The importance of the brain diseases in elderly population in Europe:

Presentation of the Lancet Neurology Dementia Commission Paper on Alzheimer's Disease

Bengt Winblad and Angel Cedazo-Minguez
Karolinska Institutet. Center for Alzheimer Research
Huddinge, Sweden

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Defeating Alzheimer's disease and other dementias: a priority for European science and society

Bengt Winblad, Philippe Amouyel, Sandrine Andrieu, Clive Ballard, Carol Brayne, Henry Brodaty, Angel Cedazo-Minguez, Bruno Dubois, David Edvardsson, Howard Feldman, Laura Fratiglioni, Giovanni B Frisoni, Serge Gauthier, Jean Georges, Caroline Graff, Khalid Iqbal, Frank Jessen, Gunilla Johansson, Linus Jönsson, Miia Kivipelto, Martin Knapp, Francesca Mangialasche, René Melis, Agneta Nordberg, Marcel Olde Rikkert, Chengxuan Qiu, Thomas P Sakmar, Philip Scheltens, Lon S Schneider, Reisa Sperling, Lars O Tjernberg, Gunhild Waldemar, Anders Wimo, Henrik Zetterberg

- Health economics in AD - Epidemiology - Prevention	- Genetic risk - Disease Biology - Diagnosis and Biomarkers
- Pharmacological treatment - Non-pharmacological treatment	- Formal and informal care - Ethics

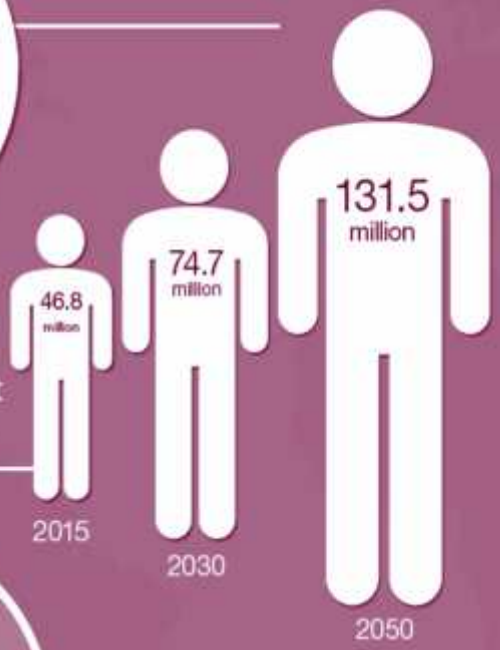
Extracted from the ADI World Alzheimer Report, August 2015

INFOGRAPHIC

The global impact of dementia

Around the world, there will be 9.9 million new cases of dementia in 2015,

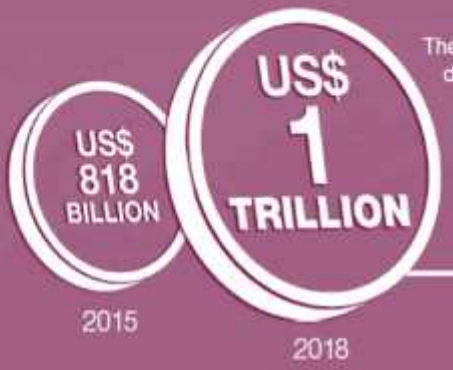
one every 3 seconds



46.8 million people worldwide are living with dementia in 2015.

This number will almost double every 20 years.

Much of the increase will take place in low and middle income countries (LMICs): in 2015, 58% of all people with dementia live in LMICs, rising to 63% in 2030 and 58% in 2050.



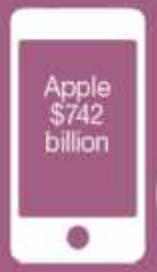
The total estimated worldwide cost of dementia in 2015 is US$ 818 billion. By 2018, dementia will become a trillion dollar disease, rising to

US$ 2 trillion by 2030

If global dementia care were a country, it would be the

18th largest economy

in the world exceeding the market values of companies such as Apple and Google



(source: Forbes 2015 ranking)

This map shows the estimated number of people living with dementia in each world region in 2015.

We must now involve more countries and regions in the global action on dementia.

Epidemiology

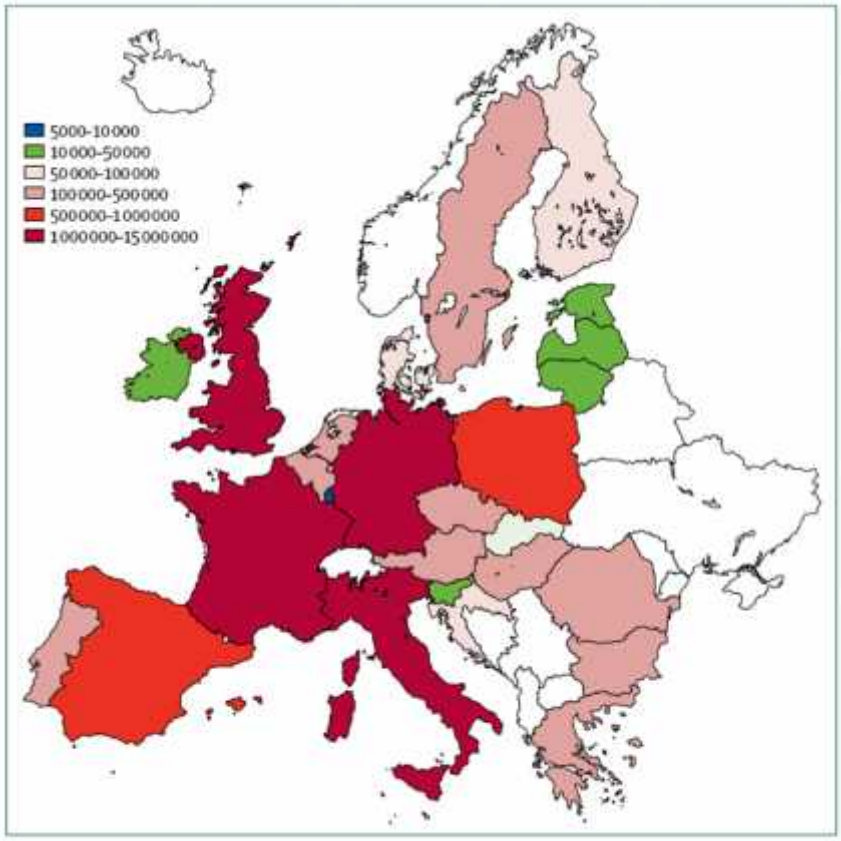


Figure 1: **Number of people with dementia in 28 European countries in 2013**
Estimates of the total number of people with dementia in each of 28 European countries were obtained from Alzheimer Europe.[36]

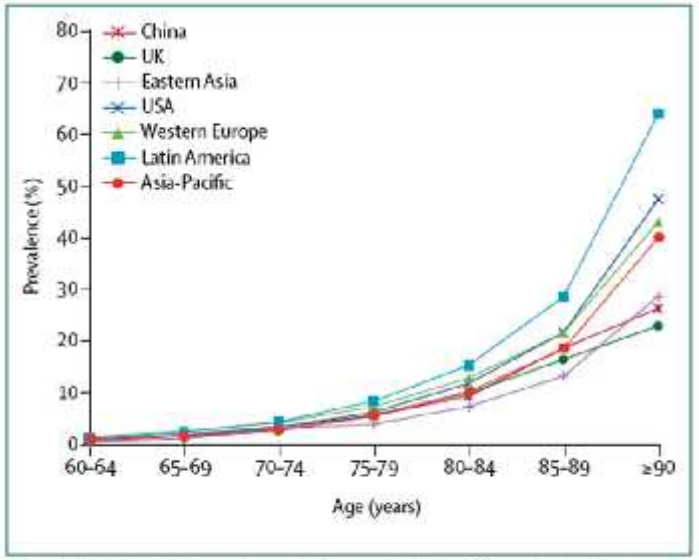


Figure 3: **Age-specific prevalence of dementia by world region and in major countries**
Patterns of age-specific prevalence of dementia are similar across worldwide regions, but with substantial variations among the oldest old (age ≥90 years).[71-75]

Prevention

RISKS FACTORS	PROTECTIVE FACTORS
• Cardiovascular diseases • Diabetes mellitus and pre-diabetes • Midlife hypertension • Midlife overweight and obesity • Midlife high serum cholesterol	• Antihypertensive drugs • Statins • Hormone replacement therapy • Non-steroidal anti-inflammatory drugs
• Saturated fats • Hyperhomocysteinaemia • Deficiencies in vitamins	• Mediterranean diet • Polyunsaturated fatty acids • Vitamin B6, vitamin B12, and folate. Antioxidant
• Sedentary lifestyle • Depression • Traumatic brain injury	• Physical activity • High education and socioeconomic status • High work complexity • Rich social network and social engagement

	FINGER	MAPT	Pre-DIVA
Multidomain intervention	Vascular care, Diet, Exercise, Cognitive training	Diet, Exercise, Cognitive training, Omega-3	Nurse-lead intensive vascular care
Age, yrs	60-75	70 -	70-78
Sample size	1200	1680	3535
Inclusion criteria	Dementia Risk Score >6 and mild degree of cognitive impairment	Frail elderly people (subj memory complaint, slow walking speed, limitation in IADL)	All elderly within GP practices
Study design	Multi-center, randomized, single-blind, parallel group	Multi-center, randomized, controlled trial	Multi-cite, open, cluster-randomized parallel group
Intervention period	2 yrs	3 yrs	6 yrs
Primary outcome	Neuropsych test battery, Trail Making, Stroop, Dementia	Change in cognitive function (Grober and Buschke memory test)	Dementia, Disability
Study completion	2014 *(Lancet 2015, Ngandu et al)*	2015	2015

Genetics of AD.

Deterministic Mutations or Individual Risk.

	Very rare (MAF <0·1%) familial variants	Variants present at low frequency (MAF <1%) in the population	Variants present as common polymorphisms (MAF >10%) in the population
Disease gene	*APP*, *PSEN1*, *PSEN2*	..	..
High impact (OR ≥2)	*SORL1*	*PLD3*, *TREM2* *APP* A673T (protective)	*APOE* ε4 allele *APOE* ε2 allele (protective)
Low impact (OR <2)	..	..	Confirmed loci: *ABCA7*, *BIN1*, *CASS4*, *CD2AP*, *CD33*, *CELF1*, *CLU*, *CR1*, *EPHA1*, *FERMT2*, *HLA DRB5–DRB1*, *INPP5D*, *MEF2C*, *MS4A6A/MS4A4E*, *NME8*, *PICALM*, *PTK2B*, *SLC24A4*, *SORL1*, *ZCWPW1* Unconfirmed loci: *ACE*, *ADAMTS20*, *AP2A2*, *ECHDC3*, *FRMD4*, *HS3ST1*, *IGH*, *NDUFAF6*, rs6678275 (intergenic), *SCIMP*, *SPPL2A*, *SQSTM1*, *TREML2*, *TRIP4*

Identified genes and loci classified according to their effect on the risk for Alzheimer's disease. Generally, causal mutations (associated with early-onset familial disease) are rare and deterministic, which means that they contribute to only a minor fraction of the total number of patients with AD but have a strong impact on the individual (very strong association), being sufficient to cause the disease. These genes are thus classified separately as disease genes. MAF=minor allele frequency. OR=odds ratio.

Table 6: **Identified loci with genetic association to Alzheimer's disease**

Uncovered mechanisms

- Aβ accumulation
- Cholesterol metabolism
- Glucose metabolism
- Inflammation
- Membrane /vesicle recycling

From Genetics to Precision Medicine

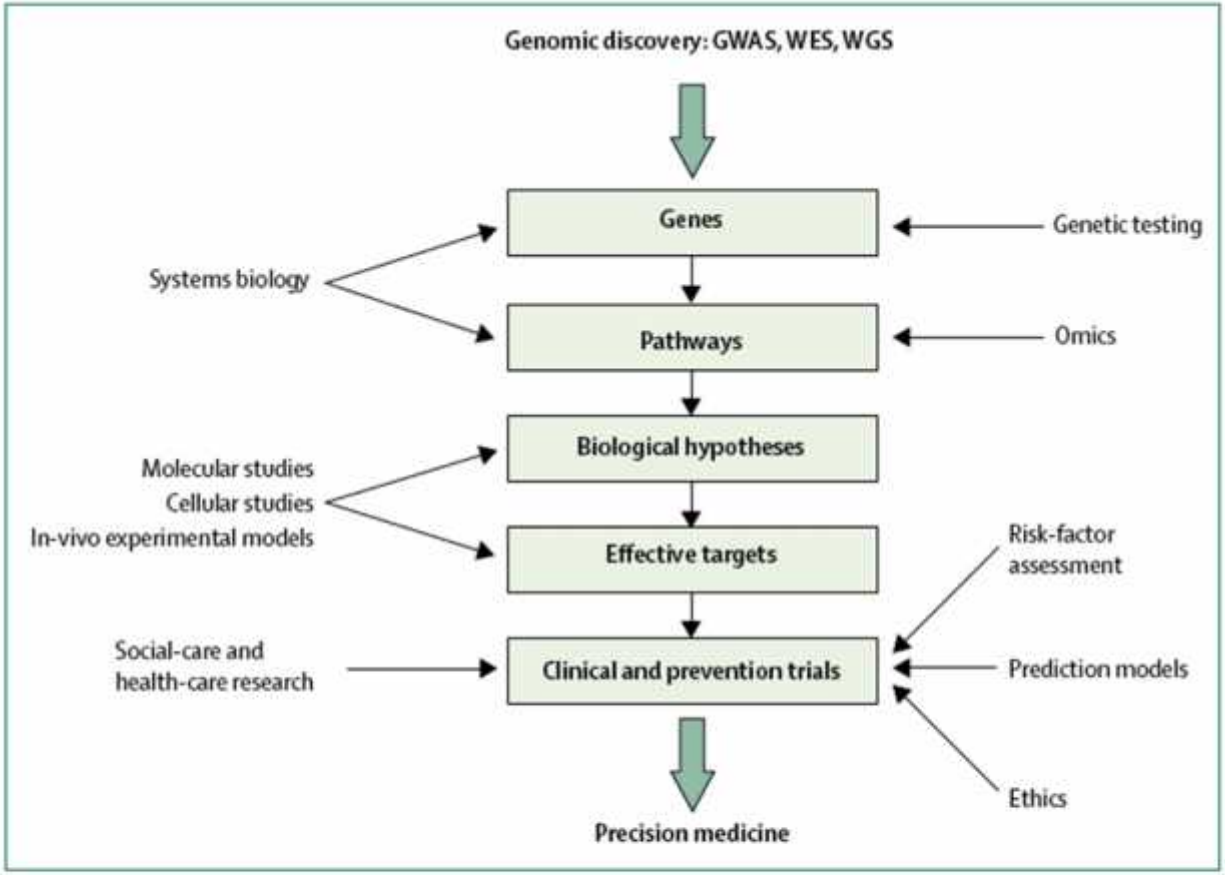
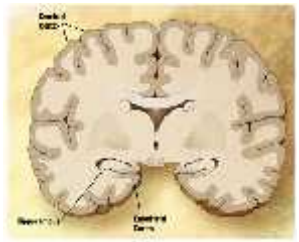
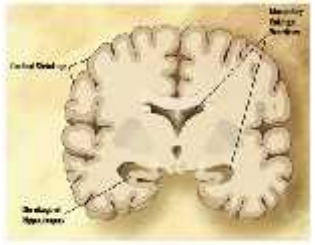
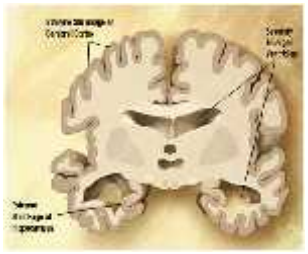


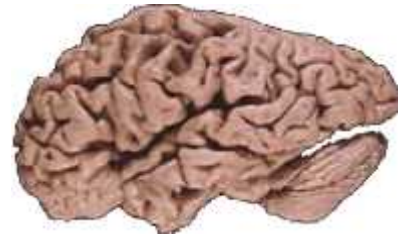
Figure 4: **From genetic and genomic discoveries to precision medicine**
Starting with genetic and genomic discoveries, future research studies need to integrate data from all research areas to construct testable hypotheses and draw meaningful conclusions about the functional consequences of the known Alzheimer's disease genes and loci. These integrated analyses could push the research frontier forward, allow personal risk profiles to be generated, and ultimately help to shape individualised strategies for intervention. GWAS=genome-wide association study. WES=whole-exome sequencing. WGS=whole-genome sequencing.

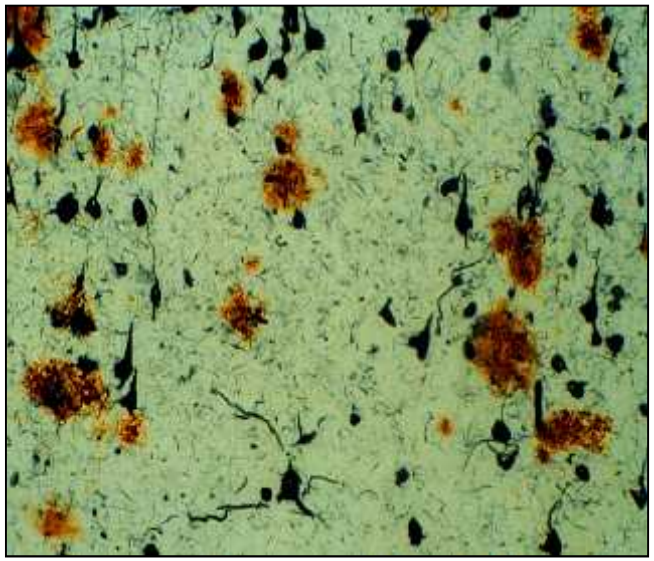
Disease Pathology





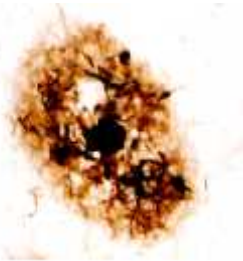




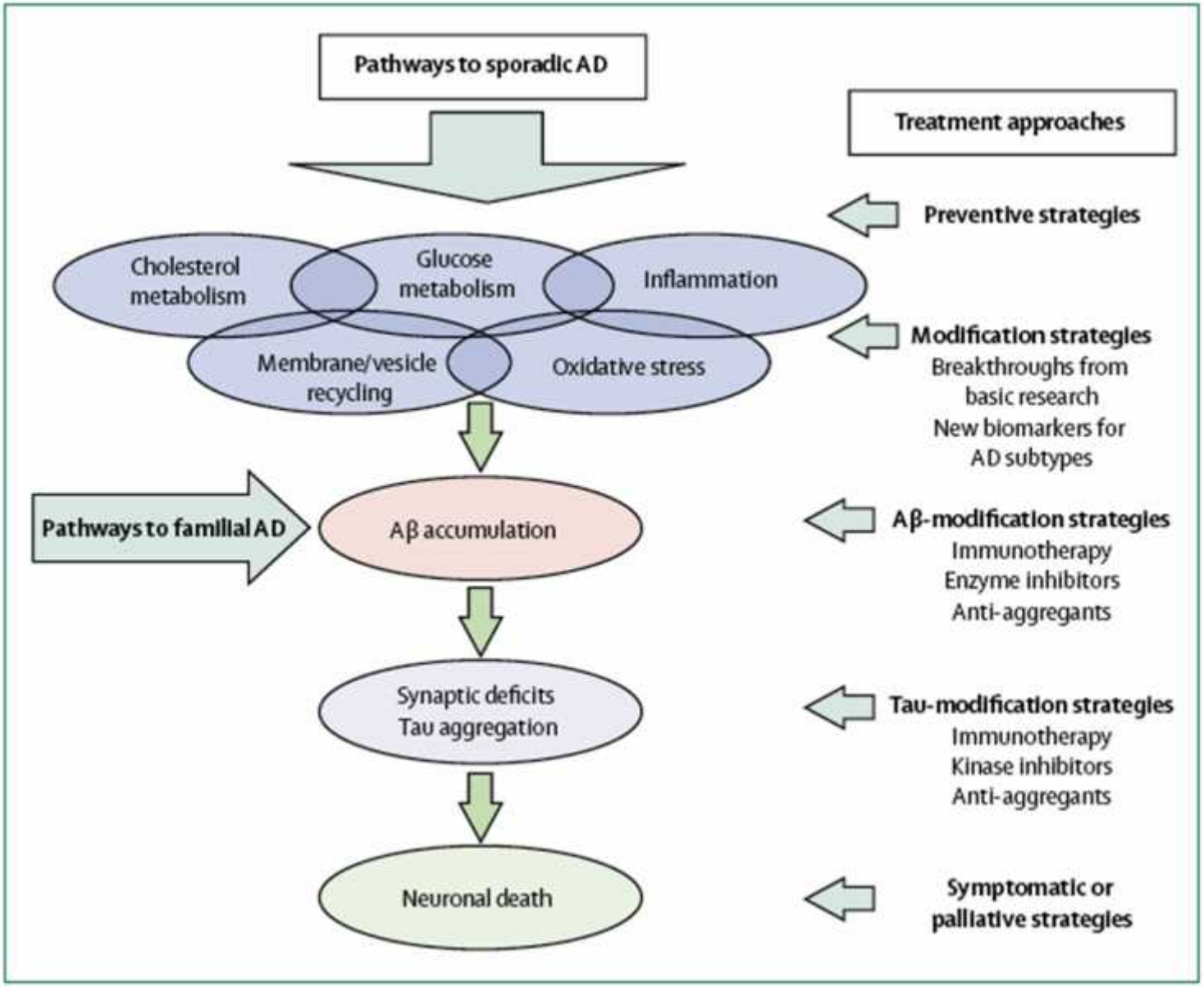


NFTs

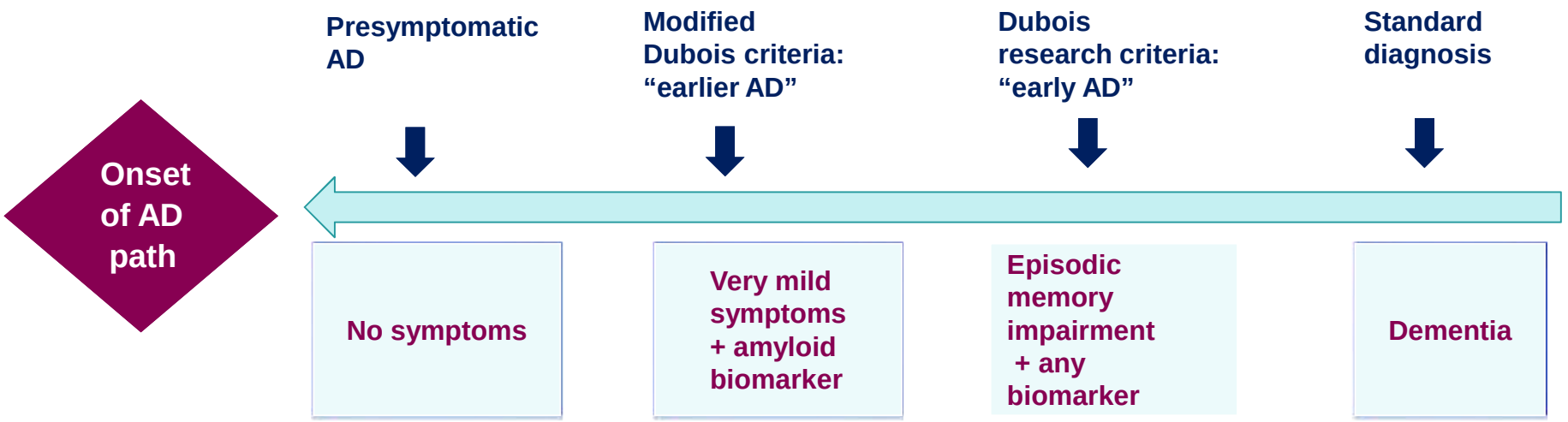
Abeta plaques



Disease Biology



AD Diagnosis Marching Leftward

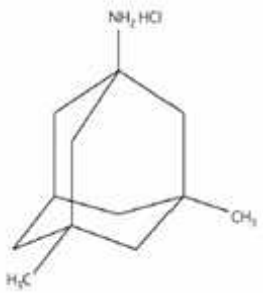


Need to define subtypes:

Individualization for Personalized Medicine

Therapy in AD: The first hundred years and looking forward…….

Memantine
NMDA
Uncompetitive
Receptor
Antagonist

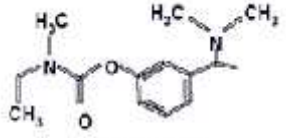


1906 1910 1974 1982 1997 2004 2010 2020

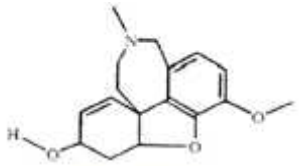
The cholinergic hypothesis

Acetylcholinesterase inhibitors

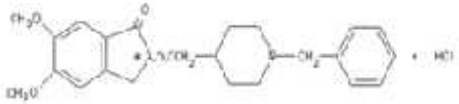
First Disease Modifying Rx?
Amyloid and tau lowering?
Next generation targets?



rivastigmine

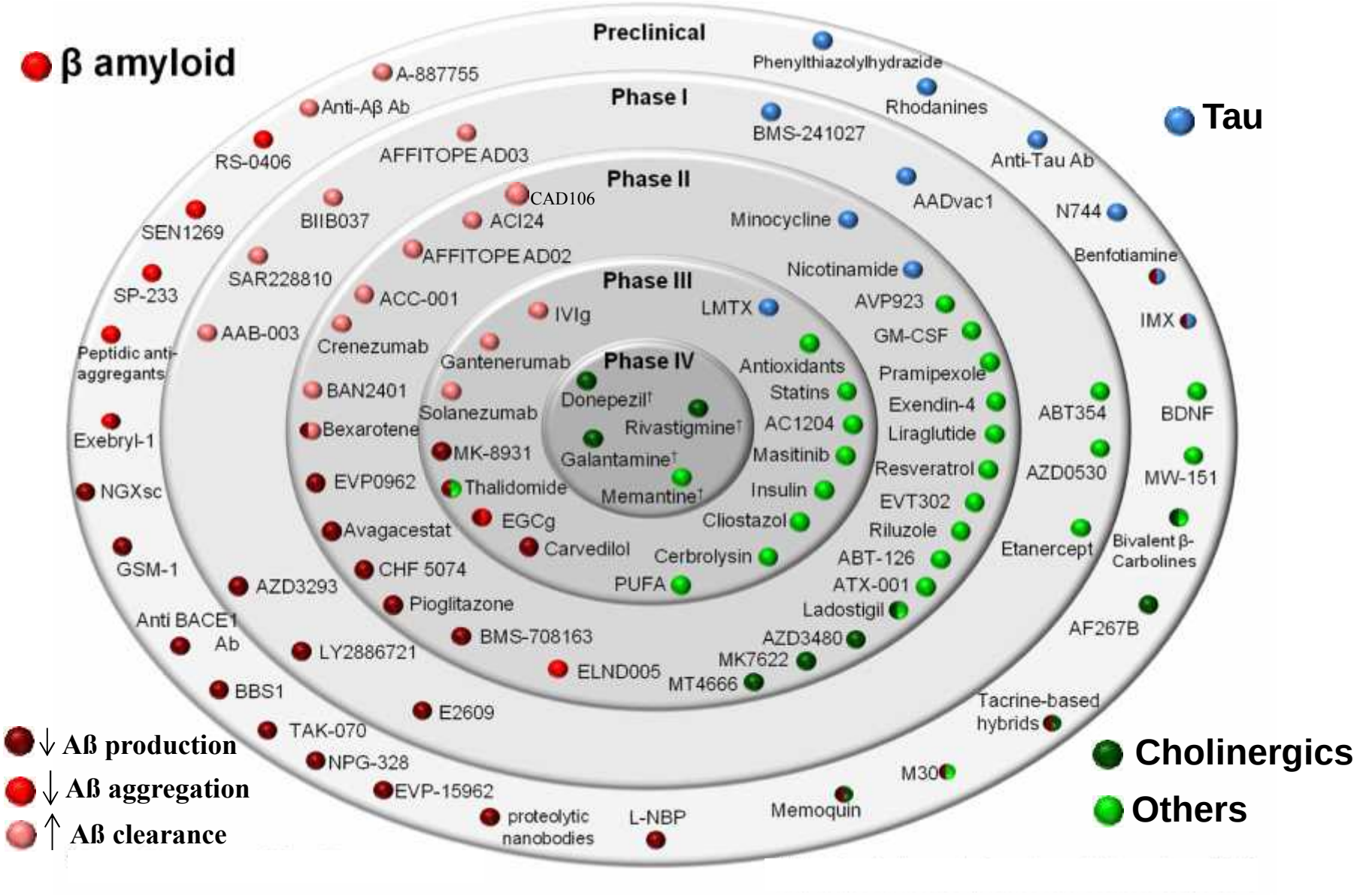


galantamine



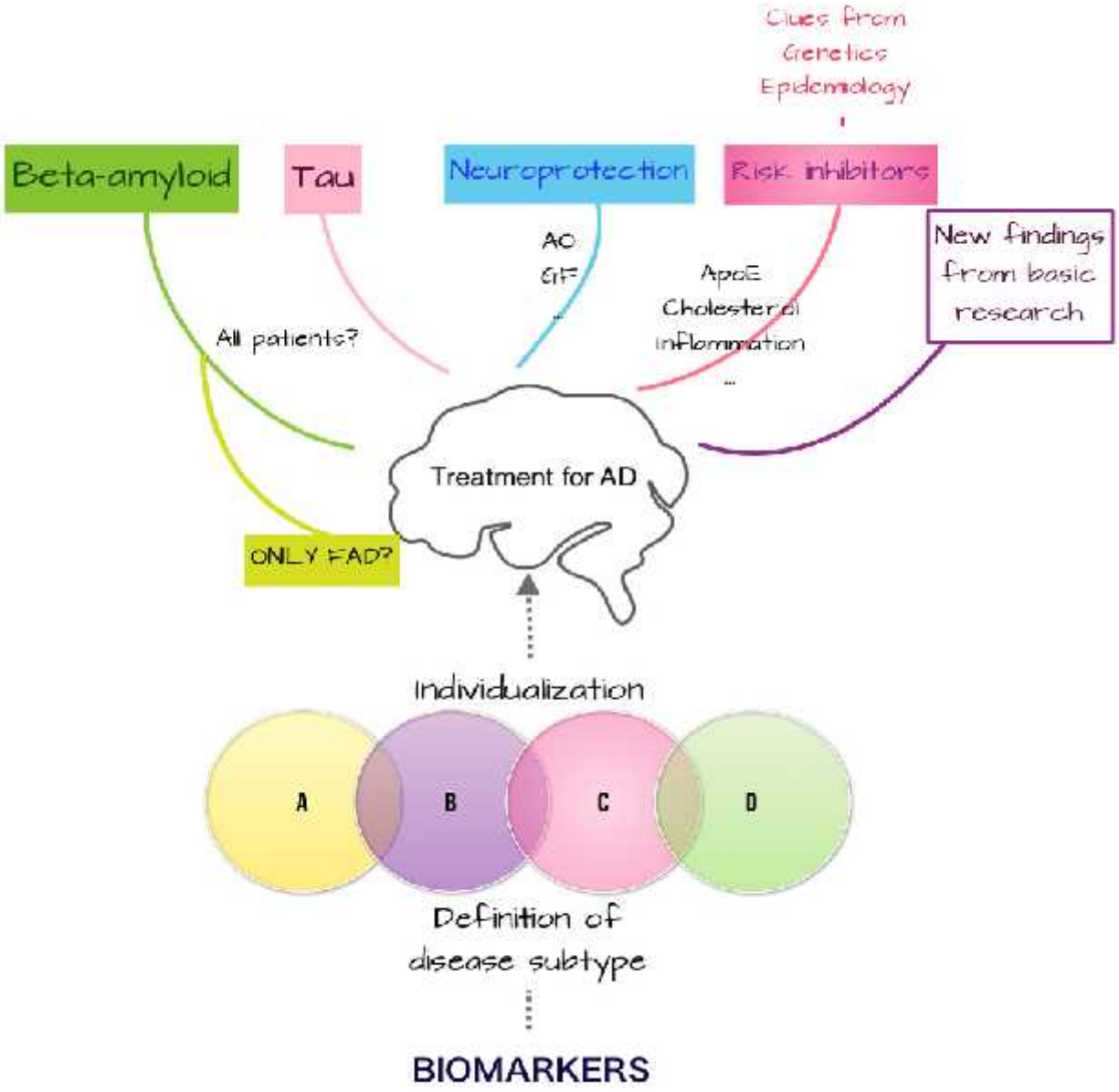
donepezil

Ongoing clinical trials in Alzheimer disease



Mangialasche et al, modified 2013 from Lancet Neurology, 2010

Research - the way forward to treatment



Formal and Informal Care for Patients

Panel 6: Formal resources to include in economic assessments of dementia care

- Formal care
- Living situation (at home or in institutions)
- Respite care
- Home social-care visits
- Home medical-care visits
- Home rehabilitation-care visits
- Visits to clinics: physician specialists
- Visits to clinics: general practitioner specialists (or similar)
- Visits to clinics: registered nurses (or similar)
- Visits to clinics: rehabilitation (similar)
- Hospital care (various specialities and departments)
- Day hospital care (eg, day surgery)
- Day care (special care for dementia)
- Day care (not specifically for dementia)
- Use of drugs
- Technical devices and equipment
- Food support (eg, meals on wheels)
- Transport services

- The care of patients with dementia **does not fit** easily into typical health-care delivery systems
- Worldwide, the **burden of care often falls on family members**
- The long-term care of people with dementia **begins at home with a collaborative partnership between informal and formal caregivers.**
- Institutional care for patients with severe dementia is **demanding and costly**
- Effective **assisted care and nursing homes with skilled staff** will become increasingly important

Ethical Considerations

Benefits and disadvantages of early diagnostics (**risk for false positive**) should be assessed from both the **biomedical and the patients' perspectives**

Increased international collaboration in research will demand **harmonised ethical standards on national and international (EU) level.**

Doing good not causing harm, respecting patient autonomy and striving for justice for all

Assessment of competency to consent cannot be based on diagnosis or staging, but on individual assessment to **maximise patients' autonomy**

End-of-life care in dementia can be improved by **advance care planning (as a routine part of primary care)** to improve quality of life

The Lancet Neurology Commission:
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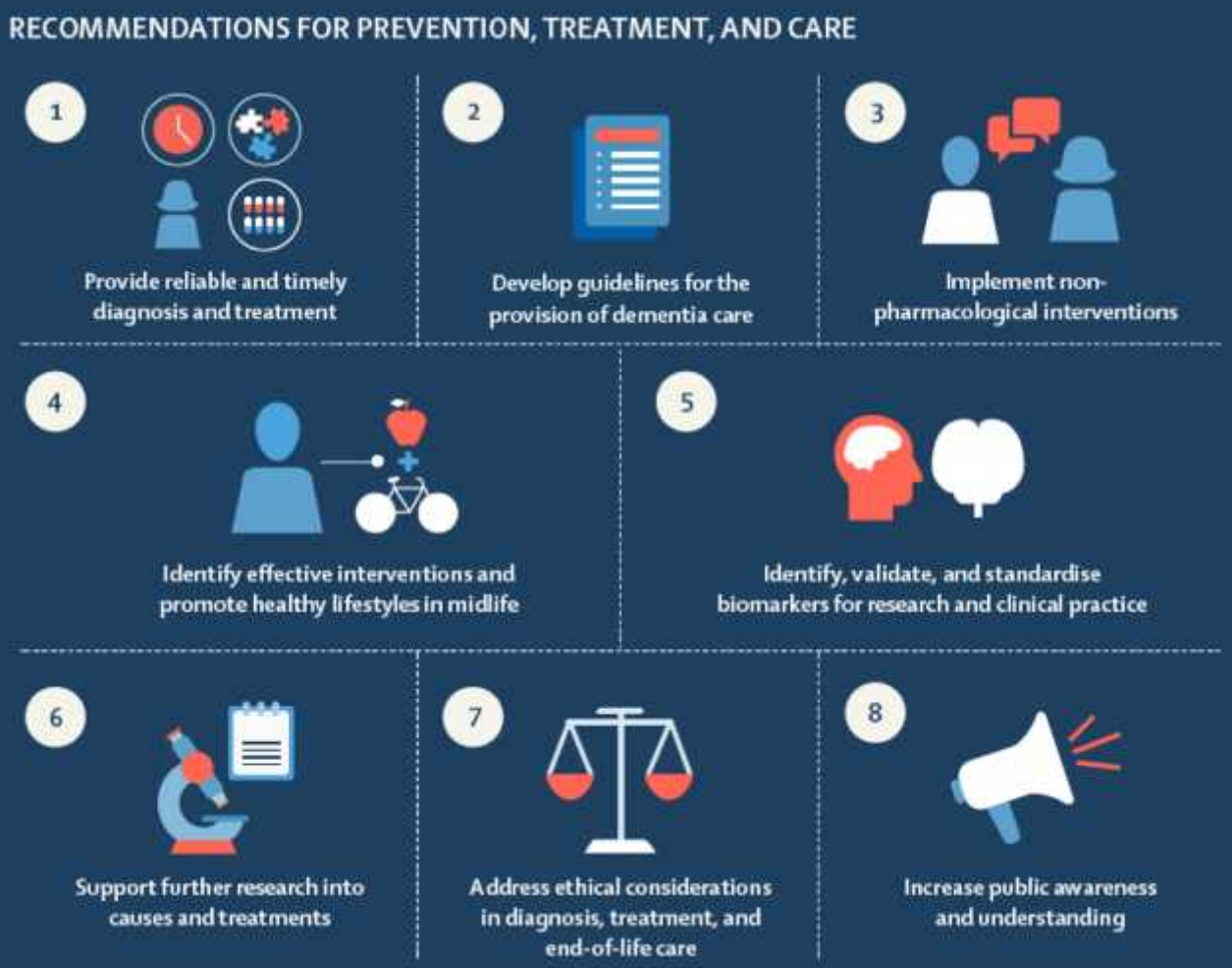

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