

# Introduction and Process

Norman L. Foster, MD

7BS.006  
**IMPROVING ACCURACY OF DEMENTIA DIAGNOSIS:  
CASE STUDIES WITH NEUROPATHOLOGY**

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University of Utah  
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**James B. Leverenz, MD**  
University of Washington  
Seattle, WA

**6:45 a.m. - 8:30 a.m.**  
**Friday, May 4, 2007**  
**Breakfast Seminar**

## Introduction and Process

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**Norman L. Foster, M.D.**  
Center for Alzheimer's Care, Imaging and Research  
Department of Neurology, University of Utah

*No conflicts to disclose*

## Overview

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- An interactive discussion of clinical cases with FDG-PET scans and autopsy diagnosis of Alzheimer's disease (AD) or frontotemporal dementia (FTD)
- Briefly review FDG-PET and its interpretation in dementia
- Briefly review the clinical criteria for AD and FTD
- Briefly review the histopathology of AD and FTD
- Cases will be presented to stimulate discussion
- We will ask the audience to vote on diagnosis

## Objectives

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- CMS recently approved the use of FDG-PET in the evaluation of dementia to distinguish AD from FTD
- Neurologists need to better understand when and how to utilize this new technology
- Improve accuracy and confidence in clinical diagnosis of dementing illnesses
- Learn when and how to use molecular imaging in dementia evaluations
- Better apply diagnostic criteria for dementing disorders in individual situations

## Why FTD and AD?

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- AD and FTD are common causes of dementia
  - AD is the most common cause of dementia in the elderly in the US
  - FTD is much less prevalent, but still the second most common neurodegenerative cause early-onset dementia
- Neither has characteristic physical findings that aid the diagnosis of other dementias
- Clinically difficult to distinguish
- FDG-PET can help this clinical decision and is CMS approved

## FTD May Mimic AD

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- Behavior disturbance is common in AD
- Language is affected early in AD
- AD is sometimes asymmetric causing prominent aphasia
- Most FTD patients develop a significant memory disturbance
- Most FTD patients also meet NINCDS-ADRDA criteria for AD (Varma et al., JNNP 1999;66:184-188)
- Clinicians depend upon relative severity of symptoms; none are pathognomonic

## Introduction and Process

Norman L. Foster, MD

### Clinical Summaries

- Collected all available medical records
- Removed personal identifiers, imaging results, and autopsy reports
- Several page clinical narrative from these records summarizing the patient's entire clinical course
- Developed by a dementia expert unaware of diagnosis who did not serve as a rater

### How We Will Consider Cases

- Review scenario and rate, then we will discuss
- Review with FDG-PET and rate, then discuss with interpretation of FDG-PET
- Present neuropathological findings
- Diagnosis - AD or FTD
  - Must decide one or the other
- Degree of Confidence
  - Very confident
  - Somewhat confident
  - Uncertain

### How to Rate Cases

- Diagnosis - AD or FTD
  - Must decide one or the other
- Degree of Confidence
  - Very confident
  - Somewhat confident
  - Uncertain

### Rating Card Example

1. What is your best diagnosis after reviewing? (select only one)
- 1)  AD
- 2)  FTD
2. What is your confidence in this diagnosis? (select only one)
- 1)  Very confident
- 2)  Somewhat confident
- 3)  Uncertain

Scenario # \_\_\_\_\_

Scenario only

Scenario and PET

# Clinical Application of FDG-PET Imaging

Norman L. Foster, MD

## Clinical Application of FDG-PET Imaging

**Norman L. Foster, M.D.**

Center for Alzheimer's Care, Imaging and Research  
Department of Neurology, University of Utah

No conflicts to disclose

## 18-F Fluorodeoxyglucose Positron Emission Tomography (FDG-PET)

- FDG-PET provides unique information, complementary to structural imaging
- Short-lived positron-labeled form of sugar that follows the early steps of glucose, but gets trapped in the cell
  - Fluorine -18: 120 min
- PET scanner uses physical properties of positrons to localize relevant radioactive emissions and discards others (improved resolution)

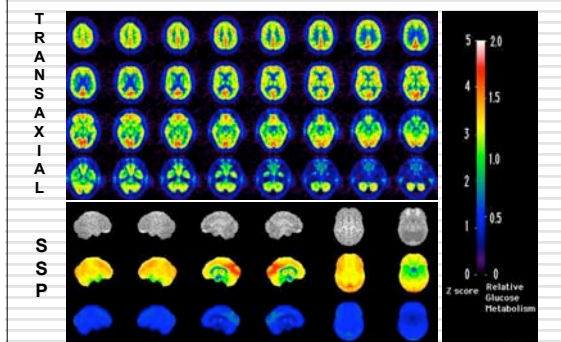
## What Glucose Metabolism Measures

- Under normal conditions the brain uses glucose as its sole source of energy
- Glucose metabolism primarily reflects synaptic activity
- Hypometabolism may not correspond to areas with greatest changes in routine neuropathology
- Routine neuropathology is better at detecting loss of neuronal cell bodies than synapses
- It is not directly affected by intracellular or extracellular inclusions

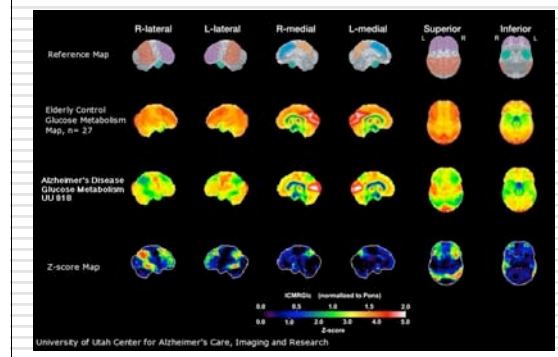
## Synapses are Lost Before Neurons Die



## FDG-PET Image Presentation Methods

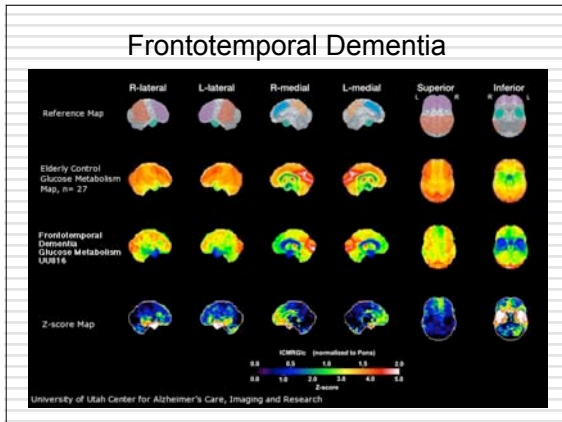


## Alzheimer's Disease



## Clinical Application of FDG-PET Imaging

Norman L. Foster, MD



### Simple Rules for FDG-PET Diagnosis in this Course

- Alzheimer's disease
  - Temporoparietal cortex hypometabolism > frontal cortex
  - Posterior cingulate cortex hypometabolic
- Frontotemporal dementia
  - Frontal cortex hypometabolism > temporoparietal cortex
  - Anterior temporal and anterior cingulate cortex hypometabolic
- When several areas affected, are AD or FTD regions most hypometabolic

# Clinical Diagnostic Criteria for AD and FTD

Edward Zamrini, MD

## CLINICAL DIAGNOSTIC CRITERIA FOR AD AND FTD

### Edward Zamrini M.D.

Center for Alzheimer's Care Imaging and Research  
Department of Neurology  
University of Utah

No conflicts to disclose

## Overview

- Clinical features and diagnostic criteria for Alzheimer's disease
- Clinical features and diagnostic criteria for frontotemporal dementia
- Reasons for difficulty with diagnosis
- Importance of making a diagnosis

## Objectives

- Improve accuracy and confidence in clinical diagnosis of dementing illnesses
- Apply diagnostic criteria for dementing disorders in individual situations
- Identify features that distinguish between AD and FTD

## Alzheimer's Disease

- Insidious onset of gradual progressive dementia
- Memory loss usually initial and most prominent symptom
- No focal weakness or sensory loss
- Gait normal and continent until late in the illness
- NINCDS-ADRDA criteria validated

## NINCDS/ADRDA

- Criteria for Diagnosis of Probable AD:
  - (a) Dementia established by clinical examination, and documented by a standard test of cognitive function, and confirmed by neuropsychological tests.
  - (b) Significant deficiencies in two or more areas of cognition, for example, word comprehension and task-completion ability.
  - (c) Progressive deterioration of memory and other cognitive functions.
  - (d) No loss of consciousness.
  - (e) Onset from age 40 to 90, typically after 65.
  - (f) No other diseases or disorders that could account for the loss of memory and cognition.

## Frontotemporal Dementia

- Insidious onset of progressive dementia
- Disturbing behavior and speech problems most prominent, less evident memory loss
- Perseveration, decreased verbal fluency
- Typical behavioral changes including apathy unrestrained and inappropriate social conduct
- Memory loss often not prominent; AD screening tests may be insensitive
- May be associated with motor neuron disease

## Clinical Diagnostic Criteria for AD and FTD

Edward Zamrini, MD

### FTD: Clinical profile

- Frontotemporal dementia (FTDbv): Character change and disordered social conduct. Instrumental functions relatively well preserved.
- Progressive nonfluent aphasia (PA): Disorder of expressive language is the dominant feature initially and throughout the disease course. Other aspects of cognition are intact or relatively well preserved.
- Semantic aphasia and associative agnosia dementia (Semantic dementia, SD): impaired understanding of word meaning and/or object identity.

### Diagnostic features of frontotemporal dementia behavioral variant

- I. Core diagnostic features of FTD
  - A. Insidious onset and gradual progression
  - B. Early decline in social interpersonal conduct
  - C. Early impairment of personal conduct
  - D. Early emotional blunting
  - E. Early loss of insight
- II. Supportive diagnostic features of FTD
  - A. Behavioral disorder
  - B. Speech and language
  - C. Physical signs

### Diagnostic features progressive non-fluent aphasia

- I. Core diagnostic features of PA
  - A. Insidious onset and gradual progression
  - B. Nonfluent spontaneous speech with: agrammatism, phonemic paraphasias, anomia
- II. Supportive diagnostic features of PA
  - A. Speech and language
    - 1. Stuttering or oral apraxia 2. Impaired repetition 3. Alexia, agraphia 4. Early preservation of word meaning, 5. Late mutism
  - B. Behavior
    - 1. Early preservation of social skills 2. Late behavioral changes similar to FTD
  - C. Physical signs: late contralateral primitive reflexes, akinesia, rigidity, and tremor

### Diagnostic features of semantic aphasia and associative agnosia

- I. Core diagnostic features of SD
  - A. Insidious onset and gradual progression
  - B. Language Disorder and/or
  - C. Perceptual disorder
  - D. Preserved perceptual matching and drawing reproduction
  - E. Preserved single-word repetition
  - F. Preserved ability to read aloud and write to dictation orthographically regular words
- II. Supportive diagnostic features of semantic dementia
  - A. Speech and language
  - B. Behavior
  - C. Physical signs

### FTD May Mimic AD

- Alzheimer's disease is much more common than frontotemporal dementia
- Behavior disturbance is common in AD
- Language is affected early in AD
- AD is sometimes asymmetric causing prominent aphasia
- Most patients with FTD have a significant memory disturbance
- Most patients with FTD also meet NINCDS-ADRDA criteria for AD (Varma et al. JNNP 1999;66:184-188)
- Clinicians depend upon relative severity of symptoms; none are pathognomonic

### AD or FTD Does it Make a Difference?

- YES!!!!
- Drug treatment differs
  - In FTD no evidence of a cholinergic deficiency
  - In FTD impaired initiative is easily confused with depression
  - In FTD amyloid strategies are inappropriate
- Management differs
  - In FTD behavior less likely to respond to usual drug treatments and appear to be more spontaneous rather than responsive to environment
  - Understanding behavior can help caregivers
- Prognosis and genetics differ

## Pathological Diagnostic Criteria:

An overview of AD and FTD pathology and diagnostic criteria

James B. Leverenz, M.D.

Departments of  
Neurology and Psychiatry and Behavioral Sciences  
University of Washington School of Medicine  
and  
VA Northwest Network Mental Illness and Parkinson's Disease  
Research, Education, and Clinical Centers

## Overview:

### Neuropathology of AD and FTD

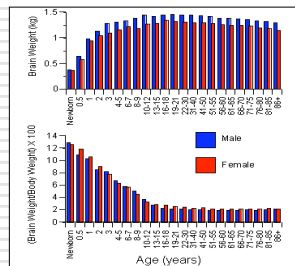
- Review of AD pathology
  - CERAD and Reagan criteria
  - Stains for detection of NP and NFT
- Review of FTD pathology
  - Pathologic subgroups
  - Stains for detection of FTD-associated pathology

## Normal Brain Weight

Mean Brain Weight:

1424g for men

1265g for women



Miller and Corsellis, Ann Hum Biol, 4:253-7, 1977.  
DeKaban and Sadowsky, Ann. Neurology, 4:345-356, 1978.

## Stains for AD/FTD neuropathology

- Histologic stains
  - Bielschowsky (silver stain): *NP, NFT, PB, BN*
  - LFB/H&E: *myelin, neurons, glia*
  - PTAH: *glia (reactive, fibers)*
- Immunohistochemistry
  - tau: *NFT, neurites in plaques, PB*
  - ubiquitin: *NFT, neurites in plaques, PB, LB, "ubiquitin-only" inclusions and neurites*
  - neurofilament: *NFT, BN*

## Alzheimer's Disease—Pathology



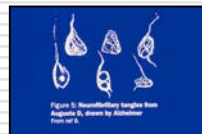
Auguste Autopsy (1906):

"...evenly affected atrophic brain..."

Bielschowsky stain:

"...fibrils arranged parallel...a tangled bundle of fibrils..."

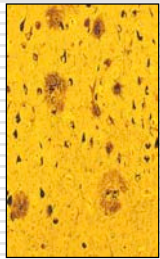
"...Dispersed over the entire cortex...miliary foci"



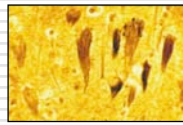
## Alzheimer's Disease—Pathology



## Alzheimer's Disease (AD)



Neuritic Plaques



Neurofibrillary Tangles

## CERAD Criteria for AD

### Neuritic Plaques

- Cortical density of neuritic plaques
  - "Infrequent"
  - "Moderate"
  - "Frequent"
- Classification "possible" or "probable"
  - Interaction of plaque stage and age (A,B,C)
- Neurofibrillary tangles are not considered in these criteria

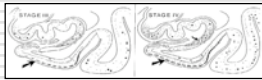
Mirra S et al. *Neurology*. 1991.

## Braak Staging of AD

### Neurofibrillary tangles



Transentorhinal Stages (I-II)



Limbic Stages (III-IV)



Isocortical Stages (V-VI)

Braak H, Braak E. *Acta Neurol Scand Suppl*. 1996;165:3-12.

## NIA-Reagan Criteria for AD

- Probability pathology accounts for dementia
  - **Low**-Braak stage I/II, CERAD infrequent plaques
  - **Intermediate**-Braak stage III/IV, CERAD intermediate plaques
  - **High**-Braak stage V/VI, CERAD frequent plaques
- Integrates plaque and tangle pathology

Neurobiol Aging. 1997 Jul-Aug;18(4 Suppl):S1-2.

## Frontotemporal Dementia (FTD)



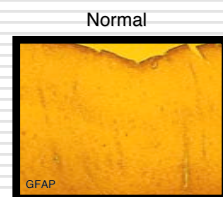
- 1892
  - Pick describes first case
  - 71 y.o. man
  - 3 yr decline including aphasia Autopsy
  - Focal temporal lobe atrophy (Chiari)



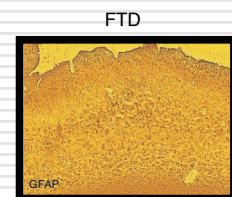
- 1911
  - Alzheimer describes Pick Bodies (PB) & Ballooned Neurons (BN)

## FTD Pathology:

### Neuronal loss and gliosis



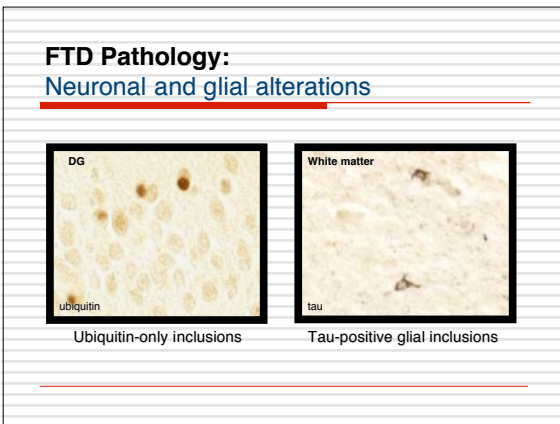
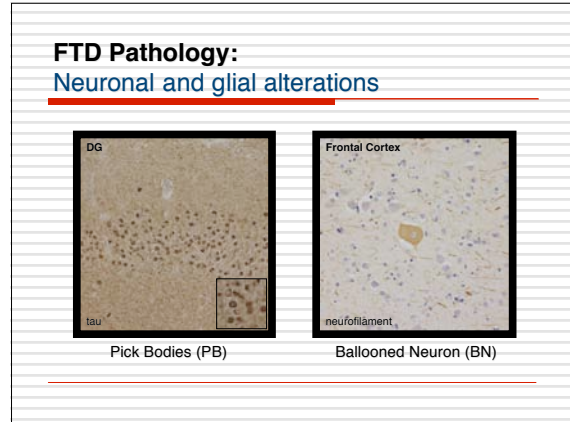
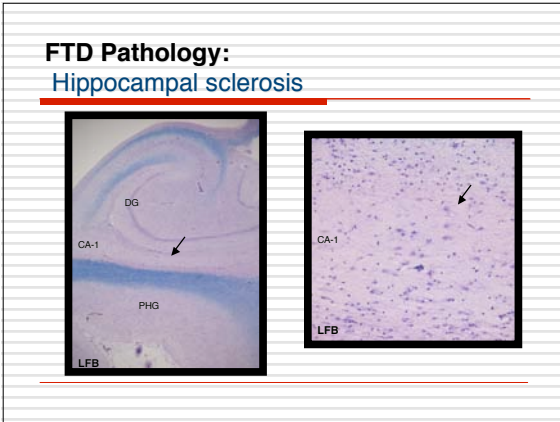
Normal



FTD

GFAP

GFAP



- ### FTD Pathologic Classifications
- **Pick-Type**
    - Severe neuronal loss and gliosis
    - Tauopathy (3R)
    - Pick bodies and ballooned neurons
  - **Corticobasal degeneration (CBD)**
    - Tauopathy (4R)
    - NFT, neuropil threads, astrocytic plaques, coiled bodies
  - **Progressive supranuclear palsy (PSP)**
    - Tauopathy (4R)
    - NFT, tufted astrocytes, coiled bodies
- Mott et al, J Neuropath Exp Neurol, 2005

- ### FTD Pathologic Classifications
- **Neurofibrillary tangle dementia**
    - Tauopathy (variable tau subtype),
    - Tau mutations
    - Variable tau pathology (neurons and glia)
  - **Frontotemporal lobar degeneration with MND or MND-type inclusions (FTLD-MND/MNI)\***
    - Variable neuronal loss and gliosis
    - "ubiquitin-only" inclusions (TDP-43 +)
  - **Dementia lacking distinctive histopathology (DLDH)**
    - Neuronal loss and gliosis without distinctive biochemical signal (e.g. tau or ubiquitin-only pathology)
- Mott et al, J Neuropath Exp Neurol, 2005

## Review Cases

- 1) Review Scenario and Vote
- 2) Review Scenario with PET and Vote
- 3) Pathology

## Scenario 2026

## Scenario 2026

- 61 yo M w 3.5y h/o progressive memory impairment.
- Sx: occ. WFD, poor concentration, difficulty following series of directions, finances, operating power tools. Able to drive.
- SH: Retired billing specialist, 12y ed.
- FH: F w probable dementia
- Neuro: Slight rest and postural tremor of UEs

## Scenario 2026

- MS: MMSE 19. Partly oriented. Trouble naming parts of objects. Impaired WORLD backwards, calculations, clock hands. 0/3 recall, 2/3 with prompting.
- 4y: can't read, name president, calculate, name items of clothing.
- 4y 9m: Can still travel. May reverse clothing, skips parts of the lawn mowing, unable to start new lawnmower.

## Scenario 2026

- 5 y: anxiety & agitation,
- 5y 9m: Cannot roll down car windows, find utensils while eating. Does not speak till spoken to. Unable to speak full sentences.
- 6.5y: brief hallucinations. Easily distracted. Speech limited to 2-word phrases.
- 8y: wandering, occ striking.
- 9y: several falls, complete care, died.

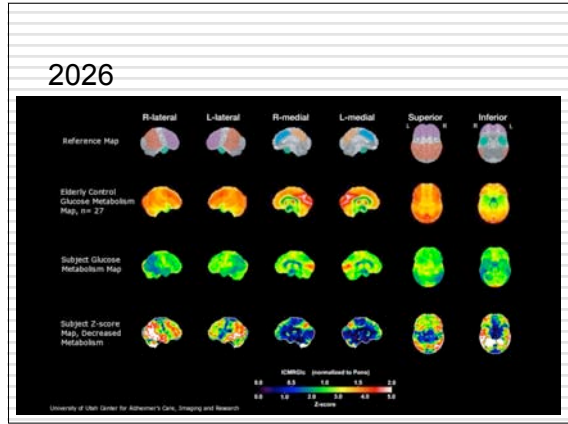
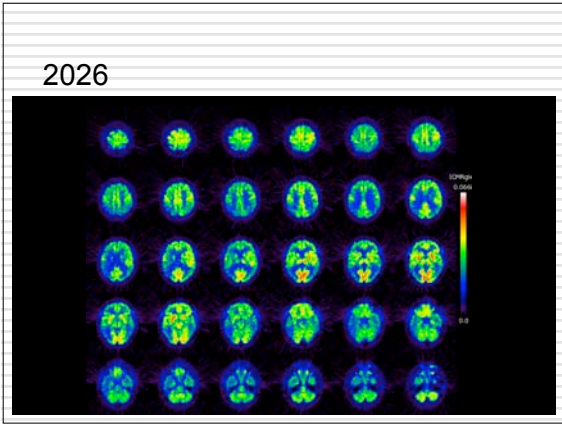
## Rate Scenario 2026

1. What is your best diagnosis after reviewing? (select only one)
- 1)  AD
  - 2)  FTD
2. What is your confidence in this diagnosis? (select only one)
- 1)  Very confident
  - 2)  Somewhat confident
  - 3)  Uncertain

Scenario # \_\_\_\_\_

Scenario only

Scenario and PET



**Rate Scenario with PET 2026**

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1. What is your best diagnosis after reviewing? (select only one)

1)  AD

2)  FTD

Scenario # \_\_\_\_\_

2. What is your confidence in this diagnosis? (select only one)

1)  Very confident

2)  Somewhat confident

3)  Uncertain

Scenario only

Scenario and PET

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2026

Pathologic Category

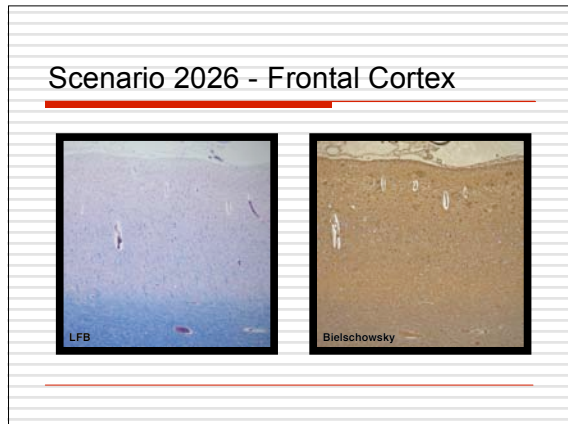
**Scenario 2026**

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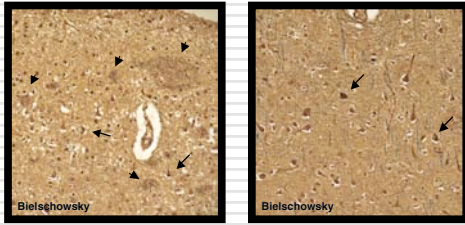
Brain wt 1160g

Moderate frontal > temporal atrophy

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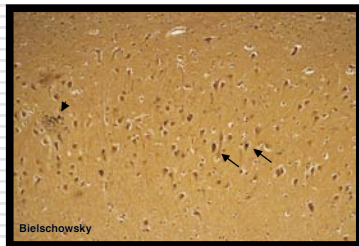
### Scenario 2026 - Frontal Cortex



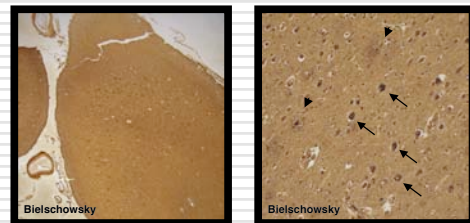
### Scenario 2026 - Hippocampus



### Scenario 2026 - Hippocampus



### Scenario 2026 - Inf. Temporal Gyrus



### Scenario 2026

- Brain wt 1160g
- Moderate frontal > temporal atrophy
  
- Histologic Findings
  - "Frequent" neuritic plaques
  - Braak Stage V
  - No Lewy bodies
  - No Strokes or other focal lesions

### 2026

#### Pathologic Category

Definite AD

## Scenario 2040

## Scenario 2040

- 62yo RHF w 2y h/o change in personality and memory loss. Doesn't participate in daily activities. No longer does housework or participates in conversations, preferring to sit in a chair all day. Stopped driving after becoming lost on familiar routes 1y into her illness. "Very forgetful". Has purchased items she does not need, and eating more. She may laugh inappropriately or become upset, and has made statements that people are "trying to dupe her".
- SH: Married, 8th grade educ. Homemaker FH: Unk.

## Scenario 2040

- Exam: O x 3/3. DS 6 forward, 5 back. Current President + 4/5 past, 4/5 serial 7s, unable to calculate nickels in \$1.35. Language intact. Draws clock, not cube. Recall 3/5 at 5'. Affect generally flat and poor awareness of cognitive changes. Slow, deliberate gait. No primitive reflexes.
- At 2y 3mo: speaking less, hums frequently. C/o being tired and hungry all the time. Sleeps frequently during the day. Needs prompting to do household chores and spends most of her day watching TV. On exam, markedly apathetic. Knows date and location. Names current but not prior Presidents. recalls 1/3 after delay. Performed simple but not complex calculations. Excellent naming but occasional paraphasias. Poor comprehension with reading.

## Scenario 2040

- 4y: Incontinent. Screams suddenly then starts to laugh. Hums almost constantly and wants to eat. On exam, humming almost constantly and picking at clothing in purposeless fashion. Paucity of spontaneous speech. Recall 3/4 at 5'.
- 6y: no intelligible speech. Agitated, distracted, and may spend time simply staring at her hands. Now needs occasional encouragement to eat. near total care for personal hygiene. On exam, had constant chewing motions. Vocalized with high pitched moans. Frequently attempted to leave the examination room. Frequently clapped. Unable to respond to any commands. Gait slightly slowed and stooped. Grasp reflexes present.
- Patient died after 14 years of symptoms.

## Rate Scenario 2040

1. What is your best diagnosis after reviewing? (select only one)

- 1)  AD
- 2)  FTD

2. What is your confidence in this diagnosis? (select only one)

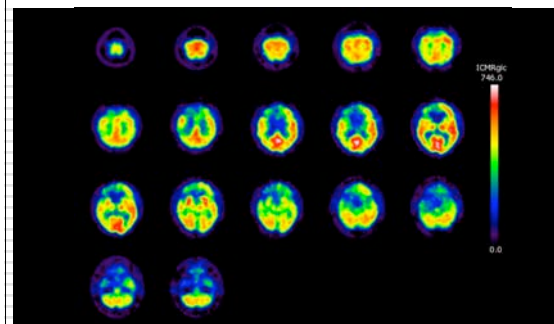
- 1)  Very confident
- 2)  Somewhat confident
- 3)  Uncertain

Scenario # \_\_\_\_\_

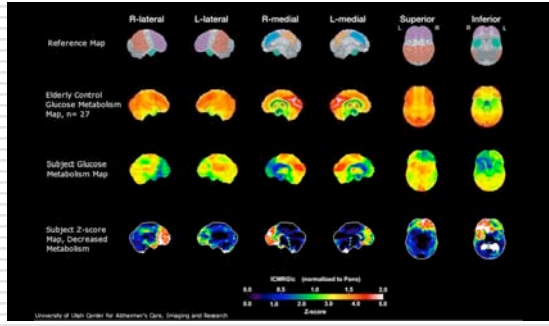
Scenario only

Scenario and PET

## 2040



2040



### Rate Scenario with PET 2040

1. What is your best diagnosis after reviewing? (select only one)
- 1)  AD
  - 2)  FTD
2. What is your confidence in this diagnosis? (select only one)
- 1)  Very confident
  - 2)  Somewhat confident
  - 3)  Uncertain

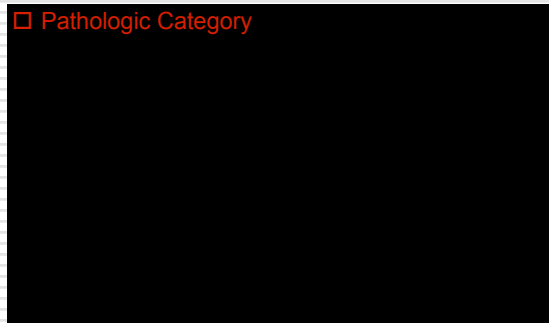
Scenario # \_\_\_\_\_

Scenario only

Scenario and PET

2040

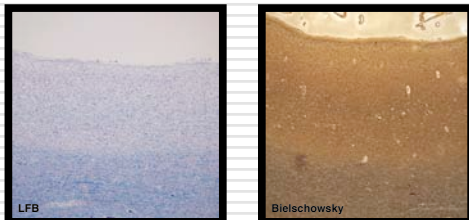
Pathologic Category



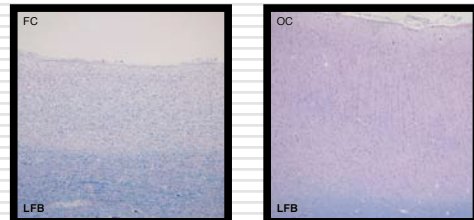
### Scenario 2040

- Brain wt 800g
- Severe fronto-temporal atrophy
  - "knife-edged" atrophy

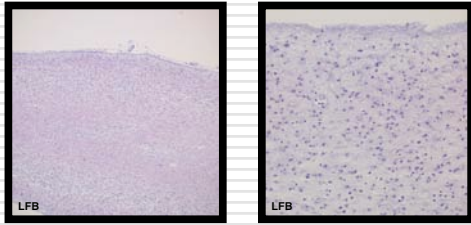
### Scenario 2040 - Frontal Cortex



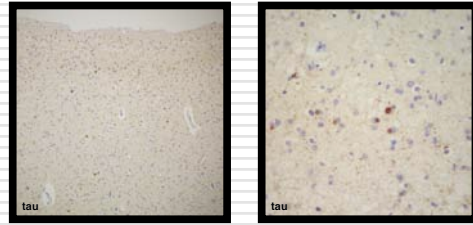
### Scenario 2040 - FC vs OC



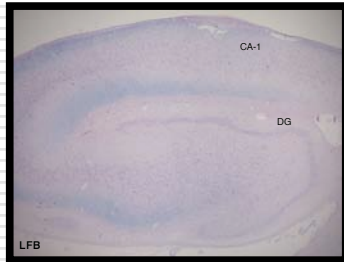
Scenario 2040 - Frontal Cortex



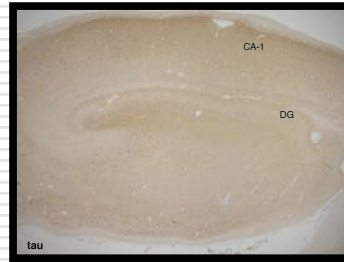
Scenario 2040 - Frontal Cortex



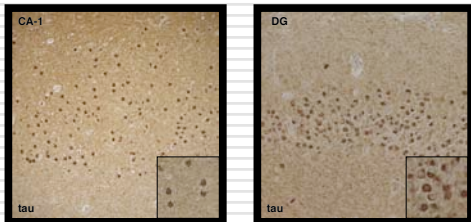
Scenario 2040 - Hippocampus



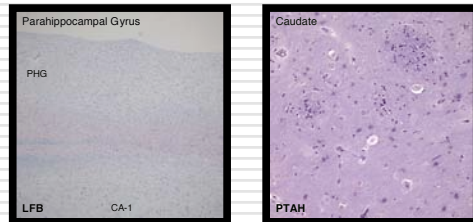
Scenario 2040 - Hippocampus



Scenario 2040 - Hippocampus



Scenario 2040 - PHG and Striatum



## Scenario 2040

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- Brain wt 800g
  - Severe fronto-temporal atrophy
    - "knife-edged" atrophy
  - Histopathology
    - Severe FC/TC neuronal loss and gliosis
    - Pick body inclusions (tau positive)
- 

## 2040

### Pathologic Category

Frontotemporal Dementia  
Pick's Disease subtype

## Review Scenario 2162

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## Scenario 2162

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- 80 yoF w 6y h/o progressive memory loss. Got lost after taking a bus downtown. Calls D several times a day w/o realizing she had called. Able to shop and prep light meals. Signif. visual and auditory impairment and bumps into objects when walking. She can no longer read or quilt.
  - SH: Unknown      FH: Unknown
  - MS: A+O to yr, season, and mo but not day of week. O to place, x county. Recalls 1/3 after 3'. Unable to subtract 7 from 100 and only 3 letters correct when spelling WORLD backwards. No difficulty with language. Mild impairment when copying a design.
  - Neuro: Unremarkable x for macular degeneration and auditory impairment.
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## Scenario 2162

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- At 6y 9m: in NH, socializes, good mood, incontinent of urine +/- stool. D/o to date & names of children & current events. Follows simple commands. 0/3 recall at 5', 2/3 w clues. Fluent.
  - At 7y 3m: can feed self, but needs help with dressing, incontinent, calm. O to city and "doctor's office". Fluent. 0/3 recall at 5'. Slight stoop.
  - At 7y 9m: wanders, paces, assists others as possible, helping them get out of restraints.
  - Patient died after 10.5 years of symptoms.
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## Rate Scenario 2162

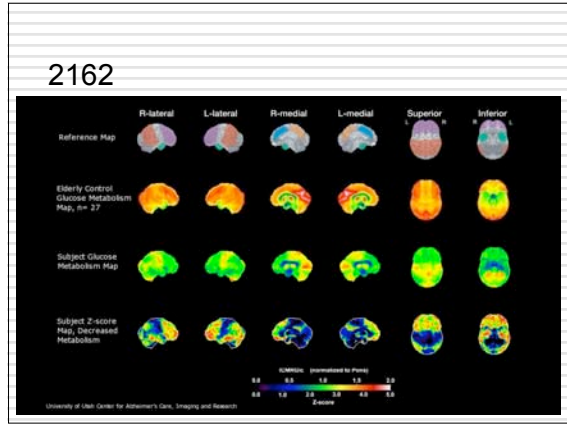
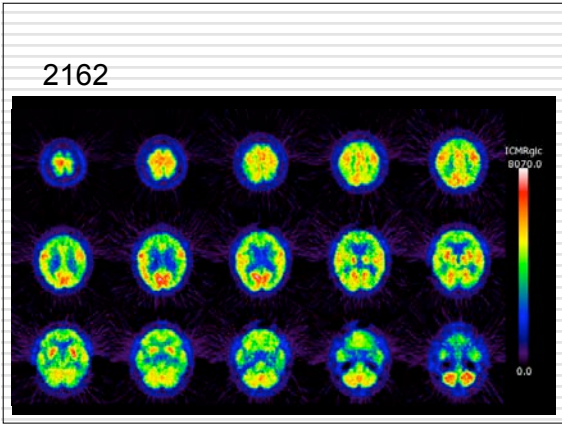
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1. What is your best diagnosis after reviewing? (select only one)
- 1)  AD
  - 2)  FTD
2. What is your confidence in this diagnosis? (select only one)
- 1)  Very confident
  - 2)  Somewhat confident
  - 3)  Uncertain

Scenario # \_\_\_\_\_

Scenario only

Scenario and PET



**Rate Scenario with PET 2162**

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1. What is your best diagnosis after reviewing? (select only one)

1)  AD

2)  FTD

Scenario # \_\_\_\_\_

2. What is your confidence in this diagnosis? (select only one)

1)  Very confident

2)  Somewhat confident

3)  Uncertain

Scenario only

Scenario and PET

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Pathologic Category

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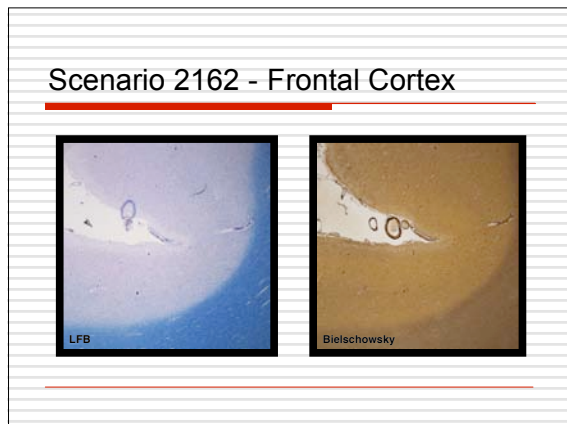
**Scenario 2162**

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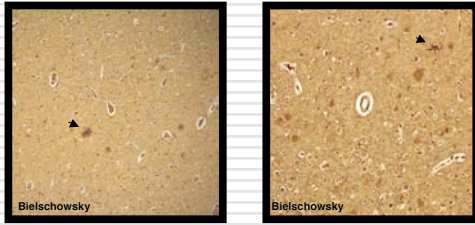
Brain wt 925g

Severe bilateral fronto-temporal atrophy

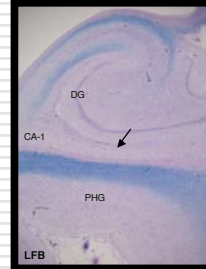
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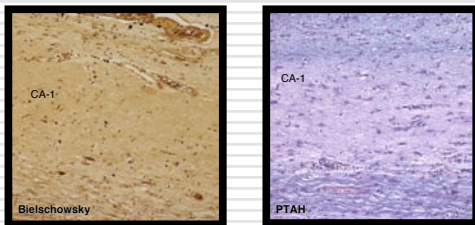
### Scenario 2162 - Frontal Cortex



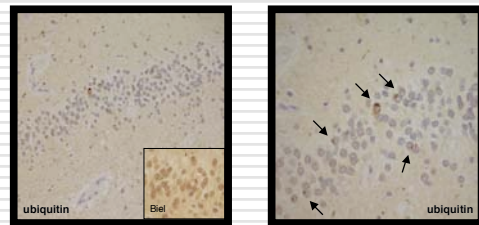
### Scenario 2162 - Hippocampus



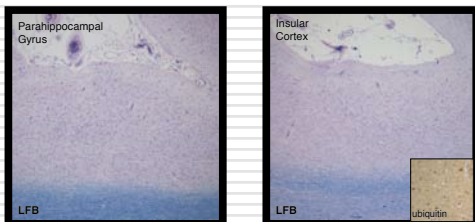
### Scenario 2162 - Hippocampus



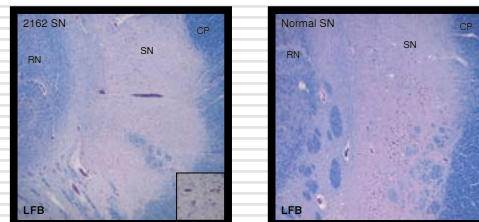
### Scenario 2162 - Dentate Gyrus



### Scenario 2162 - PHG/Insular cortex



### Scenario 2162 - Substantia Nigra



## Scenario 2162

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- Brain wt 925g
  - Severe fronto-temporal atrophy
  
  - Histopathology
    - Severe neuronal loss and gliosis, insular and temporal cortex, hippocampus ("hippocampal sclerosis", and substantia nigra
    - Ubiquitin-only inclusions/neurites DG, superficial neocortex
    - "Frequent" neuritic plaques
    - Braak stage III
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Pathologic Category - FTD

Frontotemporal Dementia:  
Motor Neuron Disease/MND-like Inclusions  
Subtype

"Intermediate" Likelihood AD