are results of quantitative image analysis available?</td>
<td>0: No, 1: Yes, 9: Unknown</td>
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</table>
# Imaging Module for diagnosis

<table>
<thead>
<tr>
<th>No</th>
<th>Yes</th>
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## 1. Was imaging obtained as part of this visit for use in diagnosis?

<table>
<thead>
<tr>
<th>No</th>
<th>Yes</th>
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**IF YES, which type(s)? (If NO, end form here.)**

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<thead>
<tr>
<th>Type</th>
<th>No</th>
<th>Yes</th>
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</table>

1a. Structural MRI imaging *(If yes, finish this section and complete Section 2 below.)*

1b. FDG-PET imaging *(If yes, finish this section and complete Section 3 below.)*

1c. Amyloid PET imaging, e.g., PiB *(If yes, finish this section and complete Section 4 below.)*

1d. CBF SPECT imaging *(If yes, finish this section and complete Section 5 below.)*

1e. Other imaging (specify below):

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<thead>
<tr>
<th></th>
<th>No</th>
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## 2. If structural MRI was done, was focal atrophy (beyond what would be expected for age) appreciated by visual inspection?

<table>
<thead>
<tr>
<th>No</th>
<th>Yes</th>
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**IF YES, where was focal atrophy appreciated?**

<table>
<thead>
<tr>
<th>Location</th>
<th>No</th>
<th>Yes</th>
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2a. Right frontal lobe

2b. Left frontal lobe

2c. Right temporal lobe

2d. Left temporal lobe

2e. Right medial temporal lobe
Next Steps

• Implement at individual centers
• Obtain funding to broaden utilization of module to cognitively normal subjects, other dementia and MCI subjects
• Integrate into UDS-3