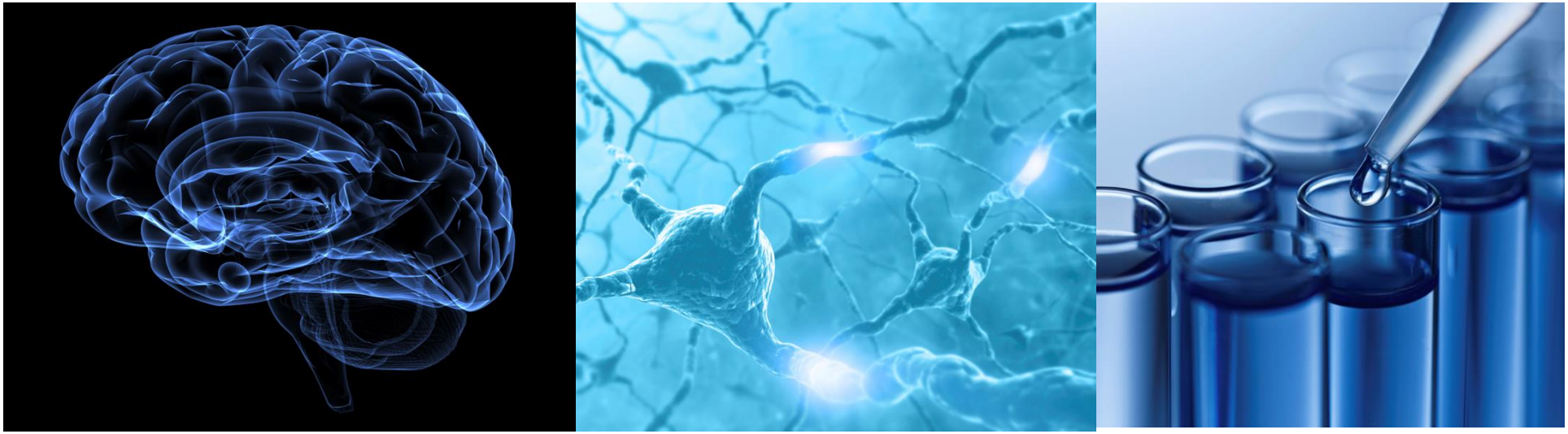

Latest in Alzheimer's Disease: The What, The How & The Hope

Heather M. Snyder, Ph.D.
Medical & Scientific Relations

alzheimer's association®

Objectives

1. Name at least two possible risk factors for Alzheimerôs
2. Discuss advances in the development of at least one type of biological marker
3. Describe current medications available for Alzheimerôs
4. Name and describe two of the five prevention efforts in Alzheimerôs disease

Topics for Discussion:

- About the Alzheimerôs Association
- Landscape of Alzheimerôs disease
- Early detection and diagnosis
- Current therapies and what is in trials today
- Next generation of clinical trials

Our vision is a world without Alzheimer's disease

Our mission:

- Advance research
- Provide care and support
- Increase Concern & Awareness
- Public Policy & Advocacy Efforts

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Research Roundtable

alzheimer's association® AAIC 14

International Research GRANT PROGRAM

alzheimer's association®

GAAIN

alzheimer's association®

ISTAART

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The Alzheimer's Association is a GLOBAL LEADER in research.

alzheimer's association®

trialmatch™

WW-ADNI

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Amyloid Imaging Taskforce (AIT)

SNMMI SOCIETY OF NUCLEAR MEDICINE AND MOLECULAR IMAGING

alzheimer's association®

the compassion to care, the leadership to conquer

alzheimer's association® | Alzheimer's & Dementia®

THE JOURNAL OF THE ALZHEIMER'S ASSOCIATION

Alzheimer

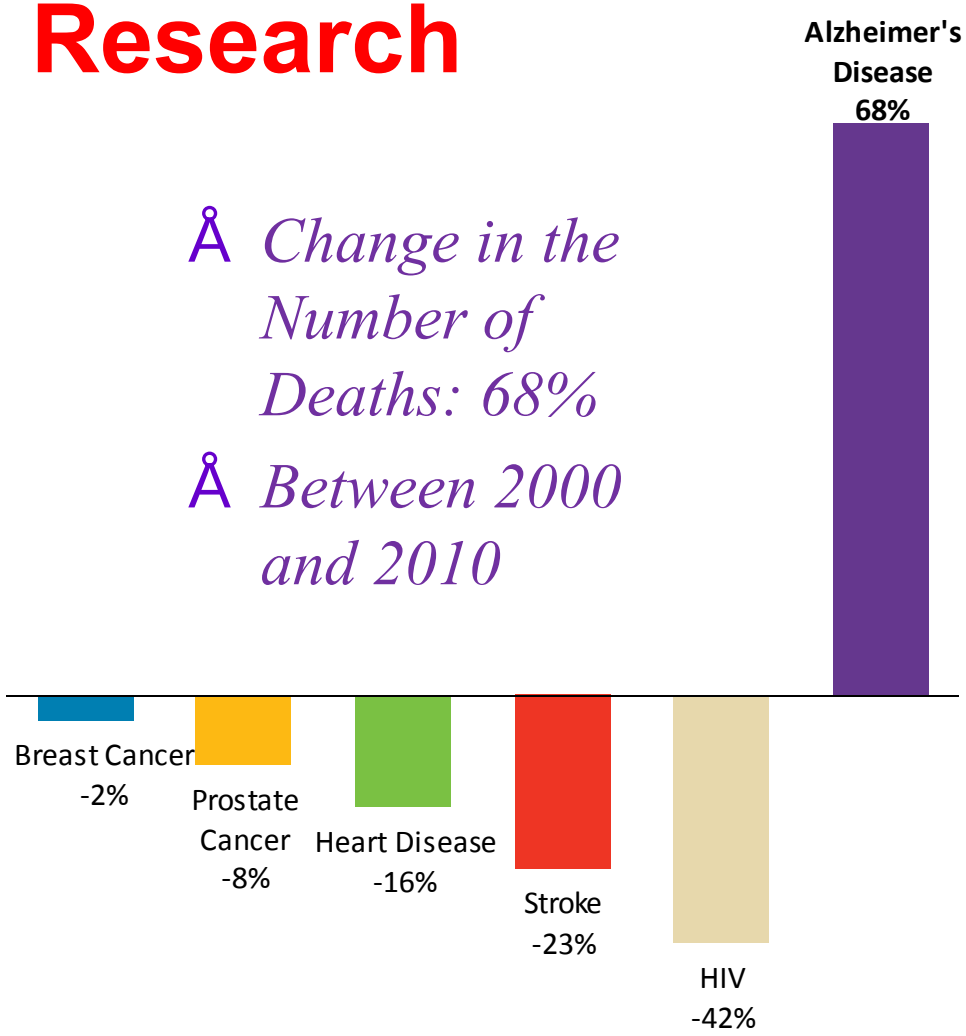
2014 Alzheimer

- More than 5 million people living with Alzheimerôs
  - Including 200,000 >65 with younger-onset.
  - 1 in 9 over age 65 and 1 in 3 over age 85
- Over 15 million people providing care / support for someone with Alzheimerôs or related dementia

Landscape of Alzheimer's Hope In Research

- 6th leading cause of death across all ages
- 5th leading cause of death for those aged 65 and older
- Only cause of death among the top 10 in America without a way to prevent, cure or even slow its progression.

- *Change in the Number of Deaths: 68%*
- *Between 2000 and 2010*



Based on preliminary 2010

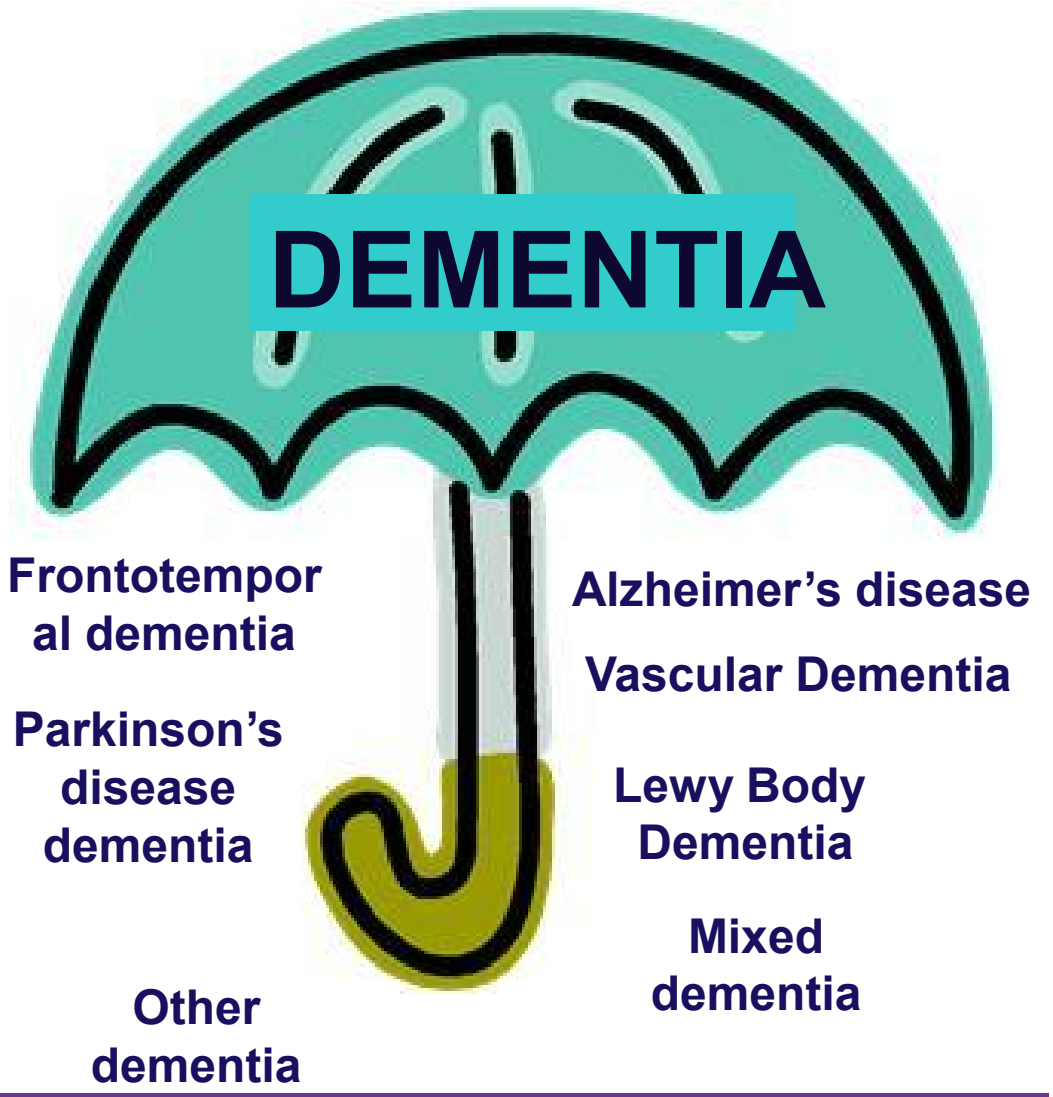
National Plan to Address Alzheimer's disease

- Goal: "Prevent and Effectively Treat Alzheimer's by 2025"
- Key strategies:
  - Increase clinical studies enrollment
  - Expand scale and scope of research
  - Accelerate drug development

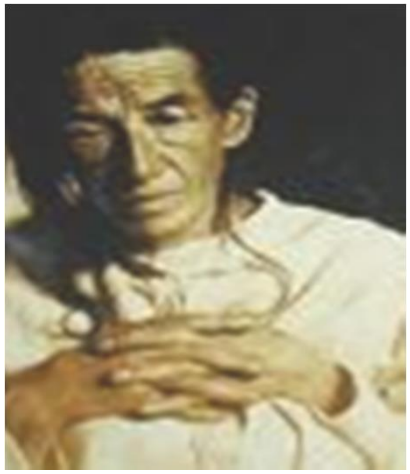
Seth Rogen Testifies Before Senate Appropriations Committee

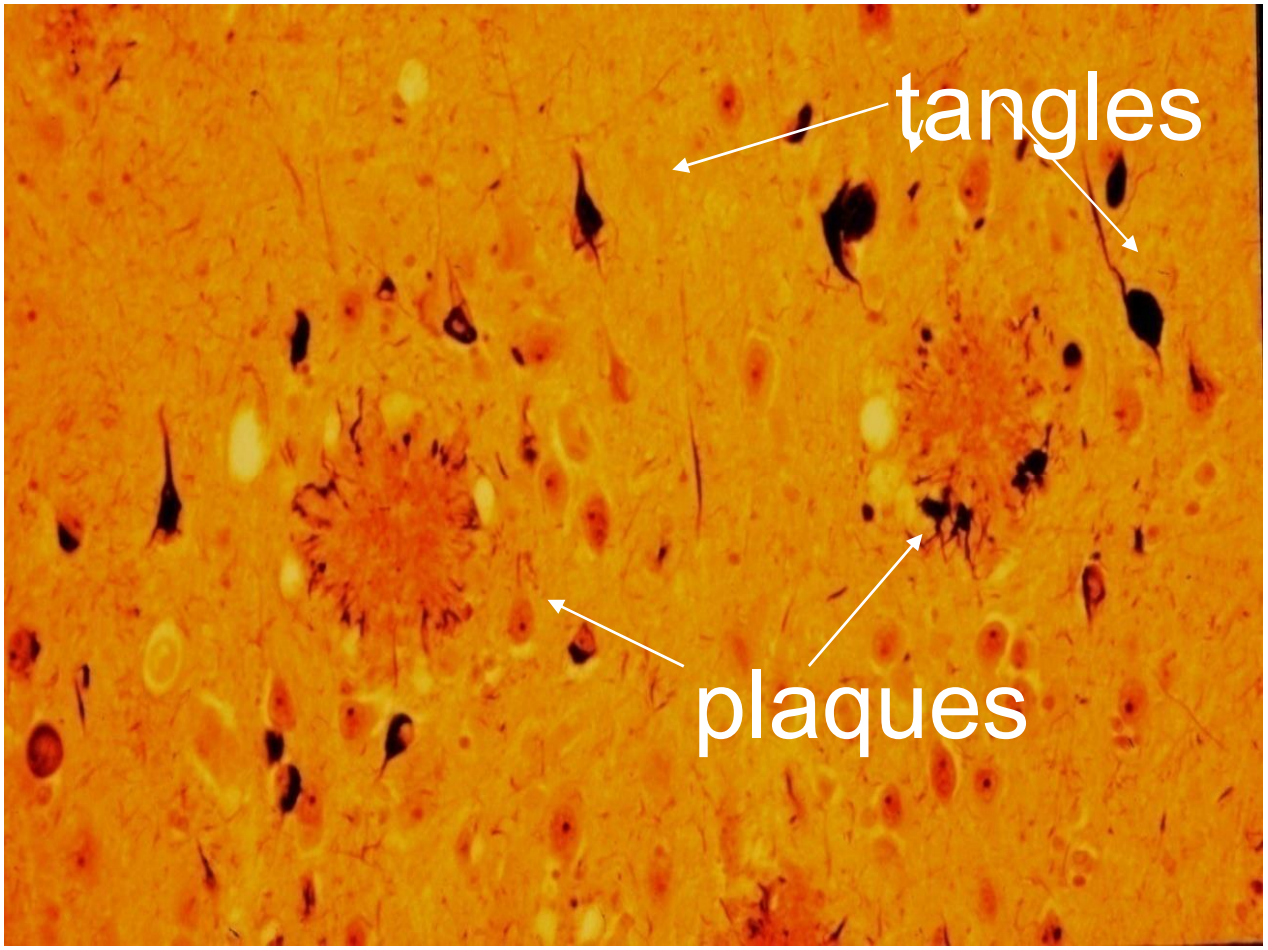
Types of Dementia

- Dementia is the loss of memory due to changes in the brain
- Alzheimer's is the most common form
- Definite diagnosis used to require autopsy
- Many mixed cases
- Many memory disorders are reversible and not truly dementia



History of Alzheimer's Disease





Risk Related to Alzheimer's

- Age: The greatest known risk factor
- Heart-head connection
  - Increased risk suspected if high blood pressure, heart disease, stroke, diabetes and high cholesterol
- Head injury
- Family History
  - Risk and deterministic genes

Understanding Genetics Linked to Alzheimer's

LETTER

doi:10.1038/nature11283

A mutation in *APP* protects against Alzheimer's disease and age-related cognitive decline

Thorlakur Jonsson[1], Jasvinder K. Atwal[2], Stacy Steinberg[1], Jon Snaedal[3], Palmi V. Jonsson[3,8], Sigurbjorn Bjornsson[3], Hreinn Stefansson[1], Patrick Sulem[1], Daniel Gudbjartsson[1], Janice Maloney[2], Kwame Hoyte[2], Amy Gustafson[2], Yichin Liu[2], Yanmei Lu[2], Tushar Bhangale[2], Robert R. Graham[2], Johanna Huttenlocher[1,4], Gyda Bjornsdottir[1], Ole A. Andreassen[5], Erik G. Jönsson[6], Aarno Palotie[7], Timothy W. Behrens[2], Olafur T. Magnusson[1], Augustine Kong[1], Unnur Thorsteinsdottir[1,8], Ryan J. Watts[2] & Kari Stefansson[1,8]

Views of the Earth, Copyright © 2010 by Christoph Hormann http://earth.imagico.de/

ORIGINAL CONTRIBUTION

Variants in the ATP-Binding Cassette Transporter (*ABCA7*), Apolipoprotein E ε4, and the Risk of Late-Onset Alzheimer Disease in African Americans

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Adam Naj, PhD
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Badri Narayan Vardarajan, PhD
Li-San Wang, PhD
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Denis Evans, MD
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Joseph D. Buxbaum, PhD
Jill R. Murrell, PhD
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Goldie S. Byrd, PhD
Walter A. Kukull, PhD
Tatiana M. Foroud, PhD
Jonathan L. Haines, PhD
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Margaret A. Pericak-Vance, PhD
Gerard D. Schellenberg, PhD
Richard Mayeux, MD, MSc

See also pp 1527 and 1533.

Author Video Interview available at www.jama.com.

Importance Genetic variants associated with susceptibility to late-onset Alzheimer disease are known for individuals of European ancestry, but whether the same or different variants account for the genetic risk of Alzheimer disease in African American individuals is unknown. Identification of disease-associated variants helps identify targets for genetic testing, prevention, and treatments.

Objective To identify genetic loci associated with late-onset Alzheimer disease in African Americans.

Design, Setting, and Participants The Alzheimer Disease Genetics Consortium (ADGC) assembled multiple data sets representing a total of 4859 African Americans (1968 case participants, 2891 control participants) 60 years or older that were collected between 1987 and 2011 at multiple sites. The association of Alzheimer disease with genotyped and imputed single-nucleotide polymorphisms (SNPs) was assessed in case-control and in family-based data sets. Results from individual data sets were combined to perform an inverse variance–weighted meta-analysis, first with genome-wide analysis and subsequently with gene-based tests for previously reported loci.

Main Outcomes and Measures Presence of Alzheimer disease according to standardized criteria.

Results Genome-wide significance in fully adjusted models (sex, age, *APOE* genotype, population stratification) was observed for a SNP in *ABCA7* (rs115550680, allele = G; frequency, 0.09 cases and 0.04 controls; odds ratio [OR], 1.79 [95% CI, 1.47-2.12]; $P = 2.2 \times 10^{-9}$), which is in linkage disequilibrium with SNPs previously associated with Alzheimer disease in Europeans ($0.6 < D' < 0.9$). The effect size for the SNP in *ABCA7* was comparable with that of the *APOE* ε4–determining SNP rs429358 (allele = C; frequency, 0.30 cases and 0.18 controls; OR, 2.31 [95% CI, 2.19-2.42]; $P = 8.9 \times 10^{-307}$). Several loci previously associated with Alzheimer disease but not reaching significance in genome-wide analyses were replicated in gene-based analyses accounting for linkage disequilibrium between markers and correcting for number of tests performed per gene (*CR1*, *BIN1*, *EPHA1*, *CD33*; 0.0006 < corrected $P < 0.01$).

Conclusions and Relevance In this meta-analysis of data from African American participants, Alzheimer disease was significantly associated with variants in *ABCA7* and with other genes that have been associated with Alzheimer disease in individuals of European ancestry. Replication and functional validation of this finding is needed before this information is used in clinical settings.

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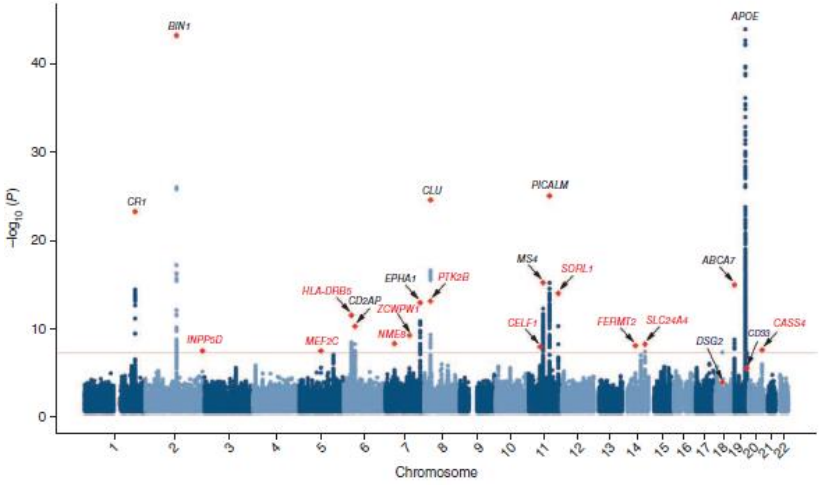
International Genomics Alzheimer's Program (IGAP)

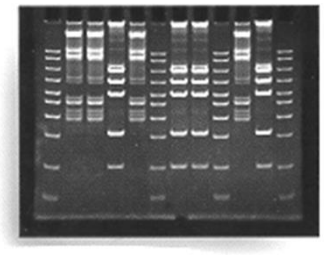
- In 2010, funded international collaboration of research groups in France, UK, & US
- Compiled nearly 75,000 individualsô genetic data Goal to understand role genes play in Alzheimerôs
- Confirmed 9 and identified 11 new genetic areas of interest

nature genetics

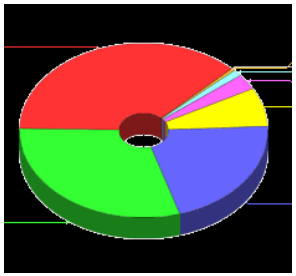
Meta-analysis of 74,046 individuals identifies 11 new susceptibility loci for Alzheimer's disease



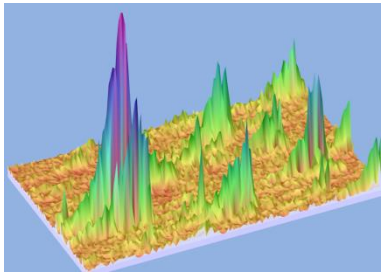
Advances in Early Detection



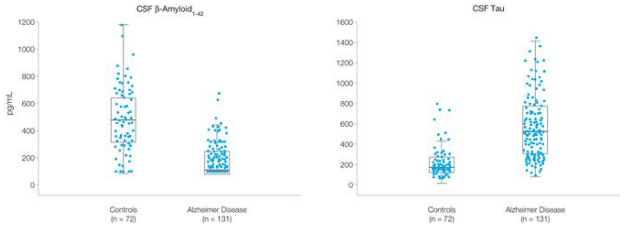
Genetics



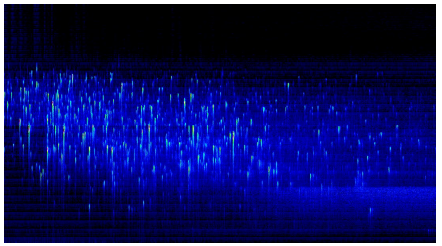
Epidemiology



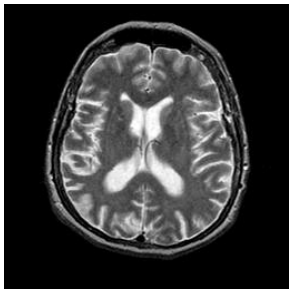
Protein production
& clearance rates



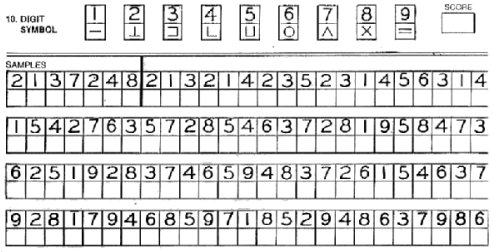
Targeted biochemical



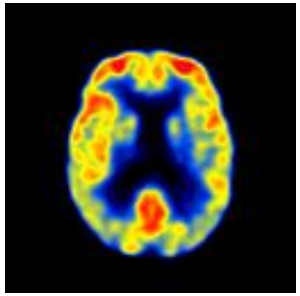
Proteomics



Structural Neuroimaging



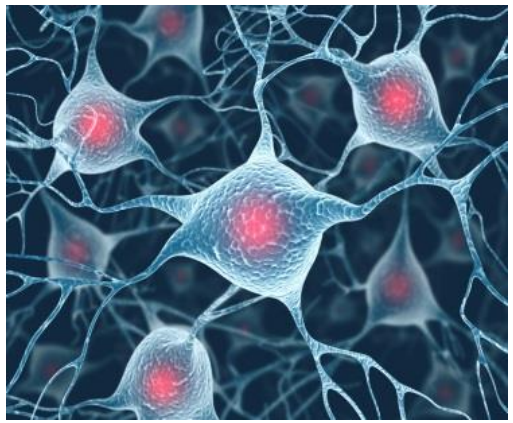
Neuropsychometric tests



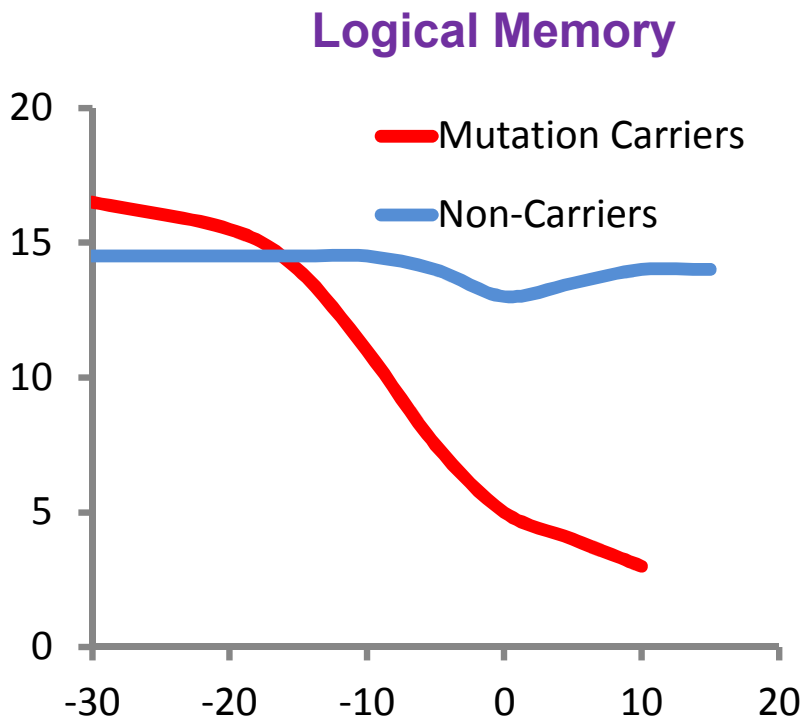
Functional and Molecular Imaging

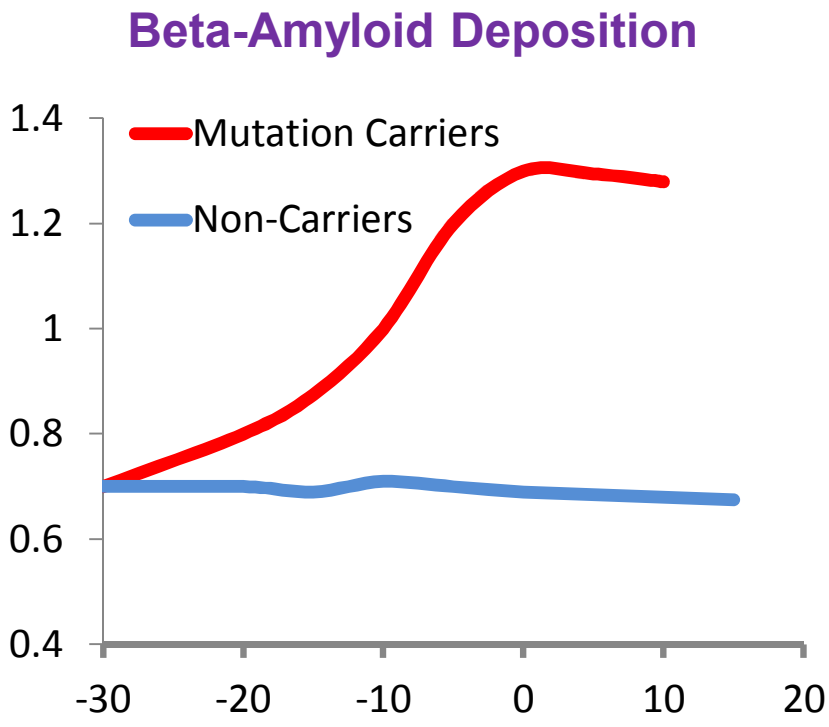
What is a Biomarker?

- Biological marker to measure change
- Reliable predictor and indicator of disease and disease progression
- Examples include:
  - Glucose for insulin resistance and diabetes
  - T cell count for HIV/AIDS



Dominantly Inherited Alzheimer Network (DIAN) Observational Trial

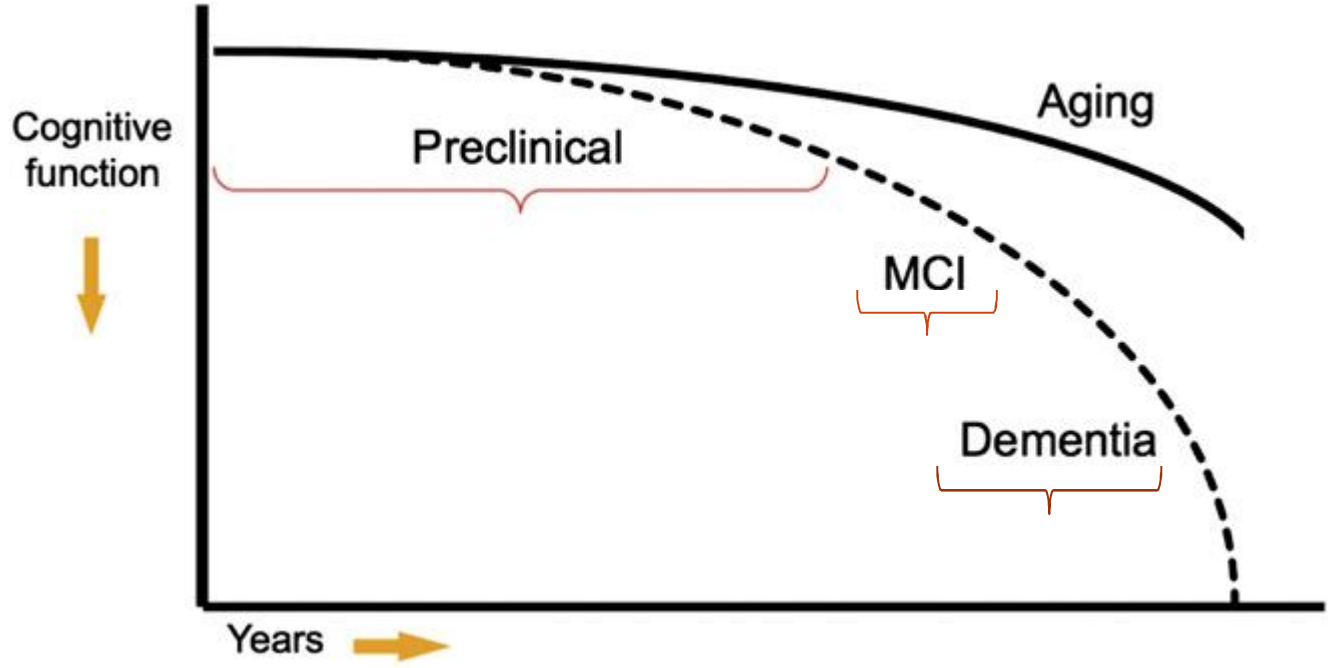




Bateman et al. (2012) N Eng J Med 367: 795- 804

Continuum of Alzheimer's Disease

Normal **Alzheimer's disease**



Adapted from Sperling et al. 2011

Modernizing the Diagnosis of Alzheimer's Based on a Continuum

The diagnosis of dementia due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease

Guy M. McKhann[a,b,*], David S. Knopman[c], Howard Chertkow[d,e], Bradley T. Hyman[f], Clifford R. Jennifer J Martin N. Ro

2011

The diagnosis of mild cognitive impairment due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease

, Bruno Dubois[e], man[i,j], William J. Jagust[k], s[o], Creighton H. Phelps[p]

Toward defining the preclinical stages of Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease

Reisa A. Sperling[a,*], Paul S. Aisen[b], Laurel A. Beckett[c], David A. Bennett[d], Suzanne Craft[e], Anne M. Fagan[f], Takeshi Iwatsubo[g], Clifford R. Jack, Jr.[h], Jeffrey Kaye[i], Thomas J. Montine[j], Denise C. Park[k], Eric M. Reiman[l], Christopher C. Rowe[m], Eric Siemers[n], Yaakov Stern[o], Kristine Yaffe[p], Maria C. Carrillo[q], Bill Thies[q], Marcelle Morrison-Bogorad[r], Molly V. Wagster[r], Creighton H. Phelps[r]

Alzheimer's & Dementia

Modernizing the Diagnosis of Alzheimer's Based on a Continuum

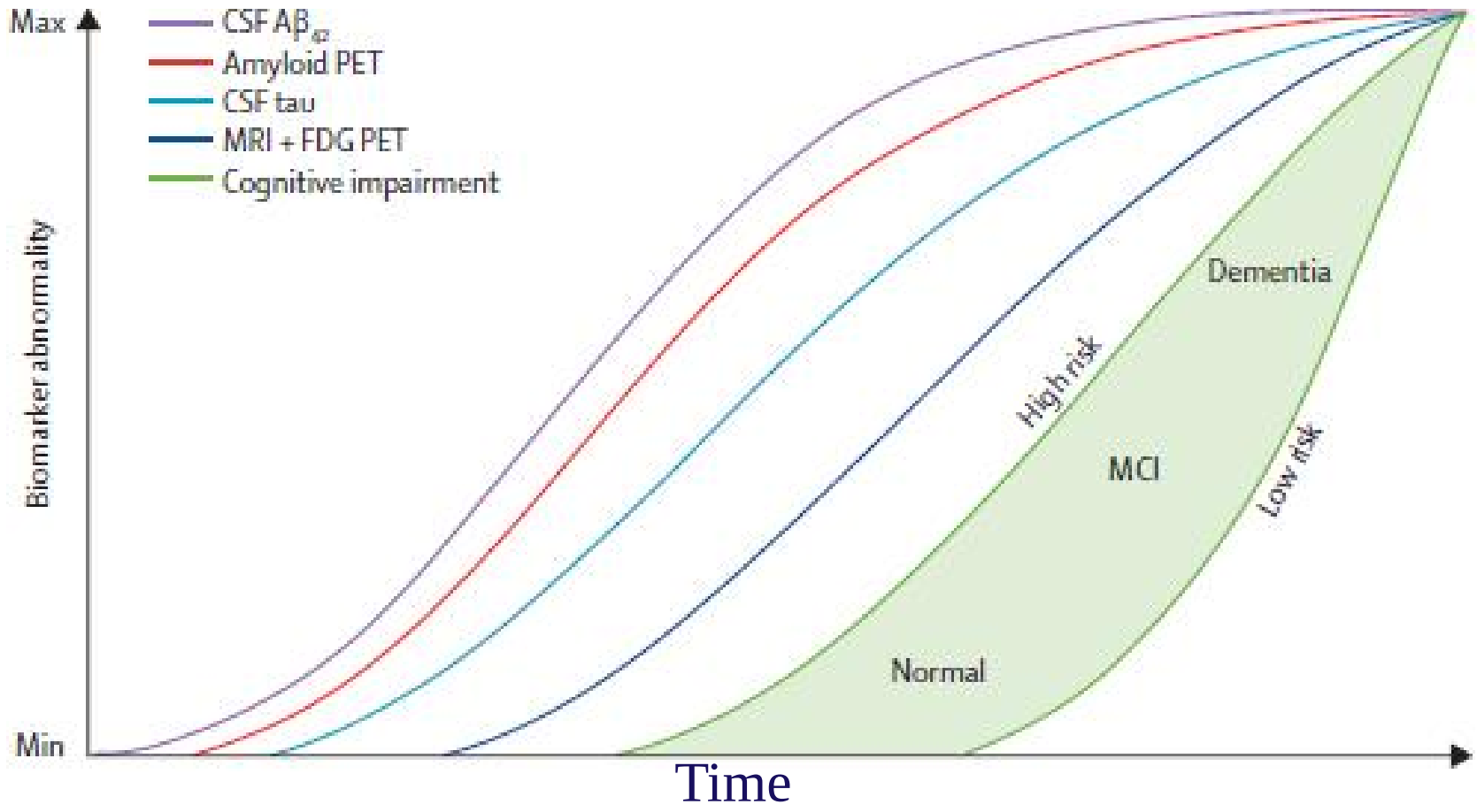
Changes that may indicate very earliest signs of disease using biomarkers.

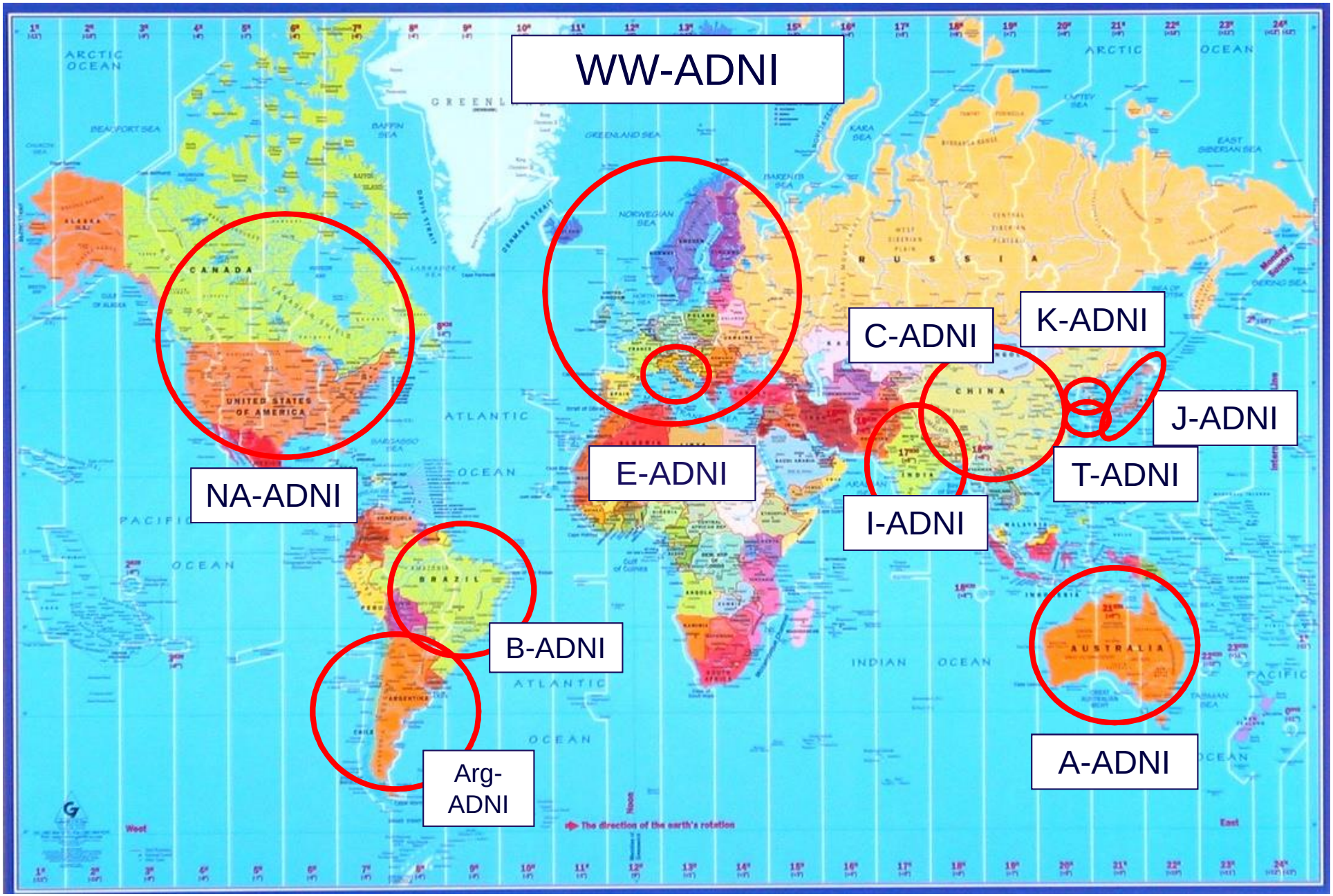
Mild changes in memory and thinking, does not compromises independence/ everyday activities. Add biomarkers to determine MCI of the AD type.

Cognitive and behavioral symptoms impair an individual's ability to function independently.

Add biomarkers to increase certainty

Underlying Biology Begins 10+ Years Before Symptoms





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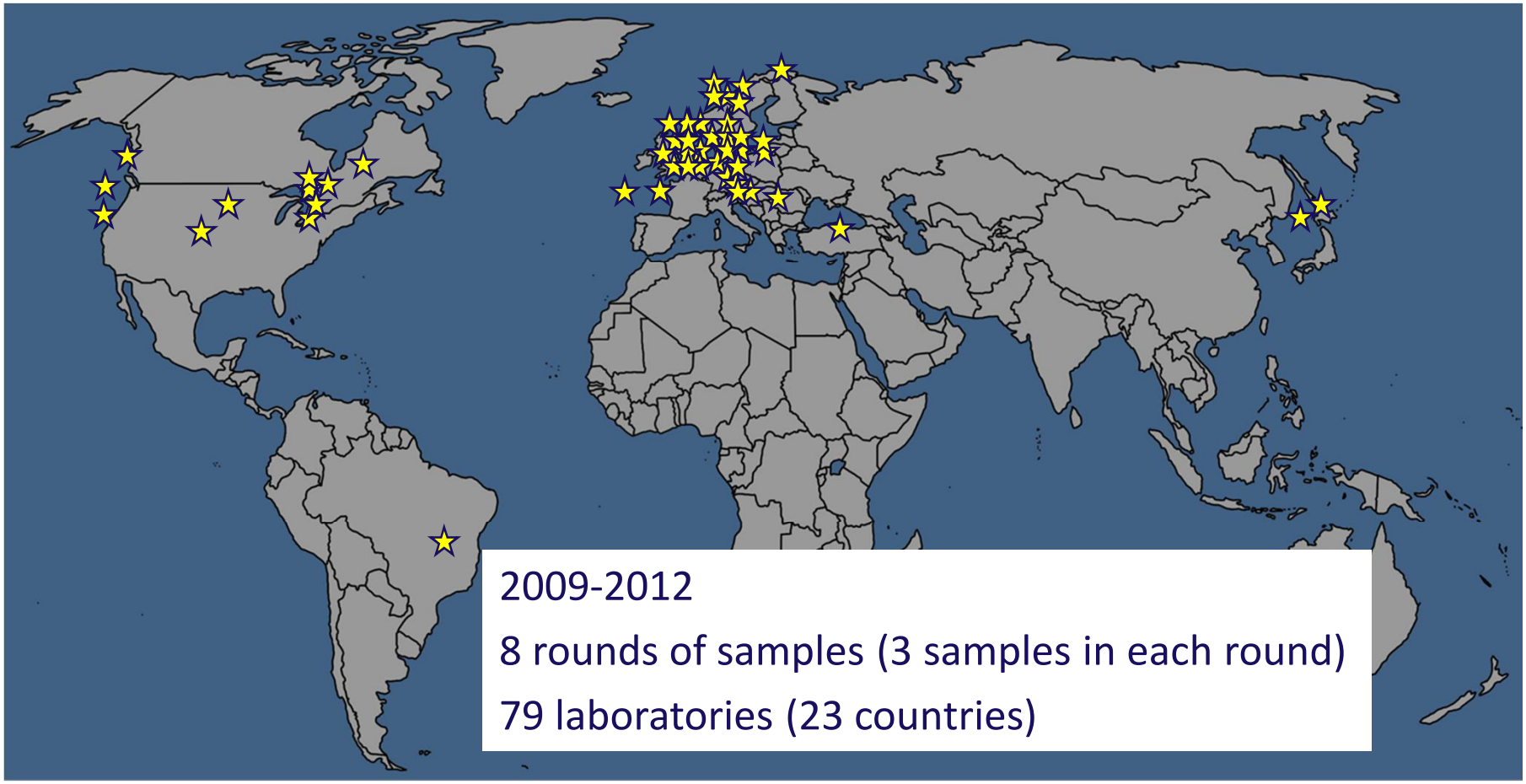
CSF as a Potential Biomarker

- On-going research to improve diagnostic accuracy
- Potentially detects early biological changes
- Requires lumbar puncture (spinal tap)
- Identify and monitor the biochemical effect of a drug candidate in clinical trials
- Global Biomarkers Standardization Consortium

Spinal column

Image from http://reidhosp.adam.com/content.aspx?productId=39&pid=1&gid=003768

Alzhiemer's Association Quality Control Program for CSF biomarkers (ELISA, xMAP, MSD)



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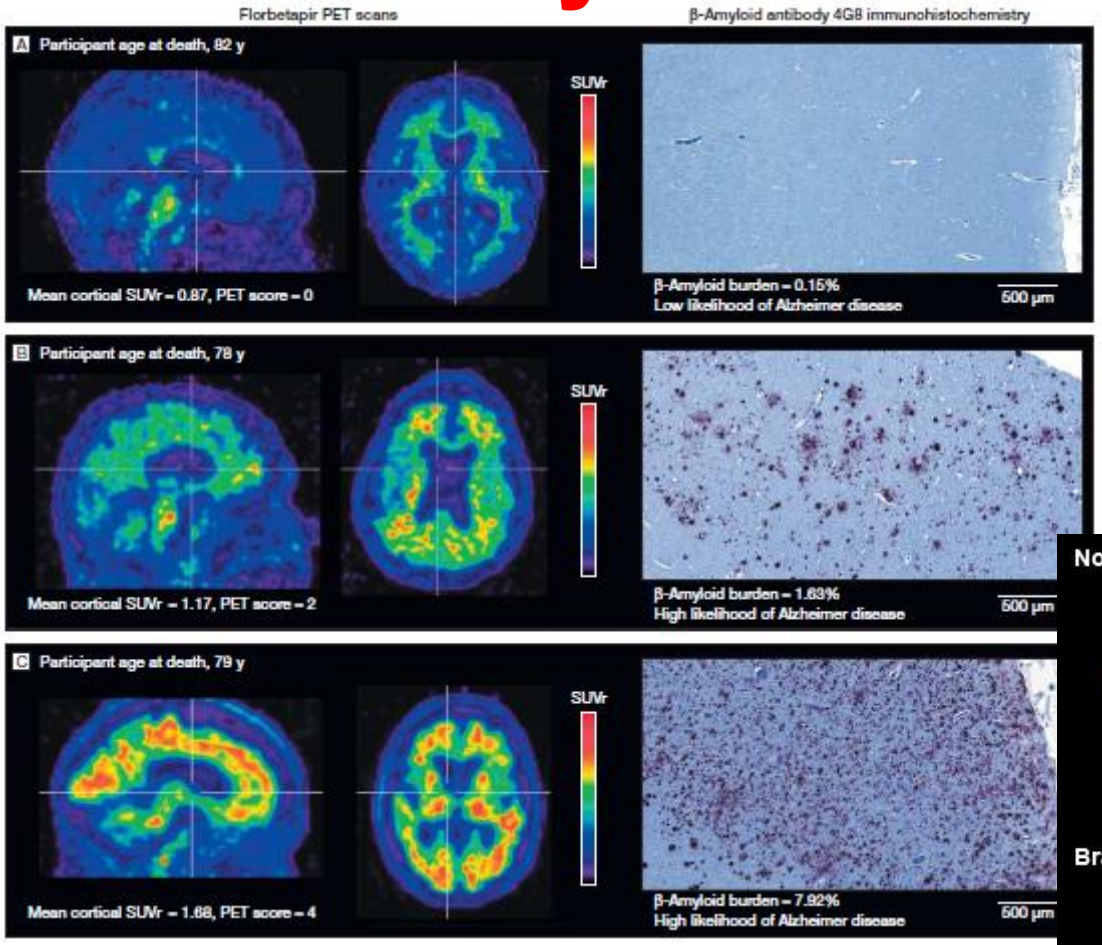
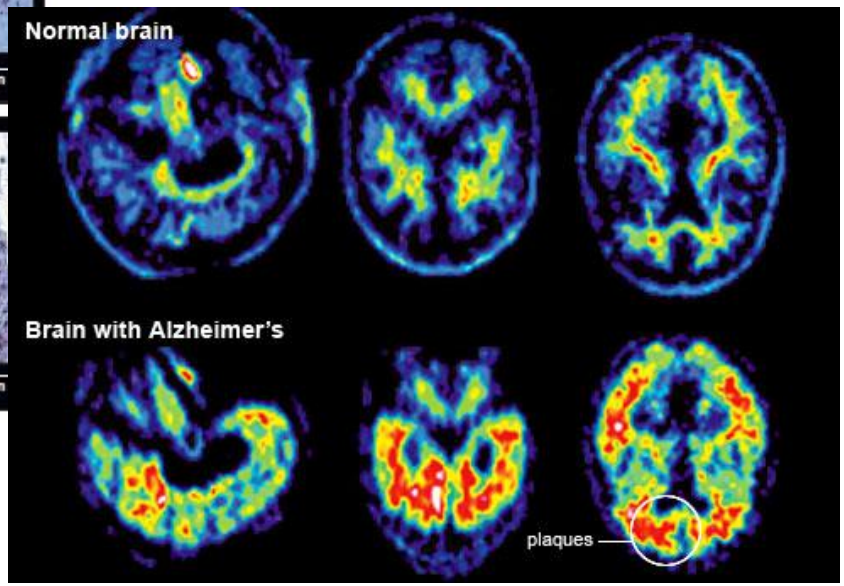
Amyloid PET Imaging



RED = maximum uptake

VIOLET = minimum uptake



Clark et al. (2011) JAMA 305(1).

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THE JOURNAL OF THE ALZHEIMER'S ASSOCIATION

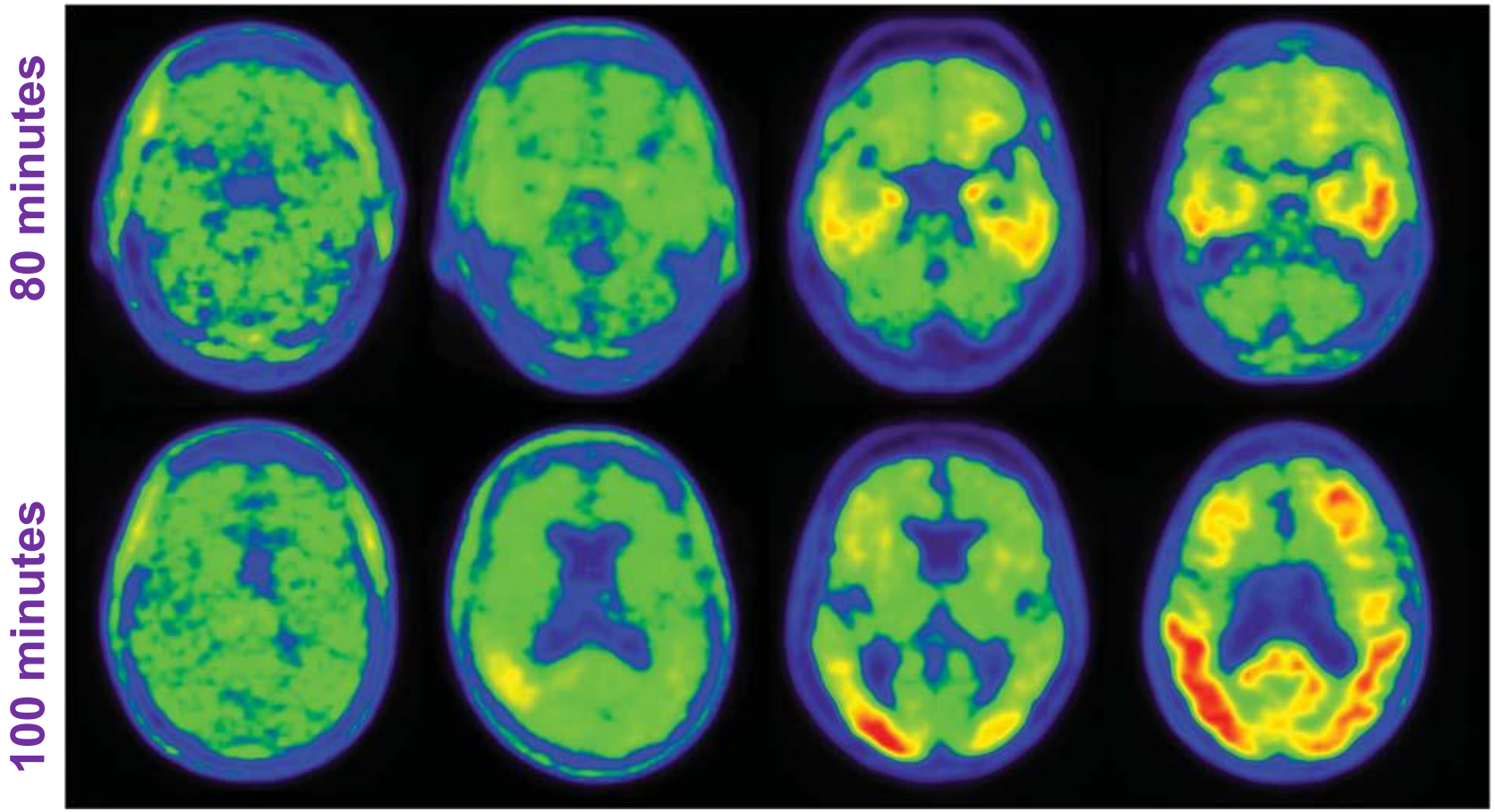
JNM
The Journal of Nuclear Medicine

Appropriate use criteria for amyloid PET: A report of the Amyloid Imaging Task Force, the Society of Nuclear Medicine and Molecular Imaging, and the Alzheimer's Association

Keith A. Johnson[a], Satoshi Minoshima[b], Nicolaas I. Bohnen[c], Kevin J. Donohoe[d], Norman L. Foster[e], Peter Herscovitch[f], Jason H. Karlawish[g], Christopher C. Rowe[h], Maria C. Carrillo[i,*], Dean M. Hartley[i], Saima Hedrick[j], Virginia Pappas[j], William H. Thies[i]

[a]*Departments of Radiology and Neurology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA*
[b]*Department of Radiology, University of Washington, Seattle, WA, USA*
[c]*Departments of Radiology and Neurology, University of Michigan, and VA Ann Arbor Healthcare System, Ann Arbor, MI, USA*
[d]*Beth Israel Deaconess Medical Center, Boston, MA, USA*
[e]*Department of Neurology, University of Utah, Salt Lake City, UT, USA*
[f]*PET Department, NIH Clinical Center, National Institutes of Health, Bethesda, MD, USA*
[g]*Department of Medicine, University of Pennsylvania, Philadelphia, PA, USA*
[h]*Department of Nuclear Medicine and Centre for PET, Austin Health, Victoria, Australia*
[i]*Division of Medical and Scientific Relations, Alzheimer's Association, Chicago, IL, USA*
[j]*Society of Nuclear Medicine and Molecular Imaging, Reston, VA, USA*

Alzheimer's disease: Tau Imaging



JT Chien et al. *Journal of Alzheimer's Disease* 2013

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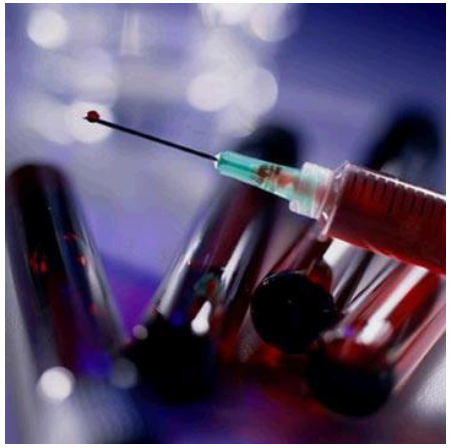
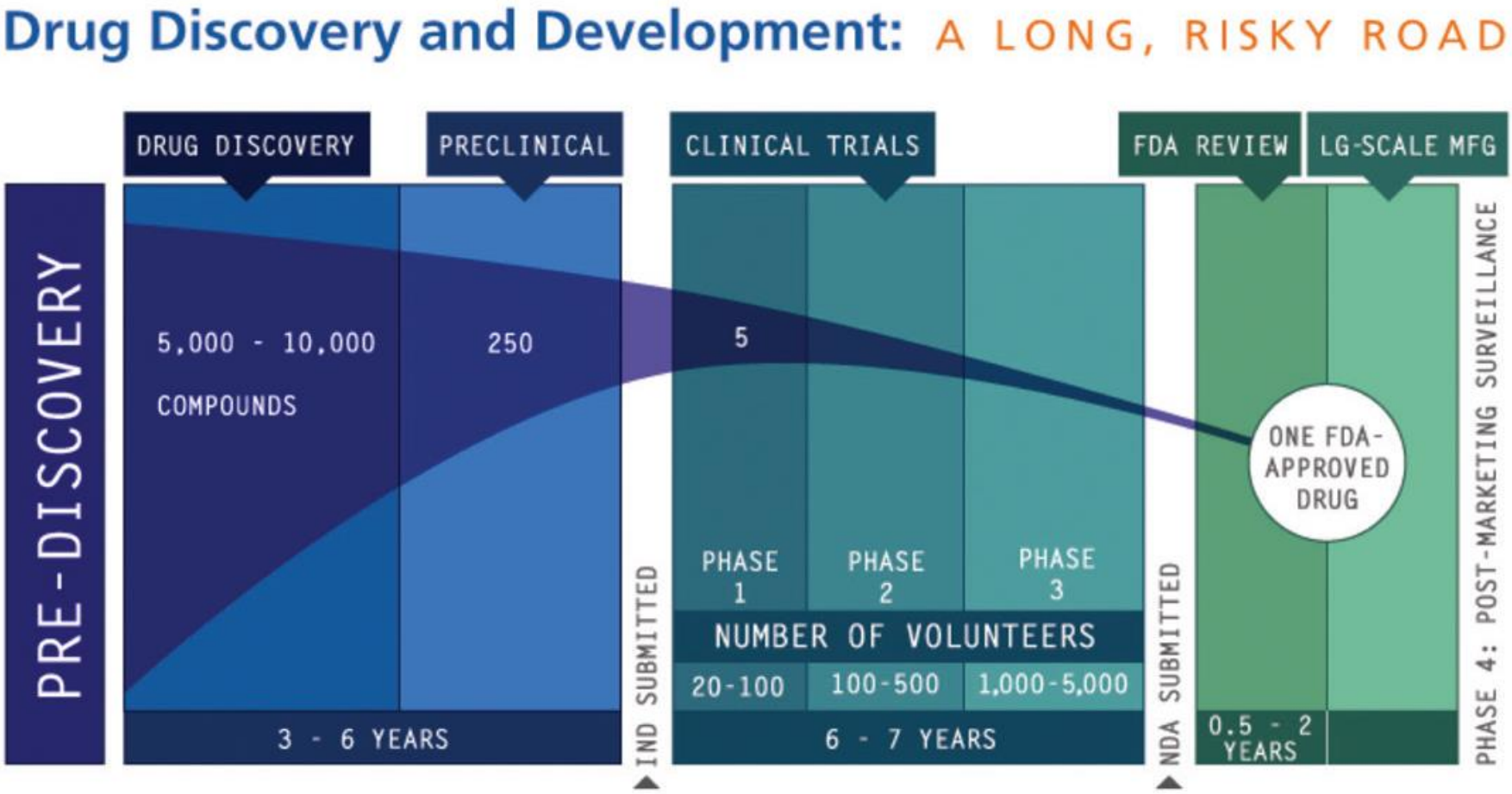
Blood Test for Early Detection?

- Active area of research
- State of Science meeting ï April 2013
- Recent study ï
  - ï Small, preliminary study suggests it may be possible to detect changes in the blood
  - ï Needs validation in larger, diverse populations
- No blood test available for use



Pathway to Your Medicine Cabinet



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Current Alzheimer's Therapies

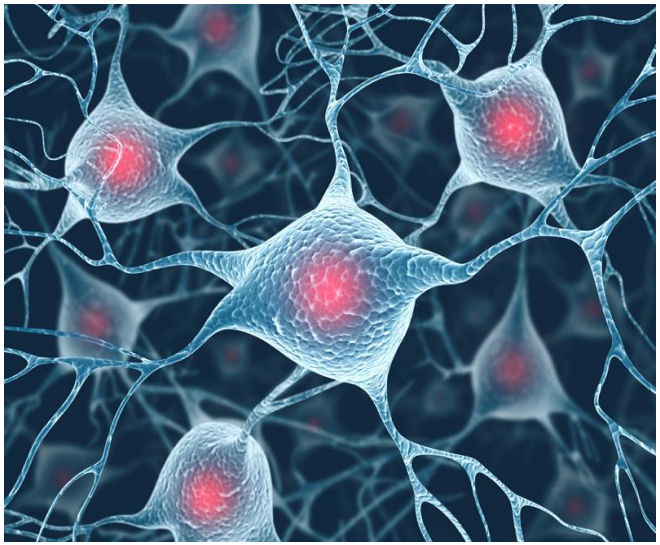
Cholinesterase Inhibitors

tacrine (Cognex)

donepezil (Aricept)

rivastigmine (Exelon)

galantamine (Razadyne)

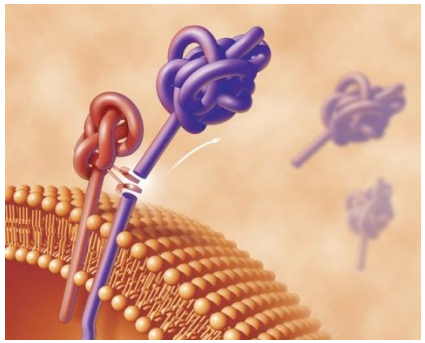


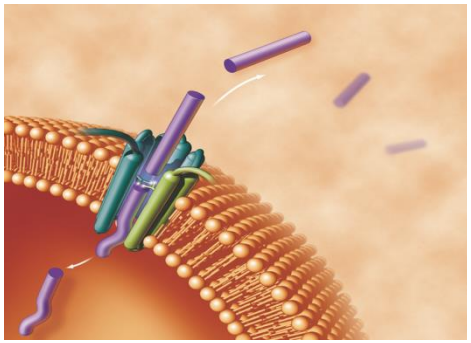
Glutamate Moderators

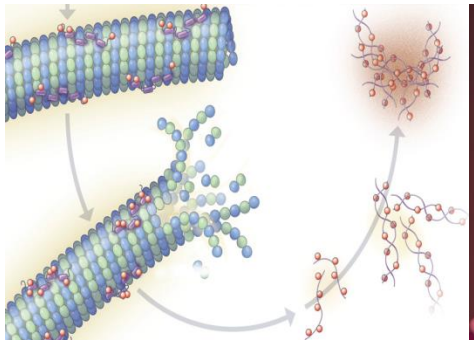
Memantine (Namenda)

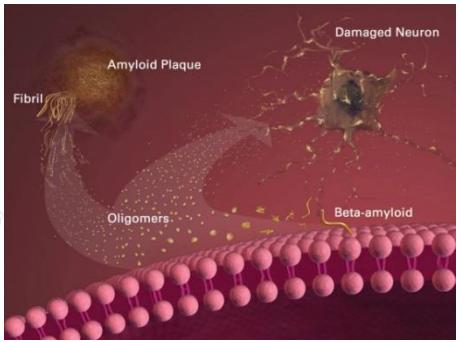
Therapeutic Pipeline for Alzheimer's

- A broad range of drugs are in clinical trials
- These drugs impact biological processes associated with AD
- More than 100 clinical trials on-going across the US today



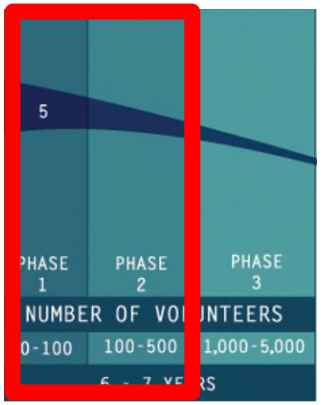






Interventional Therapies in Phase I and II Clinical Trials Target Diverse Mechanisms

AADvac1 ← Tau
ABT-126
ACC-001 (vanutide cridificar)
AFFITOPE-AD02/03
Anatabloc
Atomoxetine
AZD3293
AZD3480
BAN2401
Bexarotene
BIIB037
CERE-110 ← NGF
Crenezumab
(MABT5102A)
DBS-f (Deep brain stimulation - fornix)
Epothilone D (BMS-241027)
EVP-0962
EVP-6124 (MT-4666)
Exendin-4
Gantenerumab
GSK2647544
Insulin
Isotretinoin
IVIg
Ladostigil
L-arginine
Lipoic Acid
LY3002813
Mesenchymal stem cells
Metformin ← Insulin
Minocycline
MK-7622
NIC5-15
Nicotinamide
Resveratrol
RO4602522 ← Monoamine oxidase
R-Pramipexole
SAR228810
Saracatinib
Sargramostim
Simvastatin
Sodium oligo-mannurarate
Tetrahydrobiopterin
Thalidomide
Transcranial magnetic stimulation (TMS)



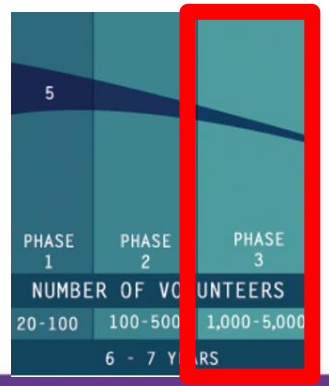
(Jan 1, 2014)

alzheimer's association®

Therapeutic Agents in Phase III Clinical Trials

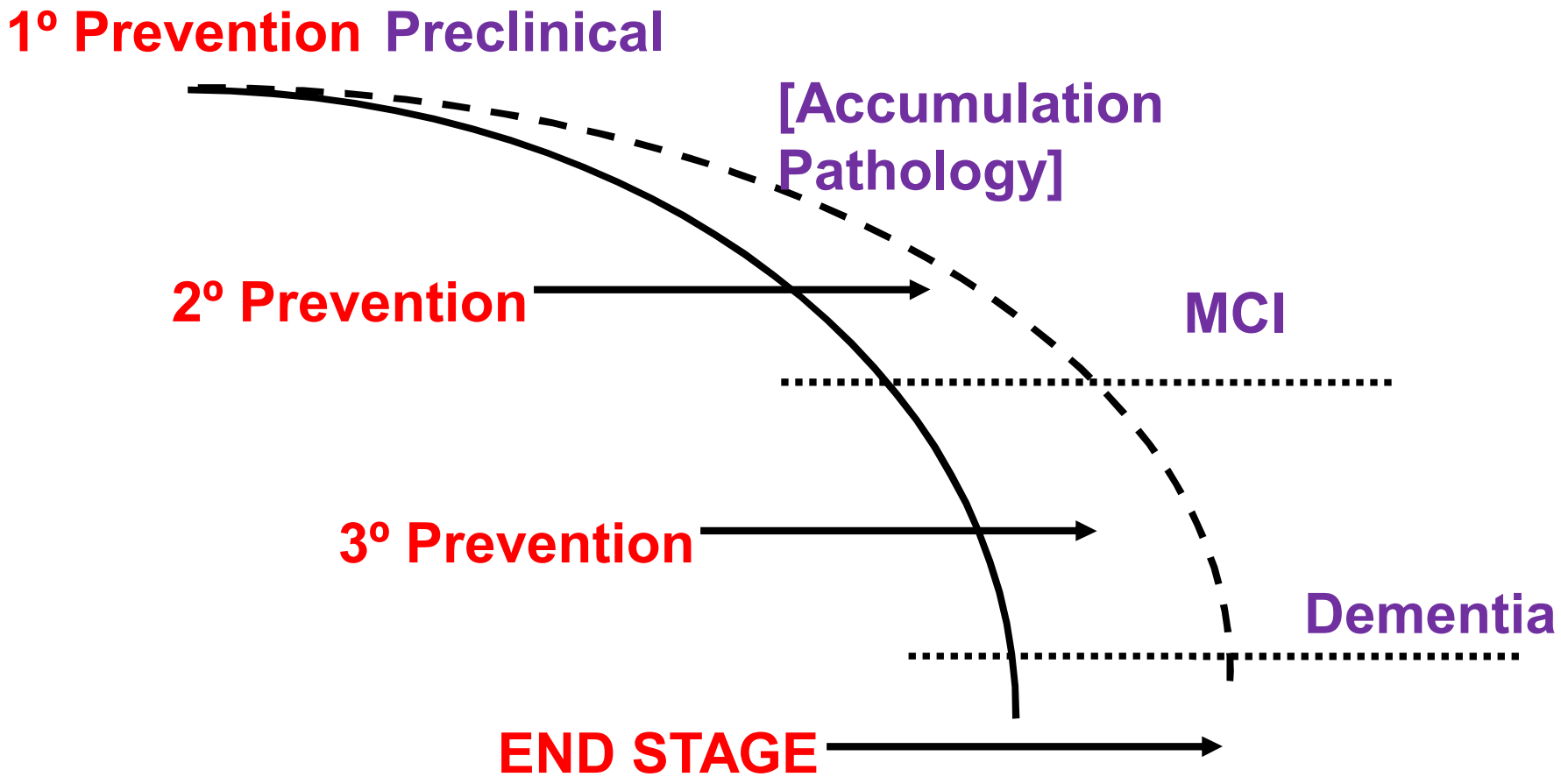
- **EVP-6124 (MT-4666)**
  - EnVivo
  - Nicotinic receptor agonist
- **Gantenerumab**
  - Hoffman-La Roche
  - Monoclonal antibody against beta-amyloid
  - Part of DIAN-TU
- **IVIg and Albumin**
  - Grifols
  - Intravenous immunoglobulin
- **LU AE58054**
  - Lundbeck
  - 5HT6 receptor antagonist
- **Masitinib**
  - AB Science
  - Inhibitor of c-KIT cell signaling
- **MK-8931**
  - Merck
  - BACE inhibitor
- **Nasal insulin**
  - Alzheimerôs Disease Cooperative Study
  - May correct insulin dysregulation in the brain

- **Nilvadipine**
  - Collaboration of European universities and pharmaceutical companies
  - Calcium channel blocker
- **Pioglitazone**
  - Takeda
  - PPAR-gamma activator
- **Solanezumab**
  - Eli Lilly
  - Humanized antibody against beta-amyloid
  - Part of DIAN TU
- **TRx0237**
  - TauRX
  - Tau aggregation inhibitor



trialmatch®

Degrees of Prevention



Possible Alzheimer's Prevention

ALZHEIMER'S
PREVENTION
INITIATIVE

TOMMORROW

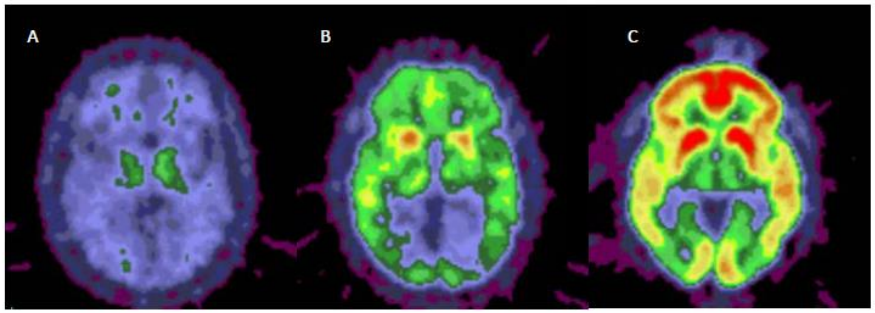
DIAN TU

Dominantly Inherited
Alzheimer Network
Trials Unit

Lead Funder of the DIAN-TU

- $4.2M grant to DIAN-TU
  - International studies in the US, UK, Japan, and Australia
  - Expansion of DIAN database
  - Three simultaneous trials to test potential therapies:
    - Gantenerumab (Roche, Monoclonal antibody to AB)
    - Solanezumab (Lilly, Monoclonal antibody to AB)
    - TBD

DIAN TU
Dominantly Inherited Alzheimer Network
Trials Unit



15 years prior to estimated symptoms | 10 Years prior to estimated symptoms | ~5 years after Alzheimer's disease symptoms

Figures courtesy of Randall Bateman, MD, DIAN-TU

Alzheimer's Prevention Initiative

API ï Colombian family

- –Largest single kindred with familial Alzheimerôs
- –Crenezumab (Genentech)
- –Received $16 million from NIH

ApoE Trial

- –Risk gene for Alzheimerôs
- –650 adults, age 60-75 with two copies APOE4
- –Anti-amyloid therapy (TBD)
- –Received $33.2 million from NIH

ALZHEIMER'S
PREVENTION
INITIATIVE

TOMMORROW Trial

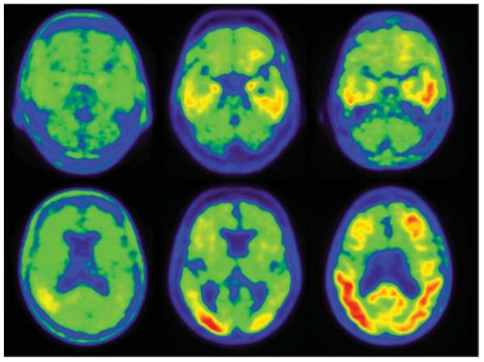
- Takeda-Zinfandel Alliance
- 5,800 volunteers enrolled
  - –End-point is conversion to Mild Cognitive Impairment
- Algorthim or enrollment:
  - –APOE status
  - –TOMM40
- Low dose Pioglitazone (Actos)

TOMMORROW

Anti-Amyloid in Asymptomatic Alzheimer's (A4) Study

- Clinically Normal, Age 65+
- Positive Amyloid PET
- Testing Solanezumab (Lilly)
- Lead Investigator: Dr. Reisa Sperling
- Leveraged study: LEARN

A4 Add On Project: LEARN



JT Chien et al. *Journal of Alz Dis* 2013

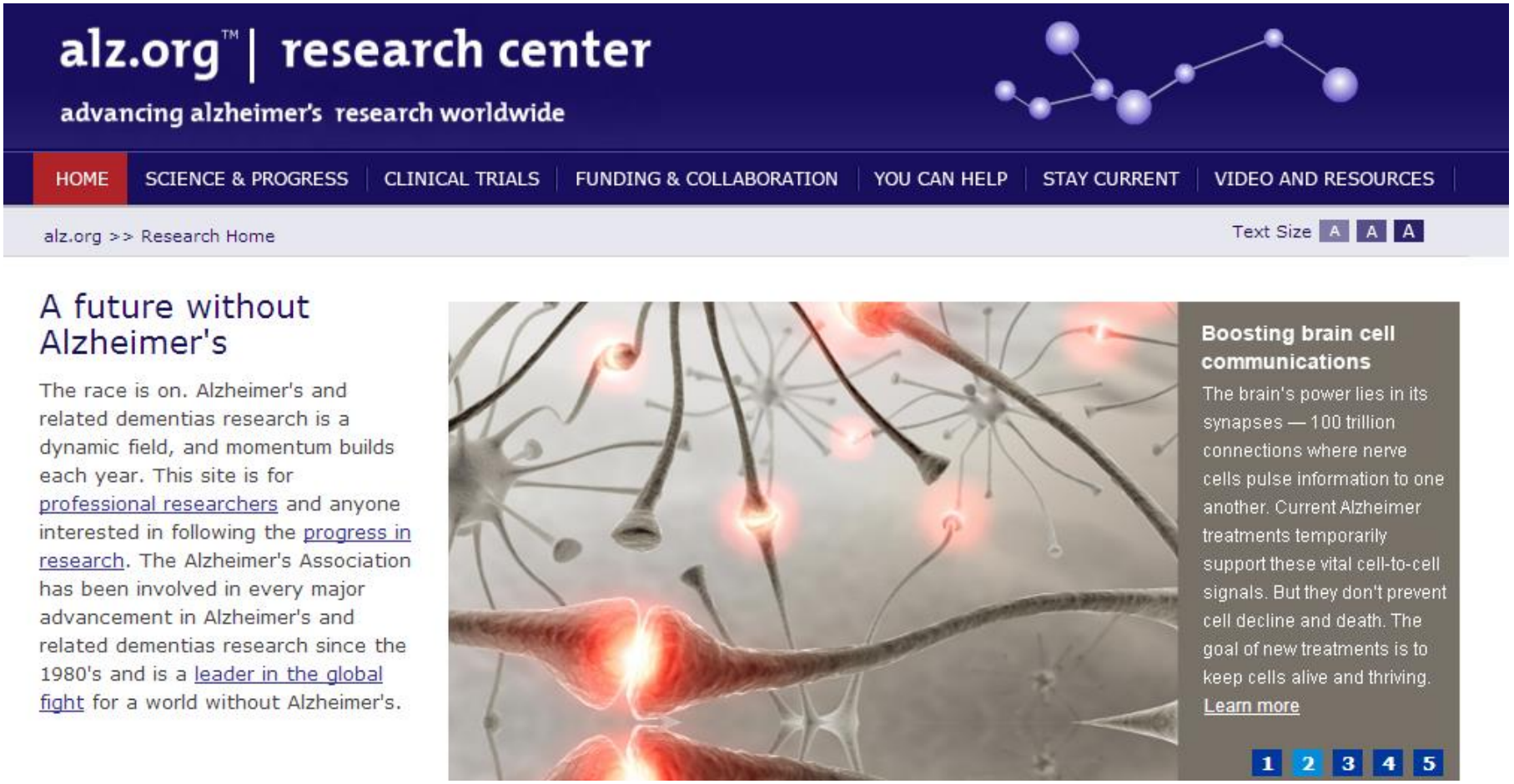
- Longitudinal Evaluation of Amyloid Risk and Neurodegeneration (LEARN)
- Natural history study of 400 people with low/intermediate levels of amyloid
- Focus on diverse populations
- ***Largest award ever given by Alzheimer's Association***
- ***First funded tau imaging study!***

  150 participants

Review of Objectives

- Possible risk factors for Alzheimerôs
- Significant advances in the development in area of early detection; moving to revised guidelines for diagnosis
- Current medications available for Alzheimerôs and advances in clinical trials, including prevention efforts
- Advocacy and awareness are key factors to advancing research
- There is HOPE through research!

Alz.org/research



THE END OF ALZHEIMER'S STARTS WITH YOU

alzheimer's association®

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