

DRUG DEVELOPMENT AND APPROVAL SESSION

Pharmaceutical Research & Development for Alzheimer's Disease

DIAD Family Conference:

Fairmont Royal York Hotel, Ballroom, Toronto, Canada

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Alzheimer's Disease – A Health Crisis

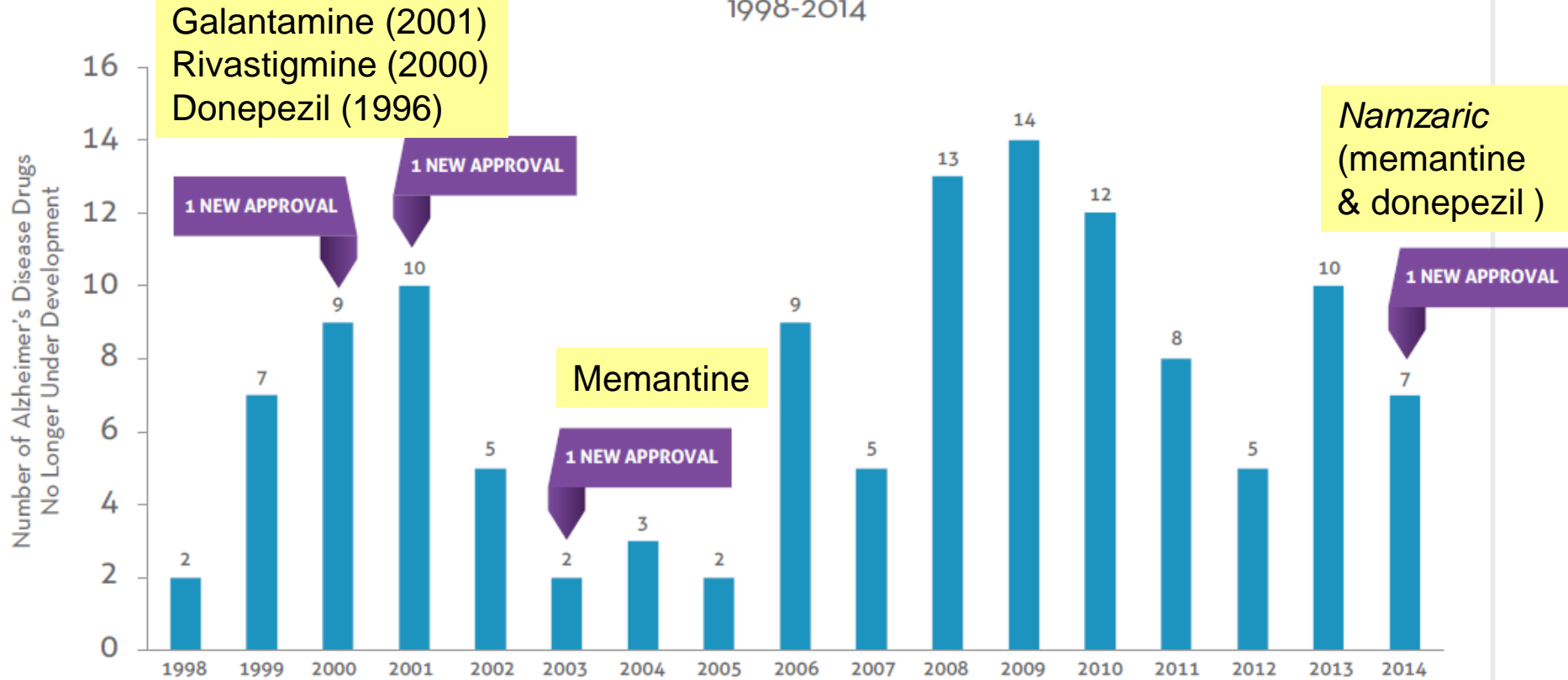
- **About 35 million people living with dementia in the world; the majority with Alzheimer's disease**
 - > 5 million people with Alzheimer's disease in the USA
- **Alzheimer's disease is growing rapidly**
 - Major patient, caregiver and health care burden
- **We need better treatments**
 - Current medicines provide modest symptomatic improvement
 - There are no “disease modifying therapies” available

Alzheimer's Medicines – Many Attempts, Few Successes so Far....

4 Approved Medicines

123 Unsuccessful Drug Programs for Alzheimer's

Unsuccessful Investigational Drugs for Alzheimer's Disease
1998-2014



Source: PhRMA analysis of Adis R&D Insight Database, 17 June 2015.

Finding a New Drug is Complex & Risky

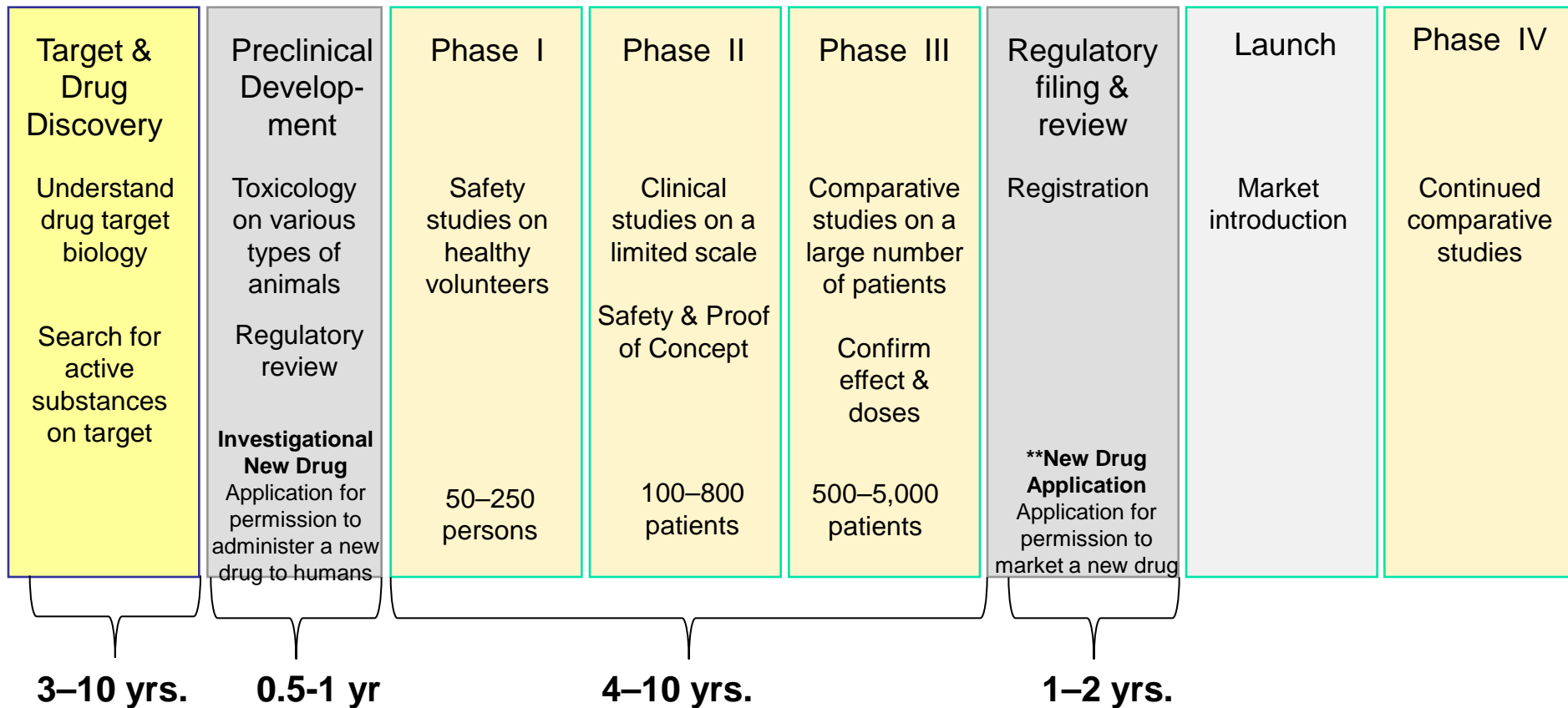
- **On average 12 % of drug molecules entering clinical studies reach the market**
 - Many more do not even make it past preclinical studies
- **On average > 10 years for one medicine to make it through the R&D process**
- **Average costs \$2.6 billion / developed medicine**
- **Failure is an inherent part of drug R&D**
 - As science grows, so does the complexity of developing new medicines

Drug Research & Development Process

Preclinical studies

Clinical studies

Commercialization



At least 15 years from idea to marketable drug

Understanding & Studying Alzheimer's Disease

Alois Alzheimer
1864 -1915

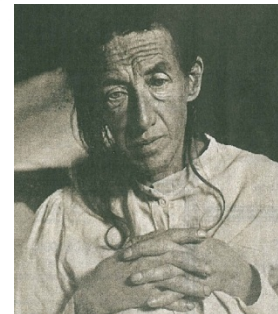


Progressive deficits in cognition (memory), activities of daily living with behavioral changes

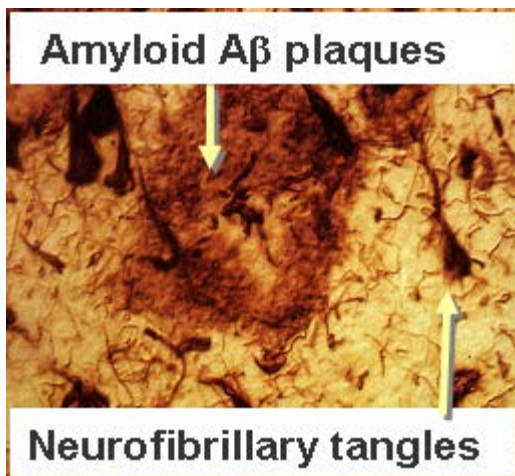
- Extracellular amyloid plaques
- Intracellular neurofibrillary tangles
- Neurodegeneration
- Neuroinflammation

- **Decreased brain metabolism**
- **Brain atrophy**

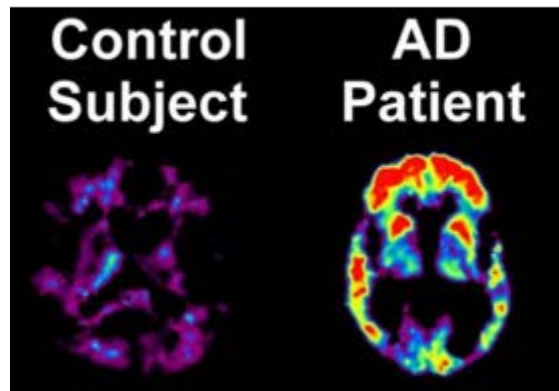
“Biomarkers”



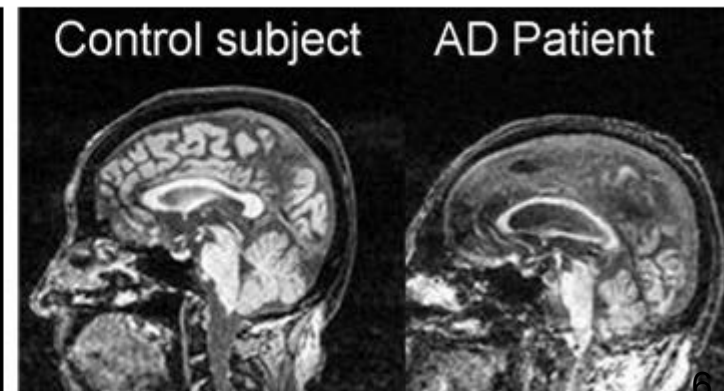
Auguste Deter
1850 –1906
(Mutation in the PSEN1 gene)



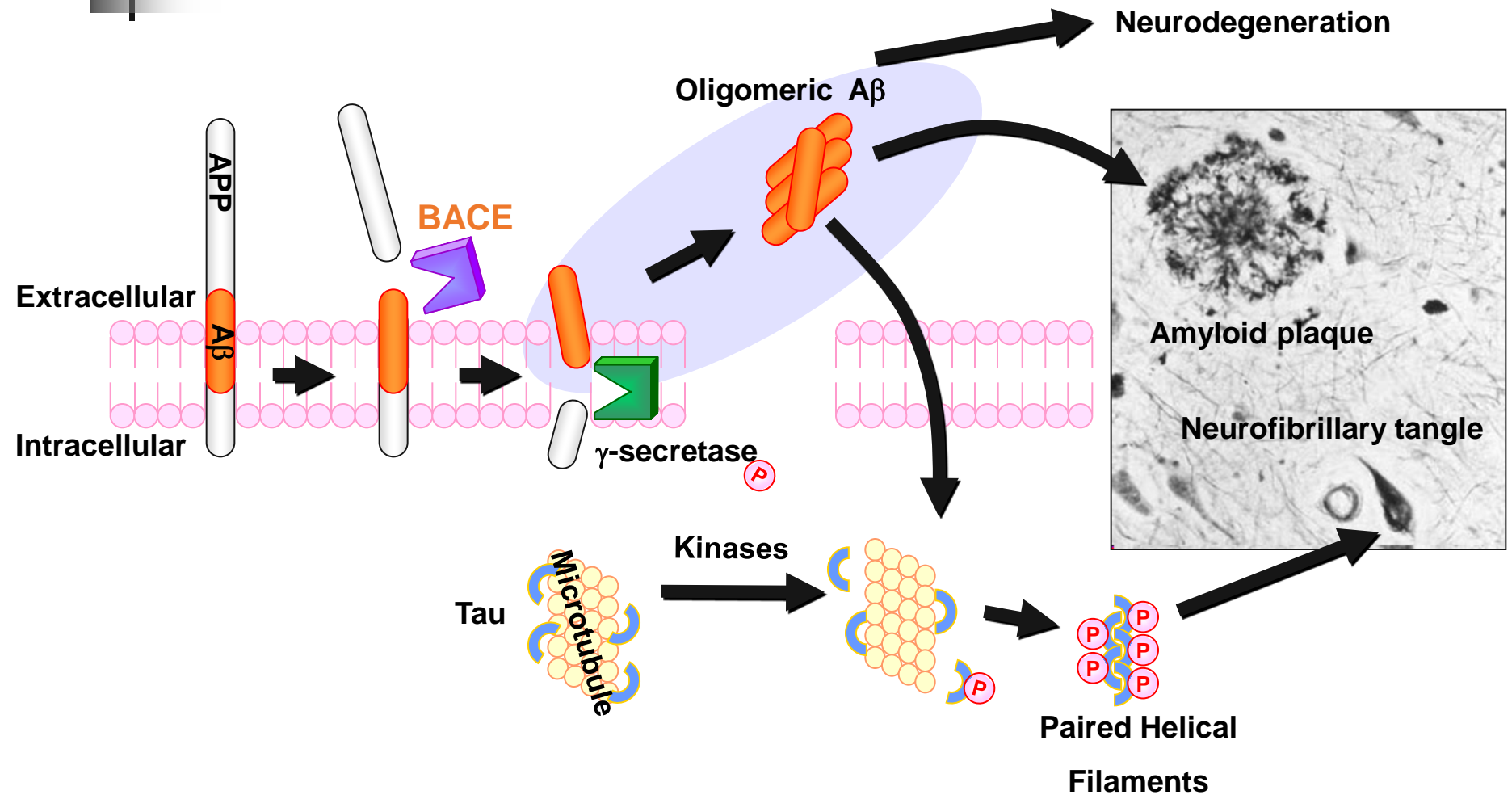
Amyloid PET Imaging



Volumetric MRI

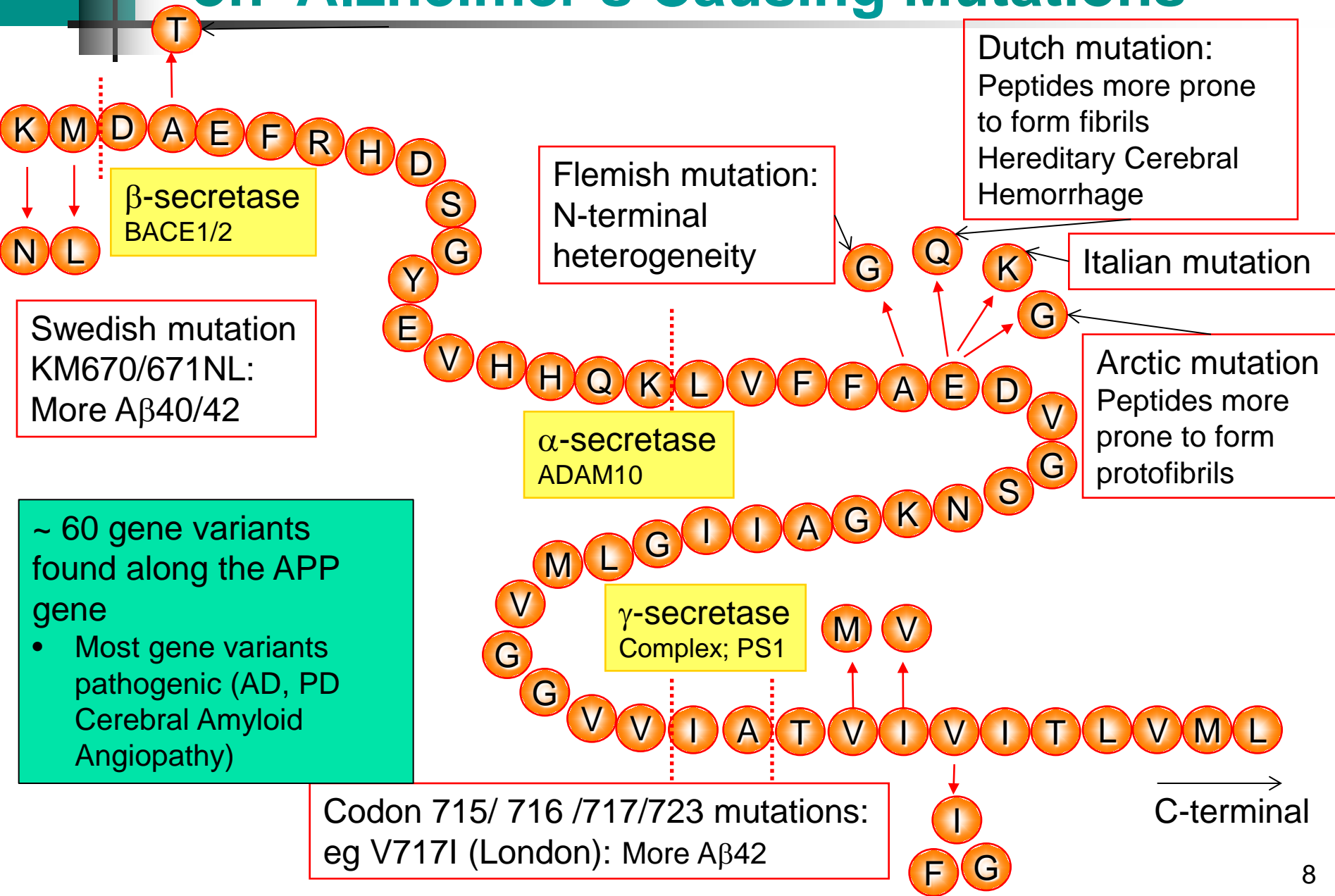


Unraveling Very Complex Biology

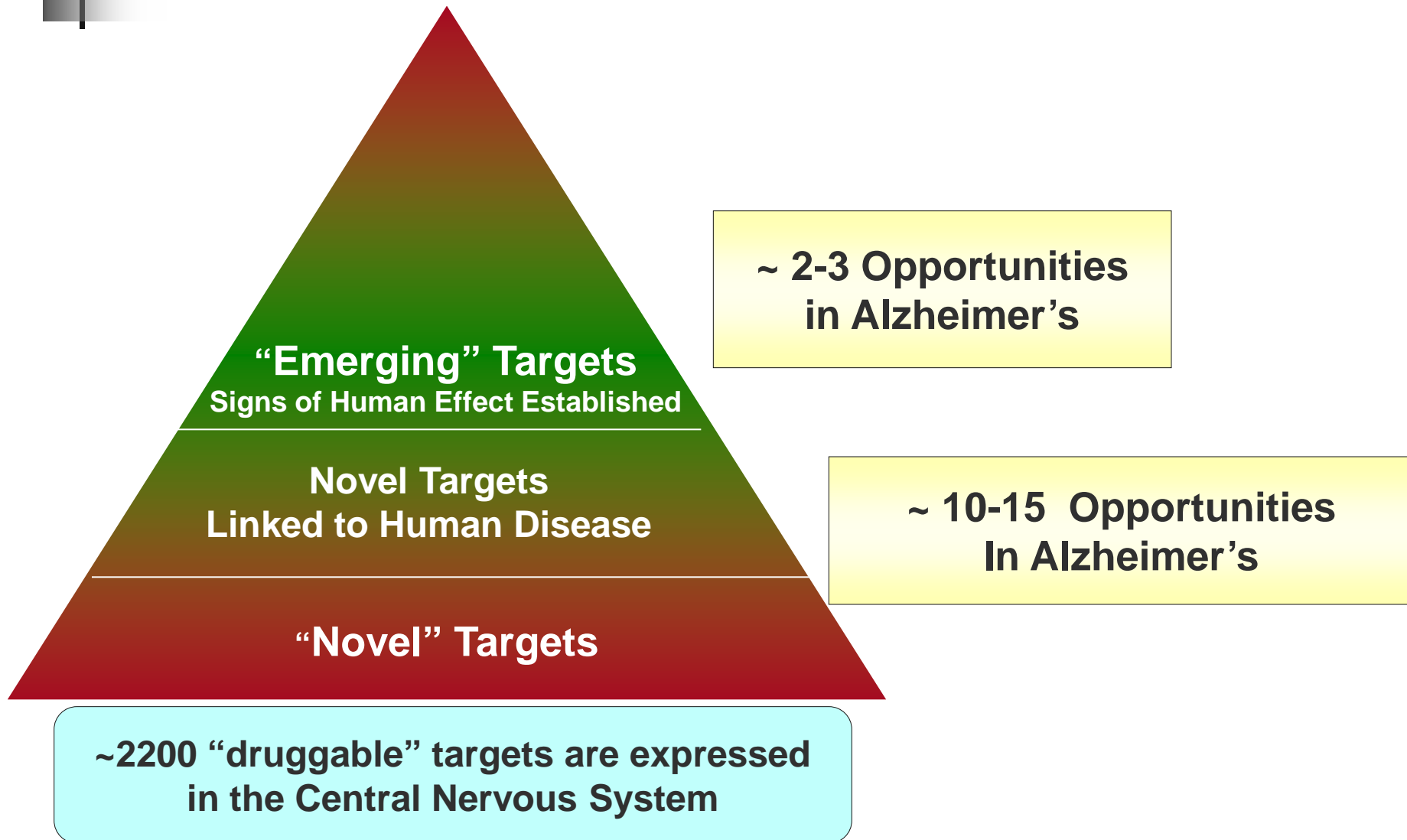


Many additional associated molecular processes
Fatty acid transporters & metabolism – e.g. ApoE
Immunological reactions & Inflammation

Critical Understanding Through Studies on Alzheimer's Causing Mutations

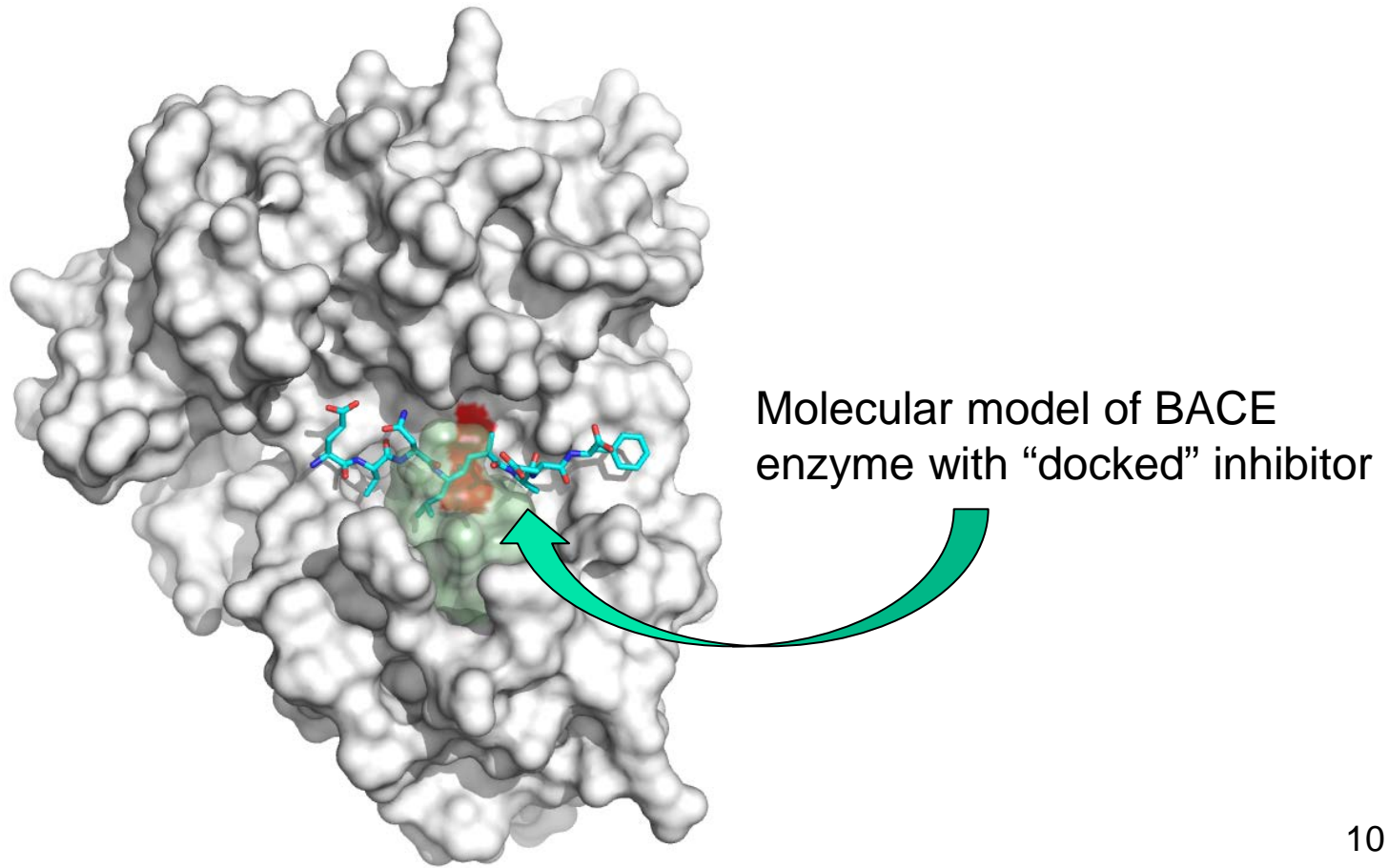


Drugs Work on Biological "Targets"

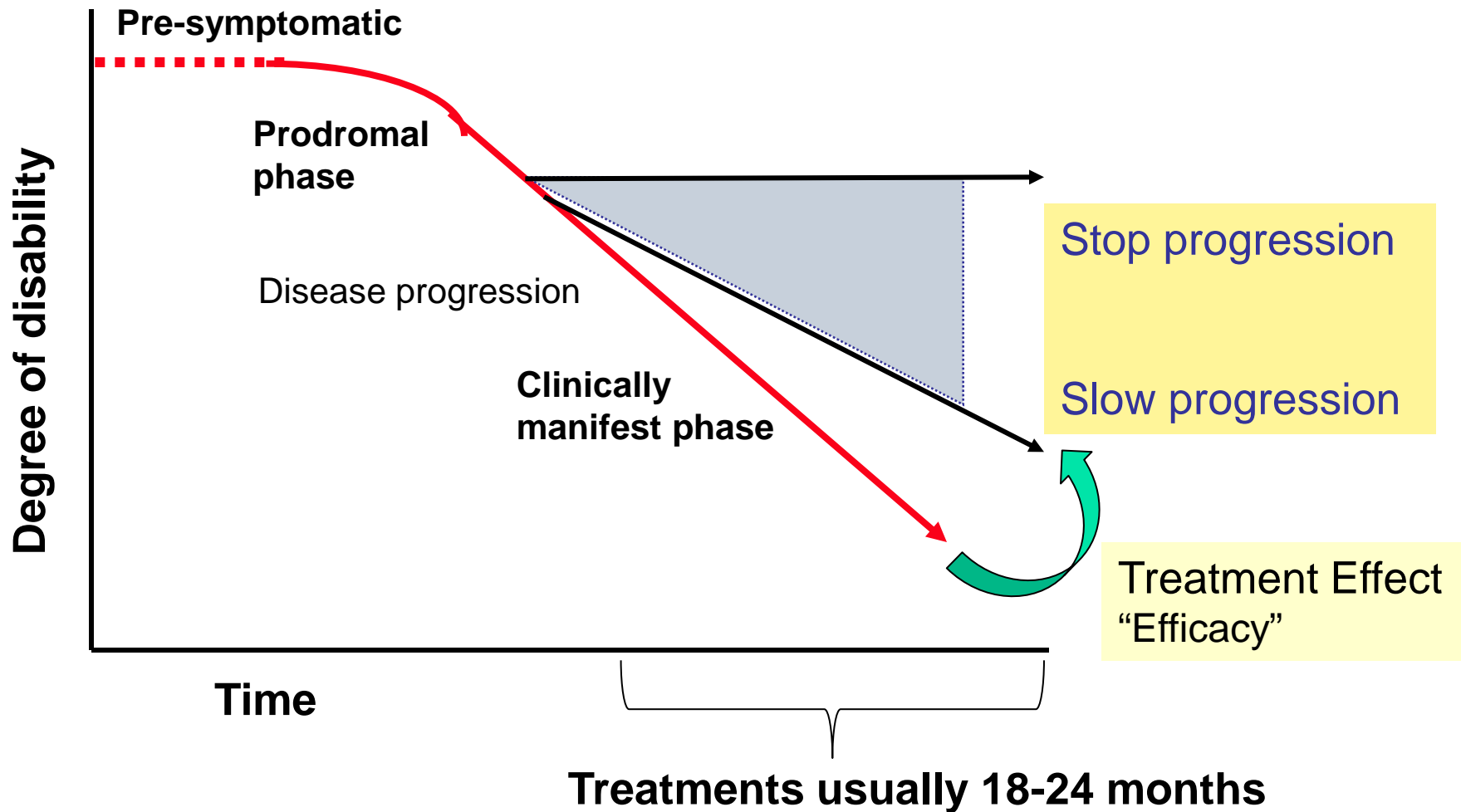


Finding Inhibitors of the BACE Enzyme Was a Major Industry Effort

- Difficult brain target for a small molecule inhibitors
 - Membrane bound intracellular protease
 - Requires potent enzyme inhibition plus brain “penetration”



How to Evaluate “Disease Modification” in Alzheimer’s



Challenges With Alzheimer's Drug Development

- **Only possible to determine that drug works late in the development process**
- **Effects measured on “rating scales”**
- **Very long trials**
- **Very expensive trials**
- **Very complex infrastructure for AD trials**
- **Very difficult getting patients to the trials**
- **Very difficult getting the “right” patients to the trials**

Alzheimer's Disease is a Continuum

Pre-Dementia → Dementia

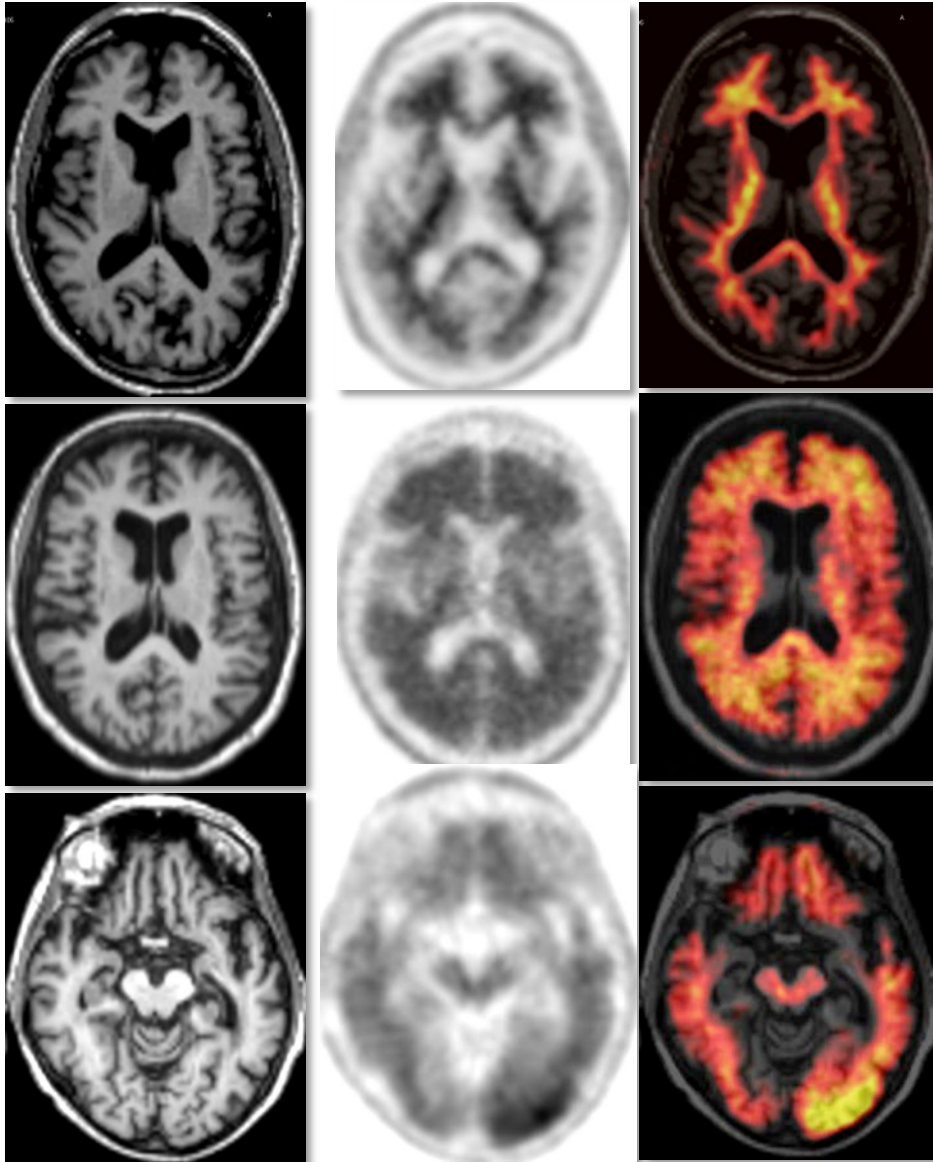
Memory complaints → *Cognitive Impairment* → *Cognitive, Functional & Behavioral deficits*
Pre-Symptomatic **MCI / Prodromal AD** **Mild** **Moderate** **Severe**
No apparent symptoms *Symptoms* *Current diagnosis & treatment*

- Risk factors; family history, old age, ApoE4 genotype, TBI, mutations
- No symptoms, or subtle cognitive deficits (memory complaints)
- **Emerging biomarker evidence of AD pathology**

- Mild cognitive impairment (MCI)
- Amnesic Mild Cognitive Impairment (aMCI) - episodic memory deficits
- aMCI combined with **biomarker evidence of AD pathology** = Prodromal AD

- AD diagnosis based on clinical symptoms; cognitive deficits & dementia of the AD type
- **Biomarker evidence of AD pathology may increase specificity of diagnosis**

Amyloid PET For Amyloid Detection

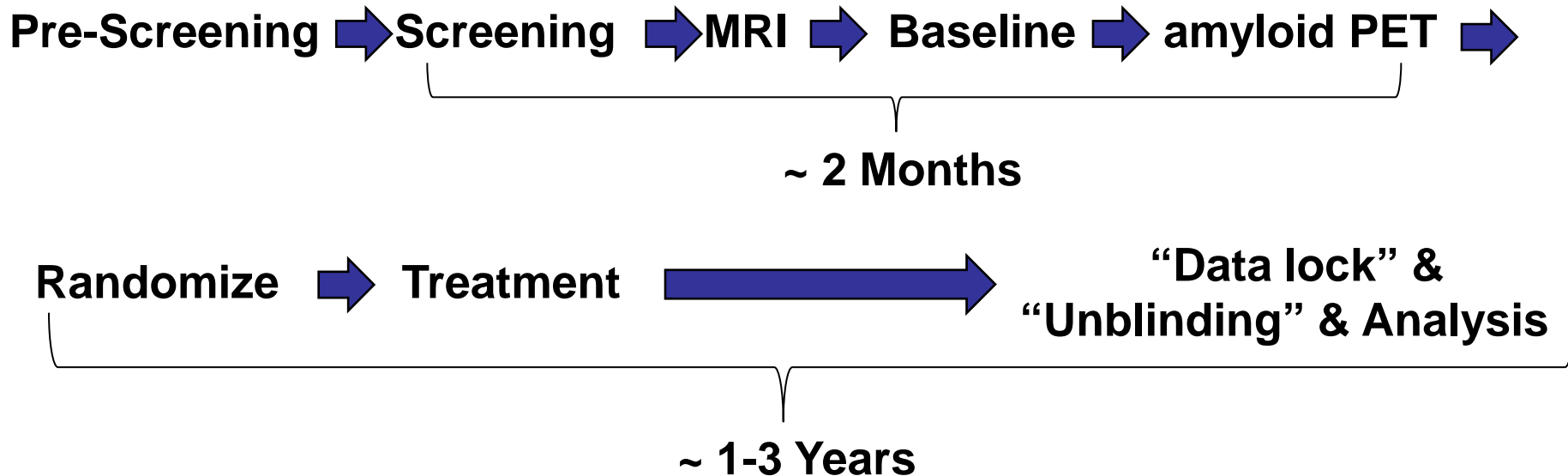


Amyloid Negative Example

**Amyloid Positive Example:
Diffuse**

**Amyloid Positive Example:
Diffuse + Focal**

A Typical Alzheimer's Drug Trial

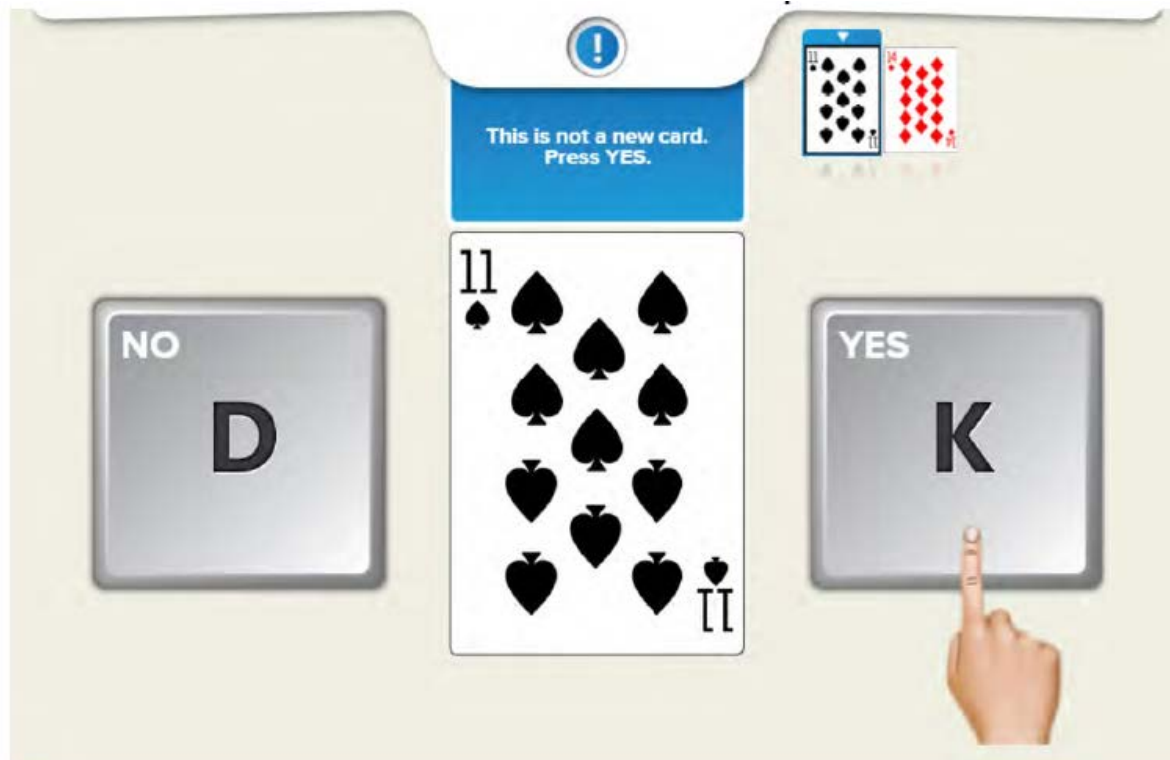


**< 75% subjects screen fail on inclusion criteria
(35-50% fail on amyloid PET)**

20-30% “drop out” during the treatment period

Web-Based Tools for Patient Enrollment Online Cognitive Assessment

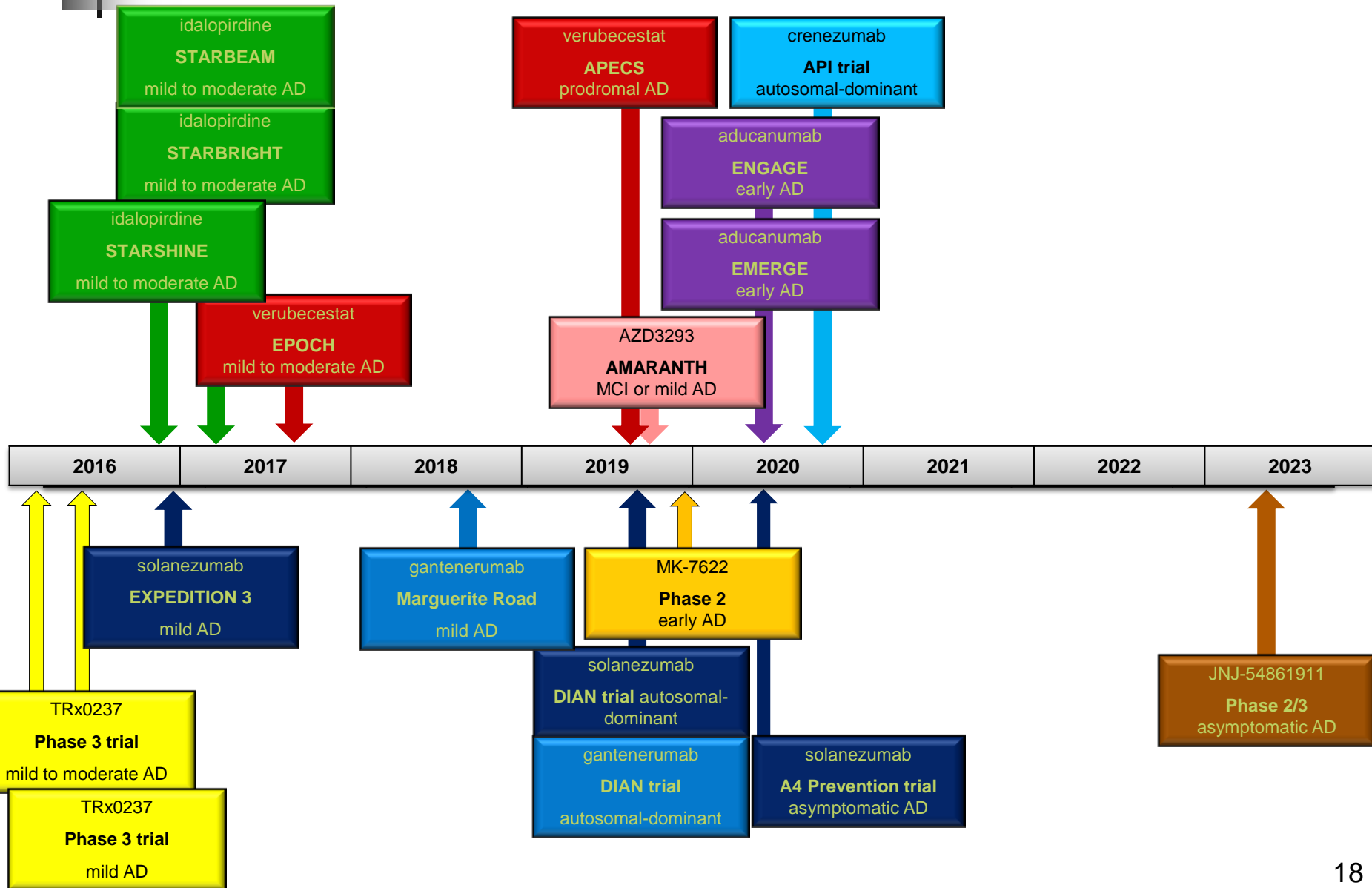
Self-assessments using a web-based online computer based cognitive test



What Do We Do to Further Improve?

- **More research – basic & clinical**
- **Developing even better diagnostics**
 - **Earlier detection**
 - **More precise definition of patients**
- **Evaluating further medicines hypotheses**
 - **Better symptomatic management (cognition and beyond)**
 - **Disease modification – delaying disease progression**
 - ***Disease prevention***

Many Ongoing Drug Trials.....



Broad Spectrum of Public Private Partnerships in Dementia R&D

Disease Understanding

Targets

New Medicines

Translational Tools & Clinical Trials

Real World Evidence

Regulators & Payers



Declaration of Conflict of Interest

I am a full time employee Eisai Inc.



I own shares in AstraZeneca and Merck Inc.

Declaration of Personal Interest



These young women had a:

- **Great-grandmother with Alzheimer's**
 - **Great-grandmother's sister with Alzheimer's**
 - **Paternal grandmother with Alzheimer's**
 - **Paternal grandmother's sister with Alzheimer's**
- and**
- **Maternal grandmother has currently MCI**

Most Critical Factor for the Alzheimer's Medicine Efforts

- **Patient & caregiver engagement to participate in trials**
 - Increased interest to enter trials
 - Increased willingness to remain in trials