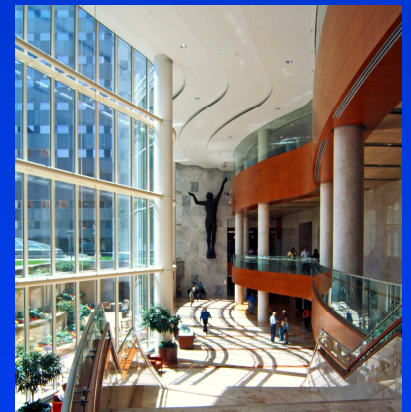


FTD and PPA

The Journey to Diagnosis

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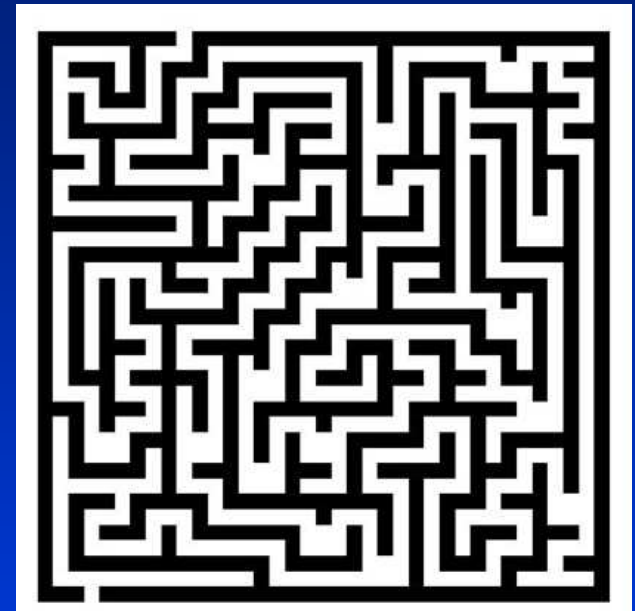
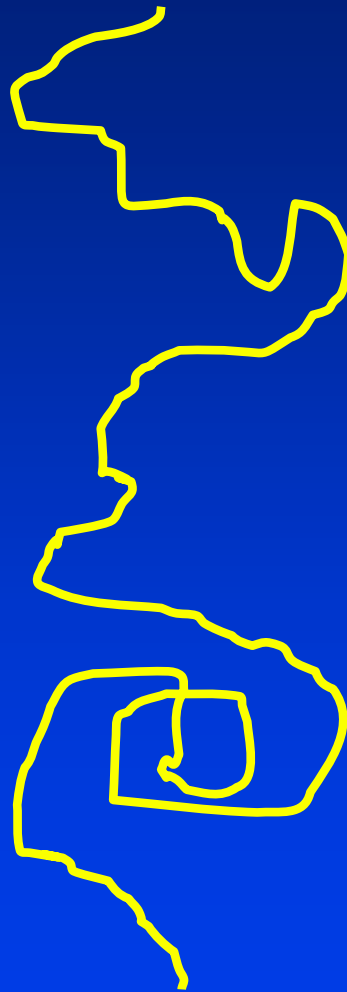
- Investigator for clinical trials sponsored by Cephalon, Inc.
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FTD/PPA: Journey To Diagnosis Outline

- **Case Examples**
- **Clinical Pearls**
- **Future Directions**

FTD/PPA: Journey to Diagnosis

Symptom Onset



Diagnosis

FTD/PPA: Journey To Diagnosis

Case Examples

Case 1 - 52 year old male executive, married, 3 children

- Not as engaged in family activities
- Little emotion at funeral of his mother
- Struggling with work productivity
- Odd purchases (3 hammers at Ace, \$4000 toolbox on TV)
- Denies being depressed; “I’m fine!”
- Family convinces to see physician ~ 1 yr after onset

FTD/PPA: Journey To Diagnosis

Case Examples

Case 1 (continued)

- MMSE 28/30, physical exam normal, labs normal
- Diagnosis: depression
- Rx antidepressant medication – apathy and work productivity slightly better
- His evolution continued...

FTD/PPA: Journey To Diagnosis

Case Examples

Case 2 - 40 yr old female homemaker, married, 4 children

- More outgoing personality
- Off-color jokes, swearing, “fat” comments to others
- Driving erratically, but no accidents
- Sleeping less
- “I’m fine – I don’t need to see a \$#%! doctor”
- Husband demands that she see an MD ~ 6 mo after onset

FTD/PPA: Journey To Diagnosis

Case Examples

Case 2 (continued)

- MMSE 30/30, physical exam normal, labs normal
- Diagnosis: bipolar disorder
- Rx valproic acid (Depakote) – mild improvement in behavioral changes, but stopped medicine due to tremor
- Her evolution continued...

FTD/PPA: Journey To Diagnosis

Case Examples

Case 3 – 47 yr old married surgeon, 2 children

- More secretive around the home, quieter
- Two bad business decisions with practice
- Sexual inuendos made to 2 female office staff – they shared this with his wife
- Surgical skills as observed by others were unchanged
- Wife was unable to convince him to seek marriage counseling; did not have primary care MD
- His evolution continued over the following year...

FTD/PPA: Journey To Diagnosis

Case Examples

**Case 4 - 61 year old male, recently divorced, 4 children
+ FH (father, sister) - “Alzheimer’s disease” – 50s**

- Forgetful
- Consuming more alcohol
- Less interested in poker, playing golf, watching NFL
- Eating M&Ms – sorts by color
- More focused on religious beliefs
- Depressed? “not really” Agrees to see MD (~ 8 mo)

FTD/PPA: Journey To Diagnosis

Case Examples

Case 4 (continued)

- MMSE 26/30, 2/3 recall
- Labs normal
- Neuropsychological testing – “more normal than not”
- MRI normal
- Diagnosis - ? Stress vs alcohol vs mid-life crisis, but daughter and clinician are worried about early Alzheimer’s disease
- His evolution continued...

FTD/PPA: Journey To Diagnosis

Possible explanations of cognitive/personality changes:

- Psychiatric/psychologic – stress, “mid-life crisis,” depression, bipolar disorder, schizophrenia, substance abuse
- Medical – hypothyroidism, profound anemia, sleep disorder, chronic fatigue, many others
- Neurologic – tumor, stroke, neurodegenerative disease (Alzheimer’s disease, Lewy body dementia, FTD, PPA)

FTD/PPA: Journey To Diagnosis

Symptom Onset



months to years

Recognition of Problem by Patient/Family



days to weeks

Evaluation by Primary Care Physician

FTD/PPA: Journey To Diagnosis

Pearl #1

Frontotemporal dementia begins insidiously and progresses gradually – this leads to a delayed recognition of a problem

- the duration of time from symptom onset to problem recognition is typically at least 6-12 months

FTD/PPA: Journey To Diagnosis

Pearl #2

Frontotemporal dementia is one of the great mimickers in clinical medicine

- the features of FTD span dozens of other psychological, psychiatric, medical, and neurologic disorders

FTD/PPA: Journey To Diagnosis

Pearl #3

*Patients don't seek medical attention –
family members drive the evaluation*

- lack of insight is almost universal among FTD patients
- spouses, adult children, or siblings are therefore required to “push” the patient, and (painfully) navigate the medical system

FTD/PPA: Journey To Diagnosis

Case Examples

Case 5 – 56 yr old married female chef, 3 children

- Speech difficulties – knows what she wants to say, but “tongue and lips don’t do what I want them to do”
- Tends to say “yes” for “no” and vice versa
- Comprehension, memory, problem-solving were OK
- Symptoms evolved slowly; nothing sudden
- Primary care MD found nothing amiss on exam
- MRI brain – normal; Diagnosis – “aging”

FTD/PPA: Journey To Diagnosis

Pearl #4

Most clinicians are not familiar with FTD or PPA

- never learned about FTD/PPA in college, medical school or residency training
- the FTD and PPA syndromes are rare – most clinicians will see 0-2 patients with FTD/PPA in their entire career

FTD/PPA: Journey To Diagnosis

Case Examples

Case 1 – 52 yr old executive with personality changes and decreased work performance

- Major blunder at work resulting in $>$ \$300,000 lost income to company
- Wife found Visa bill $>$ \$25,000 with various tools
- Patient forgot to pick up teenager at school 3 times
- Primary care MD referred him to a neurologist

FTD/PPA: Journey To Diagnosis

Case Examples

Case 2 – 40 yr old homemaker with “bipolar” diagnosis

- Friends and family increasingly concerned about disinhibition, excessive talking, lack of sleep
- Car accident due to erratic driving, totalled car, several injuries
- Primary care MD referred her to psychiatrist

FTD/PPA: Journey To Diagnosis

Case Examples

Case 3 – 47 yr old surgeon with “marital problems”

- Attempted to force sexual intercourse on 2 female patients in his examination rooms at office practice
- 1 patient pressed charges, leading to medical evaluation
- Subtle asymmetric tremor, rigidity, and masked facies found on exam by an internist – referral to neurologist

FTD/PPA: Journey To Diagnosis

Case Examples

Case 5 – 56 yr old chef with “speech” problems

- Pulled over by police officer while driving to her restaurant for speeding
- Officer noticed “slurred speech” and suspected the patient was drunk, brought into police station
- Could not explain her history adequately, police could not reach family, brought to local hospital ED

FTD/PPA: Journey To Diagnosis

Pearl #4

Unfortunately, a major financial blunder, a medical catastrophe, or a legal problem, is often the “crisis” event that triggers an MD or specialist referral

- families are then required to attempt to “fix” the problems that had occurred, many of which are then not fix-able

FTD/PPA: Journey To Diagnosis

Symptom Onset

months to years

Recognition of Problem by Patient/Family

days to weeks

Crisis

Evaluation by Primary Care Physician

weeks to years

Evaluation by Specialist

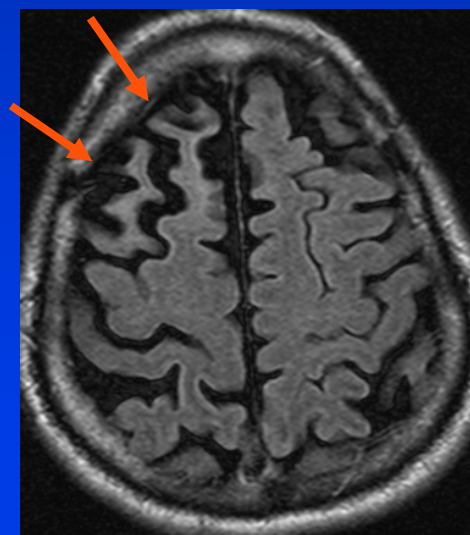
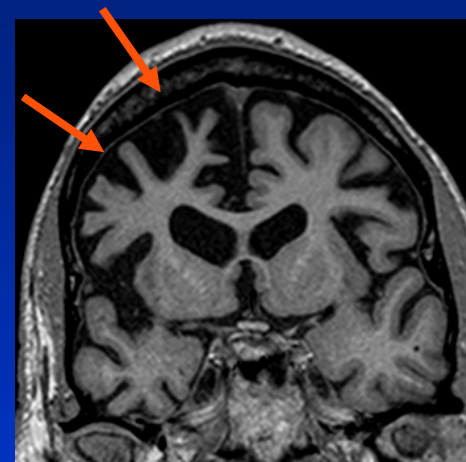
FTD/PPA: Journey To Diagnosis

Case Examples

Case 1 – 57 yr old executive

Neurologic evaluation

- MMSE 27/30
- Neurologic examination - normal
- Neuropsychological testing – executive dysfunction
- MRI – right frontal atrophy
- Diagnosis – FTD



FTD/PPA: Journey To Diagnosis

Case Examples

**Case 2 – 40 yr old female with “bipolar disorder” and
car accident**

Psychiatric treatment

- No improvement over 1 yr, referral to neurologist

Neurologic evaluation

- Clinical features, neuropsychologic testing and MRI all
consistent with FTD

FTD/PPA: Journey To Diagnosis

Case Examples

Case 5 – 56 yr old female chef with “speech” problems

Emergency department evaluation

- “this seems neurologic, but CT scan is OK”
- Referral to neurologist

Neurologic evaluation

- Exam suggests “dysarthria”
- MRI normal
- Diagnosis – “stroke that we can’t see on MRI”

FTD/PPA: Journey To Diagnosis

Case Examples

Case 5 (continued)

- Family seeks another opinion

2nd neurologic evaluation

- Exam reveals apraxia of speech, nonverbal oral apraxia, and mild expressive/nonfluent aphasia
- Speech pathologist – confirms the above findings, also notes subtle spastic/hypokinetic dysarthria features
- MRI shows subtle left inferolateral frontal atrophy
- Diagnosis – PPA

FTD/PPA: Journey To Diagnosis

Pearl #6

The diagnosis of FTD and PPA is not challenging in most patients if evaluated by a knowledgeable clinician and the appropriate diagnostic studies are performed

- the combination of clinical features, neuropsychological findings, speech/language evaluation findings, and MRI findings are highly characteristic of FTD or PPA in most individuals
- the key is seeing a clinician familiar with FTD/PPA
- requires diligent families and “good luck”

FTD/PPA: Journey To Diagnosis

Case Examples

Case 3 – 47 yr old surgeon

Neurologic evaluation

- Clinical features consistent with mild parkinsonism
- Neuropsychological testing – normal
- MRI head – normal
- Diagnosis – early Parkinson's disease

Wife was not convinced this diagnosis was accurate –
sought second opinion

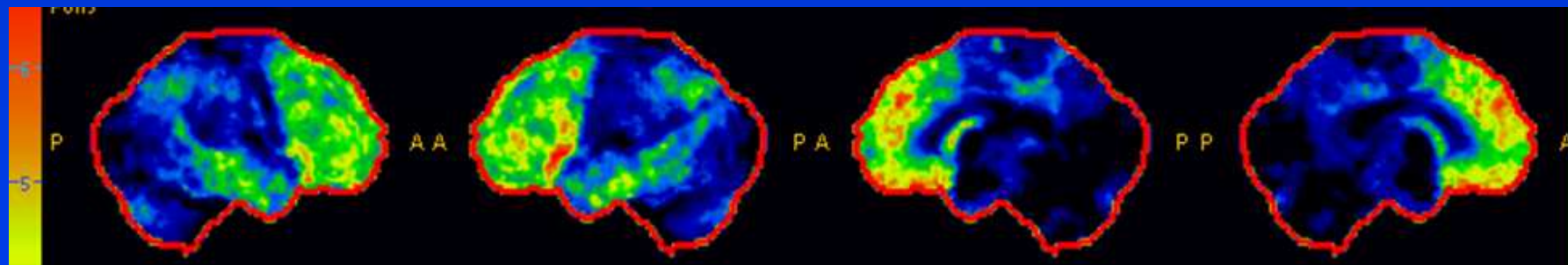
FTD/PPA: Journey To Diagnosis

Case Examples

Case 3 – 47 yr old surgeon

2nd neurologic evaluation

- Clinical features and subtle findings on exam and neuropsychological testing suggested FTD plus parkinsonism
- FDG-PET of brain – highly typical of FTD



FTD/PPA: Journey To Diagnosis

Pearl #7

In some patients with early/mild FTD, standard neuropsychological tests can be normal, leading to diagnostic confusion

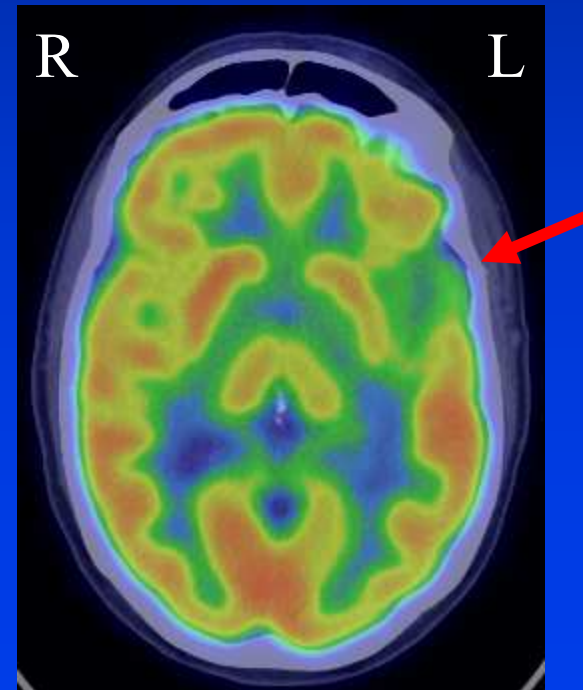
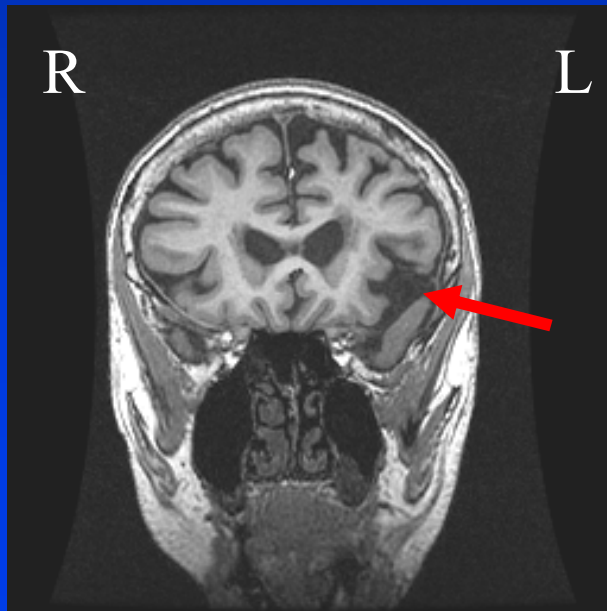
- Normal performance on mental status exam (MMSE) and neuropsychological testing does not exclude the diagnosis of FTD
- Investigators are refining neuropsychological tests to improve the sensitivity of diagnosis early in the course

FTD/PPA: Journey To Diagnosis

Case Examples

Case 5 – 56 yr old chef with PPA

- MRI head re-analyzed – shows focal atrophy
- FDG-PET of brain – highly typical of PPA



FTD/PPA: Journey To Diagnosis

Pearl #8

Abnormal findings on fluorodeoxyglucose positron emission tomography (FDG-PET) can be key to establishing a diagnosis of FTD or PPA

- FDG-PET is clearly not necessary to establish an FTD or PPA diagnosis in everyone, but in challenging cases, it can be critical

FTD/PPA: Journey To Diagnosis

Pearl #9

An expert opinion is sometimes needed if a diagnosis (and management plan) “does not seem right”

FTD/PPA: Journey To Diagnosis

Case Examples

Case 4 - 61 year old male with + FH, Dx ? stress

- Decline in problem solving, decision making, memory, and independence continued
- Daughter remained concerned about a neurologic disorder, and particularly a genetically-mediated disorder
- Daughter and primary care MD agreed neurologic and genetic evaluations were warranted

FTD/PPA: Journey To Diagnosis

Case Examples

Case 4 - 61 year old male with + FH

Neurologic evaluation

- MMSE 24, 1/3 on recall
- Neuropsychology showed impairment on executive functions, language, learning and memory
- PET showed left > right frontotemporal hypometabolism
- Genetic counseling and testing – progranulin mutation

FTD/PPA: Journey To Diagnosis

Pearl #10

When there is diagnostic uncertainty between FTD and AD, FDG-PET can provide diagnostic clarity

- FDG-PET is covered by Medicare and some insurance providers to differentiate FTD from AD

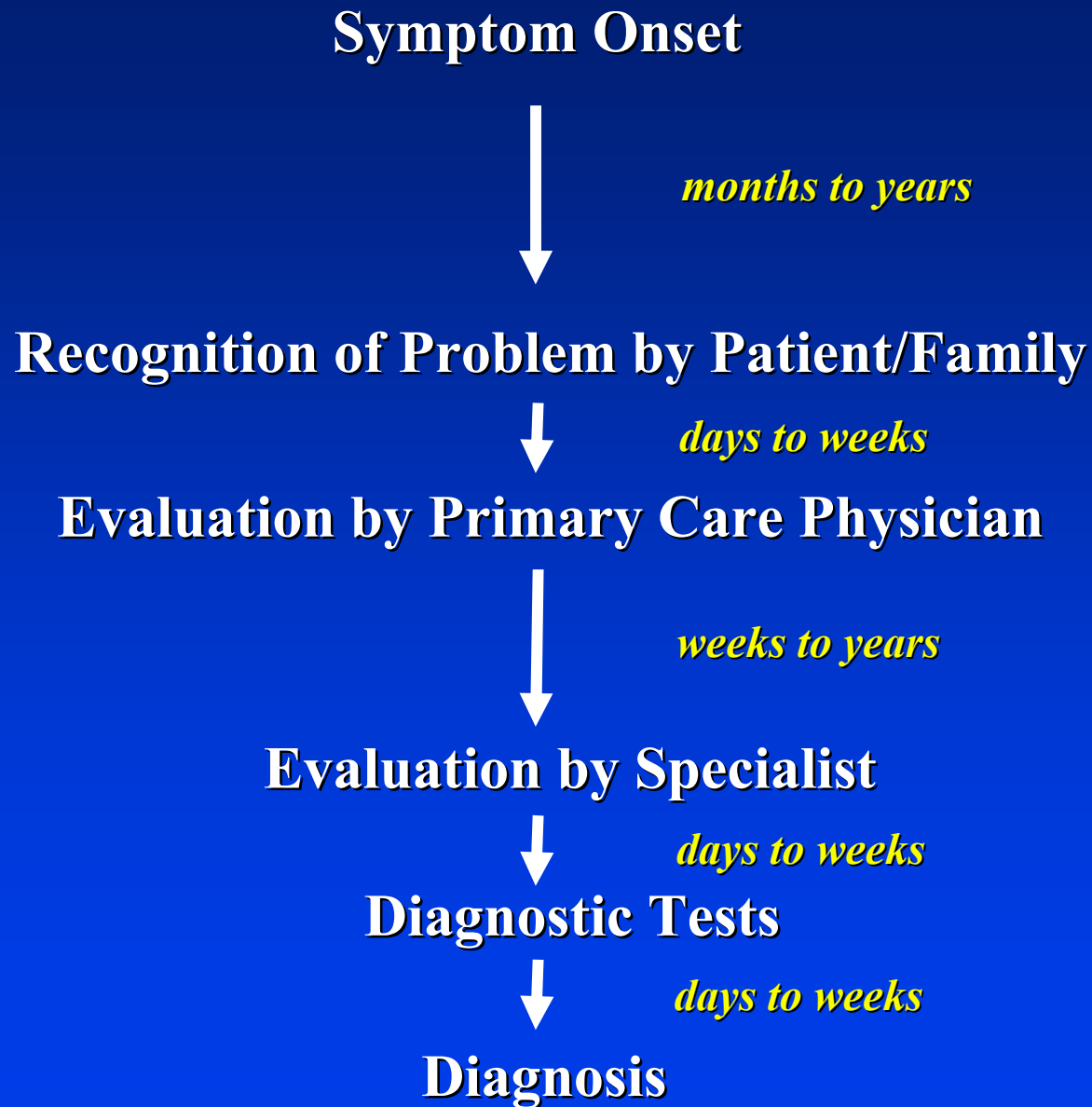
FTD/PPA: Journey To Diagnosis

Pearl #11

Genetic testing (with pre- and post-testing counseling) can sometimes establish a specific FTD disorder with certainty, and should be considered when a positive family history of dementia +/- parkinsonism +/- ALS exists

- Genetic testing is available for some of the genes involved in FTD
- This will become increasingly important as therapies become available for specific genetic mutations and their protein targets

FTD/PPA: Journey to Diagnosis



FTD/PPA: Journey To Diagnosis

Pearl #12

The journey from symptom onset to diagnosis is typically a tumultuous 1-4 year process

The repercussions are many:

- emotional
- occupational
- financial
- legal
- medical - in the future when targeted therapies for tau, TDP-43, etc., are available, the delay in diagnosis will have medical repercussions as well

Salient Points Relevant to FTD/PPA Diagnosis

- 1. FTD begins insidiously and progresses slowly, leading to delayed recognition of a problem**
- 2. FTD is a great mimicker**
- 3. FTD patients don't seek medical attention – family members do**
- 4. Lack of clinician awareness is a major barrier to FTD and PPA diagnosis**
- 5. Major event often needed to trigger an evaluation**
- 6. FTD/PPA diagnosis not challenging when seen by a knowledgeable clinician**
- 7. Standard neurologic exam and neuropsychological tests can be normal early in FTD; MRI can be essentially normal in PPA**
- 8. PET scans can be helpful to establish a diagnosis**
- 9. It is OK to seek a second opinion if diagnosis is questioned**
- 10. PET scans can help differentiate FTD from AD**
- 11. Genetic testing can help confirm an FTD/PPA diagnosis and plan for the future**
- 12. The journey to diagnosis is typically a tumultuous 1-4 years**

Future Directions

- Increase awareness of FTD and PPA among the public
 - AFTD, FTD/PPA Support Groups, local/regional conferences, TV segments, internet, educational films

YOUR INVOLVEMENT IS CRITICAL

- Increase awareness of FTD and PPA among clinicians
 - AFTD, FTD/PPA Support Groups, local/regional/national conferences, medical school/residency education, textbooks, TV, internet, educational films

Future Directions

- Improve sensitivity/specificity (neuropsychology, CSF, MRI) and availability (PET) of diagnostic tests
 - research being devoted to these
 - ensure good quality control across tests
- Increase research funding for FTD/PPA and improve insurance/Medicare coverage of evaluations and tests
 - work with local/state legislators, insurance companies, federal administration offices

YOUR INVOLVEMENT IS CRITICAL

FTD/PPA: Journey to Diagnosis

Symptom Onset



months to years

* Recognition of Problem by Patient/Family



days to weeks

* Evaluation by Primary Care Physician



weeks to years

* Evaluation by Specialist



days to weeks

* Diagnostic Tests



days to weeks

* Diagnosis

*6-24
months*

* **your involvement**

FTD/PPA: Journey to Diagnosis

Symptom Onset



months to years

* Recognition of Problem by Patient/Family



days to weeks

* Evaluation by Primary Care Physician



days to weeks

* Evaluation by Specialist



days to weeks

* Diagnostic Tests



days to weeks

* Diagnosis

*1-12
months*

* **your involvement**

Reduce the time and burden from problem recognition to diagnosis

Support and Collaboration

Foundations

Association for Frontotemporal Dementias

National Institutes of Health

National Institute on Aging

**National Institute for Neurologic
Disorders and Stroke**

Patients and Families

**Your support of each other, the AFTD,
local/regional/national organizations, and participation in
FTD/PPA research are all critical**