Chiadi U. Onyike, MD, MHS
Johns Hopkins Neuropsychiatry

NVDCC 34th Annual Caregiver's Conference
November 11, 2020

If Not Alzheimer's Disease, What Is It? Getting a Diagnosis and Care

Preface

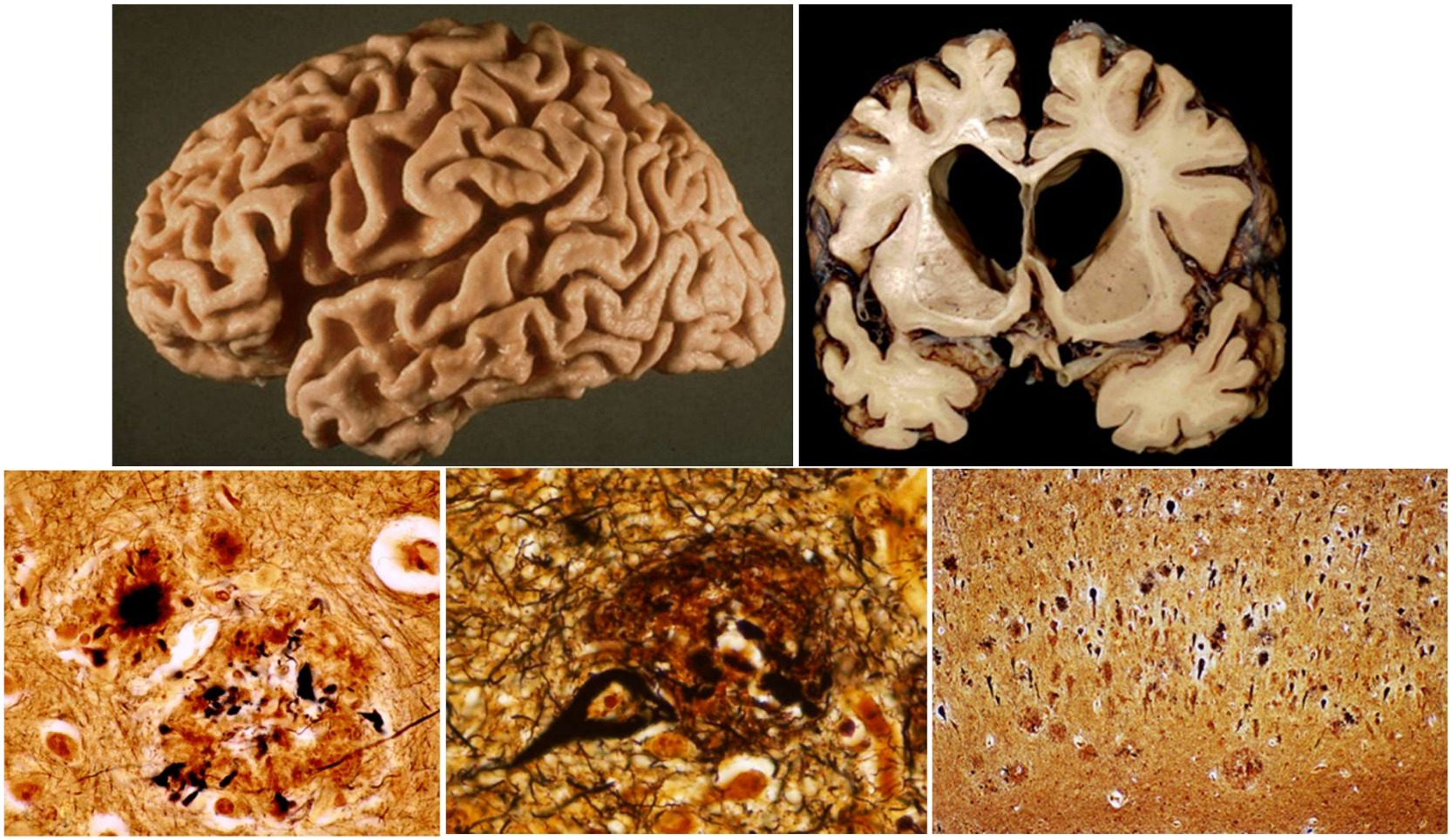
- **Topics covered:**
  - Clinical syndromes and natural history
  - Diagnostic rules and procedures, measurement methods
  - Treatments and care methods
  - Early detection for treatment development

- Disclosure:
  - PI/CI of NIH and ADDF studies of dementia and SCA
  - PI/CI of sponsored clinical trials
    - *Celecoxib and ibuprofen in AD (NIA/NIH) – Neurology 2007, 68:1800–1808*
    - *Memantine in FTD (Forest Inc.) – Lancet Neurology 2009, 12(2):149–156*
    - *LMTM in FTD (Tau Therapeutics) – TRx237-007 (NCT01626378)*
    - *Psychometric trajectories in FTD (Biogen) – just completed*
    - *AL001 in FTD (Alector) – in planning phase*
  - Discussion of “off-label” prescribing is based on experience

“Disease of Forgetfulness”

Alzheimer, A. 1907. Allgemeine Zeitschrift für Psychiatrie und Psychisch-Gerichtliche Medizin, 64, 146–148

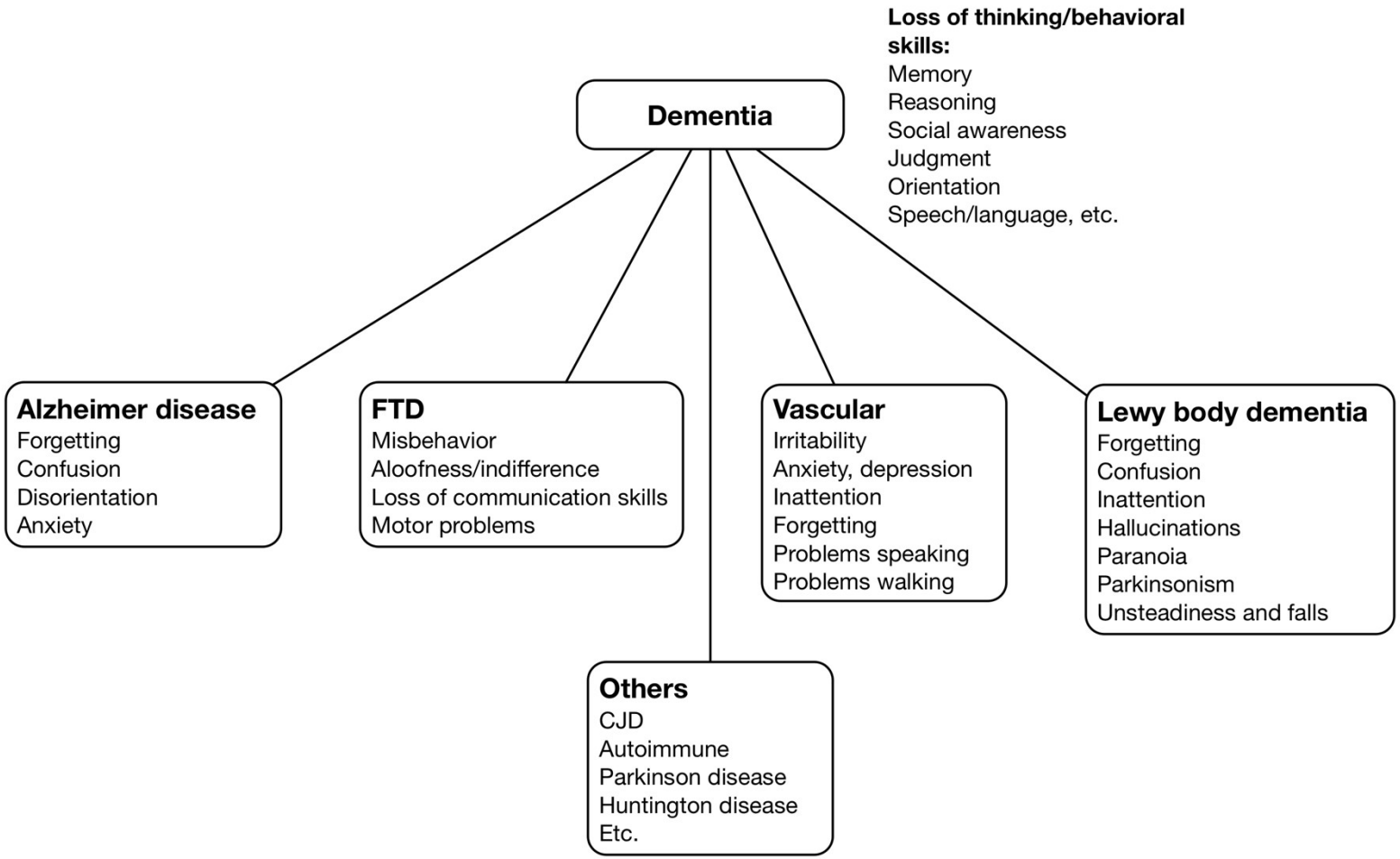
Auguste Deter developed forgetfulness, inertia, anxiety, agitation and delusions in the late 1890s. In 1901 Alois Alzheimer found confusion, rapid forgetting, poor self knowledge, disorientation, trouble naming and knowing objects. Alzheimer recorded the progress and, after her death in April 1906, examined the brain.



Pathological features of Alzheimer disease

http://neuropathology-web.org/chapter9/chapter9bAD.html

Top left, brain specimen shows diffuse cortical atrophy; top right, coronal section shows diffuse atrophy, enlarged ventricles, pallid white matter, and atrophy of both caudate nuclei; bottom left, amyloid plaques; bottom middle and right, amyloid plaques and neurofibrillary tangles


Loss of thinking/behavioral skills:
Memory
Reasoning
Social awareness
Judgment
Orientation
Speech/language, etc.
Dementia
Alzheimer disease
Forgetting
Confusion
Disorientation
Anxiety
FTD
Misbehavior
Aloofness/indifference
Loss of communication skills
Motor problems
Vascular
Irritability
Anxiety, depression
Inattention
Forgetting
Problems speaking
Problems walking
Lewy body dementia
Forgetting
Confusion
Inattention
Hallucinations
Paranoia
Parkinsonism
Unsteadiness and falls
Others
CJD
Autoimmune
Parkinson disease
Huntington disease
Etc.

Case PC

A 61 year-old former dental hygienist developed ***insidious*** *lqpses in judgment, aloofness, poor self-control and rudeness. EXAMPLES: jocularity, incongruous laughing, racial talk, telling to a vagrant he had bad teeth, exuberant dancing in public, and childlike repetitiousness. She engaged in compulsive grocery shopping. She had trouble learning new office technology. Sometimes she had word retrieval problems. Time and space orientation were preserved. She did not have difficulty with arithmetic.*

She was inefficient at work and she burned cooking at home. She maintained hygiene and grooming. Restless legs were observed during sleep, along with hypersomnia. She had a tendency to wander away. Fidgeting, finger rubbing and leg tapping had been observed.

She had mild gaze dyspraxia and right limb paratonia; the neurological examination was otherwise normal. A recent MMSE score was 28. Brain scanning showed reduced FDG-PET uptake in the frontal lobes.

Classical definition of frontotemporal dementia (FTD)

Onyike et al., 2011; Onyike & Diehl-Schmid, 2013

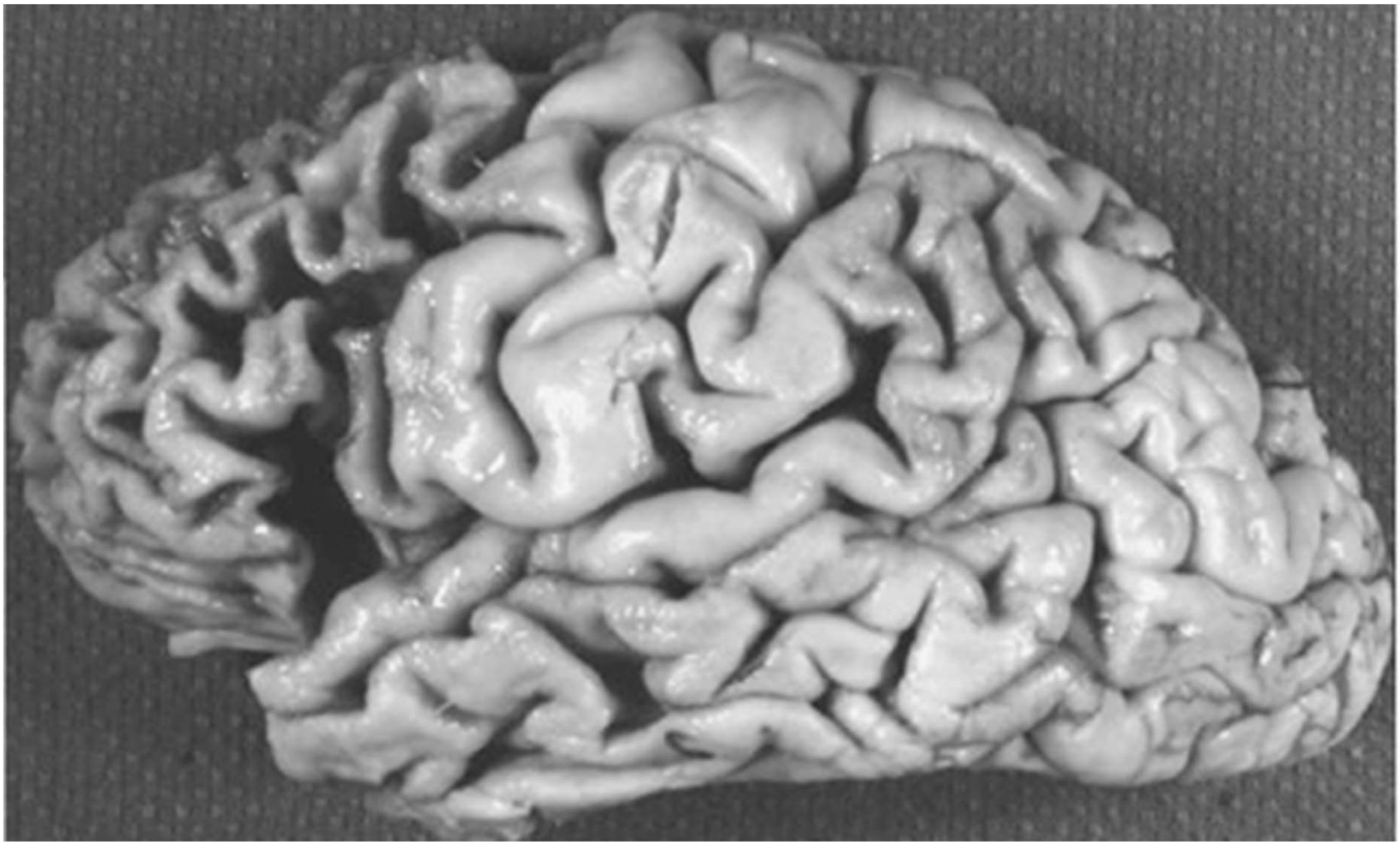
"…hallmarks are progressive decline in [conduct]: coarsening of temperament, dispositions, judgment, and comportment; dysregulation of emotions, drives and self-control; and disintegration of language and communication…"

*"Thus results a **behavioral phenotype** beginning with combinations of indifference, impatience, carelessness, jocularity, insensitivity, distractibility, impulsiveness, stereotyped behaviors, compulsions and rigid routines; **or** **language phenotypes** featuring either effortful, dysfluent, agrammatical speech, plus impaired comprehension of sentences, **or** fluent, vacuous speech, with anomia and word (and object) agnosia".*

Historical perspective

- 1891 – report of primary aphasia
- 1892 – clinicopathologic description
- 1911 – Absence of plaques and tangles noted
- 1923/26 – “Picks disease”
- 1974/75 – Types A, B and C
- 1975 – Semantic aphasia
- 1982 – Primary progressive aphasia
- 1998 – discovery of MAPT mutations
- 2004 – discovery of CHMP2B mutation
- 2006 – discovery of PGRN mutation & TDP-43
- 2011 – discovery of C9ORF72 mutation

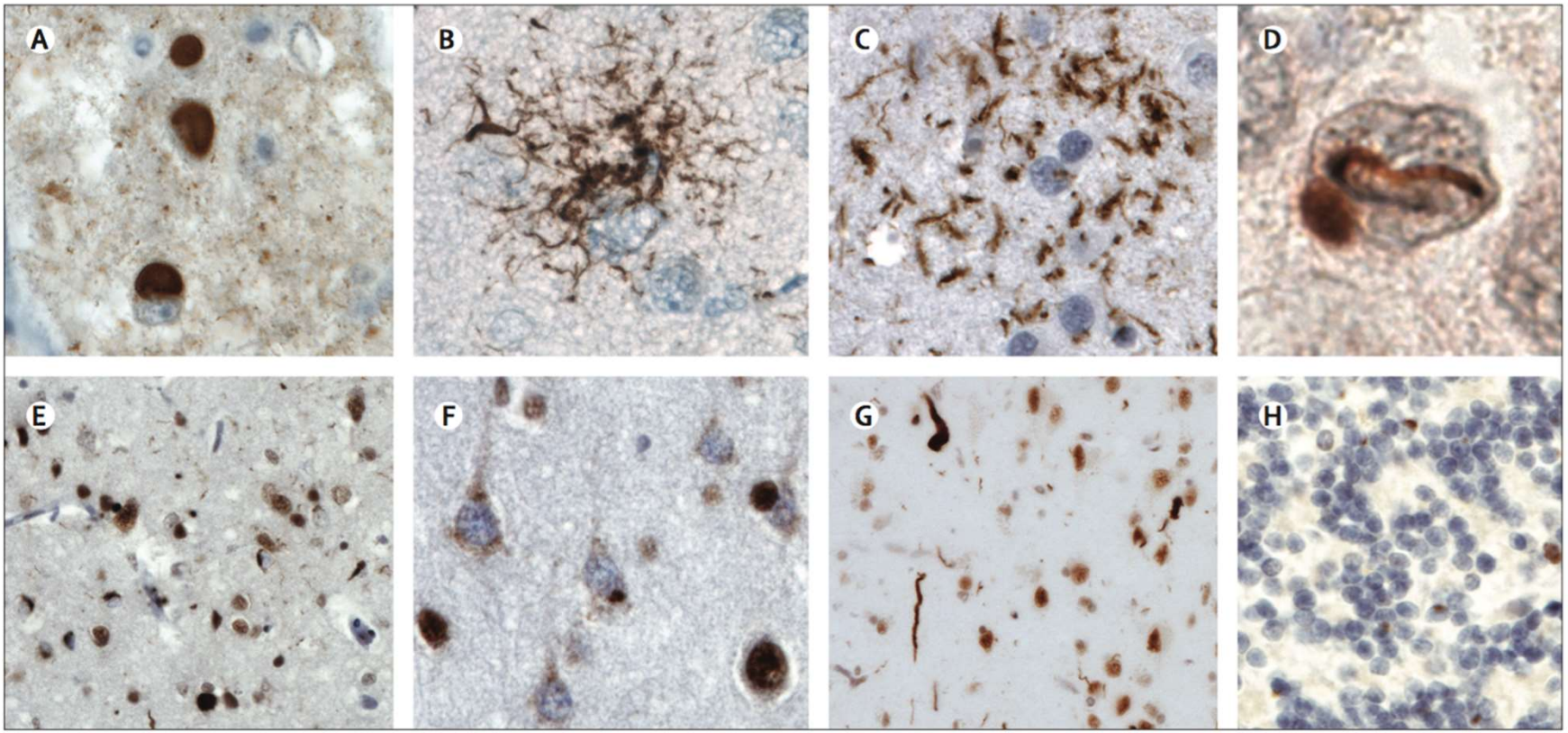
Arnold Pick
b. 1851, Velké Meziříčí, Czechia
d. 1924, Prague, Czechia



Lobar atrophy in FTD

Graff-Radford and Woodruff, 2007

Pathological appearance of the brain in Pick's Disease: "knife's edge" atrophy of the frontal lobe



Histopathology in FTD *Bang et al., 2015*

FTLD-tau (A) Pick bodies in Pick's disease; (B) a tufted astrocyte in progressive supranuclear palsy; (C) an astrocytic plaque in corticobasal degeneration; FTLD-TDP (E) small compact or crescentic neuronal cytoplasmic inclusions and short, then neuropil threads in FTLD-TDP type A; (F) diffuse or granular neuronal cytoplasmic inclusions (with a relative paucity of neuropil threads) in FTLD-TDP type B; and (G) long, tortuous dystrophic neurites in FTLD-TDP type C. TDP can be seen within the nucleus in neurons lacking inclusions but mislocalises to the cytoplasm and forms inclusions in FTLD-TDP. The remaining FTLD cases are characterised by FUS-immunoreactive inclusions that stain negatively for tau and TDP-43; a vermiform neuronal nuclear inclusion in a dentate gyrus granule cell is shown (D); this neuron contains an ovoid cytoplasmic inclusion. In patients with hexanucleotide expansions in *C9orf72*, small juxtanuclear ubiquitin-positive, TDP-negative inclusions (H) are pathognomonic for the disorder. These inclusions contain dipeptide repeat proteins translated from the GGGGCC repeat in one of six reading frames. Immunostains are 3-repeat tau (A), phospho-tau (B and C), FUS (D), TDP-43 (E–G) and ubiquitin (H). Sections are counterstained with haematoxylin. Scale bar applies to all panels and represents 50 µm in A, B, C, and H; 12 µm in D; and 100 µm in E and G. FTLD=frontotemporal lobar degeneration. TDP=TAR DNA-binding protein. FUS=fused-in-sarcoma.

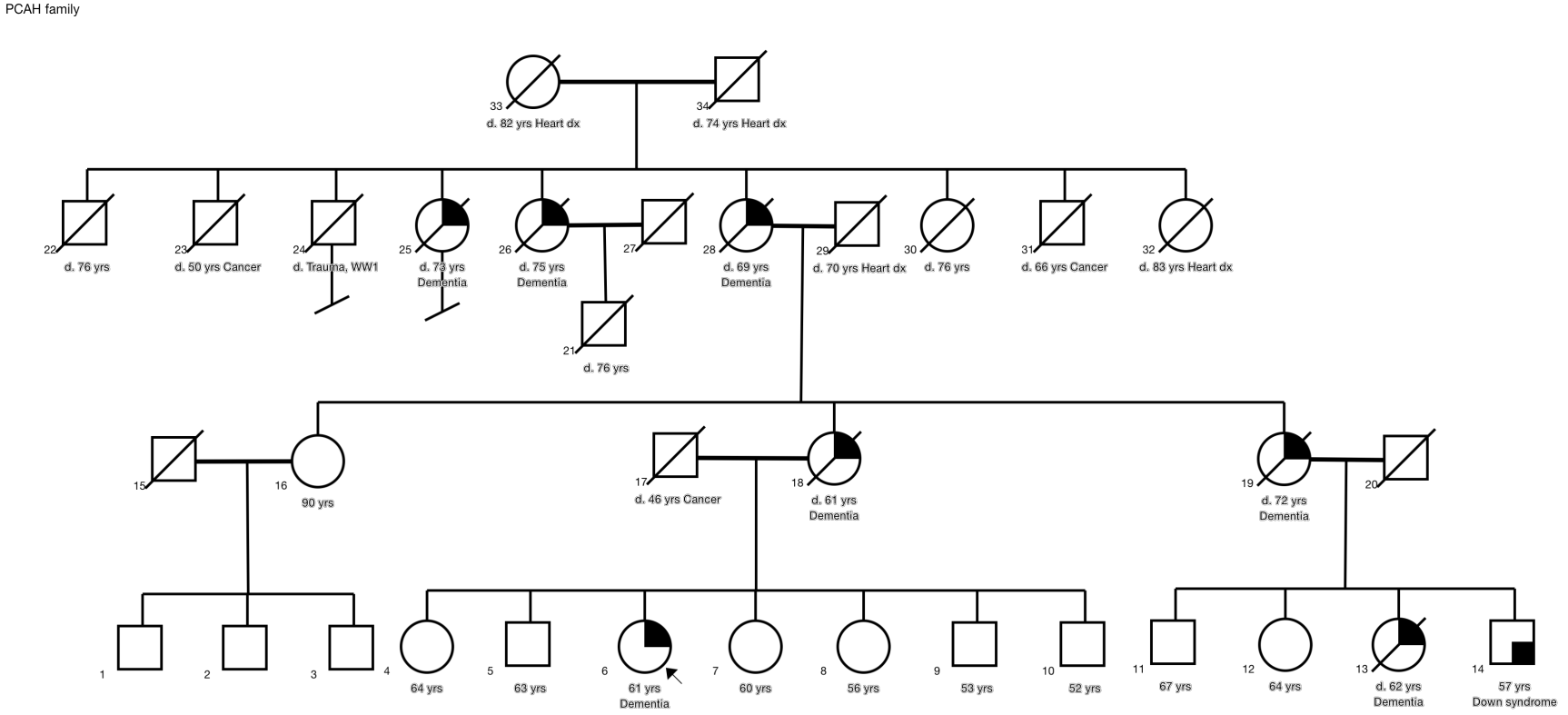
Epidemiology of frontotemporal dementia

Bird et. Al, 2003; Ratnavalli et al., 2002; Rosso et al., 2003; Onyike and Diehl-Schmid, 2013; Landquist Waldo, 2015

- Peak age of onset 53 – 58; range 21 – 75…
- Prevalence: 18 – 38 per 100,000; underestimated in elders
- M>>F in most reports
- Familial in >40%; hereditary in 10-20%

PC’s pedigree

Onyike CU, data from the JH FTD-YOD Clinic

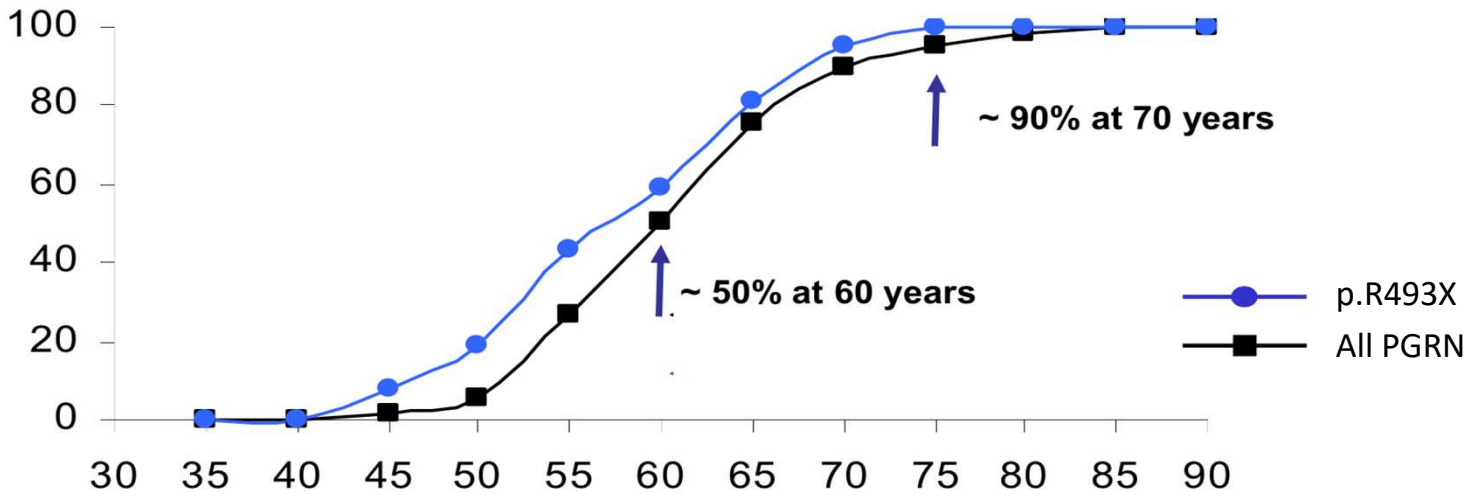


PC and affected relatives were carriers of C9ORF72

Gene	Locus	%	Phenotypes	Pathologic type
MAPT	17q21	20-25	FTD ± parkinsonism; PNFA; CBD; PSP	Tau +
PGRN	17q21	20-30	FTD; SD	TDP43 +
C9ORF72	**9p21**	**25-40**	**FTD; FTD-ALS; ALS; amnesic; psychiatric**	**TDP43 +**
CHMP2B	3p11.2	<1	FTD	Ubiquitin + Tau –, TDP43 –
VCP	9p13	<1	MSP (i.e., ± IBM ± PBD ± FTD ± ALS)	TDP43 +
TBK1	12q14.1	<1	FTD; FTD-ALS; ALS	TDP43 +

Penetrance of mutations causing FTD

Graph adapted from Hutton, 2006

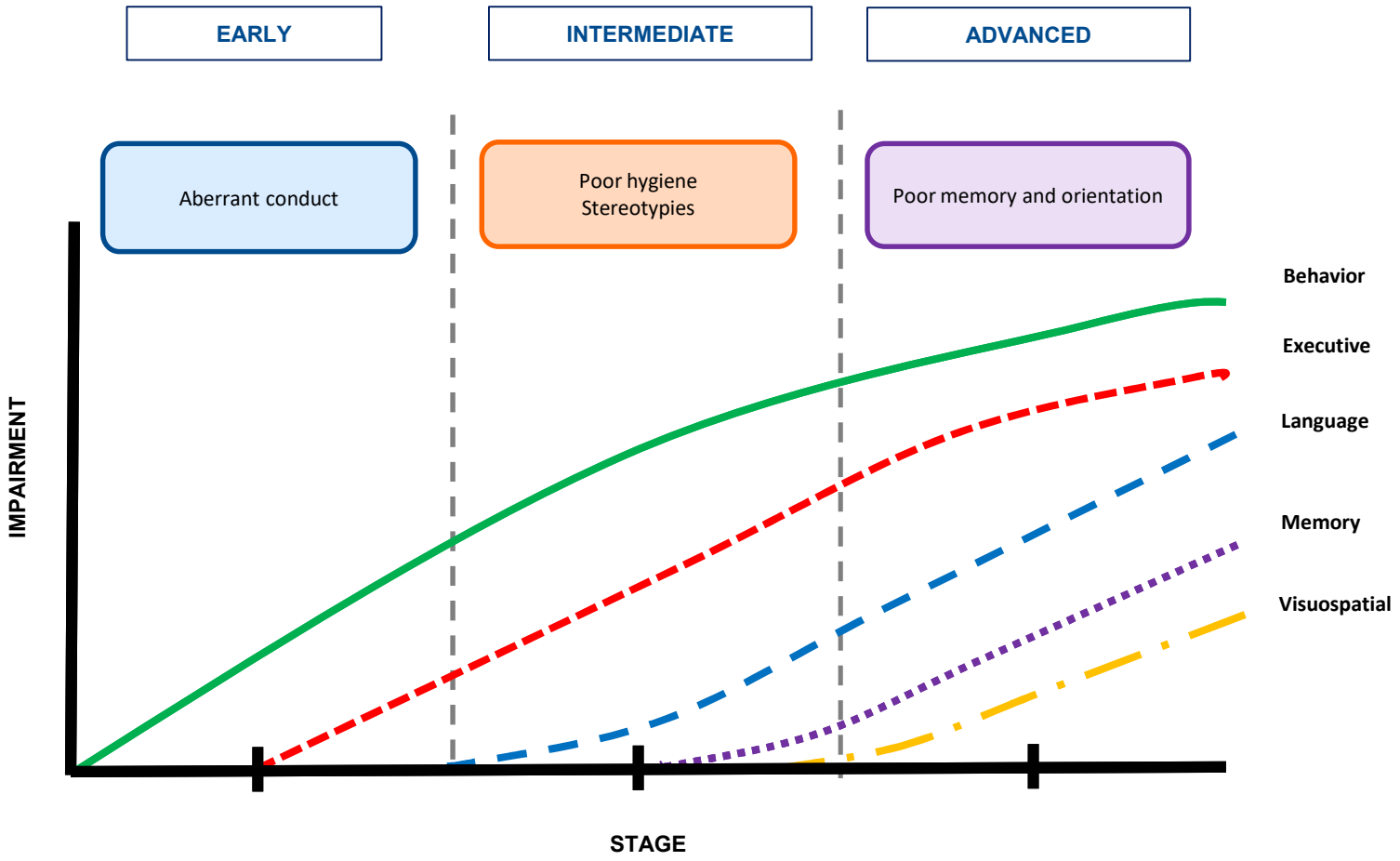


Penetrance for PGRN, MAPT and C9ORF72 mutations show larger similar profiles and time course

TMEM106B variants influence disease penetrance in carriers of PGRN and C9ORF72 mutations. *van Deerlin et al., 2010; Finch et al., 2011; van Blitterswijk et al., 2014.*

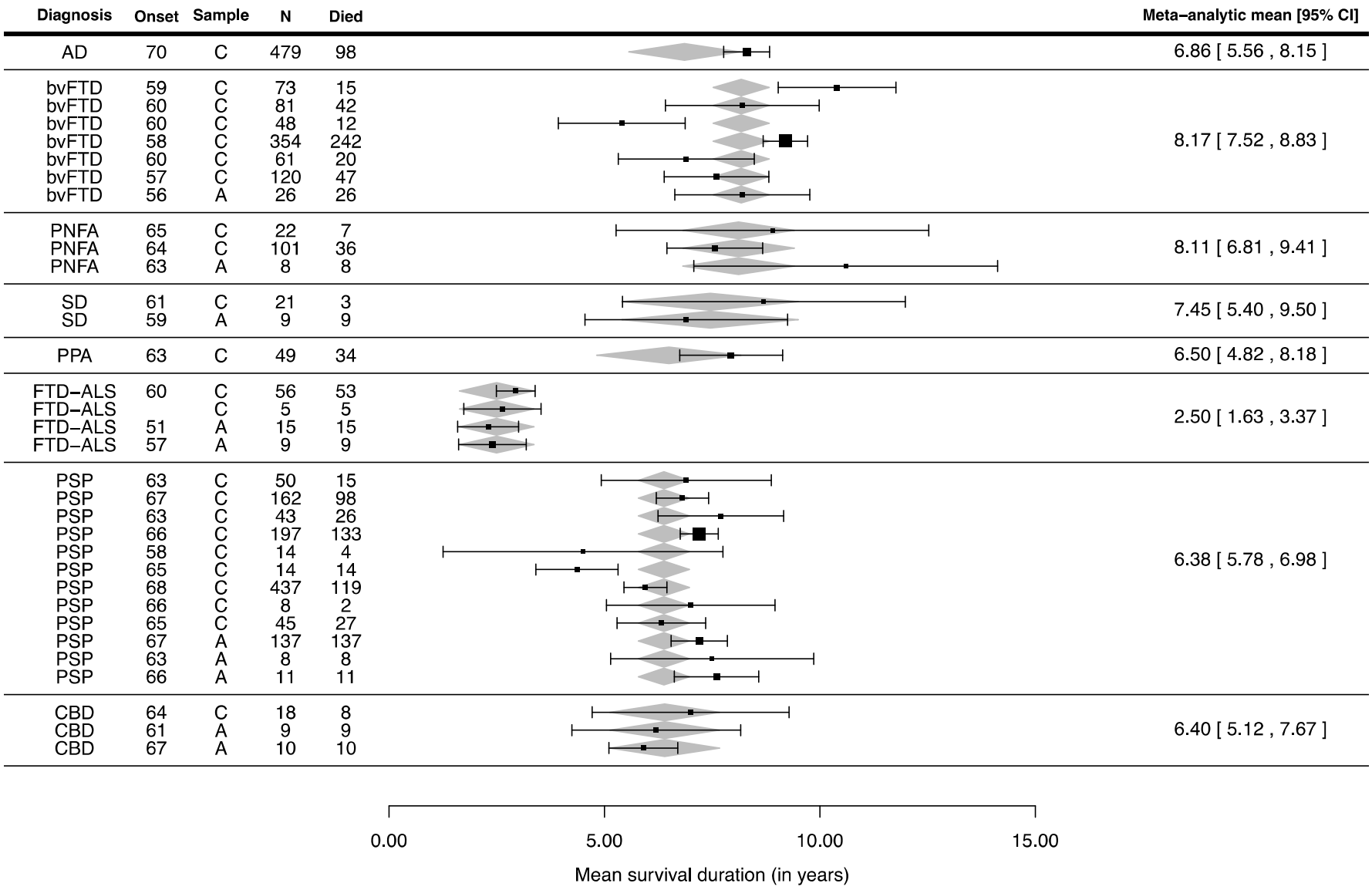
C9ORF72 repeat length has not been shown to influence penetrance or phenotype *Rutherford et al., 2012.*

Natural history of behavioral FTD



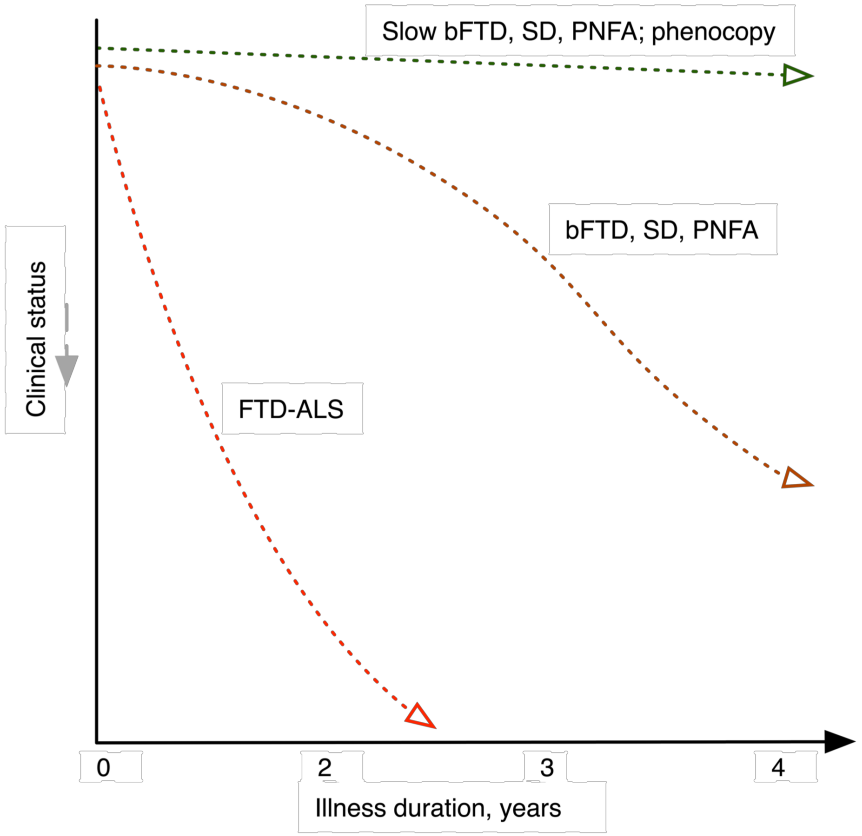
Comparing average life expectancy

Kansal et al., 2016



Differences in the rate of progression

Tempo of progression



REFERENCES:

Kipps et al., 2007: FTD phenocopy

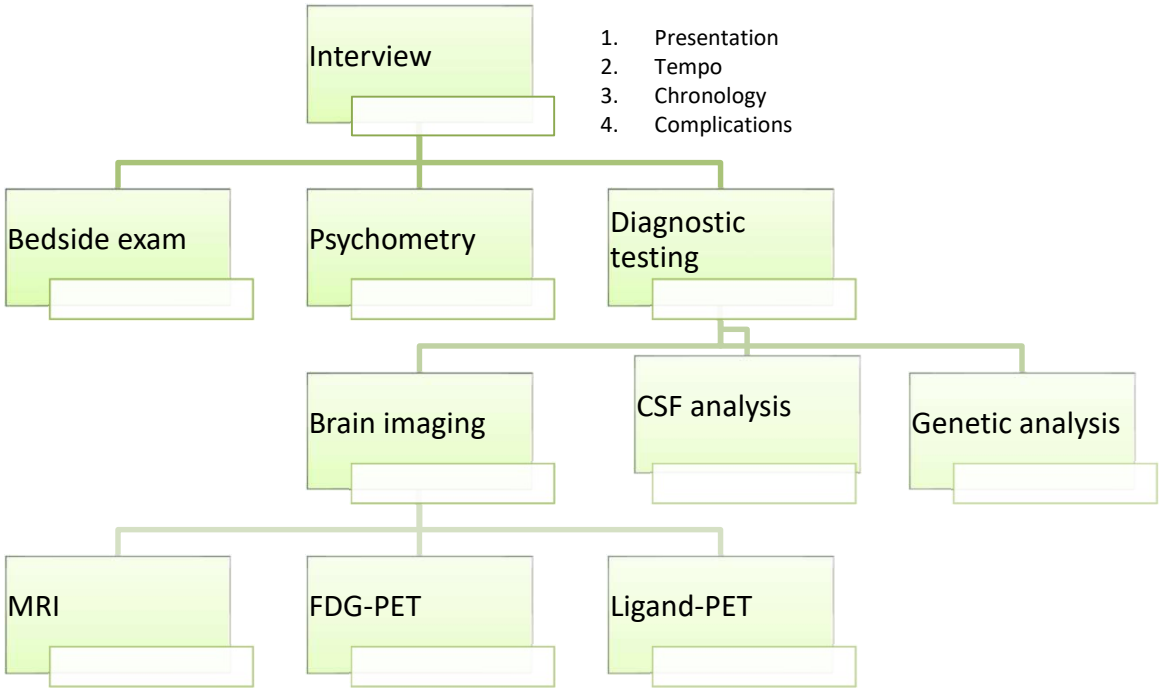
Khan et al., 2012: slow progression 4.6% in large case series

Brodtmann et al., 2013: family illness duration >20+ years

Gomez-Tortosa et al., 2013: C9ORF72 family, duration >30 years

Kansal et al., 2016: Illness duration in all phenotypes

Evaluation



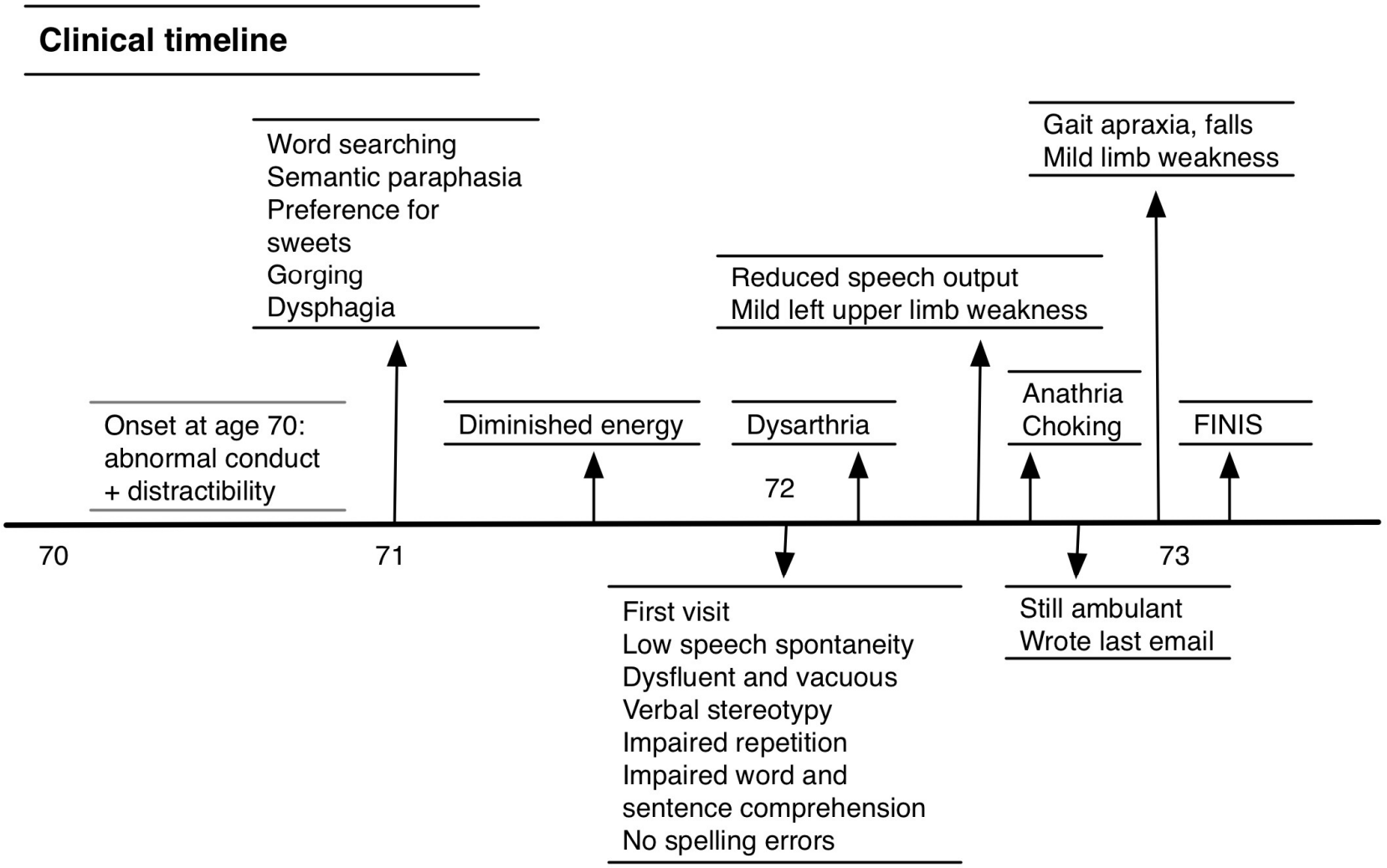
HIGHLIGHTS:

- Clinical interview
- Neurological examination
- Brain MRI and PET

- CSF analysis, ligand-PET and genetic analysis in a special situations

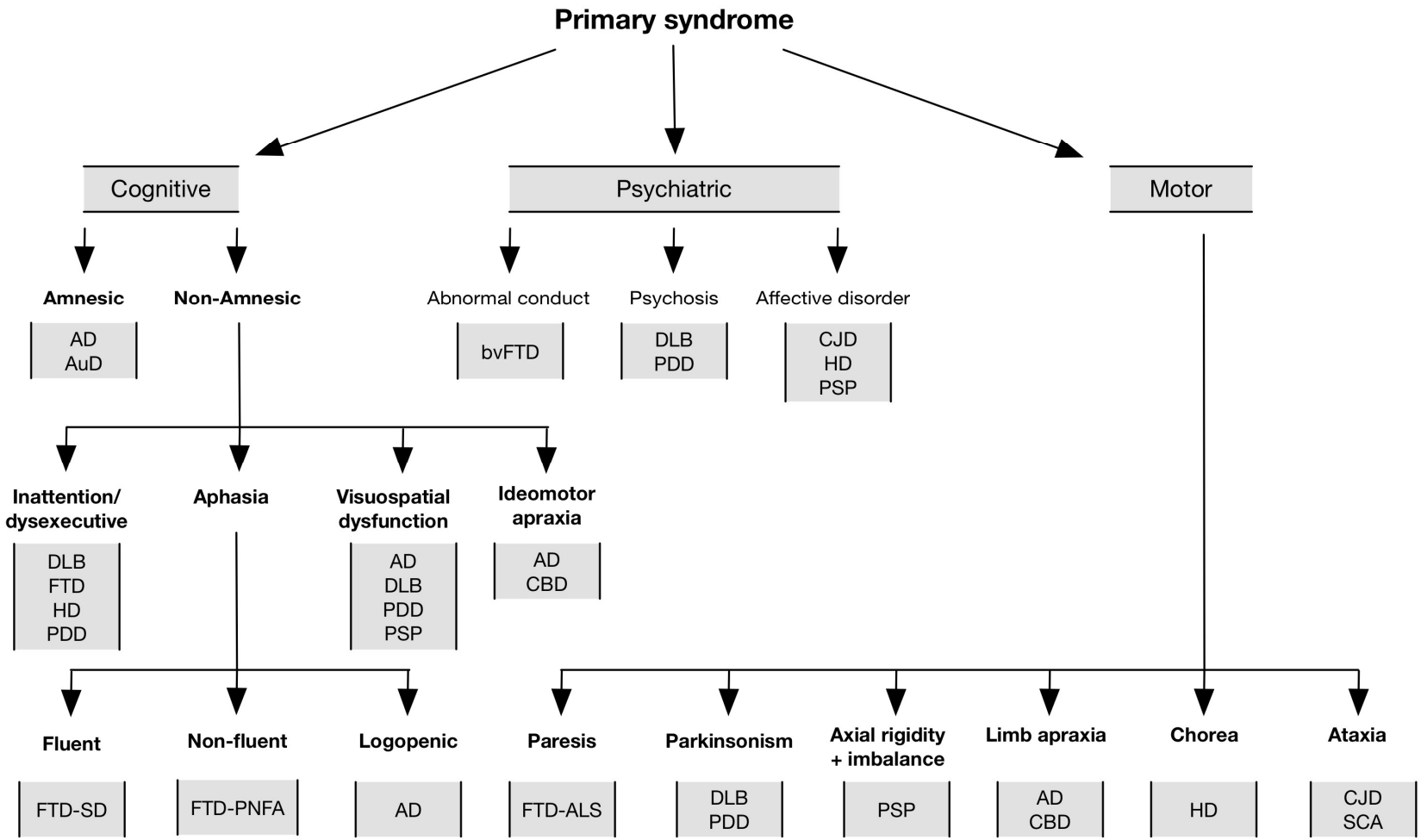
- Genetic testing requires a 3-generation pedigree

Graphical illustration of a clinical history



Clinical decision pathway

Devineni and Onyike, 2015; Onyike, in press



Flow diagram illustrating how cognitive, psychiatric and motor syndromes guide the differential diagnosis. The arrows indicate the diagnostic pathways, and grey boxes show the dementia types corresponding to the cognitive, psychiatric or motor category.
AD — Alzheimer disease; **AuD** — autoimmune dementia; **bvFTD** — behavior variant frontotemporal dementia; **DLB** — dementia of Lewy bodies; **PDD** — parkinson disease dementia; **CJD** — Creutzfeldt-Jakob disease; **HD** — Huntington disease; **PSP** – progressive supranuclear palsy; **FTD-SD** — frontemporal dementia, semantic dementia variant; **FTD-PNFA** — frontotemporal dementia, progressive non-fluent aphasia variant; **FTD-ALS** — frontotemporal dementia with amyotropic lateral sclerosis; **SCA** — spinocerebellar ataxia

Adapted from Devineni and Onyike, Psychiatr Clin North Am 2015; 38(2)233-248

Differentiating dementias from psychiatric disorders

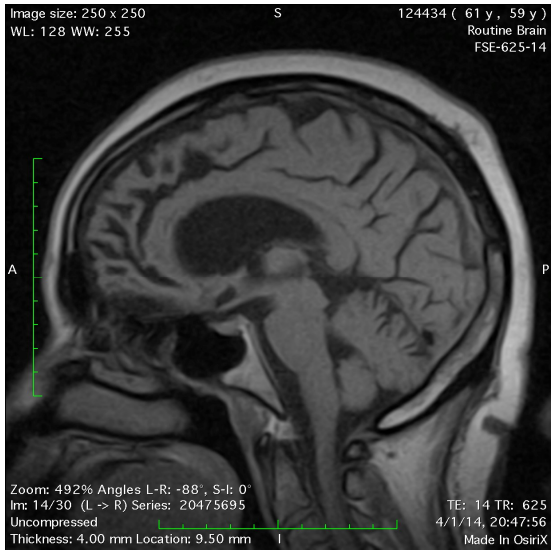
Disease/disorder	Onset	Phenotype	Features
AD	65+	Apathy, depression, anxiety, amnesia, dysexecutive	↓ cognition; global atrophy; diffuse EEG slowing
FTD	45+	↓ conduct, impulsive, dysexecutive, aphasia	↓ cognition; focal EEG slowing; focal atrophy
Vascular dementia	>60	Dysexecutive, affective disorder, psychomotor slowing, stroke/CVD	↓ cognition; neurological signs; infarcts and gliosis on MRI
DLB	>70	Hallucinations, paranoia, amnesia, fluctuations, parkinsonism	↓ cognition; global atrophy; diffuse EEG slowing
Major depression	<30	Intermittent depression with apathy and anhedonia	Normal cognition; normal EEG; no atrophy
OCD	<30	Obsessions, compulsions and anxiety	Normal insight, cognition, EEG; no atrophy
Bipolar disorder	<35	Intermittent mania and depression	Normal cognition; no atrophy
Schizophrenia	<30	Intermittent or chronic psychosis	Youth onset; chronic status; stable cognition; no atrophy
Personality disorder	<18	Sociopathic; compulsive behavior; superficial or unstable affects	Lifelong (+/- developmental); stable cognition; variable EEG; no atrophy

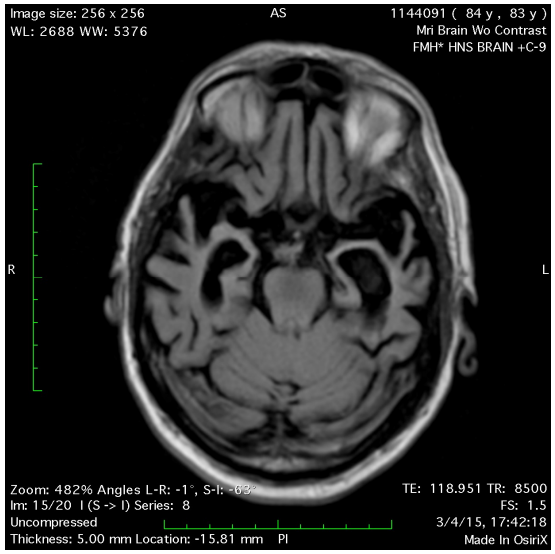
Bedside tests to measure the problem

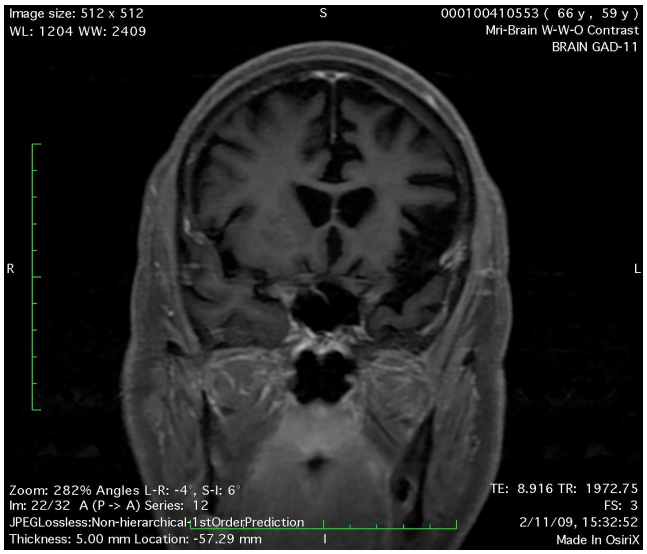
Test	Domain	Advantages	Disadvantages
MMSE	Cognition	Takes 5-10 minutes. Widely known	Poor sensitivity; low ceiling; proprietary
MoCA	Cognition	Takes ~10 minutes. Widely available; Sensitive to mild impairment	High floor; incomplete characterization
ACE	Cognition	Sensitive to mild impairment; broad measurement; tested for FTD	Takes 15-20 minutes
FRS	Illness severity	Quantitative, empirical	Takes >20 minutes
NPI; NPI-Q	Behavior	Widely used; measures many behaviors; easy to score	Incomplete coverage of FTD behaviors
FAB	Behavior	Developed for FTD; may facilitate discrimination of FTD from AD	Awkward to score; limited utility
CDR; CDR7	Illness staging	Widely used; training available; Modified version enhances utility for FTD	Original underestimates severity in early FTD

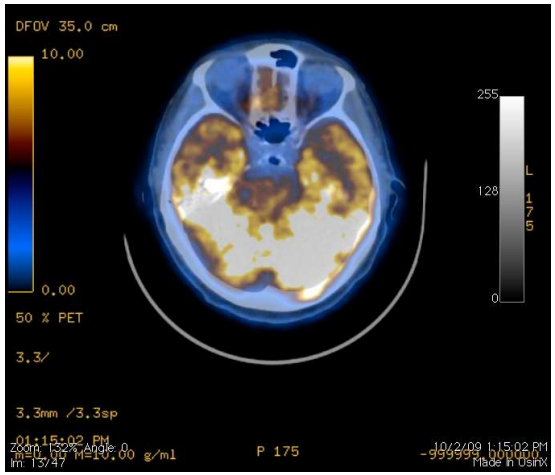
Brain imaging: MRI and FDG-PET

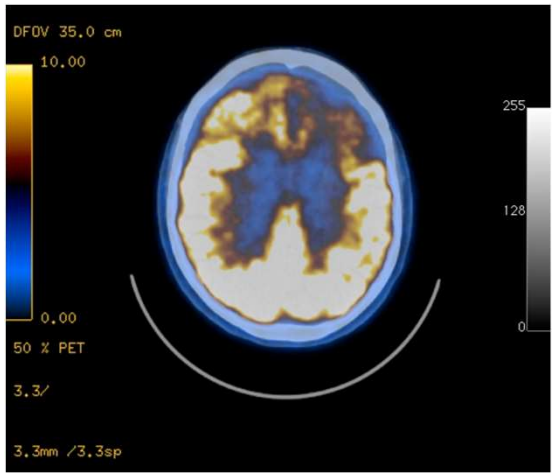
Onyike CU, images from the JH FTD-YOD Clinic archives

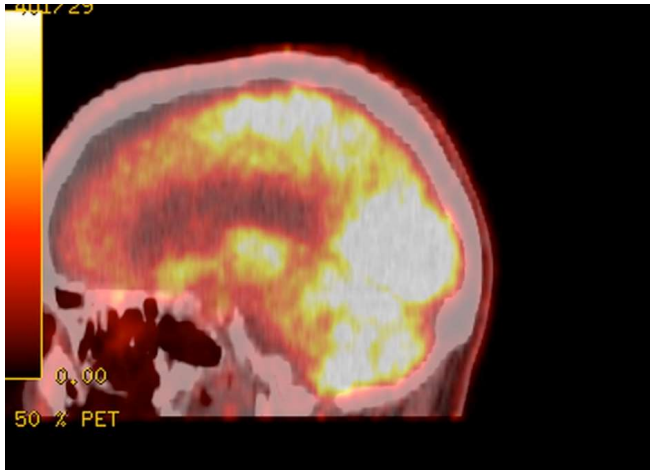






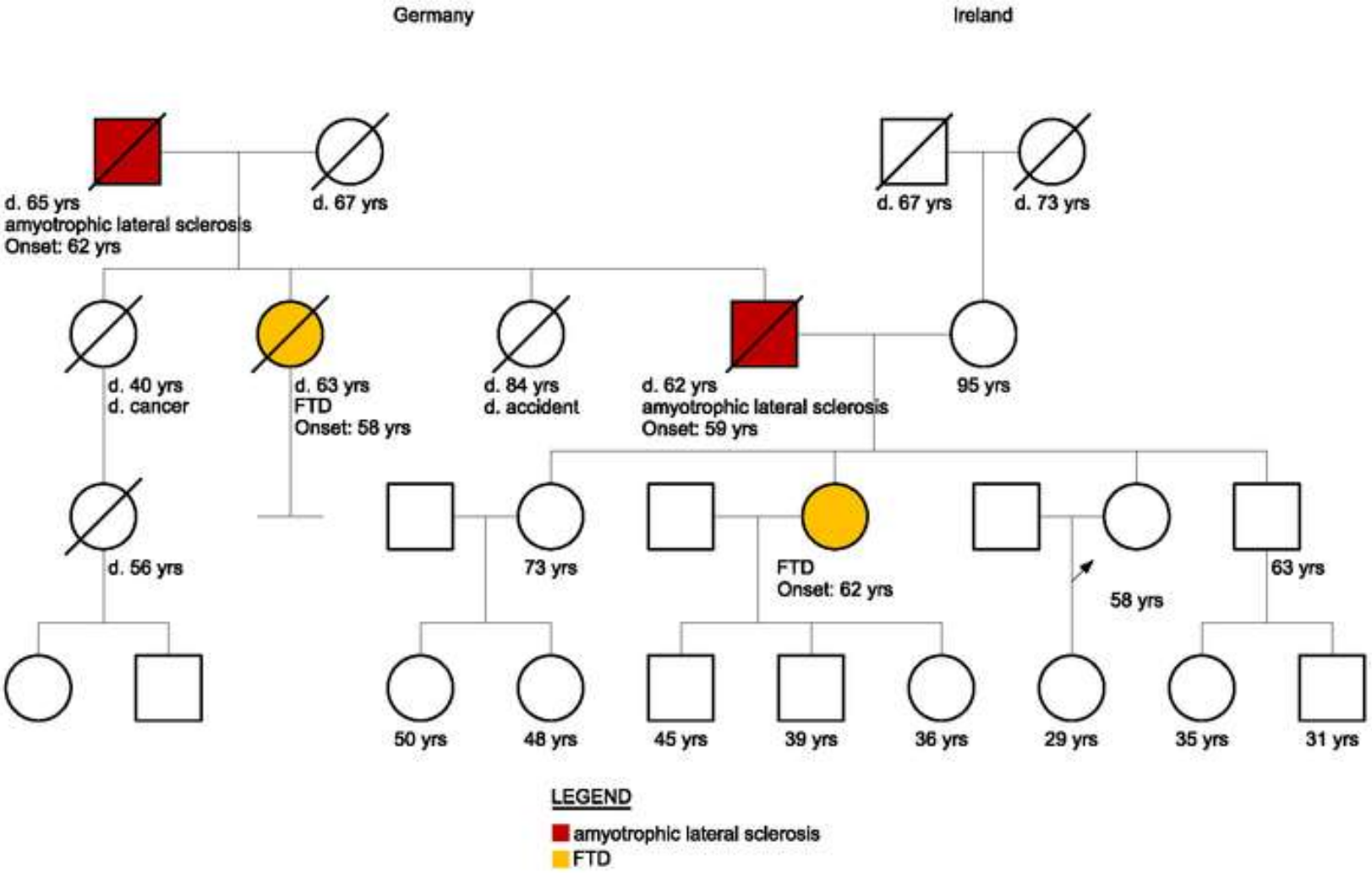






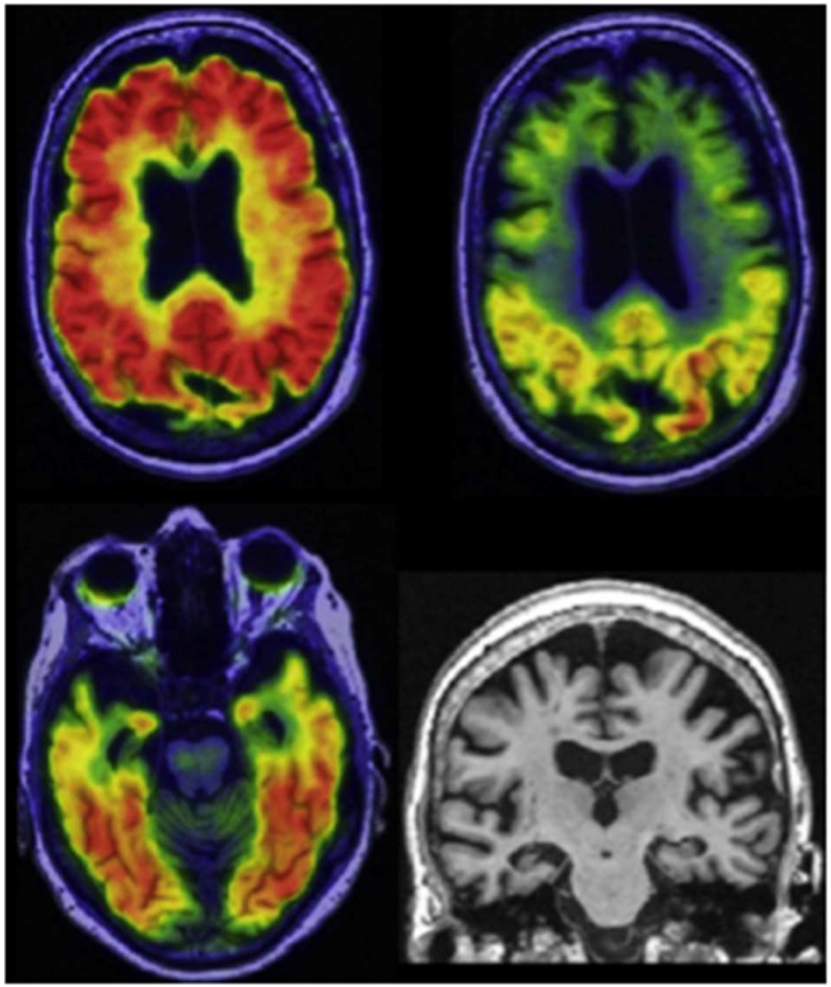
Genetic testing requires a 3-generation pedigree

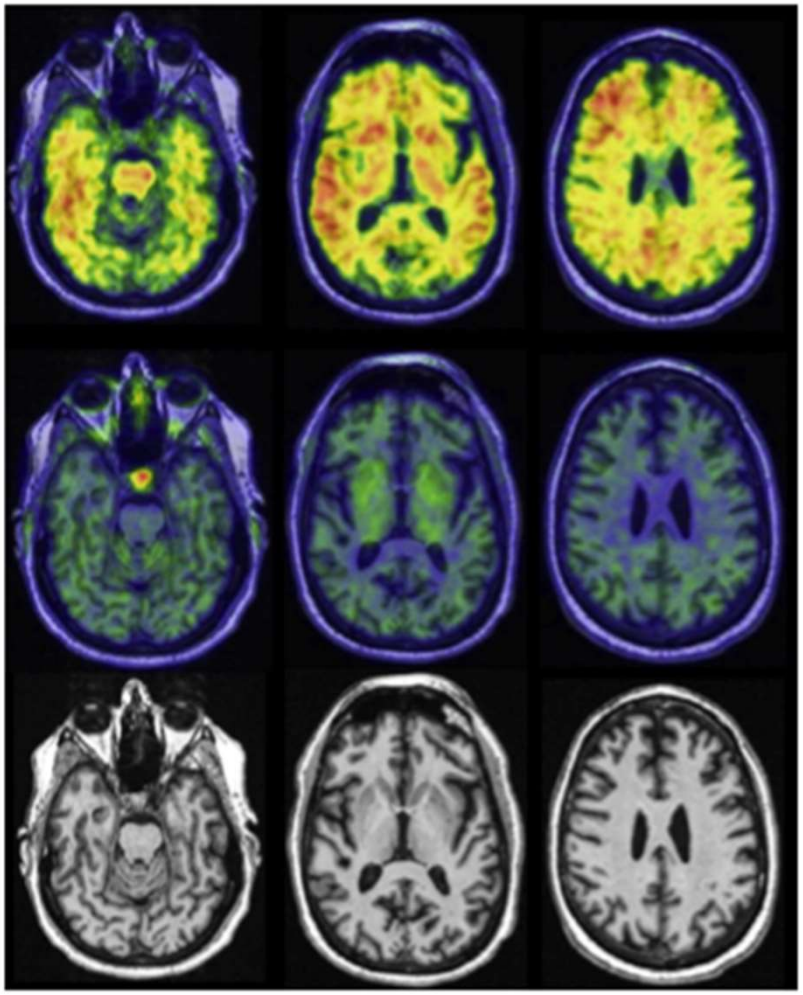
ALLFTD – https://www.allftd.org/fftld



Amyloid-PET in AD

Jack et al., 2018

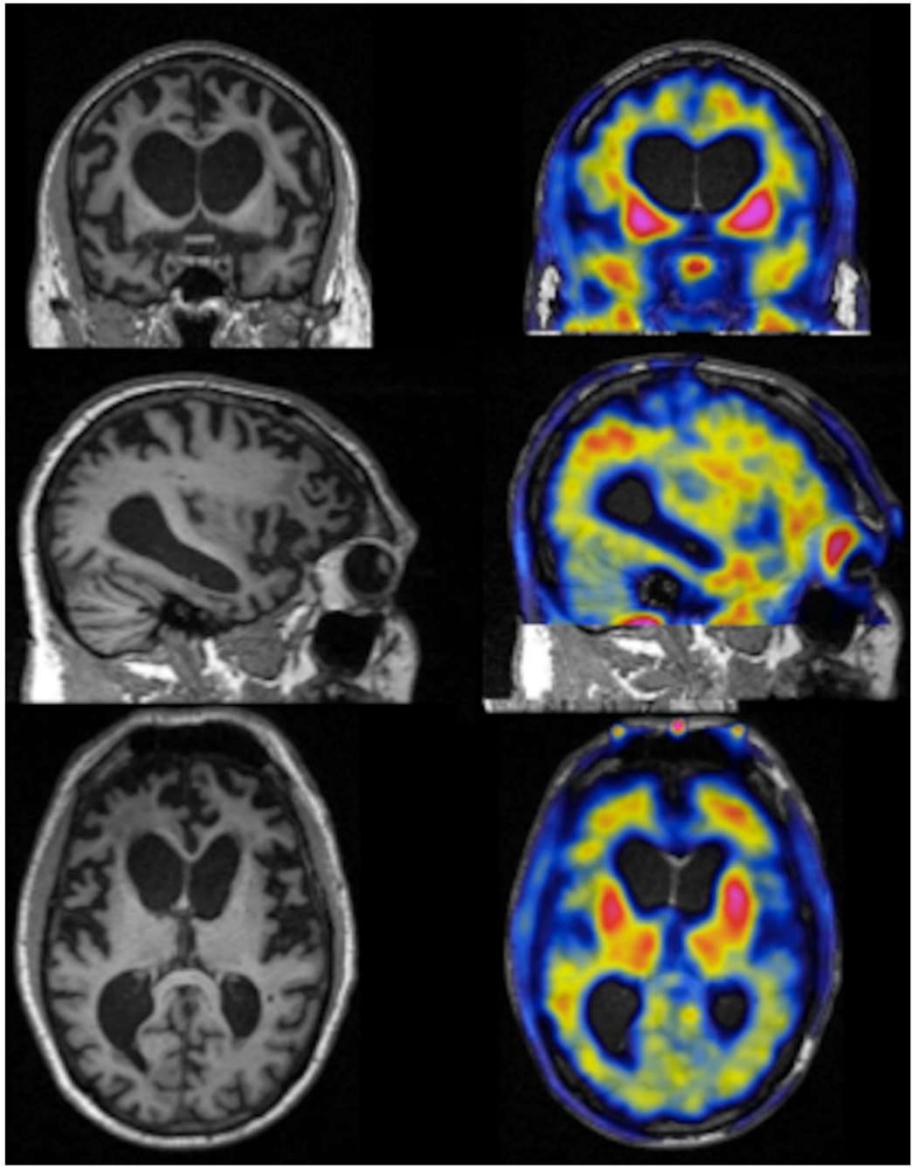




Tau-PET in FTD

Ghetti et al., 2015

[F18]-T807 ligand PET in a 56 year-old affected carrier or the P301L MAPT mutation



Visual ratings for MRI

Kipps, et al. 2007, Davies et al. 2009, Harper et al., 2015

Frontotemporal Rating Scale, FRS

Characteristics:

- T1-weighted coronal
- 5 ranks defined
- Interrater reliability = 0.7
- Intrarater reliability ~ 0.8

Sensitivity:

- 100% for SD
- 73% for PNFA
- 53% for bvFTD

Insula vital for FTD diagnosis, anterior temporal lobe for SD

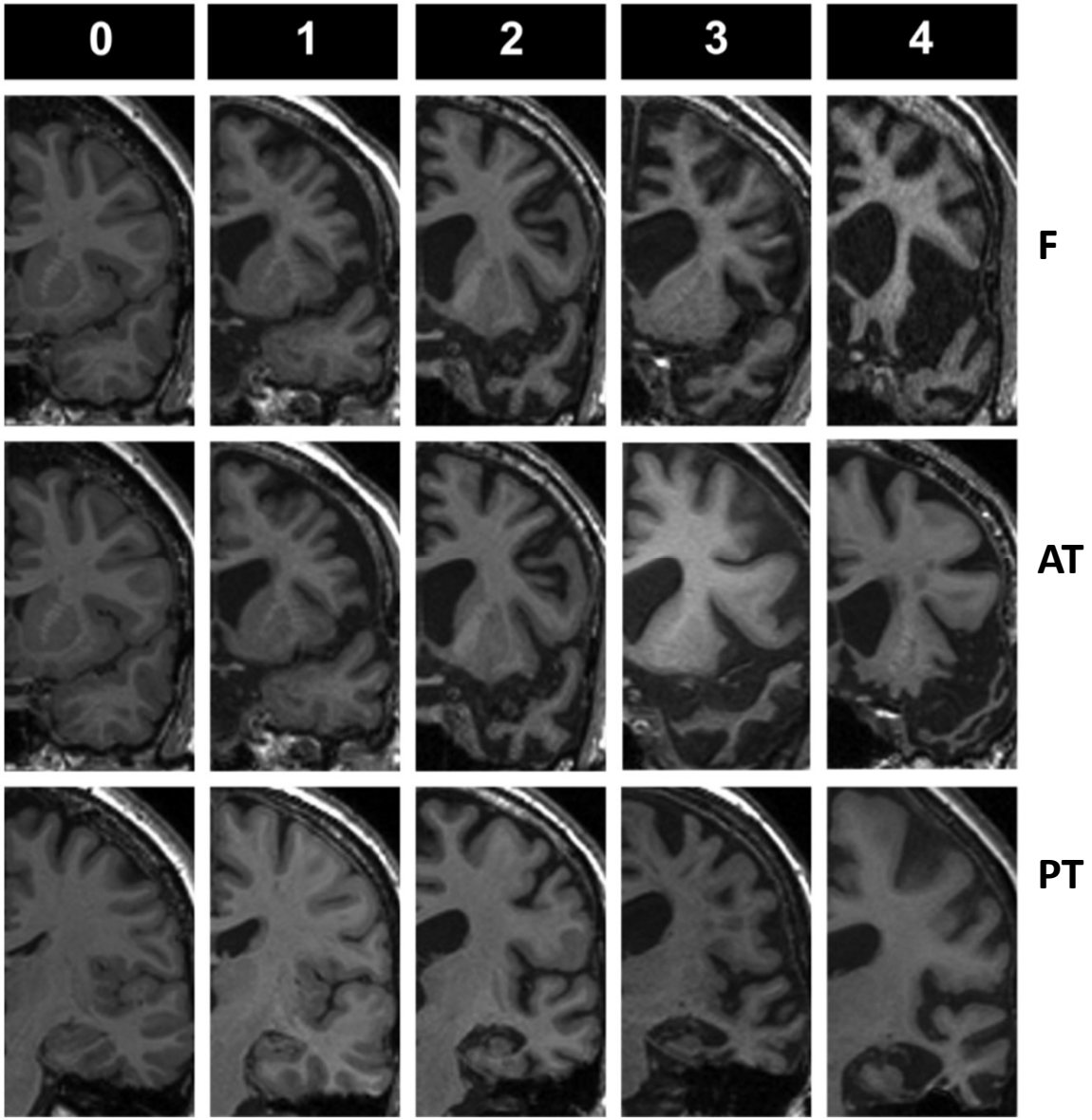


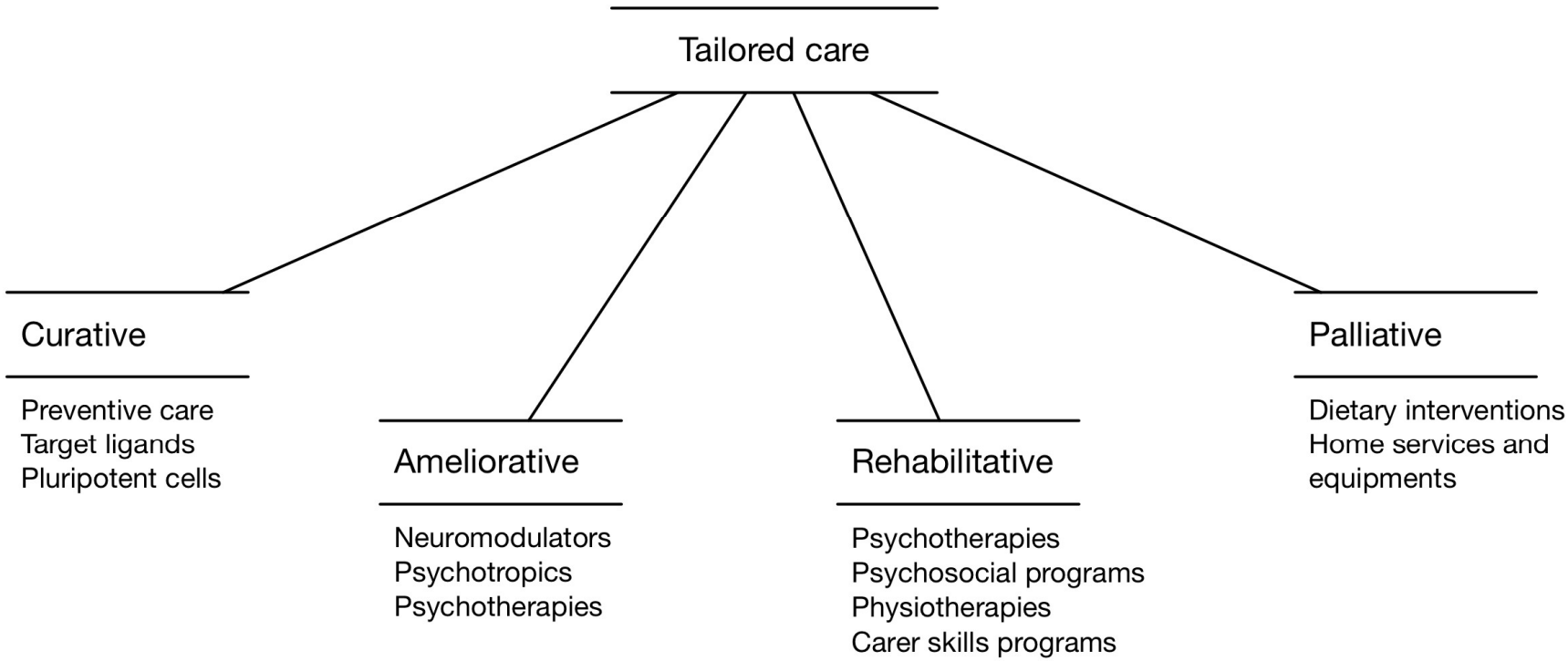
Figure. FRS, showing the 5 ranks. ROI are: F, frontal; AT, anterior temporal; PT, posterior temporal. The most widely used scoring system is binary, i.e., classifying 0-1 = normal and ≥ 2 = disease

Basis of dementia care

Onyike & Huey 2013; Wylie et al., 2013

Problem	Role	Intervention
Disease/disorder	Diagnose	Provide evaluation, direct investigation, make referrals
Disability, crisis	Solve problems	Crisis interventions and psychosocial/rehabilitative care
Distress	Provide relief	Make prescriptions
Demoralization, stress	Guidance	Provide clarification, support and direction

A universe of interventions



Existential issues → crisis or conflict *Wylie et al., 2013*

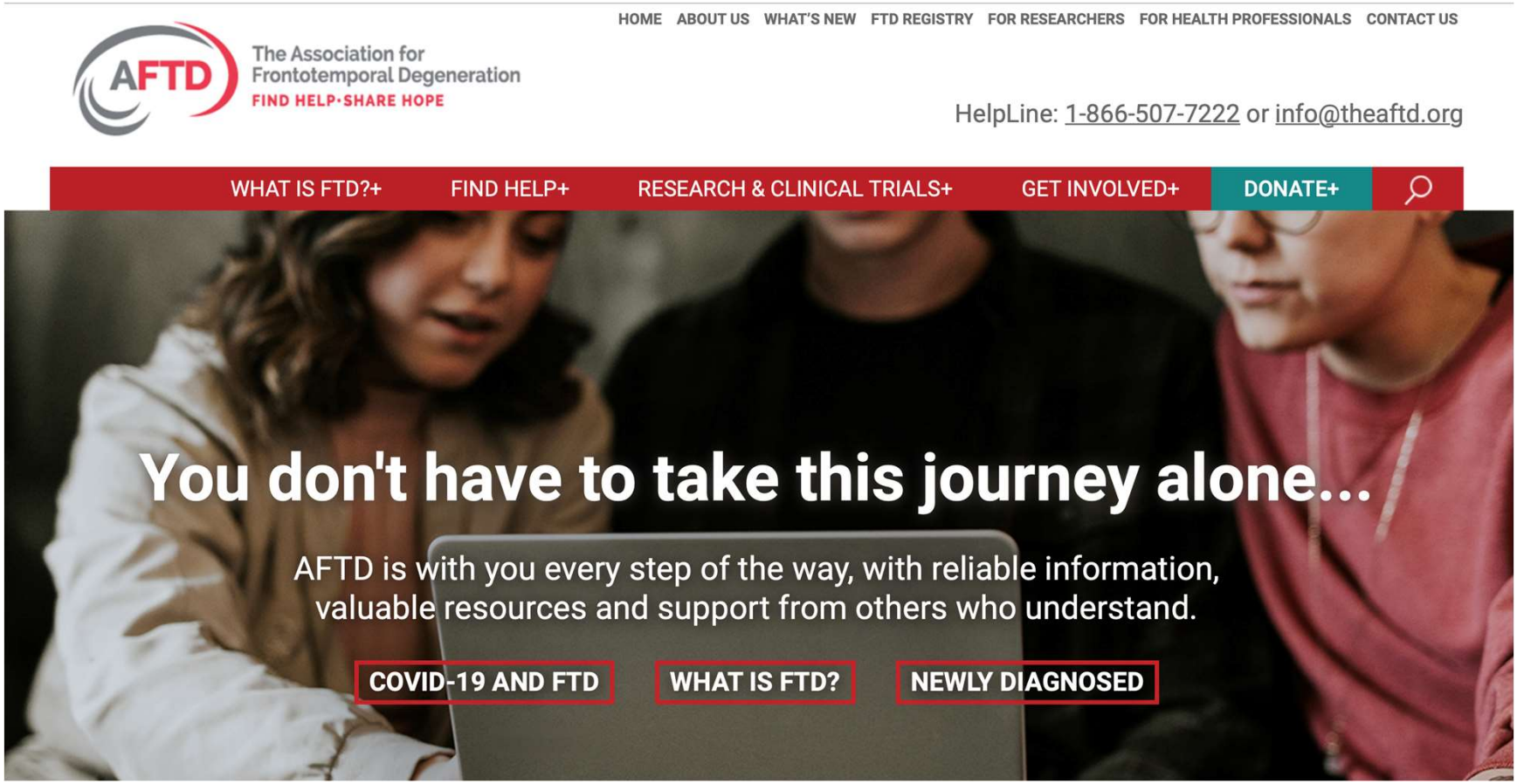
- Decisional-capacity, competence and disability
  - Diagnosis ≠ global handicaps
  - Life participation perspective
- Driving safety
  - Monitoring for accidents, mishaps and mistakes, and compliance with rules
  - Profiling of cognition and driving conduct
  - On-road assessments of skill
  - Individualized recommendations
- Advanced directives
- Residential care
- Feeding disorder
- End of life care

Pharmacologic treatments

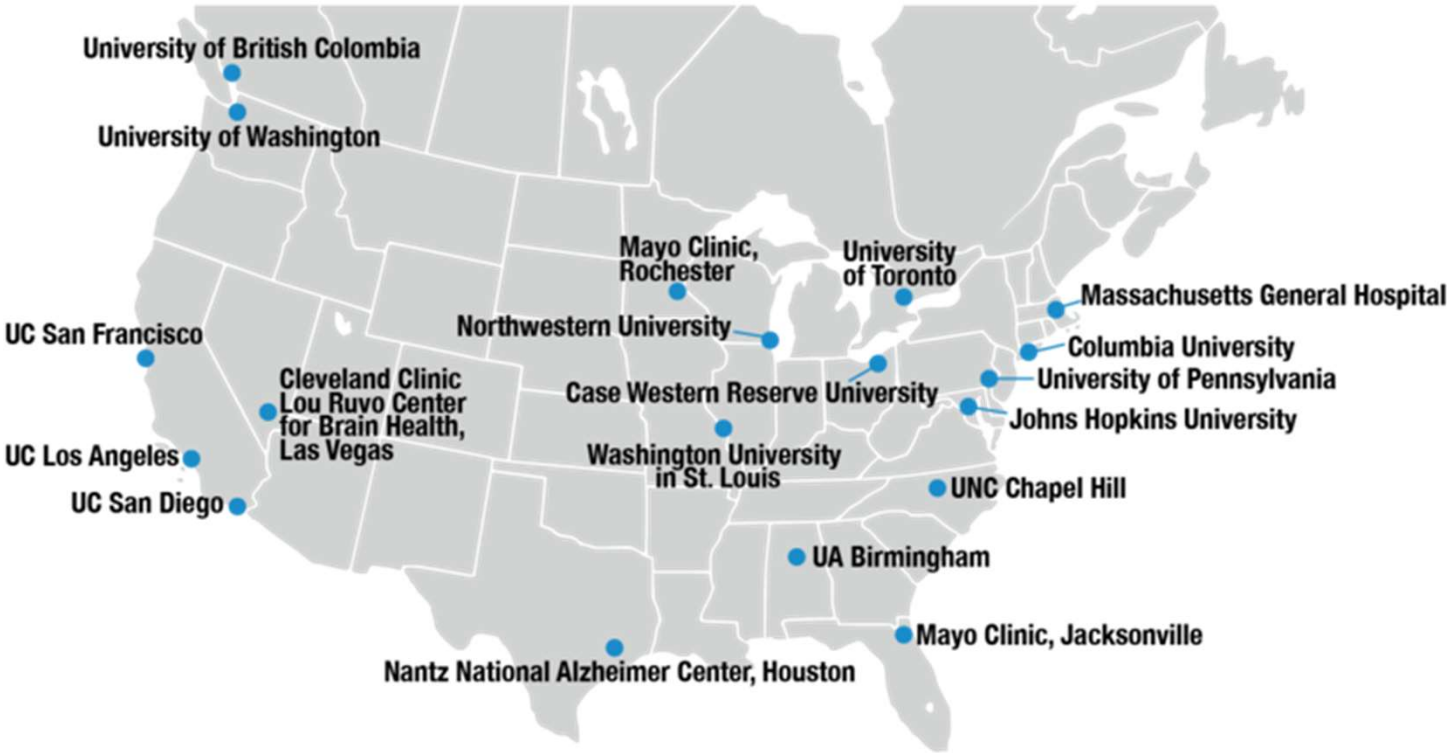
Lebert et al., 1999; Moretti et al., 2002; Ikeda et al., 2004; Lebert et al., 2004; Huey et al., 2006; Cruz et al., 2008; Singam et al., 2013

Class	Purpose
Amantadine	Stimulate cognition
SSRI & SNRI	Address depression, anxiety, irritability, compulsions
Neuroleptics	For agitation, hallucinations, delusions
Benzodiazepines	For anxiety, irritability, agitation
Methylphenidate	For inattention
Mirtazapine	To improve nighttime sleep
Zolpidem	For sleep
Topiramate	May help with overeating, roaming

Advocacy and carer support: www.aftd.org



ALLFTD Consortium



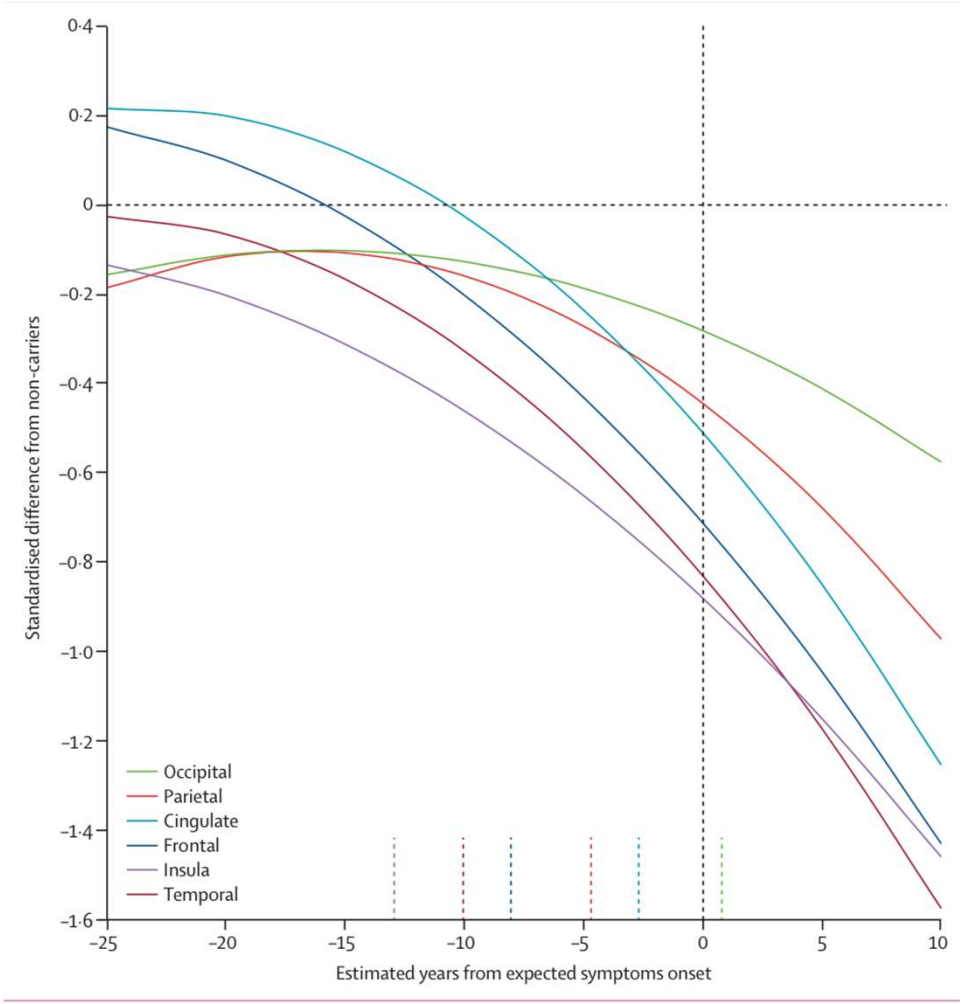
GENFI Consortium (Europe)

Preclinical states in hereditary FTD

Subclinical executive ± language dysfunction in carriers of MAPT, CHMP2B, and PGRN mutations. *Geschwind et al., 2001; Stokholm et al., 2012; Barandiaran et al., 2012*

Mild behavioral impairment has been described, but the construct lacks specificity. *Taragano et al., 2009*

Relative decline in the cortex of MAPT, PGRN, C9ORF72 mutations carriers, see graph. *Rohrer et al., 2015*

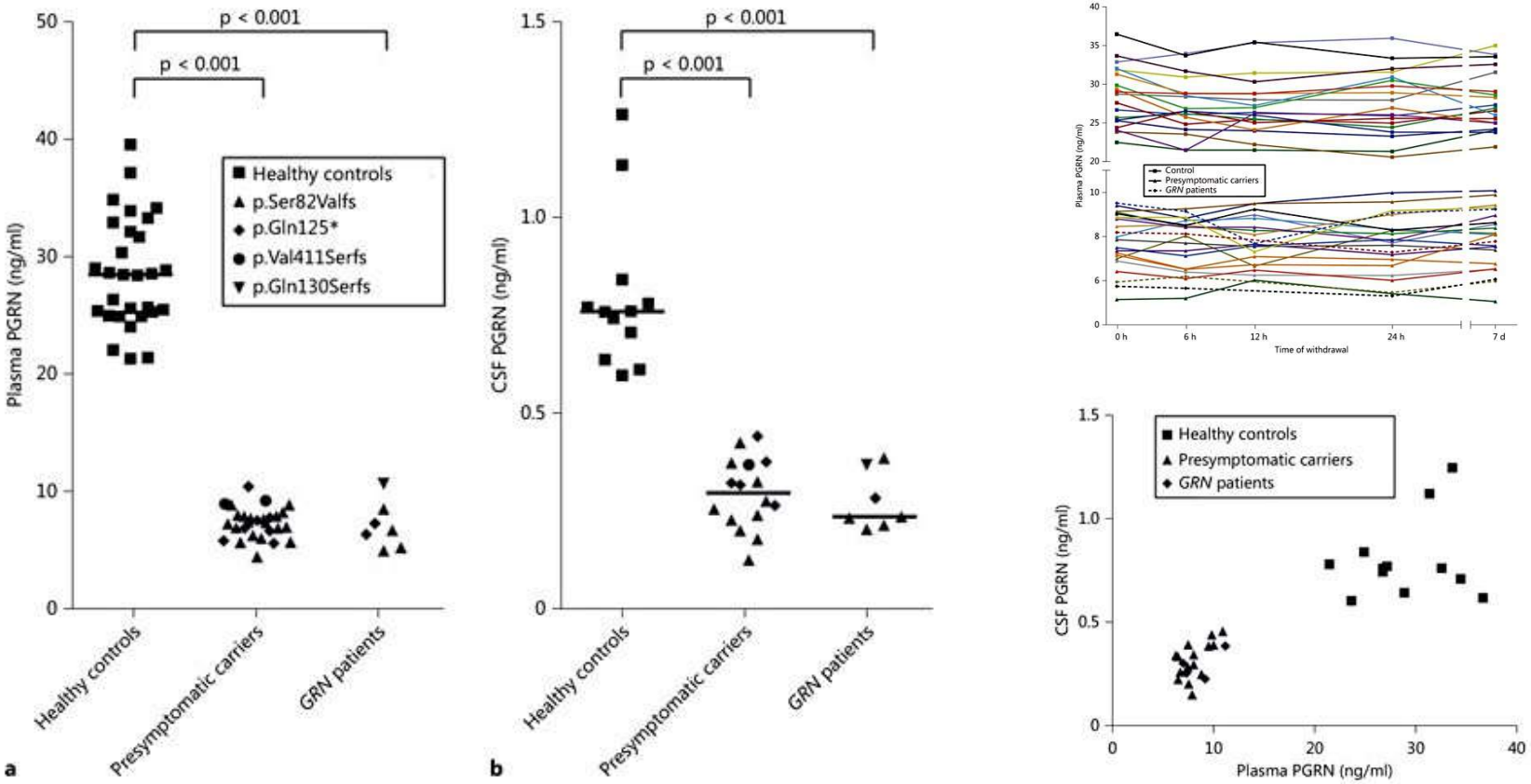


Standardised difference between all mutation carriers and non-carriers in cortical grey matter volumetric imaging measures versus estimated years from expected symptoms onset

Individual data points not plotted to prevent disclosure of genetic status. The time at which the upper 95% CI for each curve crosses zero on the y-axis (i.e., the point at which a significant difference exists between mutation carriers and non-carriers) is shown on the x-axis.

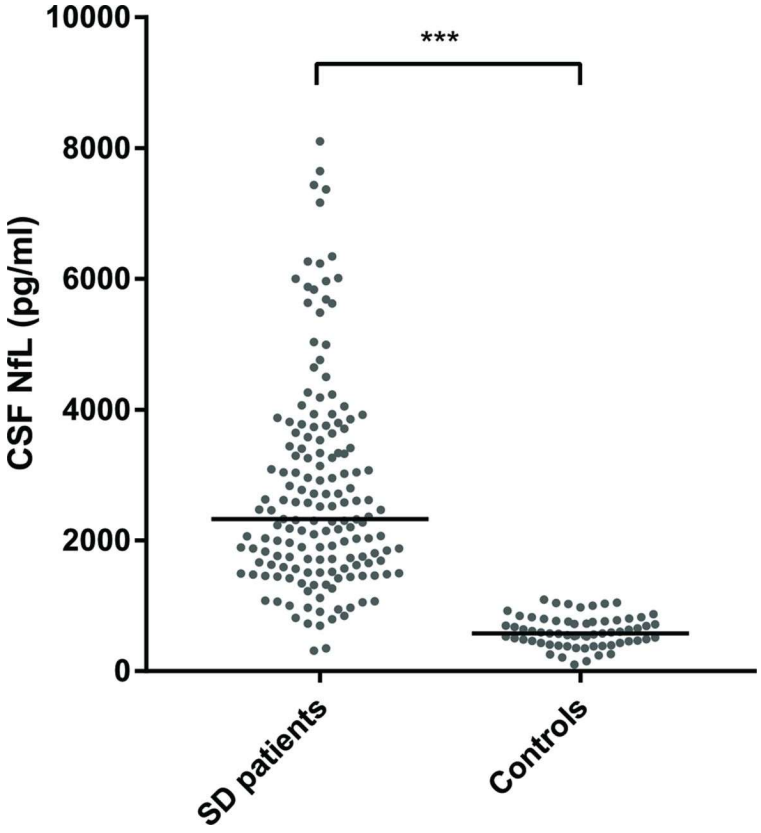
Progranulin assays in mutation carriers and non-carriers

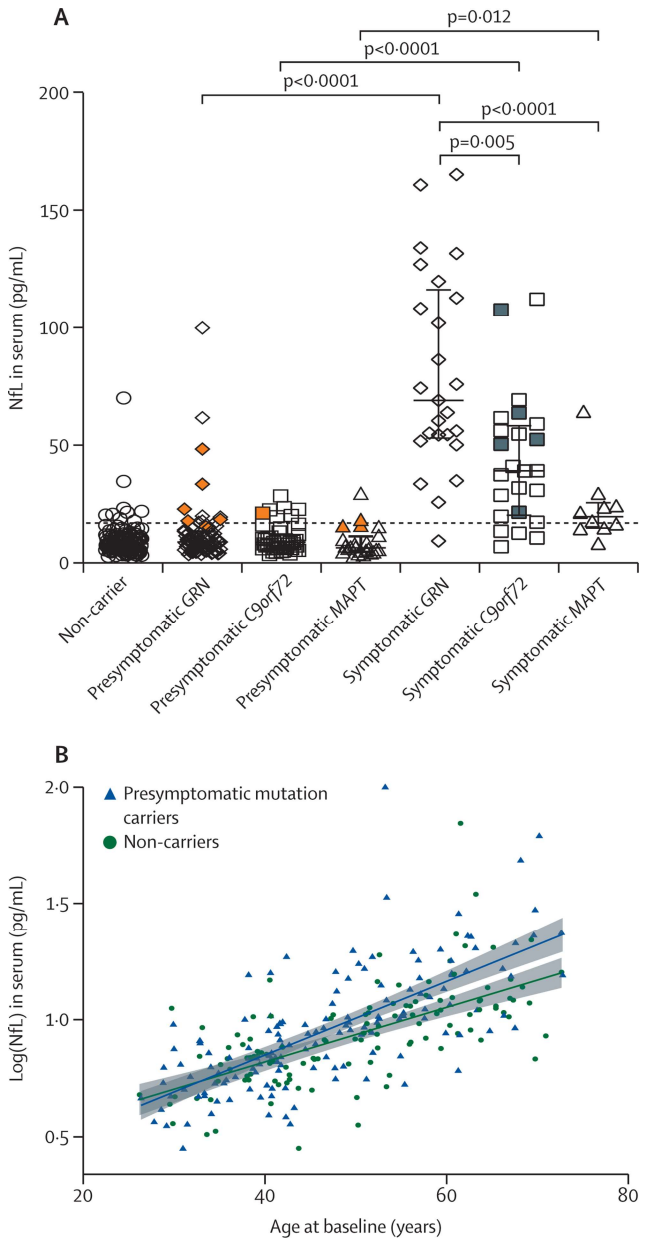
Finch et al., 2009



Neurofilament light chain assays

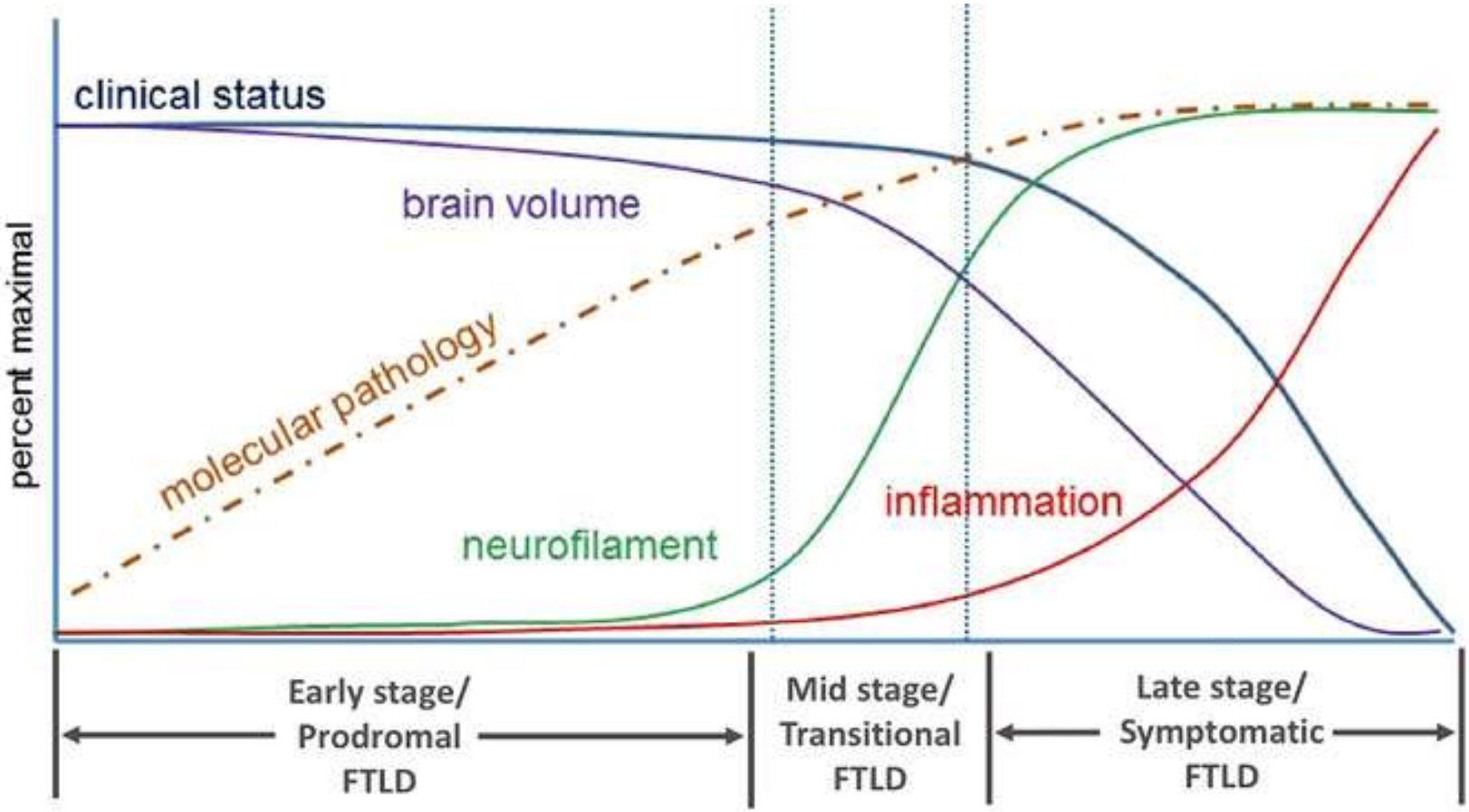
Jiskoot et al., 2016





Working model for FTD evolution

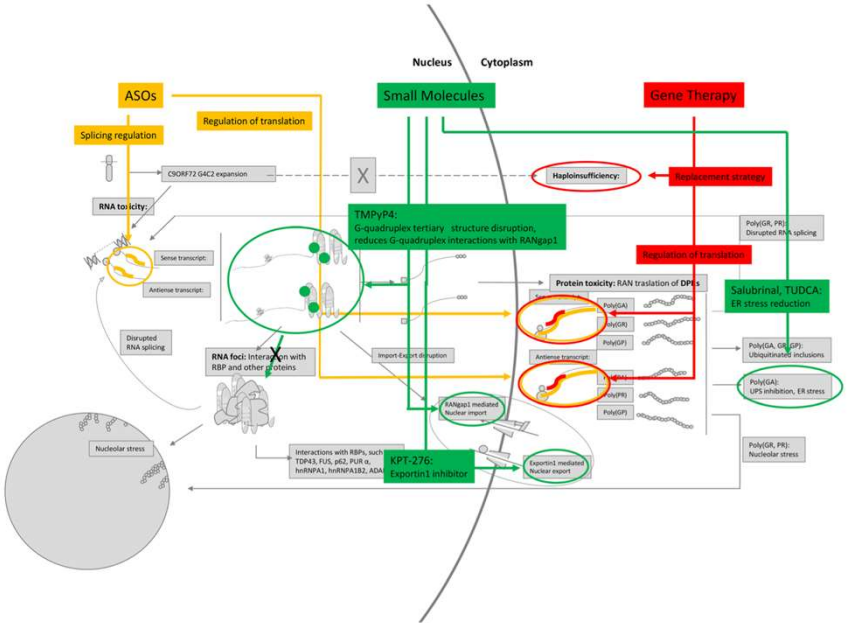
ALLFTD – https://www.allftd.org/fftld



Candidate mechanisms for disease and drug development

Nalbandian et al., 2011; Cleary and Ranum, 2013; Ling et al., 2015; Mis et al., 2016

- Dysregulation of cellular repair → apoptotis
- Tau polymerization → disruption of axonal transport
- Dysfunction of endosomal trafficking and autophagy
- Mitochondrial dysfunction – in MSP
- Activation of microglia and cytokines/interleukins
- Repeat associated non-ATG (RAN) translation – in C9 FTD/ALS, SCA8, DM1 and FXTAS – toxic dipeptide repeat proteins
- Compromise of TDP43 repression of non-conserved cryptic exons
- Prion-like propagation of neuropathology vs. regional differences in proteinopathy expression



Clinical studies at Johns Hopkins

ALLFTD

- Ann Fishman, ann.fishman@jhu.edu, 410-502-5816

Observational/translational studies for YOAD and clinical trials for FTD

- Toni White, twhite46@jhmi.edu, 410-550-6486

Neuromodulation in PPA

- Olivia Herrmann, oherrma1@jhu.edu, 410-736-2940

Observational studies and clinical trials for DLB, PSP and other parkinsonian disorders

- Diane Lanham, dlanham1@jhmi.edu, 443-287-2965

Genetic Counseling

- Weiyi Mu, wmu2@jhmi.edu, 443-287-2965

Brain donation for FTD and young-onset AD research

- Mary Anne Wylie, mwylie1@jhmi.edu, 410-502-2981

Acknowledgments

- **FTD/Young-Onset Dementia:** Kalyani Kansal, Mary Anne Wylie, Rebecca Rye, Myra Franklin, Ann Fishman, Sarah Woody Lawrence, Meghan Schultz, Toni White, Elsheba Abraham, Ashnaa Rao, Sadhvi Saxena
- **Geriatric Psychiatry/Neuropsychiatry:** Gwenn Smith, Peter Rabins, Halima Amjad
- **JH ADRC:** Marilyn Albert, Carol Gogel
- **Cognitive Neurology:** Argye Hillis, Kyrana Tsapkini
- **Neuropsychology:** Vidya Kamath, Jason Brandt, Campbell Sullivan
- **Movement Disorders Neurology:** Alexander Pantelyat
- **Neuromuscular Neurology:** Jeff Rothstein, Nicholas Maragakis, Lora Clawson
- **Rehabilitation Psychology:** Kathleen Bechtold, Connie Jacocks, Marlis Gonzalez-Fernandez
- **Neuropathology:** Juan Troncoso, Olga Pletnikova, Karen Fisher
- **Neuroradiology:** Haris Sair
- **U. Pennsylvania:** David Irwin, Murray Grossman, Katya Rascovsky, Corey McMillan, John Trojanowski
- **Columbia University:** Edward Huey
- **UCSF:** Adam Boxer, Howard Rosen, Bruce Miller
- **Mayo Clinic Rochester:** Brad Boeve
- **Harvard University:** Brad Dickerson
- **Association for Frontotemporal Degeneration**
- **Frontotemporal Dementia Study Group**
- **Alzheimer's Association of Greater Maryland**
- **Jane Tanger Black Fund for Young-Onset Dementias; Nancy Hall Fund for Geriatric Psychiatry; Trovato Fund**