

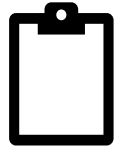
## *ALZHEIMER'S DISEASE- UPDATED INFO SHOT*

*A story of setback or success*

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**Ingenious e-Brain**

Nurturing Innovations - Fostering Business



The present paper highlight the status around **Alzheimer's**, it's advanced clinical development, available treatment, economic burden and the major challenges being faced in the **Alzheimer's**.

**The Dementia-** A loss or decline in memory and other cognitive abilities.



*"Imagine an age of 65+, already lived more than half of life and then started to forget the beautiful moments of life, it's hard to believe but one of the disease do so, and surprisingly is more responsive in case of resistance than therapy, the reason behind this is memory ignorance, called dementia".*



Alzheimer's Disease runs parallel with dementia and has a big impact on both patient & society. Dementia term is used in daily life with different intensity, it could be mild (forgotten any task) to moderate (problem in remembering events, performing daily tasks) and to severe (appearance of depression or anxiety, guidance in eating foods or wearing clothes) but when this common factor badly affects the daily life of person, it could be signs of irreversible, progressive brain disorder called Alzheimer's which according to CDC is responsible for 60% to 80% of dementia cases.



According to Alz.org, there is a 123% increase in deaths due to Alzheimer's. This death is more than combined death caused due to prostate and breast cancer. This alarm doesn't stop here, in US 1@every 65 sec is developing Alzheimer's and is estimated to reach 14 Mn by 2050.



Alzheimer's rank 6th when we talk about the cause of death, according to WHO 2016, Alzheimer's rank higher compared to the progressive development made in cancer, however in middle-upper countries it has been rank after lung cancer but again in high-income countries it has been rank above lung cancers and after heart diseases.

## Funding & need of newer or modified targets have appeared as unmet area in Alzheimer's



Aging itself comes with lots of physical and immunity-related changes & complications, this is where Alzheimer's mostly talked, it will be not wrong if age highlighted and considered as a promoter of Alzheimer's, with growing age Alzheimer's risk progresses, the most diagnosed age group is >65.



Early diagnosis can prevent Alzheimer's but proportional dementia is making it tough. The behavioral and psychological changes such as outdoor activities in nightwear, social behavior, repetitive behavior, etc. can give signs of dementia or can be correlated with Alzheimer's disease, however, this need confirmation & hence doctor visit is recommended.



We know more about Alzheimer's, but still quality treatment is lacking, biochemical targets such ACh, Glutamate & famous Tau-protein, etc. are targeted, but they seem to be more resisted than to be changed. Symptomatic targeted treatments & QoL are tried for years in addition to biochemical mediated targets, by various governments, organization, NGOs & Industry etc.



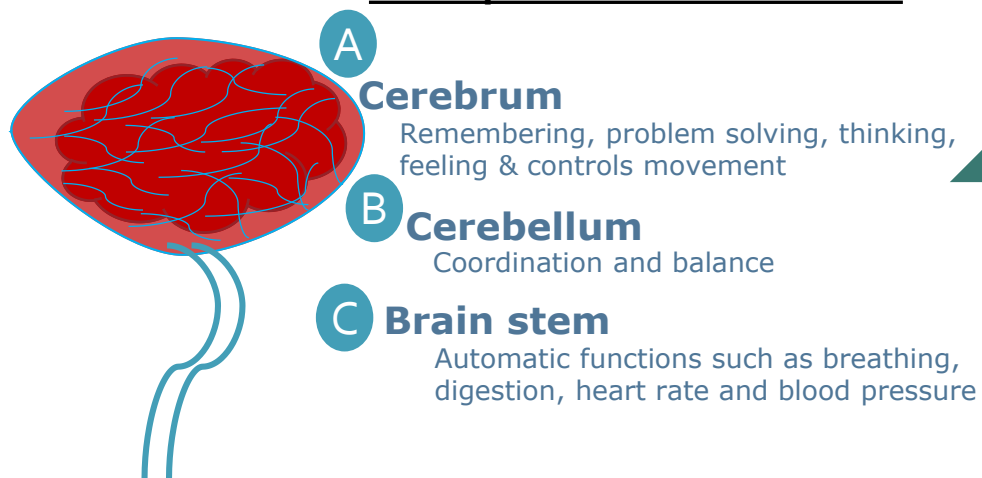
This is true that we deepen our understanding in Alzheimer's, but a promising cure is still under investigation, newer risk factors & causes are coming out, but the exact cause of Alzheimer's disease is still unknown.



Failure of clinical trials and exit of many industries from Alzheimer's are making the disease worse while prevalence pool keeps growing, it is estimated that there will be 82 million Alzheimer's patients by 2030 and will cost \$trillions as an economic burden. Various plans, initiatives have been taken by the governments and WHO to combat this mysterious disease. Science has a promising future and so is the treatment of **Alzheimer's**.

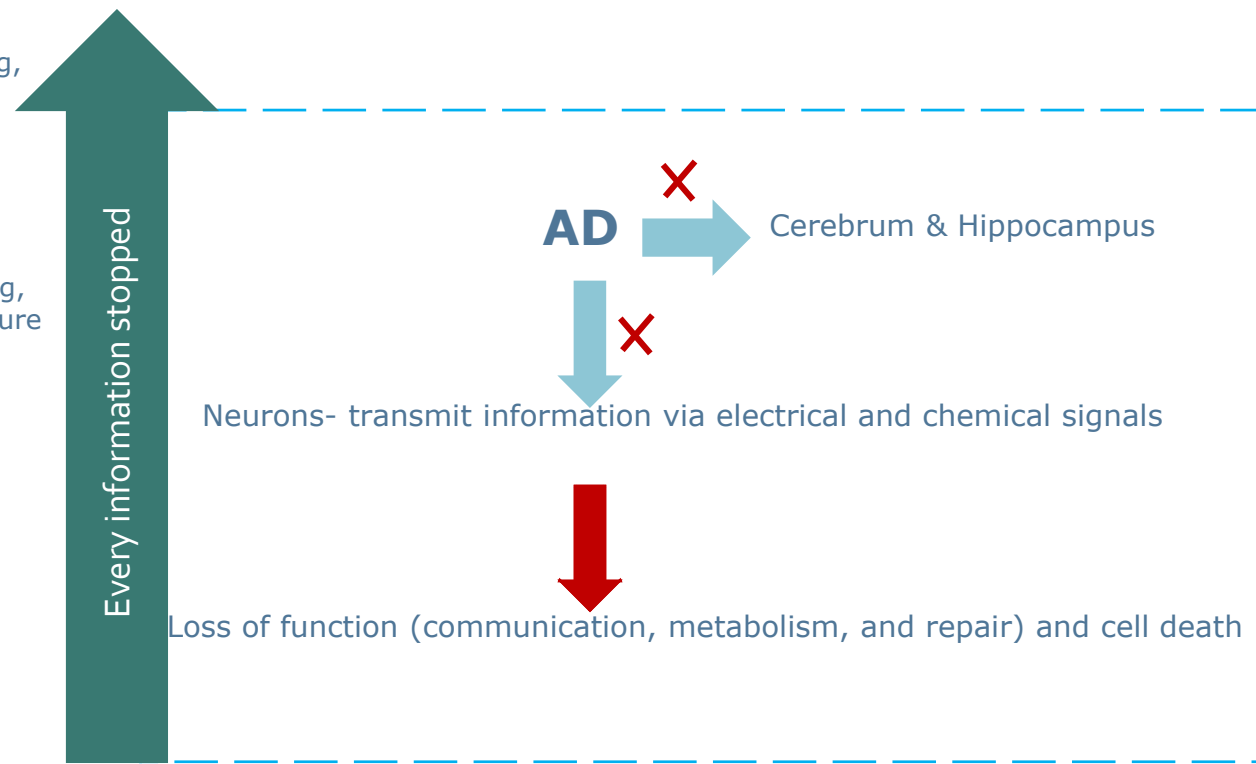
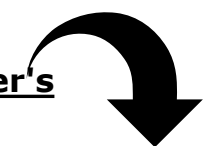
Brain functions are deeply affected due to Alzheimer's causing impairment in carrying out daily activities

**Who operate What functions?**



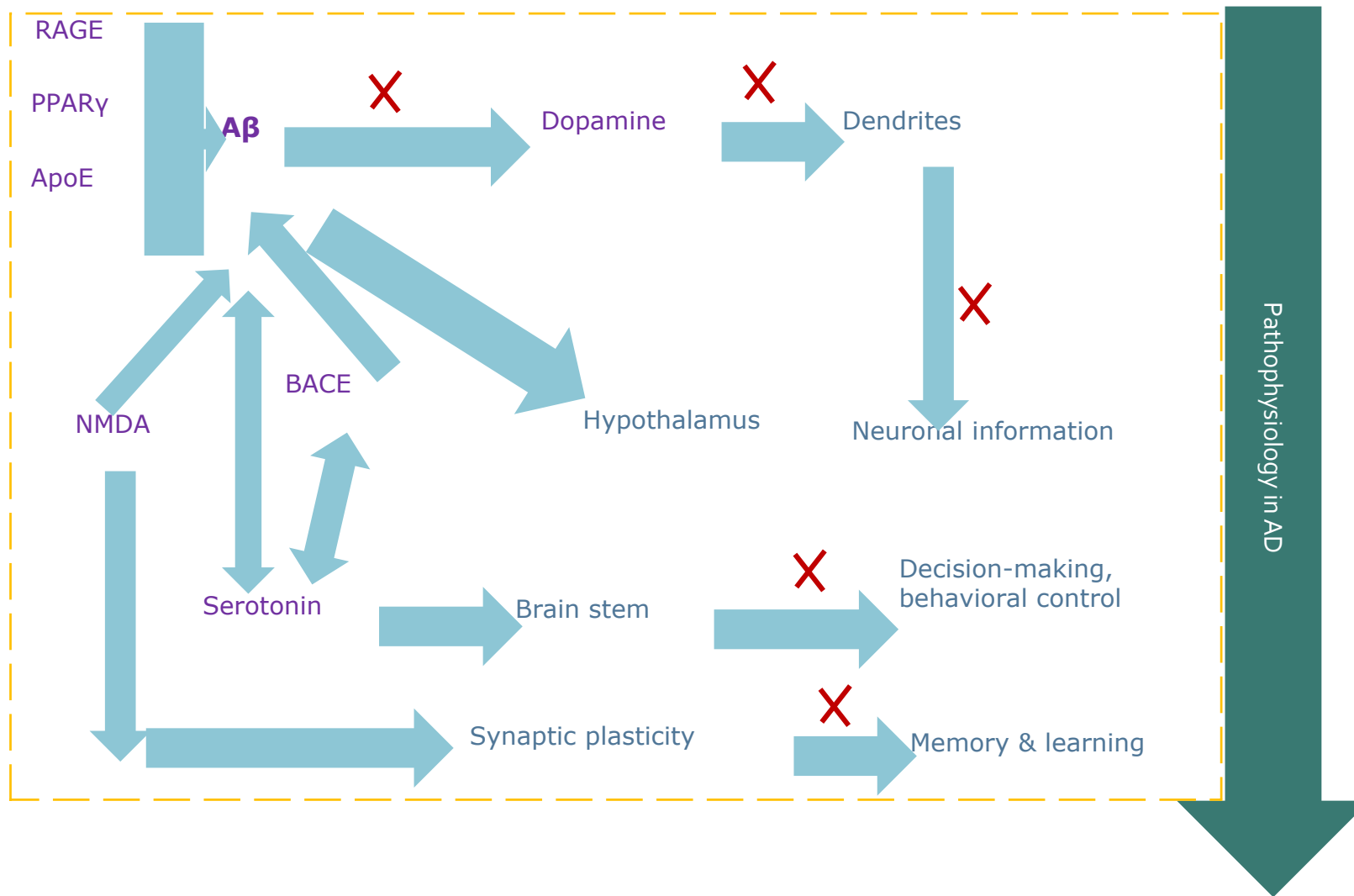
- 1 Hippocampus: Retrieval of memories
- 2 Amygdala: Emotional recall
- 3 Left hemisphere: Struggle to complete the sentence
- 4 Temporal lobe: Hard to recognize family and objects
- 5 Frontal lobe: Personality & behavior
- 6 Parietal lobe: Body sense
- 7 Occipital lobe: Shape, color, movement & dreams

**In Alzheimer's**



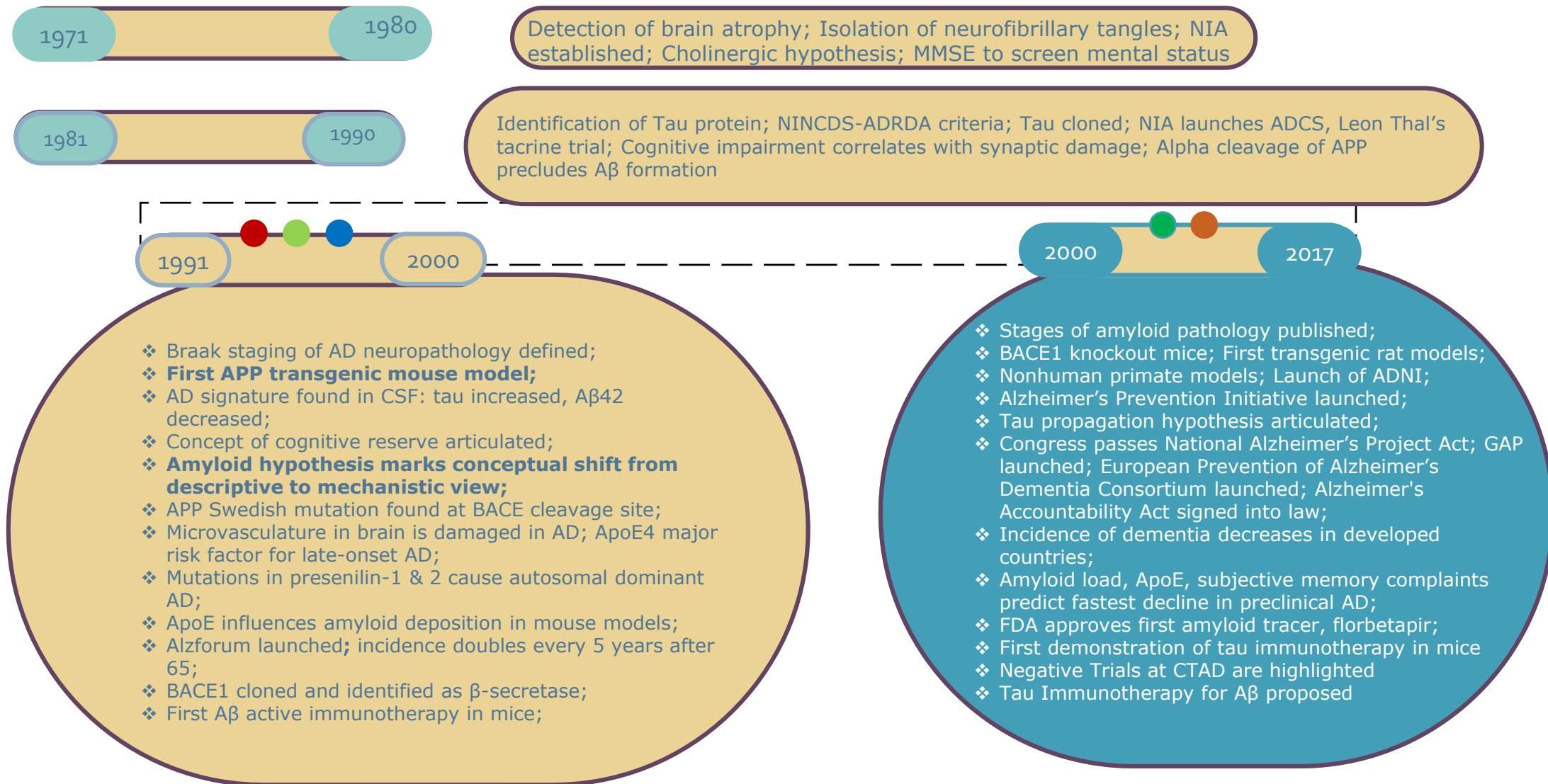
[ Impairment of brain areas and related functions ] X Negatively affected

Pathophysiology has not fully established in Alzheimer's and targets are still missing



Advance patho-physio-factors associated with Alzheimer Bio/chemical/targets  $\times$  Negatively affected

Advance research continued from 70's to 90's while extensive modern research & findings obtained from 90's onwards



● Galantamine 
 ● Memantine 
 ● Rivastigmine 
 ● Tacrine 
 ● Donepezil 
   Approval

Unlike other responded therapeutic area where diagnosis is established, Alzheimer's identity is still un-diagnosed

- Diagnosis**
- ❖ Medical history
  - ❖ Family history
  - ❖ Physical and neurological exam
  - ❖ Lab tests
  - ❖ Tests for psychological, functional, and cognitive status
  - ❖ MRI/PET/CT scan
  - ❖ CSF analysis

**As per NIA, Alzheimer in updated diagnostic guidelines**

Three stages

**Preclinical**

Brain changes, amyloid building and changes in nerve cells, conclusive clinical evidence need to be established

**Mild cognitive impairment (MCI)**

Memory or other thinking problems are highlighted where their symptoms are greater than normal for a person's age and education, MCI may or may not progress to Alzheimer's dementia.

**Alzheimer's dementia**

The final stage in which symptoms of Alzheimer's, such as memory loss, word-finding difficulties, and visual/spatial problems, are significant, their presence are enough to impair a person's ability to function independently.

**SEVERE**

- ❖ Always seeks attention in performing daily activities
- ❖ Severe memory impairment such as loss of recent incidents
- ❖ Impairment of physical performance & communications
- ❖ Raise in chances of getting pneumonia

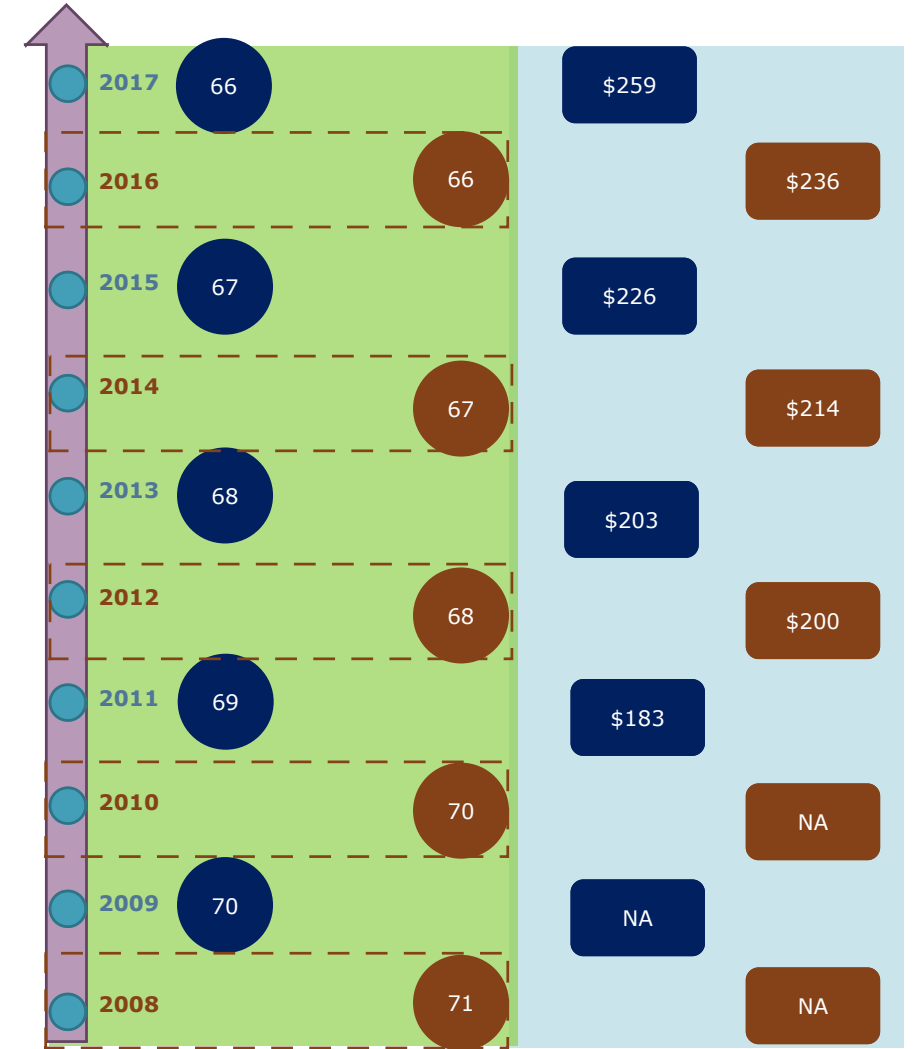
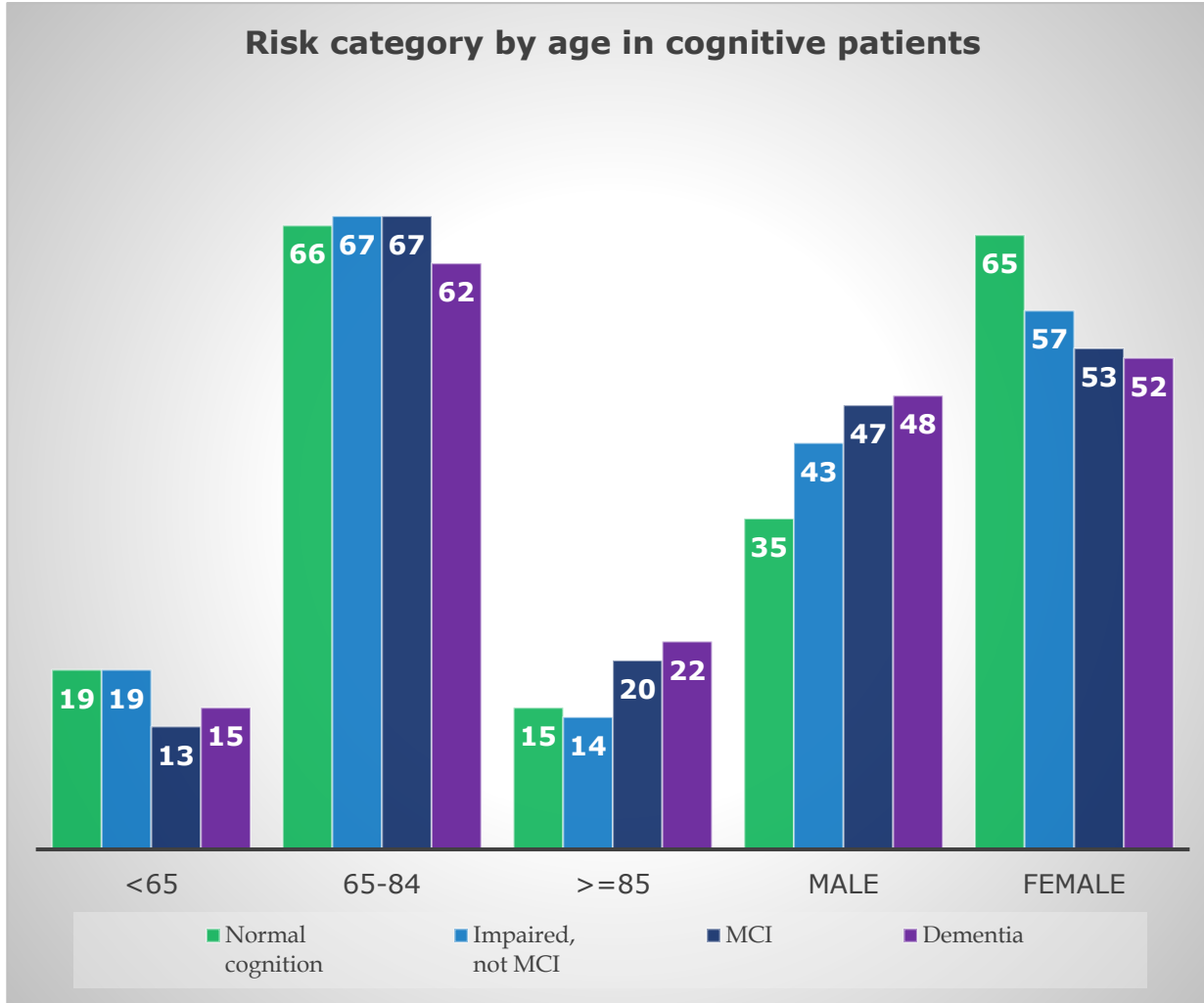
**MODERATE**

- ❖ Forgetting events or details about personal history
- ❖ Feeling moody or withdrawn, especially in pschyo-social conditions
- ❖ Trouble in recalling their own address
- ❖ Disturbances in sleeping patterns
- ❖ Personality and behavioral changes such as repetitive behavior

**MILD**

- ❖ Trouble in remembering names
- ❖ Trouble while meeting to new people
- ❖ Forgetting just recent read materials
- ❖ Work tasks performance becoming poor
- ❖ Management failure associated with planning or organizing

*With no promising therapy, Alzheimer's cases are increasing; ages are making worse, economic costs keep increasing by year*  
**Burden & Risk Categories (1)**



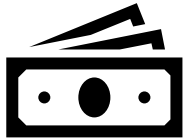
Developing AD in US (every seconds)    AD economic costs (in billions)



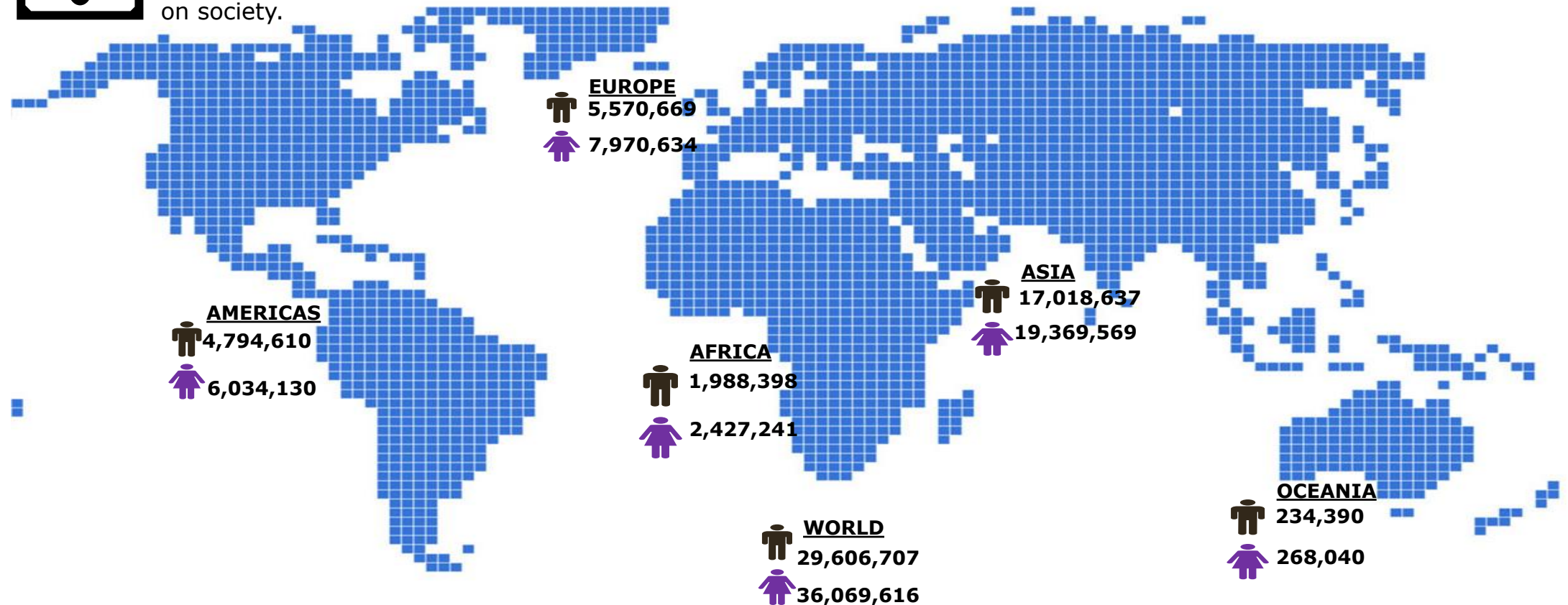
>65 age are most sensitive age group with Alzheimer's, low-middle-high income geographies, all are being affected by Alzheimer's

## Burden & Risk Categories (2)

Considering 65+ as sensitive age group of Alzheimer's Disease, by 2017, a rough yet descriptive age numbers across geographies define the big numbers, probably this is why world is trying best to get rid of this mysterious & unidentified disease.



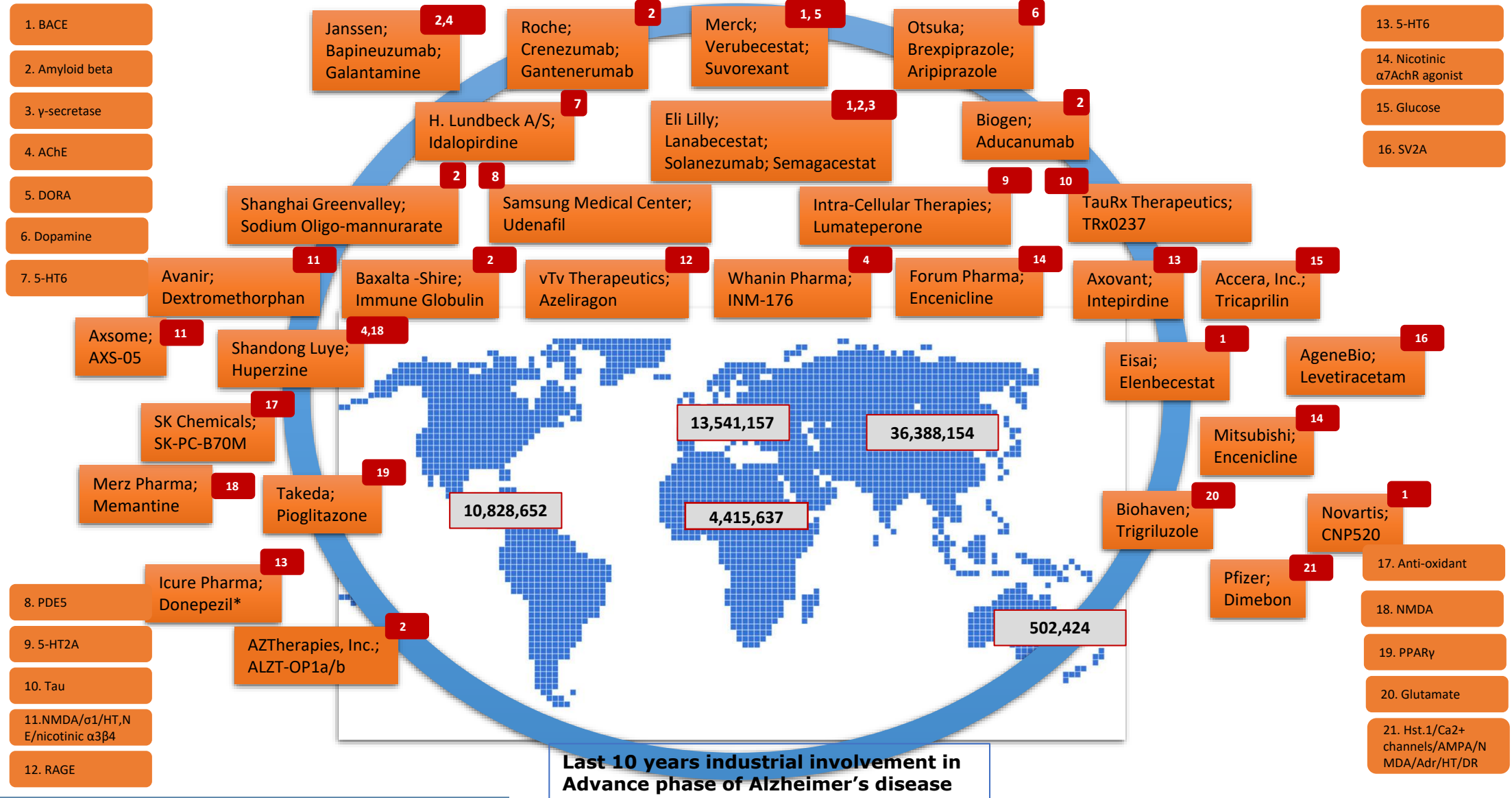
In US & as per CDC/Alz.org PR, in 2015, worldwide annual cost exceed \$818 bn, Medicare and Medicaid pay nearly 70% of applicable cost related with Alzheimer's; it is expected by 2050 annual costs can cross >\$1.1 trillion, with >400% increase in annual costs to Medicare while >350% increase on out of pocket costs, Alzheimer's is a huge burden on society.



(65+ age group, using UN Population database and applying age range & Alzheimer occurrence as only filter criteria, these numbers could be different depending on the nature of epidem model used and applied cut off criteria; by 2017)

The total possible Alzheimer's population is high, conclusive novel targets still missing in advanced industrial clinical trials

## Quest in clinical trials - Industry

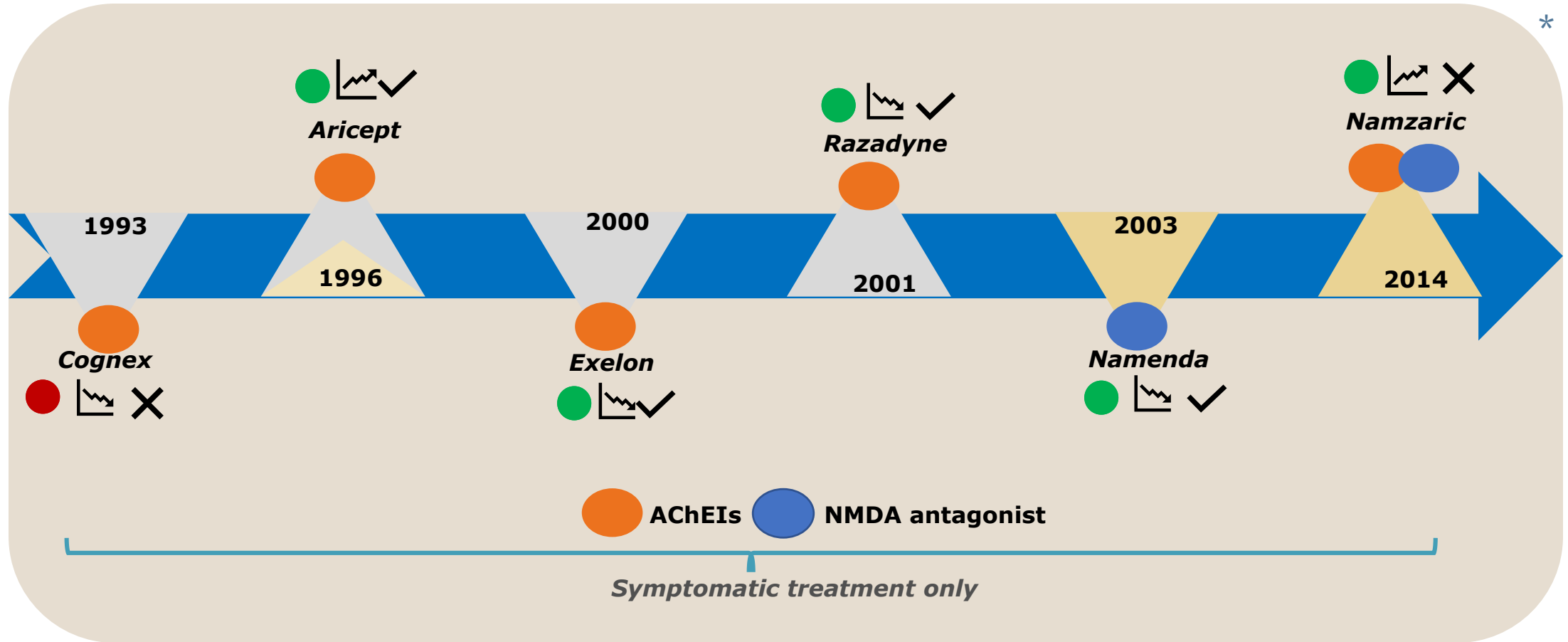


The total possible Alzheimer's population is high, conclusive novel targets still missing in advanced academic clinical trials

## Quest in clinical trials - Academic



Approvals are still around Anti-cholinesterases & NMDA, the approval timeline explains difficulties in around Alzheimer's treatment.



Toxicities

- High
- Low-Medium

Prescription intensity

- High
- Low-Medium

Generics availability

- Yes
- No

Disease stage

- Mild-Moderate
- Moderate-Severe

*Need of surrogate end points, genetic & biomarkers detailing, patient recruitment in clinical trials & early diagnosis are high unmet area, needed to address quickly & carefully*



Although scientific knowledge has been extensively expanded on molecular & cellular bases of Alzheimer's, target therapy is still missing, this has made to rethink Alzheimer's and has questioned to sum up the findings. In advance phase of trials, Industries and Academics both were fighting to identify targets for Alzheimer's. Amyloid stands to be favorite among industries and again, right therapy is still missing. On the other hand academia tried different targets for Alzheimer's, but they run parallel to the Industries with a high failure rate.



At a time when more than 1500 trials have been conducted on Alzheimer's and when right treatment is lacking, it becomes questionable and time arrives to re-think on Alzheimer's. Whether there is lack of pre-clinical models, failure of clinical trials and toxicities are prime concern for Alzheimer's study, end conclusion is still struggling to find right cure of Alzheimer's. The courageous and admirable efforts of industry and academia keeps falling, fainting future of Alzheimer's treatment. The funding in form of public-private partnership has emerged as a relief for the clinical trials while raise in changes in policy makers can be identified as the unmet need for the treatment of Alzheimer's.



Number of articles have asked questions around amyloid beta and clinical trial design, establishment of newer and precise pre-clinical models which can mimic human, genes and surrogate end points. An era where personalized medicines are being highlighted, Alzheimer's has still to walk a long distance. At a time when more than 1500 trials have been conducted on Alzheimer's and when right treatment is lacking, it Number of reports have highlighted dementia as a major problem in low and middle income countries, however, it need to be understand that 65+ age is distributed worldwide and it's should be considered as the priority disease of the world. The funding and initiatives across the globe explain severity of disease.

The failure rate is ~100% making one of this largest sensitive patient pool, never to forget the cost of burden that Alzheimer's contribute to society.



Conclusive story speaks around biomarkers, diagnosis, slow patient recruitment, clinical trials & other data findings. We have deepen our understanding of Alzheimer's, but at the same time research failure has raised questions as:

***Do we need to follow conventional thinking in Alzheimer's or it's time to re-think outside the box?***

***"All the years of research & development are questioning success?"***