UCDAVIS HEALTH

The Many Faces of Dementia and Why They Matter

Brittany N. Dugger, PhD

Assistant Professor Department of Pathology and Laboratory Medicine

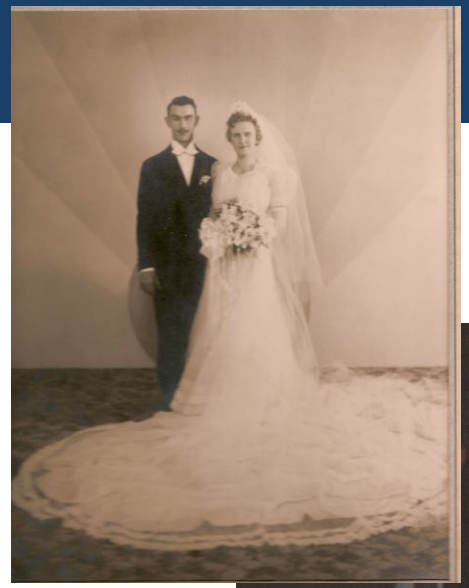
Co-Investigator UC-Davis Alzheimer's Disease Center

UCDAVIS HEALTH | Alzheimer's Disease Center

What I will cover today

- There are many faces of dementia
  - Type of symptoms
  - Underlying pathology
  - Disease stage
  - Concomitant pathologies
  - Demographic variables
- Use of Machine Learning to understand the many faces of dementia


HOUSE PUB



Two amazing persons affected by “Dementia”, but two different presentations

Grandma Dugger

- didn’t remember who I was but could remember to sit in the same pew even though it wasn’t a church she grew up in or was very familiar with before the disease

Grandma Morenski

- dementia with hallucinations and more pronounced personality changes

Clinical Classification of Dementia

Decrease in activities of daily living and cognitive impairment

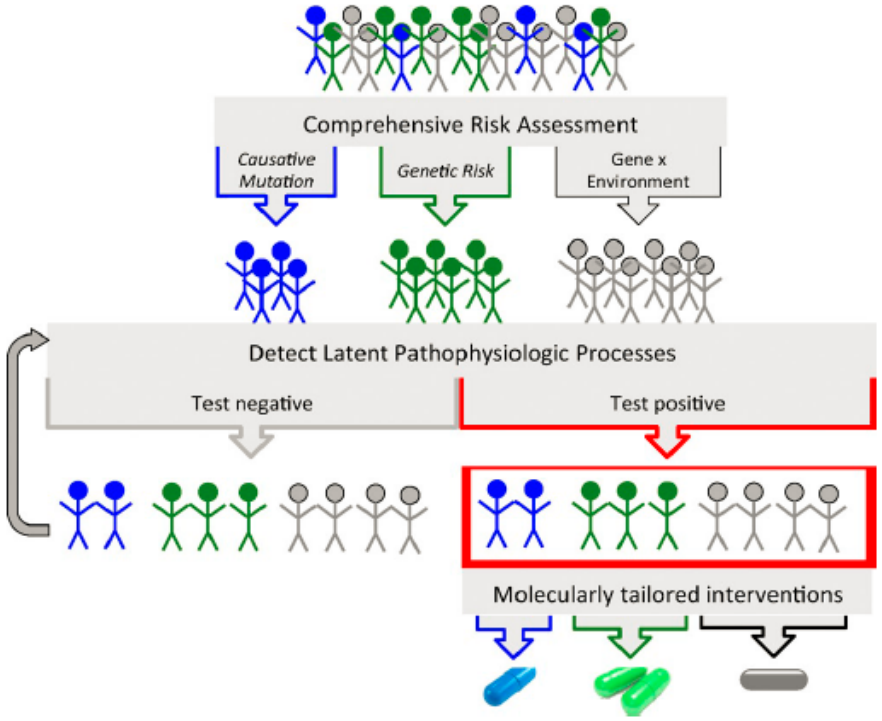
Clinical presentation vs. underlying disease

DEMENTIA

- Alzheimer's Disease (AD)
- Dementia with Lewy Bodies (DLB)
- AD & Vascular Dementia (mixed)
- Vascular Dementia (VaD)
- Frontotemporal Dementia (FTD)
- Parkinson's Disease (PD)
- Huntington's Disease (HD)
- Other Degenerative Diseases (PSP, ALS with dementia)
- Dementias Secondary to Alcohol
- Depression/Pseudodementia
- Normal Pressure Hydrocephalus (NPH)
- Structural Lesions
- Metabolic Disorders (Hypothyroidism)
- Delirium
- Infections (e.g. neurosyphillis, AIDS, CJD)
- Drug Intoxication

Why we need to understand the underlying disease

Precision Medicine
"Deliver optimally targeted and timed interventions tailored to an individual's molecular drivers of disease".



Montine, T et al. Journal of Experimental Medicine 2015

Clinical diagnosis is not an exact science

Low clinical diagnostic accuracy of early vs advanced Parkinson disease

Clinicopathologic study

Charles H. Adler, MD, PhD
Thomas G. Beach, MD, PhD
Joseph G. Hentz, MS
Holly A. Shill, MD
John N. Caviness, MD
Erika Driver-Dunckley, MD
Marwan N. Sabbagh, MD
Lucia I. Sue
Sandra A. Jacobson, MD
Christine M. Belden, PhD
Brittany N. Dugger, PhD

Correspondence to

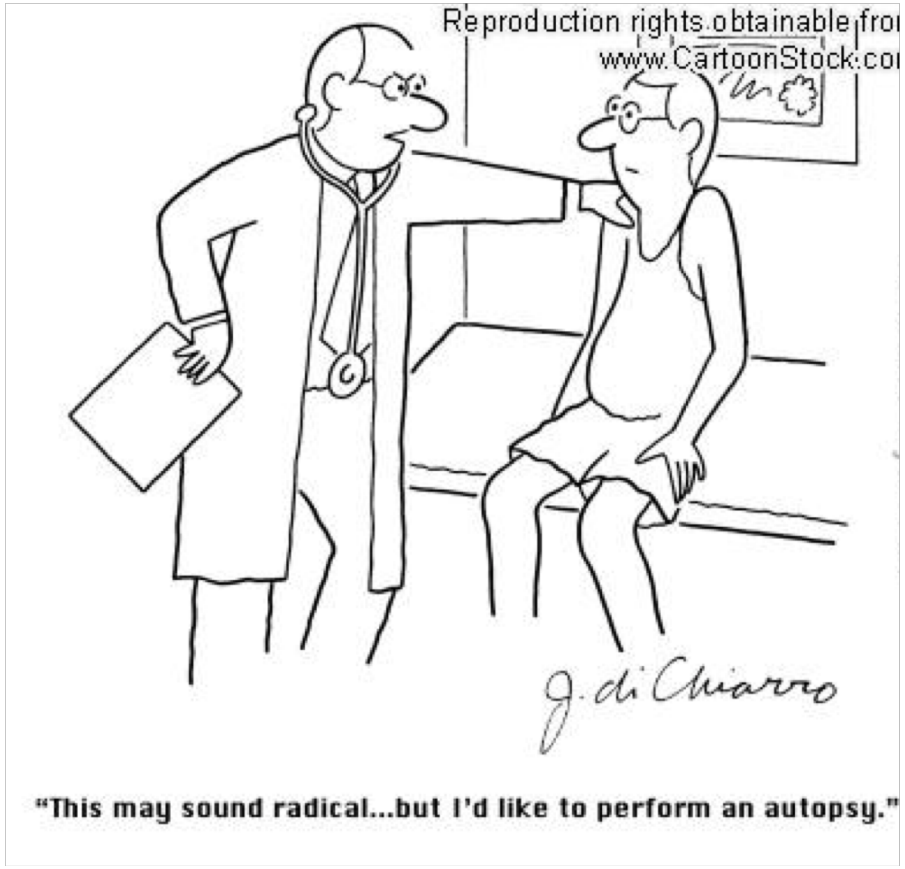
ABSTRACT

Objectives: Determine diagnostic accuracy of a clinical diagnosis of Parkinson disease (PD) using neuropathologic diagnosis as the gold standard.

Methods: Data from the Arizona Study of Aging and Neurodegenerative Disorders were used to determine the predictive value of a clinical PD diagnosis, using 2 clinical diagnostic confidence levels, PossPD (never treated or not clearly responsive) and ProbPD (responsive to medications). Neuropathologic diagnosis was the gold standard.

Results: Based on first visit, 9 of 34 (26%) PossPD cases had neuropathologically confirmed PD while 80 of 97 (82%) ProbPD cases had confirmed PD. PD was confirmed in 8 of 15 (53%) ProbPD cases with <5 years of disease duration and 72 of 82 (88%) with ≥5 years of disease duration. Using final diagnosis at time of death, 91 of 107 (85%) ProbPD cases had confirmed PD. Clinical variables that improved diagnostic accuracy were medication response, motor fluctuations, dyskinesias, and hyposmia.

Conclusions: Using neuropathologic findings of PD as the gold standard, this study establishes the novel findings of only 26% accuracy for a clinical diagnosis of PD in untreated or not clearly responsive subjects, 53% accuracy in early PD responsive to medication (<5 years' duration), and



Adler CH, *et al.* Neurology. 2014.

How does one classify dementias pathologically?

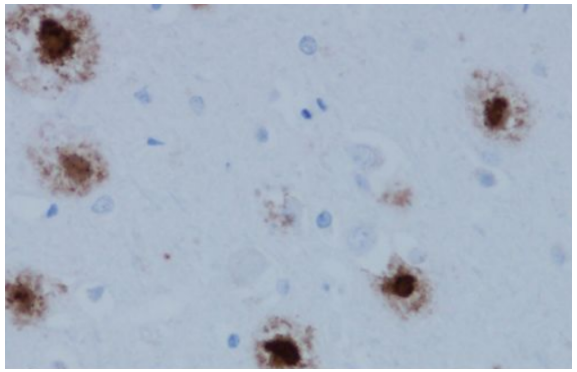
- Looking for the “car accidents”

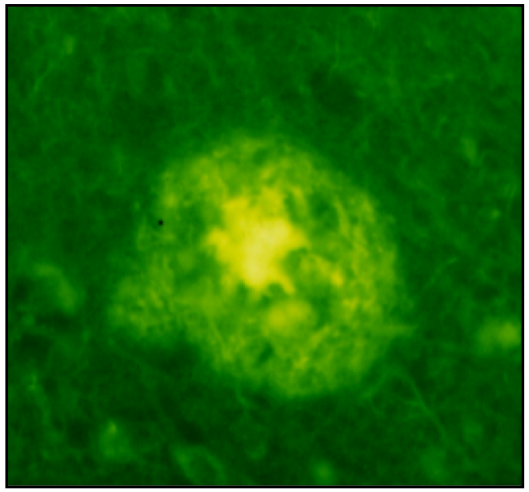
- A dementia will have abnormal aggregates (i.e. “car accidents”) of specific proteins in specific areas of the brain

This how you classify dementia pathologically

abnormal aggregates of Amyloid-β

“Amyloid Plaques” in Alzheimer’s disease



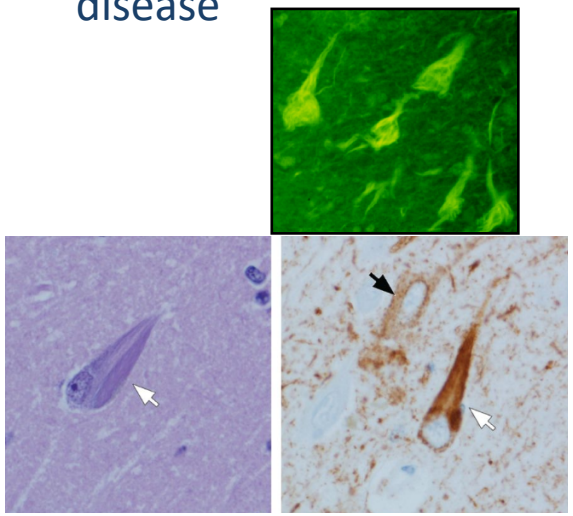


Dugger BN and Dickson DW Cold Spring Harb Perspect Biol. 2017

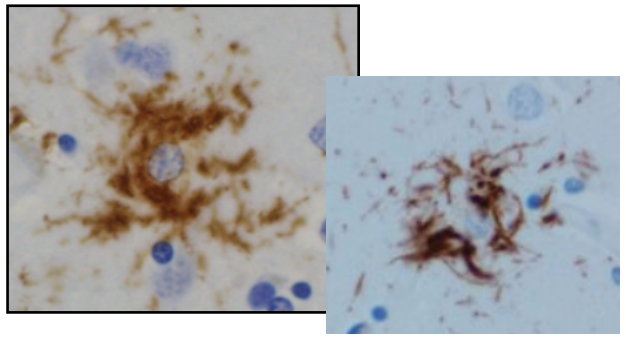
This how you classify dementia pathologically

abnormal aggregates of Tau

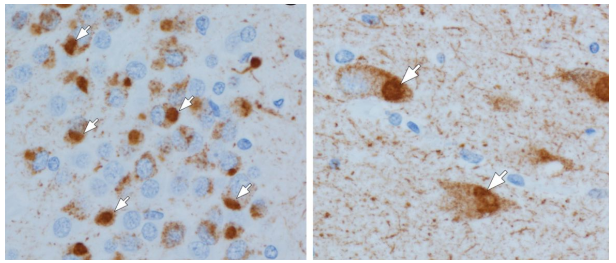
"Neurofibrillary Tangles" in Alzheimer's disease



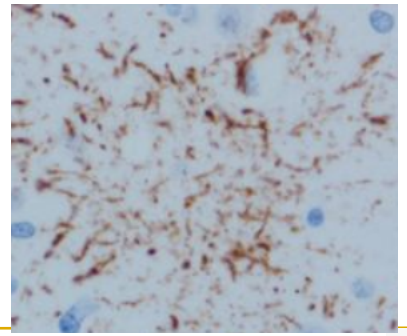
"tufted astrocytes" in Progressive Supranuclear Palsy



"Pick Bodies" in Pick's disease



"Astrocytic plaques" in Corticobasal Degeneration

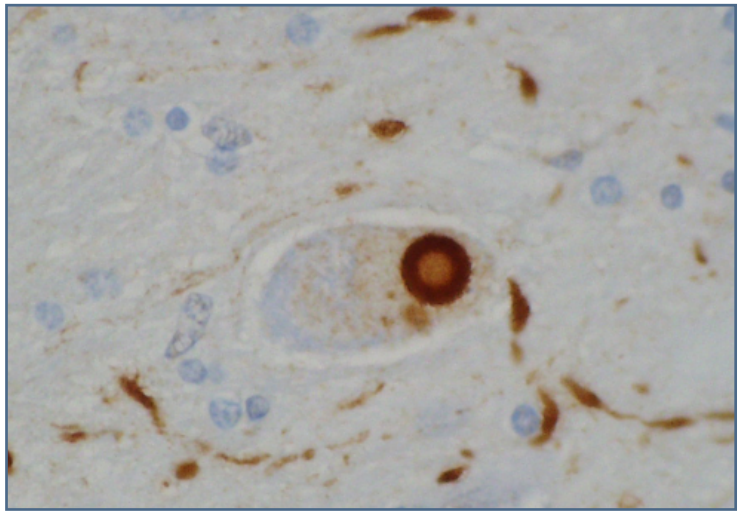


Dugger BN and Dickson DW Cold Spring Harb Perspect Biol. 2017

This how you classify dementia pathologically

abnormal aggregates of α-synuclein

“Lewy bodies” in Dementia with Lewy bodies



Dugger BN and Dickson DW Cold Spring Harb Perspect Biol. 2017

In dementias, there are similarities and differences

Disease	Clinical presentation	Pathologic presentation
Alzheimer's Disease (AD)	Dementia, forgetfulness & word finding difficulties	Plaques and Tangles
Dementia with Lewy Bodies (DLB)	Dementia, Parkinsonism, hallucinations, fluctuations, REM sleep behavior disorder	Lewy bodies
Progressive Supranuclear Palsy (PSP)	Dementia, Parkinsonism, Supranuclear gaze palsy, backwards falls (early), dysphagia	Tufted astrocytes
Corticobasal Degeneration (CBD)	Dementia, Parkinsonism, Asymmetric clumsiness, stiffness or limb jerking, alien limb phenomenon	Astrocytic plaques
Pick's Disease	Dementia; inappropriate social behavior, language problems	Pick bodies

Many studies have aided greatly in understanding the relationship between clinical symptoms and underlying pathology….

However,

- Typically focus on one diagnosis
  - Importance of:
    - Concomitant diagnoses
    - Locational aspect of pathology/disease states
- Cohorts mainly “upper middle class white Caucasians”
  - Importance of race/ethnicity:
    - Social
    - Cultural
    - Economic
    - Behavioral characteristics

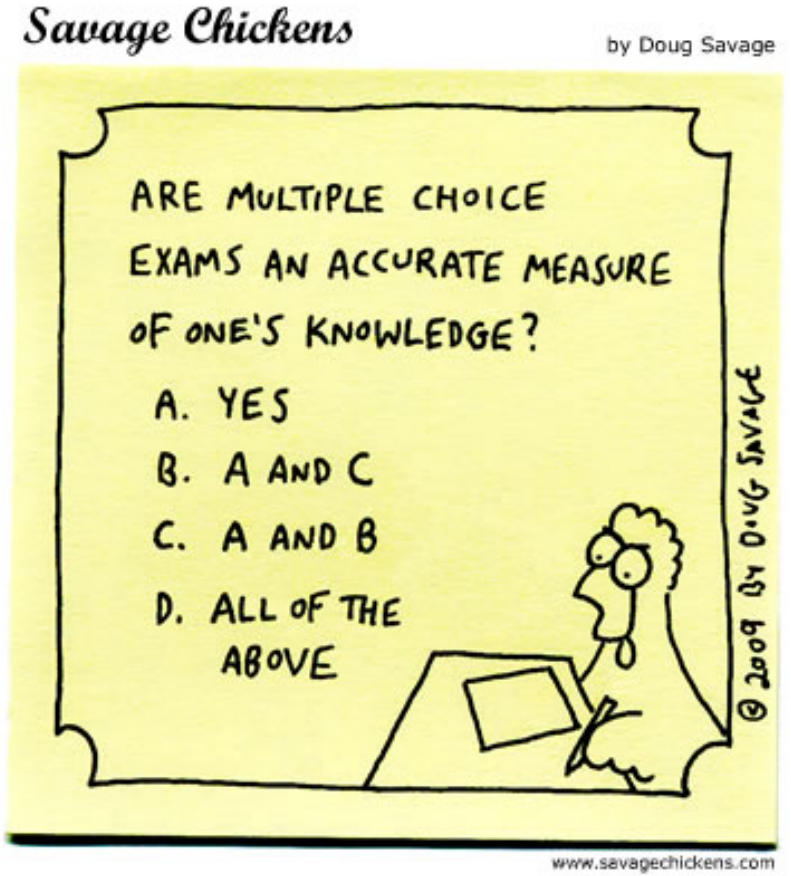


Image URL: http://bcheights.com/2017/01/25/recognizing-diversity-mental-illness/

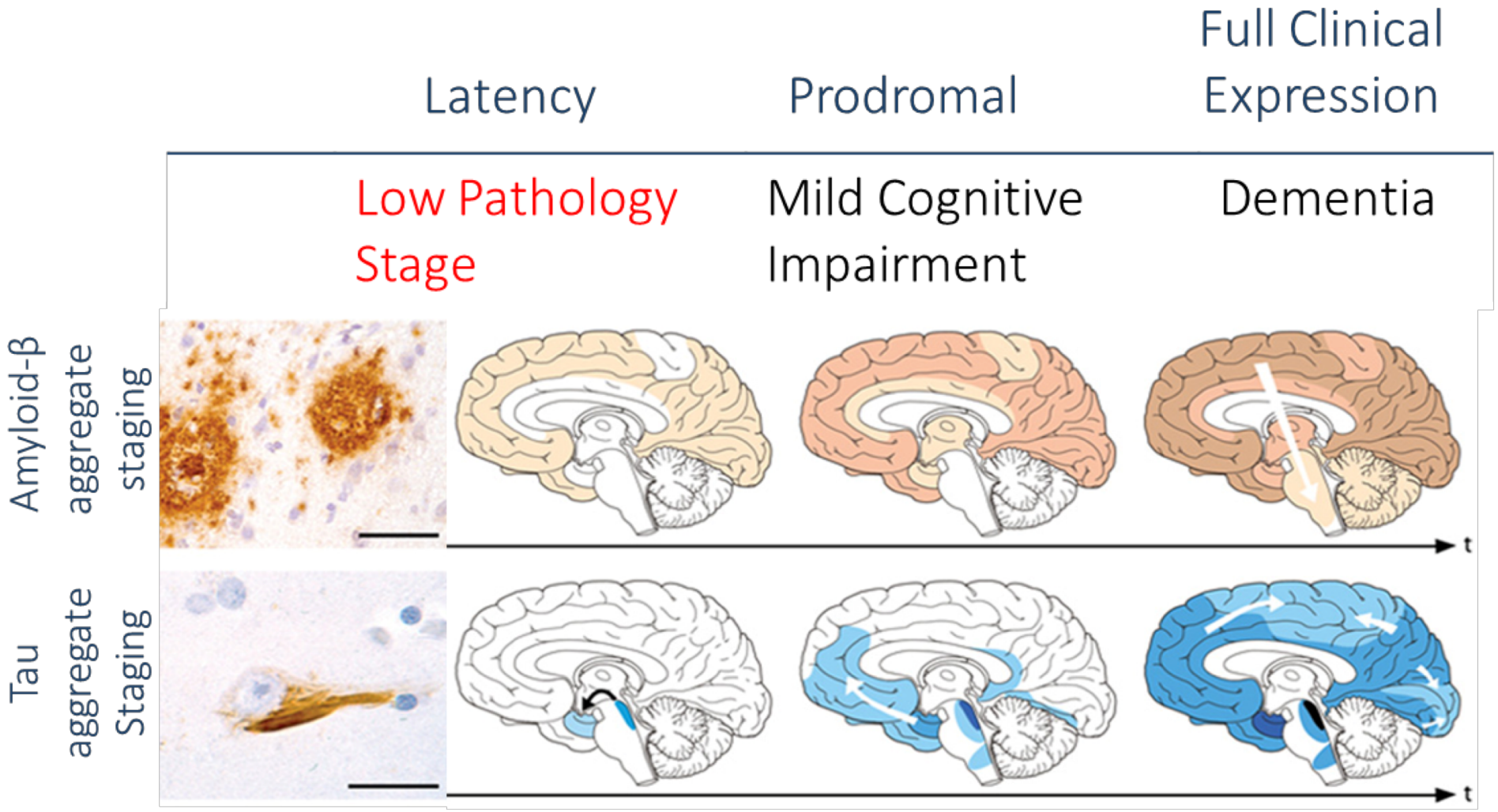
how frequent are concomitant diagnoses?

Multiple diseases can exist in one brain

30% of Alzheimer's cases have a concomitant clinicopathological diagnosis.

Dugger BN, query of the Brain and Body Donation Program database

A person just doesn't wake up one day with dementia, it is a process

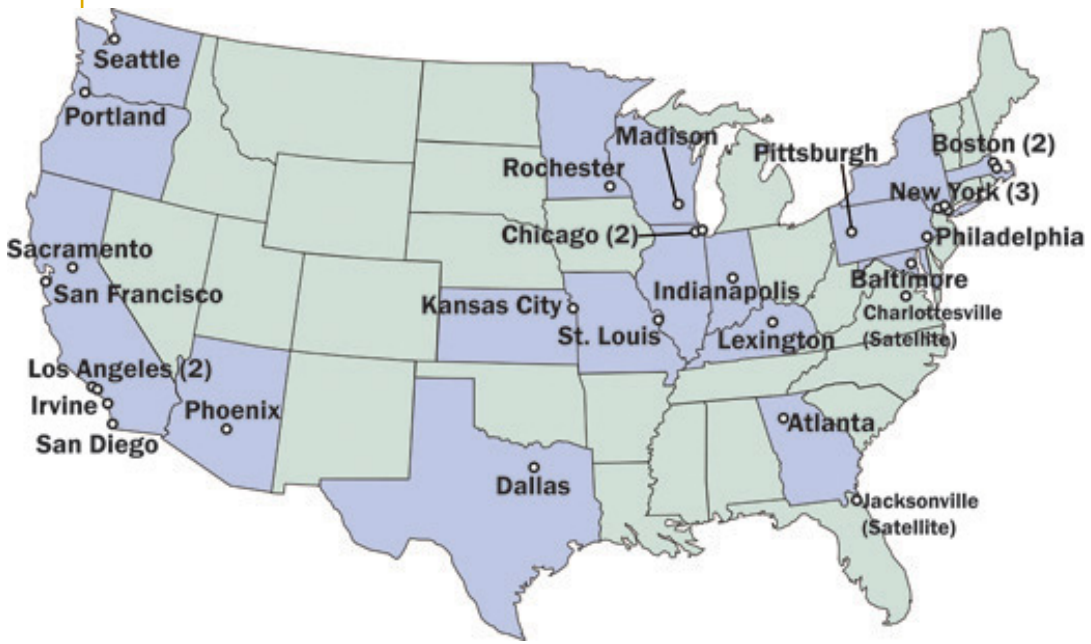


Jucker M, Walker LC. Nature. 2013.

What of cohort composition?

Diversity in research cohorts

Alzheimer's Disease Centers



Race	Frequency (n)	% of total
White	28487	79.6%
Black or African American	4479	12.5%
American Indian or Alaska Native	206	<1%
Native Hawaiian or Pacific Islander	27	<1%
Asian	860	2.4%
Multiracial	1125	3.1%
Unknown or ambiguous	584	1.6%
All	35768	

Hispanic ethnicity	Frequency (n)
No	32905
Yes	2718
Unknown	145
All	35768

2718/35768 =7.6%

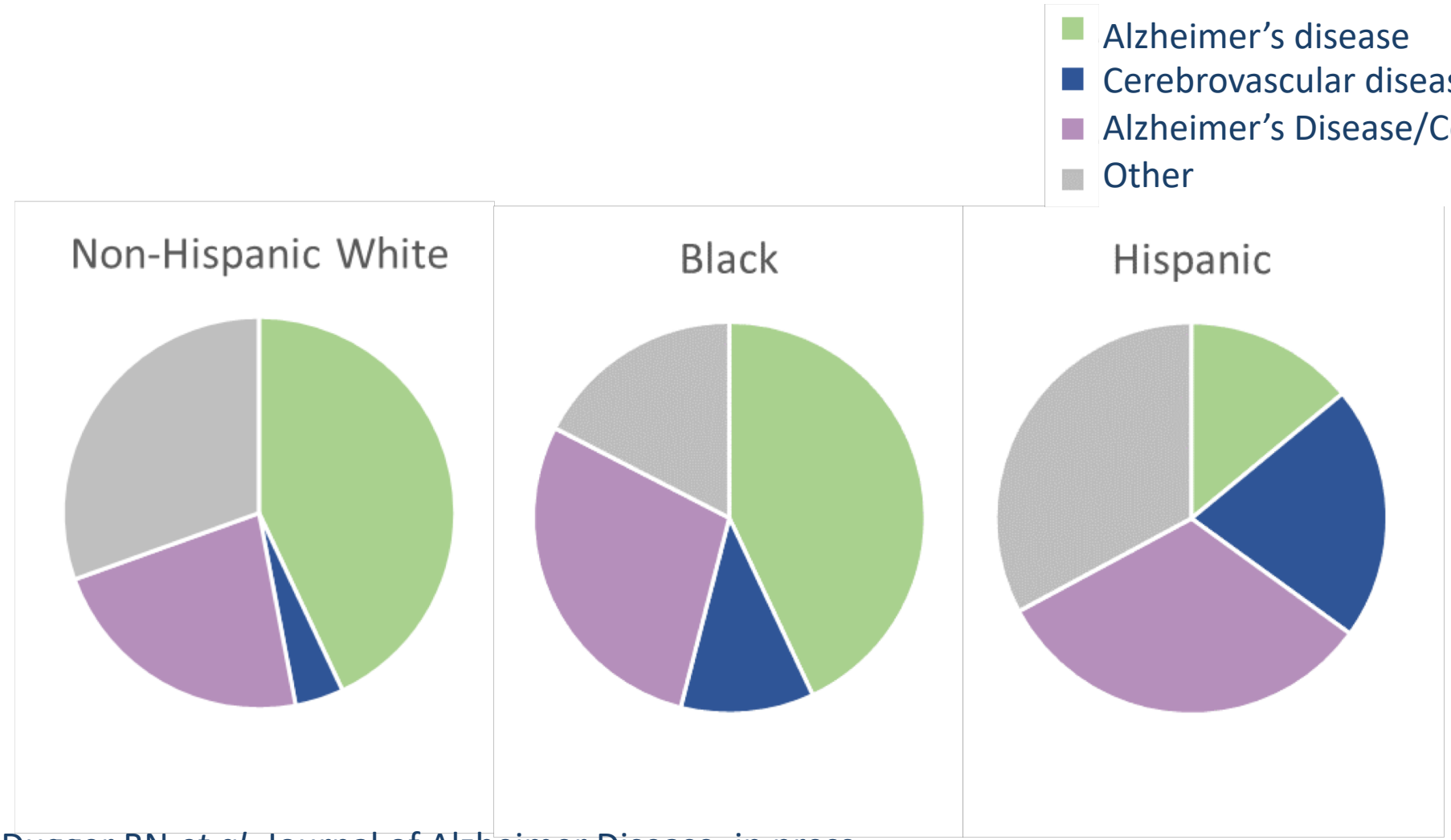
Dugger, BN unpublished, NACC query July 15, 2017

U.S. population July 2016 estimates

Race and Hispanic Origin	%
White, not Hispanic or Latino	61.3%
Black or African American	13.3%
American Indian and Alaska Native	1.3%
Hispanic or Latino	**17.8%**
Asian	5.7%
Native Hawaiian and Other Pacific Islander	0.2%

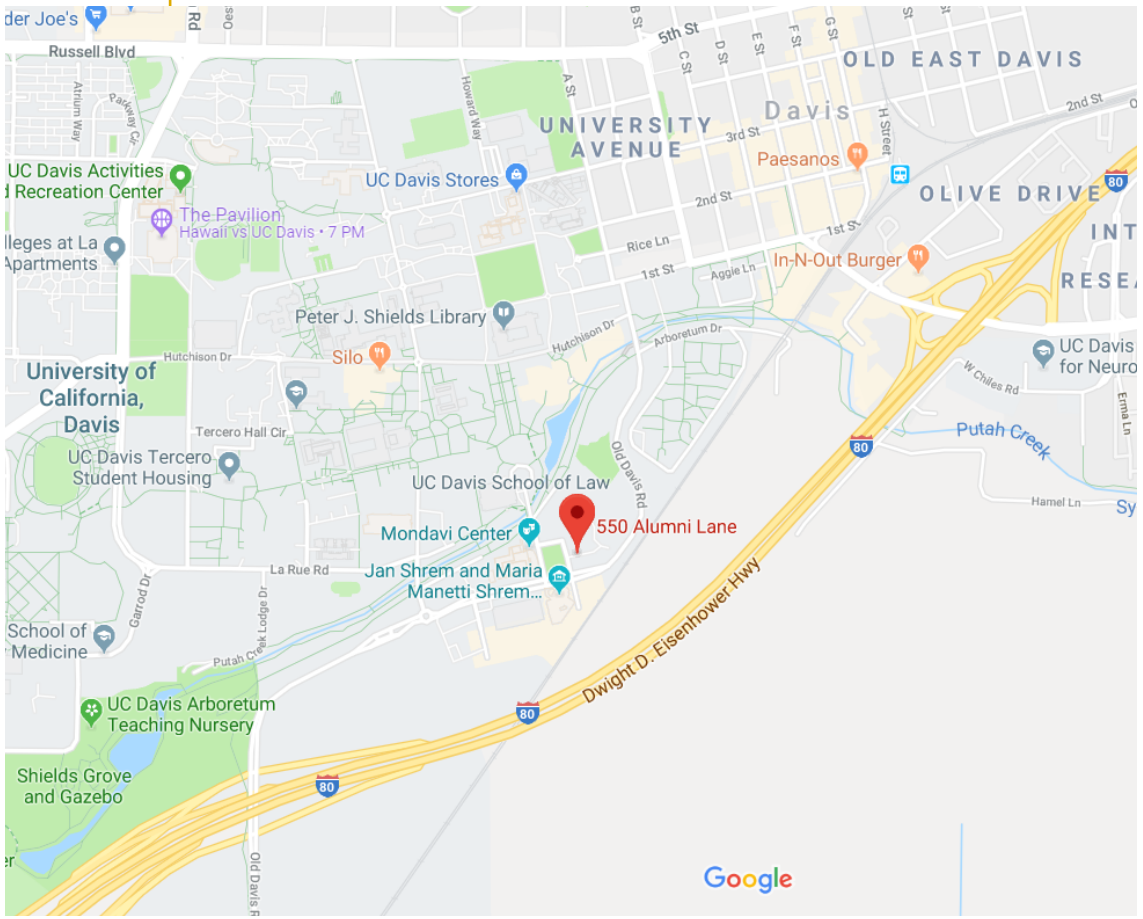
https://www.census.gov/quickfacts/

Diversity matters because dementias can differ based on demographic factors!

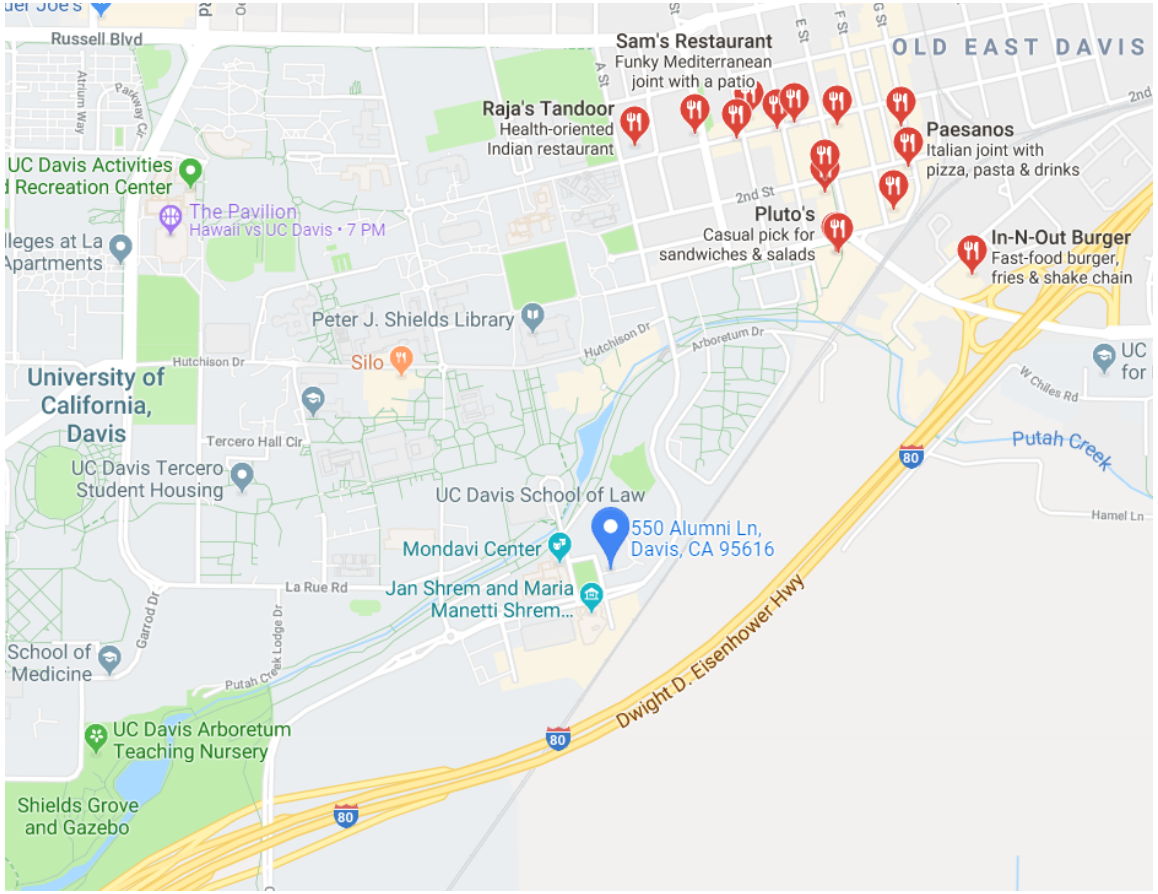


Filshtein TJ, Dugger BN *et al.* Journal of Alzheimer Disease, in press

How can we delve deeper into understanding dementia?



Location of Restaurants near UC-Davis

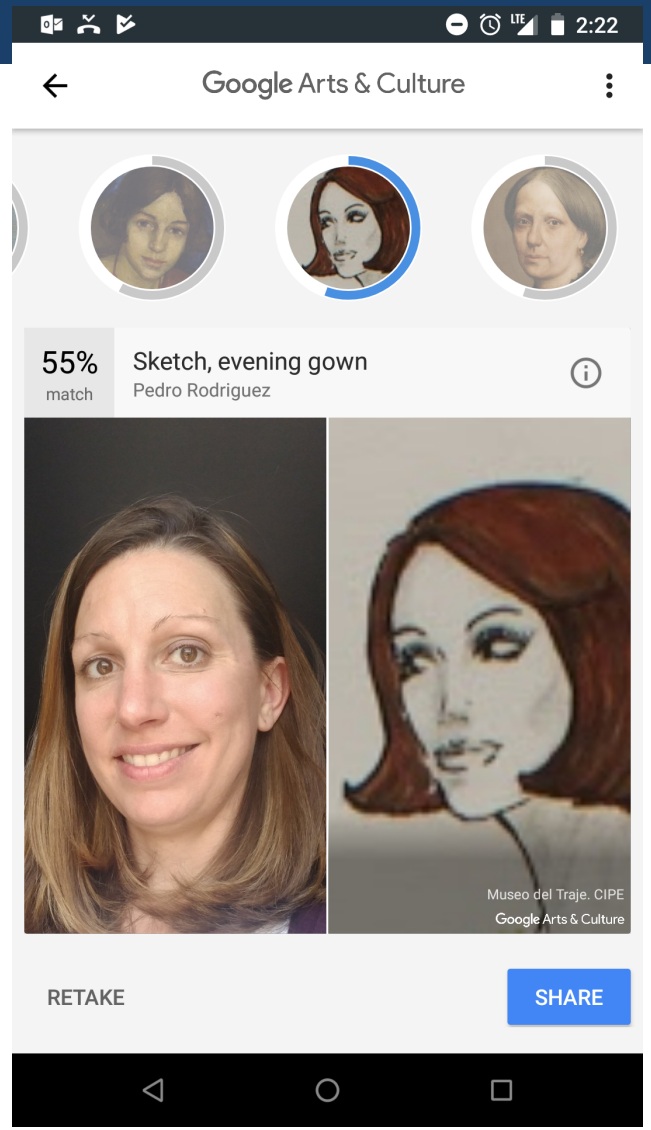


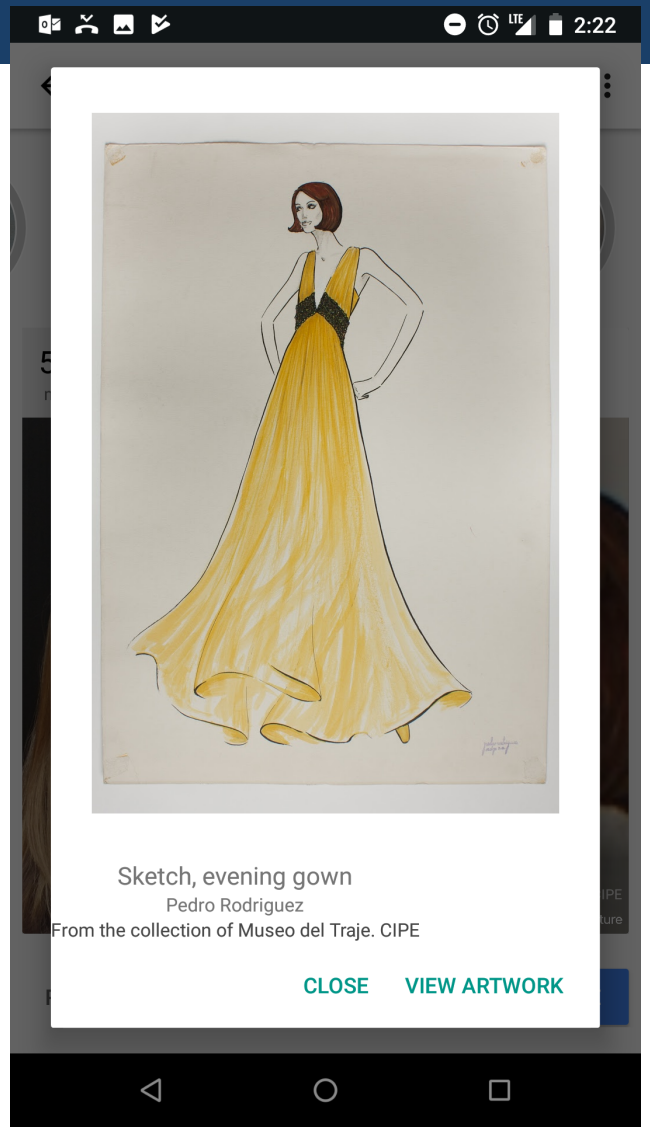
The Age of Machine Learning

"We're looking for someone with your exact qualifications, but a mechanical version."

Machine learning programs are able to make informed judgements and decisions by recognizing patterns in data

Using Machine Learning



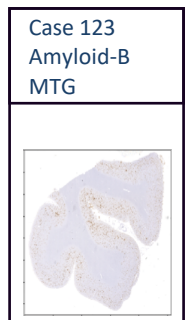


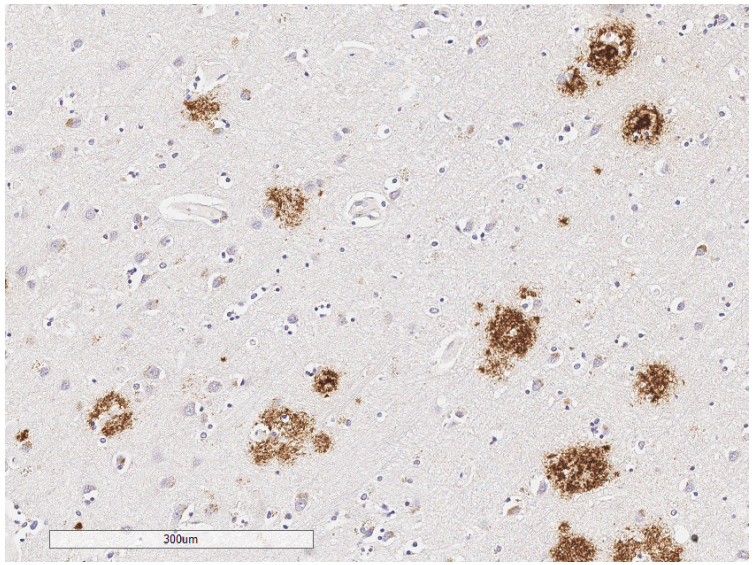
https://artsandculture.google.com/

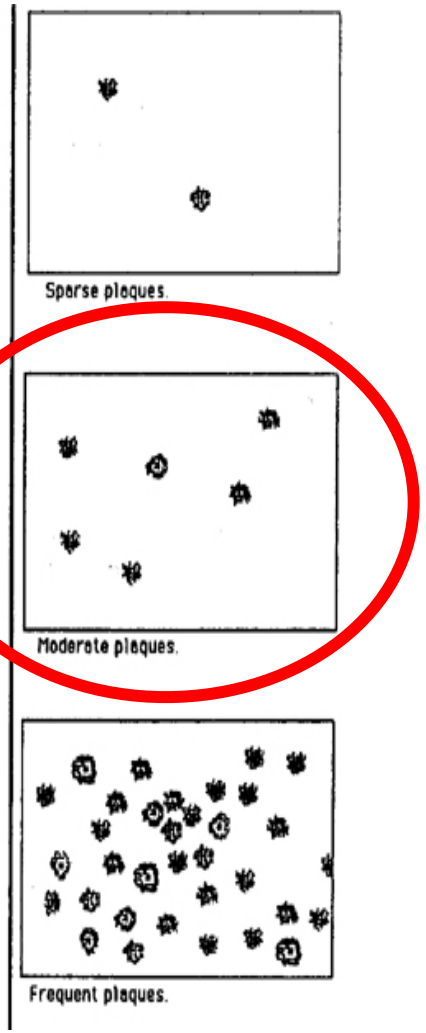
Can we utilize machine learning to aid in understanding the many faces of dementia?

Current standard way of assessing pathologies

Case 123
Amyloid-B
MTG



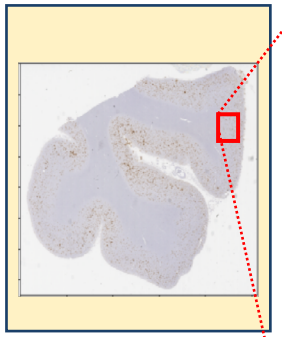




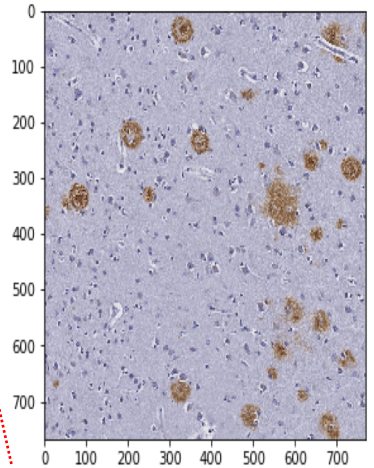
Mirra S, et al. 1991

Here's how machine learning can help

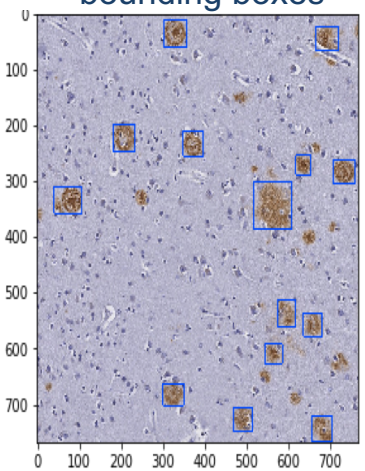
Whole slide image

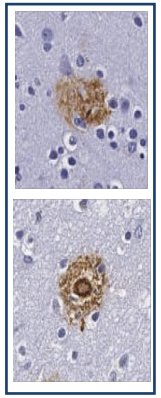


Tile (768 x 768) at 10x



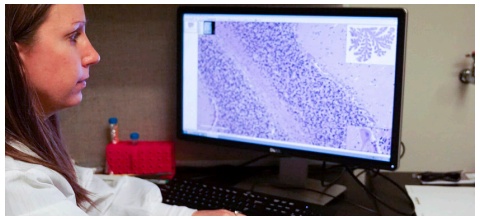
bounding boxes



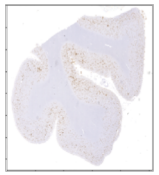


~55,000 cropped (128 x 128) tiles

Digitize glass slides



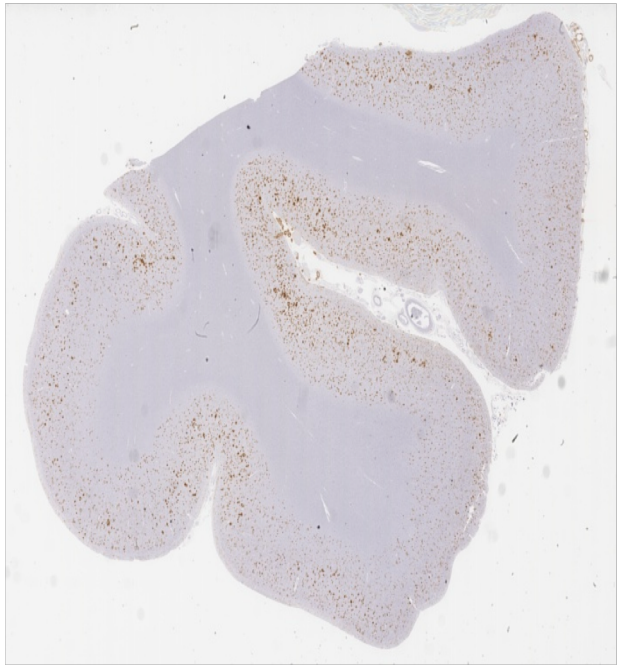
Case 123
Amyloid-B
MTG



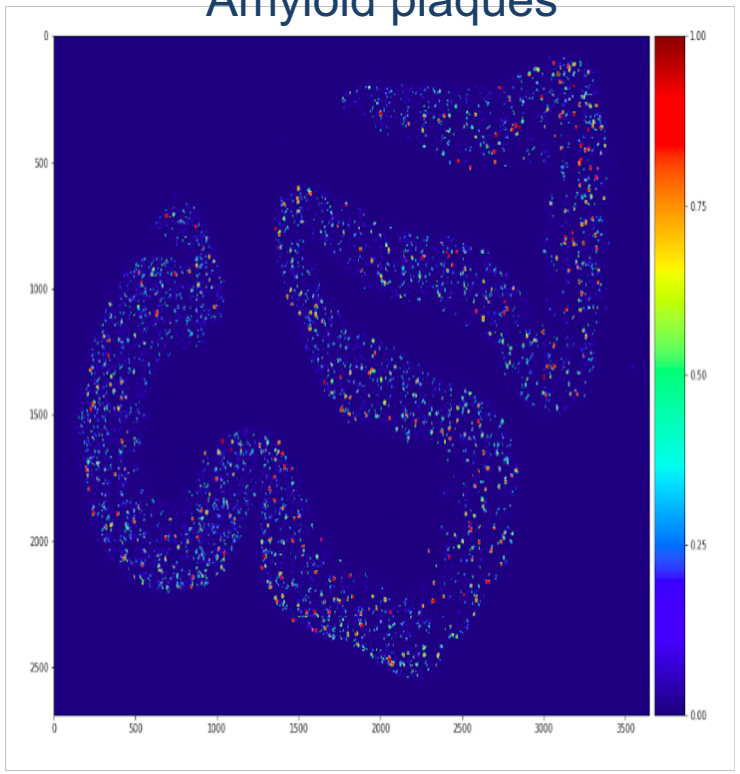
Tang, *et al.* under review

Whole slide heatmaps to see where and how much of each specific pathology is within a slide

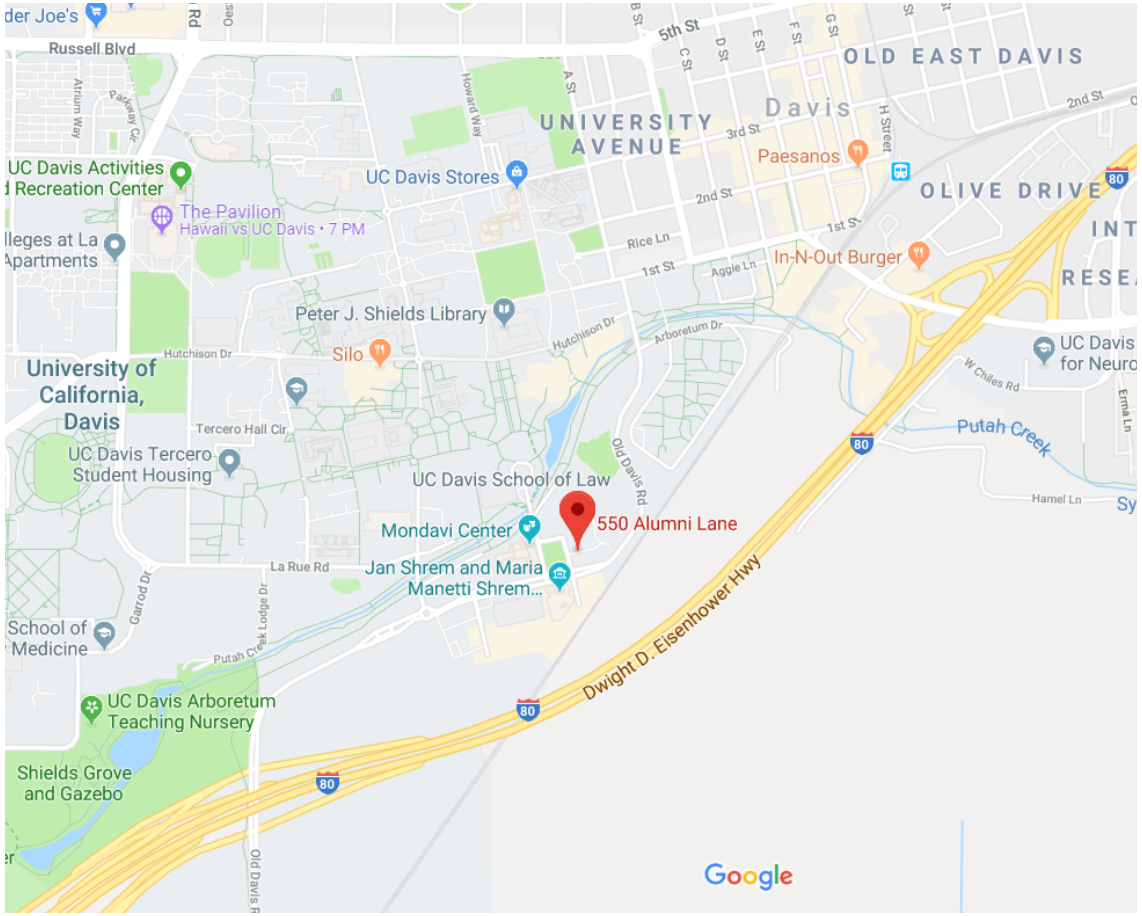
original

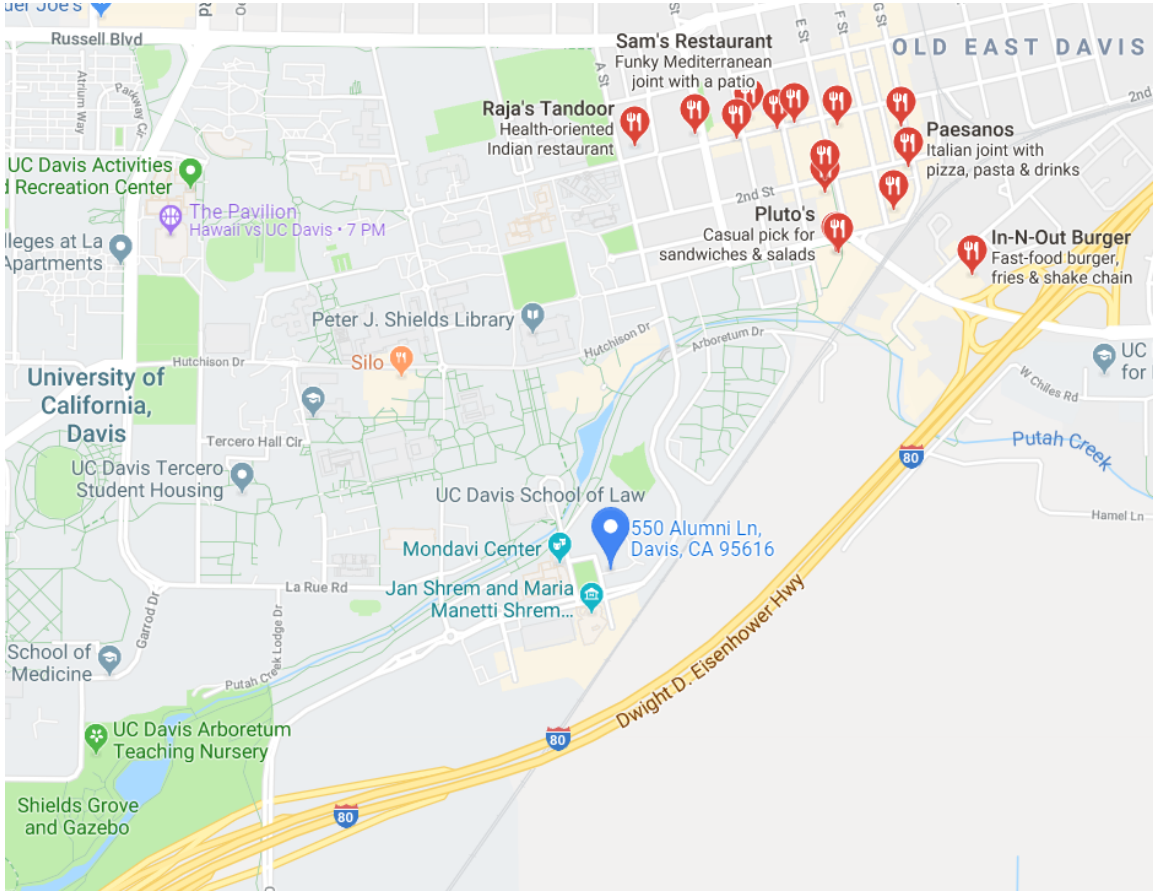


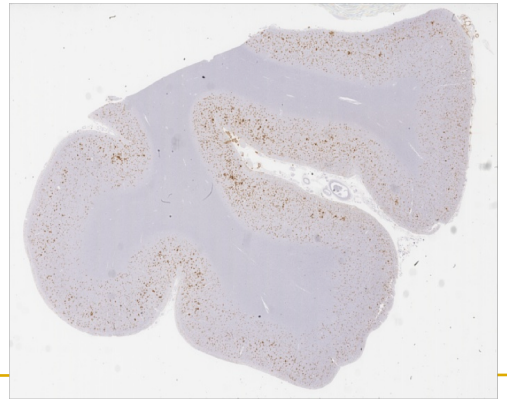
Amyloid plaques



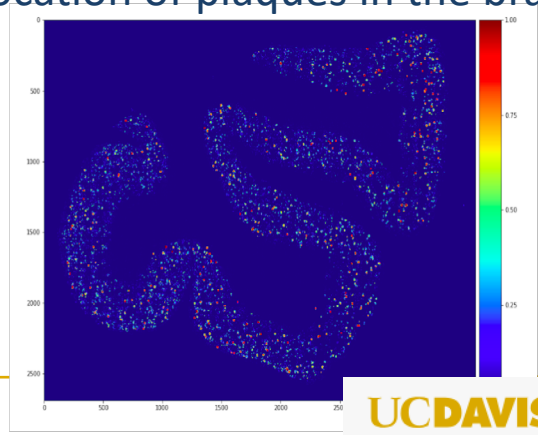
Tang, *et al.* under review







Location of plaques in the brain



What I covered today

- There are many faces of dementia
  - Type of symptoms
  - Underlying pathology
  - Disease stage
  - Concomitant pathologies
  - Demographic variables
- Use of Machine Learning to understand the many faces of dementia

Understanding these different “faces” of dementia matter as it leads to better biomarkers, treatment, and model systems for all who are affected by these devastating diseases

UCDAVIS HEALTH

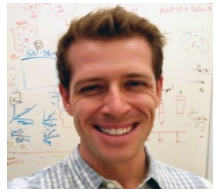
UC DAVIS HEALTH | Alzheimer's Disease Center


Charles DeCarli, MD

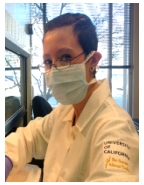

Teresa Jenica Filshtein, PhD


Luis Carvajal-Carmona, PhD


Kelsey Mifflin

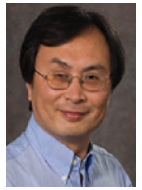

Michael Keiser, PhD (UCSF)

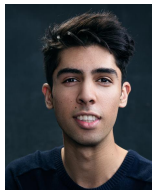

Kangway Chuang, PhD (UCSF)


Kelsey Erickson


Sarah T. Farias, PhD

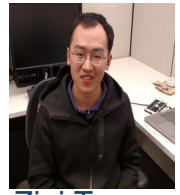

Bruce Reed, PhD


Lee-Way Jin, MD, PhD

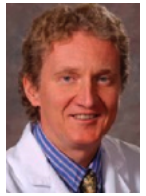

Yamah Hamsafar


Nupoor Adhikari


Harry Vinters, MD (UCLA)

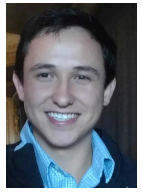

Ziqi Tang (Tisinghua University)


Justin Athey


John M. Olichney, MD


Dan Mungas, PhD


David Atkinson


Welver Suarez


Laurel Beckett, PhD


Paul Lott, PhD

Department of Pathology and Laboratory Medicine Faculty and Staff

Study participants and their families

Clinical and Research Staff


Edwin S. Monuki, MD, PhD (UC- Irvine)

UC DAVIS HEALTH

NATIONAL INSTITUTES OF HEALTH
National Institute on Aging

Thank you!