Le prospettive della genetica nella diagnosi e terapia delle demenze

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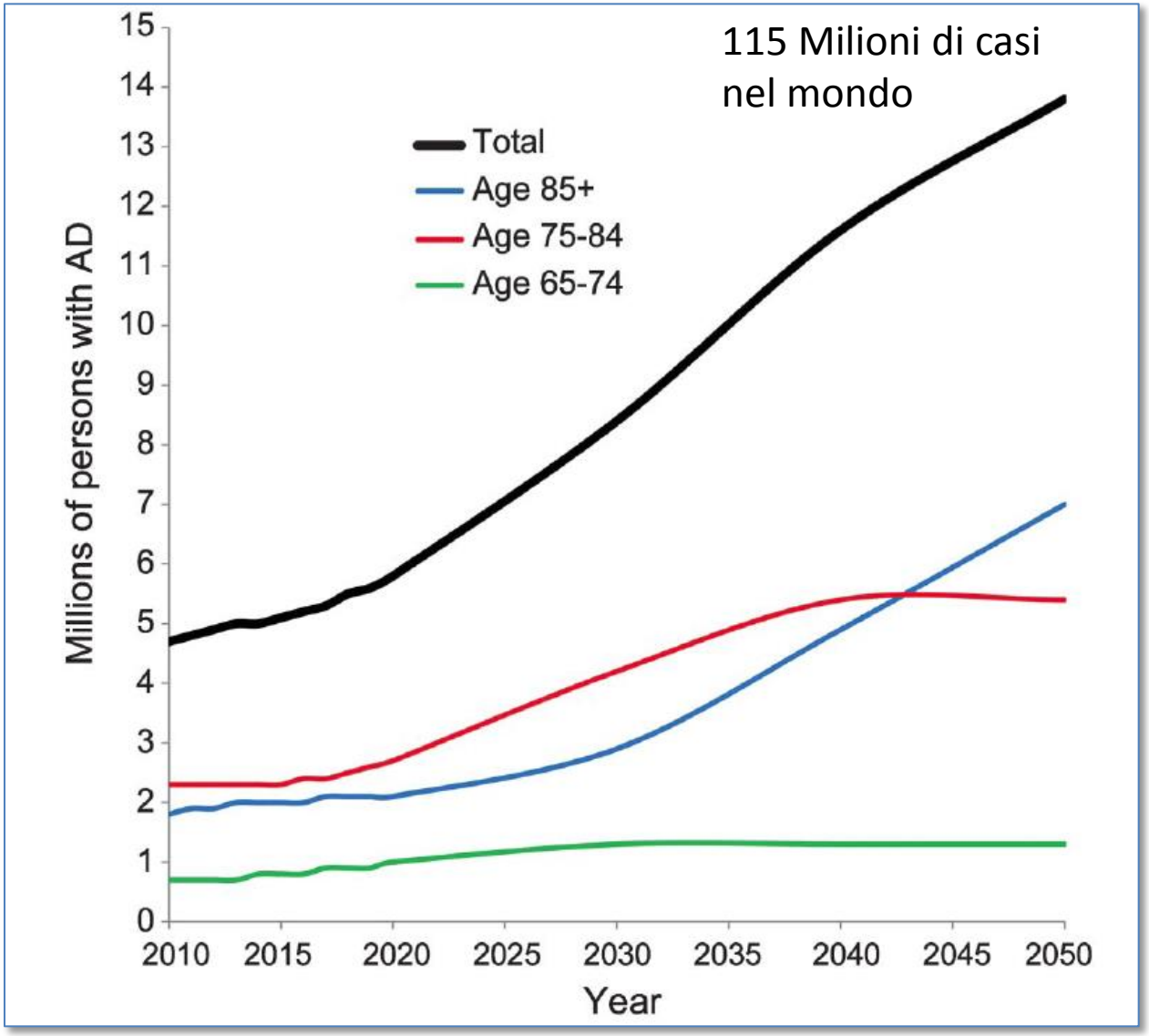
Convegno "Dottore Angelico"
Cassino
11-13 Giugno 2015

La genetica e l'Alzheimer : piano espositivo

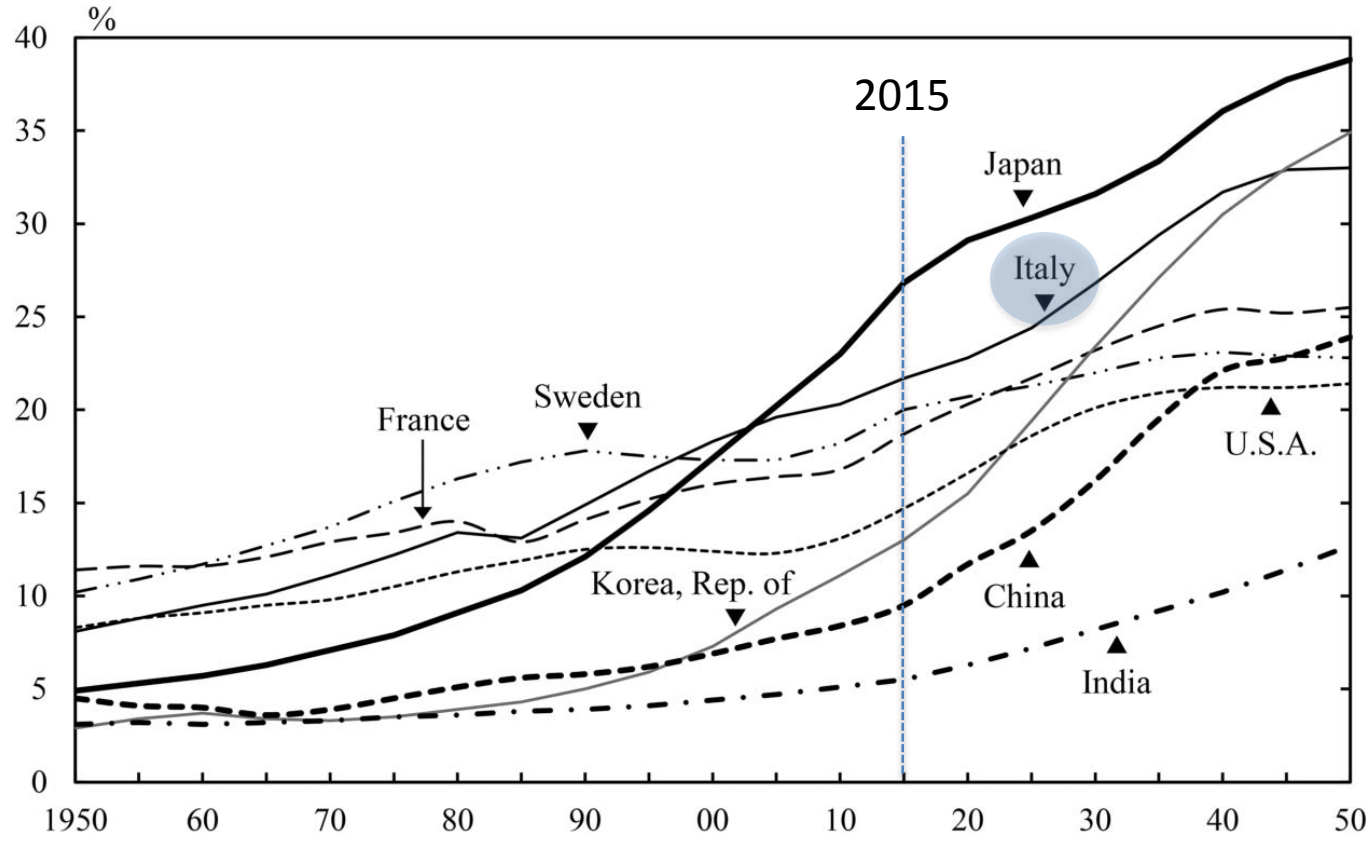
- La malattia di Alzheimer:
  - ✓ Forme ereditarie e sporadiche
  - ✓ Nuovi concetti sulla neuropatologia
  - ✓ Ruolo dei geni come causa e fattori di rischio
- Determinazione del rischio genetico:
  - ✓ Linkage studies
  - ✓ GWAS
  - ✓ Exome/genome sequencing
- Geni implicati nell'Alzheimer
- Quali prospettive offre la genetica nelle demenze?
- Update: Aducanumab trial (Biogen)

Emergenza Alzheimer: casi previsti da oggi al 2050 negli USA



Neurology 80, 2013

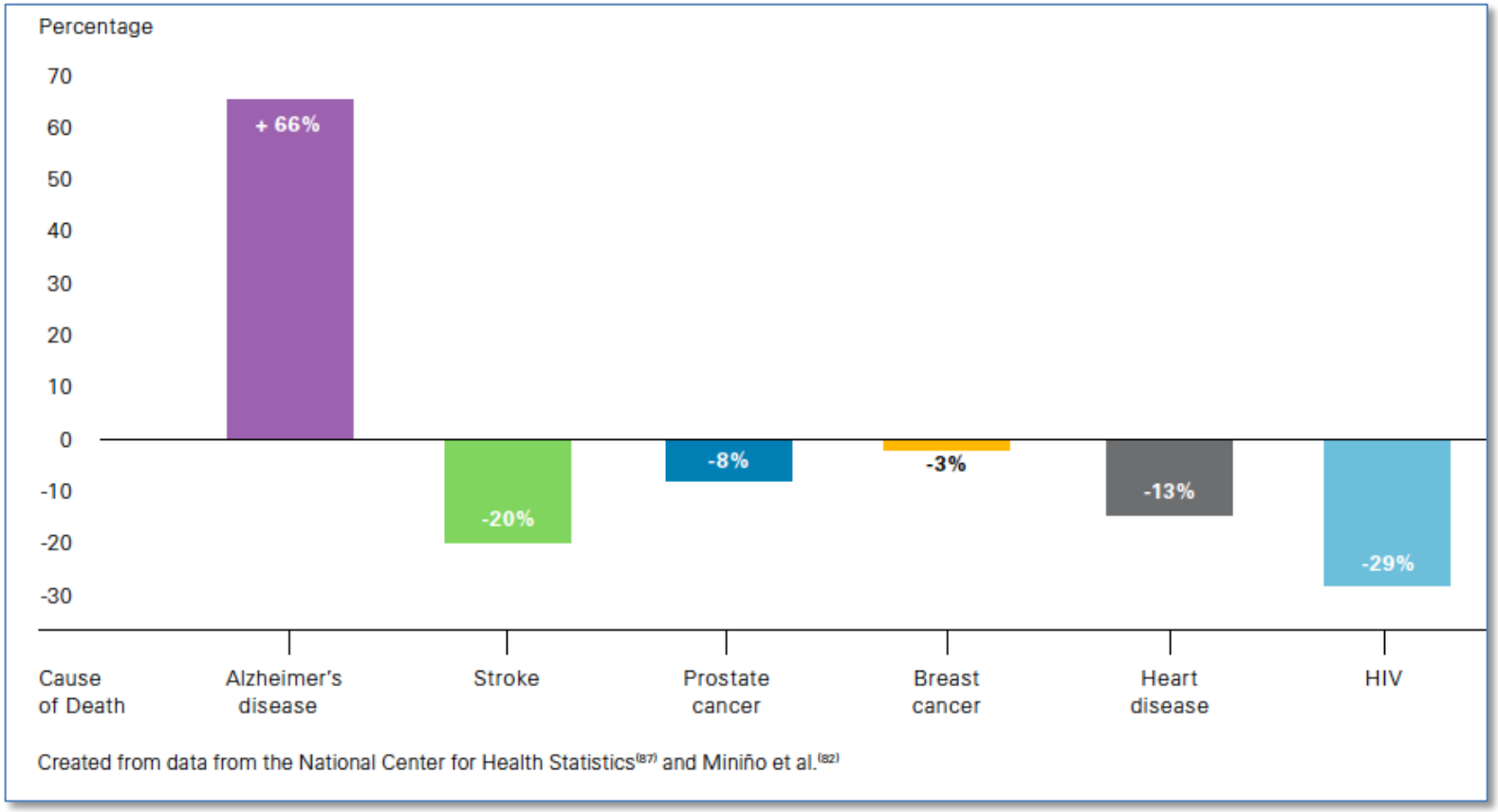
Aumento della popolazione di eta' superiore ai 65 anni (1950-2050)



Adapted from Current Status and Predictions for an Aging Society with Fewer Children. Japanese Ministry of Education, Sports, Culture, Science and Technology. Available at: http://www.mext.go.jp/english/whitepaper/1302597.htm. Reprinted with permission.

Neurology 84 March 10:1051, 2015

L’ Alzheimer e’ l’unica malattia la cui mortalita’ e’ aumentata tra’ il 2000 e il 2008



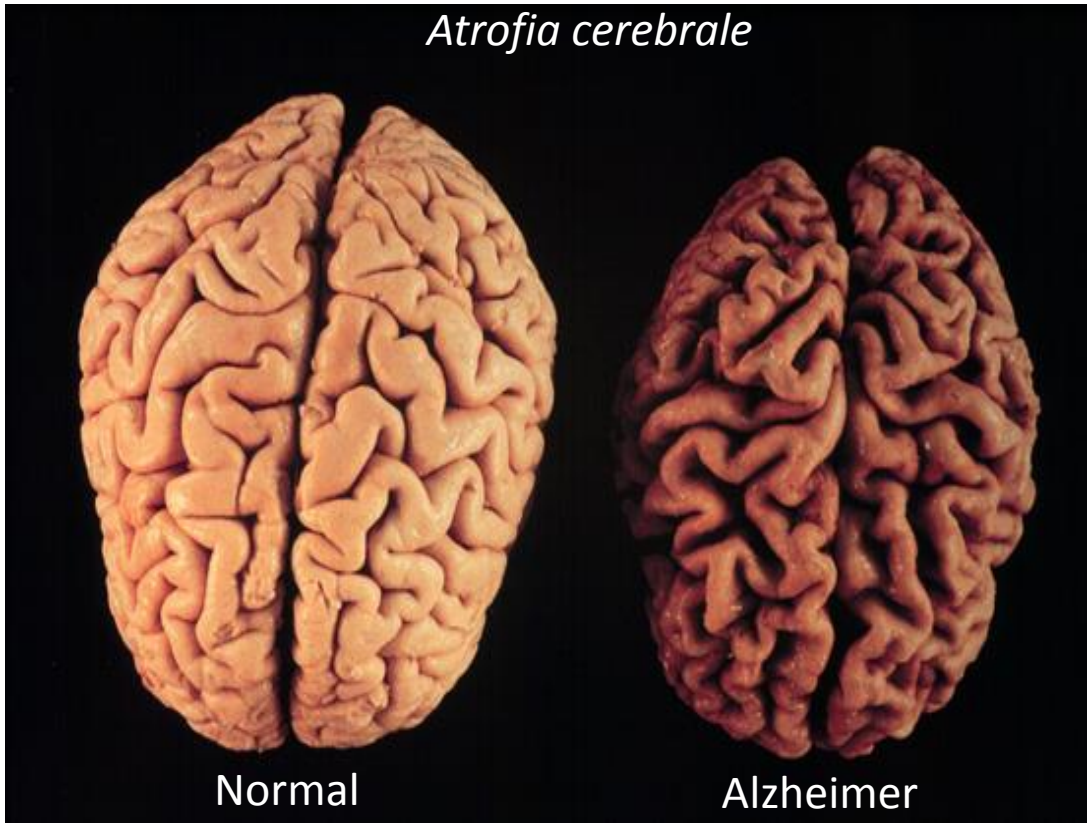
La malattia di Alzheimer

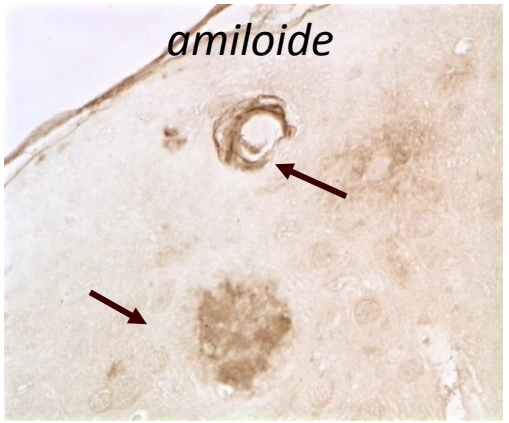
Alois Alzheimer, 1906

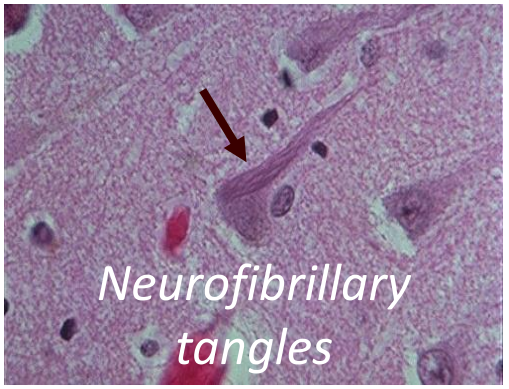
- *Deterioramento cognitivo*
- *Disturbi emozionali*

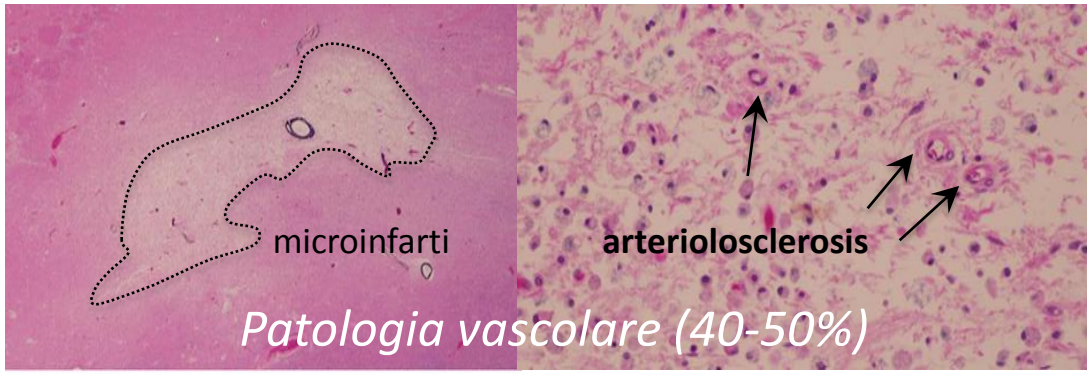
- *E' La causa piú comune di demenza nell'anziano*
- *L'incidenza aumenta con l'etá (≈1% a 65 aa, ≈10% a 80 aa; ≈50% a 95 aa)*
- *Esistono casi ereditarii, ma la maggioranza dei casi sono sporadici*

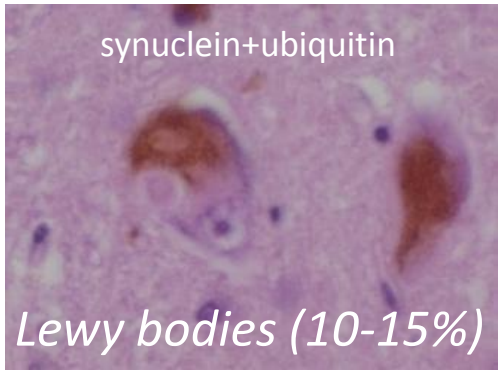
La neuropatologia del morbo di Alzheimer



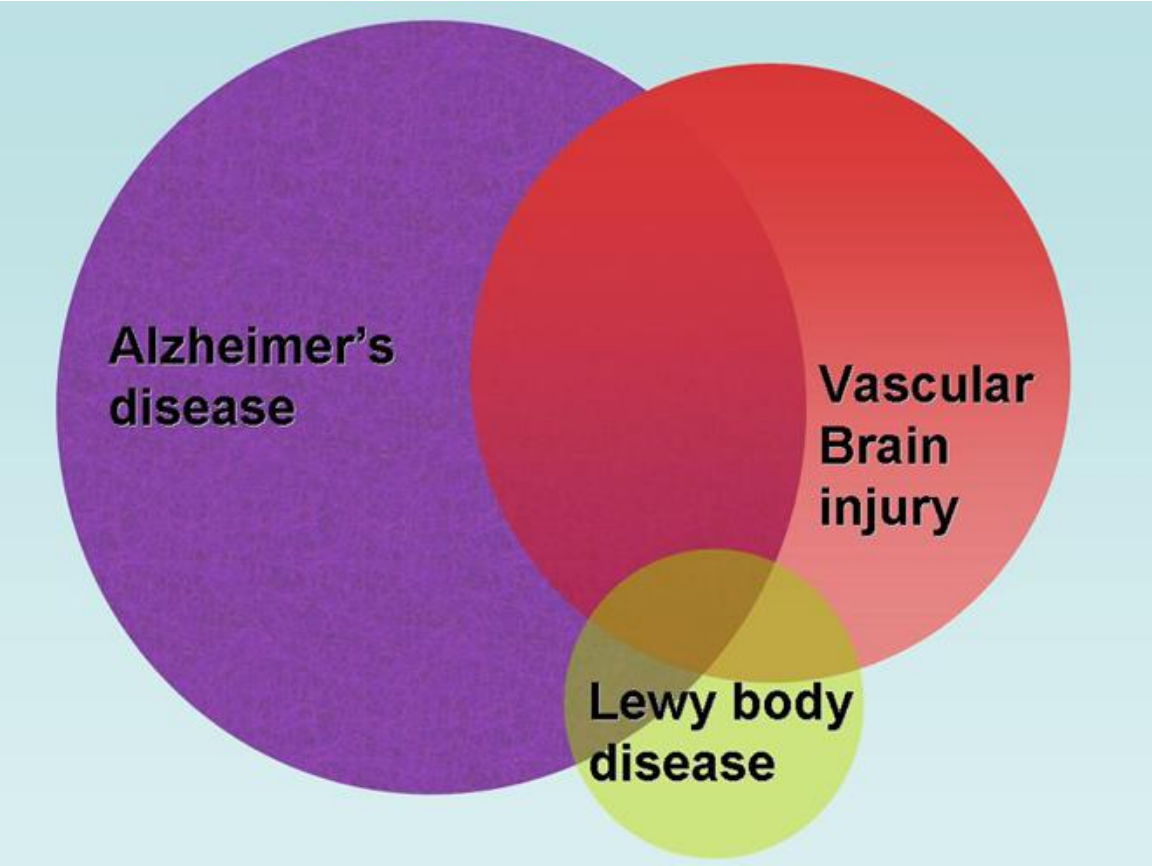




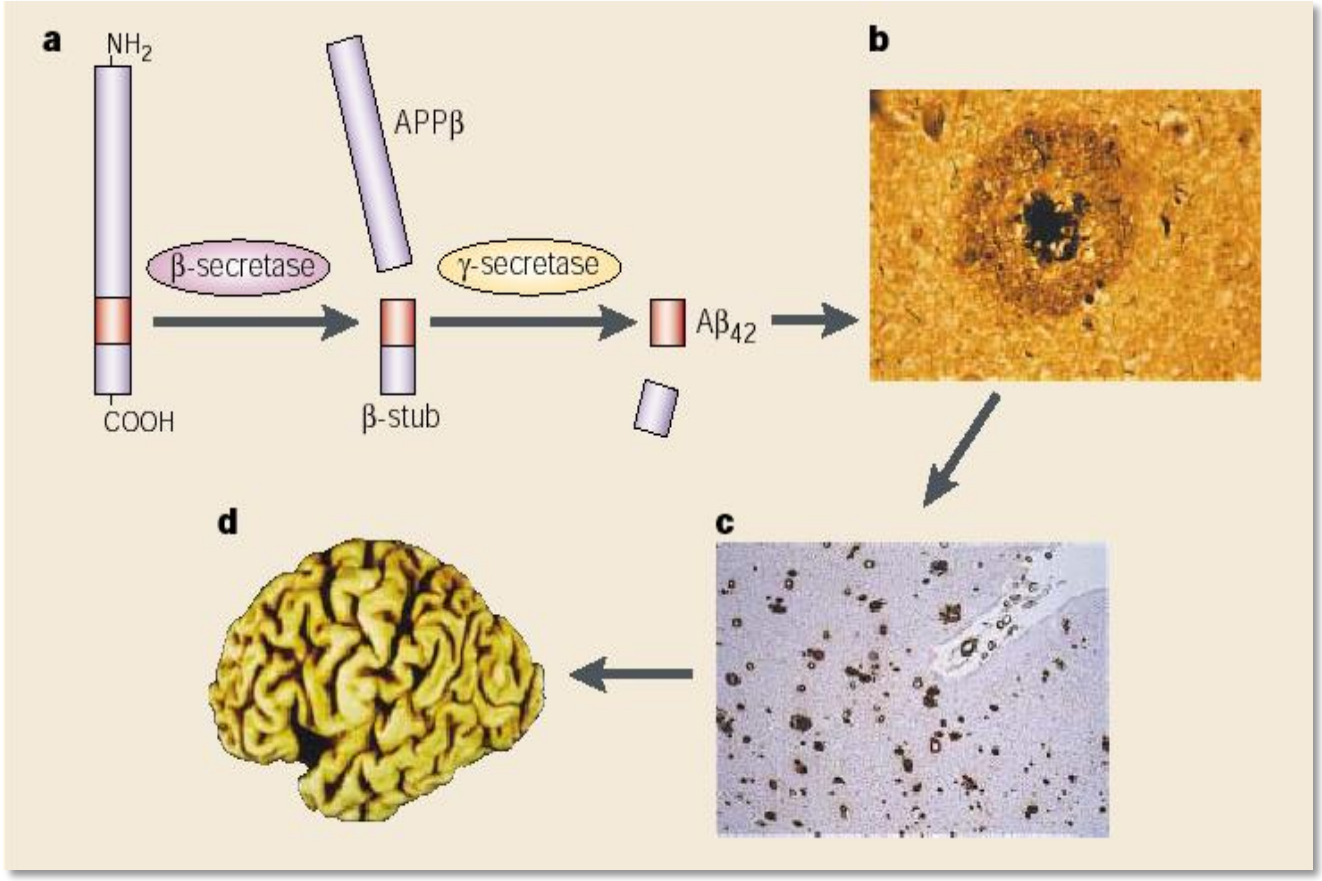




Patologie multiple coesistono specialmente nei casi sporadici

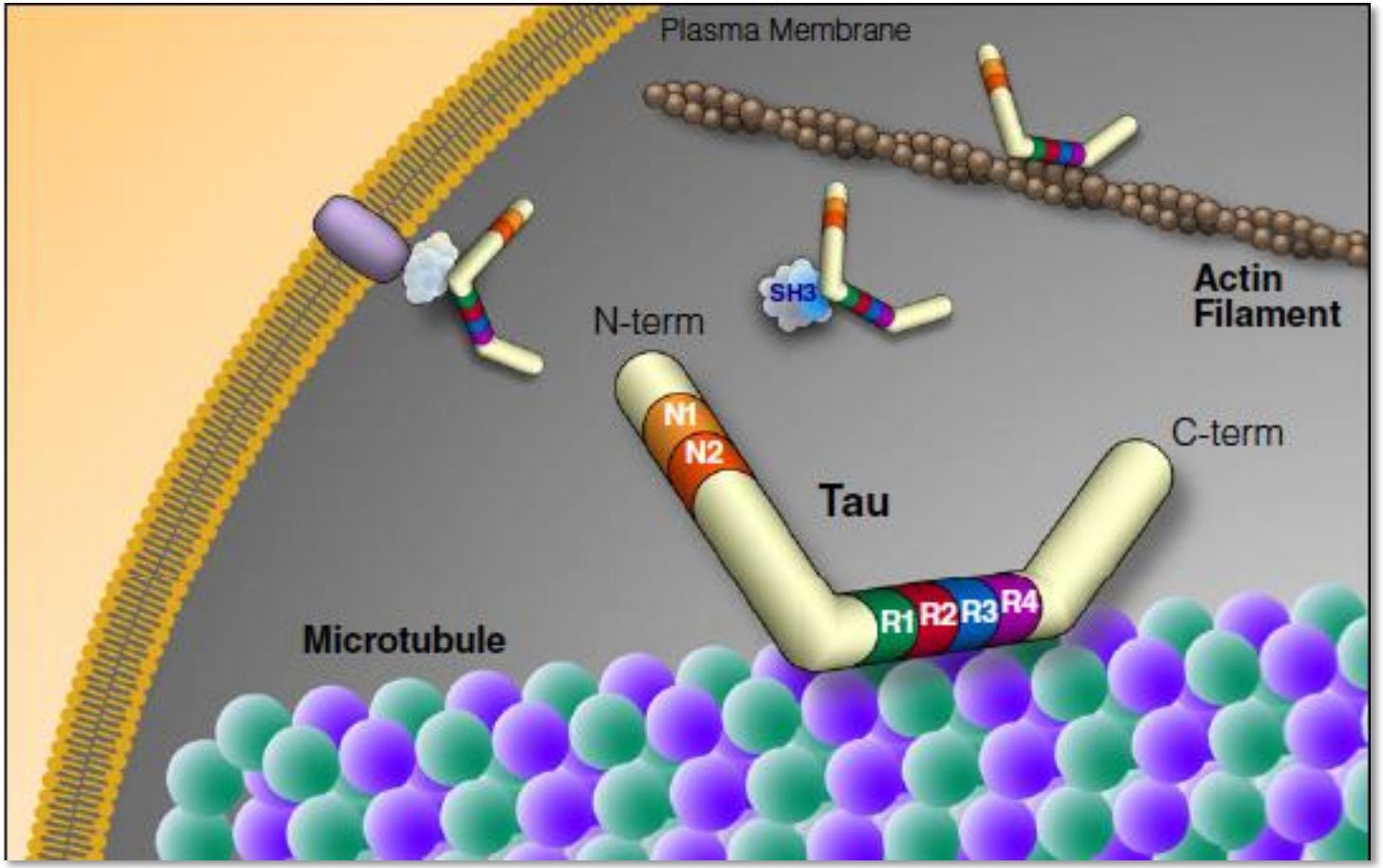


Cause del Morbo di Alzheimer: "Amyloid hypothesis"

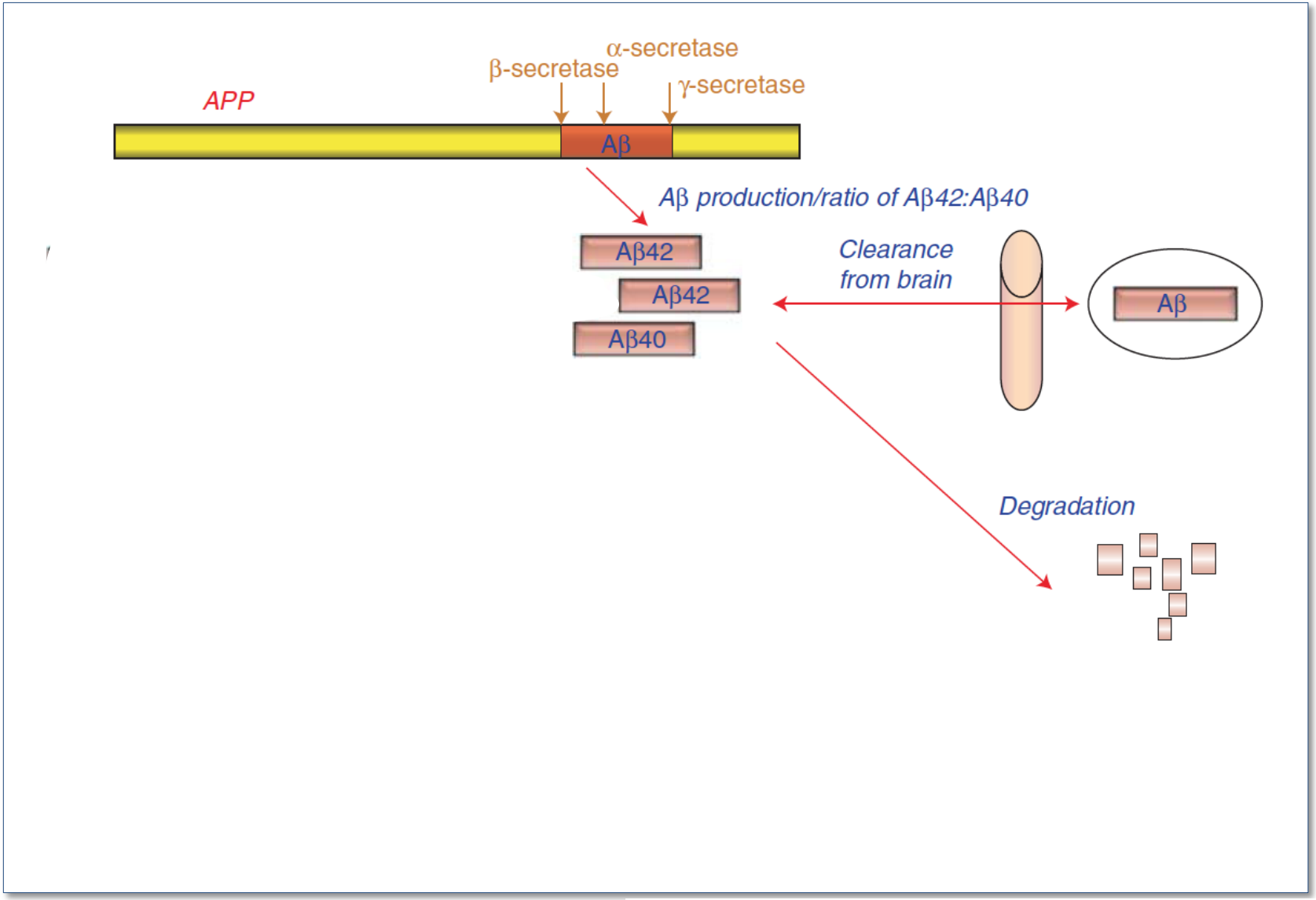


Nature Rev. Neurosci. 3:824, 2002

Cause del morbo di Alzheimer: il *tau*



Schema integrato della patobiologia dell'Alzheimer



Cold Spring Harb Perspect Med 2012;2:a006296

Demenza presenile e senile: evoluzione del concetto e ruolo della genetica

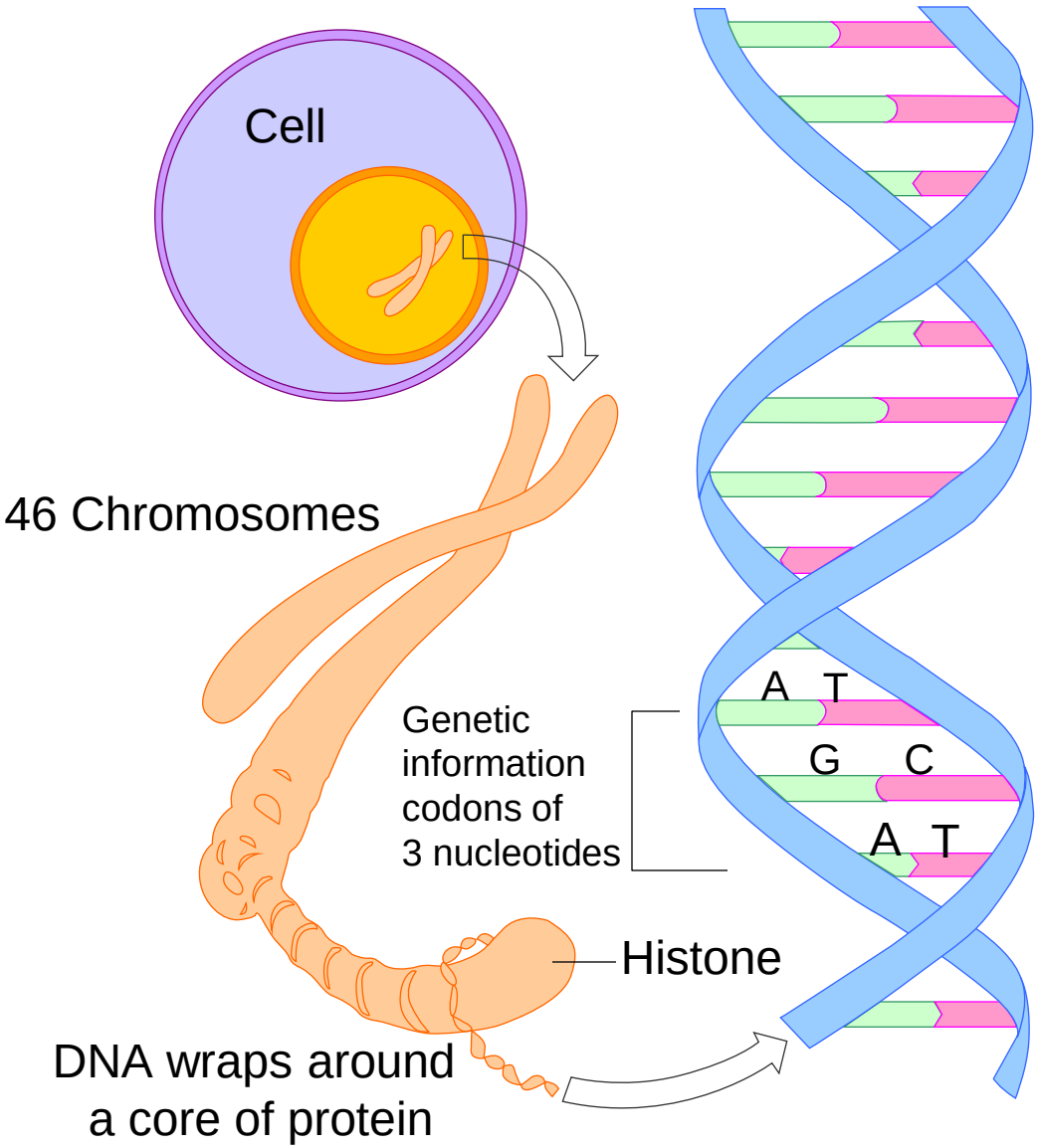
- 1906: Alzheimer/Kraepelin:
  Demenzia presenile e senile sono condizioni distinte
  Amiloide e tangles: forme presenili
  La patologia vascolare: forme senili

- 1960: Roth, Tomlinson, Blessed:
  Amiloide e tangles sono presenti anche nella demenza senile

- 1970: Katzman:
  Demenza presenile e senile sono la stessa entita' patologica

- 1990: Hardy et al.
  Le forme presenili sono interamente su base genetica (FAD)
  Le forme senili sono le piu' comuni e sporadiche (LOAD)
  Fattori di rischio su base genetica

Il DNA e' impacchettato densamente nei chromosomi nel nucleo della cellula



Helix of double-strand DNA:

- 10 metri di DNA
- 25,000 geni
- 3.2 miliardi di basi
- Solo il 5% del DNA codifica proteine (exome)
- Il 95% sono sequenze che non codificano (introns)

Identificare geni e' come cercare il proverbiale ago nel pagliaio

Linkage Analysis:

Utilizzare marcatori genetici conosciuti per localizzare approssimativamente un gene sconosciuto

Genome-wide association studies (GWAS):

Variazioni genetiche nel DNA (SNP) associate con un tratto particolare, per esempio una malattia

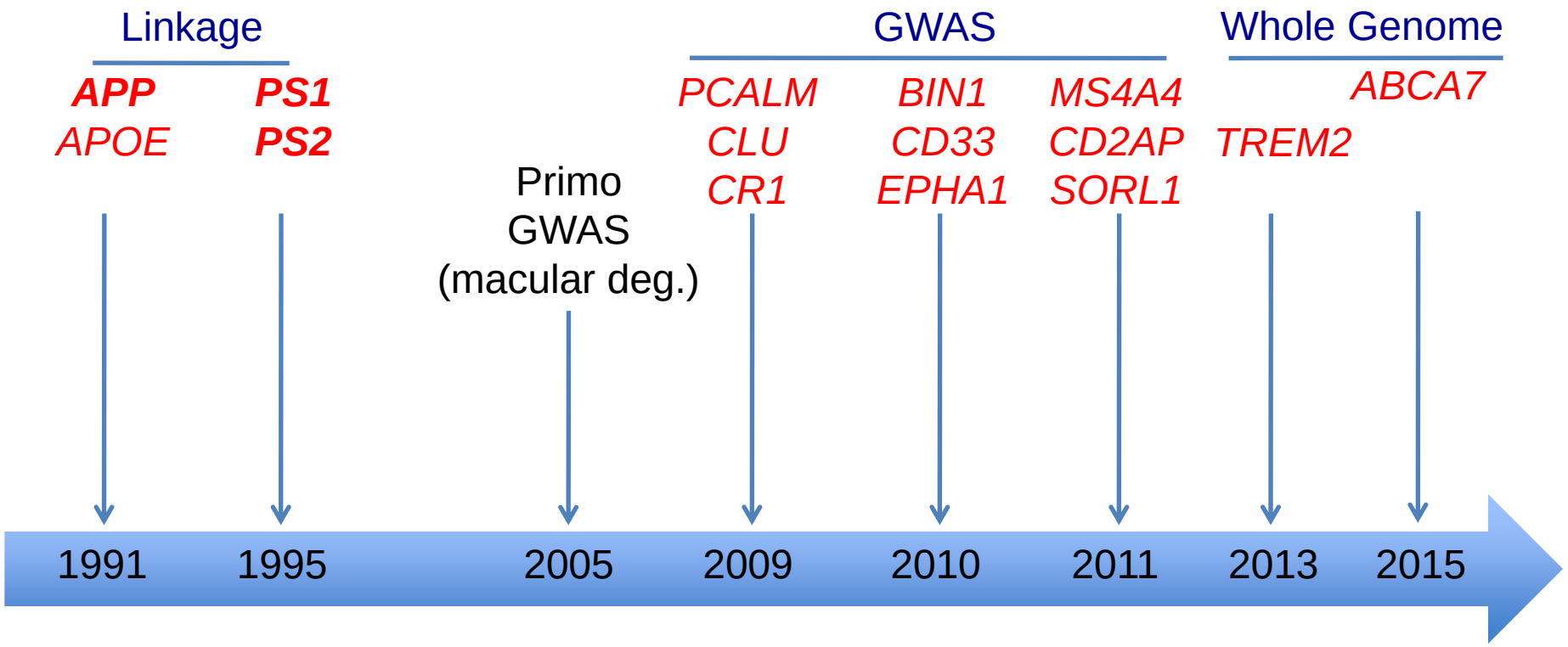
Whole exome sequencing:

Determinazione delle sequenza del DNA che codifica tutte le proteine (exome: 5% dell'intero genoma)

Whole genome sequencing:

Determinazione delle sequenza di tutto il DNA sia l'exome che le sequenze che non codificano proteine

La scoperta dei geni legati all'Alzheimer nel corso degli anni

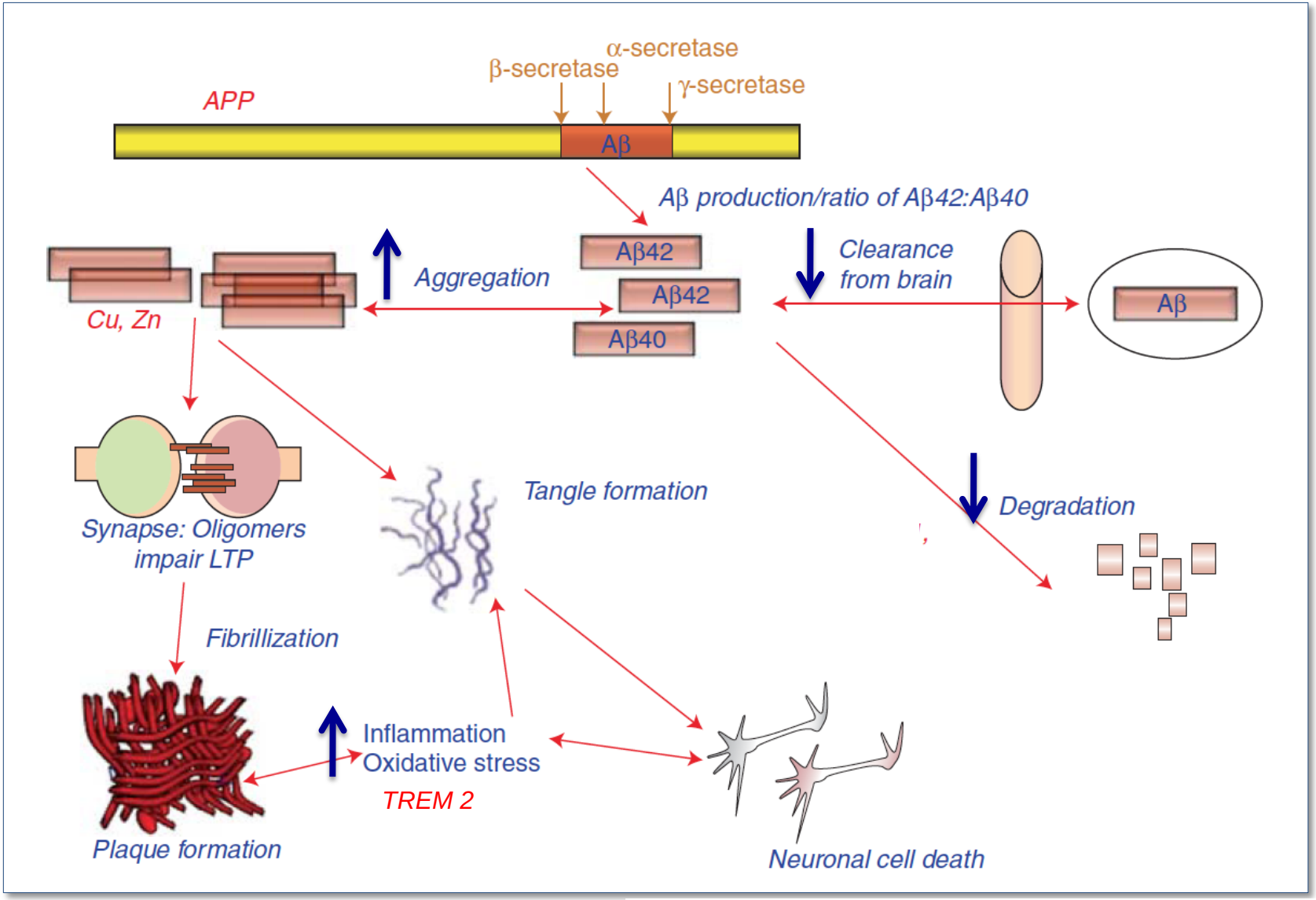


Rischio conferito dai geni legati all'Alzheimer

Gene	Protein	Location	Risk change (%)	Proposed molecular phenotype
APOE	Apolipoprotein E	19q13	~400%–1500%	Clearance of Aβ; lipid metabolism
CD33	CD33 (Siglec 3)	19q13.3	~10%	Innate immunity; degradation of Aβ
CLU	Clusterin	8p21.1	~10%	Clearance of Aβ; innate immunity
CR1	Complement component (3b/4b) receptor 1	1q32	~15%	Clearance of Aβ; innate immunity
PICALM	Phosphatidylinositol binding clathrin assembly molecule	11q14	~15%	Production and clearance of Aβ; cellular signaling
BIN1	Bridging integrator 1	2q14	~15%	Production and clearance of Aβ; cellular signaling
ABCA7	ATP-binding cassette subfamily A member 7	19p13.3	~20%	Lipid metabolism; cellular signaling
CD2AP	CD2-associated protein	6p12.3	~10%	Cellular signaling
EPHA1	EPH receptor A1	7q34	~10%	Cellular signaling; innate immunity
MS4A6A/MS4A4E	Membrane-spanning 4-domains, subfamily A, members 6A and 4E	11q12.1	~10%	Cellular signaling

Cold Spring Harb Perspect Med 2012;2:a006296

Influenza dei geni sulla patobiologia dell'Alzheimer



Cold Spring Harb Perspect Med 2012;2:a006296

Prospettive della genetica nell'Alzheimer

L'identificazione dei geni ci aiuta a capire le basi molecolari della malattia

- *Il gene dell'APP ha portato alla teoria dell'amiloide*

Determinazione del rischio e aiuto diagnostico

- *APOE genotipo aiuta nella diagnosi dell'Alzheimer*

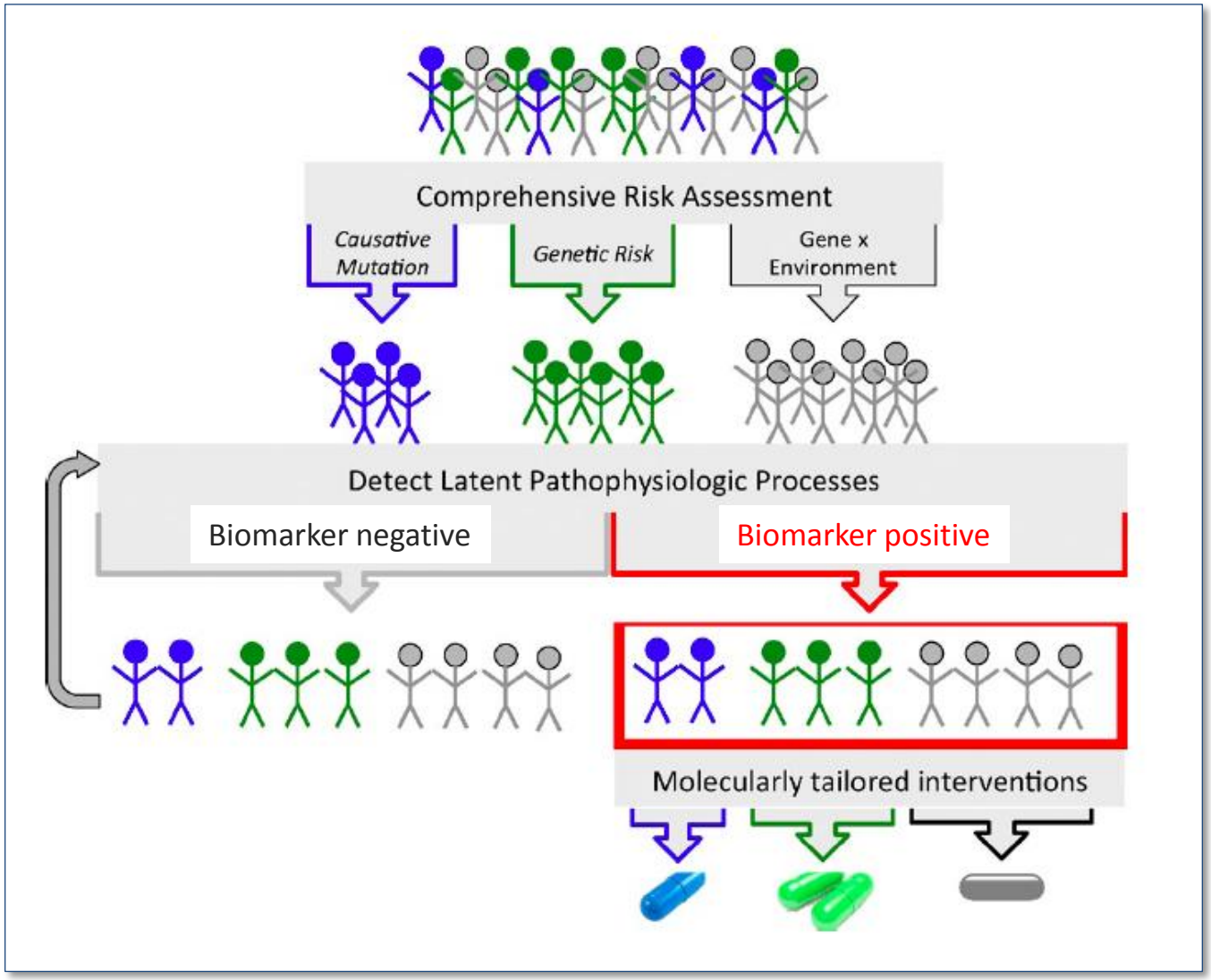
L'identificazione delle cause aiuta a sviluppare nuove terapie

- *Inhibitori della secretasi nelle FAD dovute alla mutazione della presinilina*

Medicina personalizzata (precision medicine):

- *Usare farmaci mirati al genotipo del paziente*

“Precision medicine” nella malattia di Alzheimer



J. Exp. Med. 2015 Vol. 212 No. 5 601–605

Aducanumab (Biogen Idec): il primo farmaco che rimuove l'amiloide e stabilizza la funzione cognitiva nell'Alzheimer

- Interim analysis, PRIME trial, randomized placebo controlled (Nizza, 20 Marzo 2015)
- 166 pazienti (Phase 1b) (eta' ≈70aa), PET+, deficit cognitive moderati (MMSE ≈25)

- IgG1 monoclonale amministrato mensilmente (1,3,6 oppure 10 mg/kg; i.v.) per ≈1 anno

- Placebo group: peggiorato di 3 punti con aumento dell'amiloide, 10 mg/kg group <1 punto, con riduzione dell'amiloide

- Diversi pazienti hanno avuto complicazioni (10mg/kg)(ARIA-E: cefalea, confusione, edema)

- Phase 3 trial per confermare l'efficacia in un gruppo piu' grande di pazienti

- Se il trial sara' positivo, il farmaco dovrebbe essere disponibile in 2-3 anni.

Genetica e demenze: sommario

- La malattia di Alzheimer:
  - ✓ Forme ereditarie (FAD) e sporadiche (LOAD)
  - ✓ Neuropatologia mista nei casi sporadici
  - ✓ Ruolo dei geni come causa (FAD) o fattore di rischio (LOAD)

- Determinazione del rischio genetico:
  - ✓ Linkage studies: APP, PS1, PS2 (FAD), APOE (LOAD)
  - ✓ GWAS: Variazioni genetiche comuni (SNP) che conferiscono un rischio del 10-15%
  - ✓ Exome/genome sequencing: geni piu' rari, ma con un rischio maggiore, e.g., TREM2, ABCA7

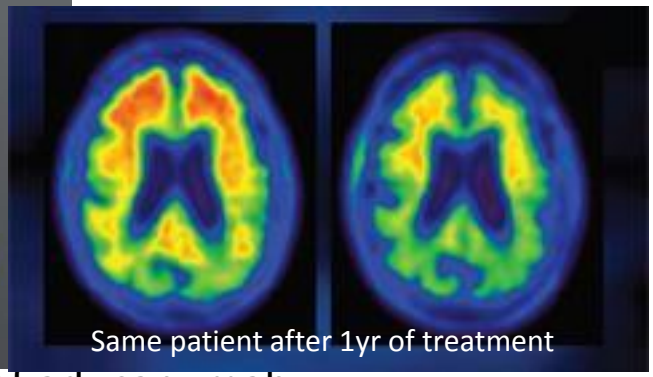
- Prospettive della genetica:
  - ✓ Nuovi fattori fisiopatologici
  - ✓ Aiutare nella diagnosi, e.g., APOE
  - ✓ Guidare il trattamento: Precision medicine

- Aducanumab: Il primo trial positivo sull' l'Alzheimer

Aducanumab (Biogen Idec): the first experimental Alzheimer's drug to reduce amyloid plaques and improve cognitive function in humans

Aducanumab is the first experimental Alzheimer's drug to convincingly reduce amyloid plaques and improve cognitive function in a human clinical trial. The drug, which is an antibody vaccine, must be administered intravenously and cannot be taken in pill form.

The results w
number of p
determine d
effectiveness



There were a
patients taking the highest—and most effective—doses of aducanumab.

Biogen aims to take this drug straight to a phase 3 clinical trial. If the results of the trial are successful, aducanumab could be available to patients within just a few years. These are the most hopeful clinical trial results I have ever seen for an Alzheimer's drug.

Triggering receptor expressed on myeloid cell 2 (TREM2)

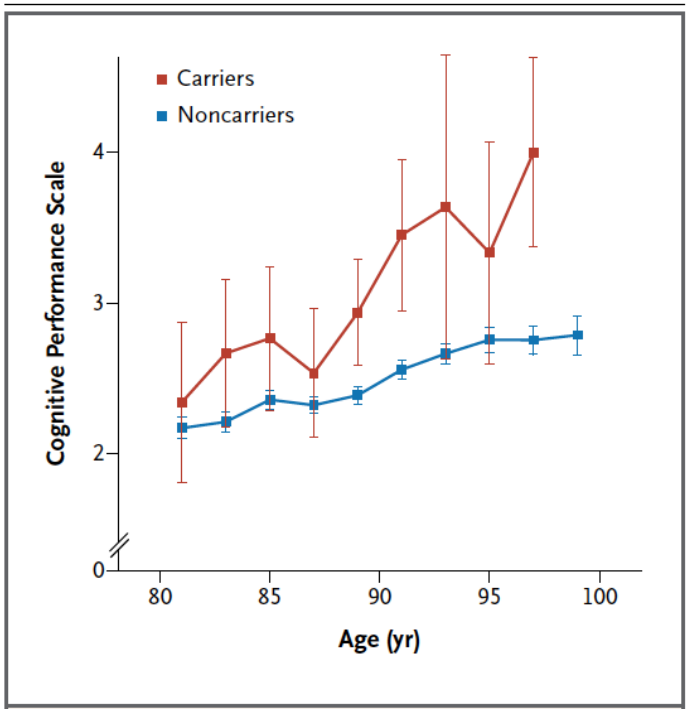
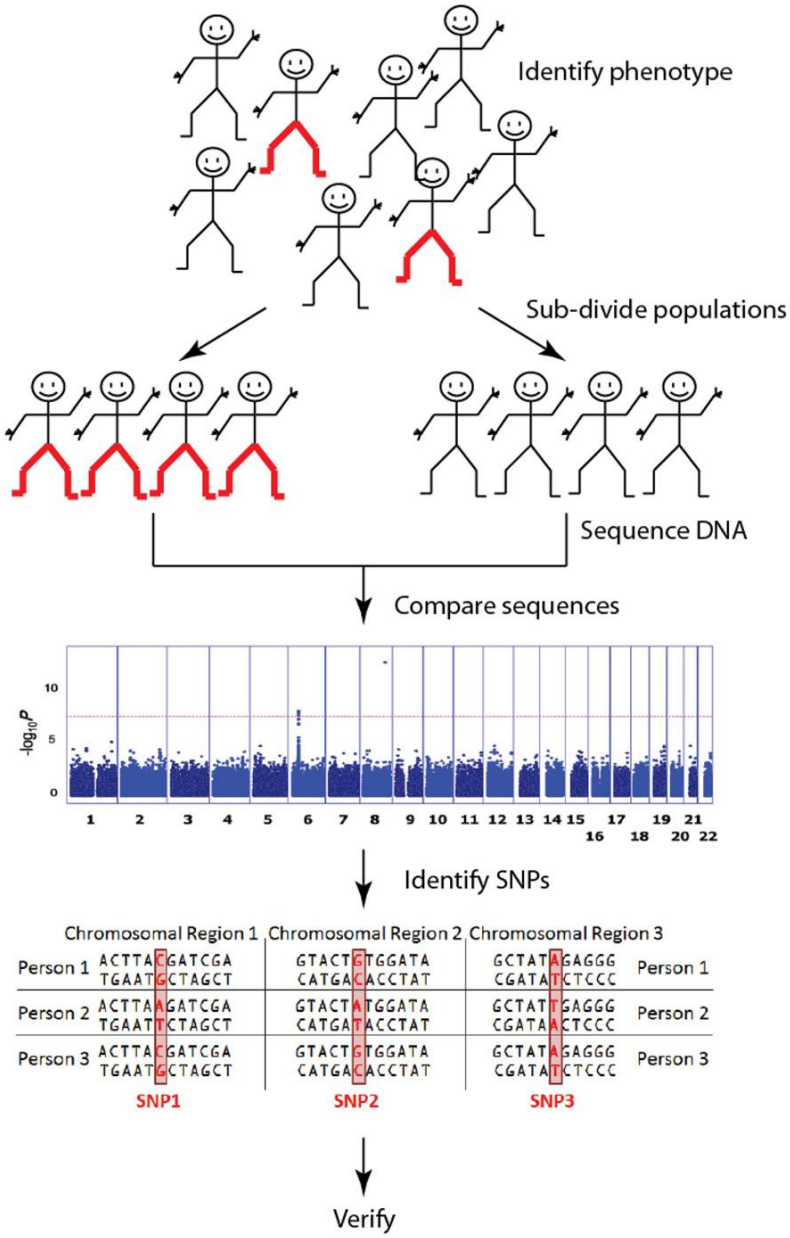
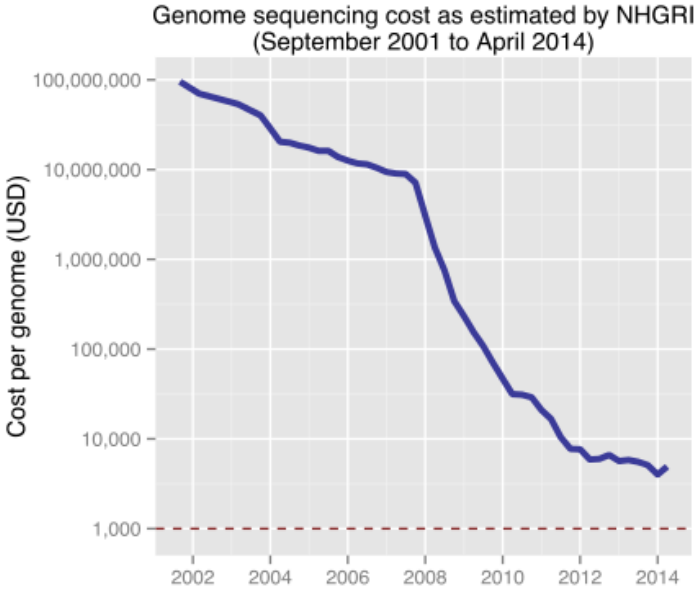


Figure 1. Cognition as a Function of Age in Controls Who Were Carriers or Noncarriers of the rs75932628-T Variant Associated with the Risk of Alzheimer's Disease.

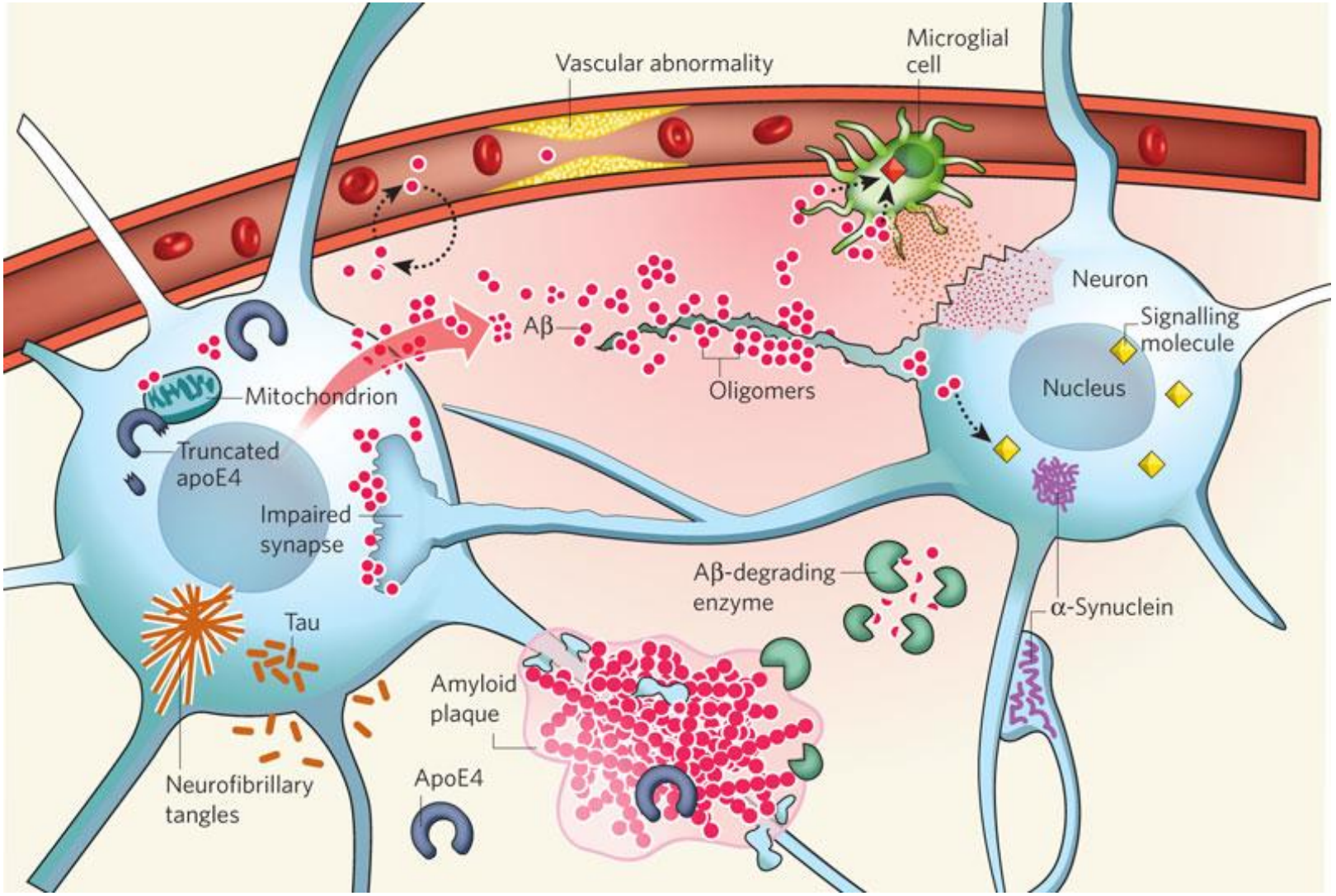
Shown are scores on the Cognitive Performance Scale (CPS) for carriers and noncarriers of the rs75932628-T variant associated with Alzheimer's disease, according to age. Scores on the CPS range from 0 to 6, with higher scores indicating more severe impairment. Values are shown in 2-year bins (i.e., the data point for 81 years of age contains data for ages 80 and 81), except for the last bin, which represents ages of 98, 99, and 100 years. No CPS data were available for carriers in the last age bin. Each data point represents the average CPS score for participants in the respective age bin. The I bars represent standard errors. The graph is based on 307 measurements from 53 carriers and 24,152 measurements from 3699 noncarriers. Patients in whom Alzheimer's disease had been diagnosed were not included in the analysis.

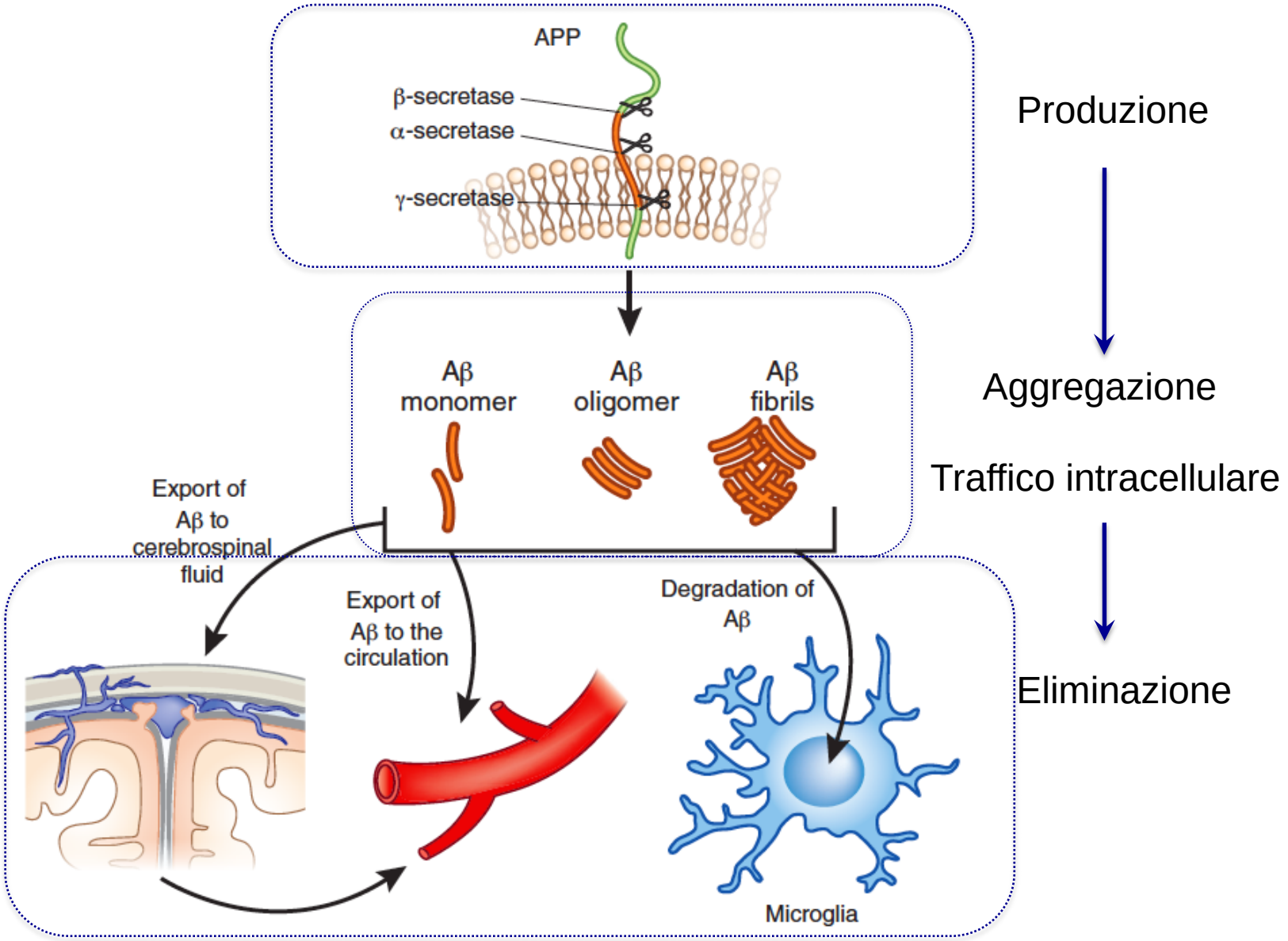
N ENGL J MED 368;2 NEJM.ORG JANUARY 10, 2013

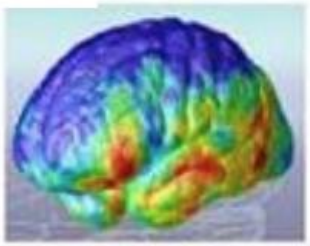

Identify phenotype
Sub-divide populations
Sequence DNA
Compare sequences
$-\log_{10} P$
10
5
0
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22
Identify SNPs
Chromosomal Region 1
Chromosomal Region 2
Chromosomal Region 3
Person 1 ACTTACGATCGA TGAATGCTAGCT GTACTGTGGATA CATGACACCTAT GCTATAGAGGG CGATATCTCCC Person 1
Person 2 ACTTAAGATCGA TGAATTCTAGCT GTACTATGGATA CATGATACCTAT GCTATTGAGGG CGATAACTCCC Person 2
Person 3 ACTTACGATCGA TGAATGCTAGCT GTACTGTGGATA CATGACACCTAT GCTATAGAGGG CGATATCTCCC Person 3
SNP1
SNP2
SNP3
Verify


Genome sequencing cost as estimated by NHGRI
(September 2001 to April 2014)
Cost per genome (USD)
100,000,000
10,000,000
1,000,000
100,000
10,000
1,000
2002
2004
2006
2008
2010
2012
2014

Il problema fondamentale nell' Alzheimer e' un difetto delle sinapsi causato principalmente da Aβ e tau




APP
β-secretase
α-secretase
γ-secretase
Aβ monomer
Aβ oligomer
Aβ fibrils
Export of Aβ to cerebrospinal fluid
Export of Aβ to the circulation
Degradation of Aβ
Microglia
Produzione
Aggregazione
Traffico intracellulare
Eliminazione



Alzheimer's Research Highlights – Gene Discovery

1991
APP
APOE

1995
PS1 *
PS2 *

1996
Transgenic
Mouse models

2005
First
published
GWAS

2009
PICALM*
CLU *
CR1 *
GWAS

2010
BIN1*

2011
MS4A4 / MS4A6E
SORL1
CD2AP,
SORL1,*

2012
TREM2
*

* Early onset Alzheimer's Disease- family based studies
* Late onset Alzheimer's Disease case control and family based studies

Range needed to identify genes: 3,000 – 27,000 cases and 11,000 – 41,000 controls

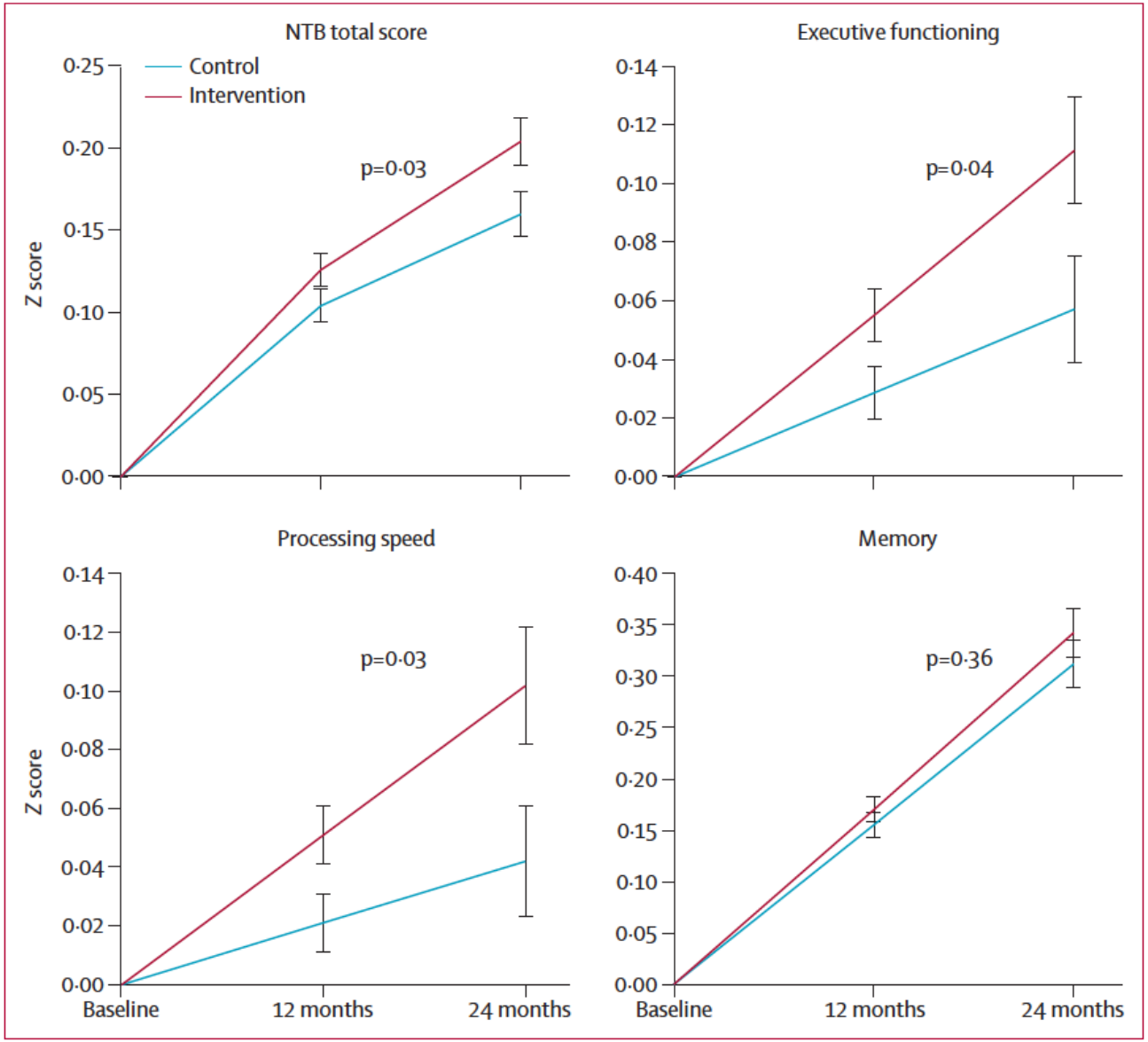
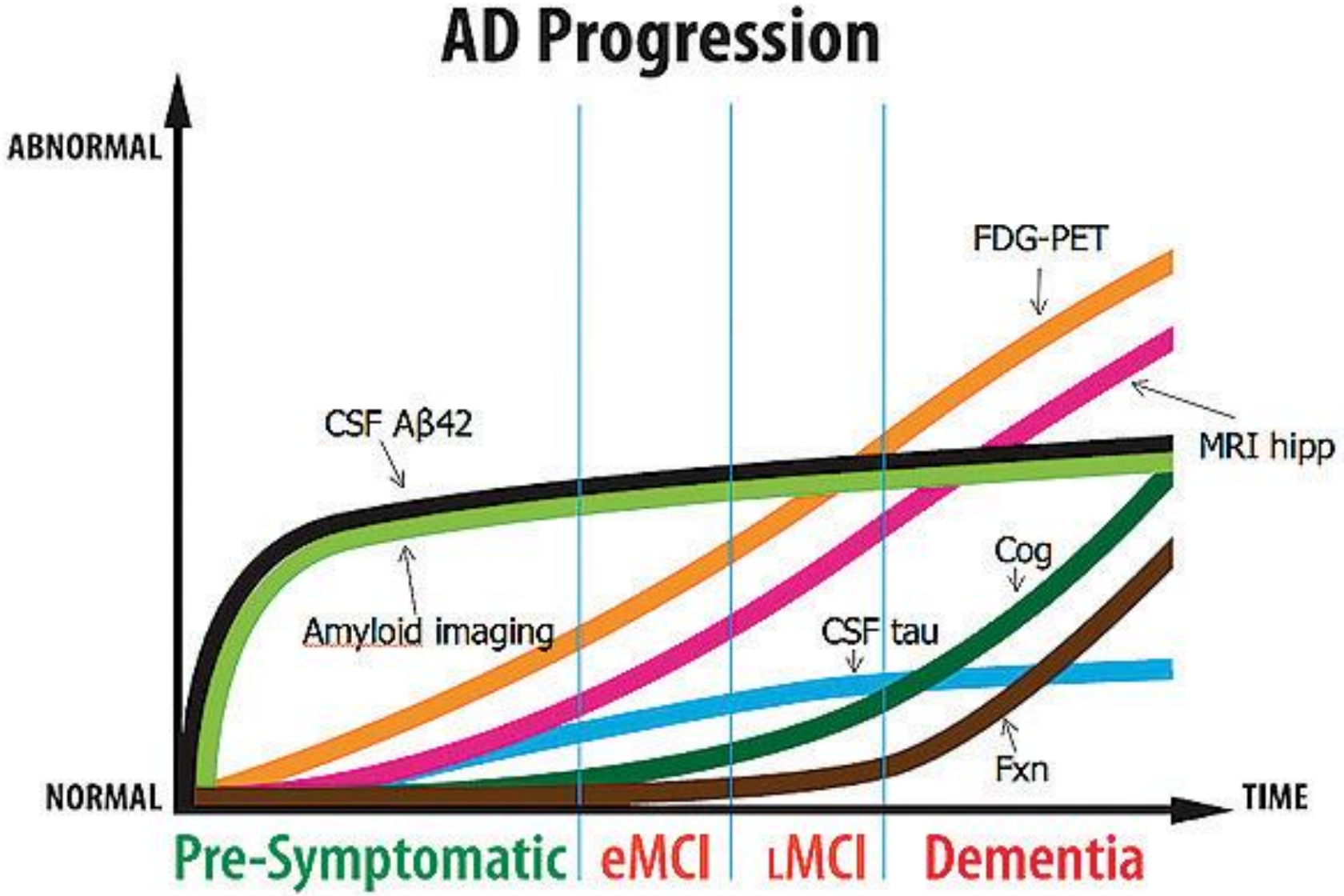


Figure 2: **Change in cognitive performance during the 2 year intervention**

www.thelancet.com **Published online March 12, 2015** **http://dx.doi.org/10.1016/S0140-6736(15)60461-5**

FINGER study



Courtesy of Paul Aisen, M.D., Alzheimer's Disease Cooperative Study, University of California, San Diego.

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Variant of *TREM2* Associated with the Risk of Alzheimer's Disease

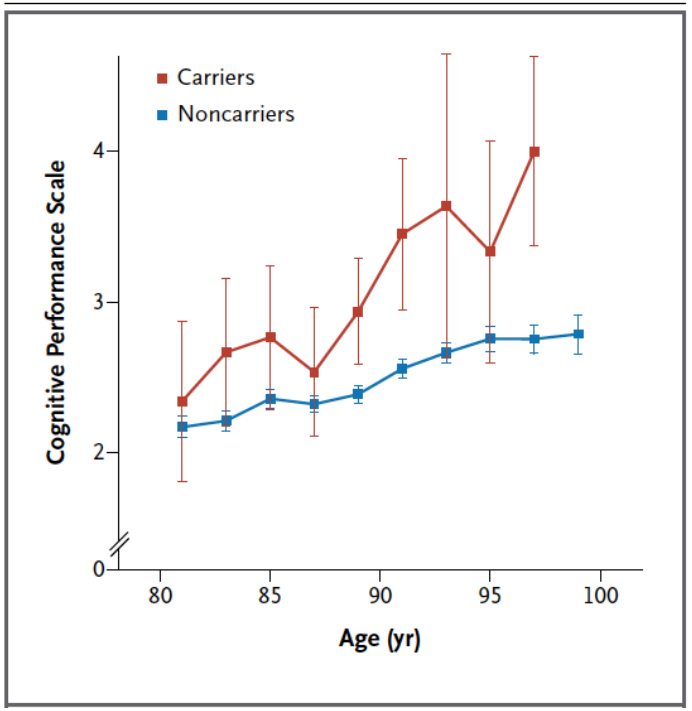
Thorlakur Jonsson, Ph.D., Hreinn Stefansson, Ph.D., Stacy Steinberg Ph.D., Ingileif Jonsdottir, Ph.D.,

TREM2 codifica una proteina delle cellule immunitarie che sopprime l'infiammazione

Aumenta il rischio dell'Alzheimer da 3 a 5 volte (come ApoE4/4)

La mutazione diminuisce la funzionalita' della proteina, aumenta l'infiammazione e riduce l' eliminazione dell'amiloide

La mutazione riduce le capacita' cognitive anche in soggetti senza l'Alzheimer.



GENETIC RISK FACTORS FOR ALZHEIMER'S DISEASE

Several genes implicated in Alzheimer's pathogenesis are involved in multiple cellular pathways, which illustrates the complexity of the disease.

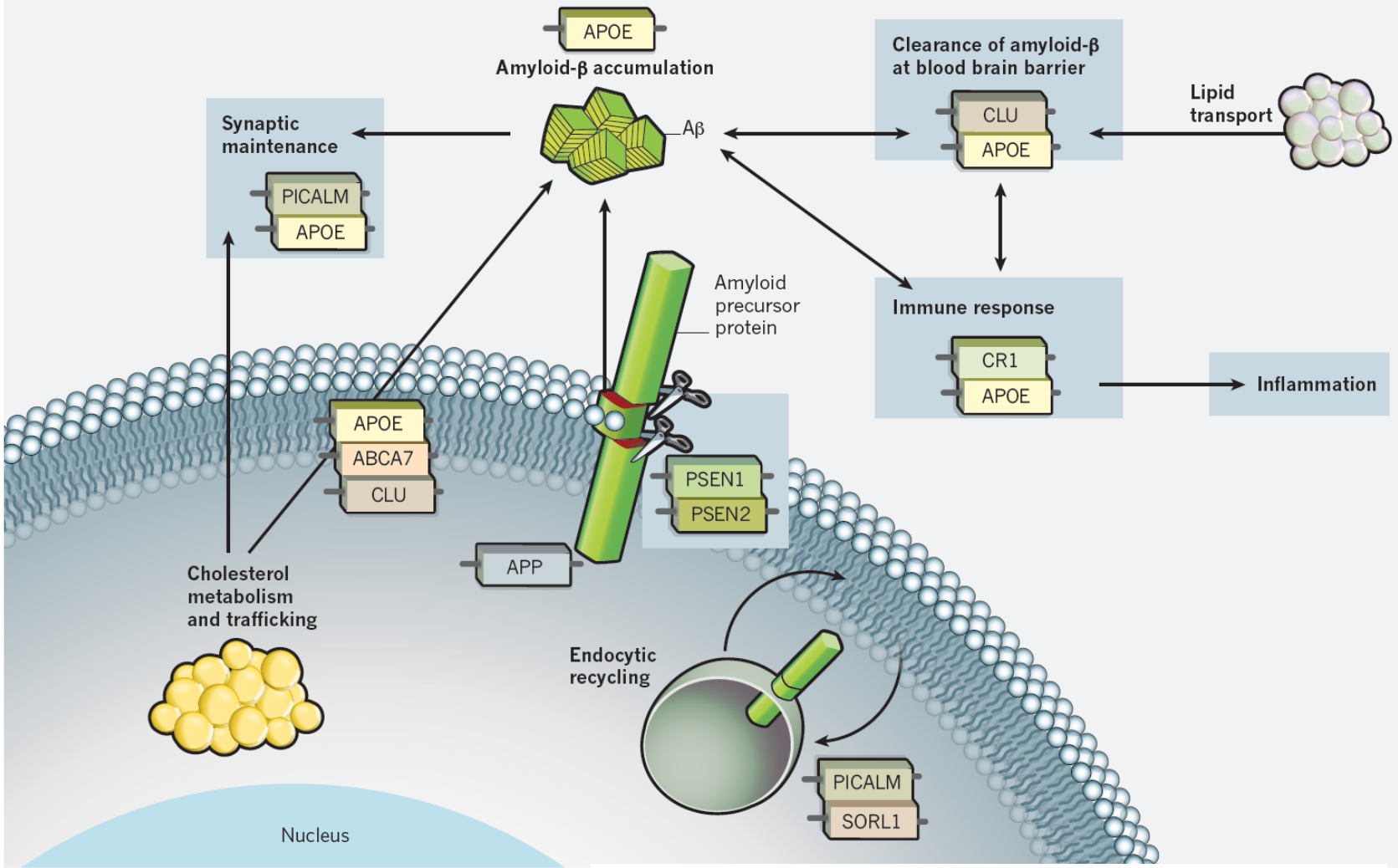


Table 1. Factors that modify the risk of Alzheimer disease

Antecedent	Direction	Possible mechanisms
Cardiovascular disease	Increased	Parenchymal destruction Strategic location ↑ Aβ deposition
Smoking	Increased	Cerebrovascular effects Oxidative stress
Hypertension	Increased and decreased	Microvascular disease
Type II diabetes	Increased	Cerebrovascular effect Insulin and Aβ compete for clearance
Obesity	Increased	Increased risk of type II diabetes inflammatory
Traumatic head injury	Increased	↑Aβ and amyloid precursor protein deposition
Education	Decreased	Provides cognitive reserve
Leisure activity	Decreased	Improves lipid metabolism, mental stimulation
Mediterranean diet	Decreased	Antioxidant, anti-inflammatory
Physical activity	Decreased	Activates brain plasticity, promotes brain vascularization

Cold Spring Harb Perspect Med 2012;2:a006296

	Chromosome	Inheritance pattern	Location of mutations or main SNP	Effect size (odds ratio [95% CI])	Proposed function*	Implicated pathway*
APP	19	Autosomal dominant or recessive	Exons 16 and 17	..†	Substrate of amyloid β peptide, cell signalling events, tau phosphorylation, GSK 3β activation	Amyloid β pathway, endocytotic receptor trafficking, tau pathway
PSEN1	14	Autosomal dominant	Whole gene	..†	γ-secretase activity, transmembrane protein processing, intracellular signalling	Amyloid β pathway, synaptic plasticity, neuronal survival
PSEN2	2	Autosomal dominant	Whole gene	..†	γ-secretase activity, transmembrane protein processing, intracellular signalling	Amyloid β pathway, synaptic plasticity, neuronal survival
APOE	19	Semi-dominant	Exon 4	ε3ε4 3·2 (2·8–3·8) ε4ε4 14·9 (10·8–20·6)‡	Amyloid β aggregation and clearance, intracellular signalling through LRP	Lipid transport and metabolism, amyloid β pathway, synaptic plasticity, neuroinflammation
CLU	8	Risk gene	Intronic *rs1136000*	0·89 (0·86–0·91)	Molecular chaperone, synapse turnover, amyloid β aggregation, clearance, and toxicity	Amyloid β pathway, lipid metabolism, immune system, inflammation, apoptosis
CR1	1	Risk gene	Intronic *rs6656401*	1·19 (1·09–1·30)	Complement system activation, amyloid β clearance	Immune system, amyloid β pathway
PICALM	11	Risk gene	Upstream *rs3851179*	0·88 (0·86–0·91)	Clathrin-mediated endocytosis	Synaptic cell functioning, amyloid β toxic effects, processing of APP
BIN1	2	Risk gene	Upstream *rs744373*	1·17 (1·13–1·20)	Synaptic vesicle endocytosis, formation of tubular membrane structures	Synaptic cell functioning, caspase-independent apoptosis
EPHA1	7	Risk gene	Upstream *rs11767557*	0·89 (0·83–0·96)	Synaptic development and plasticity	Immune system
ABCA7	19	Risk gene	Intronic *rs3764650*	1·23 (1·18–1·28)	Transportation of substrates across cell membranes	Cholesterol metabolism, immune system, processing of APP
MS4A4A, MS4A6E	11	Risk gene	Intergenic *rs610932*	0·90 (0·88–0·93)	No known functions (except MS4A2 β-subunit, which has high affinity for IgE receptors)	Immune system (MS4A2), cell surface signalling
CD33	19	Risk gene	Upstream *rs3865444*	0·85 (0·86–0·92)	Clathrin-mediated endocytosis	Immune system, synaptic cell functioning
CD2AP	6	Risk gene	Intronic *rs9349407*	1·12 (1·08–1·16)	Receptor-mediated endocytosis	Synaptic cell functioning, actin cytoskeleton

Effect size for top SNPs in risk genes is based on AlzGene meta-analysis (http://www.alzgene/org). SNP=single nucleotide polymorphism. *Selection of proposed functions and pathways; the exact functional evidence of these loci in Alzheimer's disease is often sparse. †Effect size for mutations in causal variants is nearly complete penetrance. ‡Effect for *APOE ε4* is based on Farrer et al.[26]

Table 1: **Causal and risk genes in mendelian and non-mendelian Alzheimer's disease**

	Drug	Participants	Treatment duration*	Primary endpoint	Finding
Rogers et al (1993)[204]	Indometacin 100–150 mg daily versus placebo	28 patients with AD dementia randomised 1:1	6 months	Cognitive trajectory on a battery of psychometric tests	Positive effects (after 36% attrition; p<0·003)
De Jong et al (2008)[205]	Indometacin 100 mg daily with omeprazole versus placebo	51 patients with mild-to-moderate AD randomised 1:1	1 year	Change in score on ADAS-Cog	Neutral-to-positive effects (after 25% attrition; not significant)
Aisen et al (2000)[206]	Prednisone (20 mg once daily tapered to 10 mg) versus placebo	138 patients with AD randomised 1:1	1 year	Change in score on ADAS-Cog	Neutral-to-negative effects (worsening of secondary endpoint behavioural measures; not significant)
Aisen et al (2003)[207]	Naproxen sodium 220 mg twice daily or rofecoxib 25 mg once daily versus placebo	351 patients with mild-to-moderate AD (MMSE score 13–26)	1 year	Change in score on ADAS-Cog	Neutral-to-negative effects, greater decline in rofecoxib group (p=0·09 after adjustment for multiple comparisons)
Aisen et al (2002)[208]	Nimesulide 100 mg twice daily versus placebo	40 patients with AD randomised 1:1	3 months	Composite of cognitive, behavioural, and functional outcomes	No apparent effect
Reines et al (2004)[209]	Rofecoxib 25 mg once daily versus placebo	692 patients with mild-to-moderate AD randomised 1:1	1 year	ADAS-Cog, CIBIC+	Trend towards negative effects (after 30% attrition)
Thal et al (2005)[210]	Rofecoxib 25 mg once daily versus placebo	1457 patients with MCI randomised 1:1	3·5 years	Change in status from MCI to AD dementia	Increased progression to AD dementia in rofecoxib group (p=0·011); no effects on secondary outcomes
Van Gool et al (2001)[211]	Hydroxychloroquine (200–400 mg once daily by body weight) versus placebo	168 patients with mild AD randomised 1:1	18 months	Functional status questionnaire, ADAS-Cog, behavioural symptoms	No apparent effect
ADAPT Research Group (2007 and 2008)[212,213]	Celecoxib 100 mg twice daily or naproxen sodium 220 mg twice daily versus placebo	2528 healthy individuals with family history of AD randomised 1:1:1.5	1–3 years	Onset of AD	Trend towards negative effects
ADAPT Research Group (2007 and 2008)[212,213]	Celecoxib 100 mg twice daily or naproxen sodium 220 mg twice daily versus placebo	2528 healthy individuals with family history of AD randomised 1:1:1.5	1–3 years	Cognitive decline on battery of neuropsychological tests	Trend towards negative effects
Simons et al (2002)[214]	Simvastatin up to 80 mg per day as tolerated versus placebo	44 patients with AD randomised 1:1	26 weeks	CSF biomarkers $A\beta_{1-40}$ and $A\beta_{1-42}$	No apparent effect
Sparks et al (2005)[215]	Atorvastatin 80 mg once daily versus placebo	67 patients with mild AD randomised 1:1	1 year	ADAS-Cog, CGI (co-primaries), LOCF analysis	Trend towards positive effects
Feldman et al (2010)[216]	Atorvastatin 80 mg once daily versus placebo	640 patients with mild-to-moderate AD (MMSE 13–25) randomised 1:1	72 weeks	ADAS-Cog, CGI (co-primaries)	No apparent effect
Harrington et al (2011)[217]	Rosiglitazone 2 mg or 8 mg daily	2981 patients with mild-to-moderate AD randomised 1:1	48 weeks	ADAS-Cog, CDR sum of boxes	No apparent effect
Breitner et al (2011)[218]	Celecoxib 100 mg twice daily or naproxen sodium 220 mg twice daily versus placebo	Follow-up of 2071 participants randomised in ADAPT	Follow-up 2–4 years after termination of treatments	Onset of AD, CSF tau, plasma tau, and CSF $A\beta_{1-42}$	No apparent effect for celecoxib, possible positive effects for naproxen (including reduced ratio of CSF tau to $A\beta_{1-42}$)
ADAPT Research Group (2013)[219]	Celecoxib 100 mg twice daily or naproxen sodium 220 mg twice daily versus placebo	Follow-up of 1537 participants randomised in ADAPT	Follow-up 5–7 years after termination of treatments	Onset of AD	No apparent effect

Heneka
Lancet neurology
April 2015

The results from the combined stage 1 and stage 2 data sets also identified 13 loci with suggestive evidence of association ($P < 1 \times 10^{-6}$) (**Supplementary Table 4**). Among these, we detected a signal for rs9381040 ($P = 6.3 \times 10^{-7}$), which is located approximately 5.5 kb away from the 3′ end of *TREML2* and 24 kb away from the 5′ end of *TREM2*. *TREM2* was recently reported to

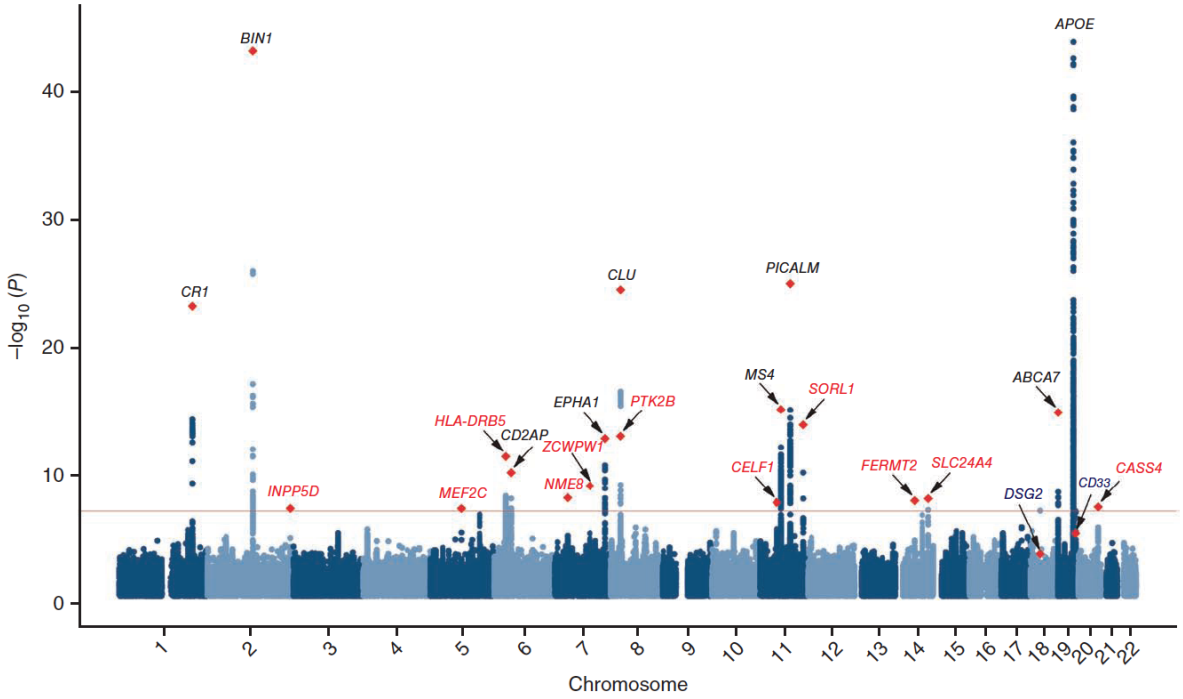
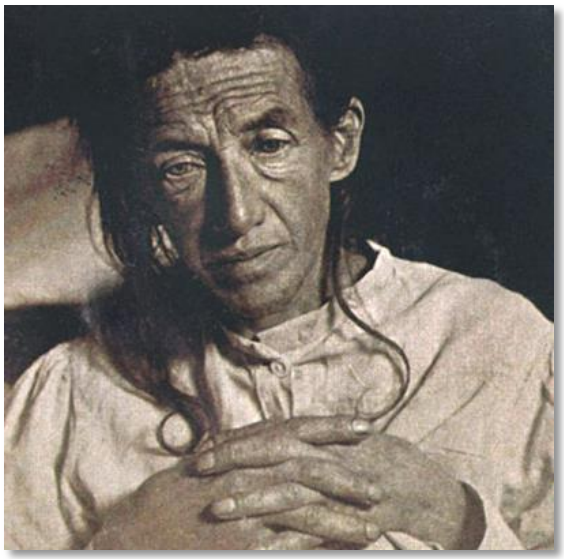


Figure 1 Manhattan plot of stage 1 for genome-wide association with Alzheimer's disease (17,008 cases and 37,154 controls). The threshold for genome-wide significance ($P < 5 \times 10^{-8}$) is indicated by the red line. Genes previously identified by GWAS are shown in black, and newly associated genes are shown in red. Red diamonds represent SNPs with the smallest *P* values in the overall analysis.

Le origini della malattia di Alzheimer

Alois Alzheimer ed alcuni collaboratori nel 1910



Auguste Deter: anni 51

Neuron *84*, November 5, 2014 ©2014 Elsevier Inc. 609

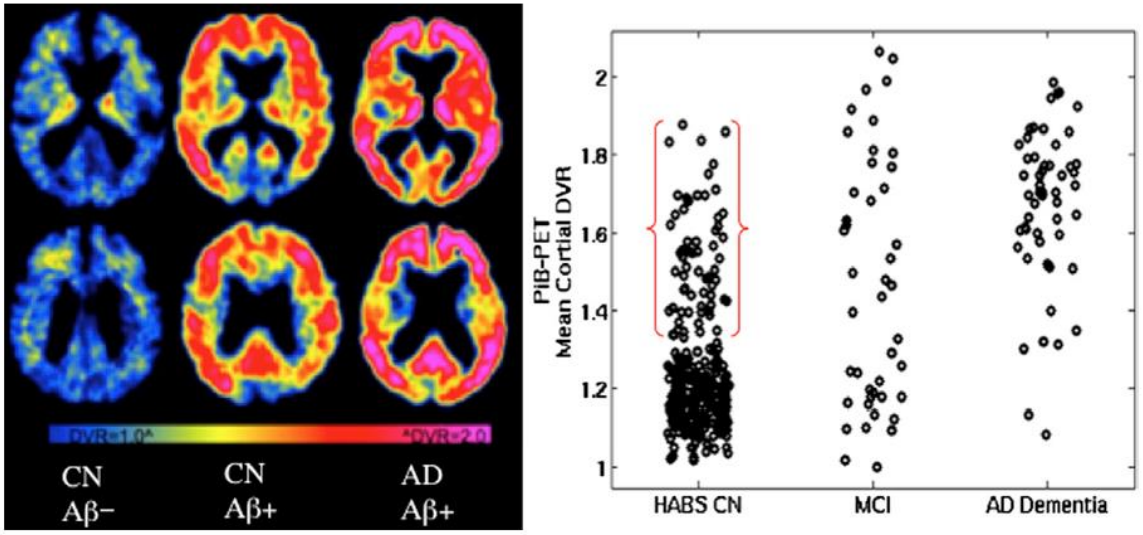


Figure 1. PET Amyloid Imaging with ^{11}C-PiB

Left: representative PET images from three older individuals; clinically normal older individual without evidence of elevated Aβ accumulation (CN Aβ−), clinically normal older individual with elevated Aβ accumulation (CN Aβ+), and patient with AD dementia with very elevated Aβ accumulation (AD Aβ+) in frontal and parietal heteromodal cortices.

Right: scattergram of PiB distribution value ratios (DVRs) by diagnostic group; Harvard Aging Brain Study clinically normal older individuals (HABS CN), mild cognitive impairment (MCI), and AD dementia. Approximately 30% of HABS CN demonstrate elevated Aβ accumulation in the range of MCI and AD dementia Aβ+.

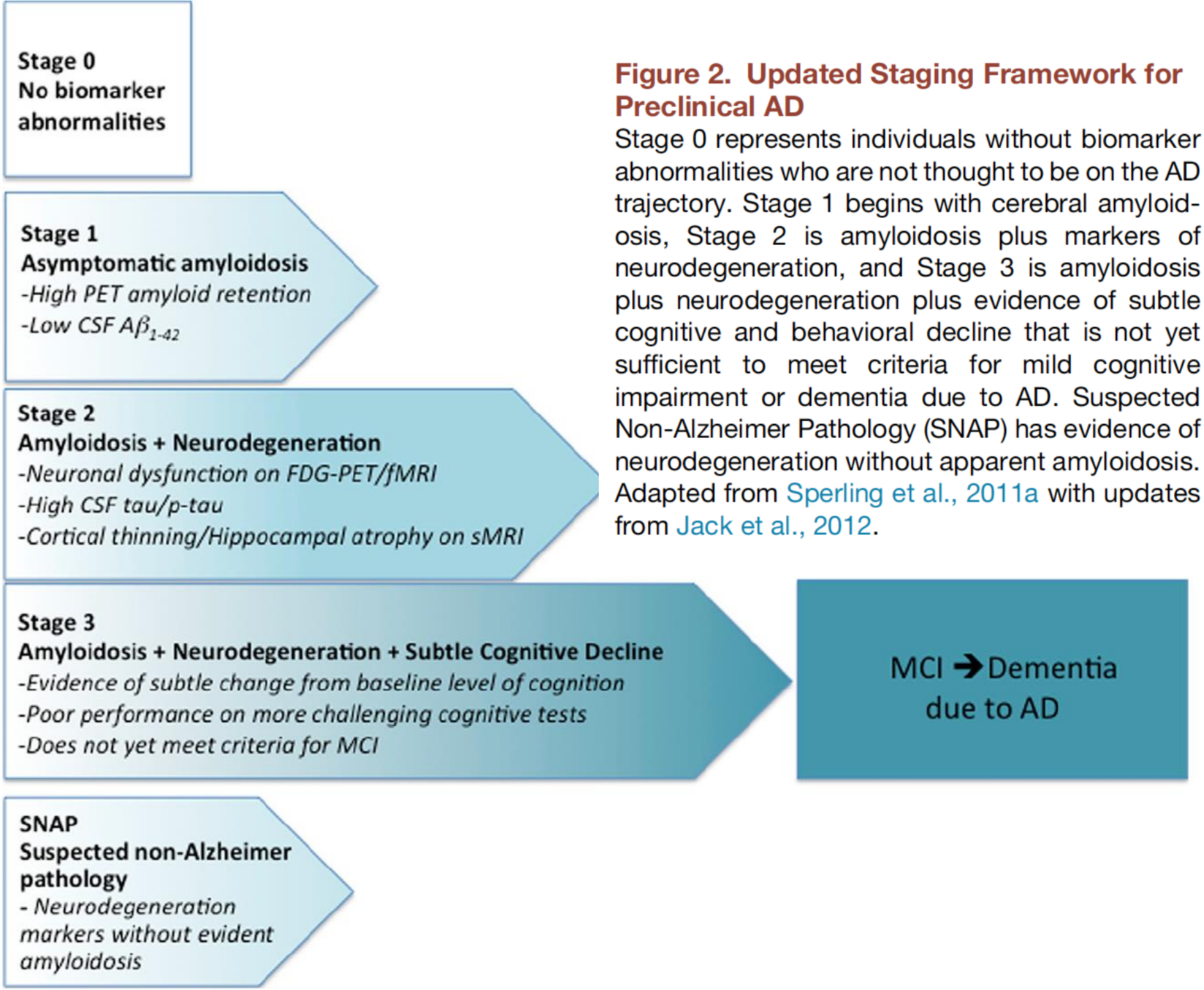


Figure 2. Updated Staging Framework for Preclinical AD

Stage 0 represents individuals without biomarker abnormalities who are not thought to be on the AD trajectory. Stage 1 begins with cerebral amyloidosis, Stage 2 is amyloidosis plus markers of neurodegeneration, and Stage 3 is amyloidosis plus neurodegeneration plus evidence of subtle cognitive and behavioral decline that is not yet sufficient to meet criteria for mild cognitive impairment or dementia due to AD. Suspected Non-Alzheimer Pathology (SNAP) has evidence of neurodegeneration without apparent amyloidosis. Adapted from Sperling et al., 2011a with updates from Jack et al., 2012.

Biomarkers della malattia di Alzheimer

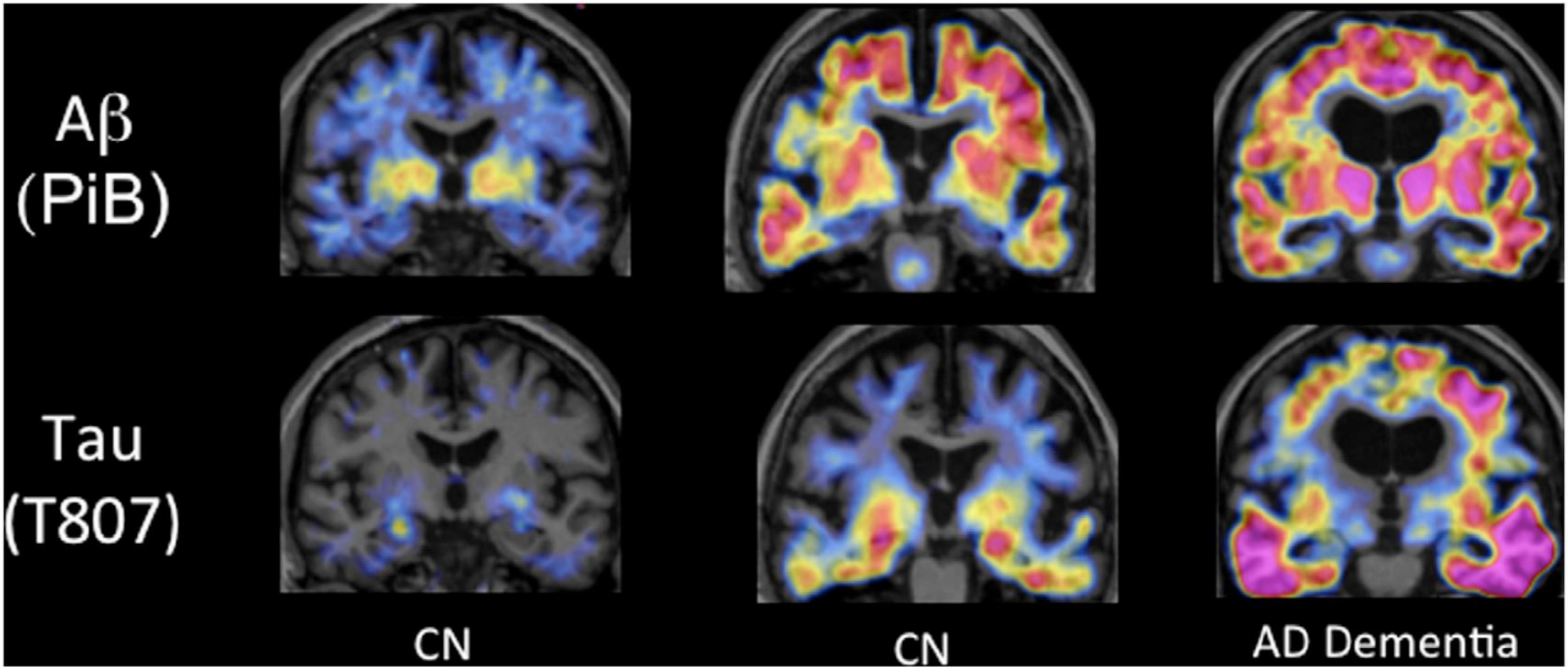


Figure 3. PET Amyloid and Tau Imaging
Coronal PET images superimposed on structural magnetic resonance of PiB Aβ (upper row) and T807 Tau (lower row) acquired on older participants in the Harvard Aging Brain Study. The first two columns of images are from clinically normal (CN) older individuals with the far right image acquired from a patient with AD dementia. Moving from left to right exemplifies increasing levels of Aβ in neocortical regions associated with increasing levels of Tau, particularly prominent in the inferior temporal cortices.

Sperling Neuron 2014

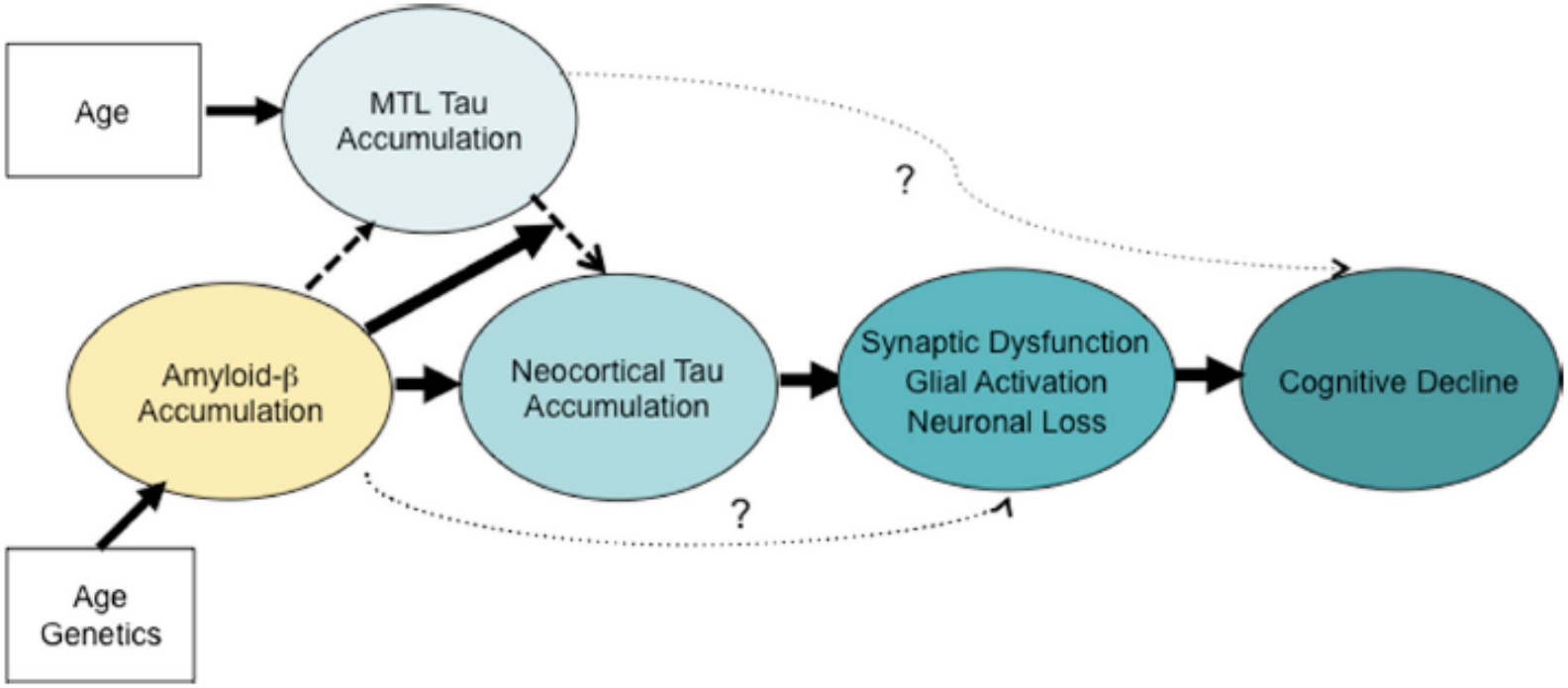


Figure 4. Hypothetical Model of the Interaction of Aβ and Tau Accumulation

Advancing age is nearly ubiquitously associated with the gradual accumulation of Tau aggregates in medial temporal lobe (MTL), but it remains unknown whether MTL tau in isolation is associated with "age-related" cognitive change. Age and genetics influence likelihood of accumulating elevated levels of amyloid-β (Aβ) aggregates. Aβ is hypothesized to increase the accumulation of Tau aggregates and in particular to accelerate the spread of Tau out of the MTL into the neocortex through local diffusion and perhaps via transynaptic spread across neural networks. Tau accumulation leads to synaptic dysfunction, glial activation, and eventually neuronal loss. Aβ may also have direct effects on synaptic toxicity resulting in network dysfunction that are not primarily mediated through Tau. The spreading of Tau into neocortex and associated neurodegenerative processes are thought to result in cognitive impairment and further progression along the clinical trajectory of Alzheimer's disease.

Panel 1: Preclinical AD stages and symptomatic AD

Normal group
CDR 0 (no dementia), no amyloid, no neuronal injury, no subtle cognitive decline

Preclinical AD stage 1
CDR 0 (no dementia), amyloid, no neuronal injury, no subtle cognitive decline

Preclinical AD stage 2
CDR 0 (no dementia), amyloid, neuronal injury, no subtle cognitive decline

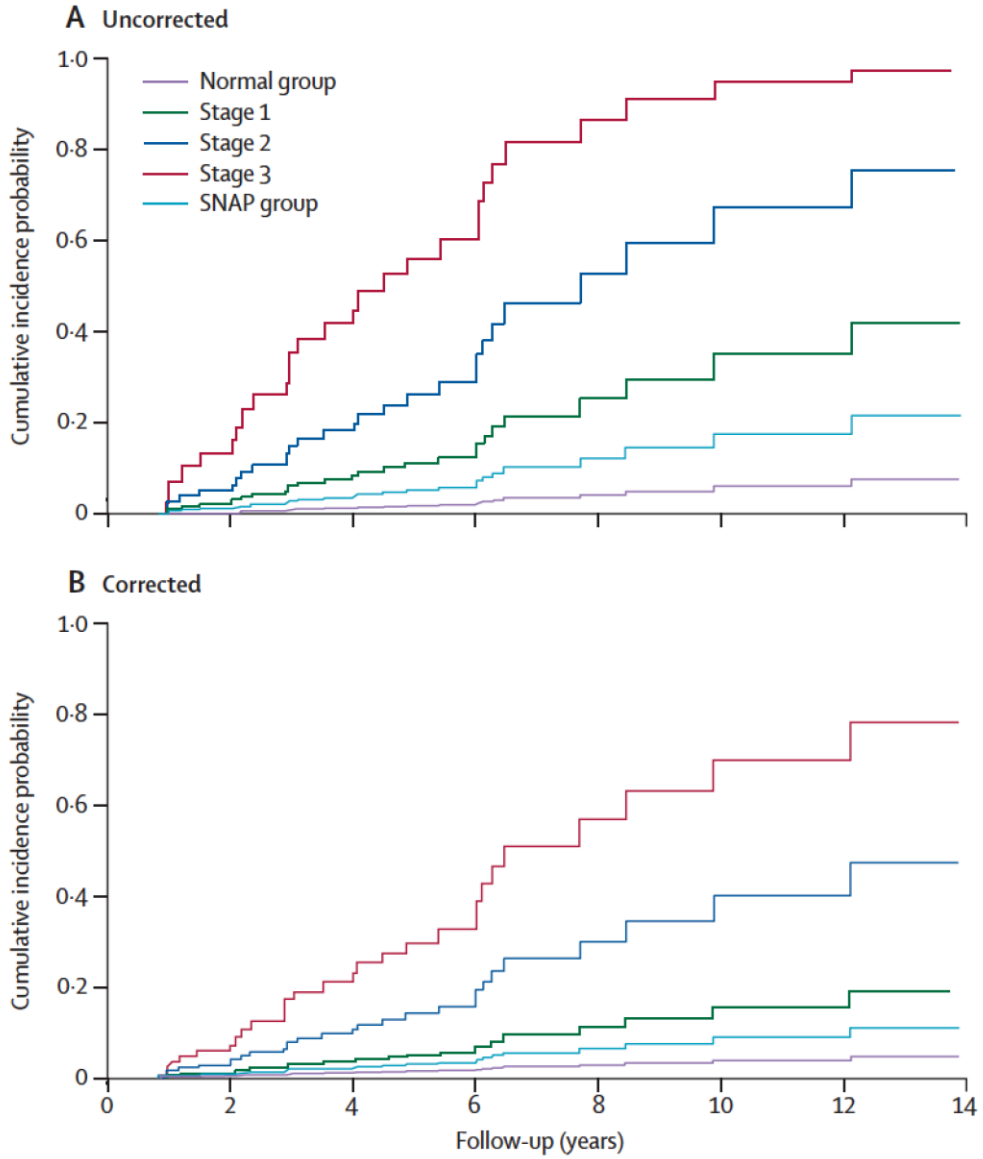
Preclinical AD stage 3
CDR 0 (no dementia), amyloid, neuronal injury, subtle cognitive decline

SNAP group
CDR 0 (no dementia), no amyloid, neuronal injury, with or without subtle cognitive decline

Unclassified group
CDR 0 (no dementia), with or without amyloid, no neuronal injury, subtle cognitive decline

Symptomatic AD
CDR>0, memory and at least one other domain received a score of ≥0·5 and the clinician felt the cognitive impairments to be due to AD (probable AD according to NINDS-ADRDA criteria), no reference to biomarkers

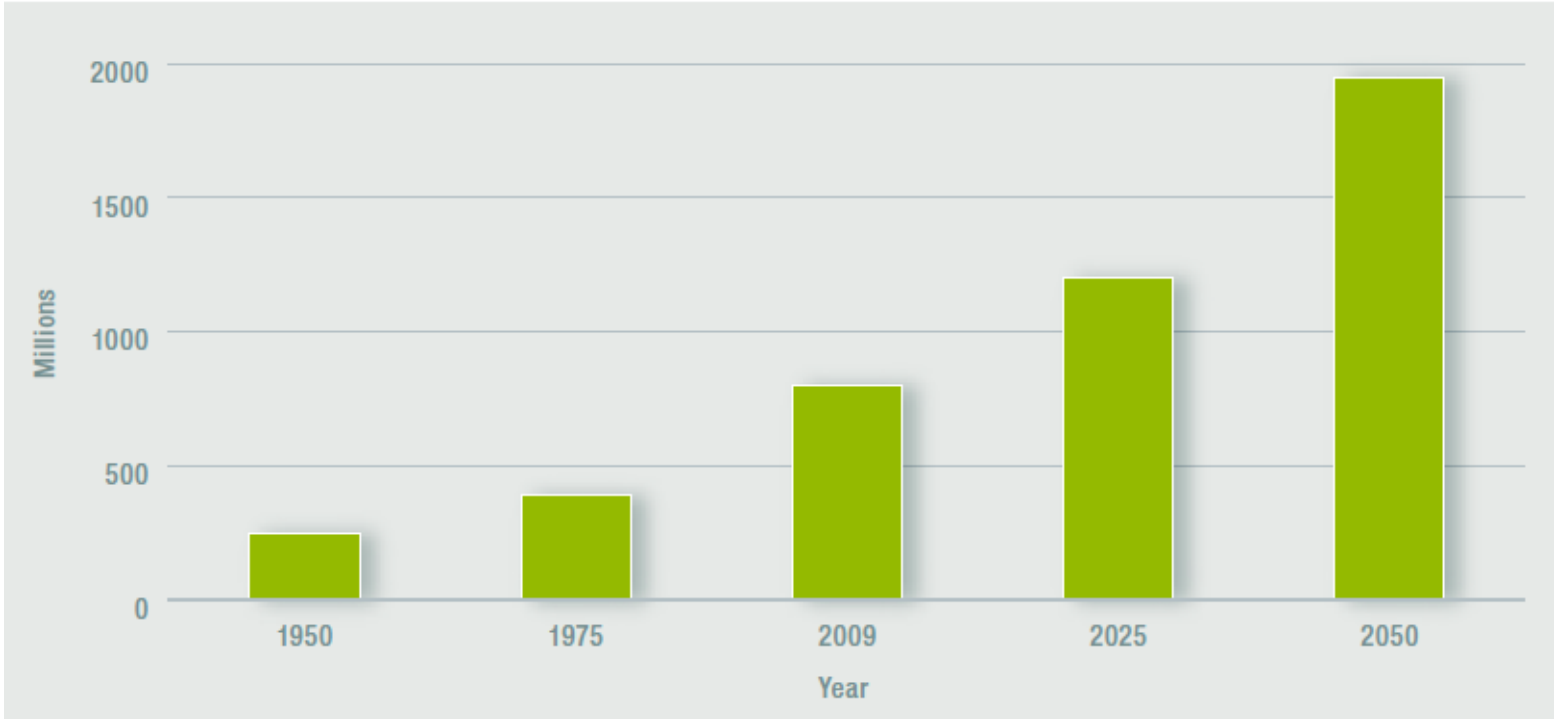
AD=Alzheimer's disease. No amyloid=CSF amyloid-β_{1-42} ($A\beta_{1-42}$) ≥459 pg/mL. Amyloid=CSF $A\beta_{1-42}$ <459 pg/mL. CDR 0=clinical dementia rating score of 0, no dementia. CDR 0·5=very mild impairment or very mild dementia. CDR 1=mild dementia. CDR 2=moderate dementia. CDR 3=severe dementia. No neuronal injury=CSF total tau (t-tau) ≤339 pg/mL and phosphorylated tau_{181} (p-tau_{181}) ≤67 pg/mL. Neuronal injury=CSF t-tau >339 pg/mL or p-tau_{181} >67 pg/mL. SNAP=suspected non-Alzheimer pathophysiology. Subtle cognitive decline=episodic memory composite score in the lowest 10th percentile. No subtle cognitive decline=episodic memory composite score in the highest 90th percentile.



Number of participants

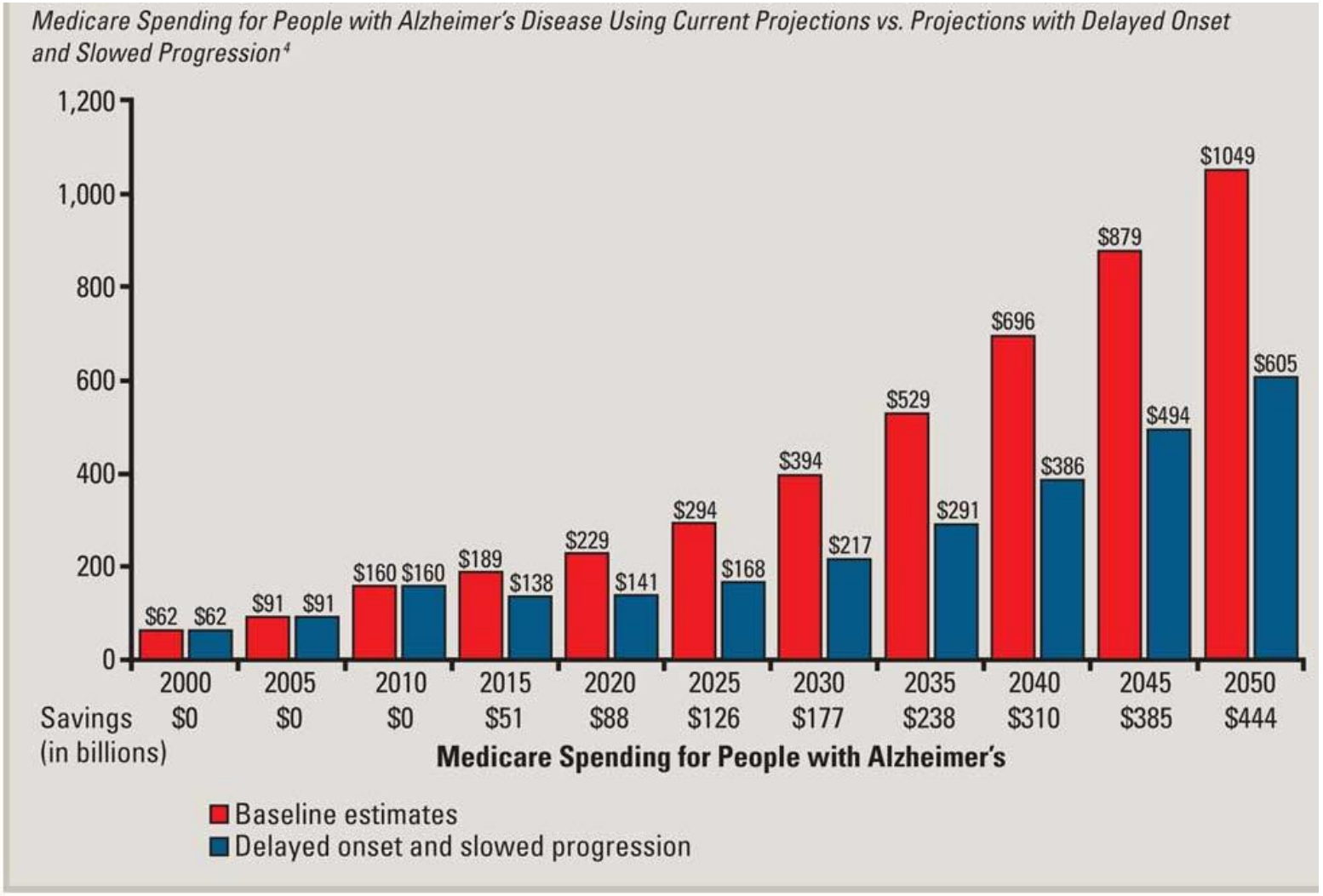
Normal	129	112	73	29	10	4	1	0
Stage 1	47	36	28	16	4	3	0	0
Stage 2	36	31	15	9	5	1	1	0
Stage 3	13	10	5	2	0	0	0	0

La popolazione mondiale di eta' superiore ai 60 anni arrivera' a quasi 2 miliardi nel 2050 (piu' del 15%)



Dementia: A public health priority.
World Health Organization, 2012

Stima della spesa pubblica per l'Alzheimer negli USA



Fattori che aumentano il rischio dell'Alzheimer

Fattore di rischio	Rischio	Tipo
Eta'	x2 ogni 10 anni, dopo i 60 anni	Non-modificabile
Sesso	Femminile >maschile	Non-modificabile
Fattori genetici	100% in casi ereditarii ApoE4: x12	Non-modificabile
Colesterolo elevato	x2	Modificabile
Diabete/obesita'	x2	Modificabile
Ipertensione	x2	Modificabile
Trauma cranico	x2	Modificabile
Stress/depressione	x2	Modificabile
Fumo	x2	Modificabile

Fattori che riducono il rischio dell'Alzheimer

Fattore benefico	Caratteristiche	Meccanismo presunto
Fattori genetici	Mutazione A673T nell'APP gene	Riduce la produzione dell'Aβ del 40%
Esercizio fisico	>30 minuti, 3 volte a settimana	Stimola il ricambio dei neuroni dell' ippocampo
Livello di educazione scolastica	Scuola superiore o laurea	Aumenta la riserva cognitiva
Attivita' intellettuale	Attivita' mentali stimolanti	Aumenta la riserva cognitiva
Interazione sociale	Vita ricca di contatti sociali	Stimola la neurogenesi
Dieta mediterranea	Pesce, frutta, verdura, pochi di grassi,	Effetti antiossidanti, riduce il rischio vascolare

Biomarkers per la diagnosi precoce dell'Alzheimer "in vivo"

***Panel*: Imaging and CSF biomarker categories in Alzheimer's disease**

Brain Aβ-plaque deposition

- CSF $A\beta_{1-42}$ ↓
- PET Aβ imaging ↑

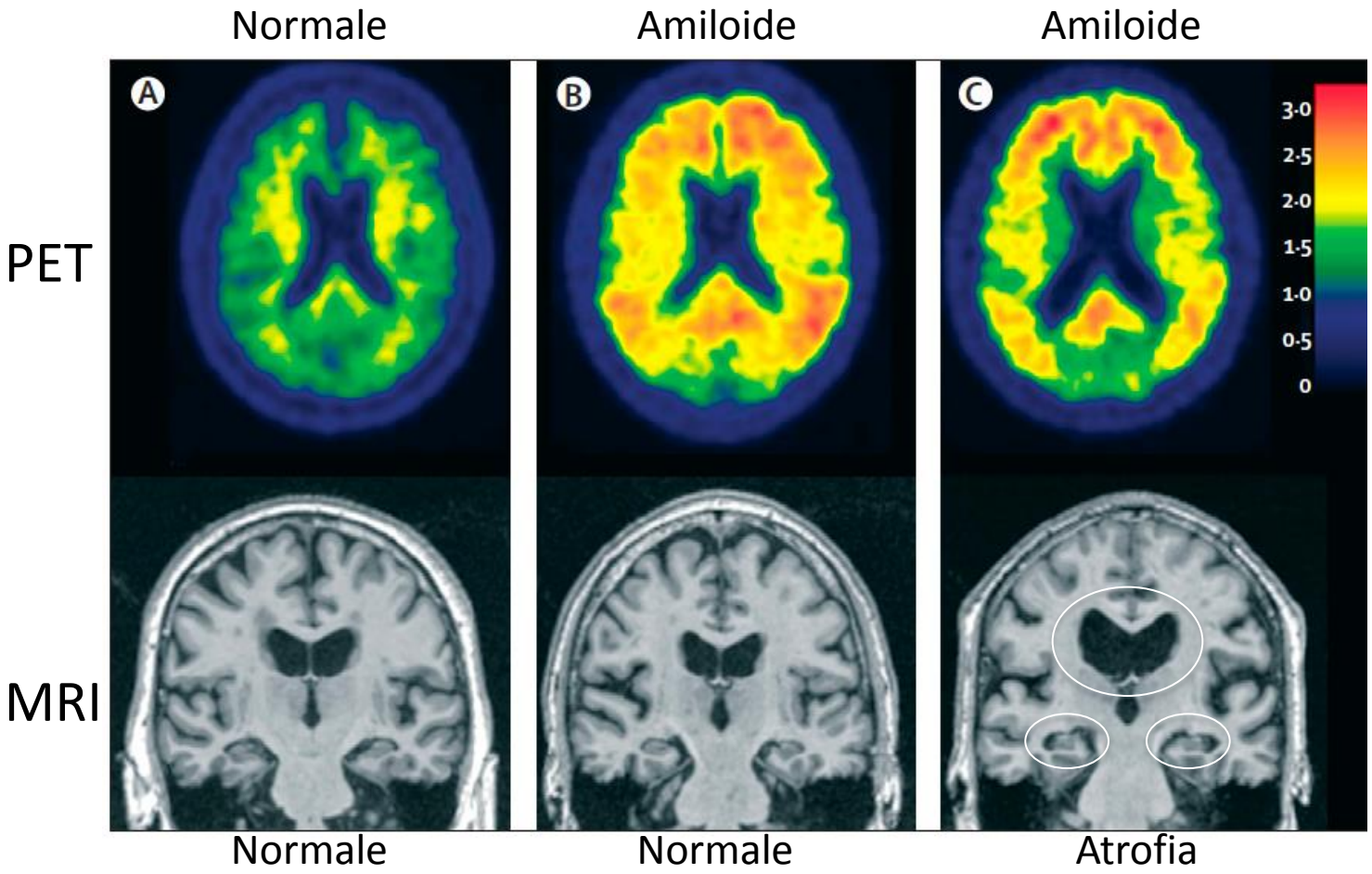
Neurodegeneration

- CSF tau ↑
- Fluorodeoxyglucose-PET ↓
- Structural MRI **(atrofia)**

Aβ=β-amyloid.

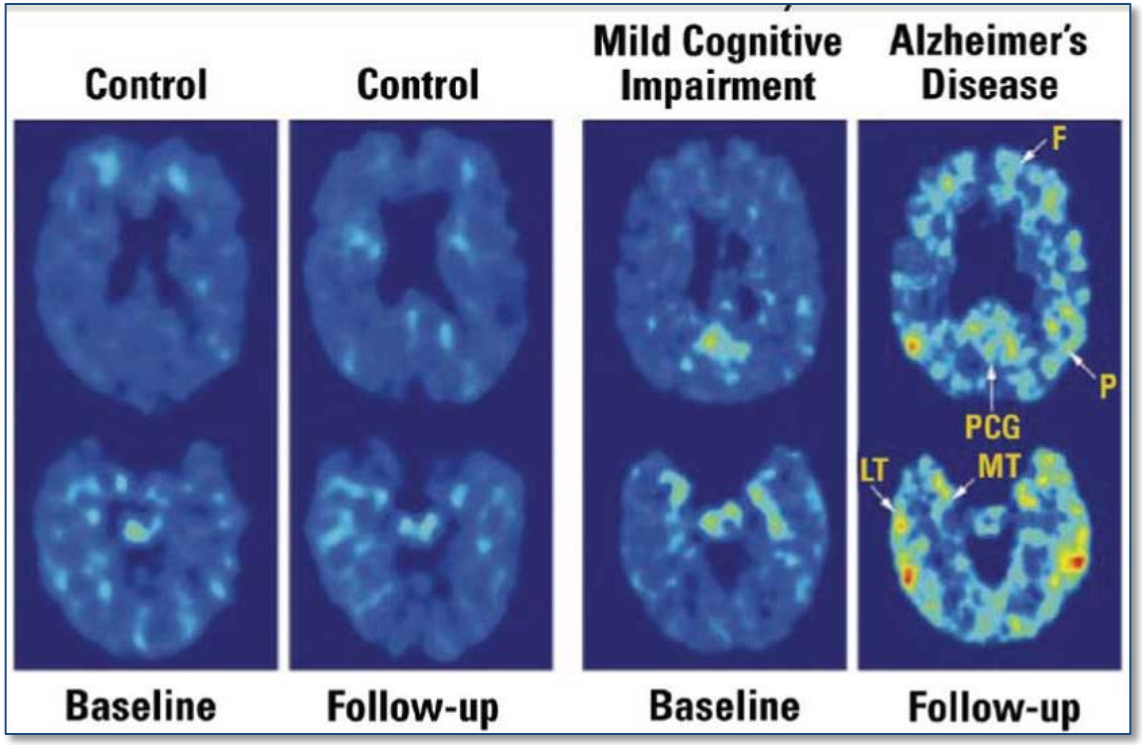
Lancet Neurol 2010; 9: 119–28

Visualizzazione dell'amiloide tramite PET con il Pittsburg compound-B (PIB)



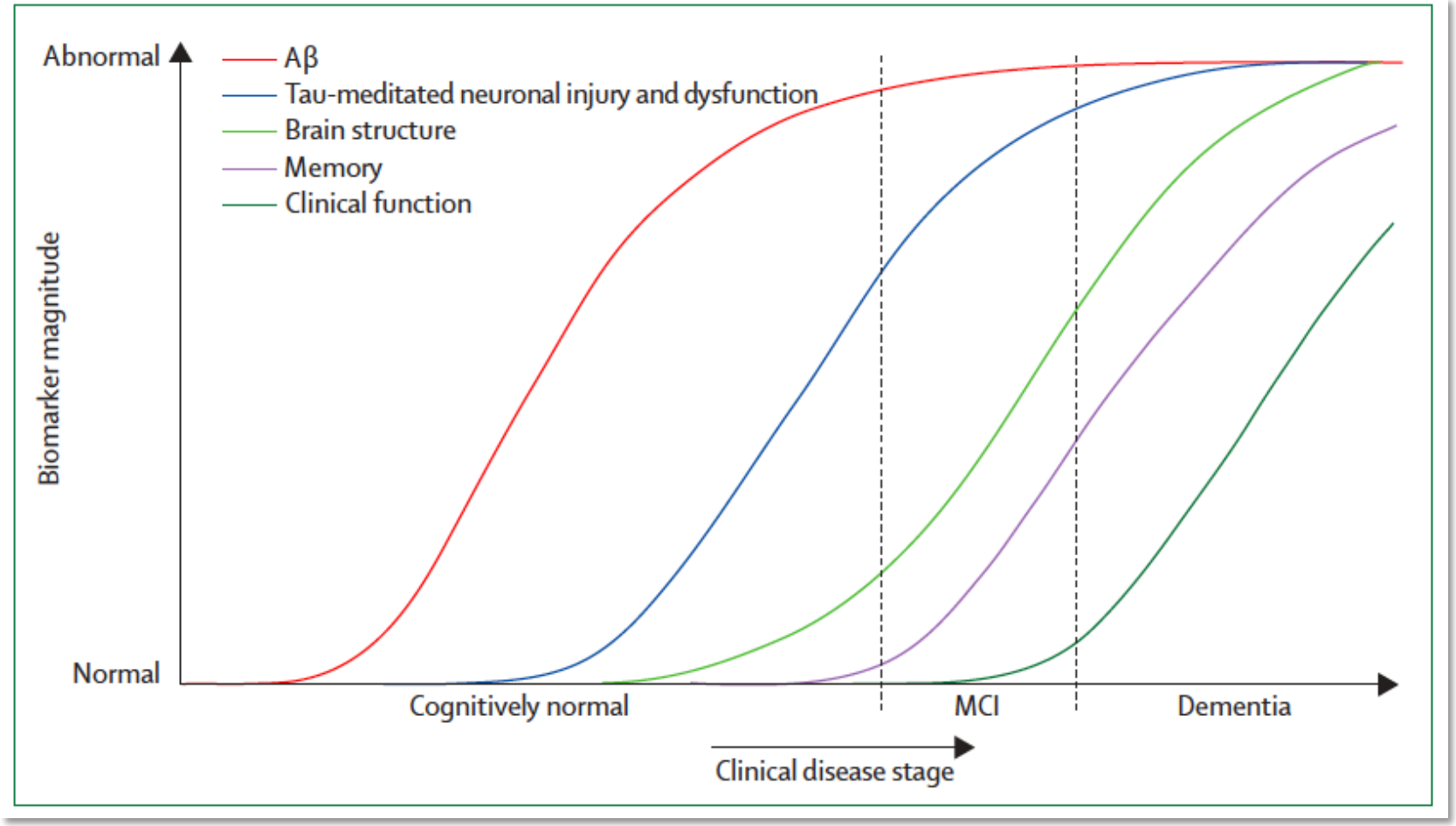
Lancet Neurol 2010; 9: 119–28

Visualizzazione dell'amiloide and della tau tramite PET con FDDNP

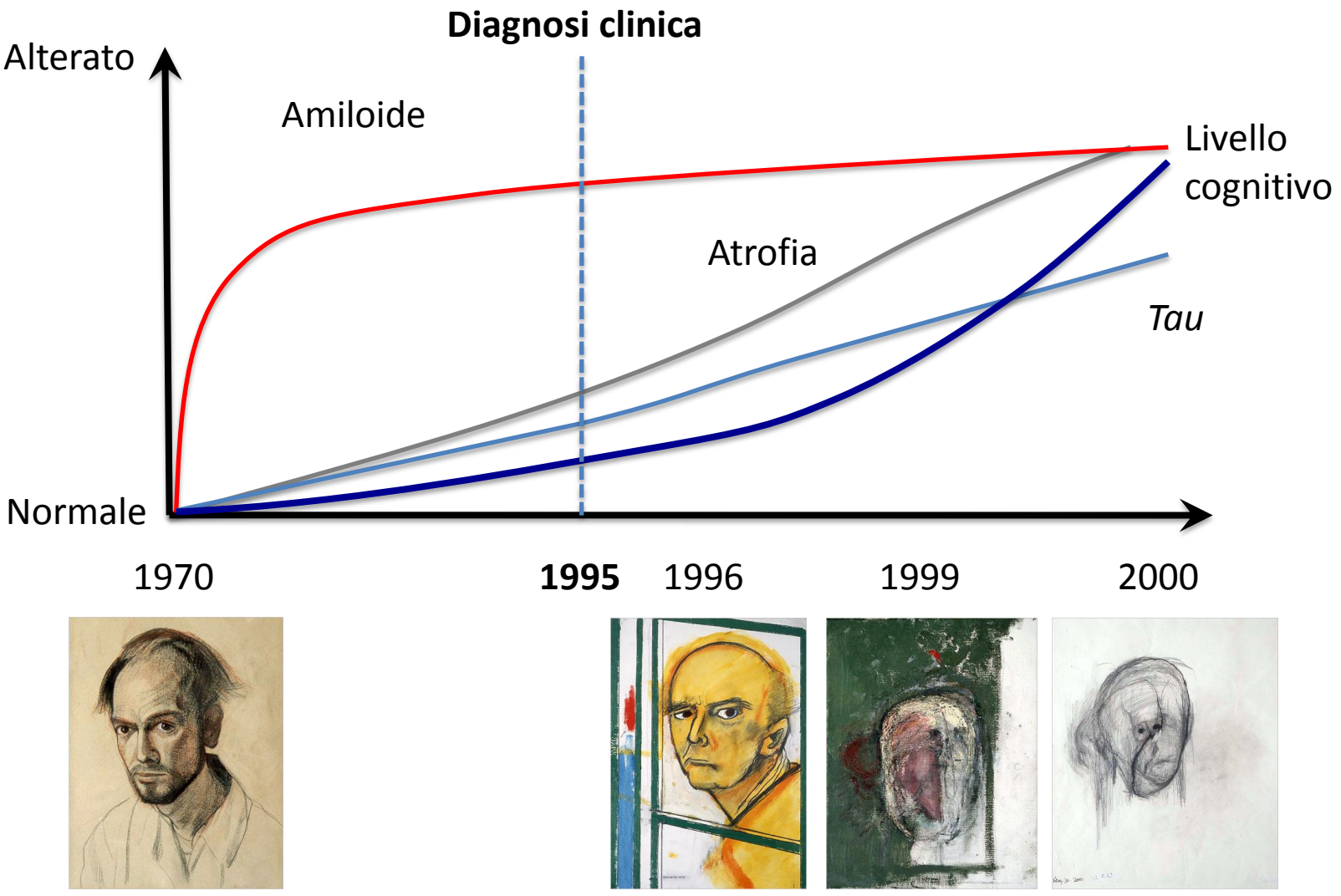


NEJM 355:2652, 2006

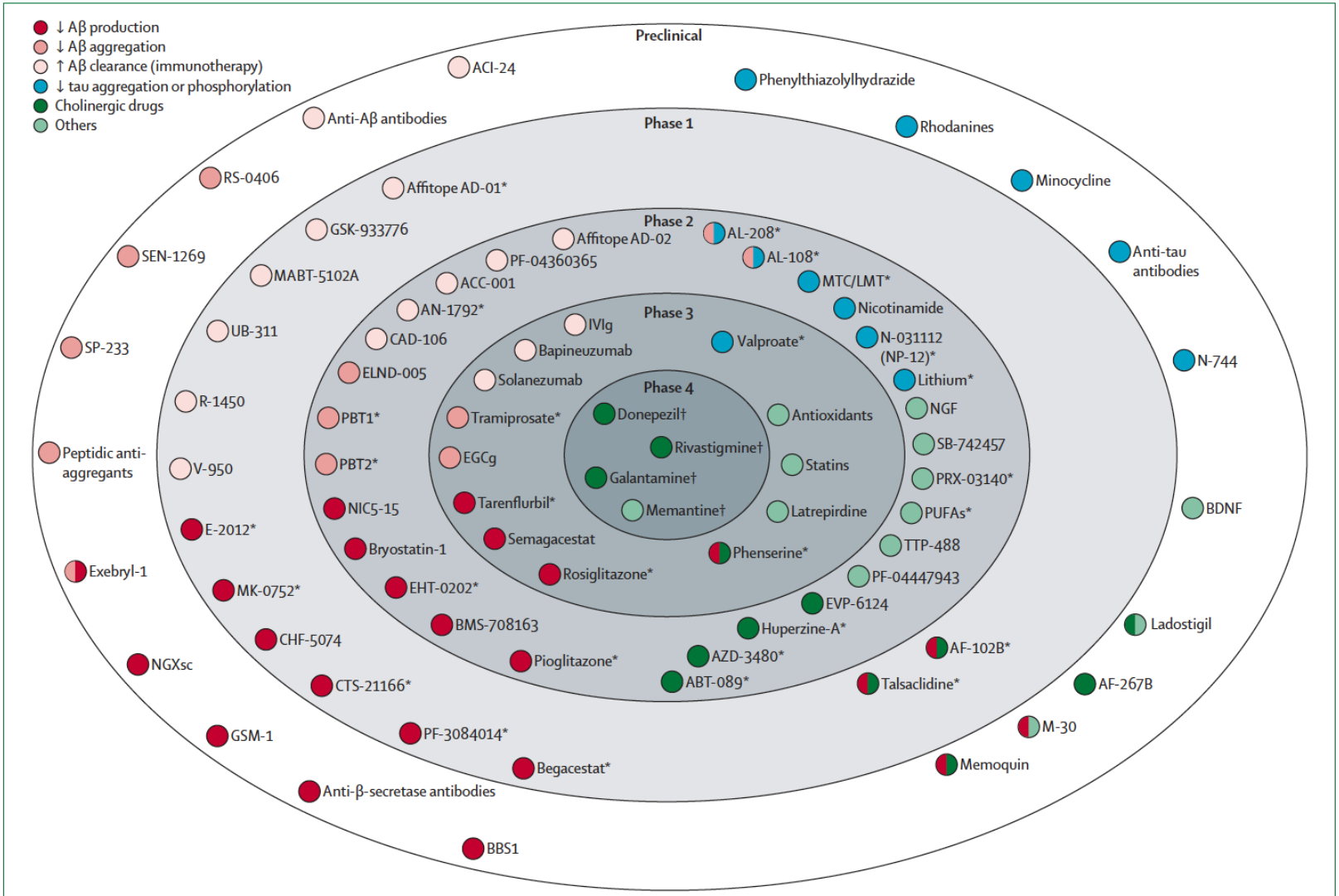
La pathologica dell' Alzheimer comincia 15-20 anni prima dei sintomi iniziali



Lancet Neurol 2010; 9: 119–28


Diagnosi clinica
Alterato
Amiloide
Livello cognitivo
Atrofia
Tau
Normale
1970
1995
1996
1999
2000

Farmaci per l'Alzheimer in varie fasi di sviluppo



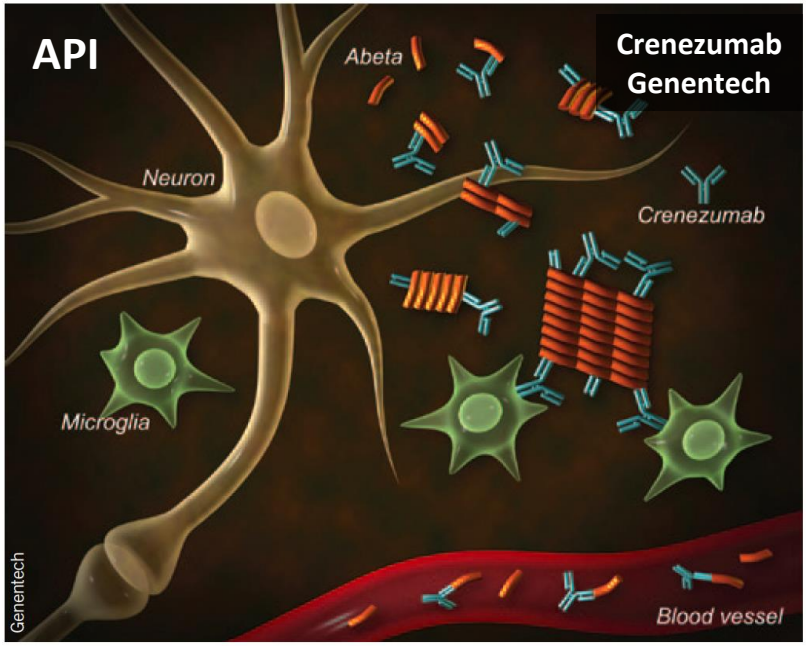
Trial clinici in pazienti ad alto rischio, ma ancora pre-sintomatici

Table 1 Presymptomatic Alzheimer's disease clinical trials

Principal sponsor	Population	Biomarkers	Start date	Duration	Cost
Alzheimer's Prevention Initiative	Mainly PS1 mutation carriers in Colombia	FDG and amyloid PET; MRI; CSF tau and Aβ-42	End 2012 or early 2013	5 years; interim analysis at 2 years	$96 million
Dominantly Inherited Alzheimer's Network	PS1, PS2 and APP carriers in N. America, Europe, Australia	FDG and amyloid PET; MRI; CSF tau and Aβ	End 2012 or early 2013 (NIA funding pending)	2 years for first stage, 5 years total	~$60 million for first stage
Alzheimer's Disease Cooperative Study	Asymptomatic 70+ year olds in N. America with high Aβ burden	Amyloid PET, MRI, CSF tau and p-tau in subset	Mid-2013 (NIH funding pending)	3 years double-blind treatment, 2 years follow-up	$109 million

p-tau, phospho-tau; CSF, cerebrospinal fluid, Aβ: amyloid-β.

Sources: API, DIAN and ADCS.



DIAN

- Gantenerumab (Roche)
- Solenazumab (Eli Lilly)
- BACE inhibitor (Eli Lilly)

ADCS

- Solenazumab (Eli Lilly)

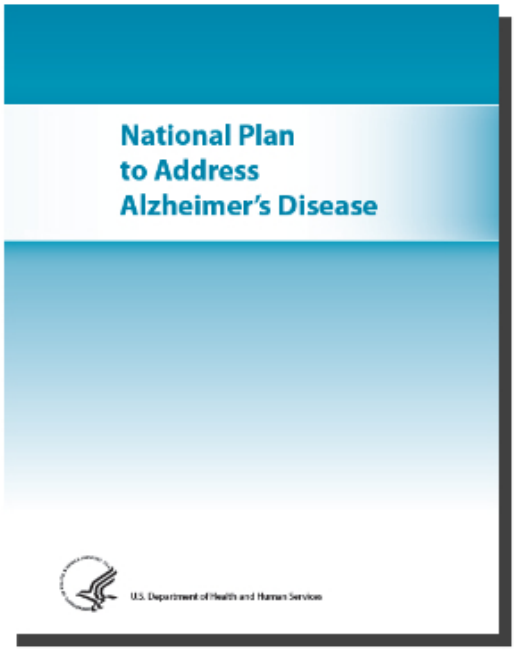
Progetti nazionali per l'Alzheimer

Country	Policy / plan / strategy title	Vision / aim / objectives	Areas of actions	Timeline	Source
Australia	*The Dementia Initiative: Making Dementia a National Health Priority*	"A better quality of life for people living with dementia and their carers and families"	• Community care packages • Training for aged care staff • Dementia Behaviour Management Advisory Service • Support and information for individuals with dementia and families • Research funding • Community support grants	2005–2011 Funding continuing to 2013	*Reference 122*
England	*Living well with dementia: A National Dementia Strategy*	"For people with dementia and their family carers to be helped to live well with dementia, no matter what the stage of their illness or where they are in the health and social care system"	The strategy has 17 recommendations, comprising three main themes: • Raising awareness and understanding • Early diagnosis and support • Develop services to assist people in living well with dementia	2009–2014	*Reference 121*
France	*French Alzheimer's Disease Plan*	• To improve the quality of life for people with dementia and their caregivers • To develop our understanding of the disease for future action • To mobilise society for the fight against dementia	• Increasing support for caregivers • Strengthening coordination between all actors involved • Enabling patients and their families to choose support at home • Improving access to diagnosis and care pathways • Improving residential care for better quality of life for Alzheimer's Disease sufferers • Recognising skills and developing training for health professionals • Making unprecedented efforts in research • Organising epidemiological surveillance and follow up • Providing information for general public awareness • Promoting ethical considerations and an ethical approach • Making Alzheimer's Disease a European priority	2008–2012	*Reference 125*
Japan	*Emergency Project for Improvement of Medical Care and Quality of Life for People with Dementia*	"To build a society, where people can live life safely without anxiety even after being affected by dementia, where they can be supported by appropriate and integrated services of medical care, long-term care and community care"	• Investigation of situation • Acceleration of the research and development • Promotion of early diagnosis and provision of appropriate medical care • Dissemination of adequate care and support • Measures for people with early-onset dementia	2008 (no end date)	*References 126 and 127*
Korea (Republic of)	*War on Dementia*	Dementia is a national health care priority	2008–2010: • Early diagnosis • Prevention and treatment • Infrastructure building	2008–2013	*References 128 and 129*

World Health Organization, 2012

Il progetto USA per l'Alzheimer e' stato lanciato nel gennaio 2011

The National Plan to Address Alzheimer's Disease (NAPA)



Strategia nazionale coordinata per affrontare l'Alzheimer: Ricerca scientifica, nuove terapie, educazione, strutture di supporto per pazienti e caregivers, ecc.

Approccio all'Alzheimer nel 2050

Determinazione del rischio all'eta' di 50 anni (e poi ogni 10 anni):

- Anamnesi familiare, esame neurologico e neuropsicologico
- Screen genetico per geni di rischio
- Se necessario: Imaging (Aβ, tau, MRI, FDG-PET)
  Esame liquorale (tau, Aβ, etc.)

Trattamento in base al rischio:

- Paziente asintomatico senza depositi di Aβ ma ad alto rischio:
  - Terapia di riduzione della sintesi di Aβ
- Paziente asintomatico con depositi di Aβ/tau:
  - Terapia di riduzione della sintesi+Aβ anticorpi+terapia anti-tau
- Paziente sintomatico con depositi di Aβ/tau:
  - Terapia di riduzione della sintesi+Aβ anticorpi+terapia anti-tau+farmaci neuroprotettivi+stimolanti colinergici

Cold Spring Harb Perspect Med 2012;2:a011585

Stato dell'Arte sull'Alzheimer: Sommario

- E' la causa principale di demenza nell'anziano, dovuta all'accumulo di Aβ e tau
- Raggiungera' livelli epidemici con costi proibitivi, progetti nazionali puntano ad un strategia integrata
- Il rischio maggiore e' su base genetica ma anche dovuto a fattori modificabili, e.g., lifestyle, rischio vascolare
- La malattia comincia 15-20 anni prima dei sintomi, nuovi biomarkers permettono la diagnosi precoce
- Nuovi trials puntano alla riduzione dell' amiloide e tau in pazienti ad alto rischio ma pre-sintomatici
- In futuro, l'approccio terapeutico sara' stratificato in base alla quantificazione del rischio.

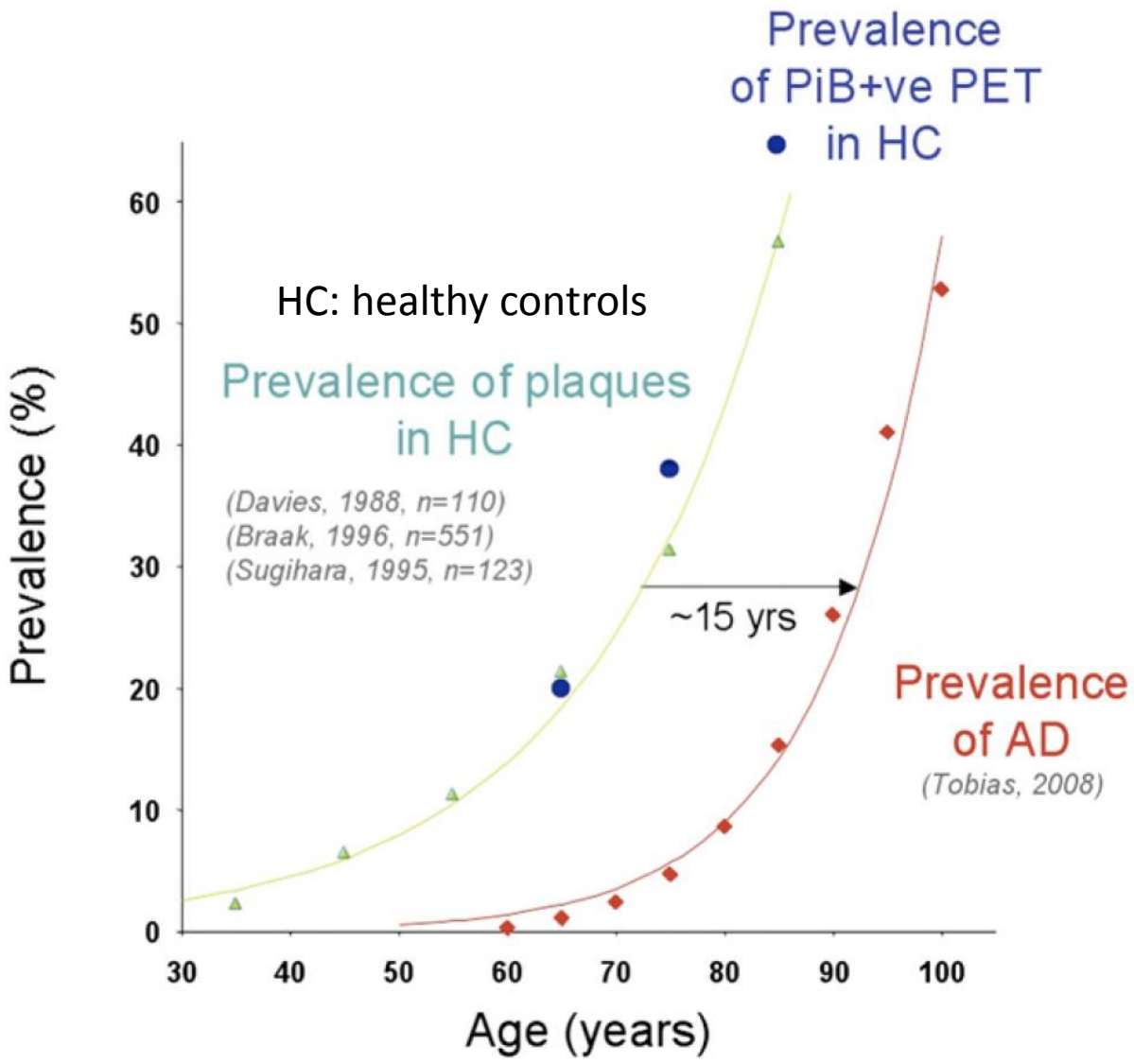

Prevalence of PiB+ve PET in HC
HC: healthy controls
Prevalence of plaques in HC
(Davies, 1988, n=110)
(Braak, 1996, n=551)
(Sugihara, 1995, n=123)
~15 yrs
Prevalence of AD
(Tobias, 2008)
Prevalence (%)
Age (years)
0
10
20
30
40
50
60
30
40
50
60
70
80
90
100

Table 2. A new paradigm for managing AD based on the AD risk category into which a person falls

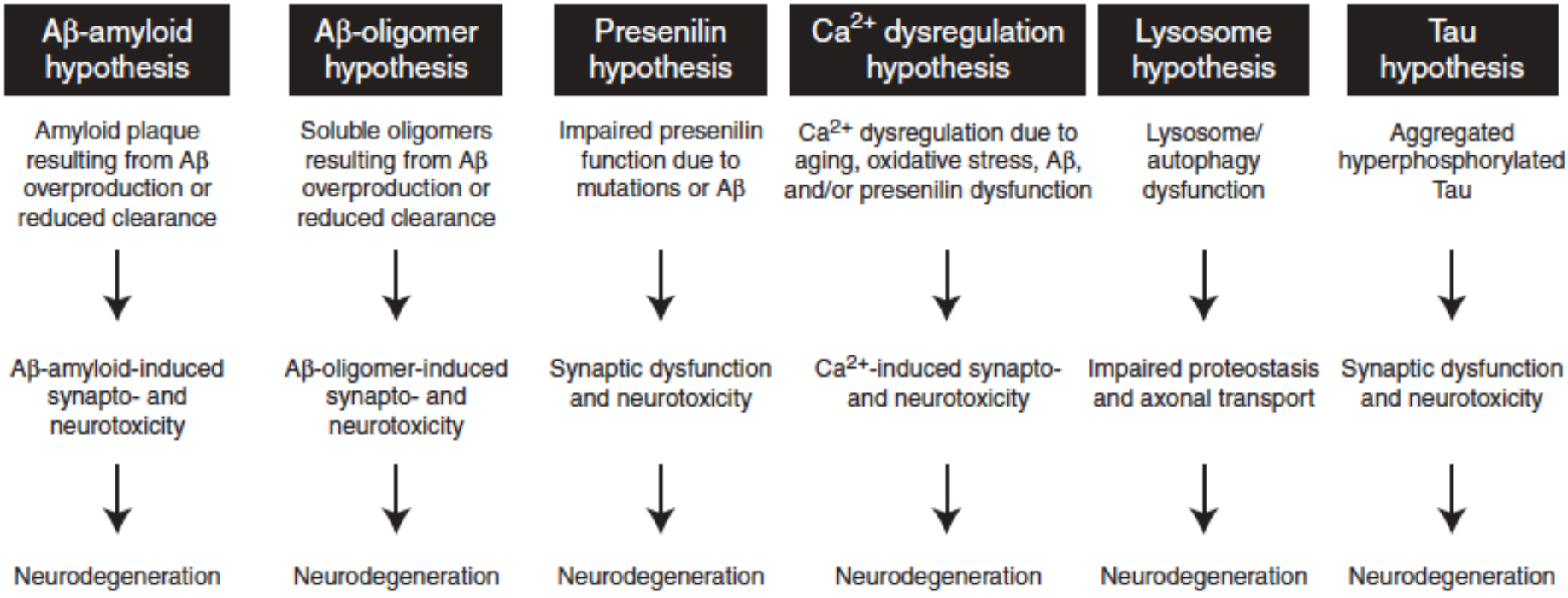
Risk category	Treatment
1. Presymptomatic subjects with no evidence of Aβ accumulation in the brain and high risk based on genetic, plasma, or CSF studies	1. Aβ synthesis or oligomer inhibitor 2. Aβ synthesis or oligomer inhibitor Aβ vaccination (active or passive)
2. Presymptomatic subjects with evidence of Aβ accumulation in the brain	3. Aβ synthesis or oligomer inhibitor + Aβ vaccination (active or passive) Anti-tau/anti-synuclein therapy
3. Presymptomatic subjects with evidence of Aβ and tau/synuclein accumulation in the brain	4. Aβ synthesis or oligomer inhibitor + Aβ vaccination (active or passive) Anti-tau/anti-synuclein therapy Neuroprotective agents
4. Symptomatic subjects with evidence of Aβ and tau/synuclein accumulation in the brain	Symptomatic agents, e.g., cholinesterase inhibitors, memantine, other neurotransmitter modulators, other psychotropic treatments

Table 1. Alzheimerology in 2020

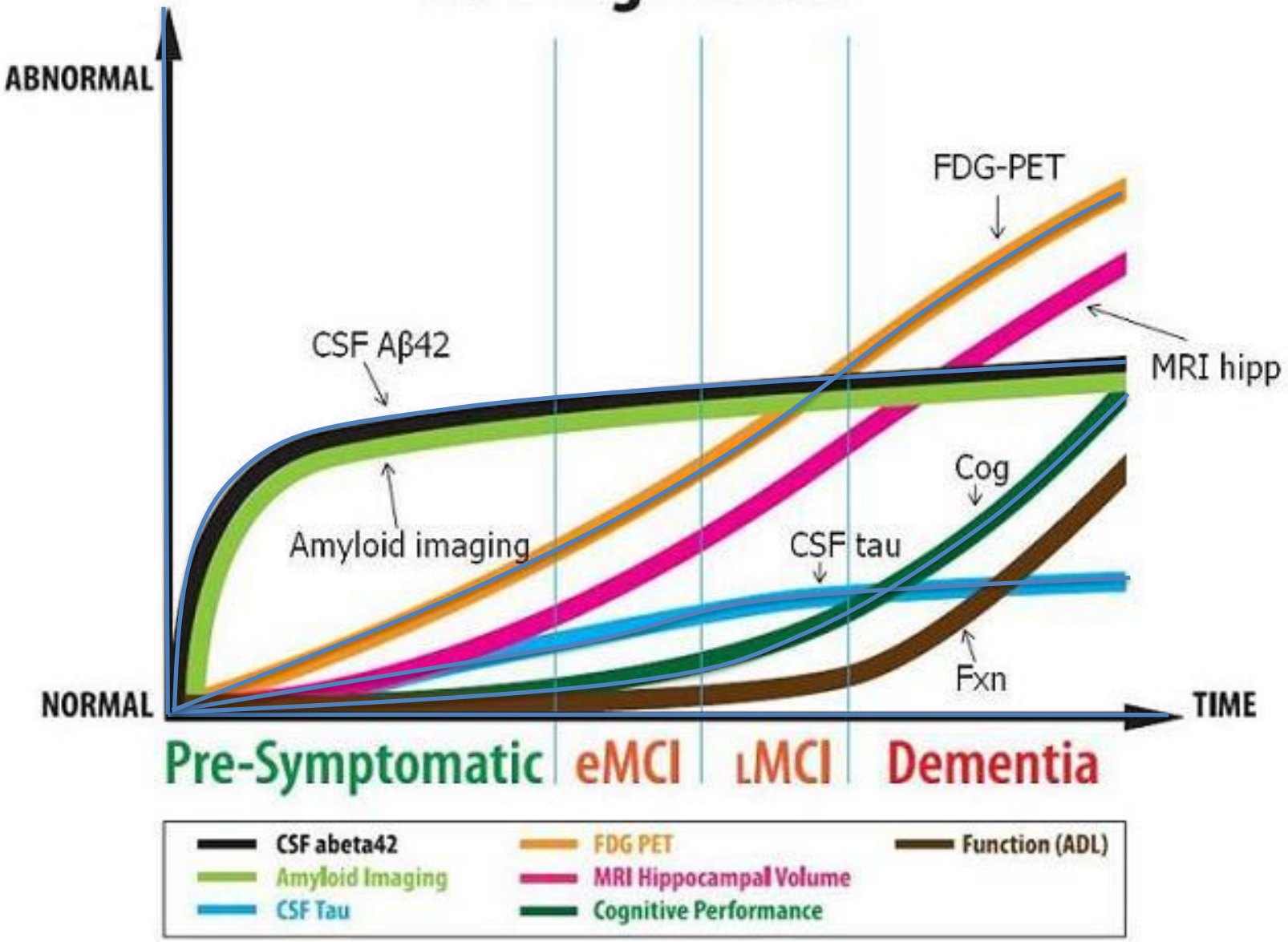
- Risk assessment at around age 50 and then every 10 years:
  - History (emphasizing family history) and neurological exam
  - Brief cognitive screen and neuropsychological testing
  - Gene screen on "AD risk chip" (+ other familial dementias)
  - Imaging—Aβ scan, tau scan, MRI
  - Blood "Aβ antibody challenge": basal and evoked Aβ levels
  - CSF assays for Aβ, tau, and other biomarkers
- Outcome: a numerical AD risk score

Farmaci approvati dalla FDA per l'Alzheimer

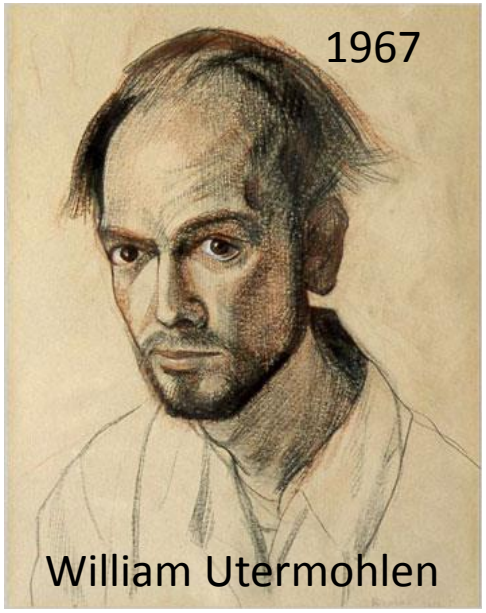
Farmaco	Nome commerciale	Meccanismo di azione	Anno di approvazione
Donepezil	Aricept	Inibitore della colinesterasi	1996
Galantamine	Razadyne	Inibitore della colinesterasi	2001
Memantine	Namenda	Antagonista dei recettori glutamatergici	2003
Rivastigmine	Exelon	Inibitore della colinesterasi	2000
Tacrine	Cognex	Inibitore della colinesterasi	1993

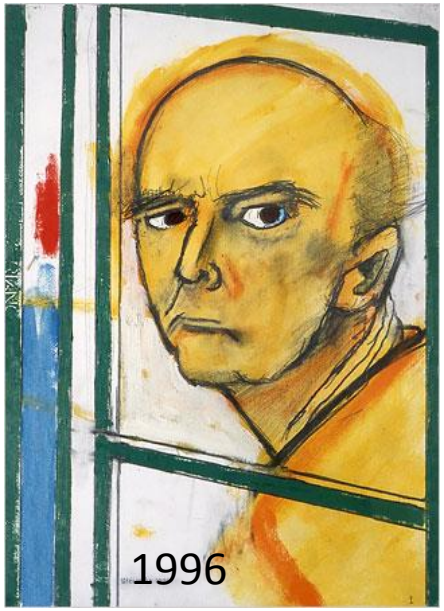

Aβ-amyloid hypothesis
Amyloid plaque resulting from Aβ overproduction or reduced clearance
Aβ-amyloid-induced synapto- and neurotoxicity
Neurodegeneration
Aβ-oligomer hypothesis
Soluble oligomers resulting from Aβ overproduction or reduced clearance
Aβ-oligomer-induced synapto- and neurotoxicity
Neurodegeneration
Presenilin hypothesis
Impaired presenilin function due to mutations or Aβ
Synaptic dysfunction and neurotoxicity
Neurodegeneration
Ca2+ dysregulation hypothesis
Ca2+ dysregulation due to aging, oxidative stress, Aβ, and/or presenilin dysfunction
Ca2+-induced synapto- and neurotoxicity
Neurodegeneration
Lysosome hypothesis
Lysosome/ autophagy dysfunction
Impaired proteostasis and axonal transport
Neurodegeneration
Tau hypothesis
Aggregated hyperphosphorylated Tau
Synaptic dysfunction and neurotoxicity
Neurodegeneration

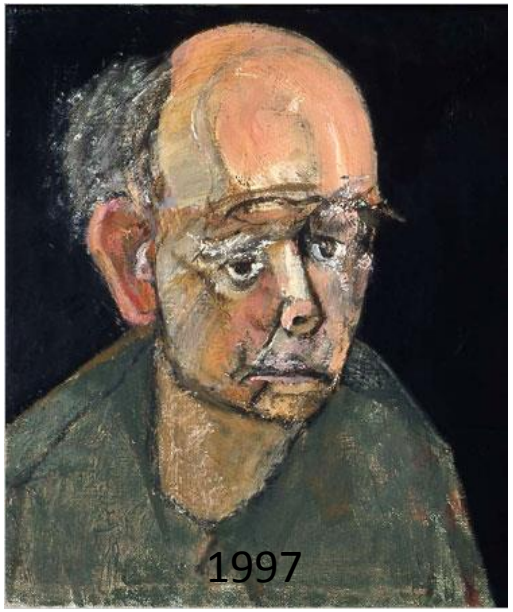
AD Progression

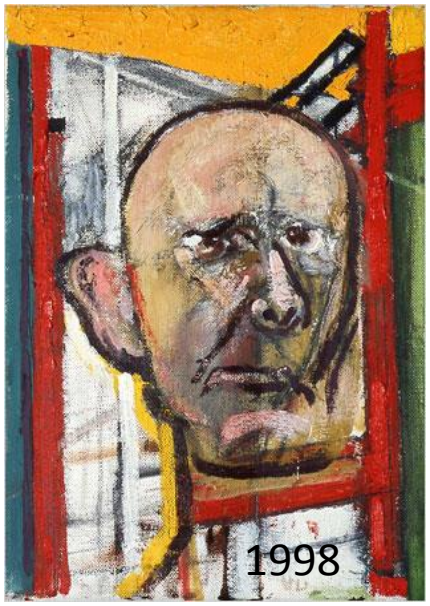


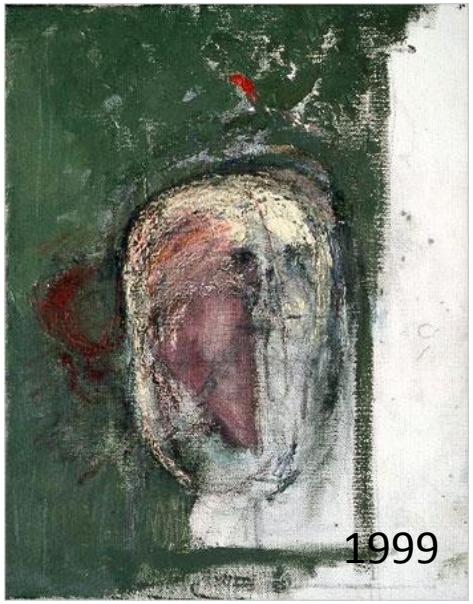
William Utermohlen ed il suo morbo di Alzheimer

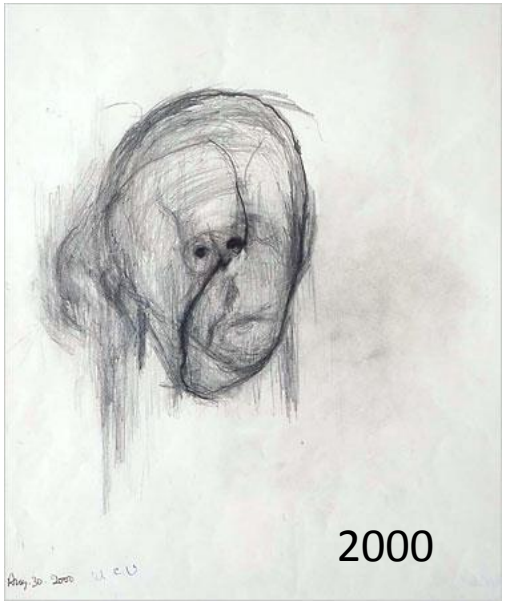


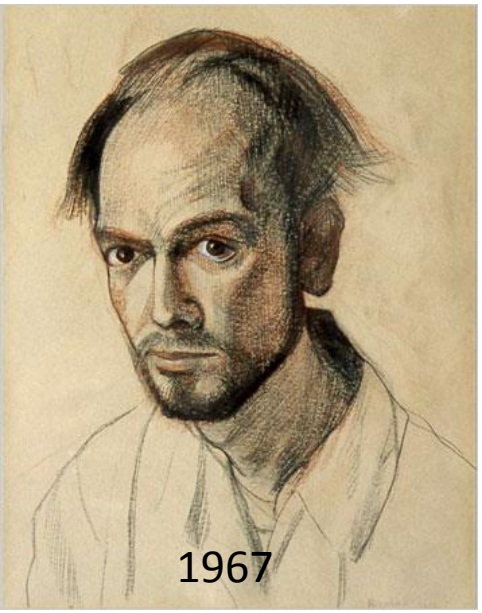


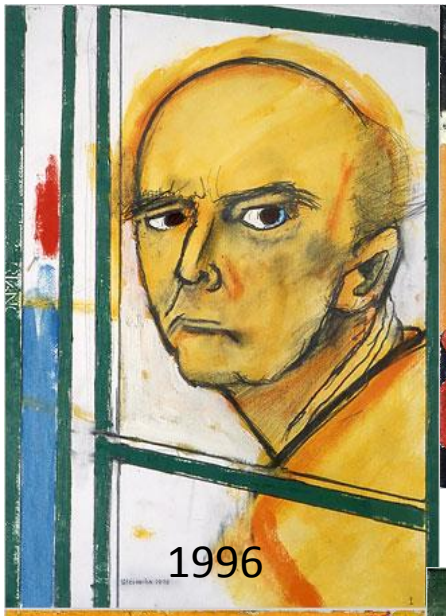




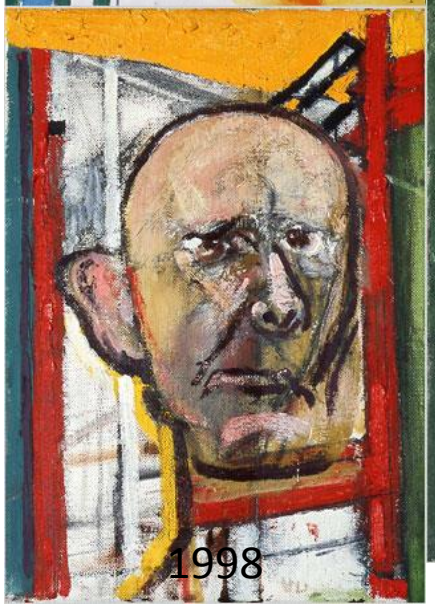


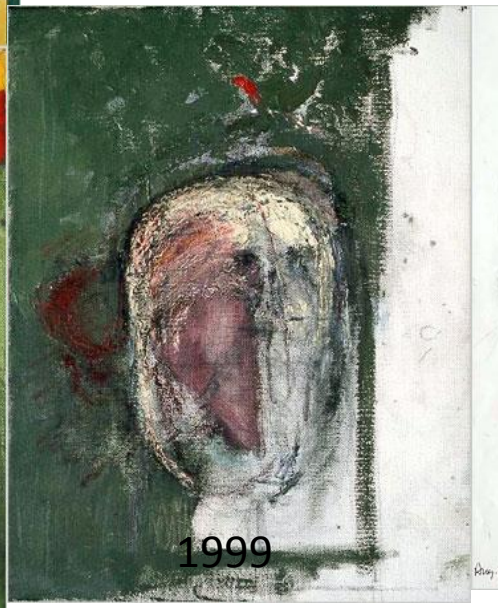


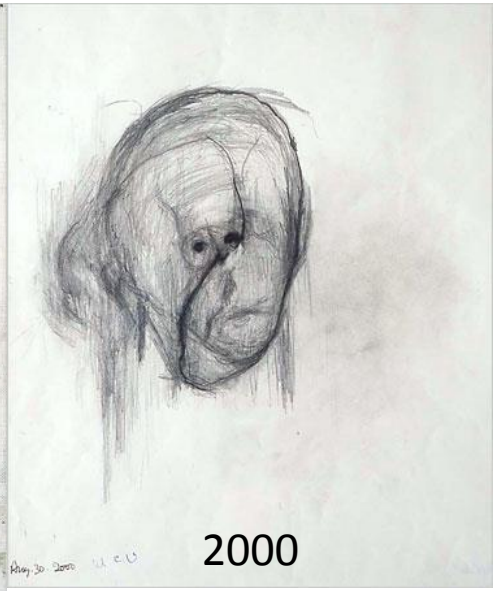

1967


1996


1997


1998


1999

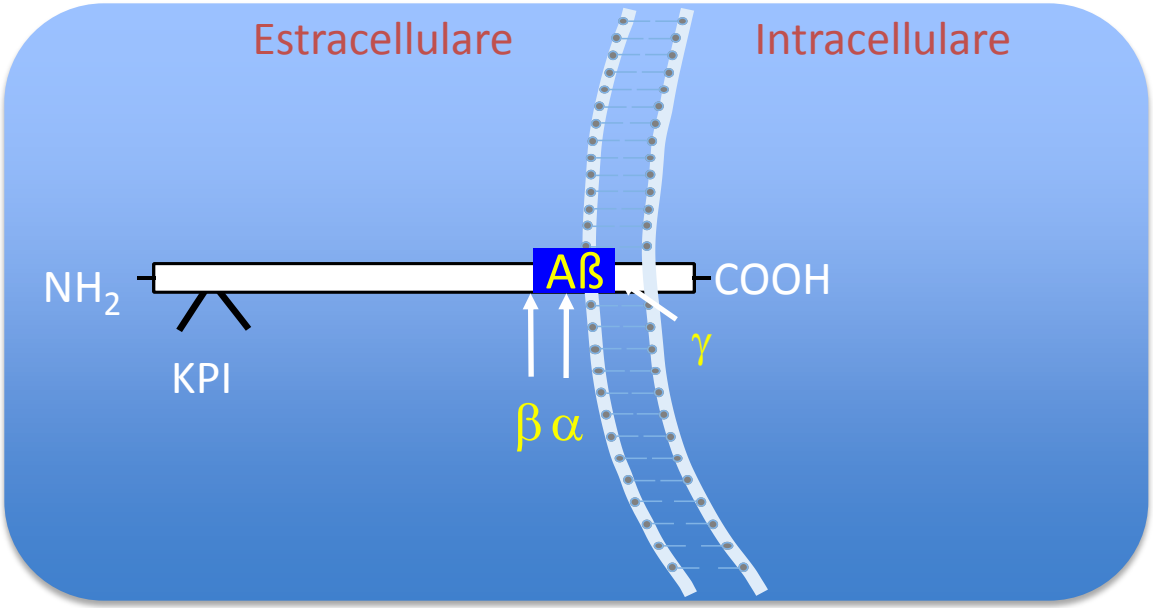

2000

Proc Natl Acad Sci U S A. 2013 Mar 5. [Epub ahead of print]
Genome-wide scan of healthy human connectome discovers SPON1 gene variant influencing dementia severity.
Jahanshad N, Rajagopalan P, Hua X, Hibar DP, Nir TM, Toga AW, Jack CR Jr, Saykin AJ, Green RC, Weiner MW, Medland SE, Montgomery GW, Hansell NK, McMahon KL, de Zubicaray GI, Martin NG, Wright MJ, Thompson PM; the Alzheimer's Disease Neuroimaging Initiative.

The posterior cingulate and superior parietal cortex show early disturbances (25), including volumetric atrophy (26, 27), impaired glucose metabolism (28), altered activity during task-based functional imaging studies (29), and disrupted resting state functional connectivity (21)—

25. Thompson PM, et al. (2001) Cortical change in Alzheimer's disease detected with
a disease-specific population-based brain atlas. Cereb Cortex 11(1):1–16.
26. Buckner RL, et al. (2005) Molecular, structural, and functional characterization of
Alzheimer's disease: Evidence for a relationship between default activity, amyloid,
and memory. J Neurosci 25(34):7709–7717.
27. Thompson PM, et al. (2003) Dynamics of gray matter loss in Alzheimer's disease.
J Neurosci 23(3):994–1005.
28. Braskie MN, et al. (2011) Common Alzheimer's disease risk variant within the CLU gene
affects white matter microstructure in young adults. J Neurosci 31(18):6764–6770.
29. Celone KA, et al. (2006) Alterations in memory networks in mild cognitive impairment
and Alzheimer's disease: An independent component analysis. J Neurosci 26(40):
10222–10231.

Amyloid Precursor Protein (APP) ed Aß



1. Il peptide Aß e' il costituente maggiore della placca amiloide e deriva dalla proteolisi della APP;

2. Alcune forme genetiche dell'Alzheimer sono associate con mutazioni della APP;

3. Overexpressione della APP in animali transgenici riproduce I tratti salienti della malattia di Alzheimer (Placche amiloidi, disturbi cognitivi).

TABLE 1 | ONGOING CLINICAL TRIALS FOR TREATING ALZHEIMER'S DISEASE

Approach or drug	Proposed mechanism of action	Phase
β-Secretase inhibition	Decreases formation of Aβ from amyloid precursor protein	II
γ-Secretase inhibition	Decreases formation of Aβ from amyloid precursor protein	II/III
Active immunization with Aβ peptides	Generates anti-Aβ antibodies that interact with Aβ and remove it from the brain by uncertain downstream mechanisms	II
Passive immunization with anti-Aβ antibodies	The antibodies interact with Aβ and remove it from the brain by uncertain downstream mechanisms	III
Intravenous pooled immunoglobulins	May enhance clearance of Aβ and other harmful proteins from the brain; may decrease harmful inflammatory processes	III
Scyllo-inositol	Decreases formation and stability of pathogenic Aβ assemblies	II
Latrepirdine	Prevents mitochondrial dysfunction	III
Inhibition of receptor for advanced glycation end products (RAGE)	Blocks stimulation of the cell-surface receptor RAGE, which binds Aβ, decreasing Aβ levels in the brain and preventing Aβ from activating pathogenic pathways	II
Stimulation of insulin signalling	Prevents hyperglycaemia; may overcome insulin resistance in the brain	II
Selective oestrogen-receptor modulator	Promotes neuroprotective effects of oestrogen without eliciting its harmful effects	II
Neurotrophic and neuroprotective agents	Stimulate neurotrophic and antioxidant pathways or pathways that protect against excitotoxicity	II

The above selection focuses on potentially disease-modifying strategies and is based on a review of websites, oral reports at scientific meetings, and discussions with Paul Aisen (University of California, San Diego) and Laurie Ryan (National Institute on Aging).

Phase II and phase III trials assess the safety and efficacy of new treatments; phase III trials involve many more subjects, are conducted in multiple centres, and are required for drug approval by regulatory agencies.

Table 1 | **Proposed mechanisms of action of compounds in trials for Alzheimer's disease modification***

Name (initial sponsor)	Description	Proposed mechanism of action	Selected refs
Semagacestat (Eli Lilly and Company)	γ-secretase inhibitor	Reduces Aβ synthesis	20,108
Bapineuzumab (Elan and Wyeth)	Humanized monoclonal antibody to Aβ	Binds to Aβ deposits and reduces amyloid load primarily through microglial clearance	59,67
Solanezumab (Eli Lilly and Company)	Humanized monoclonal antibody to Aβ	Binds to soluble Aβ and reduces amyloid load via peripheral sink mechanism	61,65
Intravenous immunoglobulin G (Baxter)	Human immunoglobulin preparation containing endogenous polyclonal antibodies to Aβ	Primarily binds to soluble Aβ and reduces amyloid load via peripheral sink mechanism	54,66

Aβ, amyloid-β. *This table lists the four molecules that are currently in Phase III trials for Alzheimer's disease modification. In addition, dimebon (an antihistamine with neuroprotective properties[100] developed by Medivation and Pfizer, is currently in several Phase III trials to confirm the symptomatic benefits that were observed in Phase II trials[99].

Jagust, JAMA NEUROL/VOL 70 (NO. 3), MAR 2013 WWW. Page 299

The biomarkers of greatest interest have been separated into 2 categories:

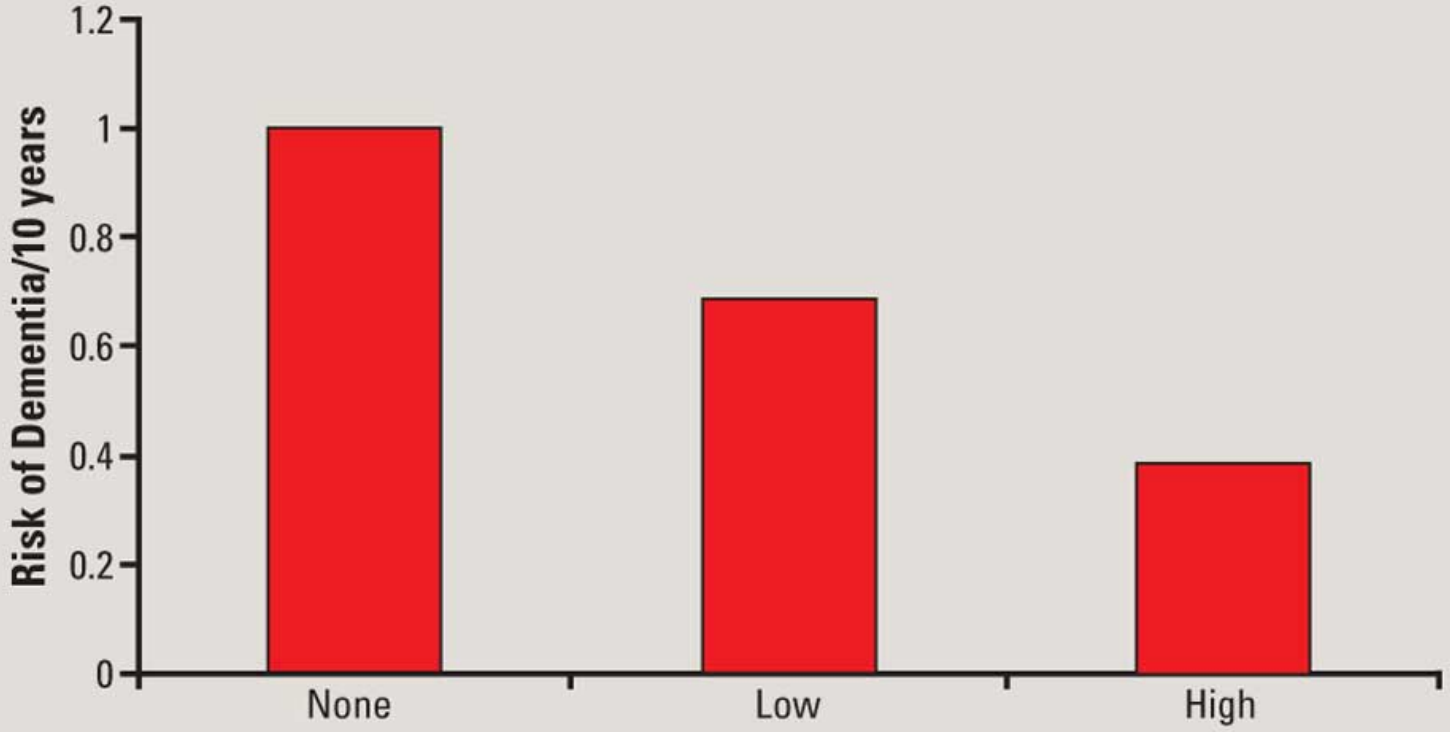
one of which is the measurement of the AD hallmark protein beta-amyloid (Abeta), apparent as reduced concentration in cerebrospinal fluid or increased retention of positron emission tomography (PET) tracers that bind to fibrillar Abeta.

The second category includes biomarkers that are presumptive measures of neurodegeneration, such as atrophy of the hippocampus and cerebral glucose hypometabolism in the temporoparietal cortex.

In the Dominantly Inherited Alzheimer Network study, evidence of brain Abeta deposition, glucose hypometabolism, and hippocampal atrophy were seen in asymptomatic mutation carriers 10 to 15 years prior to the expected age at disease Onset. (Bateman RJ, Xiong C, Benzinger TL, et al; Dominantly Inherited Alzheimer Network. Clinical and biomarker changes in dominantly inherited Alzheimer's disease. *N Engl J Med. 2012;367(9):795-804.*)

SLIDE 3

Exercise and Risk of Dementia [16]



High >30 min, 3x per week; Low <30 min, 3x per week.

Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade. Jack et al.

Currently available evidence strongly supports the position that the initiating event in Alzheimer's disease (AD) is related to abnormal processing of β-amyloid (Aβ) peptide, ultimately leading to formation of Aβ plaques in the brain. This process occurs while individuals are still cognitively normal. Biomarkers of brain β-amyloidosis are reductions in CSF Aβ42 and increased amyloid PET tracer retention. After a lag period, which varies from patient to patient, neuronal dysfunction and neurodegeneration become the dominant pathological processes. Biomarkers of neuronal injury and neurodegeneration are increased CSF tau and structural MRI measures of cerebral atrophy. Neurodegeneration is accompanied by synaptic dysfunction, which is indicated by decreased fluorodeoxyglucose uptake on PET. We propose a model that relates disease stage to AD biomarkers in which Aβ biomarkers become abnormal fi rst, before neurodegenerative biomarkers and cognitive symptoms, and neurodegenerative biomarkers become abnormal later, and correlate with clinical symptom severity.

Lancet Neurol 2010; 9: 119–28

NeuroImage 61 (2012) 505–516

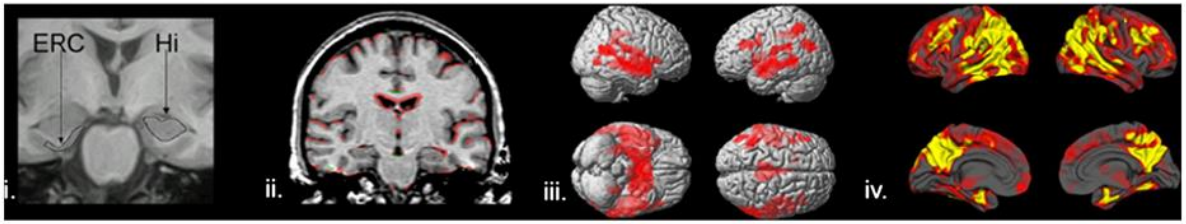


Fig. 1. Volumetric MRI in the detection and tracking of AD, including (i) accelerated rates of atrophy in the hippocampus (Hi) and entorhinal cortex (ERC) regions-of-interest (Mike Weiner, with permission); (ii) accelerated rates of whole brain atrophy using sequential MRIs, as shown in red in a symptomatic AD patient (Nick Fox, with permission); (iii) regional gray matter loss, as shown in this statistical brain map comparing symptomatic AD patients and controls; and (iv) regional thinning in cerebral cortex comparing symptomatic AD patients and controls.
(iii) reprinted from Baron et al. (2001), Copyright (C) 2001 with permission from Elsevier. All rights reserved. (iv) reprinted with permission from Du et al. (2007), Copyright © 2007 Oxford University Press. All rights reserved. This figure was reproduced with permission from Reiman and Langbaum (2009), Copyright © 2009 Oxford University Press. All rights reserved.

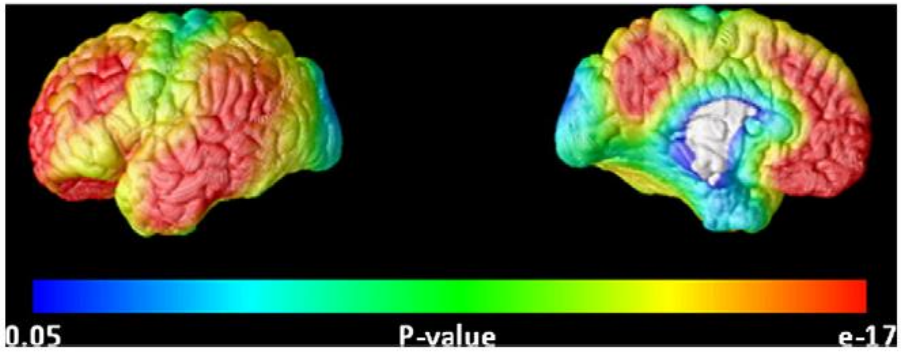
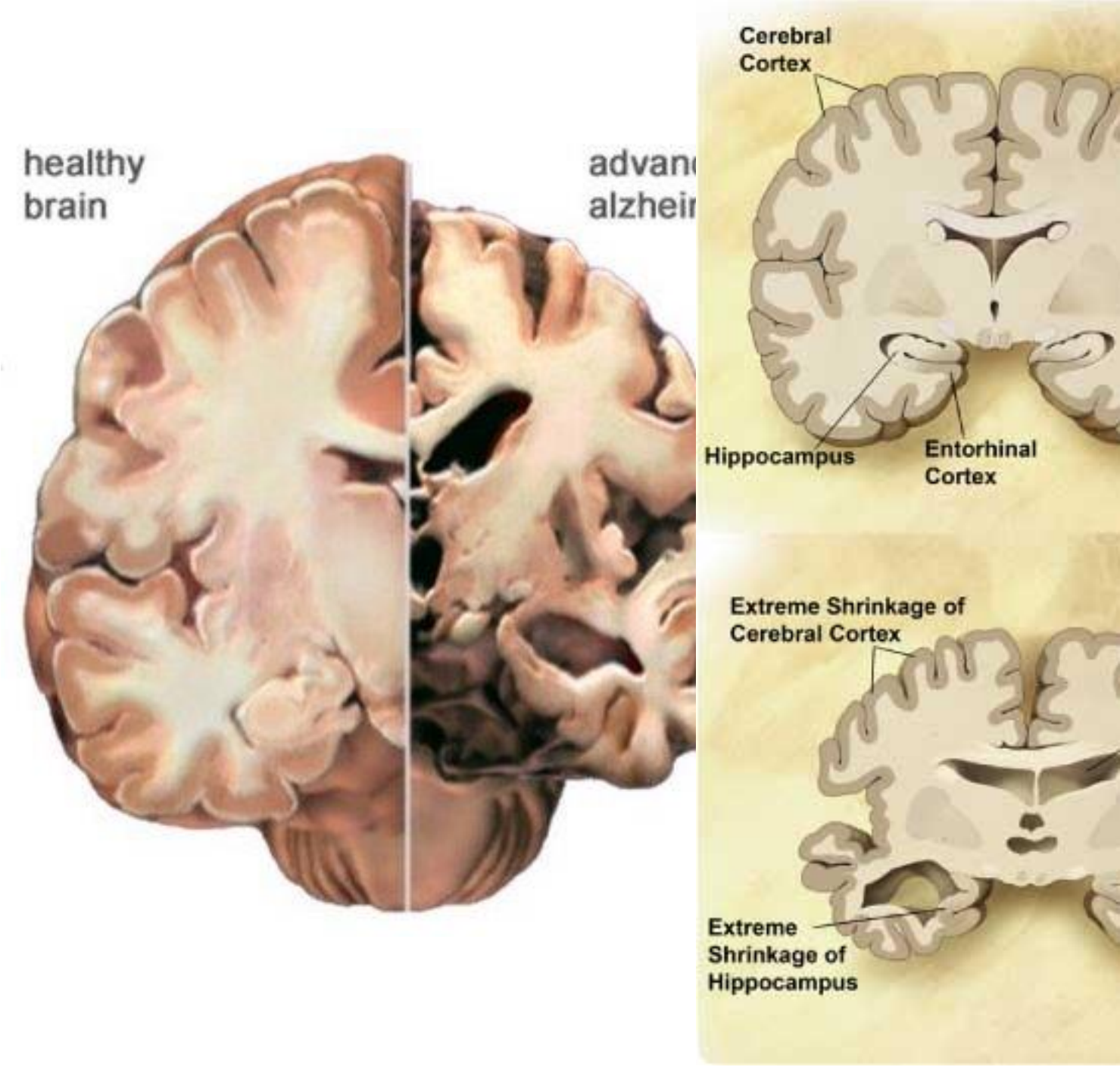


Fig. 3. Fibrillar amyloid imaging in the study of AD. Increases in Pittsburgh Compound-B PET measurements of fibrillar amyloid-β in symptomatic AD patients.
Adapted with permission from Reiman et al. (2009, 2010), Copyright © 2009 National Academy of Sciences, USA. All rights reserved.


CONTROL


healthy
brain
advan
alzhei
Cerebral
Cortex
Hippocampus
Entorhinal
Cortex
Extreme Shrinkage of
Cerebral Cortex
Extreme
Shrinkage of
Hippocampus

NeuroImage 61 (2012) 505–516

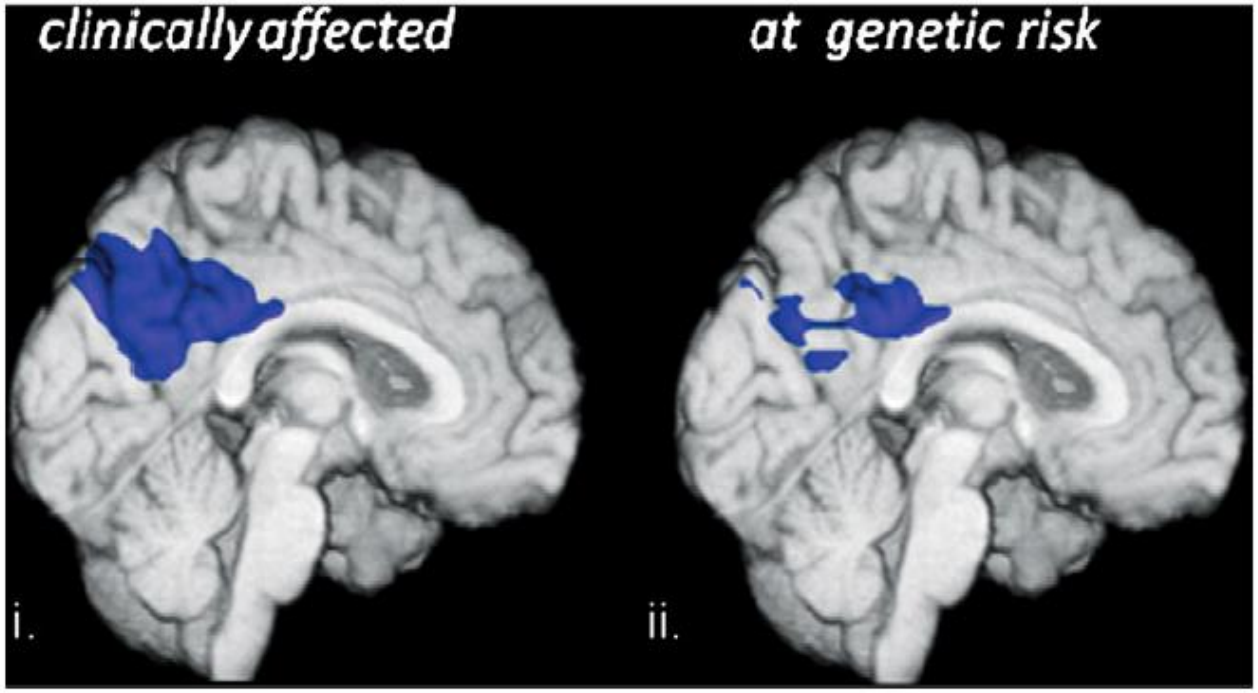


Fig. 2. FDG PET in people who are clinically affected by or at increased genetic risk of AD. Characteristic CMRgl reductions (compared to normal controls) are displayed on the medial surface of a brain MRI in clinically affected AD patients and in cognitively normal young adult with one copy of the *APOE ε4* allele, the major AD susceptibility gene.

Adapted with permission from Reiman et al. (1996), Copyright © 1996 Massachusetts Medical Society, all rights reserved, and Reiman et al. (2004), Copyright © 2004 National Academy of Sciences, USA. All rights reserved.

NeuroImage 61 (2012) 505–516

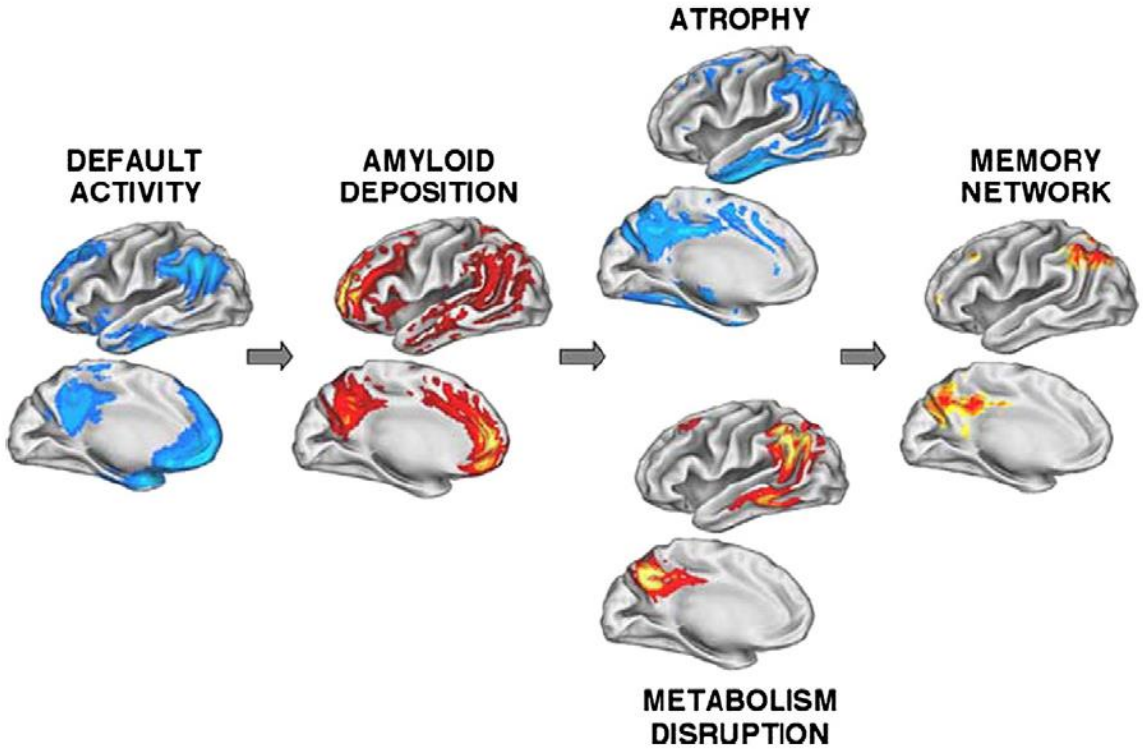


Fig. 4. Spatial relationships (and postulated causal connections) among the brain regions implicated in the Default Mode Network and successful episodic memory retrieval in young adults, the regions preferentially associated with fibrillar amyloid-β deposition, and the regions preferentially associated with atrophy and CMRgl decline. Reprinted with permission from Buckner et al. (2005), Copyright © 2005 Society for Neuroscience. All rights reserved.

Biomarkers

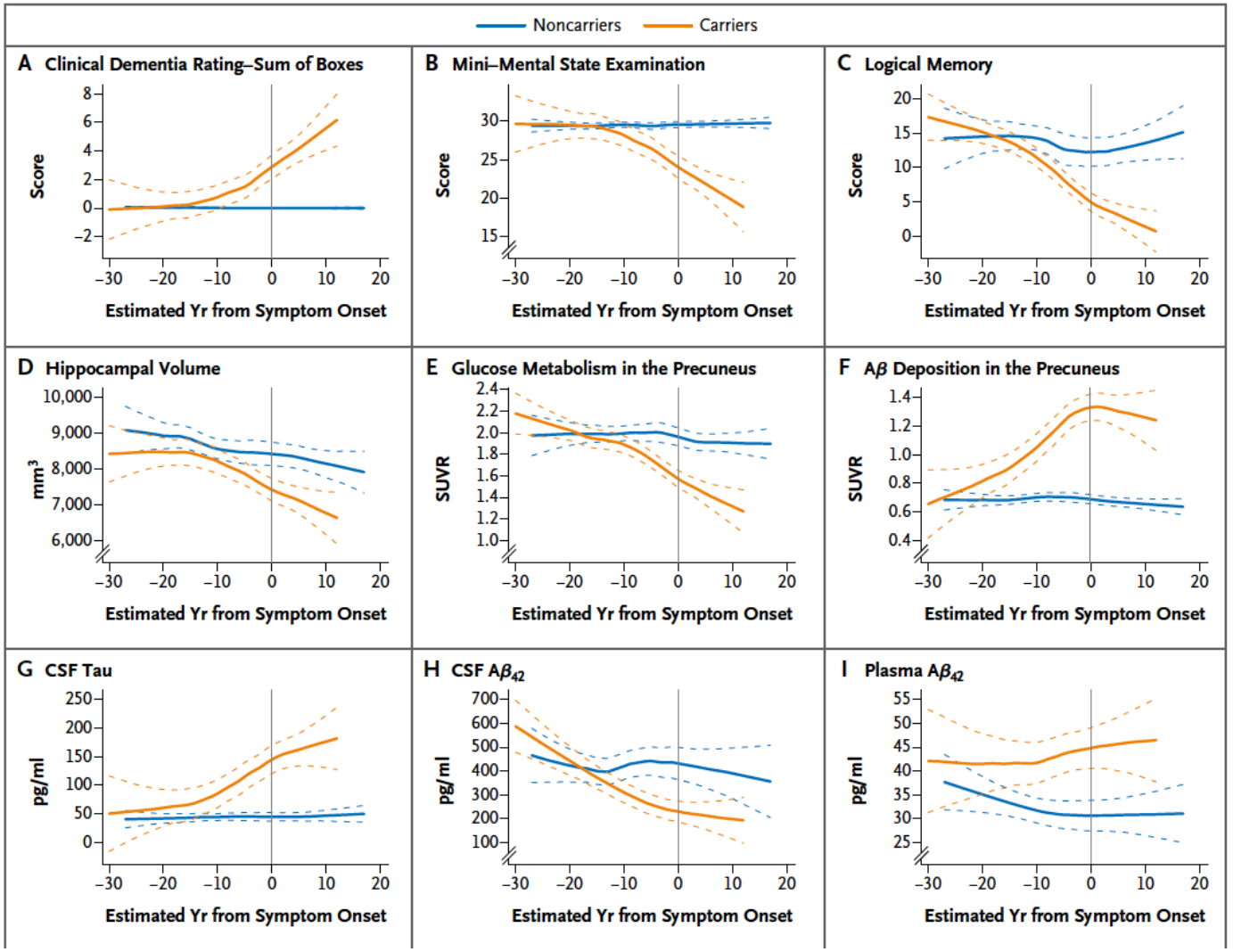
- Cognitive assessment

- Imaging:
  - Hippocampal volume
  - PET Abeta imaging
  - PET Glucose utilization

- CSF Tau, Abeta

- Plasma Abeta

-


Noncarriers
Carriers
A Clinical Dementia Rating–Sum of Boxes
Score
Estimated Yr from Symptom Onset
B Mini–Mental State Examination
Score
Estimated Yr from Symptom Onset
C Logical Memory
Score
Estimated Yr from Symptom Onset
D Hippocampal Volume
mm3
Estimated Yr from Symptom Onset
E Glucose Metabolism in the Precuneus
SUVR
Estimated Yr from Symptom Onset
F Aβ Deposition in the Precuneus
SUVR
Estimated Yr from Symptom Onset
G CSF Tau
pg/ml
Estimated Yr from Symptom Onset
H CSF Aβ42
pg/ml
Estimated Yr from Symptom Onset
I Plasma Aβ42
pg/ml
Estimated Yr from Symptom Onset

Genetics

- At least 12 susceptibility genes
- Pooled GWAS
- Whole genome sequencing
- TREM2 increases risk by 3 folds (NEJM 2013)

- Protective APP mutations (Nature 2012): 80% risk reduction
- 40% reduction in BACE activity ex vivo

Mechanisms

- Misfolded tau in extracellular space propagates into neurons
- PRION like mechanism of propagation across the brain

Neuron 2012;
PNAS 2013;
J Exp Med 2012

Clinical trials

•*Bapineuzumab (Janssen Pharmaceutical):* Humanized monoclonal antibody against Aβ.

- •Bapineuzumab is a passive immunotherapy approach, in which patients are treated with humanized monoclonal antibodies with specificity to Aβ peptides.
- •In August 2012 Phase III clinical trials of intravenous bapineuzumab were halted in patients with mild to moderate Alzheimer's disease due to disappointing results.

• *Solanezumab (Lilly)*: humanized monoclonal antibody against Aβ.

- •Solanezumab binds specifically to soluble amyloid-β and therefore may act to draw the peptide away from the brain through the blood to be cleared peripherally.
- •Phase III clinical trial failed primary endpoint;
- •Subgroup analysis may show slowing in patients with mild dementia

Clinical trials

- *Gamma secretase inhibitor (*Bristol-Myers Squibb)*:*
  - 11 December 2012. New York City-based Bristol-Myers Squibb recently announced that it will halt all clinical development of its γ-secretase inhibitor avagacestat, including an ongoing trial in people with prodromal Alzheimer's

- *BACE inhibitor (*Merck, Lilly)*:*
  - Merck compound MK-8931) in phase 3 (started enrolling December 2012
  - Eli Lilly and Company launched a Phase 2 study of its BACE1 inhibitor (LY2886721) in 129 people with mild cognitive impairment, and who tested positive for brain amyloid by PET scanning

- *IVIg:*
  - *Feb 2013 Phase II* **Octapharma IVIg Iffy failed endpoint**
  - **Baxter Gammagard** *Phase III to be released in July 2013*

Clinical trials

Diversify portfolio

Combination treatment

Prevention trials:

- DIAN: Autosomal dominant AD treat with BACE inhibitor
- ADCS4

Alzheimer prevention initiative

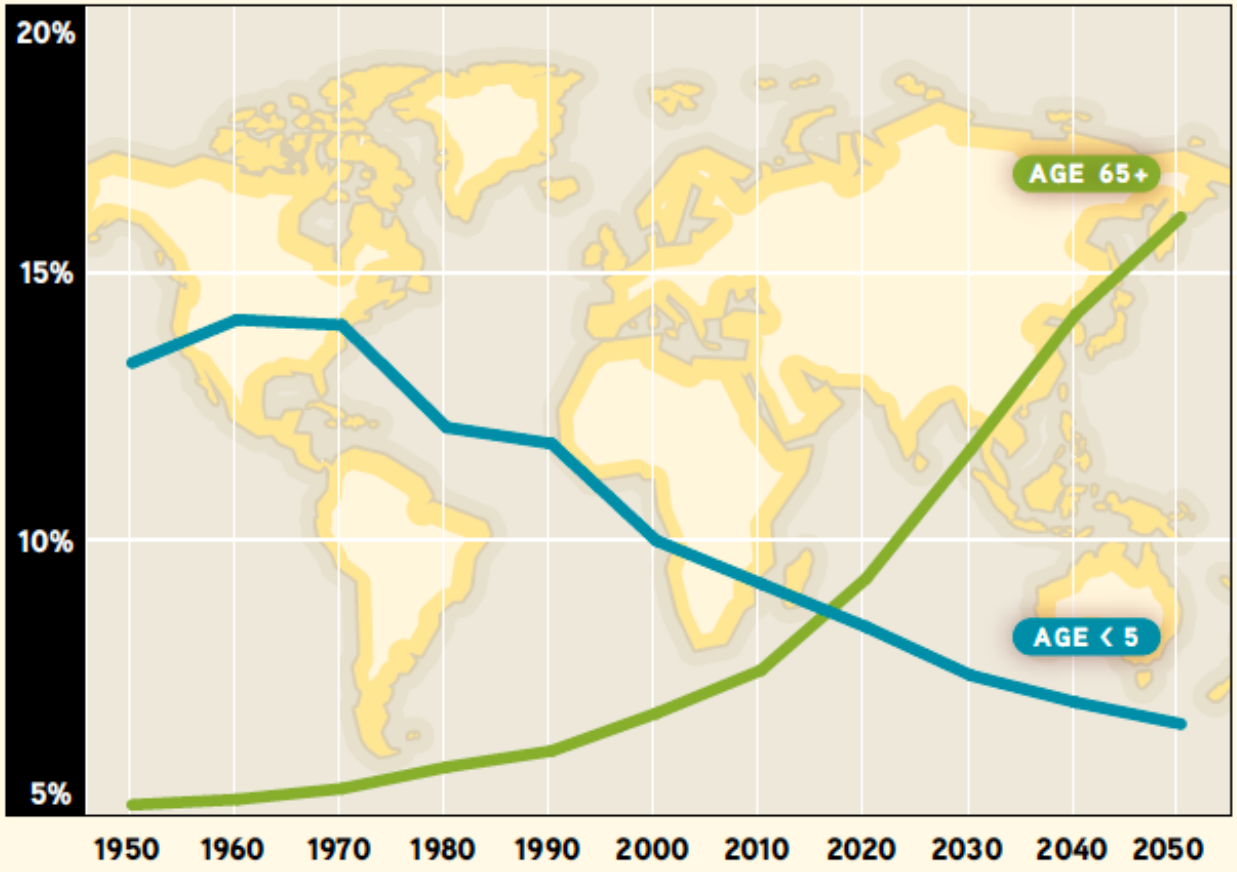
National initiatives

USA: Alzheimer's national plan
Reduce AD by 2025

German DZNE, Munich Dementia Center

France AD initiative

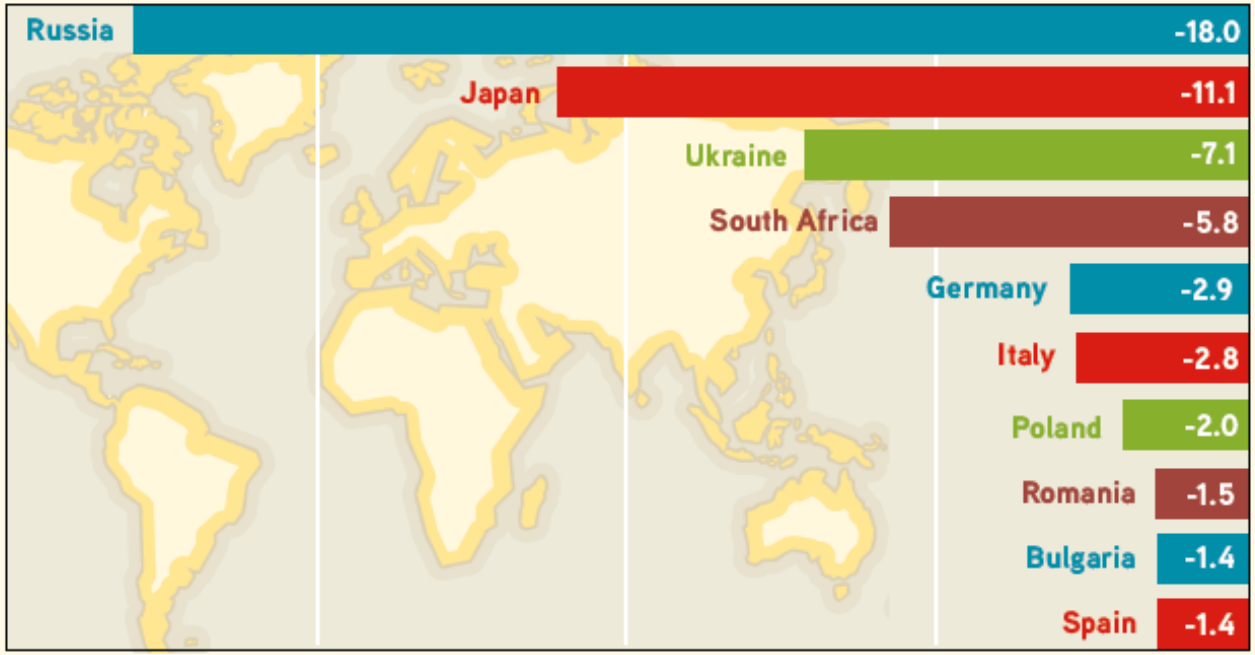
YOUNG CHILDREN AND OLDER PEOPLE AS A PERCENTAGE OF GLOBAL POPULATION



Source: United Nations Department of Economic and Social Affairs, Population Division. *World Population Prospects. The 2004 Revision.* New York: United Nations, 2005.

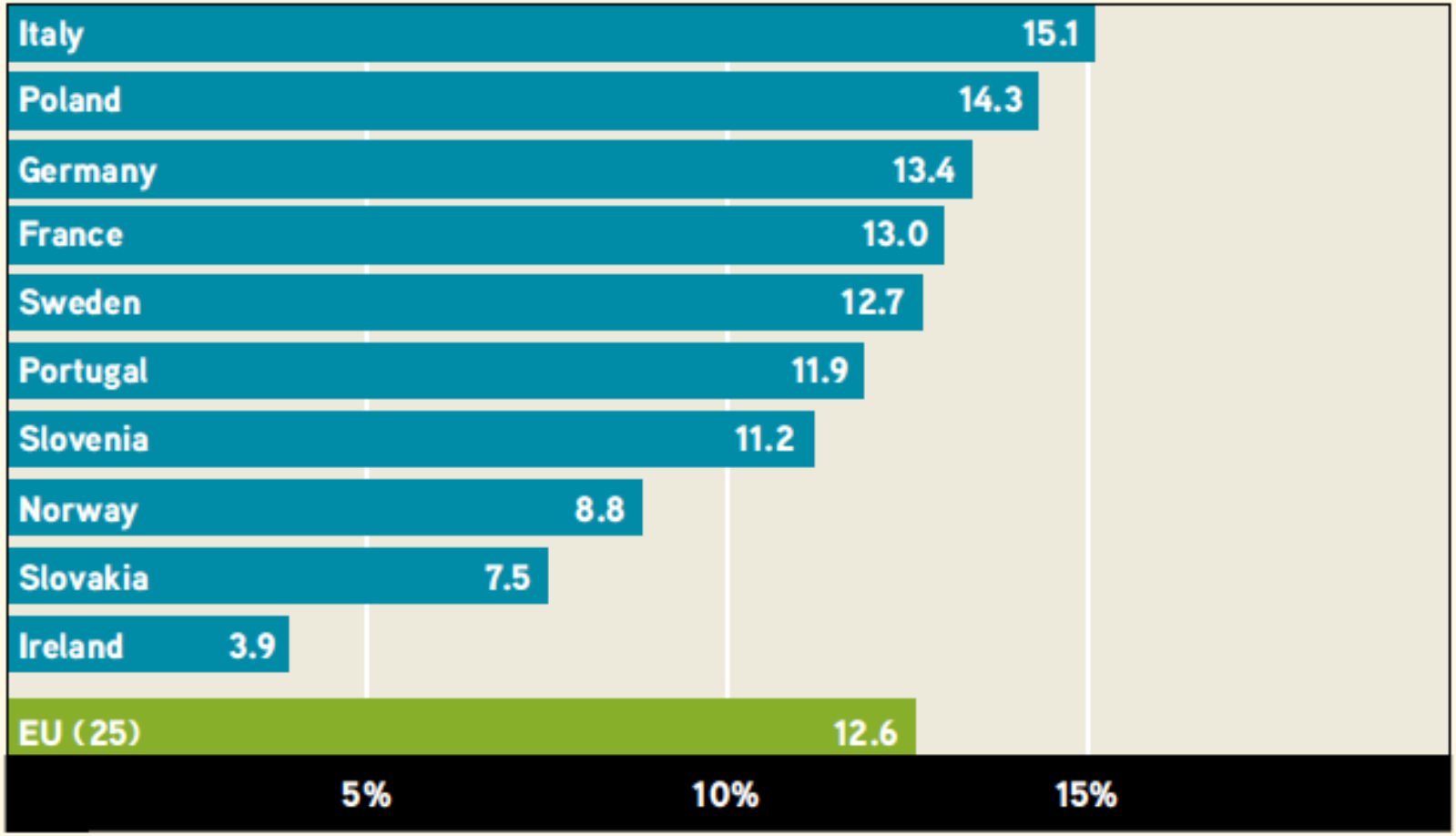
Figure 7:

PROJECTED POPULATION DECLINE BETWEEN 2006 AND 2030 (IN MILLIONS)



Source: U.S. Census Bureau International Data Base. Available at: http://www.census.gov/ipc/www/idbnew.html. Accessed January 8, 2007.

PENSION EXPENDITURES IN THE EUROPEAN UNION AS A PERCENTAGE OF GROSS DOMESTIC PRODUCT: 2003



Note: Pensions include old-age, anticipated old-age, partial, and disability benefits, as well as early retirement benefits due to reduced capacity to work.

Source: European Statistical System (EUROSTAT). Available at: http://epp.eurostat.ec.europa.eu. Accessed January 8, 2007.

KEY MESSAGES

- Dementia is not a normal part of ageing.
- 35.6 million people were estimated to be living with dementia in 2010. There are 7.7 million new cases of dementia each year, implying that there is a new case of dementia somewhere in the world every four seconds. The accelerating rates of dementia are cause for immediate action, especially in LMIC where resources are few.
- The huge cost of the disease will challenge health systems to deal with the predicted future increase of prevalence. The costs are estimated at US$ 604 billion per year at present and are set to increase even more quickly than the prevalence.
- People live for many years after the onset of symptoms of dementia. With appropriate support, many can and should be enabled to continue to engage and contribute within society and have a good quality of life.
- Dementia is overwhelming for the caregivers and adequate support is required for them from the health, social, financial and legal systems.
- Countries must include dementia on their public health agendas. Sustained action and coordination is required across multiple levels and with all stakeholders – at international, national, regional and local levels.
- People with dementia and their caregivers often have unique insights to their condition and life. They should be involved in formulating the policies, plans, laws and services that relate to them.
- The time to act is now by:
  - promoting a dementia friendly society globally;
  - making dementia a national public health and social care priority worldwide;
  - improving public and professional attitudes to, and understanding of, dementia;
  - investing in health and social systems to improve care and services for people with dementia and their caregivers;
  - increasing the priority given to dementia in the public health research agenda.

Dementia: a public health priority. World Health Organization, 2012

BOX 3.1

THE ALZHEIMER'S DISEASE INTERNATIONAL KYOTO DECLARATION 2004

10 AREAS FOR ACTION:

- Provide treatment in primary care.
- Make appropriate treatments available.
- Give care in the community.
- Educate the public.
- Involve communities, families and consumers.
- Establish national policies, programs and legislation.
- Develop human resources.
- Link with other sectors.
- Monitor community health.
- Support more research.

Source: Reference 141.

ADI, an international federation of Alzheimer associations around the world, released the Kyoto Declaration in 2004 *(141) providing* minimum recommendations for dementia care based on overall recommendations from WHO's World health report 2001 which focused on mental health *(142). Recognizing that countries are at* different levels of resource development, it proposes a feasible, pragmatic series of objectives and actions for health systems at all levels of development. It defines responses to each of the 10 actions at three levels of attainment: for countries with low, medium and high levels of resources (Box 3.1).

FIG 5.1 The integrated caregiving system

Country	Policy / plan / strategy title	Vision / aim / objectives	Areas of actions	Timeline	Source
Netherlands	Caring for people with dementia	"To improve the quality of life of people with dementia and their carers; and to provide professionals with the tools they need to care effectively"	• Creating a coordinated range of care options that meet the client's needs and wishes • Sufficient guidance and support for people with dementia and their caregivers • Measuring quality with dementia care indicators • The key outcome should be to secure the continuum of care.	2008–2011	*Reference 130*
Northern Ireland	*Improving Dementia Services in Northern Ireland*	"To improve the quality of life of people with dementia and their carers; and to provide professionals with the tools they need to care effectively."	• Reducing the risk or delaying the onset of dementia • Raising awareness • Promoting early assessment and diagnosis • Supporting people with dementia • Supporting caregivers • Legislation • Research	2011–2015	*Reference 131*
Norway	*Dementia Plan 2015*	"To improve the care for persons with dementia, the family carers and professional caregivers"	• Improving the quality of care through development measures and research • Raising knowledge / skills of workforce and increasing numbers • Improving collaboration between professions • Support "active care", such as day-care programmes • Support partnership between families and professionals	2007–2015	*Reference 132*
Scotland	*Scotland's National Dementia Strategy*	"Deliver world-class dementia care and treatment in Scotland, ensuring that people with dementia and their families are supported in the best way possible to live well with dementia"	Focusing on two key service delivery areas: • Improved post-diagnostic information and support • Care in general hospitals, including alternatives to admission	2010–2013, with annual progress reports and a commitment to review plan by 2013	*Reference 133*
Switzerland (Subnational plan in Canton of Vaud)	Maladie d'Alzheimer et maladies apparentées	Improve lives of persons with dementia and health care recognition of their needs	• Geriatric assessment and formation/education of medical and health professionals • Care coordination • Respite for family caregivers	2010–2013	*Reference 134*

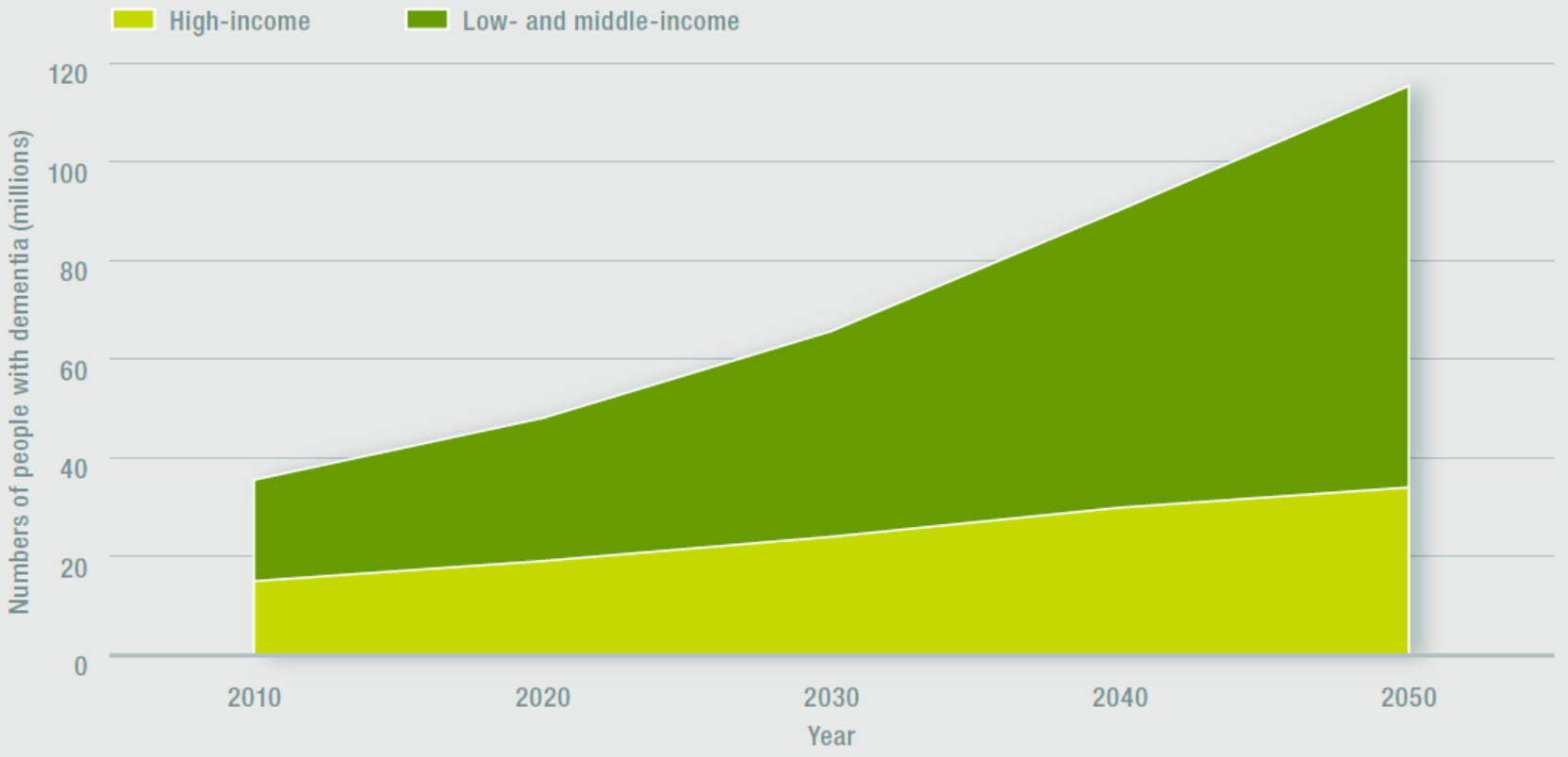


FIG 2.3 Growth in numbers of people with dementia in high-income and low- and middle-income countries

Le prospettive della genetica nella diagnosi e terapia delle demenze

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