Appreciation of John Trojanowski & aging-related TDP-43 pathology (LATE)

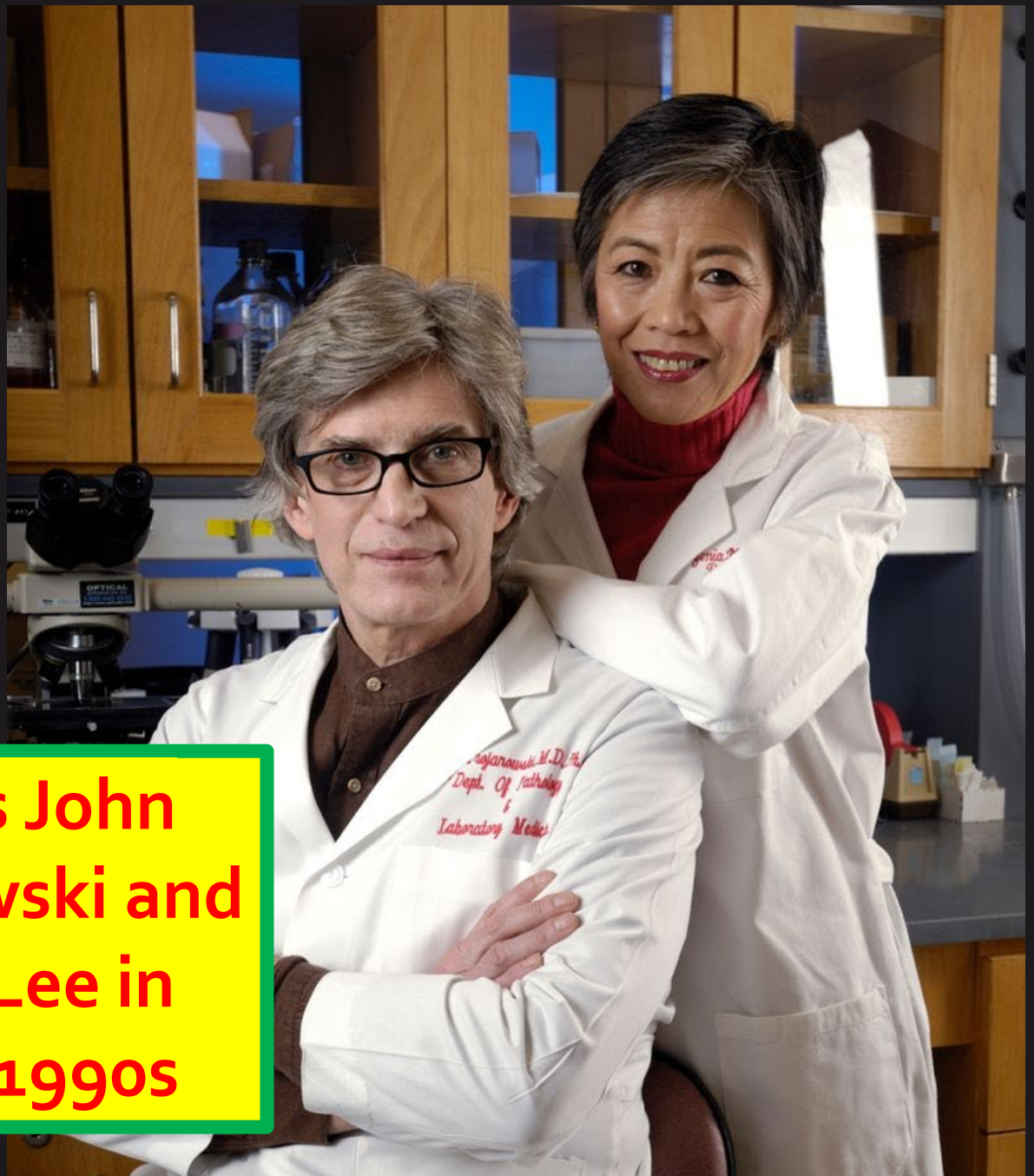
Pete Nelson

University of Kentucky
College of Medicine

A man lives for as long as we carry him inside us,
for as long as we carry the harvest of his dreams,
for as long as we ourselves live, holding memories in common,
a man lives.

Brian Patten*

*-This is an excerpt from *So Many Different Lengths Of Time* – a poem by Brian Patten. Thanks to Dr. Bernardino Ghetti for showing me this poem which was evocative to him of Dr. Trojanowski's memory.



I met Drs John Trojanowski and Virginia Lee in the mid-1990s

Pre-mid-1990s paradigm:

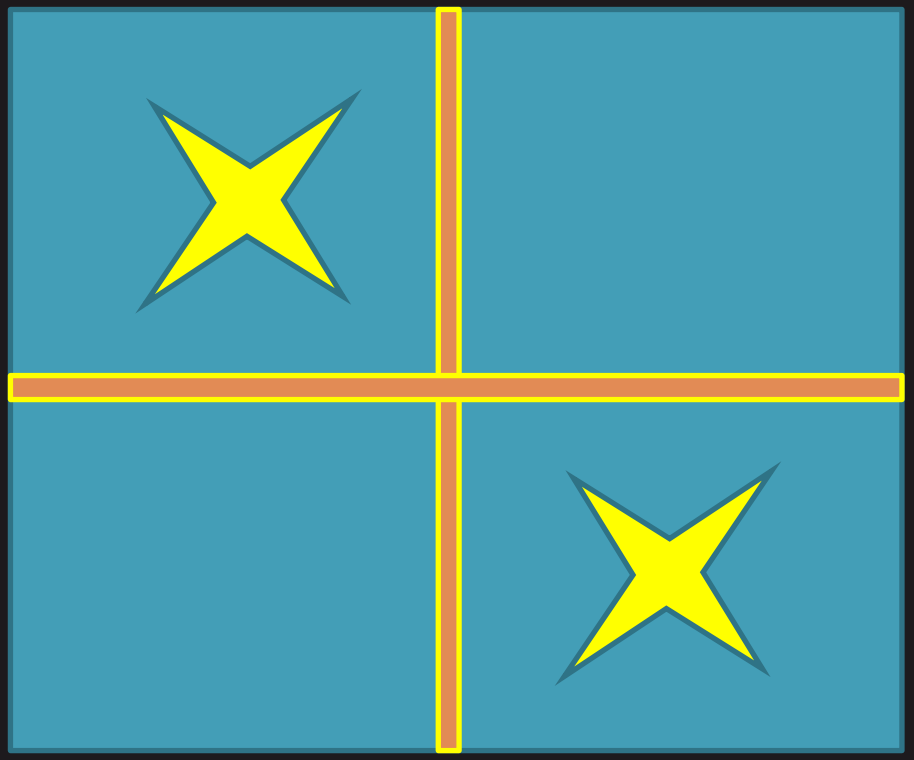
Alzheimer's disease pathology

NO YES

Dementia

NO

YES



Progress in understanding dementia phenotypes

Two recurrent themes:

Roles of Dr. Trojanowski

Roles of the ADRC system

Brain degeneration linked to “fatal attractions” of proteins in Alzheimer’s disease and related disorders

John Q. Trojanowski and Virginia M.-Y. Lee*
The Center for Neurodegenerative Disease Research, Department of Pathology and Laboratory Medicine, University of Pennsylvania School of Medicine, Philadelphia, PA, USA

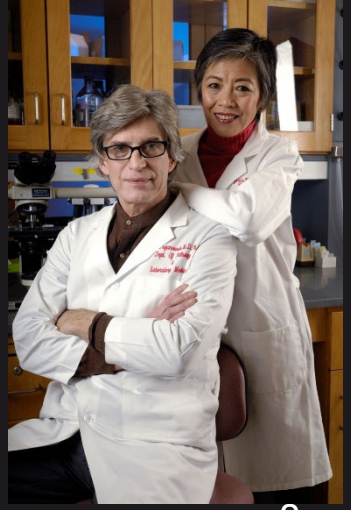
Table 1
Fatal protein attractions in neurodegenerative diseases

Disease	Lesion/Protein
AD	Plaques/Amyloid-beta
	Tangles/Tau
DS	Plaques/Amyloid-beta
	Tangles/Tau
	Lewy Bodies/Alpha-synuclein
	Lewy Neurites/Alpha-synuclein
LBVAD (AD + DLB)	Plaques/Amyloid-beta
	Tangles/Tau
	Lewy Bodies/Alpha-synuclein
	Lewy Neurites/Alpha-synuclein
PD	Lewy Bodies/Alpha-synuclein
	Lewy Neurites/Alpha-synuclein
	Neurites/Alpha-, Beta-synuclein
	Axonal Spheroids/Gamma-synuclein
DLB	Lewy Bodies/Alpha-synuclein
	Lewy Neurites/Alpha-synuclein
	Neurites/Alpha-, Beta-synuclein
	Axonal Spheroids/Gamma-synuclein
MSA	Glial Inclusions/Alpha-synuclein
NBIA 1	Lewy Bodies/Alpha-synuclein
	Lewy Neurites/Alpha-synuclein
	Glial Inclusions/Alpha-synuclein
PSP/CBD	Tangles/Tau
Pick’s Disease	Tangles/Tau
FTDP-17	Tangles/Tau
ALS	Axonal Spheroids/Neurofilaments, SOD1
Trinucleotide Repeat Diseases	Nuclear Inclusions/Polyglutamine Tracts
NIID	Nuclear Inclusions/Polyglutamine Tracts
Prion Diseases	Plaques/Prions

J. Alzheimers Dis.
2001 Feb;3(1):117-119

1997/8:

Helluva year



2007 & 2009
FTLD Consortium

2013
ARTAG

2013
PART

2017
DLB
Consortium

Timeline →

Dr. Trojanowski
1997/1998:
Potamkin Prize
President of AANP
NIA-Reagan
Consensus
Synuclein paper

2006
TDP-43

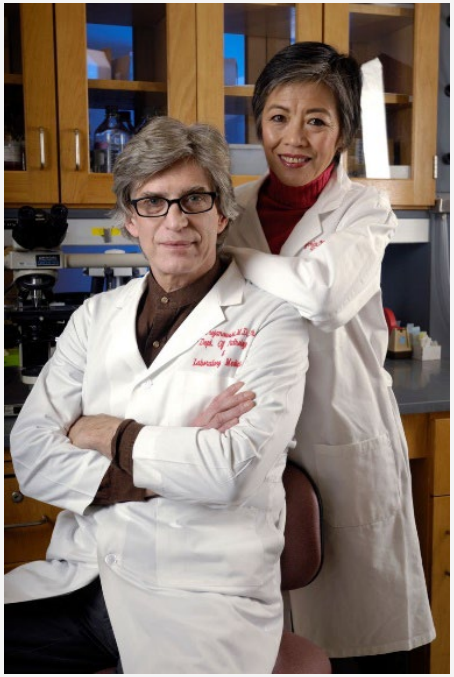
2008
Consensus
on MSA

2012
NIA-AA ADNC
Consensus

2019
LATE
Consensus

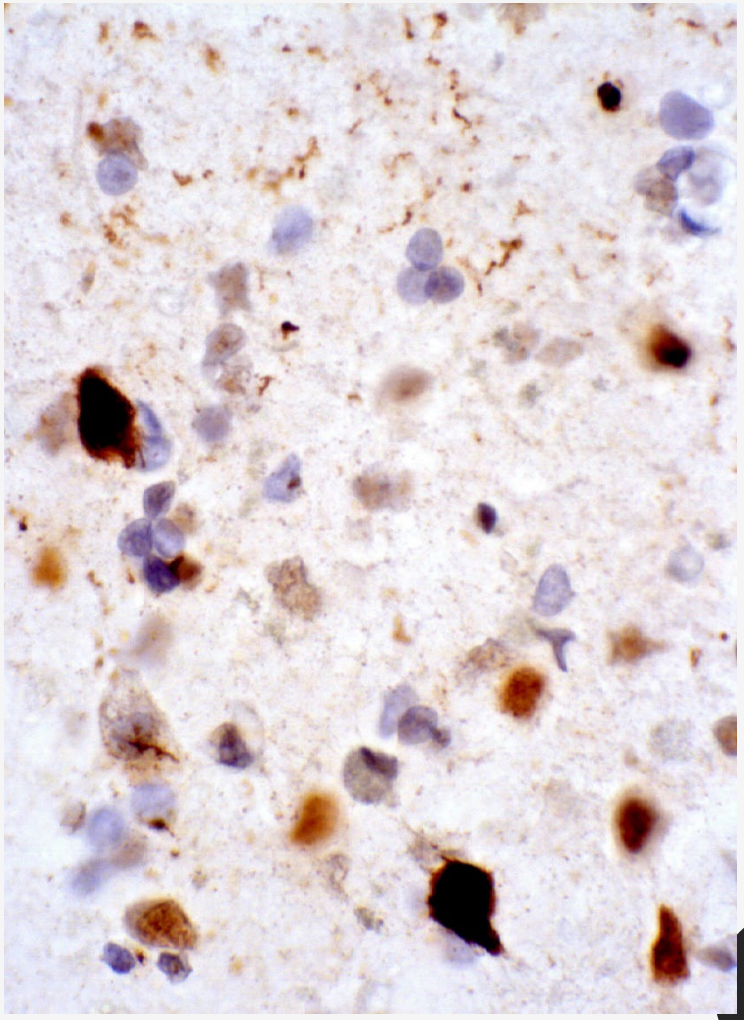
John Trojanowski was coauthor on all of these!

ALS/FTLD spectrum



Dr. Manuela Neumann
Dr. John Trojanowski
Dr. Virginia Lee
Et al
2006, *Science*

TDP-43 proteinopathy



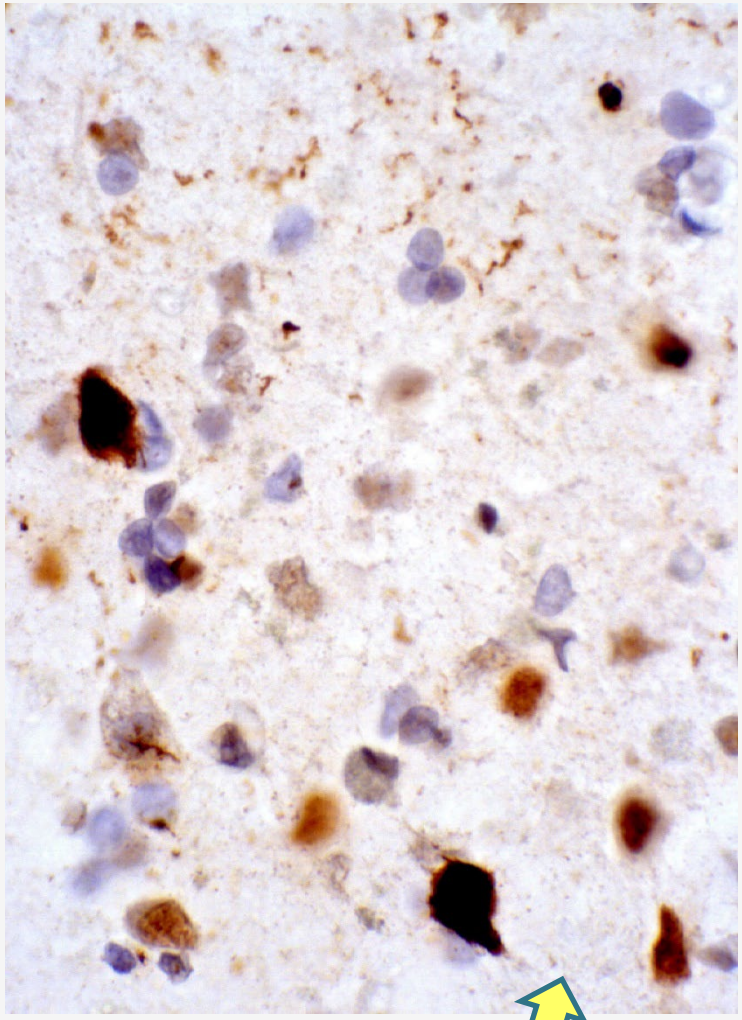
ALS/FTLD-TDP spectrum

Brain trauma (chronic)

Various degenerative conditions

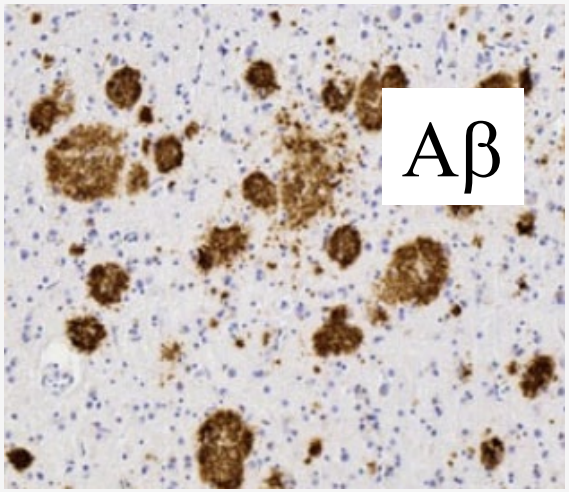
Developmental, neoplastic, & other diseases

TDP-43 proteinopathy



MOST COMMON: LATE

Misfolding proteinopathies are complex, and prevalent comorbid pathologies strongly influence the clinical and pathologic phenotypes



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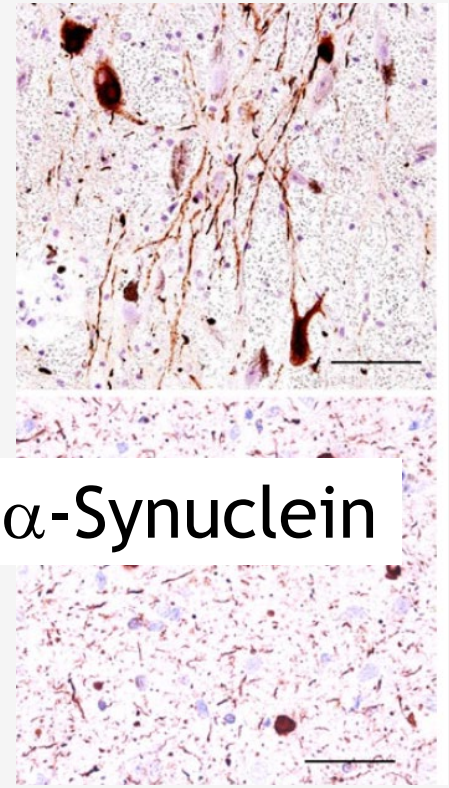
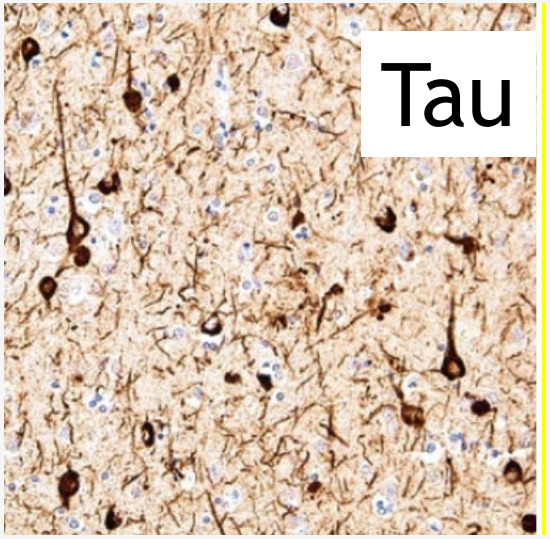
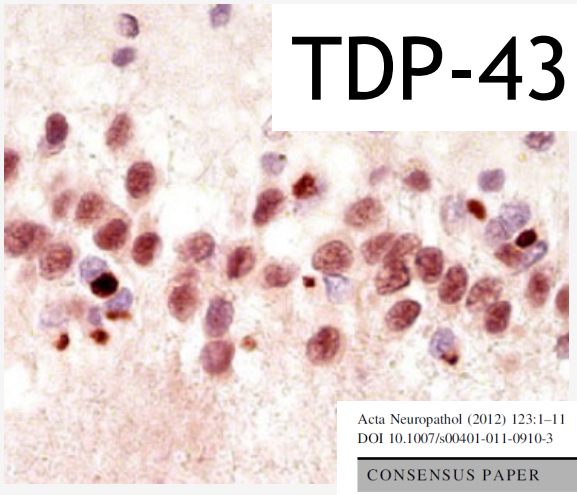






Acta Neuropathol (2012) 123:1–11
DOI 10.1007/s00401-011-0910-3

CONSENSUS PAPER

National Institute on Aging–Alzheimer's Association guidelines for the neuropathologic assessment of Alzheimer's disease: a practical approach

Thomas J. Montine · Creighton H. Phelps · Thomas [illegible]ach · Eileen H. Bigio · Nigel J[illegible]rns · Dennis W. Dickson · Charles Duyckaerts · Matthew [illegible]rosch · Eliezer Masliah · Suzanne [illegible]Hirra · Peter T. Nelson · Julie A. Schneider · Dietmar Rud[illegible]thal · John Q. Trojanowski · Harry V. Vinters · Bradley T. Hyman

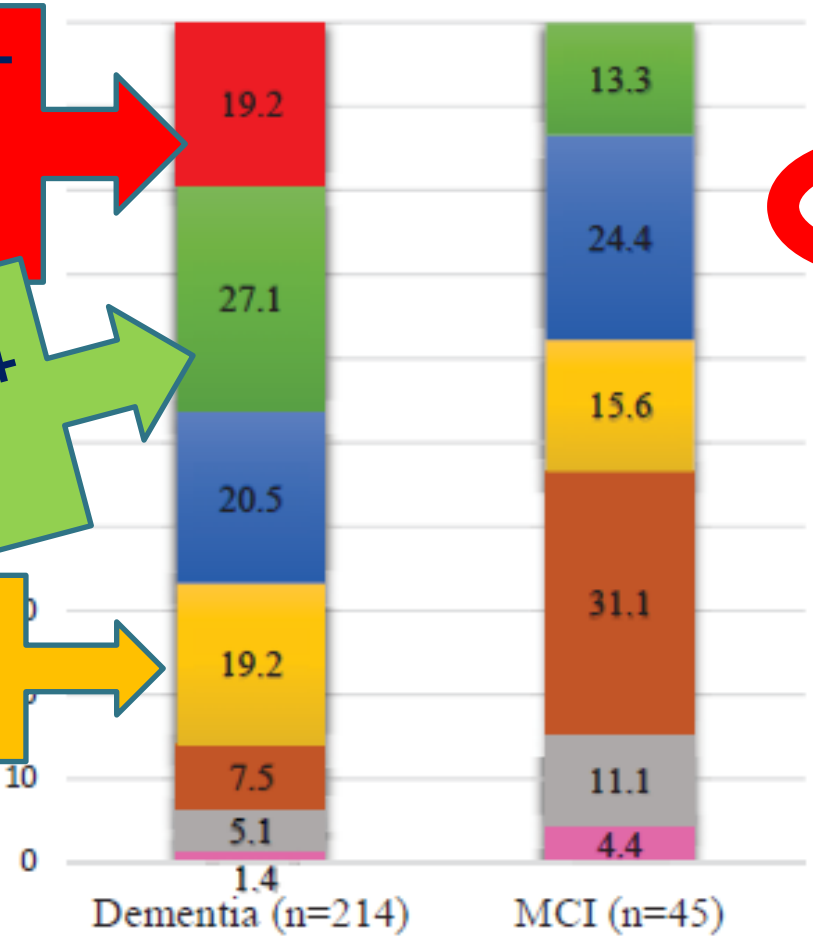
Dr. Shama Karanth

Dr. Erin Abner

LATE+ AD+ LBD

LATE+ AD

"Pure AD"

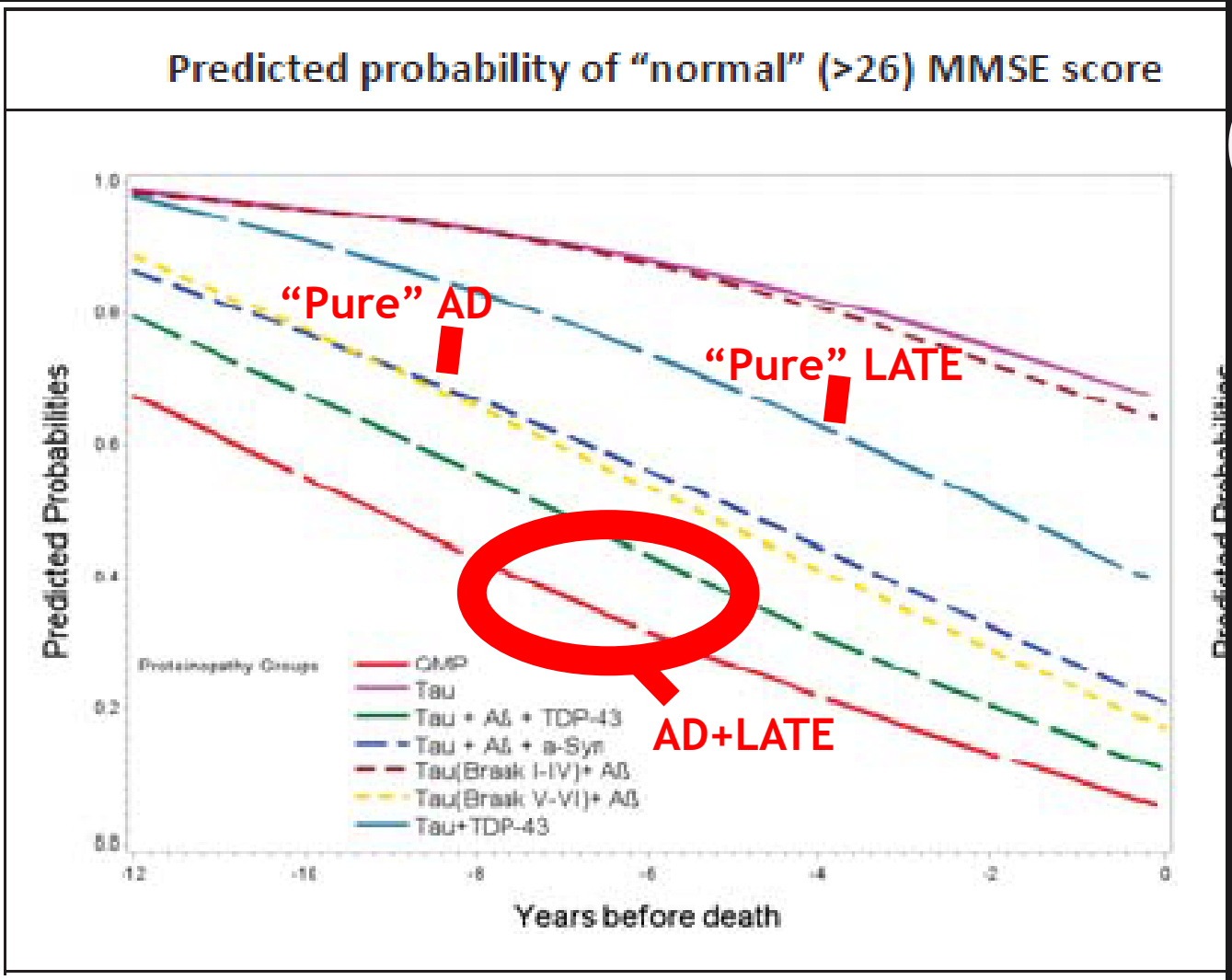


Karanth et al, JAMA Neurol 2020

Average length of yearly longitudinal follow-up: over 10 years

Dr. Shama Karanth

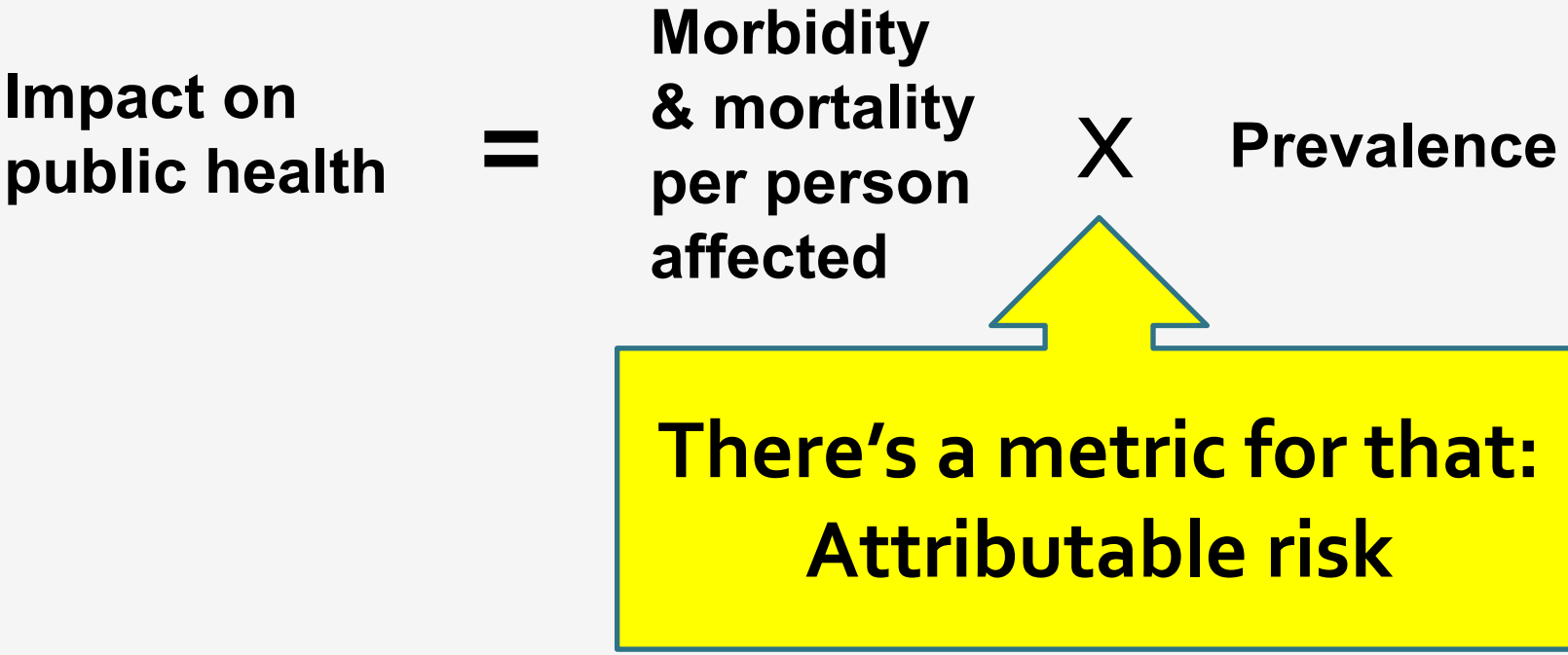
Dr. Erin Abner



Karanth et al, JAMA Neurol 2020

Impact on public health = Morbidity & mortality per person affected X Prevalence

There's a metric for that: Attributable risk



What %age of AD-type (amnestic) dementia in a population is attributable to LATE-NC?

Kudos to Dr. Schneider & Rush U team!

LATE-NC

Implication: ~15-20% of assigned "AD-type dementia" risk attributable to LATE-NC

Table 2 A statistical analysis of attributable risk from research volunteers in two clinical pathological studies of ageing from Rush University

Neuropathological indices	Fraction attributable % (95% CI)[a]
Alzheimer's disease (ADNC)	39.4 (31.5–47.4)
Vascular disease pathology[b]	24.8 (17.3–32.1)
LATE-NC	**17.3** (13.1–22.0)
α-Synucleinopathy/Lewy body pathology	11.9 (8.4–15.6)

Shown are fractions of dementia of the Alzheimer type cases that were attributable to individual neuropathological indices in advanced age. In this sample, the mean age of death was 89.7 years (SD 6.5 years, range 65–108 years). For these analyses, multivariable logistic regression models examined associations of neuropathological indices with the outcome of Alzheimer's-type clinical dementia and quantified the percentage of cases attributable to each. Methods have been described in detail previously (Boyle *et al.*, 2019). These data give strong indication that the public health impact of LATE is large, on the same order of magnitude as ADNC, vascular pathologies, and Lewy body pathology.

[a]95% CIs were derived using bootstrapping.

[b]Vascular pathologies included: cerebral amyloid angiopathy, atherosclerosis, arteriolosclerosis and gross infarcts.

~40% of assigned "AD-type dementia" risk is attributable to ADNC (plaques/tangles)

Brain, 2019

Challenges (prior to 2019)

No prior consensus-based effort had tackled TDP-43 in aging.

There was no standard or even common terminology.

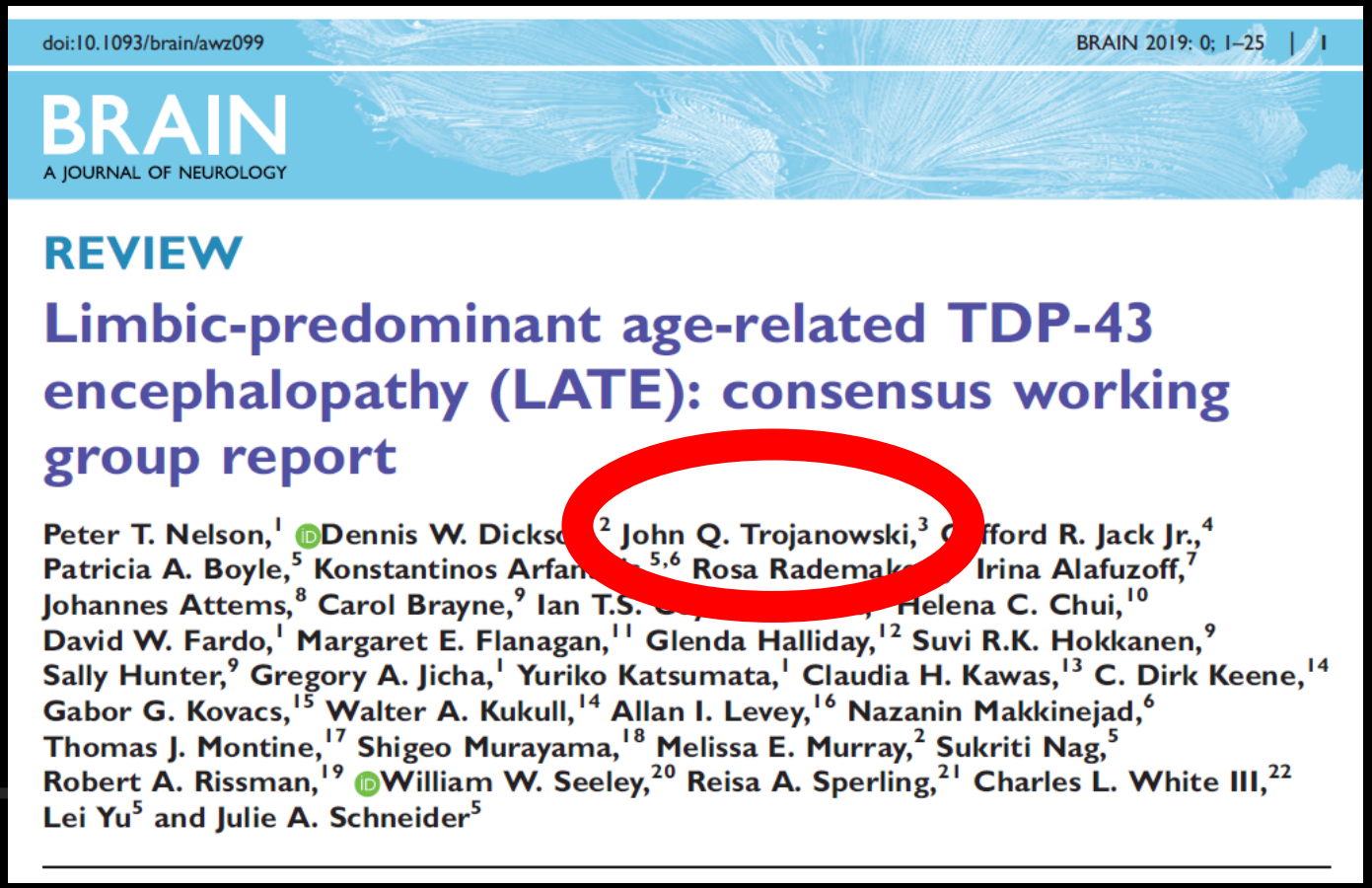
A very under-appreciated, under-studied clin-path phenomenon.

Opportunities

Classification and terminology were needed to help…

- **Enable autopsy diagnosis (“standardize the gold standard”)**
- **Increase awareness of this condition**
- **Catalyze research**
  - **Diagnostic studies – specific biomarkers required**
  - **Important therapeutic target in its own right**
  - **Key consideration in AD clinical trials**
  - **Animal models and other experimental contexts**
  - **Genetics, risk factors, and many other correlates**
- **Enable a “common language” across disciplines**

NIH-sponsored, international, multi-disciplinary group of experts, after 6 months in subcommittees, teleconferences, and then a 2 day in-person meeting, wrote a report with recommendations



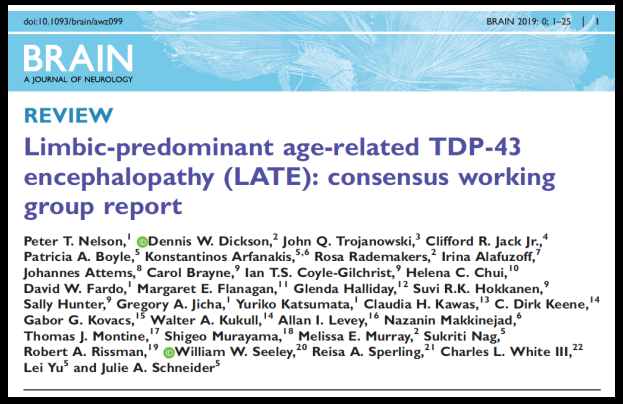
doi:10.1093/brain/awz099 BRAIN 2019: 0; 1–25 | 1

BRAIN
A JOURNAL OF NEUROLOGY

REVIEW

Limbic-predominant age-related TDP-43 encephalopathy (LATE): consensus working group report

Peter T. Nelson,[1] Dennis W. Dickso[2] John Q. Trojanowski,[3] C[ ]fford R. Jack Jr.,[4] Patricia A. Boyle,[5] Konstantinos Arfan[ ][5,6] Rosa Rademak[ ] Irina Alafuzoff,[7] Johannes Attems,[8] Carol Brayne,[9] Ian T.S. C[ ] Helena C. Chui,[10] David W. Fardo,[1] Margaret E. Flanagan,[11] Glenda Halliday,[12] Suvi R.K. Hokkanen,[9] Sally Hunter,[9] Gregory A. Jicha,[1] Yuriko Katsumata,[1] Claudia H. Kawas,[13] C. Dirk Keene,[14] Gabor G. Kovacs,[15] Walter A. Kukull,[14] Allan I. Levey,[16] Nazanin Makkinejad,[6] Thomas J. Montine,[17] Shigeo Murayama,[18] Melissa E. Murray,[2] Sukriti Nag,[5] Robert A. Rissman,[19] William W. Seeley,[20] Reisa A. Sperling,[21] Charles L. White III,[22] Lei Yu[5] and Julie A. Schneider[5]



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Brain, 2019

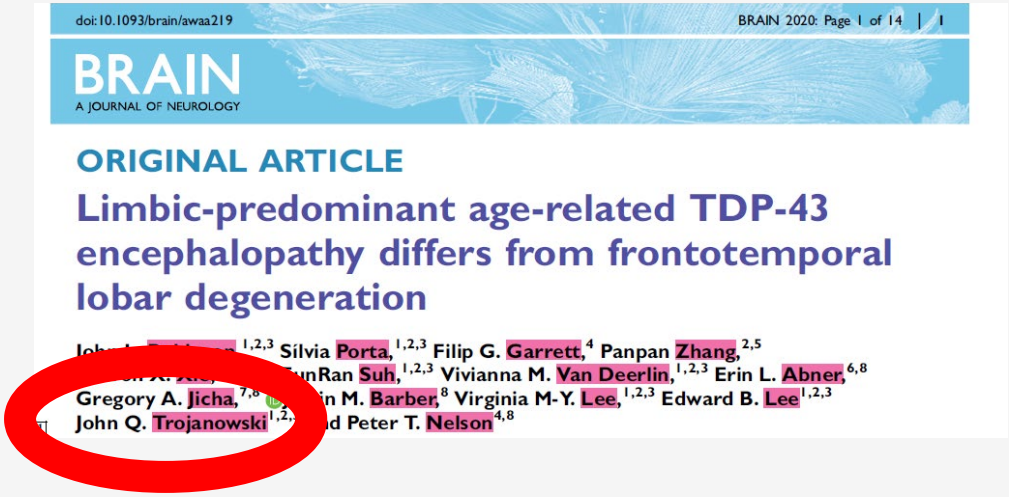
Neuropathology-based diagnosis, classification, and staging

LATE-NC features

- A sampling and staging system for routine autopsy diagnosis is proposed to characterize the anatomical distribution of TDP-43 proteinopathy
  - Stage 1: amygdala only
  - Stage 2: + hippocampus
  - Stage 3: + middle frontal gyrus
- Hippocampal sclerosis pathology may be observed (and should be reported), but is neither necessary nor sufficient for diagnosis of LATE-NC

Kudos to Drs. Dickson and Josephs & Mayo Clinic team!

How specific is the pathology of LATE?


doi:10.1093/brain/awaa219 BRAIN 2020: Page 1 of 14 | 1

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ORIGINAL ARTICLE

Limbic-predominant age-related TDP-43 encephalopathy differs from frontotemporal lobar degeneration

[illegible][1,2,3] Sílvia Porta,[1,2,3] Filip G. Garrett,[4] Panpan Zhang,[2,5] [illegible]unRan Suh,[1,2,3] Vivianna M. Van Deerlin,[1,2,3] Erin L. Abner,[6,8] Gregory A. Jicha,[7,8] [illegible]n M. Barber,[8] Virginia M-Y. Lee,[1,2,3] Edward B. Lee[1,2,3] John Q. Trojanowski[1,2,] [illegible]d Peter T. Nelson[4,8]

U. Kentucky & UPENN ADRCs

JL Robinson et al, *Brain* 2020

The pathology of LATE-NC is *significantly* different from the pathology of FTLD-TDP

LATE vs FTLD-TDP

- Both: TDP-43 pathology
- Different neuroanatomy
- Mostly different symptoms
- Mostly different age predisposition
- LATE far (~100x) more prevalent

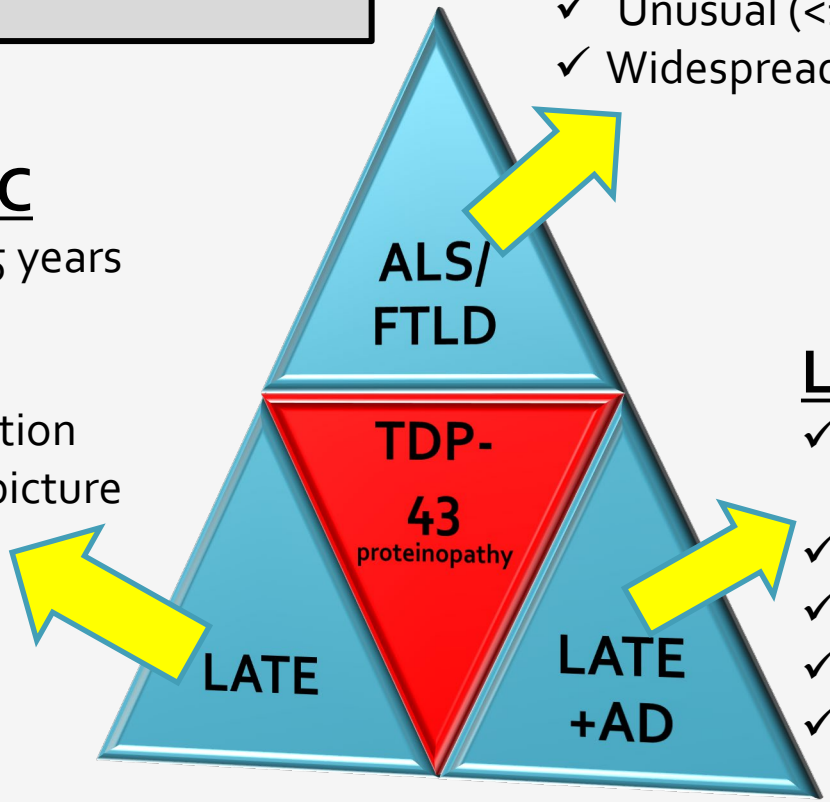
Clinical and pathological phenotypes of age related TDP43 proteinopathy

FTLD-TDP

- ✓ Average age at autopsy <75 years
- ✓ Behavioral, psychiatric, or language predominant presentation
- ✓ Unusual (<1:1000 lifetime risk)
- ✓ Widespread neocortical pathology

"Pure" LATE-NC

- ✓ Age at autopsy >85 years
- ✓ Duration of MCI prolonged
- ✓ Amnestic presentation
- ✓ Not a FTD clinical picture
- ✓ Common (~1:10)
- ✓ Limbic TDP-43



LATE-NC + ADNC

- ✓ Average age at autopsy >80years
- ✓ Swiftest clinical course
- ✓ +LBs – even worse
- ✓ Very common (~1:3)
- ✓ Limbic TDP-43

Thanks to Dr. Jicha

Follow-up questions:

Does LATE-NC *often* occur in the absence of either AD pathology or FTD clinical syndrome?

Does LATE-NC tend to *eventually* progress to FTLD-TDP?

Follow-up questions and answers:

Does LATE-NC *often* occur in the absence of either AD pathology or FTD clinical syndrome?

YES

Does LATE-NC tend to *eventually* progress to FTLD-TDP?

NO

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Editorial | Open Access | Published: 12 April 2022

Remembering John Q Trojanowski, in his own words: A life dedicated to discovering building blocks and using them to build bridges of knowledge, collaboration, and discovery

Hilal A. Lashuel

When (Dr. Trojanowski was) asked … to name one pathway that is the cause of (Alzheimer's) disease…?

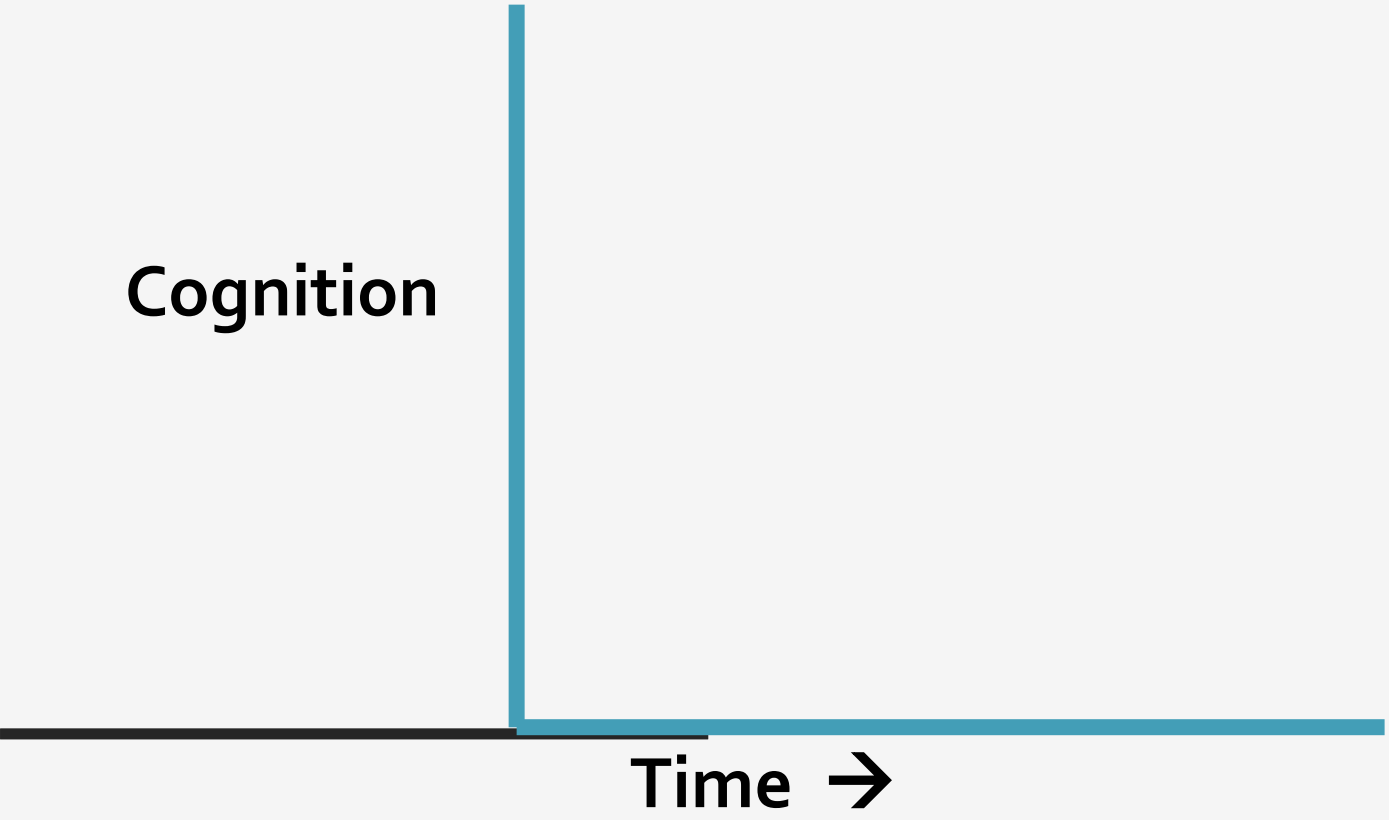
"Well, I think that's erroneous because AD is not one disease. …"

"I think the scientific community appreciates that we should think of Alzheimer "diseases" rather than one disease and the public, I hope, will also appreciate that. There are many forms of this dementia we call AD."

—John Trojanowski

LATE

Phenotypes addressed by clinical trials



LATE

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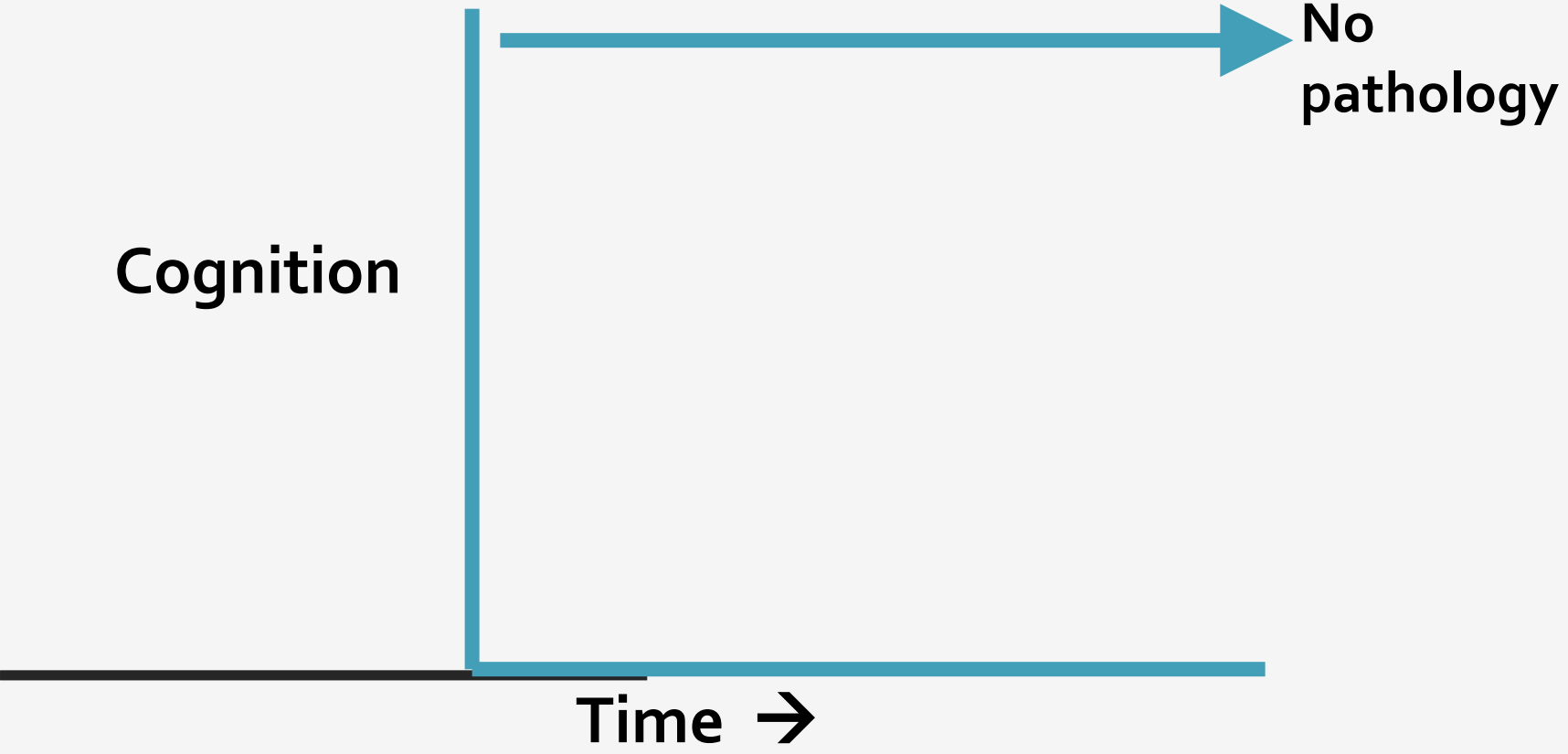

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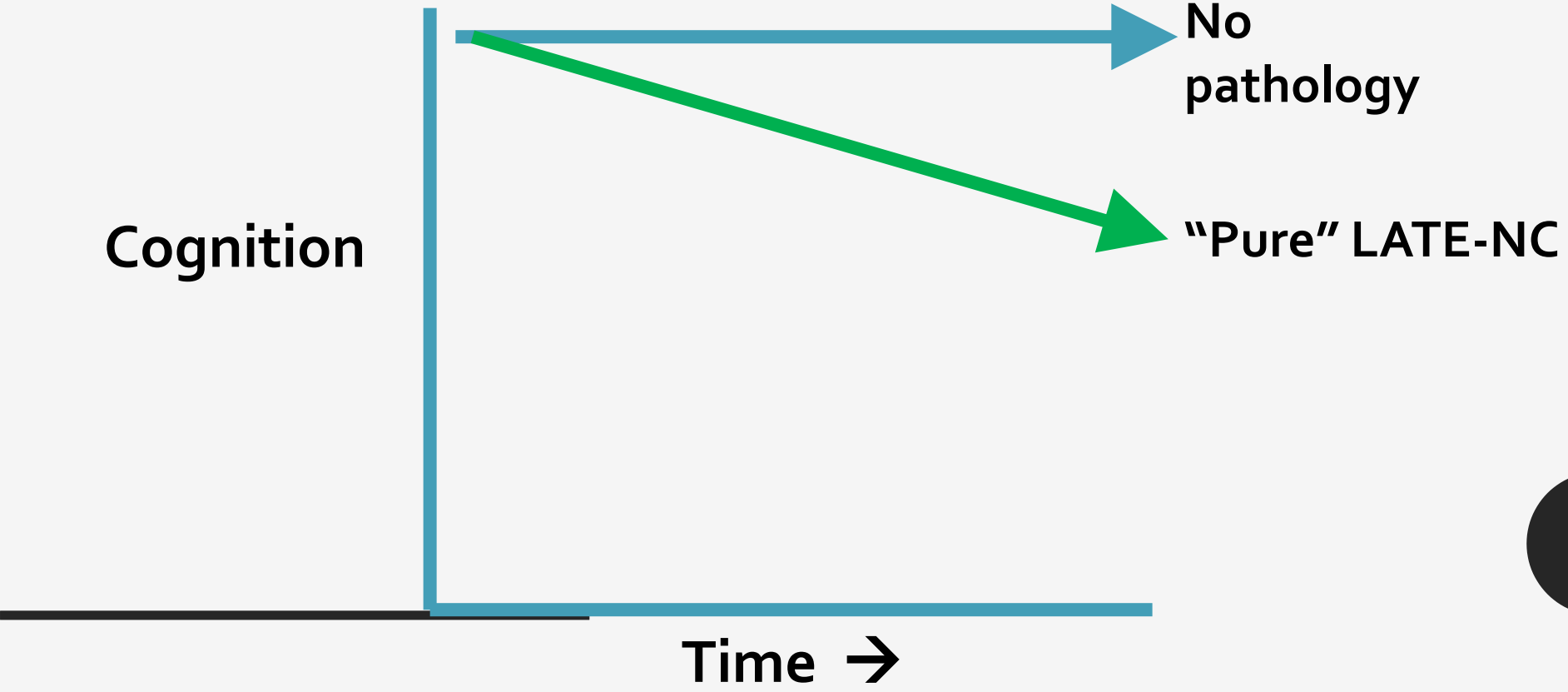

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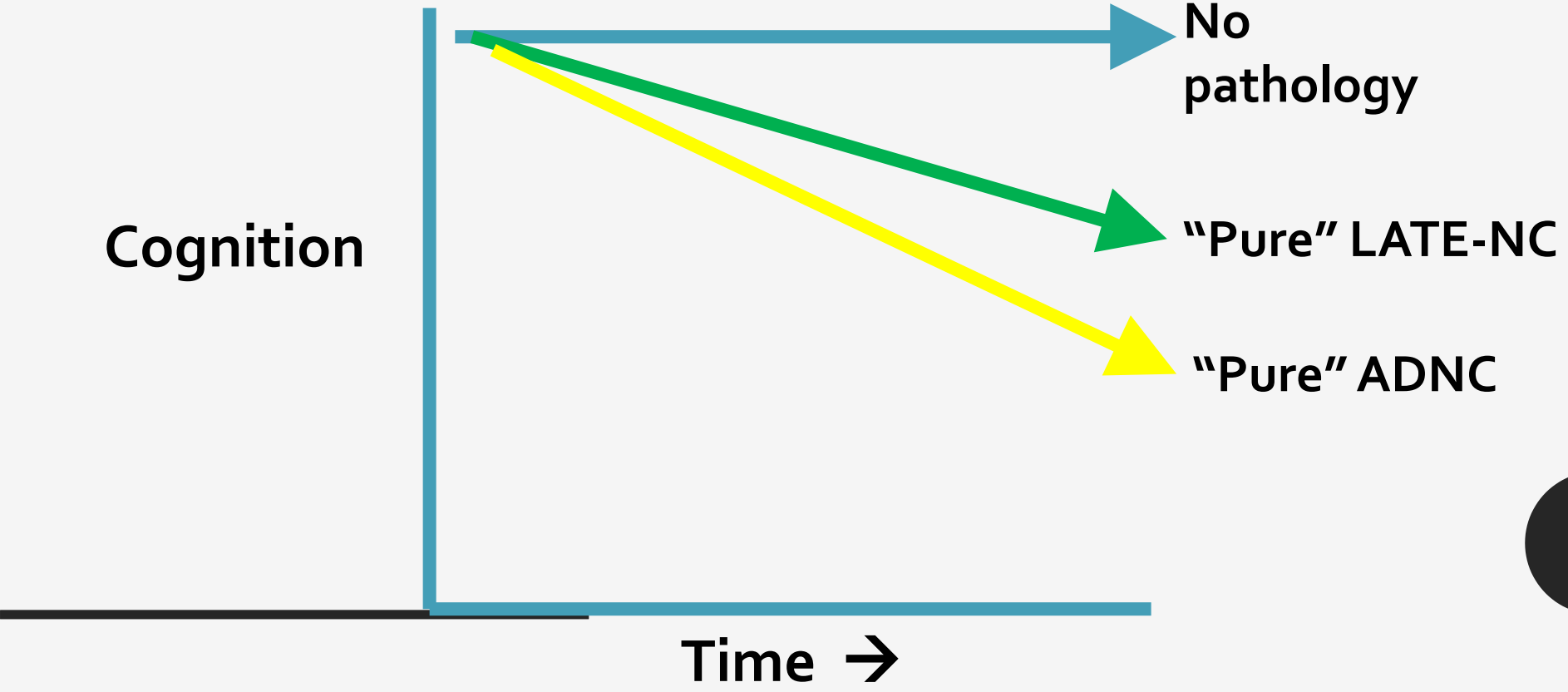

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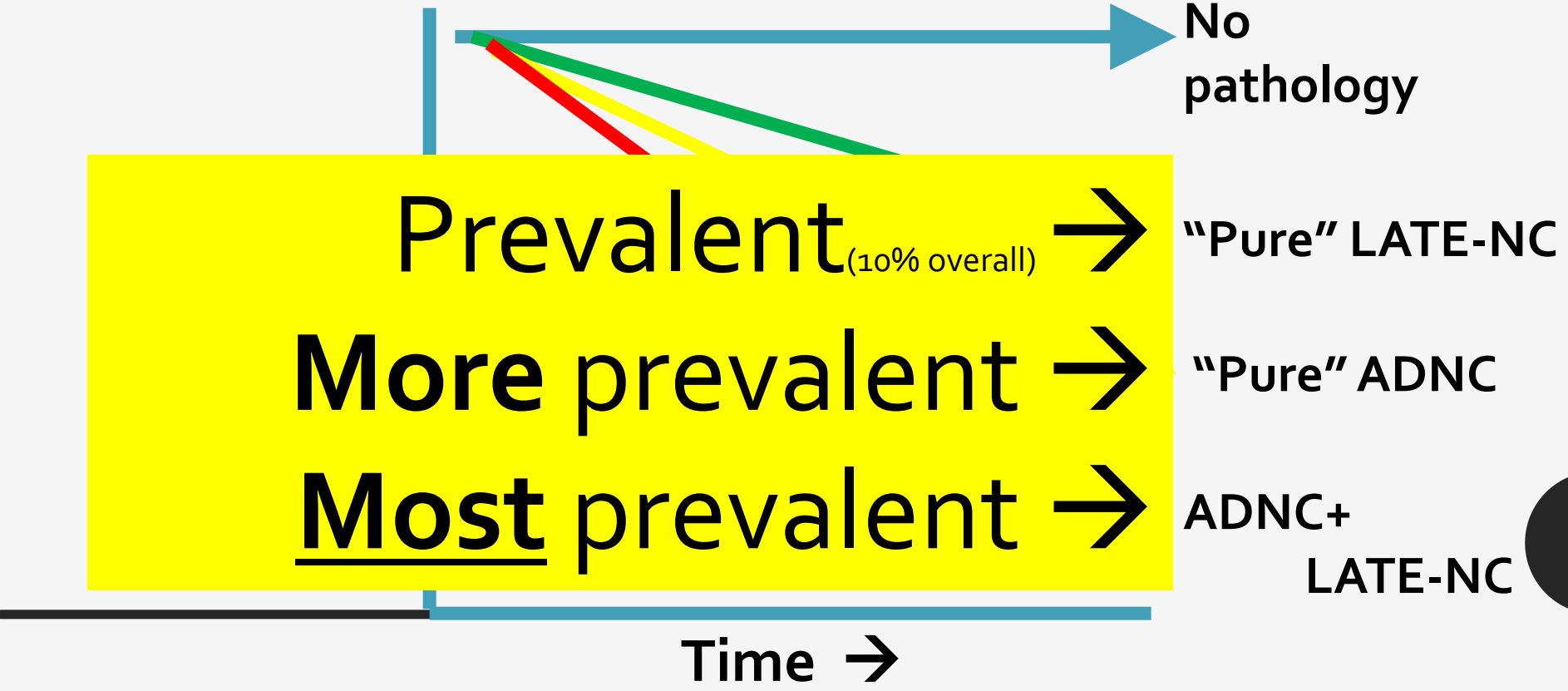

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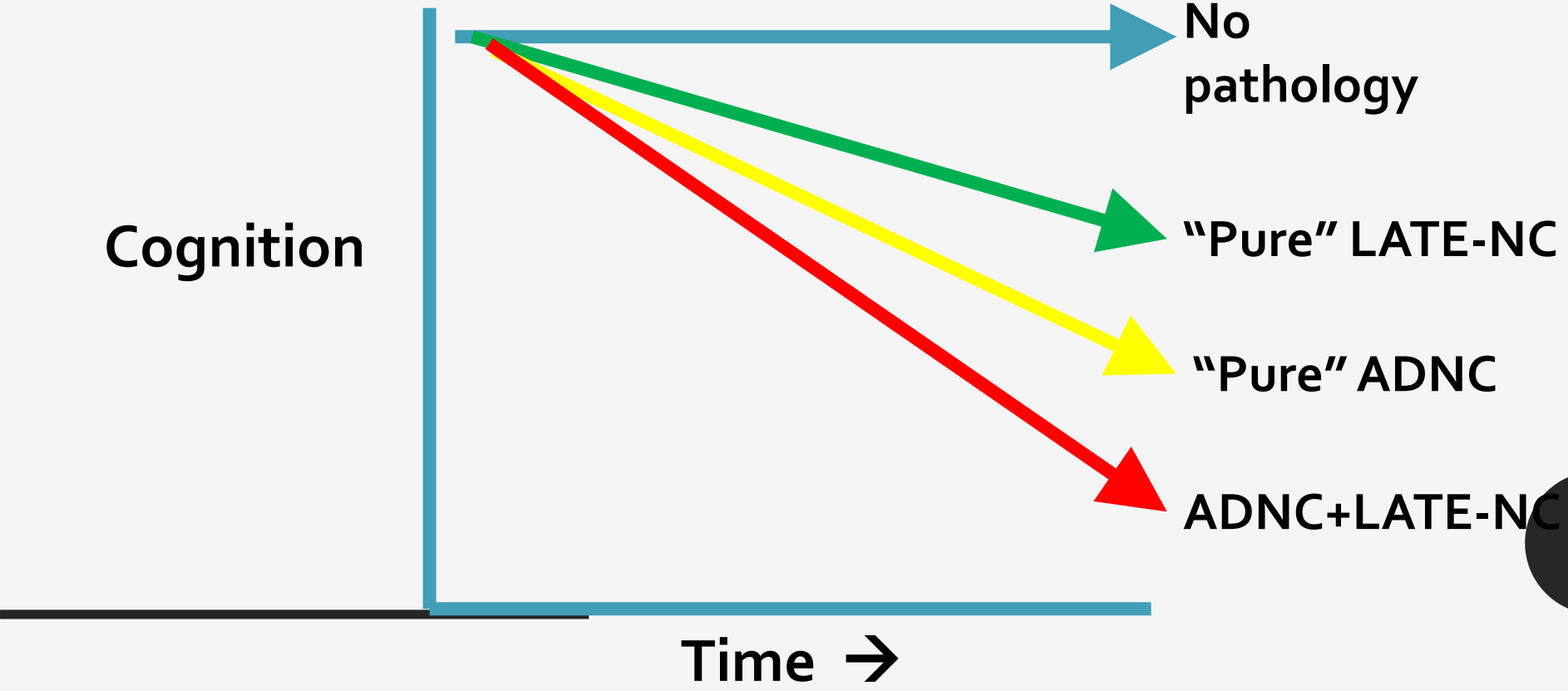
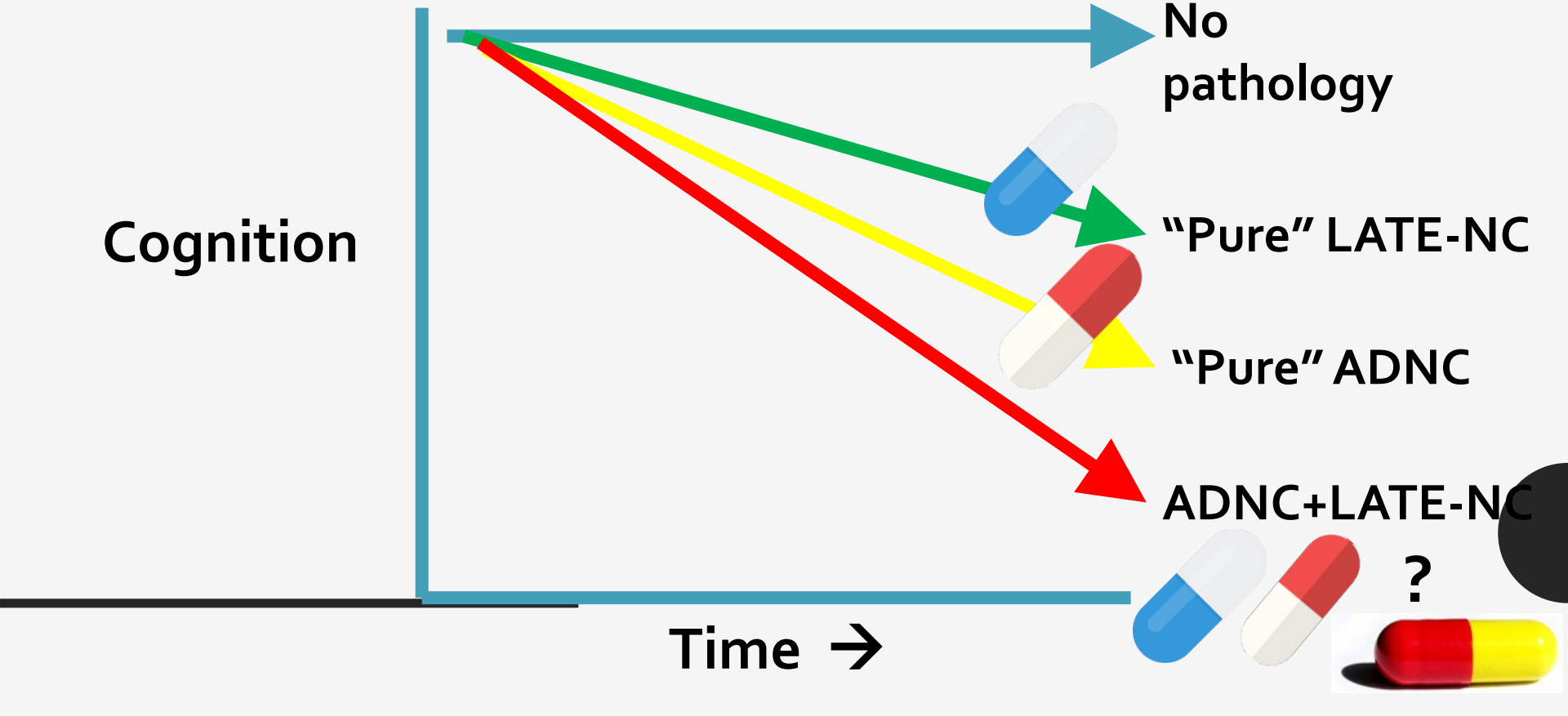
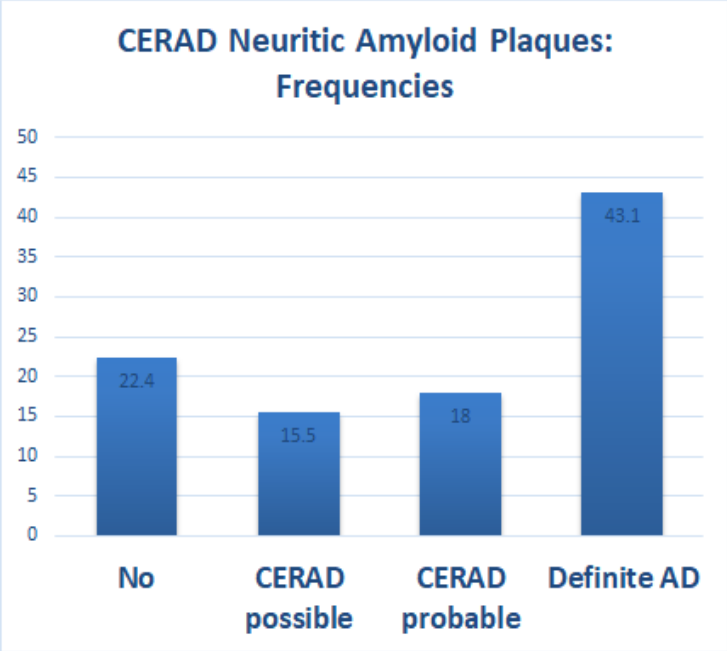


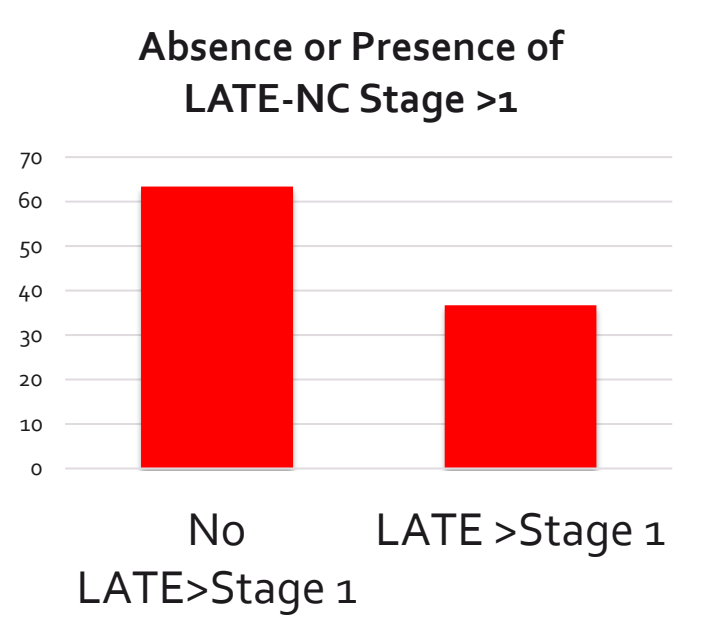
LATE

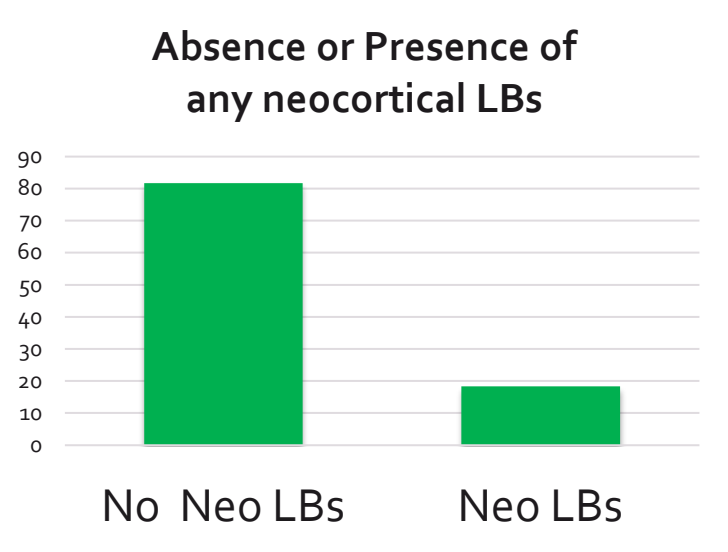
The future of clinical trials



2019-2021 Autopsied cases, UK-ADRC; n=60







LATE:

What it is:

Limbic-predominant age-related TDP-43 encephalopathy

Why it's important:

- **A common high-morbidity brain disease**
- **A helpful disease-related concept**
- **Part of a movement away from "dichotomous dementia/ dichotomous pathology" paradigm**

Roles of Dr. Trojanowski:

Many and various!

THANKS JOHN !!!!!