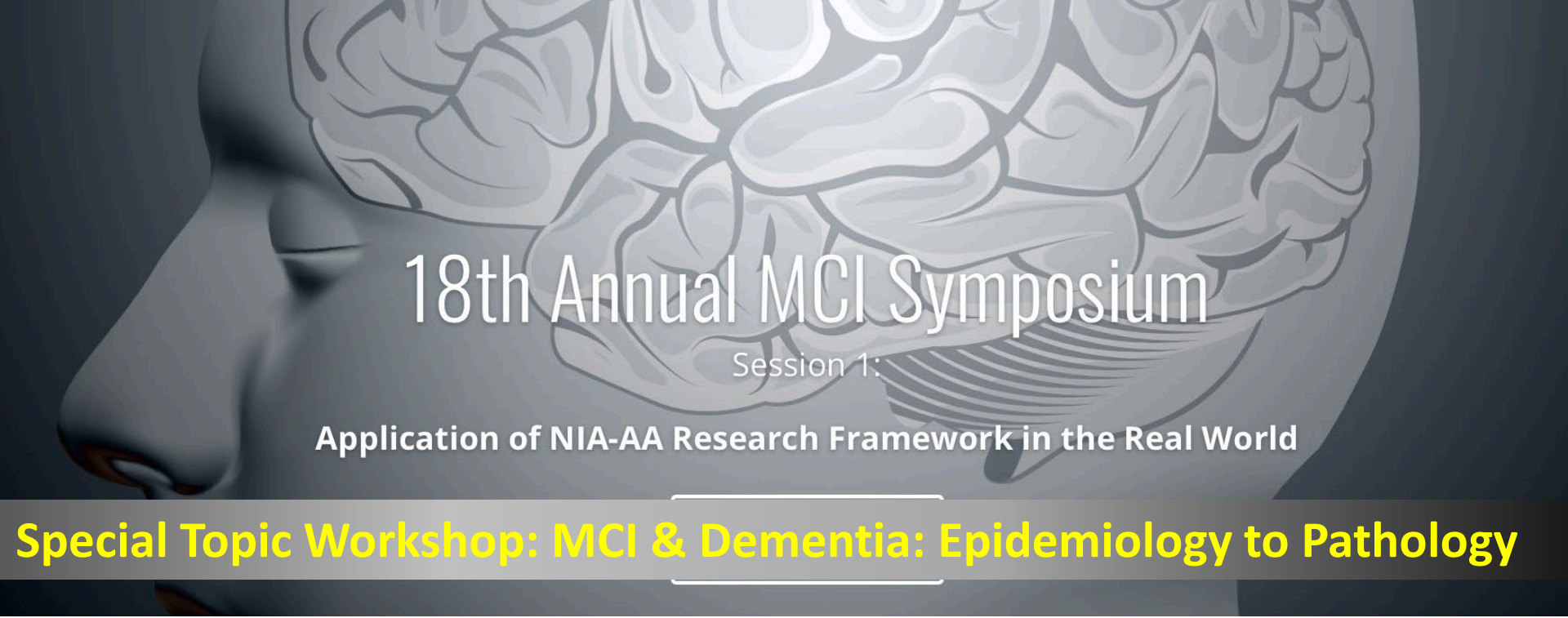


Special Topic Workshop: MCI & Dementia: Epidemiology to Pathology

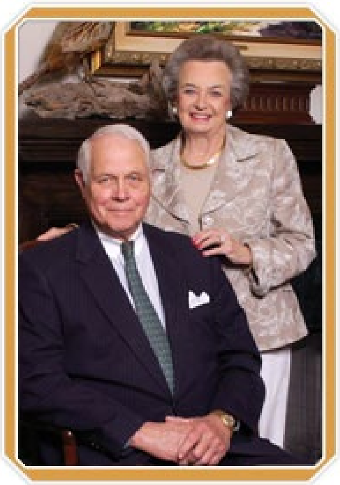
The NIA-AA Research Framework: Implications for Clinical Care, Epidemiological and Genetic/Biology Studies

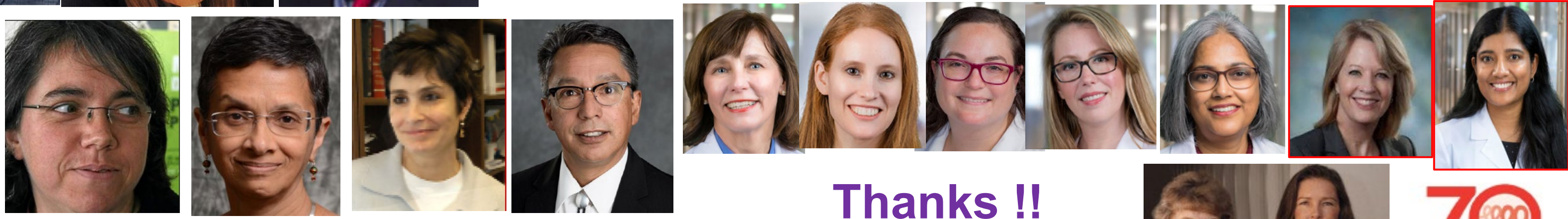
Sudha Seshadri, MD
Director, Glenn Biggs Institute For Alzheimer's
& Neurodegenerative Diseases; Senior Investigator, The Framingham Heart Study

Potential Conflicts of Interest:

None

Acknowledgements





UT Health San Antonio

Glenn Biggs Institute for Alzheimer's & Neurodegenerative Diseases

https://biggsinstitute.org/

Thanks !!

70 1948·2018 THANKS TO YOU

FRAMINGHAM HEART STUDY

BOSTON UNIVERSITY

NIA: U01 AG049505, U01 AG058589, R01 AG033040, AG061872
R01 AG049607, U01 AG052409, R01 AG054076, AG059421

NINDS: R01 AG017950, UH2 NS100605

NIDDK, NHLBI, Alzheimer Association

Greetings to Our Friends at the 18th Annual MCI Conference from the Biggs Family!

https://biggsinstitute.org/research/south-texas-alzheimers-conference/ Feb 23rd to 26th San Antonio, TX

Outline of Talk

A-T-N Criteria, Stages of Cognitive Impairment: Imperfectly Aligned Axes

A-T-N in Epidemiology: Impractical, Insufficient Explanation

A-T-N Framework in Clinical Care & Clinical Trials: Overlapping Biology

A-T-N in Genetic & Biological Studies: More Targets, Better Outcomes?

A-T-N Plus: What Next?

The Cognitive Continuum

- Age-related Cognitive Decline
- Subjective Cognitive Impairment or Objective Decline in 'normal' range
- Mild Cognitive Impairment
- **Dementia**

Normal Aging Versus Dementia

• Making a bad decision once in a while	• Making poor judgments and decisions a lot of the time
• Missing a monthly payment	• Problems taking care of monthly bills
• Forgetting which day it is and remembering later	• Losing track of the date or time of year
• Sometimes forgetting which word to use	• Trouble having a conversation
• Losing things from time to time	• Misplacing things often and being unable to find them
Occasional	Frequent, Persistent

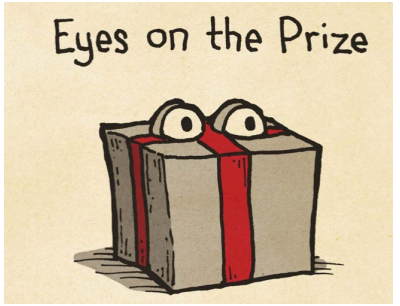
versus

Slow
versus
not at all!

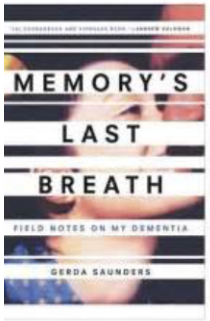
All dementia does NOT begin with memory or language problems;

Vision, personality, mood, walking, sleep changes can be 1st signs

What is Dementia?



- A syndrome
- Loss of memory and thinking abilities or changes in behavior
- Affects the person's ability to function as they used to and wish to



William Utermohlen:

Self potraits; dementia diagnosis at age 61, 1995

Alzheimer's Disease

1984

NINCDS-ADRDA Criteria

Clinical-Pathological definition

2011

NIA-AA Criteria

Clinical syndrome with biomarkers for amyloid and neurodegeneration

2018

NIA-AA Framework

Alzheimer's disease as a biological entity
defined by positive biomarkers for amyloid and tau

Clinical Spectra Independent

How early can we diagnose Alzheimer disease (and is it sufficient)?

The 2017 Wartenberg lecture

Ronald C. Petersen, PhD, MD

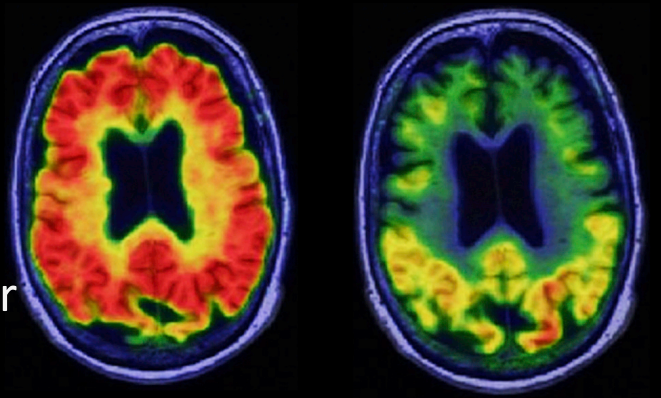
Neurology® 2018;91:395-402. doi:10.1212/WNL.0000000000006088

Correspondence
Dr. Petersen
peter8@mayo.edu

2018 ATN Alzheimer Disease Criteria: *the most frequently diagnosed dementia*

Amyloid+

A+ (amyloidosis) = Alzheimer
A- = No Alzheimer



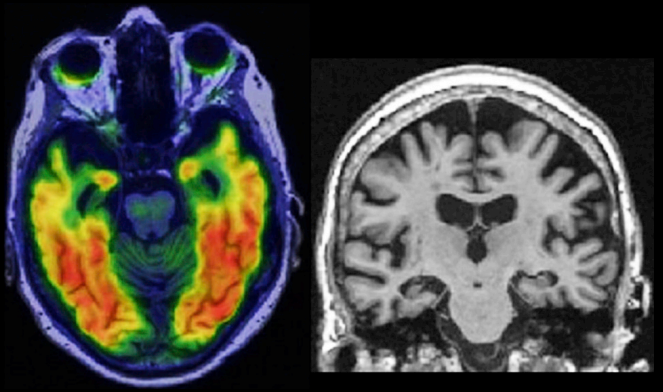
Tau +

CSF: Amyloid, p-tau

PET Imaging

Tau +

T-= Pathophysiological continuum
T+ = Disease



Neurodegeneration+

Alzheimer's & Dementia: The Journal of the Alzheimer's Association 2018 14, 535-562DOI: (10.1016/j.jalz.2018.02.018)

2018 National Institute on Aging—Alzheimer's Association (NIA-AA) Research Framework

NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease

AT(N) profiles	Biomarker category	
A-T-(N)-	Normal AD biomarkers	
A+T-(N)-	Alzheimer's pathologic change	A +
A+T+(N)-	Alzheimer's disease	Alzheimer's continuum
A+T+(N)+	Alzheimer's disease	
A+T-(N)+	Alzheimer's and concomitant suspected non Alzheimer's pathologic change	
A-T+(N)-	Non-AD pathologic change	
A-T-(N)+	Non-AD pathologic change	
A-T+(N)+	Non-AD pathologic change	

Initial Rationale: We should only treat people with X (amyloid) 'lowering' drugs if X levels are 'high', so A+

Supporting Rationale:
If we treat persons with high amyloid early, before clinical symptoms, perhaps we can prevent clinical symptoms

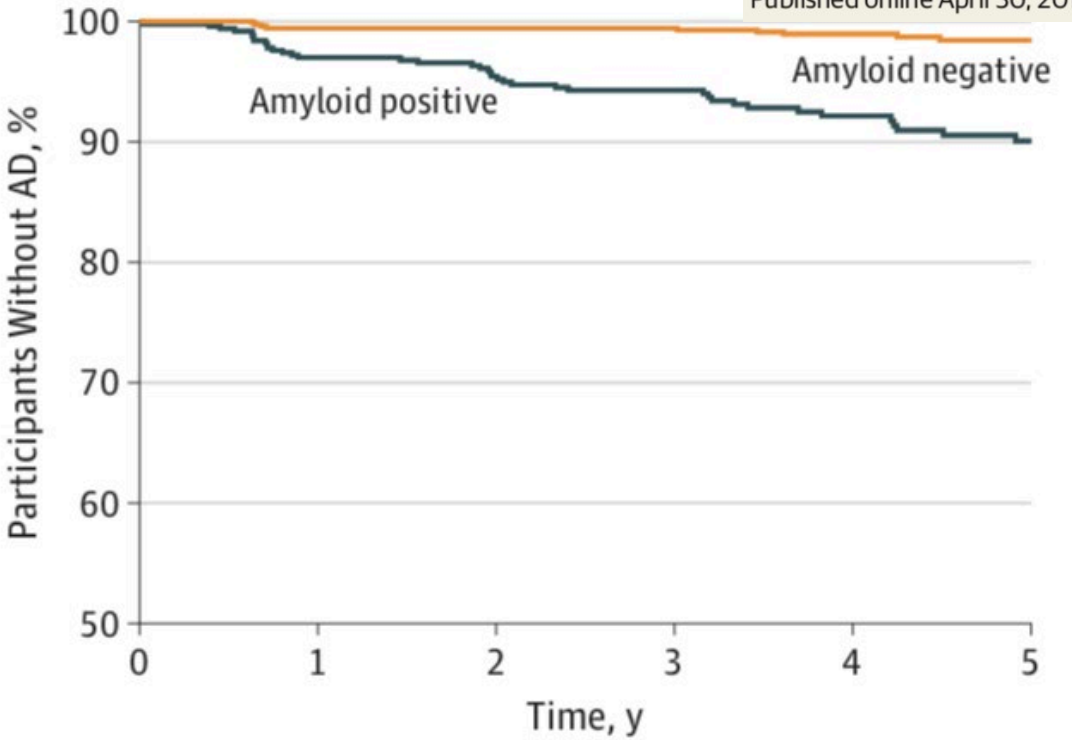
PET Imaging

CSF Levels

Blood levels

Percentage of participants with no cognitive impairment or aMCI without AD dementia over time

JAMA Neurol. 2018;75(8):970-979. doi:10.1001/jamaneurol.2018.0629
Published online April 30, 2018.



No. at risk (events)						
Amyloid positive	520 (0)	481 (15)	420 (22)	334 (27)	248 (34)	193 (39)
Amyloid negative	1110 (0)	1048 (6)	903 (6)	669 (6)	418 (9)	294 (11)

Population prevalence of amyloid +ve status in Rochester, MN:

3% at 50-59
41% at 80-89

AT(N) profiles	Biomarker category	
A-T-(N)-	Normal AD biomarkers	
A+T-(N)-	Alzheimer's pathologic change	Alzheimer's continuum
A+T+(N)-	Alzheimer's disease	
A+T+(N)+	Alzheimer's disease	
A+T-(N)+	Alzheimer's and concomitant suspected non Alzheimer's pathologic change	
A-T+(N)-	Non-AD pathologic change	
A-T-(N)+	Non-AD pathologic change	
A-T+(N)+	Non-AD pathologic change	

2018 National Institute on Aging—Alzheimer's Association (NIA-AA) Research Framework

NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease

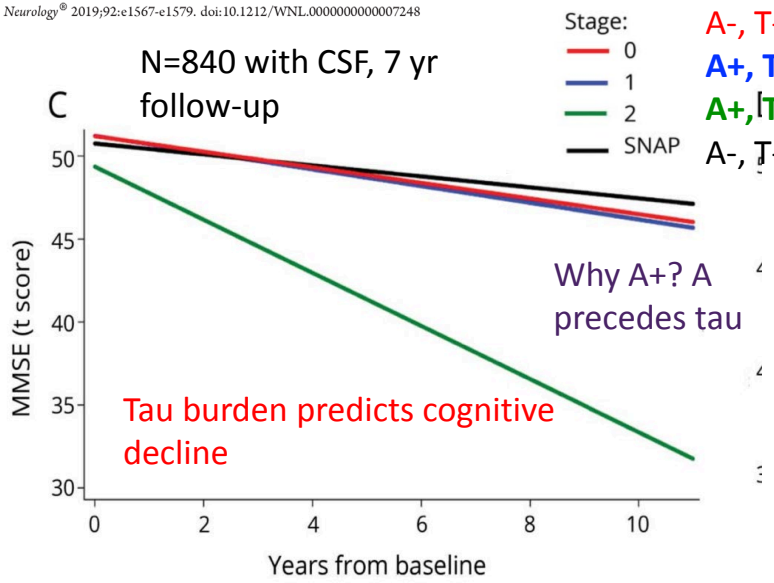
ATN profiles among cognitively normal individuals and longitudinal cognitive outcomes

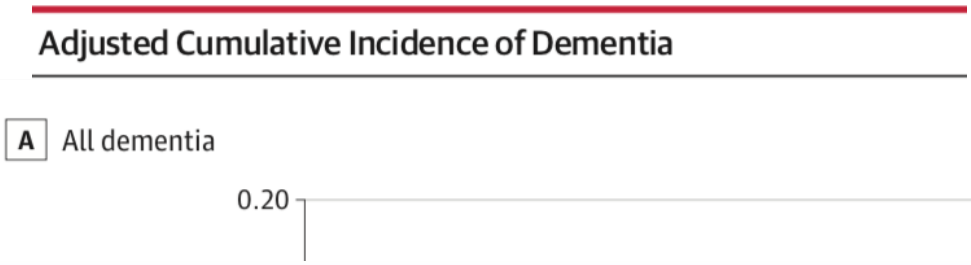
Anja Soldan, PhD, Corinne Pettigrew, PhD, Anne M. Fagan, PhD, Suzanne E. Schindler, MD, Abhay Moghekar, MBBS, Christopher Fowler, PhD, Qiao-Xin Li, PhD, Steven J. Collins, MD, Cynthia Carlsson, MD, Sanjay Asthana, MD, Colin L. Masters, MD, Sterling Johnson, PhD, John C. Morris, MD, Marilyn Albert, PhD, and Alden L. Gross, PhD

Correspondence
Dr. Soldan
asoldan1@jhmi.edu

Neurology® 2019;92:e1567-e1579. doi:10.1212/WNL.0000000000007248

N=840 with CSF, 7 yr follow-up





JAMA Neurology | Original Investigation

Assessment of Plasma Total Tau Level as a Predictive Biomarker for Dementia and Related Endophenotypes

Matthew P. Pase, PhD; Alexa S. Beiser, PhD; Jayandra J. Himali, PhD; Claudia L. Satizabal, PhD; Hugo J. Aparicio, MD; Charles DeCarli, MD; Geneviève Chêne, MD, PhD; Carole Dufouil, PhD; Sudha Seshadri, MD

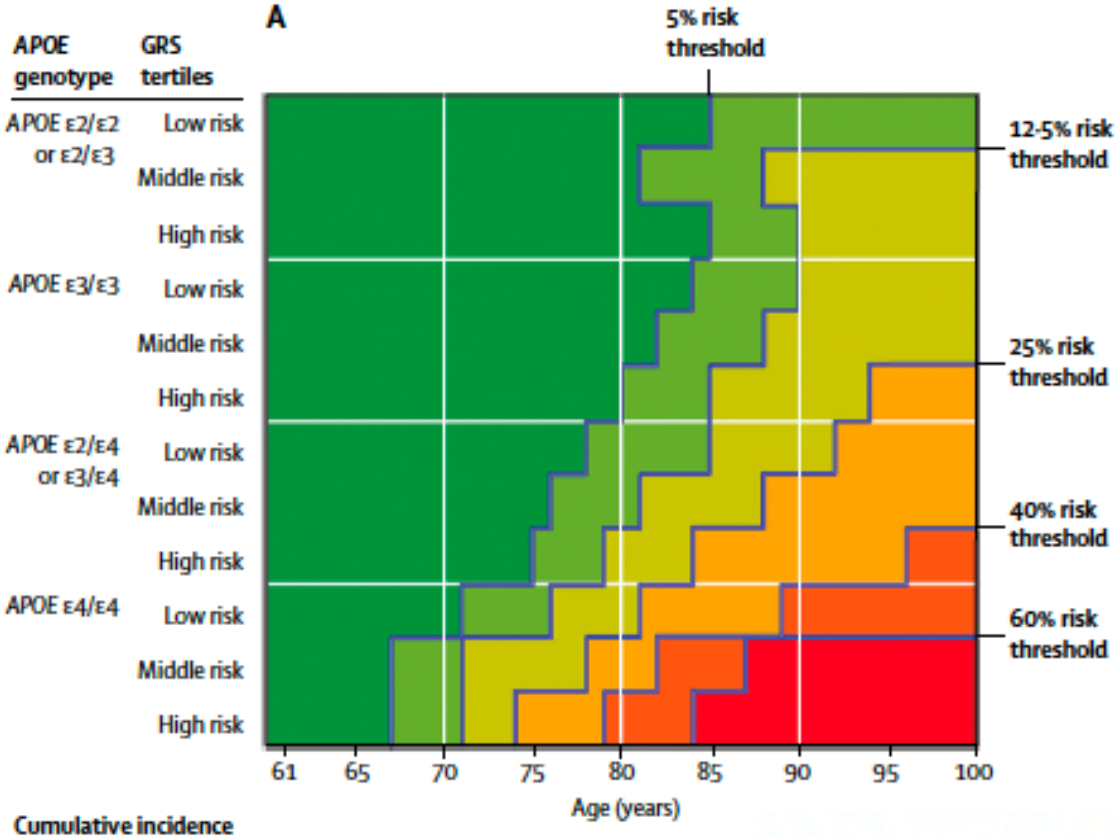
JAMA Neurol. 2019;76(5):598-606. doi:10.1001/jamaneurol.2018.4666
Published online March 4, 2019.

Association of Plasma Total Tau With Cognition and Hippocampal Volume in the Framingham Heart Study[a]

	Model 1[b]		Model 2[c]	
Outcome	β (SE)	*P* Value	β (SE)	*P* Value
Episodic memory				
Logical memory, No. correct	−0.12 (0.06)	.049	−0.14 (0.06)	.03
Paired associate learning, No. correct	−0.05 (0.02)	.04	−0.04 (0.02)	.06
Verbal reasoning: similarities, No. correct	−0.18 (0.05)	<.001	−0.17 (0.06)	.003
Visual memory: visual reproductions, No. correct	−0.14 (0.05)	.002	−0.14 (0.05)	.003
Visuospatial integration: Hooper Visual Organization Test, log unit[d]	−0.02 (0.01)	.01	−0.02 (0.01)	.02
Processing speed: Trail Making Test A, log unit[e,f]	−0.02 (0.01)	<.001	−0.02 (0.01)	.004
Executive function: Trail Making Test B-A, log unit[e]	−0.010 (0.004)	.005	−0.009 (0.004)	.01
Premorbid function				
Wide-Ranging Achievement Test, log unit[g]	−0.009 (0.010)	.37	−0.001 (0.010)	.95
Hippocampal volume, %	−0.002 (0.001)	.003	−0.003 (0.001)	.001

Polygenic Risk Scores: Helpful for Risk Stratification Enrollment in Prevention Trials

Chouraki V et al. J Alz Dis,2016



Lancet Neurol 2018; 17: 434-44

Outline of Talk

A-T-N Criteria, Stages of Cognitive Impairment: Imperfectly Aligned Axes

A-T-N in Epidemiology: Impractical; Insufficient Explanation

A-T-N Framework in Clinical Care & Clinical Trials: Overlapping Biology

A-T-N in Genetic & Biological Studies: More Targets, Better Outcomes?

A-T-N Plus: What Next?

Concerns about equating “Cerebral Amyloidosis” with Alzheimer Continuum (not Alzheimer Disease)

Social Justice Arguments

- Cost of Screening (1 Amyloid PET = Cost of Effective BP control for 10 years)
- Limited Knowledge on Prevalence in Minorities

Polypill for Cardiovascular Disease Prevention in an Underserved Population

Daniel Muñoz, M.D., Prince Uzoije, M.D., Cassandra Reynolds, B.S., Roslynn Miller, M.S., David Walkley, Susan Pappalardo, Phyllis Tousey, M.S.P.H., Heather Munro, M.S., Holly Gonzales, M.D., Wenliang Song, M.D., Charles White, M.P.H., William J. Blot, Ph.D., and Thomas J. Wang, M.D.

N ENGL J MED 381;12 NEJM.ORG SEPTEMBER 19, 2019

Editorial

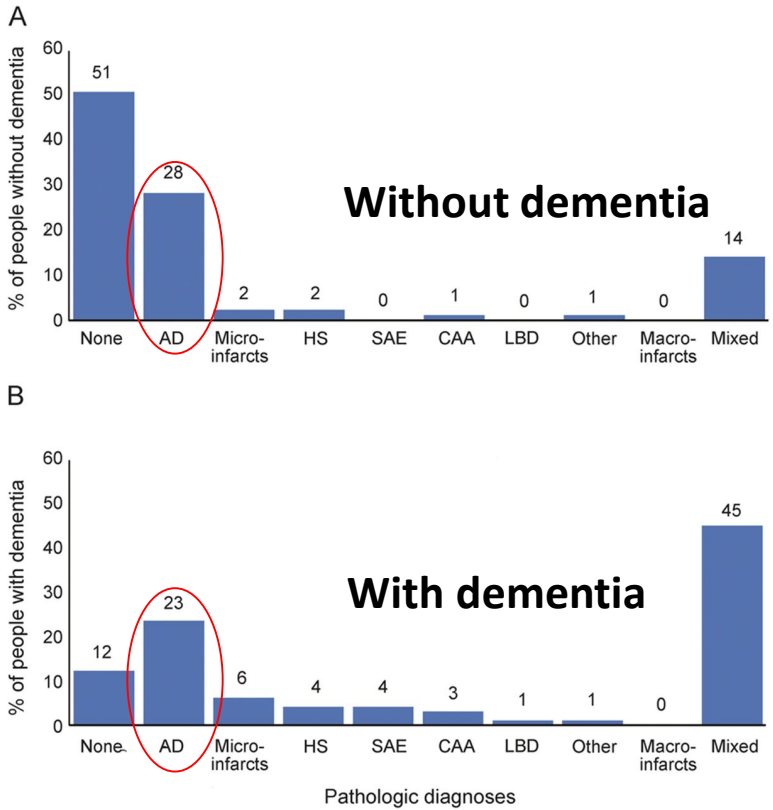
January 7, 2019

Biomarkers for Alzheimer Dementia in Diverse Racial and Ethnic Minorities—A Public Health Priority

Lisa L. Barnes, PhD[1]

For example, African-Americans may have less tau but more clinical dementia

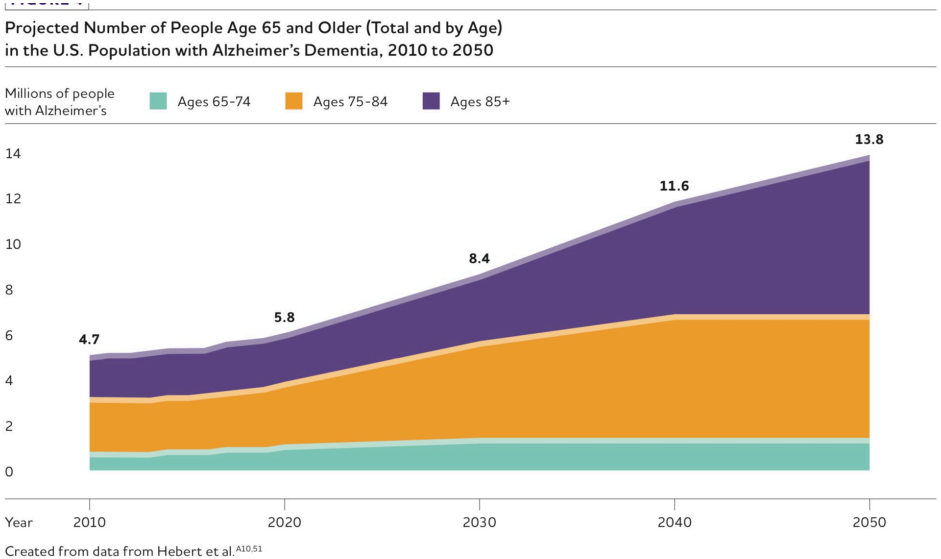
Distribution of single and multiple pathologies in 90+ Study



Claudia H. Kawas et al. Neurology 2015;85:535-542

AD = Alzheimer disease; CAA = cerebral amyloid angiopathy; HS = hippocampal sclerosis; LBD = limbic/neocortical Lewy bodies; macroinfarcts = 2 or more; microinfarcts = 3 or more;; SAE = white matter disease/subcortical arteriolosclerotic leukoencephalopathy.

Cannot Ignore Disease in 85+



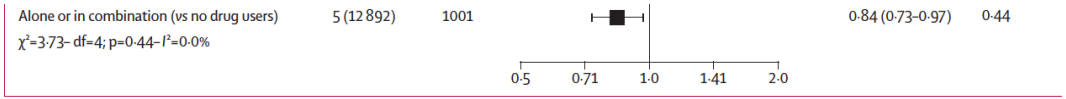
Alzheimer Association, Facts and Figures, 2019:

By 2050, 50% of clinical AD will be in 'oldest-old'

Multiple tau, TDP-43, Vascular etc.

Risk and Protective Factors Over Lifespan

- Prenatal Care, Education & Nutrition: Reserve
- Unknown factors: Infections, Lead, Pollution
- Cognitive engagement, hearing



Vascular

Figure 2: Associations of antihypertensive medication use with incident Alzheimer's disease in the high blood pressure stratum

- Physical Activity, Sleep
- Social interactions
- Stress, Diet

Antihypertensive medications and risk for incident dementia and Alzheimer's disease: a meta-analysis of individual participant data from prospective cohort studies

Jie Ding, Kendra L Davis-Plourde, Sanaz Sedaghat, Phillip J Tully, Wanmei Wang, Caroline Phillips, Matthew P Pase, Jayandra J Himali, B Gwen Windham, Michael Griswold, Rebecca Gottesman, Thomas H Mosley, Lon White, Vilmundur Guðnason, Stéphanie Debette, Alexa S Beiser, Sudha Seshadri, M Arfan Ikram, Osorio Meirelles, Christophe Tzourio, Lenore J Launer

A-T-N: Sufficient to Explain Dementia Risk Predictors?

Are vascular, lifestyle factors acting through amyloid and tau?

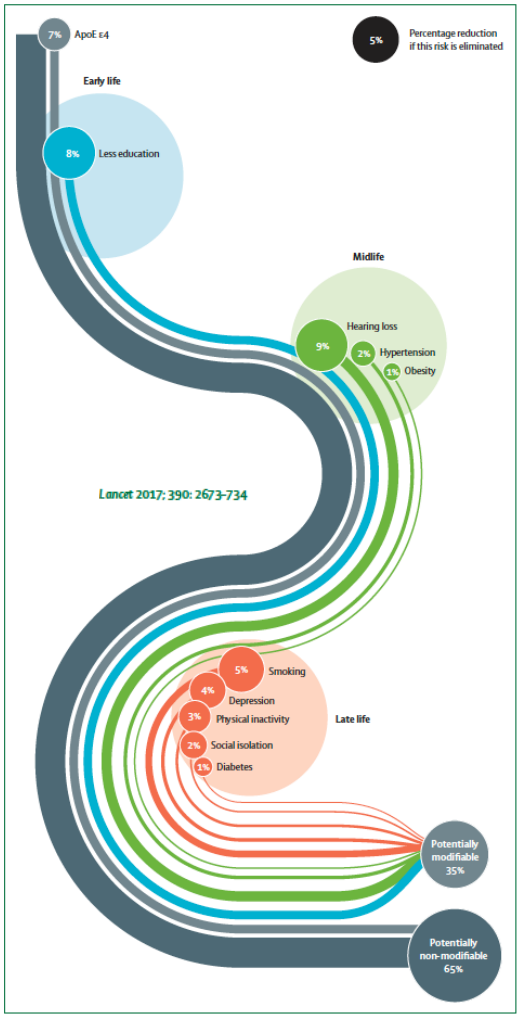


Figure 4: Life-course model of contribution of modifiable risk factors to dementia
Numbers are rounded to nearest integer. Figure shows potentially modifiable or non-modifiable risk factors.

Framingham Heart Study: Neurology, 70+ years

1948 → 2019

Gen 1

1975 onwards, dementia surveillance

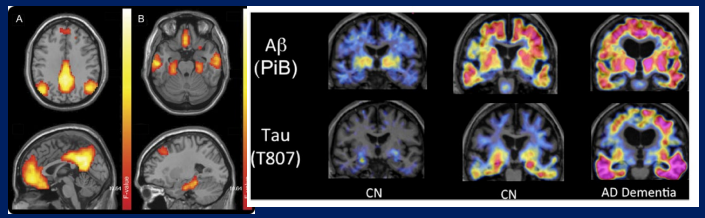
1999 onwards: 4 rounds MRI
Cognition ~ once in 6 yrs

Healthy Brain Aging, **MCI, Dementia, AD, VCID,** Stroke, PD, Epilepsy, Tremor

1971 → 2019

Gen 2/ Omni 1

Since 2015: MRI/NP and Novel Imaging
Functional MRI, Amyloid and Tau PET



2002 → 2019

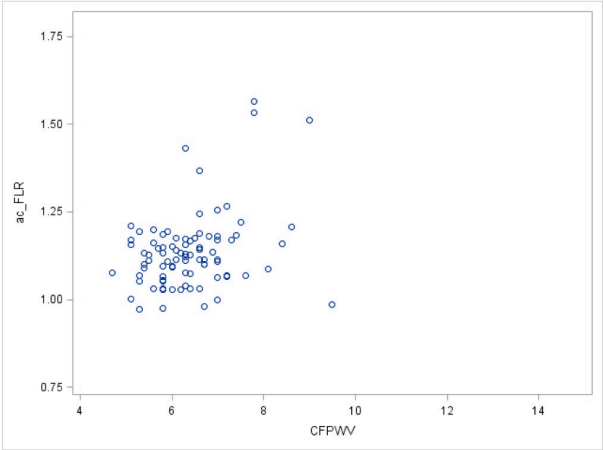
Gen 3/ Omni2

Exams 2 & 3: 2 rounds
MRI & NP; mean age 42

Brain Bank: 1997

Amyloid and Tau PET associations in FHS

- 280 persons, 46% F, age 35-75 years (expect N=900 by end of study)
- Framingham Stroke Risk Profile, Arterial Stiffness
  - Not associated with amyloid burden overall
  - CFPWV associated in women (46%) and APOE 4+ (24%)
- Plasma total tau (N+, blood marker)
  - Associated with Dementia, Cognition, not PET amyloid
  - Cingulate, insular and transverse temporal tau
- Walking Speed (Clinical Biomarker)
  - Associated with 2-3X risk of dementia
  - Lower brain volume (N+)
  - Entorhinal tau burden, not amyloid



Searching for 'biomarkers' and risk predictors/biological underpinnings of individual endophenotypes

JAMA Neurology | Original Investigation

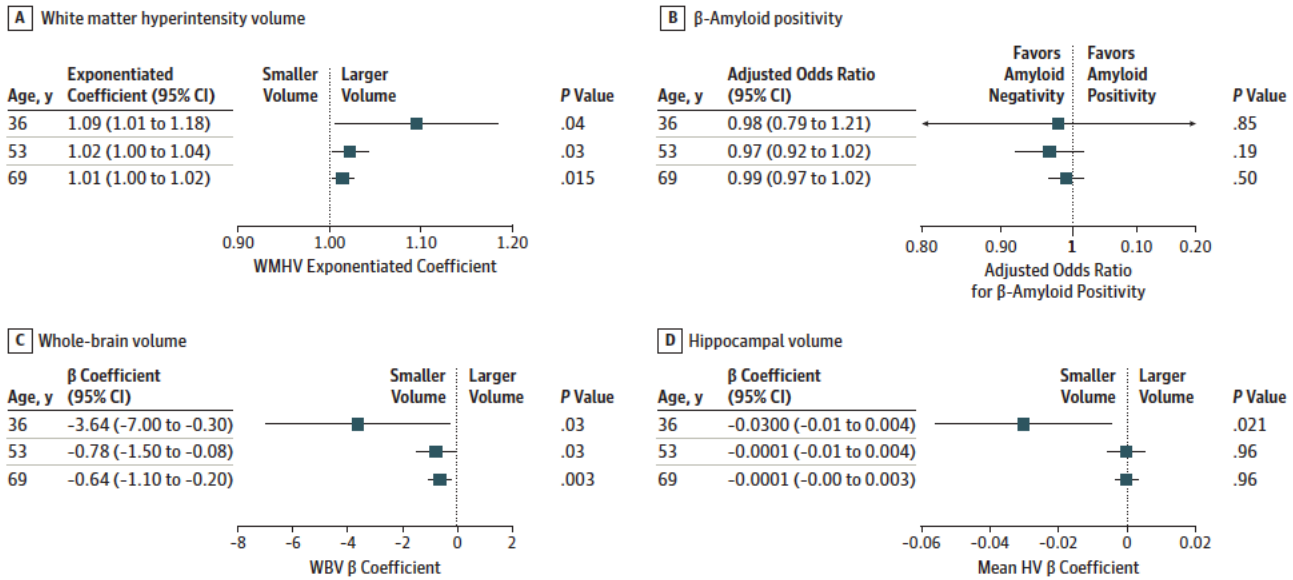
Associations Between Vascular Risk Across Adulthood and Brain Pathology in Late Life

Evidence From a British Birth Cohort

JAMA Neurology Published online November 4, 2019

Christopher A. Lane, MD, PhD; Josephine Barnes, PhD; Jennifer M. Nicholas, PhD; Carole H. Sudre, PhD; David M. Cash, PhD; Ian B. Malone, PhD; Thomas D. Parker, MRCP, PhD; Ashvini Keshavan, MRCP, PhD; Sarah M. Buchanan, FRACP; Sarah E. Keuss, MRCP; Sarah-Naomi James, PhD; Kirsty Lu, MA; Heidi Murray-Smith, MSc; Andrew Wong, PhD; Elizabeth Gordon, MSc; William Coath, MSc; Marc Modat, PhD; David Thomas, PhD; Marcus Richards, PhD; Nick C. Fox, FMedSci; Jonathan M. Schott, MD, FRCP

Figure. Plots Showing the Effect Sizes of a 1% Increase in Framingham Heart Study–Cardiovascular Risk Score at Ages 36, 53, and 69 Years on Imaging Outcome Measures at Age 69 to 71 Years



HV indicates hippocampal volume; WBV, whole-brain volume; WMHV, white matter–hyperintensity volume.

Prevention of Dementia—Thinking Beyond the Age and Amyloid Boxes

Sudha Seshadri, MD

(Midlife) Vascular Factors Adversely Impact Brain Structure

[Increase Risk of Dementia]

But do not increase brain amyloid

129 FHS participants; stroke risk profile (DM, HTN, AF, CVD, smoking)

Associations of vascular risk burden and neuropathology outcomes. *Ann Clin Transl Neurol. 2019;6:2403-2412*

	Mid-life vascular risk Model 1		Mid-life vascular risk Model 2		Late-life vascular risk Model 3	
Outcome	**OR (95% CI)**	**p**	**OR (95% CI)**	**p**	**OR (95% CI)**	**p**
Cerebrovascular pathology						
Cortical infarcts	3.99 (1.65, 9.65)	0.002*	3.83 (1.55, 9.45)	0.004*	1.04 (1.00, 1.08)	0.049*
Subcortical infarcts	1.95 (1.07, 3.54)	0.029*	1.85 (1.01, 3.40)	0.047*	1.02 (0.99, 1.06)	0.129
Atherosclerosis	1.89 (1.17, 3.06)	0.009*	1.90 (1.16, 3.10)	0.011*	1.02 (1.00, 1.05)	0.070
Arteriosclerosis	1.86 (1.15, 3.02)	0.012*	1.78 (1.09, 2.90)	0.022*	1.03 (1.00, 1.05)	0.024*
Proteinopathy						
Braak NFT stage	1.15 (0.73, 1.82)	0.554	1.18 (0.74, 1.89)	0.484	1.03 (1.01, 1.05)	0.012*
Cerebral amyloid angiopathy	1.15 (0.71, 1.86)	0.575	1.19 (0.72, 1.95)	0.494	1.02 (1.00, 1.05)	0.061
CERAD neuritic plaque score	0.86 (0.54, 1.37)	0.525	0.86 (0.54, 1.39)	0.547	1.02 (1.00, 1.05)	0.052

OR: Odds ratio, CI: confidence interval, P: p-value, CERAD: Consortium to Establish a Registry for Alzheimer's Disease.

*$p<0.05$.

Model 1: Adjusted for sex, presence of ApoE ε4, and elapsed time between mid-life vascular risk and death (with quadratic term for atherosclerosis and arteriosclerosis).

Model 2: Model 1 additionally adjusted for late-life vascular risk.

Model 3: Adjusted for sex, presence of ApoE ε4, and elapsed time between late-life vascular risk and death.

Outline of Talk

A-T-N Criteria, Stages of Cognitive Impairment: Imperfectly Aligned Axes

A-T-N in Epidemiology: Impractical, Insufficient Explanation

A-T-N Framework in Clinical Care & Clinical Trials: Overlapping Biology

A-T-N in Genetic & Biological Studies: More Targets, Better Outcomes?

A-T-N Plus: What Next?

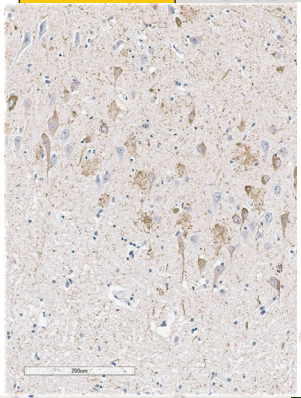
Final Diagnosis: One ‘typical’ patient

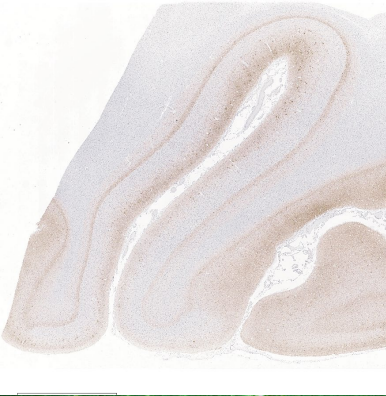
Definite AD, by any criteria

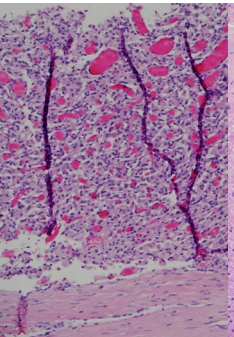
- High ADNC
- Stage 2 LATE-NC
- Limbic (transitional) Lewy body pathology
- Mild cerebral amyloid angiopathy
- Moderate cerebrovascular disease, non-occlusive
  - Moderate arteriolosclerosis and HTN changes
- Small subdural

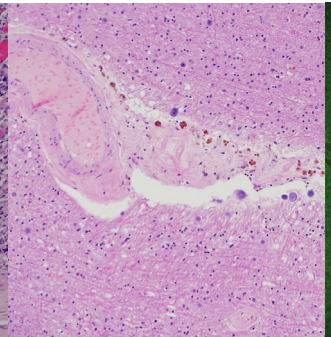
Table 3 “ABC” score for level of AD neuropathologic change

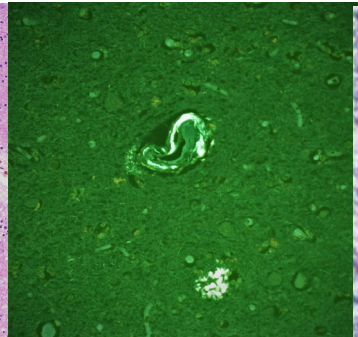
AD neuropathologic change		B[a]		
A[b]	C[c]	0 or 1	2	3
0	0	Not[d]	Not[d]	No
1	0 or 1	Low	Low	Lo
	2 or 3[f]	Low	Intermediate	Interme
2	Any C	Low[g]	Intermediate	Interme
3	0 or 1	Low[g]	Intermediate	Interme
	2 or 3	Low[g]	Intermediate	Hi

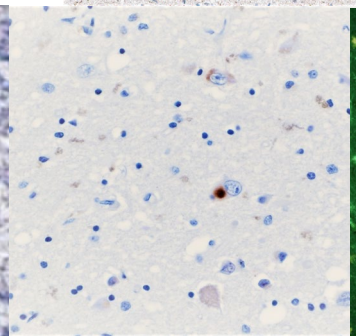


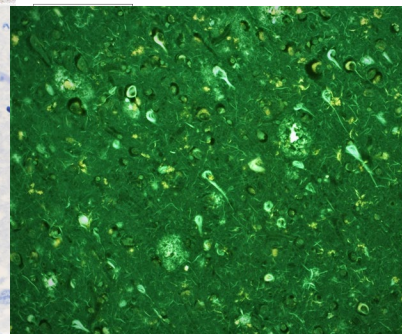












NIA-AA Research Framework	
Amyloid (A)	Cerebrospinal fluid Aβ42, or Aβ42/Aβ40 ratio
	Amyloid-positron emission tomography
Tau (T)	Cerebrospinal fluid phosphorylated-tau
	Tau positron emission tomography
Neuro-degener-ation (N)	Anatomic MRI
	Fluorodeoxyglucose-positron emission tomography
	Cerebrospinal fluid total tau
Clinical Linkages for Individuals With Symptoms	
$A^+T^+N^-$	Prodromal Alzheimher's disease/mild cognitive impairment due to Alzheimer's disease
$A^+T^+N^+$	Alzheimer's disease dementia (can still be mixed dementia)
$A^-T^+N^-$	Cerebrovascular disease, prion disease, early tauopathies
$A^-T^+N^+$	Vascular dementia, tauopathies, dementia with Lewy bodies, primary age-related tauopathy
$A^-T^-N^+$	Limbic-predominant age-related TDP-43 encepha-lopathy

- Valuable in Differential Diagnosis of Clinical Dementia

  Causal or Incidental?

  Problem of Missing Pathologies we cannot yet screen for

- For 'Worried Well' and 'Persons with Subjective Cognitive Impairment'

  Stigma, Anxiety, Impact on Family

  Potentially Unnecessary or Harmful Treatment Changes

- Extrapolating data gathered with old to new criterion based Alzheimer Disease diagnosis

IDEAS Trial: *"In participants who joined the study with MCI and scans revealed amyloid, clinicians were twice as likely to prescribe Alzheimer's drugs (~40% to 80%). Doctors discontinued drugs in some with little amyloid"*

JAMA April, 2019

Outline of Talk

A-T-N Criteria, Stages of Cognitive Impairment: Imperfectly Aligned Axes

A-T-N in Epidemiology: Impractical, Insufficient Explanation

A-T-N Framework in Clinical Care & Clinical Trials: Overlapping Biology

A-T-N in Genetic & Biological Studies: More Targets, Better Outcomes?

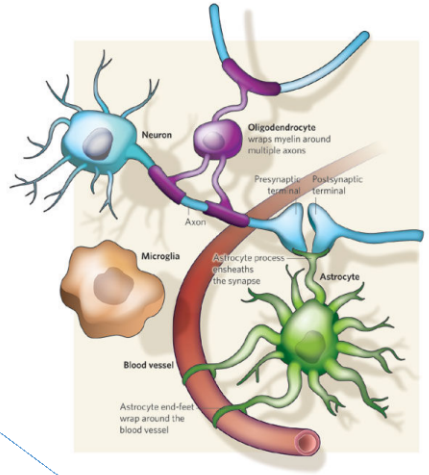
A-T-N Plus: What Next?

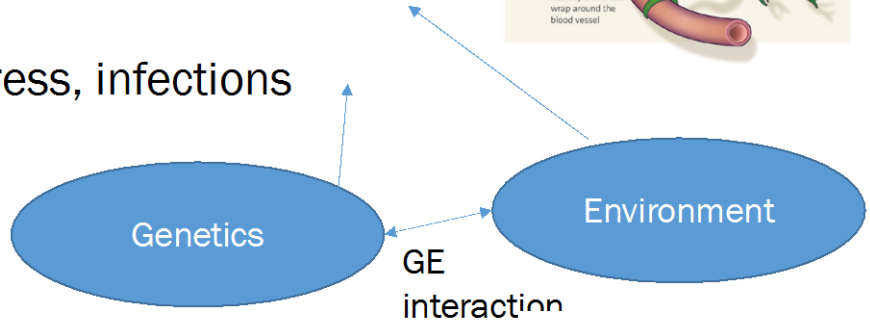
What Causes Dementia?

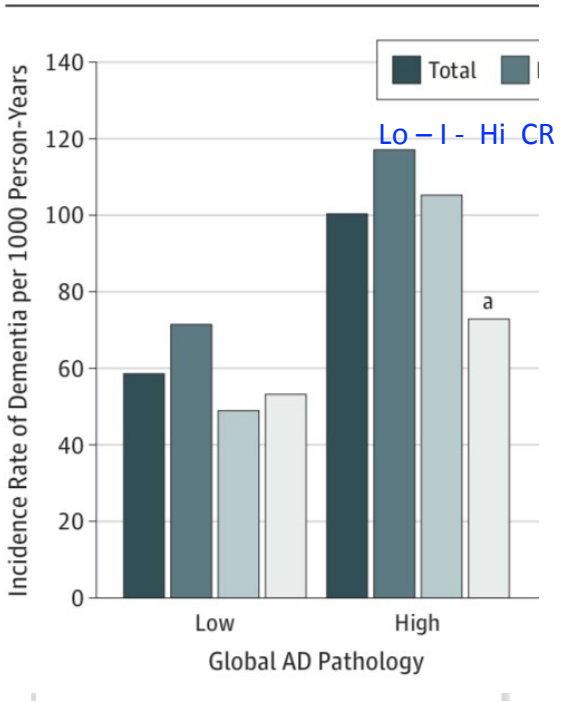
Cog Reserve Indicator: Education + Social

JAMA. doi:10.1001/jama.2019.9879
Published online July 14, 2019.

- Things that injure the brain overcome it's resilience/reserve
  - Neurodegenerative Diseases
  - Vascular Brain Injury
  - Age, inflammation
  - Trauma, stress, infections

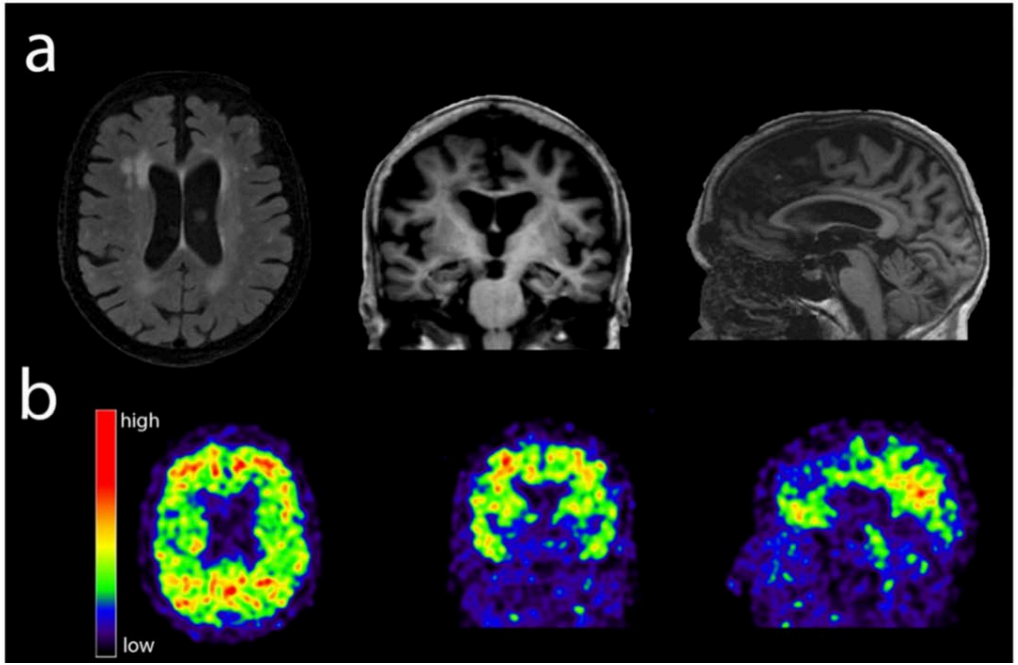


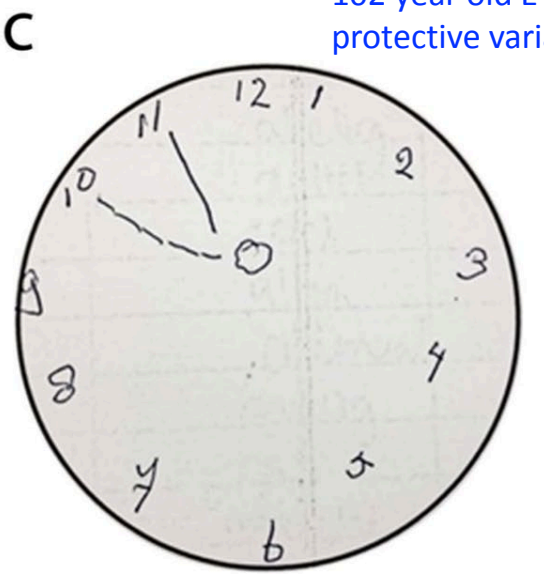




Association of Lifespan Cognitive Reserve Indicator With Dementia Risk in the Presence of Brain Pathologies

rs72824905-G allele in *PLCG2*





102 year old E4/4 carrier with protective variant in PLCG2

10 minutes before 11

Acta Neuropathologica (2019) 138:237–250
https://doi.org/10.1007/s00401-019-02026-8

ORIGINAL PAPER

Check for updates

A nonsynonymous mutation in *PLCG2* reduces the risk of Alzheimer's disease, dementia with Lewy bodies and frontotemporal dementia, and increases the likelihood of longevity

Association with:	N-cases	N-controls	Odds-ratio	P-value
Alzheimer's disease (AD)	4,985	8,492	0.57 [0.41-0.78]	0.00063*
Dementia with Lewy-bodies (DLB)	1,446	5,286	0.54 [0.30-0.99]	0.045*
Frontotemporal dementia (FTD)	2,437	10,647	0.61 [0.41-0.89]	0.011*
Progressive supranuclear palsy (PSP)	882	3,187	1.46 [0.83-2.58]	0.19
Amyotrophic lateral sclerosis (ALS)	10,953	20,673	1.07 [0.87-1.33]	0.52
Parkinson's disease (PD)	28,448	108,438	1.18 [0.97-1.44]	0.10
Multiple sclerosis (MS)	4,476	5,714	0.99 [0.74-1.32]	0.95
Reaching the age of >90 years	3,516	9,677	1.50 [1.13-2.00]	0.0051*

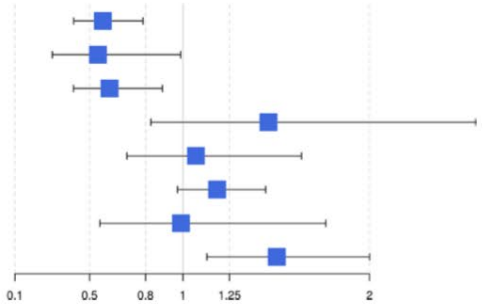
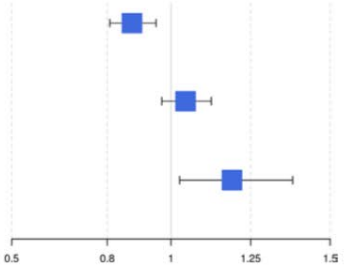


Fig. 1 Association results of rs72824905-G with seven brain diseases and longevity. *P values < 0.05. Numbers (N) of cases (patients or long-lived individuals) and controls studied. The figure shows the odds-ratio (box) of the rs72824905-G with the 95% confidence intervals (whiskers)

Protective against all types of dementia and increasing longevity?

Association with:	Comparing:	Odds-ratio	P-value
Parental dementia	16,968 father cases vs. 358,468 father controls + 32,262 mother cases vs. 346,999 mothers controls	0.88 [0.81-0.95]	0.0018*
Parental age >90 years	17,558 father's age =90 years vs. 353,100 father age <90 years + 35,256 mother's aged =90 years vs. 342,810 mother's aged <90 years	1.05[0.97-1.13]	0.24
Parental age >95 years	3043 father's age =95 years vs. 353,100 father's age <90 years + 7790 mother's aged =95 years vs. 342,810 mother's aged <90 years	1.19 [1.03-1.38]	0.021*



Association results of rs72824905-G with dementia by-proxy and longevity by-proxy analysis in the UK Biobank. *P values < 0.05. The figure shows the odds-ratio (box) of the rs72824905-G with the 95% confidence intervals (whiskers)

A-T-N Based Diagnoses of Clinical Dementia (ADRD)

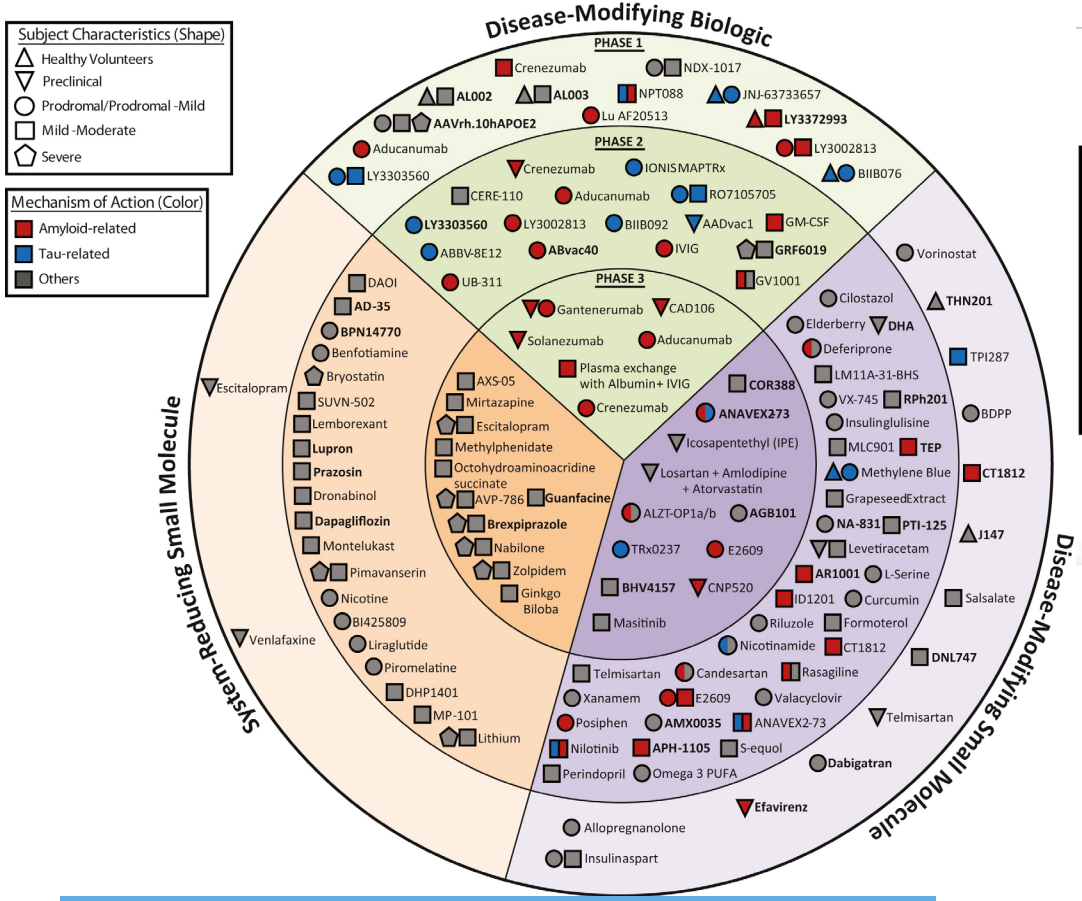
- Will likely need addition of markers for-
  - Vascular
  - Inflammatory
  - Mitochondrial
  - Genetic (common variants)
  - Genetics (rare variants)
  - Other omic, molecular markers

  - Environmental (built, social, behavioral)
  - Lifestyle (sleep, physical activity, diet)

May not be acting through A or T pathways

Avoid the 'peptic ulcer' fallacy

2019 Alzheimer's Drug Development Pipeline



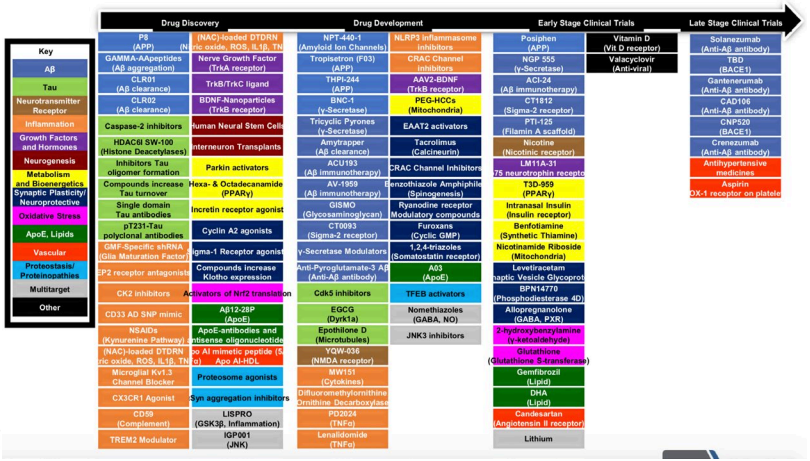
Alzheimer's disease drug development pipeline: 2019

Cummings, Lee, Ritter, Sabbagh, Zhong

https://doi.org/10.1016/j.trci.2019.05.008

NIA-AD clinical trials pipeline toward 2025

NIA Program Directors: Laurie Ryan, Zane Martin, Larry Refolo



Promising therapies based on animal models and Phase 1, 2 studies of 'pure tau,' 'vascular' and other models

Outline of Talk

A-T-N Criteria, Stages of Cognitive Impairment: Imperfectly Aligned Axes

A-T-N in Epidemiology: Impractical, Insufficient Explanation

A-T-N Framework in Clinical Care & Clinical Trials: Overlapping Biology

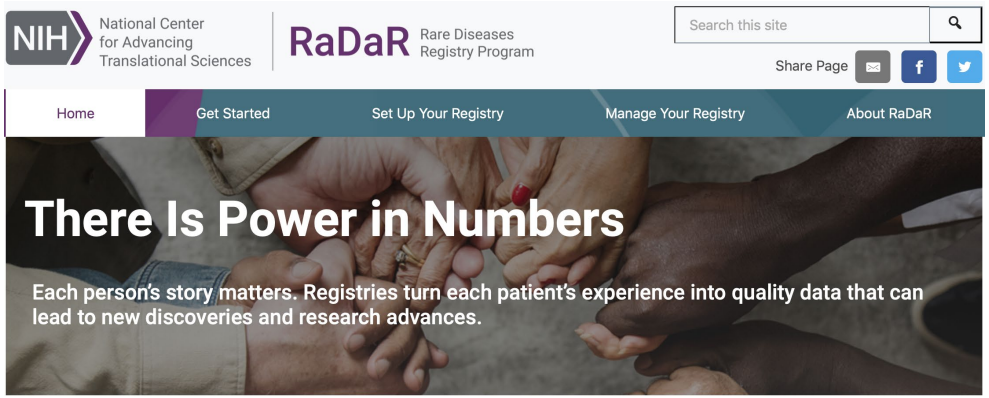
A-T-N in Genetic & Biological Studies: More Targets, Better Outcomes?

A-T-N Plus: What Next?

How Might we move beyond A-T-N?

Explore, define dementia subtypes in

- International Collaborative Clinical Dementia Registries
- By clinical, imaging, genetic and omic endophenotypes
- Dementia, Cognitive (x-MIND) clinical trial datasets
- Biobanks and Longitudinal Cohorts



Rare Diseases Registry Program (RaDaR) Helps You:

Recognize 'Alzheimer disease' as defined by A+/T+
Is likely only one part of the problem (? 50%) of dementia

Summary: Uses of A-T-N Classification: Research

- Tracking Prevalence of and Prognosis with Biomarkers
  - 'Cerebral Amyloidosis'? 'Alzheimer?'
- Selecting Subjects for and Tracking Response in *Specific* Clinical Trials
- Differential Diagnosis in Persons with Dementia
- Genetics/Biology of Endophenotypes

GOOD

- Other Markers of Cognitive Decline
- Oldest-Old, Other Race-, Ethnic-, SES groups
- Some Risk Factors not acting through A or T
- Anxiety, Stigma, Costs
- Missing Concomitant Pathology
- Assuming Risk Factors and Treatments Identified with old criteria apply to new
- Opportunity Cost of not finding treatable causal and modifying biology

CONCERNING