Development of new medicines for the treatment of Alzheimer Disease: issues for discussion at a regulatory level

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Dementia in Europe: a challenge for our common future

Roma, 14 November 2014

Public Declaration of transparency/interests*

Interests in pharmaceutical industry	NO	Currently	Last 2 years	More than 2 years but less than 5 years ago	More than 5 years ago (optional)
Direct interests:					
Employment with a company	X				
Consultancy for a company	X				
Strategic advisory role for a company	X				
Financial interests	X				
Ownership of a patent	X				
Indirect interests:					
Principal investigator	X				
Investigator				X	
Individual's Institution/Organisation receives a grant or other funding	X				
CME Courses	X				

***Valentina Mantua**, in accordance with the Conflict of Interest Regulations approved by AIFA Board of Directors (26.01.2012) and published in the Italian Government Official Journal on 20.03.2012 according to 0044 EMA/513078/2010 on the handling of the conflicts of interest for scientific committee members and experts

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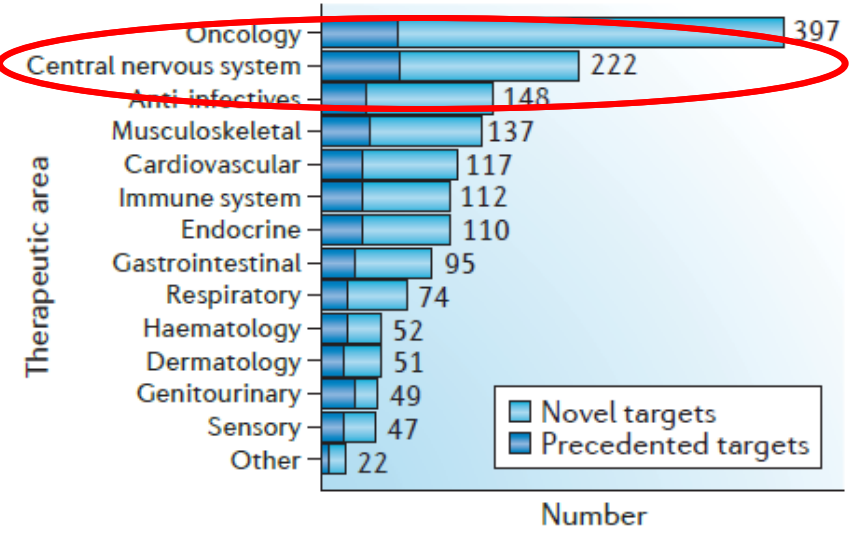
Note: For this presentation I am not receiving any compensation

The innovation challenge and beyond

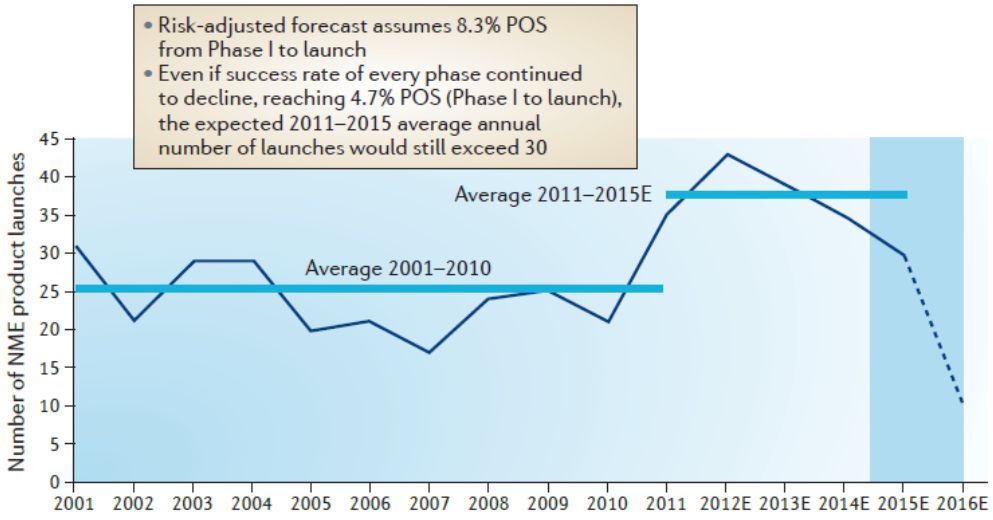
Outlook for the next 5 years in drug innovation

Roy Berggren, Martin Møller, Rachel Moss, Pawel Poda and Katarzyna Smietana

Number of targets in development by therapeutic area: 2011

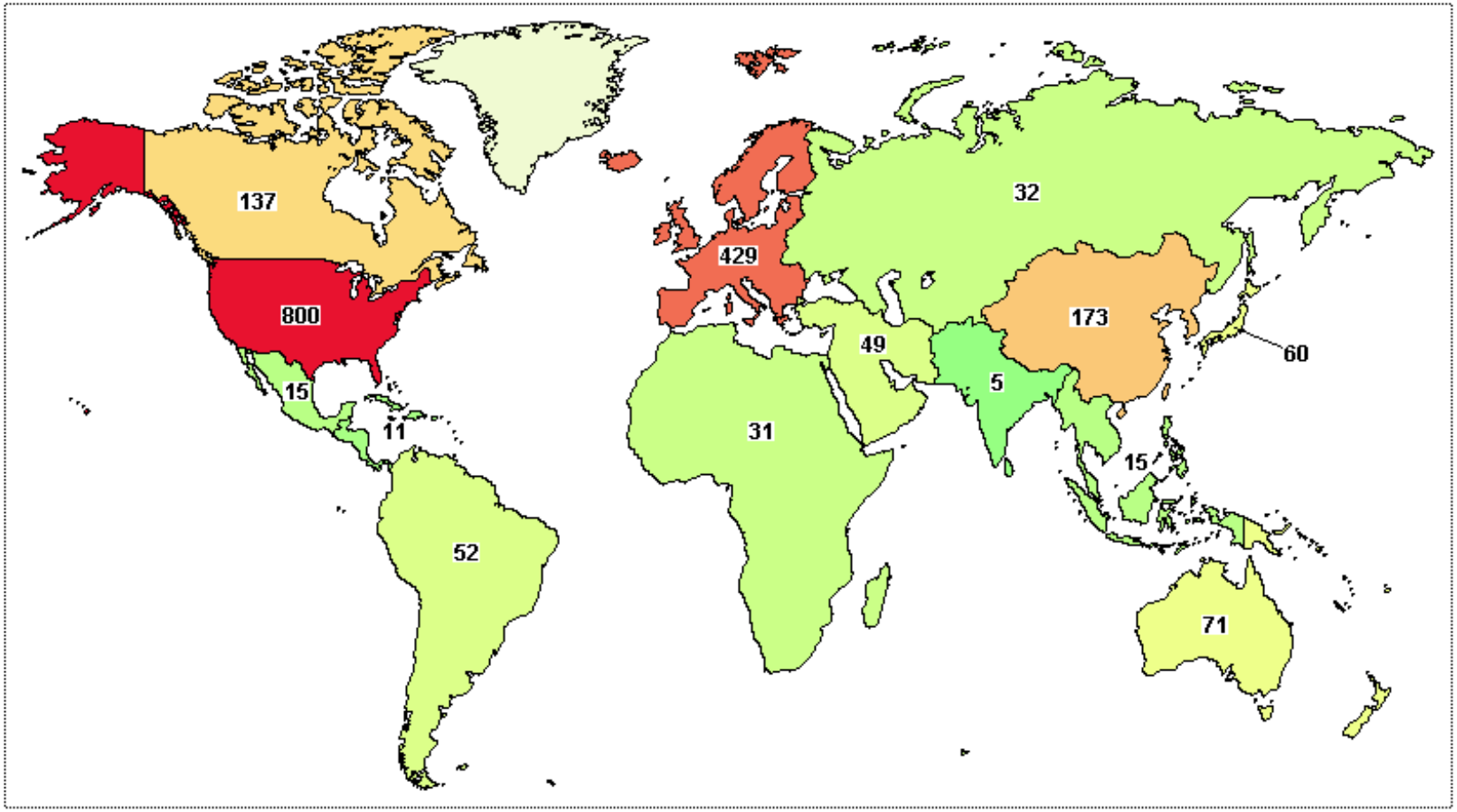


Historic and forecasted number of launches.



Average peak-year sales of innovative products are forecasted to continue to decline, from around $900 million for products launched in 2012 to around $600 million for products launched in 2015.

1507 studies found for Alzheimer Worldwide



The centralized procedure (1995)

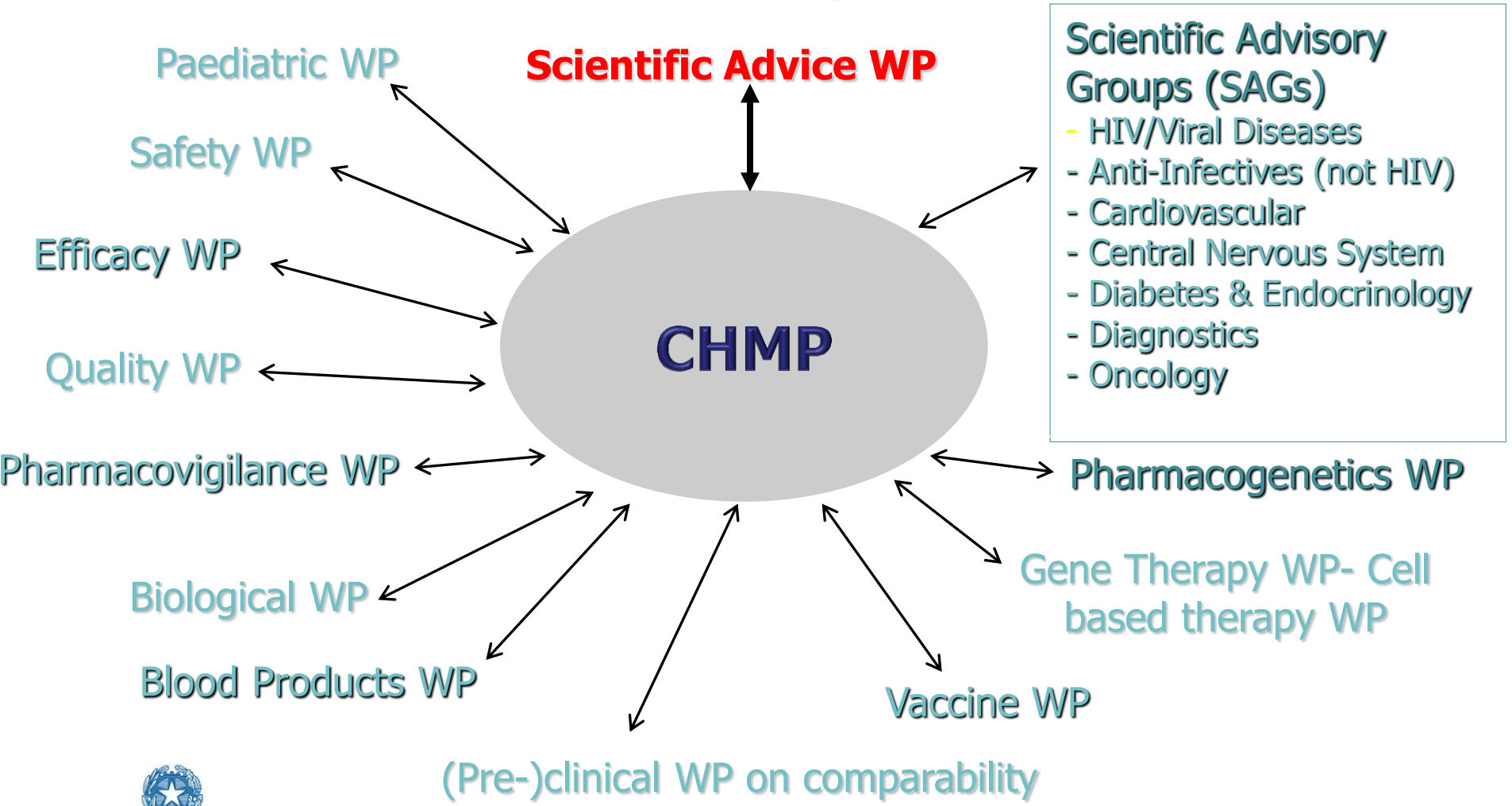
Regulation (EC) No 726/2004

Marketing authorisation that is valid throughout the EU.

It is compulsory for medicinal products:

- using biotechnological processes,
- for orphan medicinal products
- treatment of AIDS, cancer, **neurodegenerative disorder** or diabetes.

CHMP Working Parties



Scientific Advisory Groups (SAGs)

- HIV/Viral Diseases
- Anti-Infectives (not HIV)
- Cardiovascular
- Central Nervous System
- Diabetes & Endocrinology
- Diagnostics
- Oncology

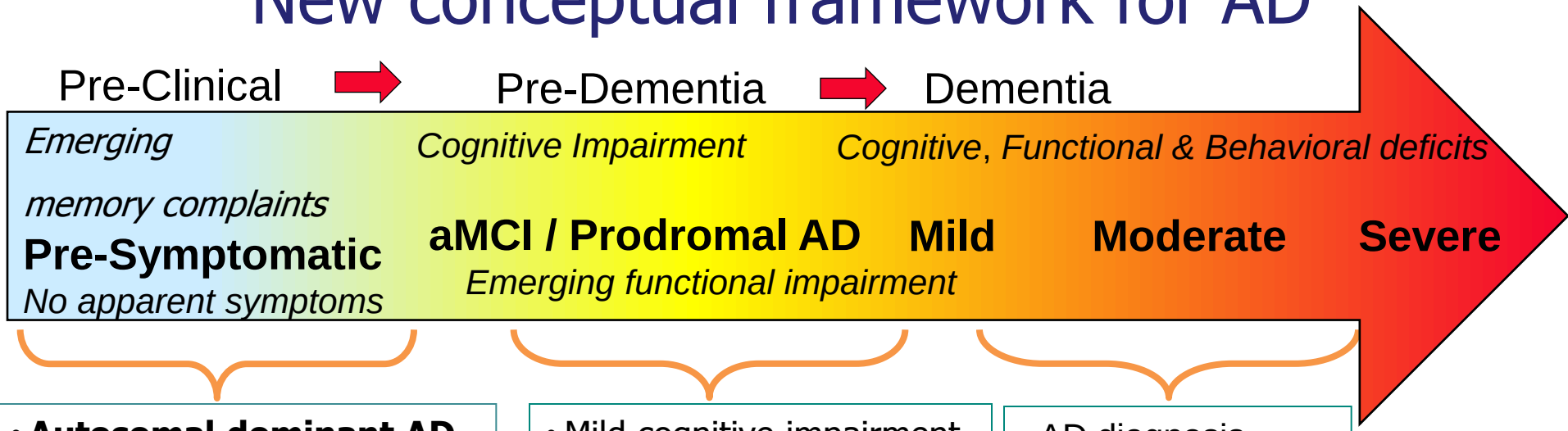
The strategic role of AIFA in the regulatory field of Dementia

In the last 2 years AIFA coordinated almost 90% of all EMA requests for scientific advice from Companies:

- 5 Qualification OPINION of novel methodologies
- 3 Qualification ADVICE procedures
- 17 Scientific Advice procedures
- 1 parallel Scientific Advice/HTA procedure

Since 2012 AIFA is National Competent Authority for clinical trials evaluation:
4 phase II/III CTs were approved out of 12 running in EU

New conceptual framework for AD



- **Autosomal dominant AD**, presence of APP, PS1, PS2 mutations in absence of symptoms (**5%**)
- **Preclinical AD**: no symptoms, emerging biomarker evidence of AD pathology (**95%**)

- Mild cognitive impairment (**MCI**)
- Amnestic MCI (**aMCI**) - episodic memory deficits
- **Prodromal AD** - aMCI combined with biomarker evidence of AD pathology (also termed **MCI due to AD**

- AD diagnosis based on clinical symptoms; cognitive deficits & **dementia** of the AD type

Need for a harmonization of the criteria to define the prodromal/MCI population

IGW (EU)	**NIA-AA** (US)	**DSM5** (APA)
Objective memory impairment	Objective or subjective memory impairment	Subjective and objective cognitive decline
No functional impairment not even in iADL	Accept minor problems in performing iADL	No functional impairment but increased compensatory strategies
Positive biomarker (amyloid PET of CSF Aβ1-42 and Tau)	Positive biomarker supportive but not mandatory	No need for biomarker

AD Biomarkers

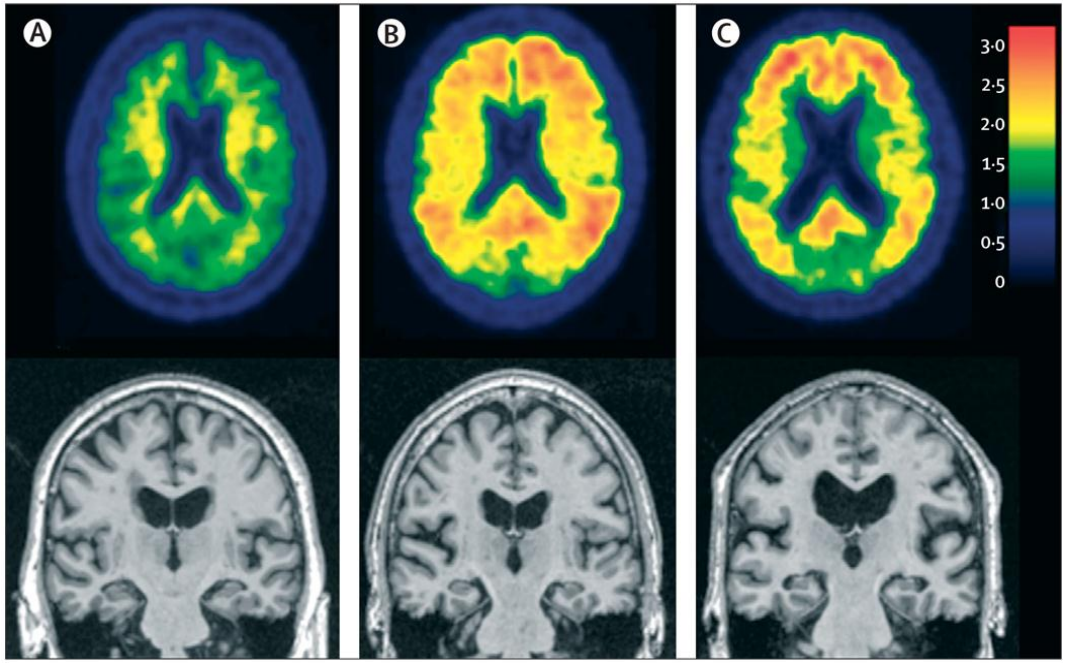
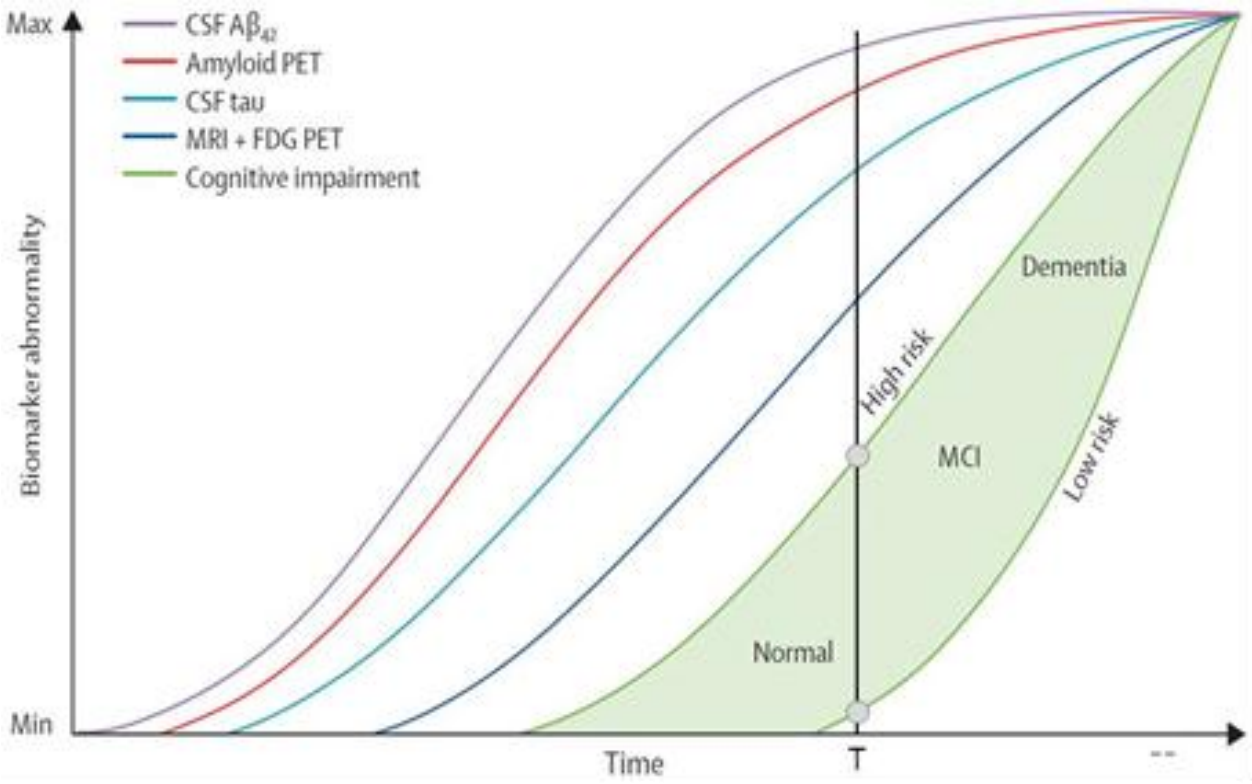


Illustration of biomarker staging of Alzheimer's disease Three elderly individuals are placed in order from left to right by use of our proposed biomarker staging scheme. (A) A cognitively normal individual with no evidence of Aβ on PET amyloid imaging with PiB and no evidence of atrophy on MRI. (B) A cognitively normal individual who has no evidence of neurodegenerative atrophy on MRI, but has significant Aβ deposition on PET amyloid imaging. (B) An individual who has dementia and a clinical diagnosis of Alzheimer's disease, a positive PET amyloid imaging study, and neurodegenerative atrophy on MRI. Aβ=β-amyloid. PiB=Pittsburgh compound B.

Biomarkers are variables (physiological, biochemical, anatomical) that can be measured ***in vivo*** and that indicate specific features of disease-related pathological changes.

Lancet Neurol. Jan 2010; 9(1): 119. Clifford R J et al

Model of dynamic biomarkers of the AD associated pathological changes (after Jack et al. 2013)



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Diagnosis: from a clinical to a biological entity

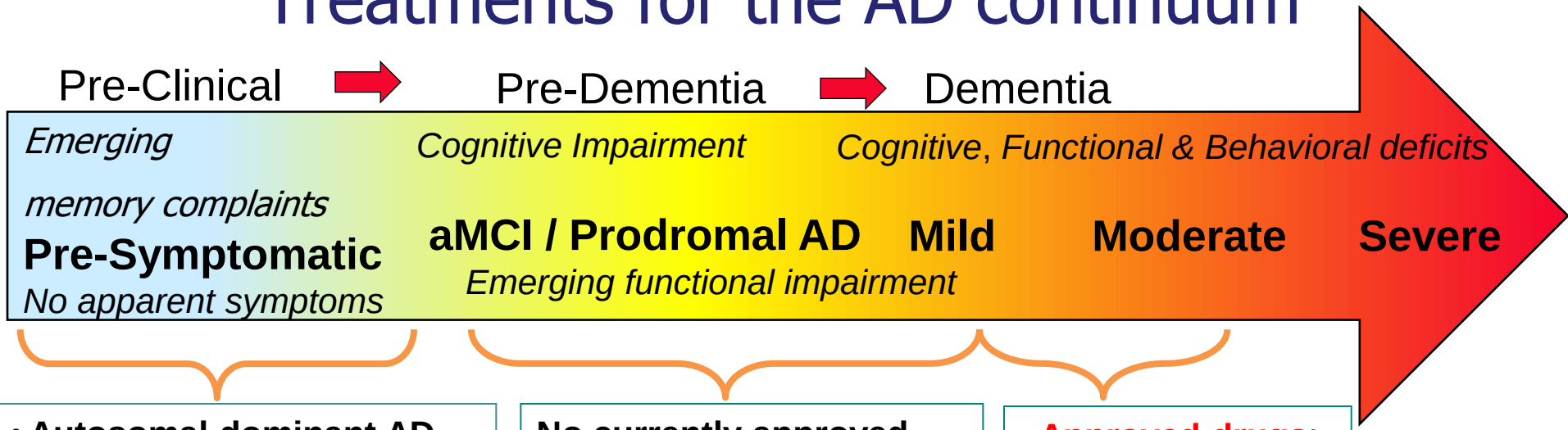
AD is a continuum with pathological processes beginning years before the onset of symptoms and a spectrum of phenomenology

- AD can be diagnosed *in vivo* with different degrees of certainty depending on the disease stage. When shall we start treatment?
- Criteria to diagnose prodromal stages (Prodromal AD or MCI due to AD or Minor Neurocognitive Impairment) are not harmonized. Do IWG, NIA-AA, DSM5 criteria select different study populations?
- Preclinical (sporadic) AD diagnosis only relies on the presence of biomarkers which are not validated for this purpose. Do these patients exist?

Regulatory validation of role of biomarkers

- Target engagement
- Proof of mechanism
- Proof of concept
- Enrichment
- Diagnosis (supportive or mandatory)
- Outcome (supportive)
- Outcome (disease modification)

Treatments for the AD continuum



- **Autosomal dominant AD**, DIAN, DIAN-2 Study,
- **Preclinical AD**: A4 Study

No currently approved drug. In development for disease modification:

- Monoclonal antibodies
- γ secretase inhibitors
- BACE 1 inhibitors

- **Approved drugs**: Donepezil, Rivastigmine, Galantamine

- **Approved drugs**: Memantine

- **In development for adjunctive therapy**:
- α7 nicotinic agonists, 5-HT-6 antagonist

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Why do development programs fail?

Mechanism of action	Drug name	Clinical phase	Key results from each trial	Current status (August 2014)	Reference
Active immunisation with Aβ	AN1792	2	Plaque Cleared. NFT reduced in neuronal processes, but not cell bodies. Very few antibody responders (25/239). Reports of encephalitis.	Discontinued	[49,50]
	CAD106	2	Favourable safety profile. Prolonged antibody titre in responders.	Ongoing	[51]
	ACC001	2	Co-administration of adjuvant required for strong antibody response. Generally safe and well-tolerated, no adverse related event.	Discontinued	[52]
	AD02	2	Favourable safety and tolerability profile. Did not reach primary or secondary outcome measures in phase 2.	Ongoing	[53]
Passive immunization against Aβ	Solanezumab	3	Worsening cognition compared to placebo, multiple adverse events.	Terminated	[54]
	Bapinezmab	3	Engaged target. Reduction in cerebrospinal fluid phospho-tau in APOE4 carriers. Decreased rate of amyloid accumulation in APOE4 carriers. No improvement in clinical outcomes in carrier or non-carriers of APOE4. Negative amyloid scans in 36% of non-carriers.	Discontinued	[55]
	Gantenerumab	2/3	Safe and well-tolerated at phase 1. Focal inflammation in areas with amyloid reduction a concern. Amyloid reductions compared to placebo.	Recruiting for Phase 3 DIAN trial	[56]
	Crenezumab	2	Did not meet co-primary endpoints. Trend of improved cognition in people with mild disease.	Ongoing	[57]
	Ponezumab	2	Safe and well-tolerated at phase 1. Plasma Aβ40 increased at phase 2. No effect on primary endpoints in phase 2.	Recruiting for further Phase 2 trials	[58]
γ-Secretase inhibitors	Avagacestat	2	Gastrointestinal and dermatological side effects at Phase 1. Also dose-dependent pharmacodynamic effects on CSF biomarkers in some patients. Trend towards worsening cognition at higher doses compared to placebo. Amyloid related imaging abnormalities.	Discontinued	[59]
	Semagacestat	3	Dose-dependent reduction in Aβ synthesis at Phase 1. Reduced plasma Aβ at Phase 2, but no differences in cognition. No improvement in cognition and worsening cognition at higher doses compared to controls at Phase 3.	Discontinued	[60]
γ-Secretase modulators	CHF5074	2	Anti-inflammatory at Phase 2. Trend towards improved function in APOE4 carriers.	Ongoing	[61]
	EVP-0962	2	Does not inhibit cleavage of γ-secretase substrates other than APP.	Ongoing	[62]
	Tarenflurbil	3	Small functional benefit at higher doses in mild AD but no cognitive benefit at Phase 2. No changes in CSF Aβ42. Failed to meet primary and secondary endpoints at phase 3.	Discontinued	[63]
β-Secretase modulators	MK-8931	3	Reduced CSF Aβ compared to controls. Safe and tolerable at Phase 2.	Recruiting for Phase 3	[64]
	CTS-21166	1	Dose dependent reduction in plasma Aβ.	Completed	[65]

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Adapted: GP Morris et al. Acta Neuropathologica Communications 2014, **2**:135

Scientific hypotheses: familiar and sporadic AD

- Familiar and sporadic AD share common symptomatology but different age of onset
- Familiar AD is hereditary and genetic mutations have been characterized
- The two diseases may have a completely different etiopathogenesis
- Many assumptions on the role of APP and amyloid proteins, derived by familiar form, need to be carefully considered in the contest of both diseases.

Extrapolation of scientific hypotheses from familiar to sporadic AD may be wrong!
(*e.g.* other neurologic disorders like ALS)

Scientific hypotheses:
Drug development of disease modifying agents

- Agents directly targeting Aβ by active and passive immunization
- Agents targeting inhibition or modulation of the γ-secretase APP cleaving enzyme
- Agents targeting the APP β-secretase cleavage enzyme BACE1

The supremacy of the amyloid hypothesis!

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Gary P Morris et al. Acta Neuropathologica Communications 2014, **2**:135

Preclinical models do not reflect human pathophysiology of AD

- Little evidence of APP overexpression in humans
- Additional biological mechanisms responsible for AD onset (inflammation, insulin resistance) are not modelled
- Behavioural experiments are often not run

Endpoints in Prodromal / MCI patients

- In the domain of functional activities some patients may present subtle symptoms at baseline also at prodromal stages
- Currently available instruments such as the ADAS-Cog have ceiling effects with MMSE scores around 24
- The CDR-SB could be a suitable candidate, however the rate of CDR-SB increase in prodromal patients is estimated to be 0.59 points per year (CI 95%: 0.53 to 0.44) (Monsell et al. 2012). This obliges to run long trials that recruit a large number of patients
- New tools development requires years for prospective validation in relevant clinical populations

Disease modification definition (2 steps)

1) Improvement in the rate of decline (cognition and function)

2) Evidence of biomarker change

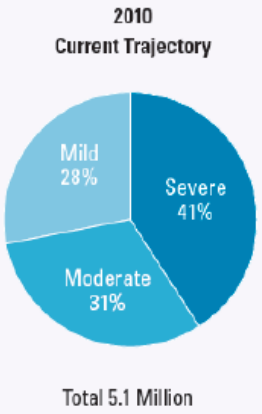
This definition relies on uncertain biological evidence. In other neurodegenerative disorders biological defects translate into heterogeneous clinical manifestation

How should biomarker data be interpreted?

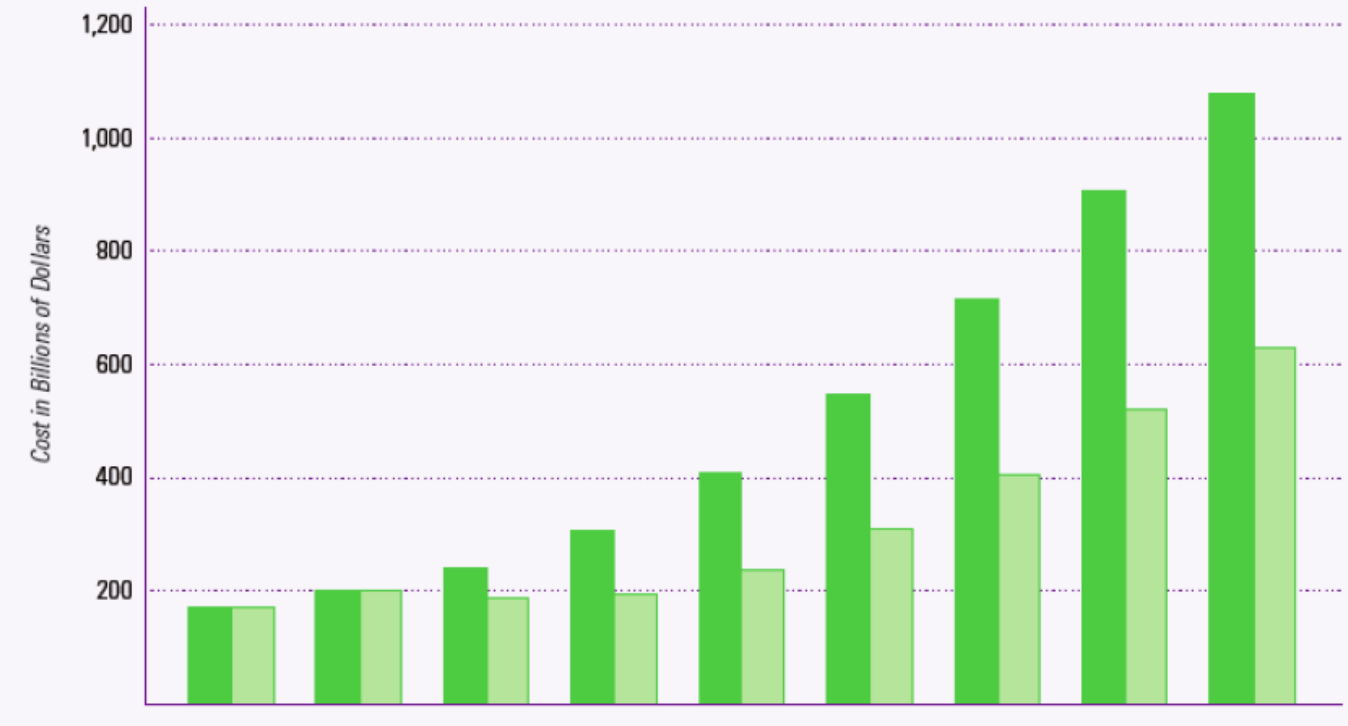
Clinical meaningful benefit is the ultimate goal of dementia therapy. If a clinical improvement is shown that changes or delays the course of the disease, a more comprehensive label such as delay in cognitive decline or disability could be granted

Alzheimer's Disease: challenging the progression

Proportion of America
Azheimer Disease by St



Impact of a 5-year delay on the onset by stage of disease, Americans aged 65 and older with AD, 2050



	2010	2015	2020	2025	2030	2035	2040	2045	2050
Current Trajectory	$172	$202	$240	$307	$408	$547	$717	$906	$1,078
Delayed Onset	$172	$202	$190	$196	$239	$311	$407	$522	$631
Reduced Cost	$0	$0	$50	$111	$170	$236	$310	$384	$447

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So @ regulatory level discussion is still open

- Common agreement as to what data can be extrapolated from current studies in familiar early onset AD is needed
- Longitudinal clinical validation of diagnostic criteria for prodromal AD
- Harmonization of endpoints for earlier stages
- Harmonization of basic requirements for clinical trials (type of analysis and length)
- Alternative labels such as delay in disability for effective products in absence of biomarker data

In Conclusion Challenges Ahead!

- Multi-stakeholder task
- Industry should share placebo data
- Private-public consortium (e.g. ADNI)
- Regulatory-academia dialogue

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Are We Ready?


Thank you