Dementia and Research

Jennifer Heidmann, MD, FACP
Medical Director, Redwood Coast PACE
Humboldt Senior Resource Center

1

How Does Research Science Work?

- A question with a hypothesis is identified, a study is designed to answer the question and prove (or disprove) the hypothesis
- The study must meet ethical review standards (institutional review board or IRB looks at study and approves if appropriate)
- A good study will have many *diverse* participants, be randomized, and have a placebo-control to compare, over a long enough period of time to ensure validity of results
- A good study can be reproduced by other scientists and should be peer-reviewed

2

How Does Science Work with Dementia Research?

- We have a variety of things to figure out: what actually causes AD (not just associated with it but really causes it)? If people with symptoms have irreversible damage to their brains, how can we identify people without symptoms who are at risk of developing AD? If we do studies on people without AD who are at risk, it could take decades to know what works and what does not, and what do we do in the meantime? Who funds the research and what side benefits might they get from raising hopes? Are drugs/treatments the only thing researchers work on?

3

What is dementia?

The word itself is not very nice or concise (Latin, "out of one's mind")

Meeting criteria for a diagnosis requires both objective testing and a real impact on day to day function

Mild cognitive impairment (MCI) = memory loss without loss of function

Dementia is not a "normal" part of the aging process, however prevalence of dementia increases with age

There are many causes of dementia

In order to treat or even cure dementia, we need to know the cause(s) down to the cellular level

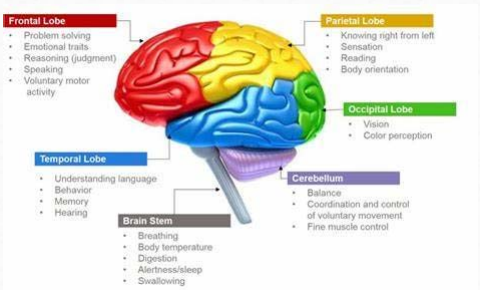
4

Most common types of dementia

- Alzheimer type dementia
- Lewy Body dementia
- Vascular dementia
- Frontotemporal dementia
- All defined by their pathology + associated symptoms
- Often there is overlap

5

Brain Anatomy



6

Global Pandemic

- New case about every 4.1 seconds worldwide
- >60% people living with dementia are in low/middle income countries
- Western Europe/the Americas-peak incidence age 80-89, Asia 75-84, Africa 70-79
- Studies demonstrate worldwide caregiver struggles: time spent caregiving and not doing other activities, emotional strain with more anxiety and depression, economic strain with costs of care + needing to work less to provide care

Epidemiology & Impact of Dementia, Current State & Future Trends. World Health Organization 2015

7

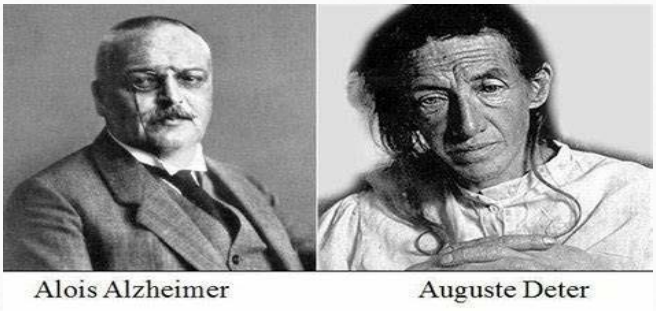
Global Pandemic

- In 2010, global costs of dementia care about $604 billion, estimated increase about 85% by 2030
- % costs more in high income countries despite lower % of dementia cases
- Costs mainly around social care needs (high income countries-more likely to hire care or place into care)
- In all countries dementia syndromes have largest impact on care needs in older people (much more so than other chronic diseases)

Epidemiology & Impact of Dementia, Current State & Future Trends. World Health Organization 2015

8

Auguste Deter and Dr. Alzheimer



Alois Alzheimer Auguste Deter

9

Presenilin-1 mutation

- Auguste's brain showed amyloid plaques and neurofibrillary tangles
- Modern scientists found slides of her brain with mutations in PSEN1 on chromosome 14 when they extracted DNA
- This shows she had autosomal dominant early-onset Alzheimer's Disease
- <2% AD is due to autosomal dominant inherited trait
- A family history of dementia does not mean you will develop dementia

10

Early-onset AD

- Age <65 years old
- <10% cases
- Might be partly due to inheriting gene mutations such as amyloid precursor protein (APP), Presenilin 1(PSEN1-like Auguste) or Presenilin 2(PSEN2)

11

ApoE

Apolipoprotein E is a gene on chromosome 19, may affect how much tau and amyloid in brain

Certain variants of this gene might increase risk of developing AD

Certain variants of this gene might decrease risk of developing AD

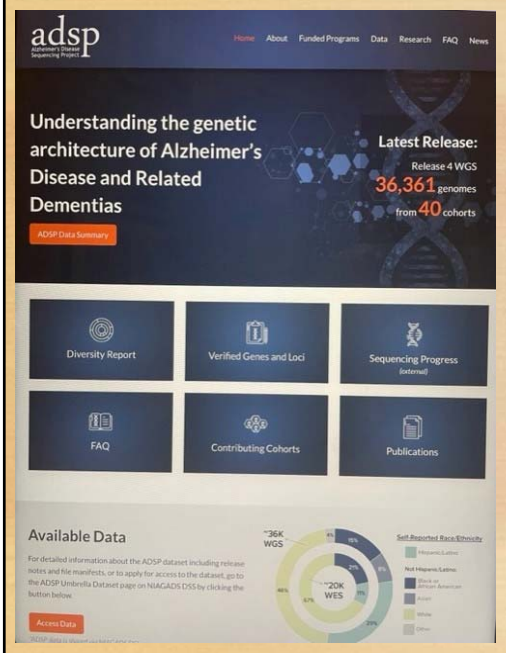
12

What to do with Genes?

- Early onset (like Auguste Dieter) best understood, typically autosomal dominant inheritance
- Late onset AD still may have genetic component, but less clear, and testing usually reserved for research studies
- If genetic testing done, need consent, and need to consider implications for all involved
- Genetic testing can help us understand more about disease, theoretically help develop treatments
- NIA has ongoing studies to better understand the dozens of genes involved in Alzheimer and Alzheimer related dementias

https://www.nia.nih.gov/research/ad-genetics

13



Gene research (NIA)

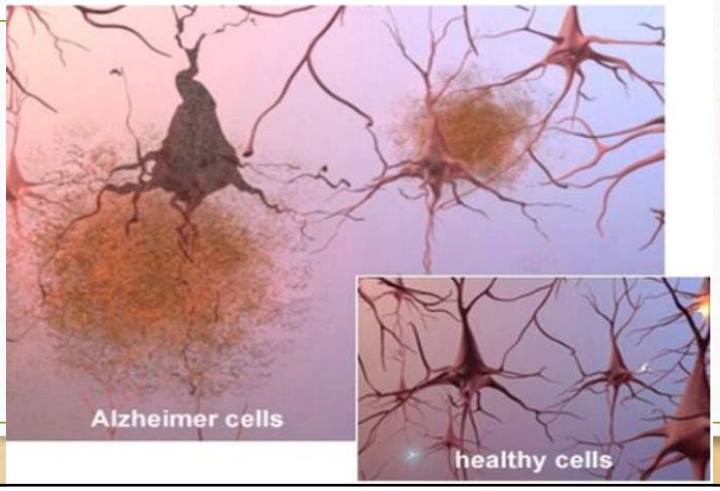
- Finding genes that are associated with increased or decreased risk of AD
- Understanding the actual function of those genes
- Look for genetic subtypes of disease to work toward targeted clinical trials
- Understand AD and ARD across diverse groups of people

AD Sequencing Project: >345 scientists from >62 institutions globally: to capture as much information as possible about genetic component
Alzheimer's Disease Sequencing Project Consortia | National Institute on Aging (nih.gov)

14

Amyloid plaques and neurofibrillary tangles are associated with Alzheimer's Disease

- BUT still not exactly clear what role they play



15

What other tests can we do?

- Cerebrospinal fluid obtained by lumbar puncture (Beta-amyloid, total tau and phosphorylated tau)
- Blood tests-being studied, not ready for prime-time (not clear yet regarding accuracy, significance)
- PET scan-detect amyloid in brain and maybe tau, high resolution MRI (still mainly used in research)
- Looking for other underlying causes (including thyroid disease, vitamin deficiency, severe depression, alcohol, drugs, medications, head trauma, electrolyte disorders)
- Brain biopsy-ante and postmortem, can diverge clinically (can have disease in brain but no clinical symptoms, can have more than one type of dementia causing lesion)
- EEG
- But still mainly a clinical diagnosis (examination and history)
- Recent Progress in Alzheimer's Disease Research, Hane, et al, Journal of Alzheimer's Disease 57 (2017) 645-665
- https://emedicine.medscape.com/article/1134817-workup?form=fpf#c1
- www.ucsfhealth.org/conditions/alzeimers-disease

16

Disease Trajectory

Before people develop symptoms, damage is starting to occur, perhaps decades prior

We would like to use biomarkers (blood, CSF, imaging tests) to try to capture a diagnosis early & be able to study potential treatments to slow progression of disease-no consensus yet on exactly how to use biomarkers in diagnosis

17

Potential Targets for Treatment

- Cholinergic deficits
- Neuritic plaques (composed of amyloid-beta peptide)
- Phosphorlyated tau (neurofibrillary tangles)
- Oxidative damage (more promising in animals than humans)
- Gene mutations
- Ideally a drug could target more than one factor associated with AD

18

Studies and Treatments- cholinesterase inhibitors

Cholinesterase inhibitors-Donepezil (1996), Rivastigmine (2000) Galantamine(2001), increase cholinergic levels in brain, as we think degradation of acetylcholine contributes to neuronal damage in AD

Usually offered in mild to moderate AD

Unlikely to change trajectory of disease, might help some with symptoms

Most data is in Alzheimer dementia, but sometimes used in other forms of dementia

K Sharma, Molecular Medicine Reports June 11, 2019

19

Studies and Treatments- cholinesterase inhibitors

Mild cognitive impairment: evidence of memory loss on testing, not yet affecting functional status

Studies in people with MCI shows little to no affect on progression to dementia or on test scores

Studies show higher rate of side effects in the drugs than placebo, especially gastrointestinal symptoms

Russ & Morling, Cochrane database review, 2012 Sep:2012 (9)

20

Studies and treatments-NMDA receptor antagonist

N-methyl-D-aspartate receptor blockers (keeping glutamate from docking there), possibly slowing influx of calcium and lessening nerve damage (memantine 2003)

Used in moderate to severe AD, off label in mild AD

Effect in moderate AD very small (symptomatic improvement), no benefit seen yet in mild AD

Well-tolerated (not many side effects)

Memantine: efficacy and safety in mild-to-severe Alzheimer's disease, Tampi & van Dyck, Neuropsychiatr Dis Treat 2007 Apr;3(2):245-258

,McShane, et al Memantine for dementia, Cochrane Database of Systematic Reviews, 2019, issue 3

21

Studies and Treatments-monoclonal antibody against amyloid beta

- Aducanumab (2021)-FDA approved last year for mild AD or MCI
- Benefit unclear—although it does reduce amyloid, to date there is no real evidence it helps clinically
- Requires PET scan and/or LP, brain MRI prior to dose 1, and MRIs prior to doses 7 and 12 to assess for microhemorrhages or edema caused by the drug (may be more common in those with APOE4 gene)
- Very expensive ($56,000 per year, not including imaging studies)
- Troubling messaging—hopefully at least it will spur further research rather than slow it (by taking us further down a path that might not benefit patients)

N Lundebjerg, My head just exploded, now what? Aducaumab, J Am Geriatr Soc, 2021;1-3;

Alexander and Karlawish, The problem of Aducanumab for the treatment of Alzheimer Disease, Ann Intern Med, 18 June 2021

22

Lecanemab

- Rushed FDA approval July 2023
- Reduces amyloid beta plaques in the brain
- Tested in early Alzheimer Disease, 1795 people, 18 months, Europe, North America, Asia, age 50-90, placebo-controlled, Black and LatinX people underrepresented
- Less decline cognitively in treatment group than placebo (both with decline), measured by a small difference in a scored test, the CDR-SB scale, with 0.45 point difference noted in trial- not clearly a significant difference in real day to day life

Jan 5, 2023 N Engl J Med 2023; 388:9-21 Lecanemab in Early Alzheimer's Disease

https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(22)02480-1/fulltext

23

Lecanemab

- Controversy among experts: concern about the methods, the loss to follow-up, safety issues (including brain hemorrhage and patient deaths)
- Does it work well enough to justify burden to patients, cost of treatment and risk of ARIA (amyloid-related imaging abnormalities—leaky blood vessels, brain swelling-13% of patients in trial developed ARIA).
- There is some brain shrinkage with the medication-is this worrisome or not?
- Some groups at higher risks of side effects, including Down Syndrome and people who test positive for APOE genotype
- Medications in same family being studied

April 6, 2023 N Engl J Med 2023; 388 Ensuring Public Trust in an Empowered FDA

https://depts.washington.edu/mbwc/news/article/lecanemab#:~:text=What%20is%20the%20controversy%20about,of%20ARIA%20are%20not%20clear.

24

Should people take lecanemab?

- Perhaps something to consider for people with MCI/very early dementia who can understand and agree to all the risks, who can afford the cost, and who have access to the infusion center every 2 weeks (we don't know yet how long people need treatment-indefinitely?) and have access to the ongoing PET scans and/or MRIs and/or lumbar punctures needed to get the treatment.

25

Studies and Treatments- antioxidants

- Vitamin E, selegiline and selenium
- Vitamin E does not prevent progression to dementia or improve cognitive function, might help a little in delaying functional decline in mild to moderate AD
- Vitamin E may be harmful at high doses, including risk of bleeding and hemorrhagic stroke
- Studies of selenium thus far no clinical benefit, high doses may have side effects, can interact with other medications
- No clear benefit seen with selegiline
- Kryscio, et al, Assoc of antiox suppl use & dementia in prevention of AD by Vit E ad Selenium trial, JAMA Neurol. 2017, 74(5):567-573
- Farina et al, Vit E for AD and MCI, Cochrane Database Syst Rev 2017
- Browne et al, Vit E and AD, Clin Interv Aging 2019;14:1303-1317
- Birks & Flicker, Selegiline for Alzheimer's disease. Cochrane Database Sys Rev 2000

26

Vaccine?

- 2023 meeting of Basic Cardiovascular Sciences Scientific Sessions-abstract presented by group from Tokyo about vaccine tested in mice that targets cells expressing senescence-associated glycoprotein (SAGP)
- Reduced amyloid deposits and reduced some inflammatory markers
- The mice who received the vaccine appeared to do better than those not vaccinated (placebo)
- https://newsroom-heart.org (abstract P3004)

27

Other research: diagnostic scales and tests

CDRS is used to score severity of dementia (from normal to severe)

MMSE, MOCA, RUDAS, SLUMS to screen for dementia and/or monitor progression

Must be validated (studied in enough people and correlated with other data to predict accuracy)

28

Clinical Dementia Rating Scale

- Looks at memory, orientation, judgement and problem solving, community affairs, home and hobbies, personal care. Studied for interrater reliability and neuropathological concurrence
- Continued studies needed to evaluate scale in diverse populations

Hughes, et al, The British Journal of Psychiatry, Volume 140, Issue 6, June 1982, pp 566-572

Morris, JC. Neurology, 1993;43(11)

29

Montreal Cognitive Assessment (MoCA)

- Developed in 1995 for detection of MCI
- Available in more than 30 languages
- May have better sensitivity for executive and language dysfunction than other tests (eg MMSE)
- Biased toward education level
- Validated in people aged 55-85, in a variety of conditions

MoCA Validation Study Nasreddine et al, JAGS 2005

30

Rowland Universal Dementia Scale (RUDAS)

- Developed to address influence of educational, culture, gender and language on screening tests for dementia
- Compares favorably to other tests (eg MMSE)
- Sensitivity 94%, specificity 54% (MoCA 97/31) for detection of MCI and dementia

Goudsmit, M, et al, Dement Geriatr Cogn Disord Extra 2018;8:290-305

C. Brymer, etal, Innovation in Aging, Volume 1, 30 June 2017

31

The St Louis University Mental Status (SLUMS)

- Tested in mostly white male VA patients
- Follow up studies show probably helpful screening tool in older adults with complex medical issues, similar to MMSE
- Still need more studies in diverse populations

Clinical gerontologist Volume 45, 2022

32

Screening versus testing?

- Dementia tests try to look at different aspects of brain function. Most used in people who have concerns about memory (thus a TEST), with fair ability to pick up mild to moderate cognitive issues.
- Screening implies looking for a disease in someone who is asymptomatic (eg mammograms, pap smears, colonoscopies at certain age)
- No clear direction on a full population dementia screen
- If a test is done, need to know what to do with results. AN ABNORMAL TEST DOES NOT=A DIAGNOSIS OF "DEMENTIA"
- Another way to test is through an "informant questionnaire" (family members/care givers/friends)

33

Other Research: Driving

Review of studies determined useful criteria for predicting risk for unsafe driving:	-Clinical Dementia Rating Scale (CDRS)	-Caregiver report that driving is unsafe or marginal	-a history of automobile crashes or citations
-person is driving less miles or self-reports avoiding situations	-Mini Mental Status Exam (MMSE) 24 or less	-impulsive/aggressive personality characteristics	Iverson, DJ et al, Neurology 2010;74(16)1316

34

Other research: wandering

- Who is at risk? All people wth dementia, maybe men>women, regardless of setting
- About 65% people with dementia are in presence of a caregiver we they get lost, Constant supervision can decrease risk, including day centers
- Use of GPS tracking devices and having identification with the person at all times can reduce risk of harm
- Alzheimer Association and MedicAlert have program call 24/7 Wandering Support (fees involved) *medicalert.org/alz*

Rowe MA, et l Mayo Clinic Proc. 2004;79(11):1417

35

Other research: living alone

- How can we predict who might be harmed?
- Study of 139 people, 65 yo+, memory loss, lived alone, followed for 18 mos
- Harm predictors: feeling they had fewer social supports, lower score on MMSE, COPD, CVD
- 21.6% participants had incident of harm

Tierney, MC et al, J Am Geriatr Soc. 2004;52(9):1435

36

How to involve people in research?

- The study looking at living alone faced challenges: it took 3 years to recruit the 139 people. How to track them down if they have difficulty coming to appointments, etc?
- Who signs the consent for research?
- People may be reluctant to participate for fear of losing independence (valid concern)

Soniat BA, Dementia Patients who live alone:research and clinical challenges, J Am Geriatr Soc:204;52(9):1576

37

Other Research-Decision making and finances

- A few studies look at financial capacity. Difficult to measure with clearly attached outcomes. Do show correlation between all stages of dementia and reduced capacity to manage finances, risk for fraud schemes, difficulty with planning.
- Could studies look at interventions to promote financial independence for as long as possible?

Okonkwo, OC et al, J Am Geriatr Soc. 2006;54(11):1745

Griffith, HR et al, Neurology 2003;60(3):449

Martin, R et al, Am J Geriatr Psychiatry.2008;16(3):209

38

Other research-"behaviors"

- Psychosis (hallucinations and delusions) –can occur with any of the common causes of dementia
- Antipsychotic drugs are used off label, but have side effects and may increase risk of death in older people with dementia
- HARMONY trial looking at safety and efficacy of pimavanserin-works differently than other antipsychotics
- Age 50-90, dementia, psychotic symptoms for 2+ mos, reliable caregiver to report symptoms, followed validated scoring scales for symptoms, did randomized discontinuation arm (looking at relapse rate)
- Promising results but small study, mixed dementia types, data not enough to start using, need more studies

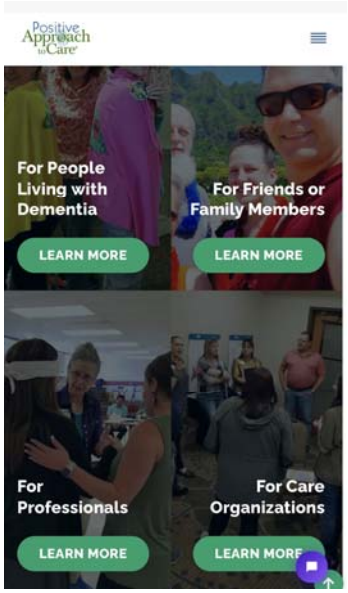
Pierre N., et al, Trial of Pimavanserin in Dementia-Related Psychosis, N Engl J Med 2021;385:309-319

39

Teepa Snow

Positive Approach to Care: team made up of people living with dementia, experts, mentors, trainers

Developing ways to better care for each other while we await the treatments and cures



40

Too Good to be True

- Pills or other things (like apps/games) sold OTC to prevent/cure dementia is a huge business
- Supplements for "brain health" are projected to reach $5.8 billion in sales by 2023
- Might be better to put money toward other things to improve day to day life

UCSF Magazine summer 2021, Elizabeth Daube

41

Can video games prevent memory Loss?

- Virtual reality game (Labyrinth-VR) being studied for potential to reduce decline in people with mild cognitive impairment
- Players wear head mounted VR display, and go through neighborhoods with increasingly difficult levels of navigation. Requires walking in place and moving body.
- 48 people, mean age 69, average cognition, half played the game, half "placebo" (just regular video games), 12 hours over 4 weeks. People in test group showed improvement in "high fidelity" memory (long term memory with ability to tell apart new objects with similar ones seen before) compared with placebo group.
- UCSF Magazine March 22, 2021 Emily Hayes
- Wais, P.E., et al Virtual reality video game improves high-fidelity memory in older adults. Sci Rep 11, 2552 (2021)

42

Study of Modifiable Risk Factors for Dementia

- Focus on heart health in early adulthood-smoking, lack of exercise, unhealthy diet and obesity at younger age correlates with higher risk of cognitive decline later in life

Study looking at data from 4 studies, 15,000 adults, ages 18-30 and 45-95

Yaffe, K et al, Cardiovascular Risk factors Across the Life Course and Cognitive Decline, A Pooled Cohort Study, Neurology Apr 2021, 96 (17) e2212-e2219

43

44

Exercise and learning new things, social connections, adequate sleep improve cognition.

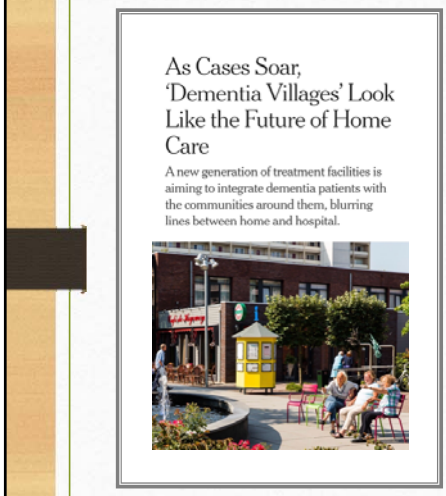
- You do not have to buy a product to add these things to your repertoire of dementia prevention.
- Still, we should continue to study affects of activities on the mind so we have more insight into what helps, and can better understand the brain and memory.

45

What goals should we have when doing dementia research?

- Cure? ($$-where the money is)
- Prevention? ($$)
- Managing symptoms and behaviors? ($)
- Reducing burdens on caregivers? (should be an economic and humanitarian priority)
- Making our society more dementia-friendly? (where the money isn't)

46


As Cases Soar, 'Dementia Villages' Look Like the Future of Home Care

A new generation of treatment facilities is aiming to integrate dementia patients with the communities around them, blurring lines between home and hospital.

NYT July 2,2023 Joann Plockova

WORLD ALZHEIMER REPORT 2020

- "Design, dignity, dementia: Dementia-related design and the built environment"
- "global perspective of dementia-related design that takes a cross cultural approach, reflects regional and economic differences in low-, middle- and high-income countries and considers urban versus rural settings"
- alzint.org

47

Future Directions

- Yes, let's keep working to find a cure or prevention
- We need people to participate in trials and to fund them. Even treatments that do not work in trials gets us closer to a better understanding of the disease and potential ways to fight it
- Alzheimer's and Related Dementias Education and Referral Center, national Institute on Aging https://www.nia.nih.gov/health/about-adear-center
- TrialMatch Alzheimer's Association https://www.alz.org/alzheimers-dementia/research-progress/clinical-trials/trialmatch

48

Future Directions

- While researching medical treatments and improved ways to diagnose AD, we should also direct funding toward:

-Support for caregivers and families

-Promoting independence for as long as possible in those with AD

-Better designing society to allow access for the less abled

-Rethinking institutionalization

49

Thank you!

50