What's New in Dementia?

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Disclosures

- I am a paid consultant to BioArctic AB

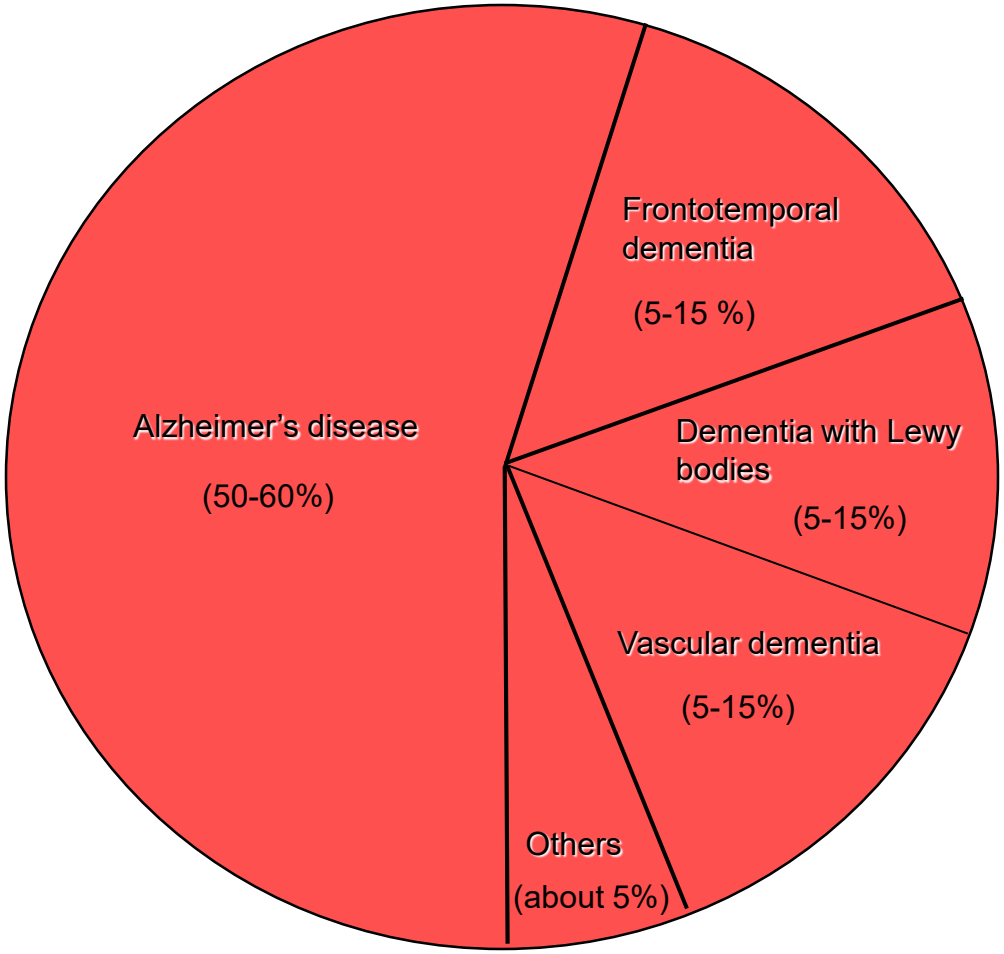
Today's presentation

Background

The novel disease modifying drugs

- Are they effective?
- Are they safe?
- Can we afford them?
- How prepared is the Canadian health care system?

Alzheimer's disease- our most common dementia disorder

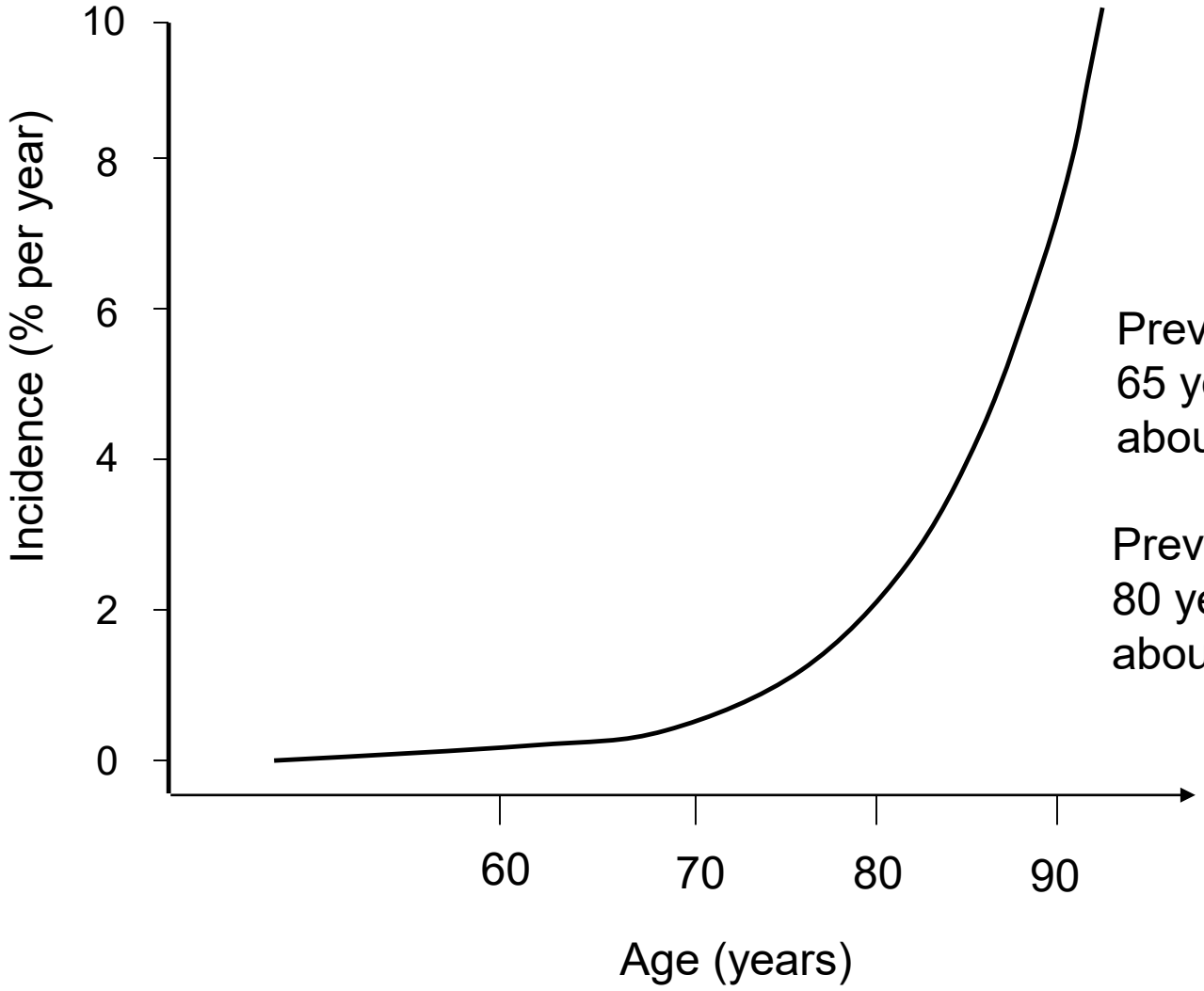


597,000 with dementia in Canada in 2020 (61.8% women).
955,900 with dementia in Canada in 2030.
124,000 were diagnosed with dementia in Canada in 2020 alone.

Over $10.4 billion- The annual cost of dementia to the Canadian economy and healthcare system.

Alzheimer Society (alzheimer.ca)

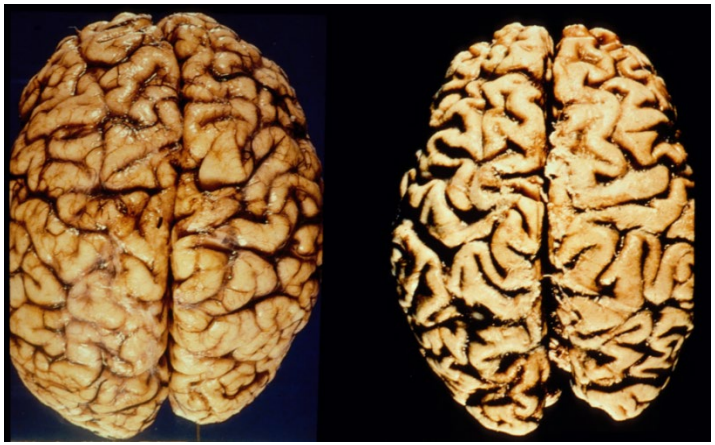
Age is the strongest risk factor for Alzheimer's disease



Prevalence among those 65 years and older: about 5%

Prevalence among those 80 years and older: about 20%

What does the Alzheimer's disease brain look like?

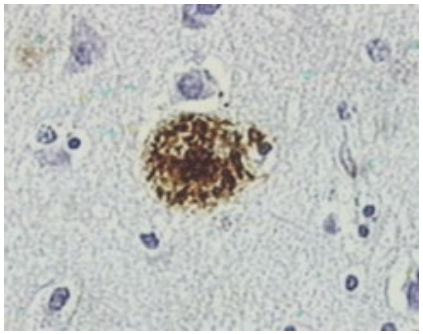


Healthy brain

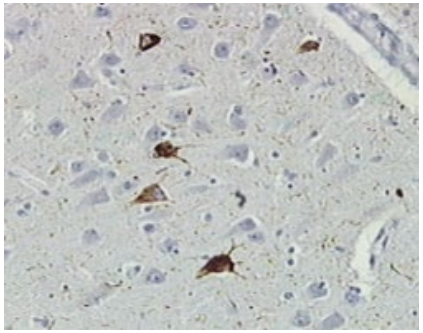
Alzheimer brain

Pathological hallmarks

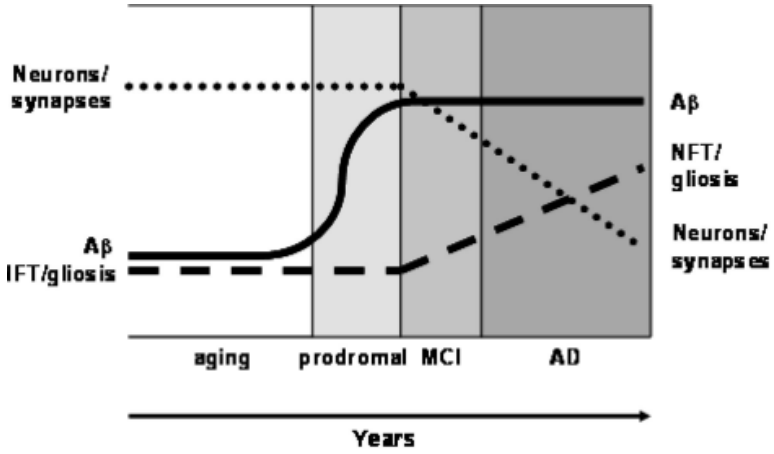
Plaques (amyloid-beta)
Neurofibrillary tangles (tau)
Degeneration of synapses and cells
Inflammation (astrocytosis and gliosis)



Amyloid plaque

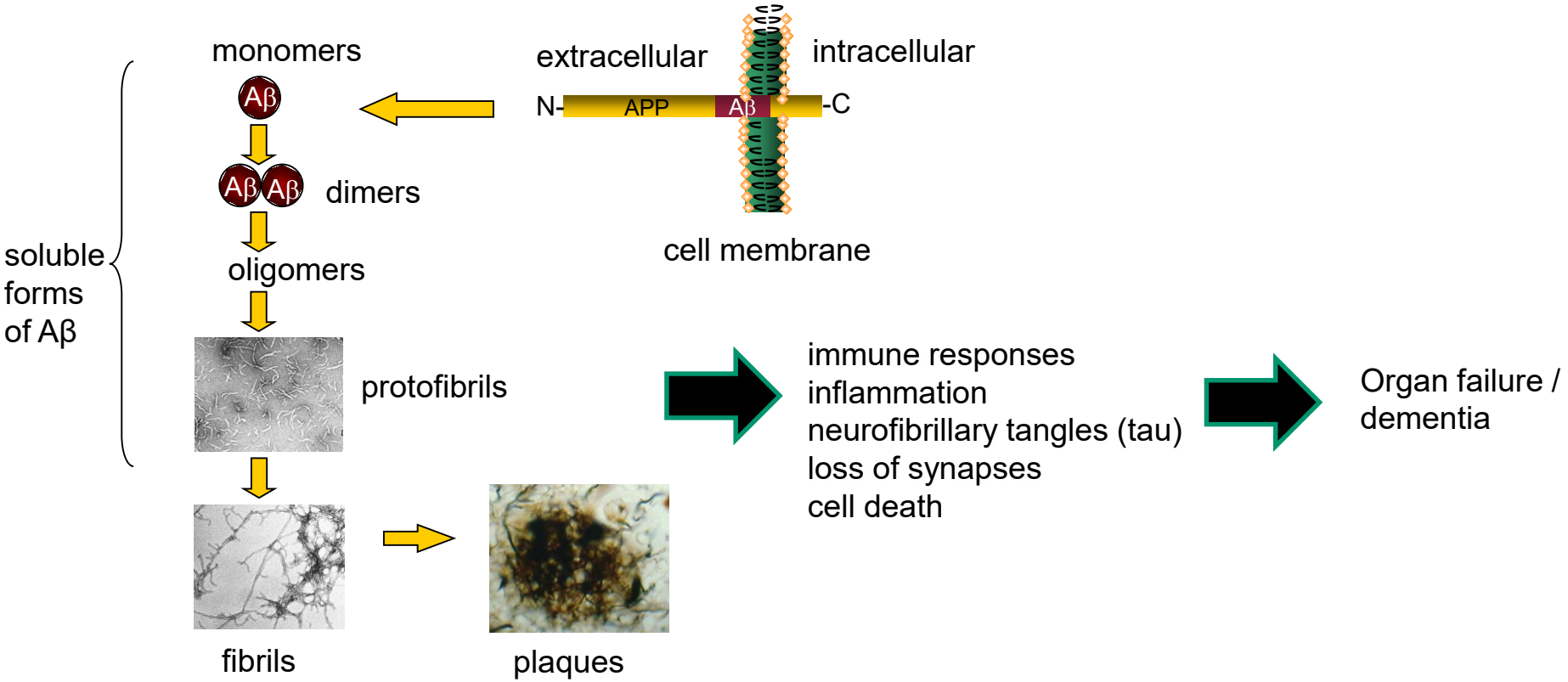


Neurofibrillary tangles

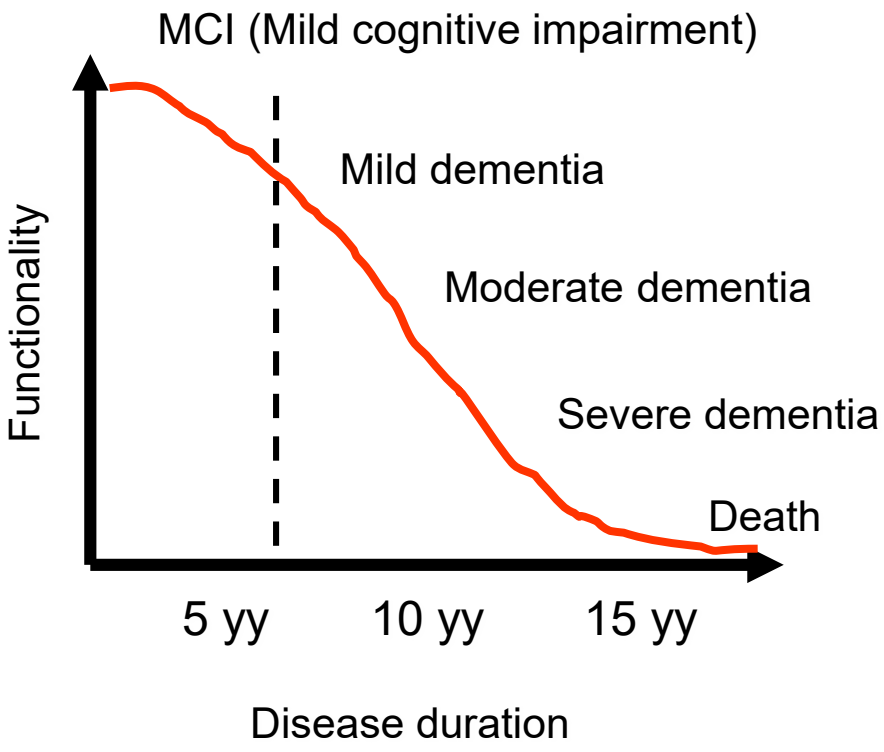


Ingelsson et al., Neurology 2004

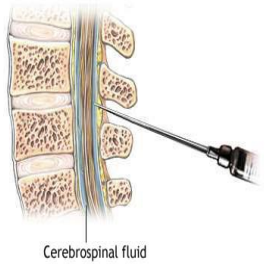
The amyloid cascade of Alzheimer's disease

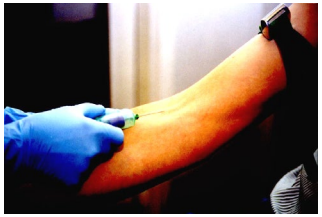


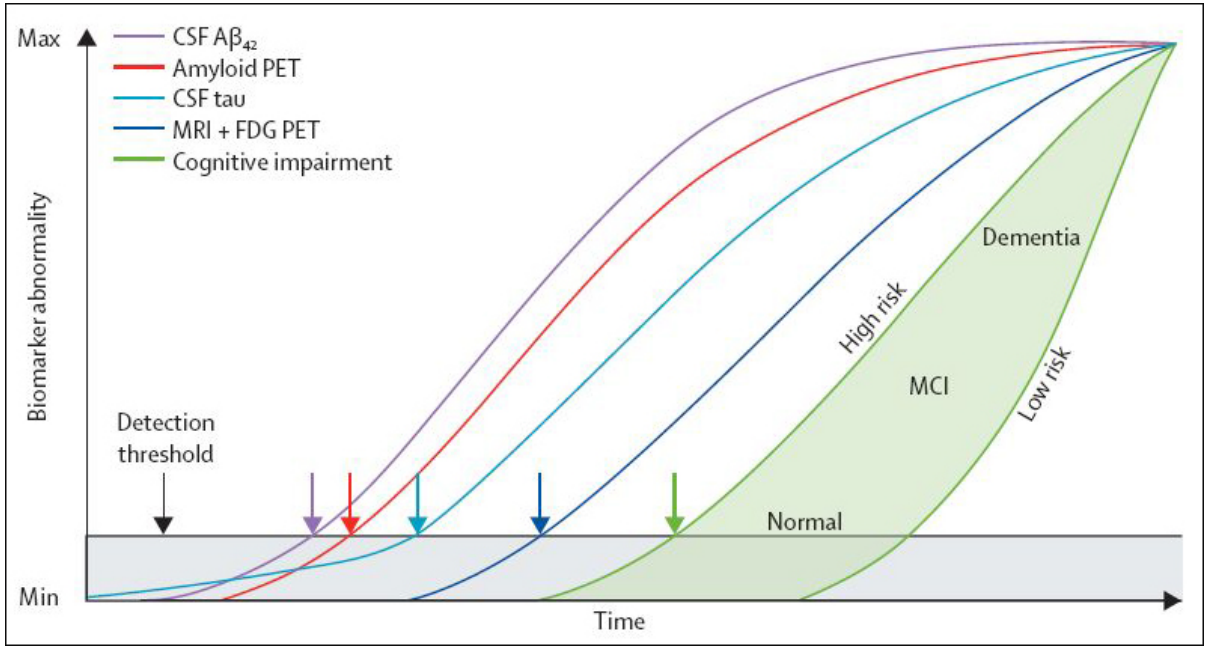
The natural evolution of Alzheimer's disease



Alzheimer's disease biomarkers

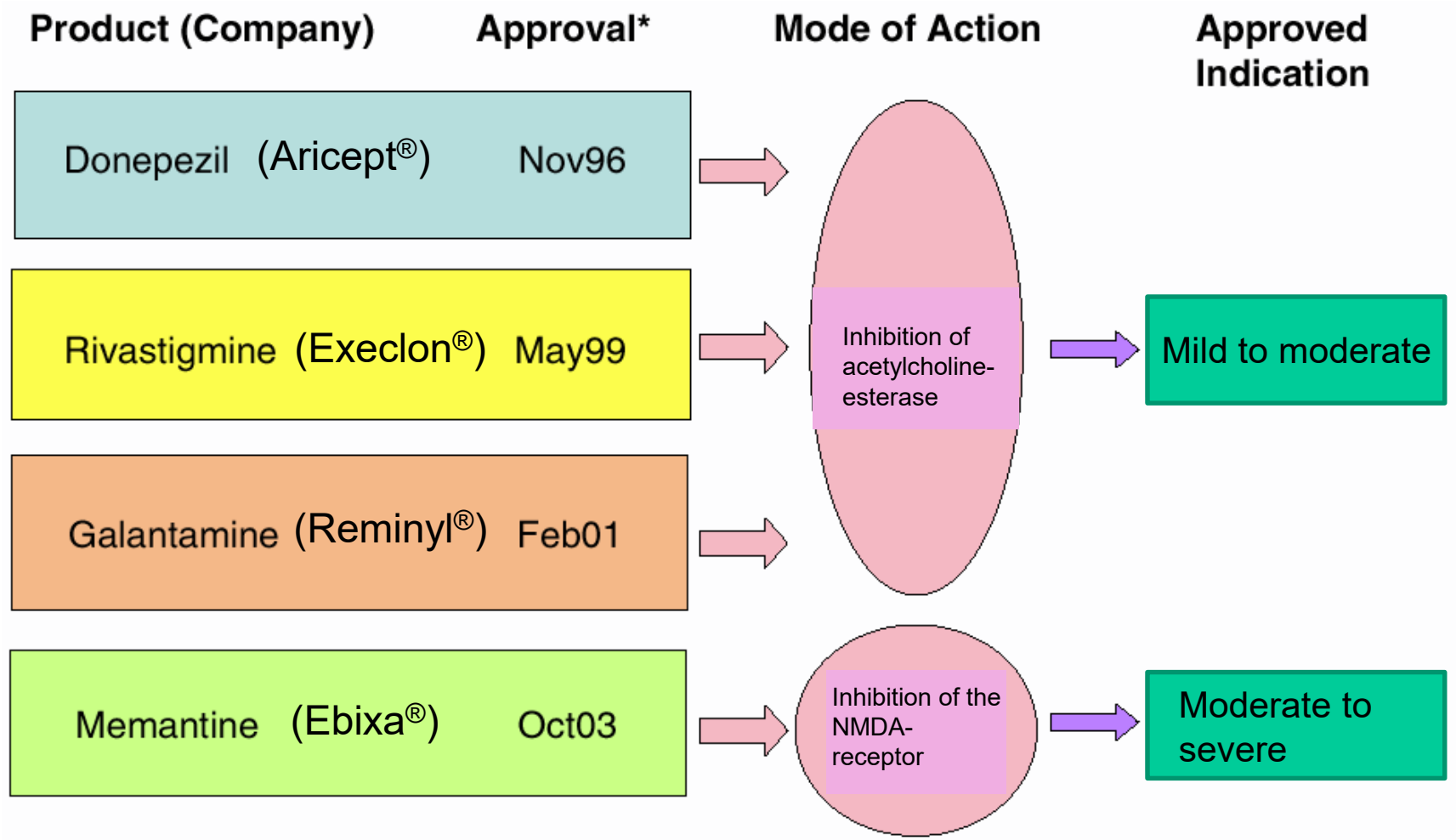






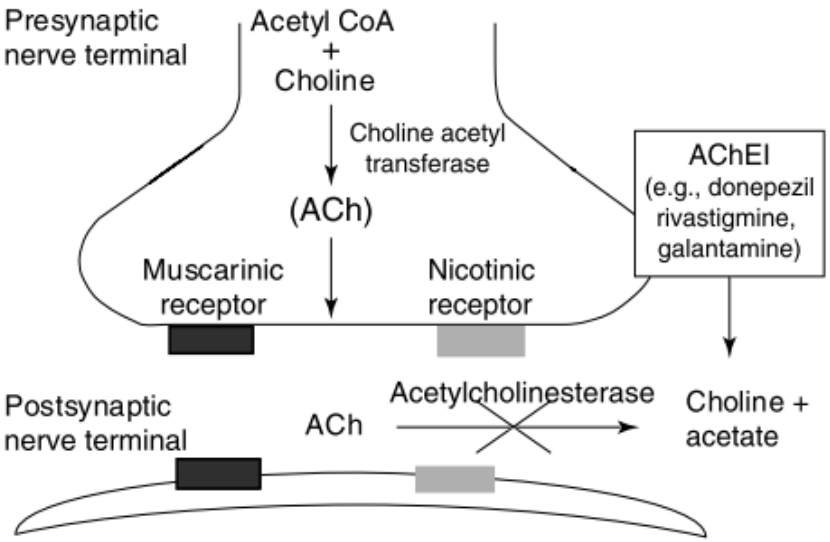
Modified from Hardy & Selkoe, EMBO Mol Med 2016

Currently approved drugs for Alzheimer's disease



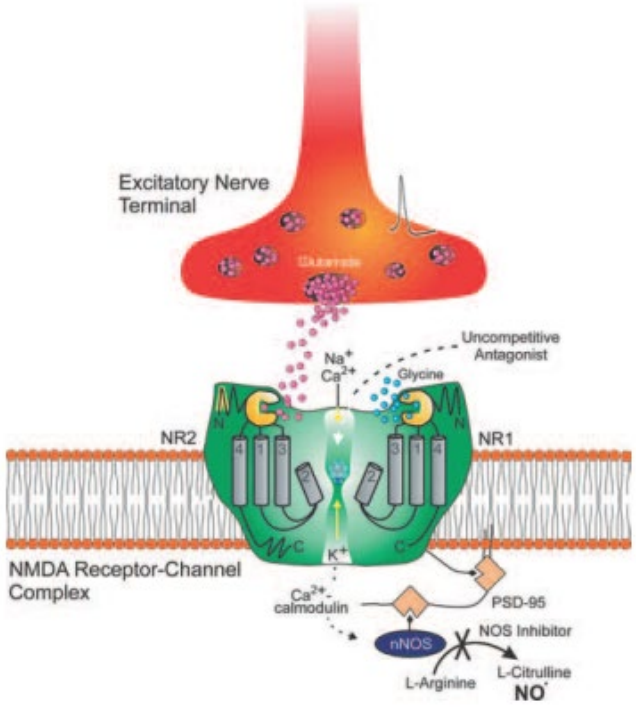
Current Alzheimer's disease drugs – modes of action

Donepezil (Aricept®), Rivastigmine (Exelon®) and Galantamine (Reminyl®)



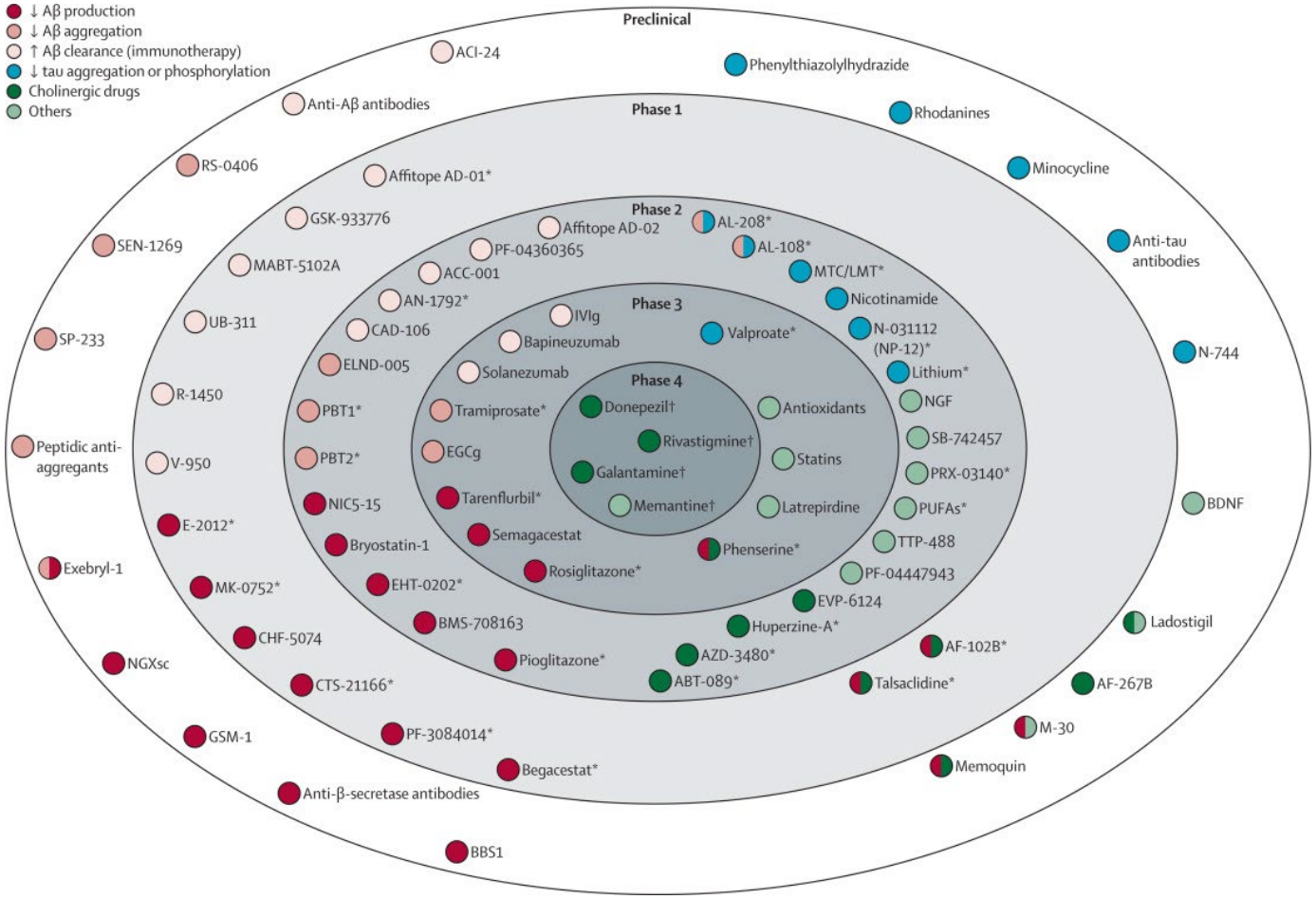
Moghul & Wilkinson, Expert Rev Neurotherapeutics, 2001, 1 (1).

Memantine (Ebixa®)



Rogawski & Wenk, CNS Drug Reviews, 2003 Vol. 9, No. 3, pp. 275–308

Large number of novel drug candidates for Alzheimer's disease

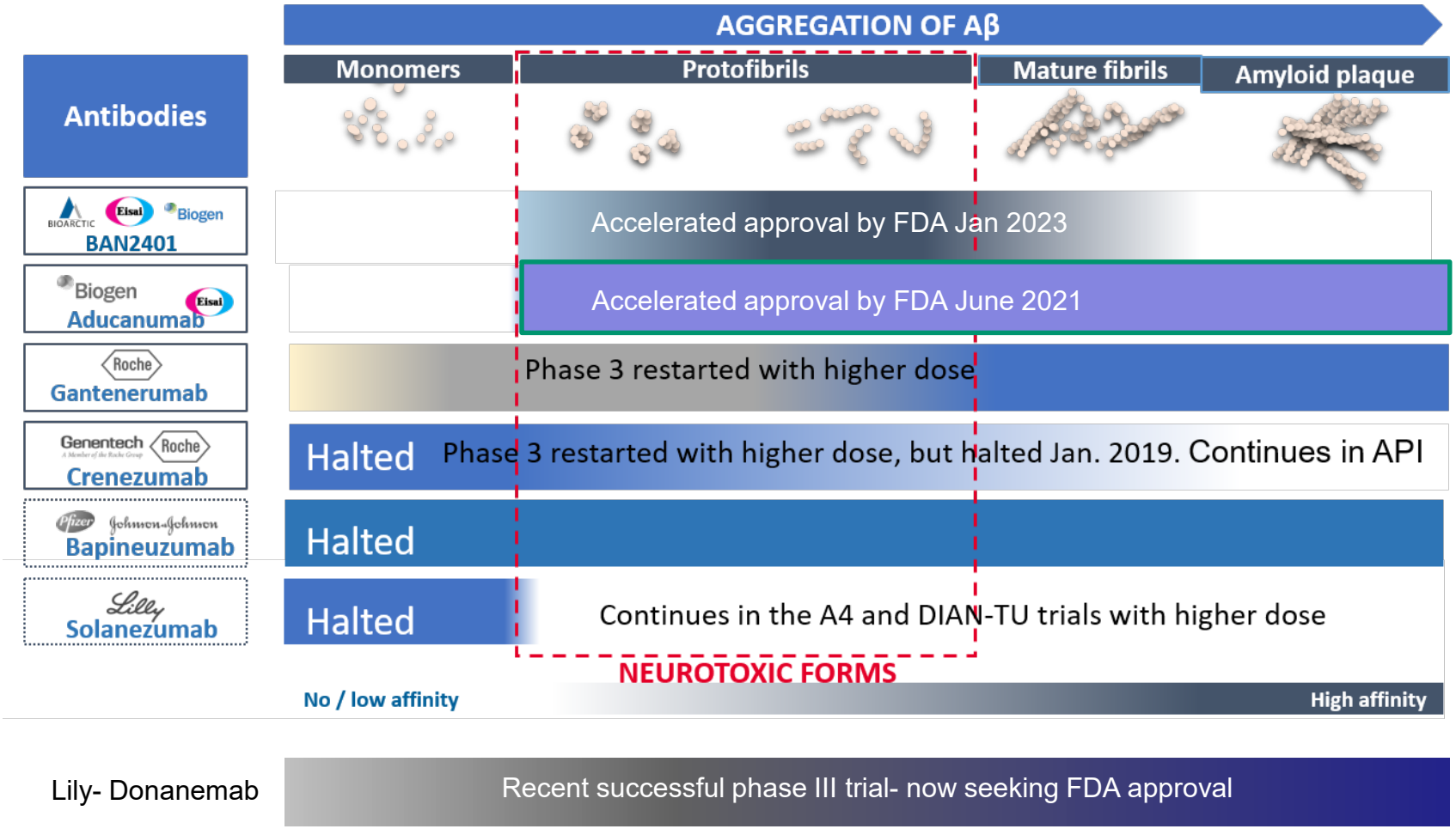


Mangialasche et al., Lancet Neurol, 2021, 9 (7), 702-716

Increasing numbers of human disorders are treated with immunotherapy

Non-CNS disorders	Target
Reumatic disorders (RA, Mb Bechterew, psoriasis arthritis)	anti-TNFa rec
Inflammatory bowel disease	anti-TNFa rec
Macular degeneration	anti-VEGF
Osteoporosis	anti-RANKL
Malignancies (e.g. CLL, colon cancer, breast cancer)	Various (e.g. anti-CD52,, anti-VEGF, anti-ErbB2)
Hyperlipidemia	anti-PCSK9
CNS disorders	
Multiple sclerosis	anti-integrin a4
Alzheimer’s disease	anti-Aβ
(Parkinson’s disease)	anti-α-syn (in phase I/II trials)

Immunotherapy for Alzheimer's disease: completed and ongoing trials with Aβ antibodies

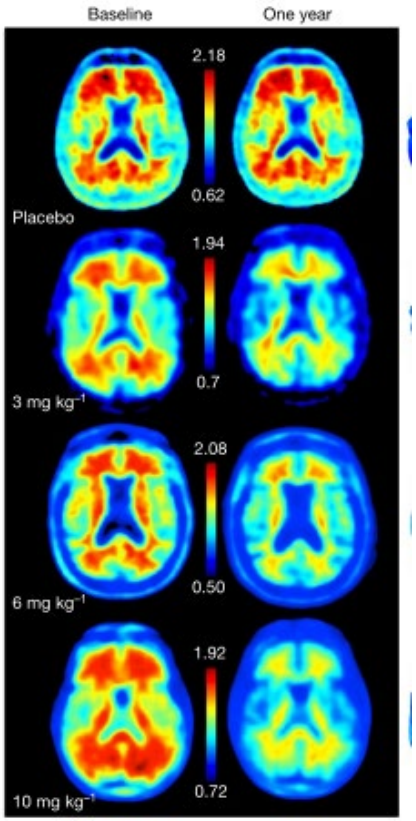


Modified from Ingelsson et al., Neurology in Sweden. 2019 No 4, 58-66

The new drugs- how efficient are they?

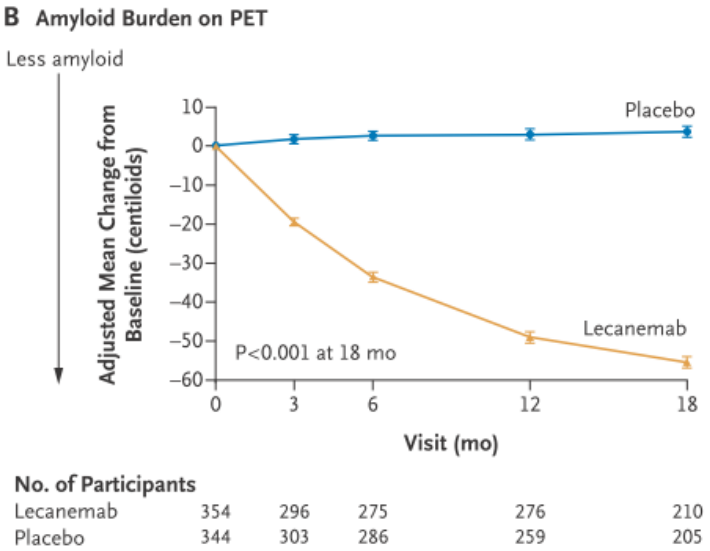
Amyloid burden on PET

Aducanumab (Aduhelm®)



Sevigny et al_Nature 2016

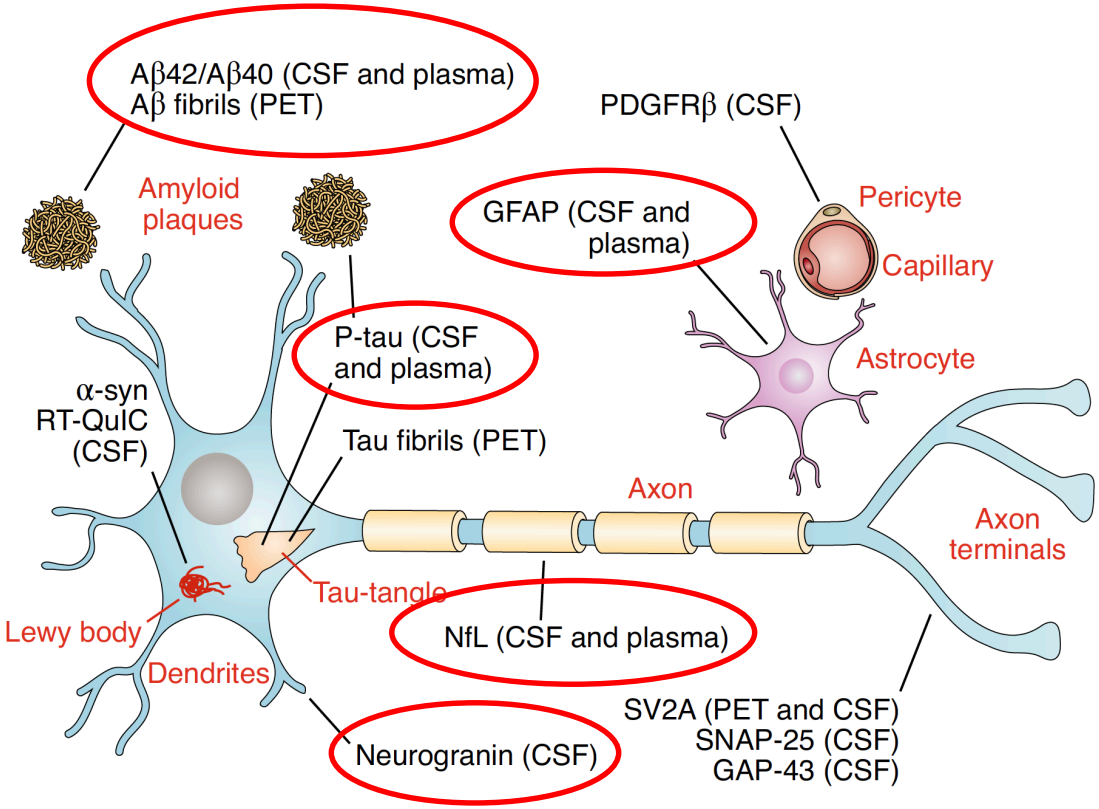
Lecanemab (Leqembi®)



Van Dyck et al., New Engl J Med, 2023

The new drugs- how efficient are they?

Effect on downstream biomarkers



Effects of Lecanemab (Leqembi®) in the Clarity Phase III trial:

CSF:

Partial correction of Aβ42, t-tau, p-tau and neurogranin.

Plasma:

Partial correction of GFAP and NFL

Hansson et al, Nature Med 2021

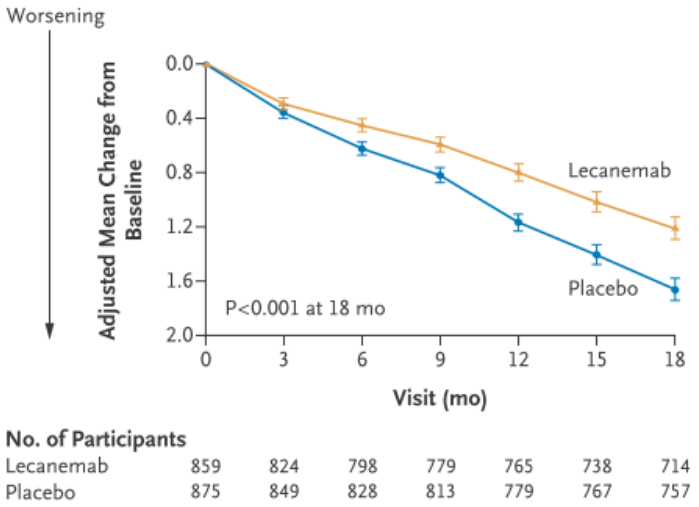
The new drugs- how efficient are they?

Effects on cognition

The cognitive scale CDR-Sum of Boxes

Table 2. Primary and secondary endpoints at week 78

Endpoint	EMERGE			ENGAGE		
	Placebo decline ± SE (n=548)	Difference vs placebo (%) | | 95% CI P: Low dose (n=543)	Difference vs placebo (%) | | 95% CI P: High dose (n=547)	Placebo decline ± SE (n=545)	Difference vs placebo (%) | | 95% CI P: Low dose (n=547)	Difference vs placebo (%) | | 95% CI P: High dose (n=555)
Primary						
CDR-SB*	1.74±0.11	−0.26 (−15%)	−0.39 (−22%)	1.56±0.11	−0.18 (−12%)	0.03 (2%)
		−0.57, 0.04	−0.69, −0.09		−0.47, 0.11	−0.26, 0.33
		.090	.012		.225	.833



CDR-SB/best effect: -0.39 (high dose compared to placebo)

Budd Haeberlein[n] et al., J Prev Alzheimer's Dis, 2022

Van Dyck et al., New Engl J Med, 2023

The new drugs- how efficient are they?

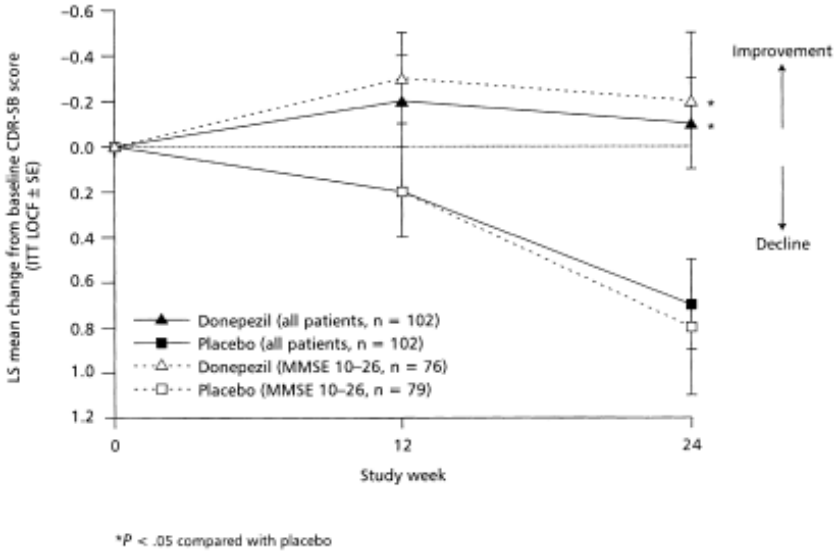
How clinically meaningful are the effects on cognition?

Table 3. Sum of Boxes Staging Category

CDR Sum of Boxes Range	Staging Category
0	Normal
0.5-4.0	Questionable cognitive impairment
0.5-2.5	Questionable impairment
3.0-4.0	Very mild dementia
4.5-9.0	Mild dementia
9.5-15.5	Moderate dementia
16.0-18.0	Severe dementia

Abbreviation: See Table 1.

O'Bryant et al., *Arch Neurol.* 2008;65(8):1091-1095



Tariot PN, et al. J Am Geriatr Soc. 2001

Homma A, et al. Dement Geriatr Cogn Disord. 2000

The new drugs- are they safe?

Side effects

Most common side effects

Infusion-related reactions
Perivascular edema (ARIA-E)
Microhemorrhages (ARIA-H)
Localized superficial siderosis (ARIA-H)

Headaches
Falls
Nasopharyngitis
Dizziness

Amyloid-Related Imaging Abnormalities (ARIA)

ARIA-E: Between 18% (non-*APOEε*4) and 43% (*APOEε*4) in high-dose EMERGE (2% placebo). 13% in CLARITY (2% placebo).

Microhaemorrhages: 20% (9% placebo), in the EMERGE high-dose group. 17% in CLARITY (9% placebo)

Serious ARIA: 1.5% high dose EMERGE (0.2% placebo). No clear difference between non-*APOEε*4 and *APOEε*4. 3% symptomatic ARIA in CLARITY.

Budd Haeberlein et al., J Prev Alzheimer's Dis, 2022
Van Dyck et al., New Engl J Med, 2023

The new drugs – can we afford them?

Costs

Aducanumab (Aduhelm): 28 000 USD/year (decreased from 56 000 USD/year)

Lecanemab (Leqembi): 26 500 USD/year

Estimated eligible number of people for treatment with lecanemab in the 27 EU countries.

Age	Amyloid-positive MCI			Mild AD dementia			Total
	Women	Men	Total	Women	Men	Total	
60–64	136,232 (60,550–282,555)	126,724 (56,322–262,837)	262,956 (116,872–545,392)	90,364 (61,415–126,604)	51,538 (34,310–72,191)	141,902 (95,725–198,795)	404,858 (212,597–744,187)
65–69	176,392 (102,121–311,009)	155,504 (90,029–274,176)	331,896 (192,150–585,185)	125,827 (85,208–176,013)	68,617 (45,052–98,684)	194,444 (130,260–274,697)	526,340 (322,410–859,882)
70–74	218,419 (151,211–319,222)	183,374 (126,950–268,005)	401,793 (278,161–587,227)	181,241 (117,172–255,434)	89,483 (58,780–127,829)	270,724 (175,952–383,263)	672,517 (454,113–970,490)
75–79	268,664 (167,518–414,059)	207,405 (129,323–319,646)	476,069 (296,841–733,705)	221,750 (145,459–314,968)	99,231 (64,619–141,181)	320,981 (210,078–456,149)	797,050 (506,919–1,189,854)
80–84	440,981 (266,252–687,814)	297,492 (179,618–464,016)	738,473 (445,870–1,151,830)	318,326 (204,567–457,219)	120,752 (78,749–175,391)	439,078 (283,316–632,610)	1,177,551 (729,186–1,784,440)
85+	752,473 (516,231–1,026,626)	371,188 (254,655–506,430)	1,123,661 (770,886–1,533,056)	527,724 (335,530–775,911)	145,232 (92,253–212,695)	672,956 (427,783–988,606)	1,796,617 (1,198,665–2,521,662)
Total	1,993,161 (1,263,883–3,041,285)	1,341,687 (836,897–2,095,110)	3,334,848 (2,100,780–5,136,395)	1,465,232 (949,351–2,106,149)	574,853 (373,763–827,971)	2,040,085 (1,323,114–2,934,120)	5,374,933 (3,423,894–8,070,515)

The estimates are based on population statistics from EuroStat (2021), combined with prevalence estimates for amyloid-positive MCI and AD dementia derived from Gustavsson et al.[13] The proportion of patients with mild AD dementia out of all patients with AD dementia is estimated to 48% (uncertainty interval 38%–58%), based on data from the Global Burden of Disease Study 2019 [31]. Numbers are adjusted for the assumption that one third of patients with amyloid-positive MCI will be eligible for treatment. Further details on the calculations are provided in the Supplement.

Jönsson et al., Lancet Reg Health Eur, 2023

Total cost if all AD patients were to be treated: 133 billion Euros / year (>50% of the current total pharmaceutical expenditures in the EU)

Leqembi now approved by the Veteran Affairs. Not yet approved by the Centers for Medicare and Medicaid Services.

The new drugs – can we afford them?

Factors that can reduce the costs

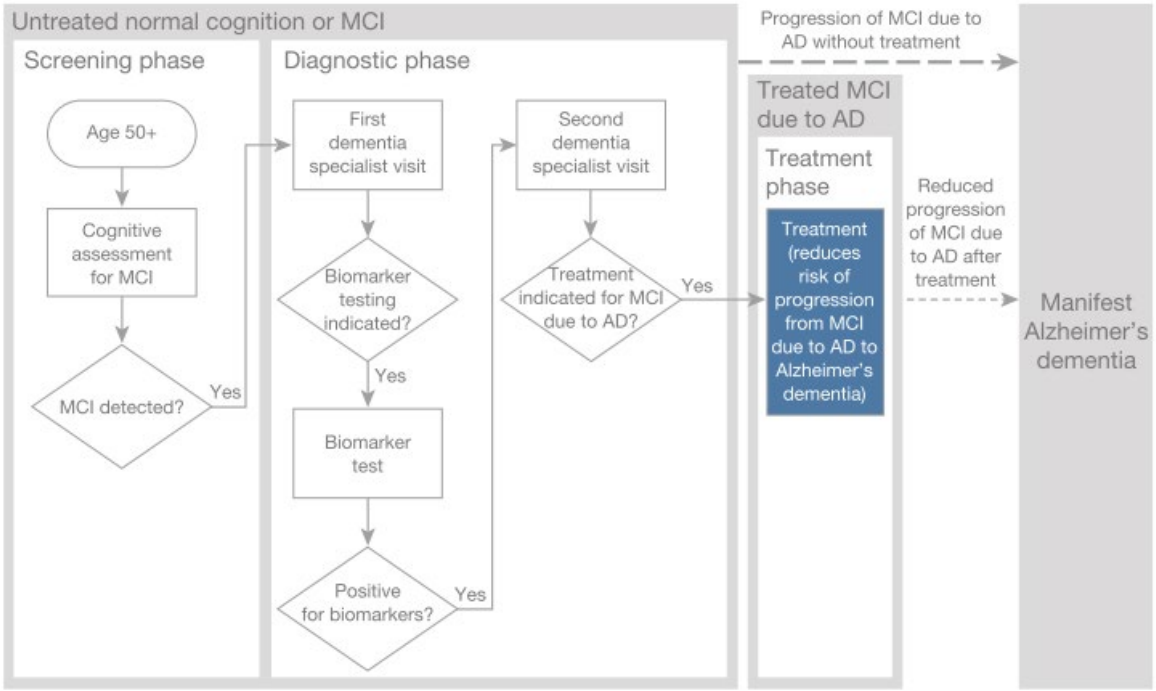
- CSF instead of PET biomarkers for eligibility.
- Use of novel plasma tau-biomarkers for eligibility.
- Development of biomarkers to discriminate between patients with and without CAA- may reduce/eliminate the need for MRI monitoring.
- Future developments of the immunotherapies (s.c. instead of i.v. administration, e.g. donanemab, lecanemab).
- Intermittent treatment (e.g. ALZN002).

The new drugs - how prepared is the Canadian health care system?

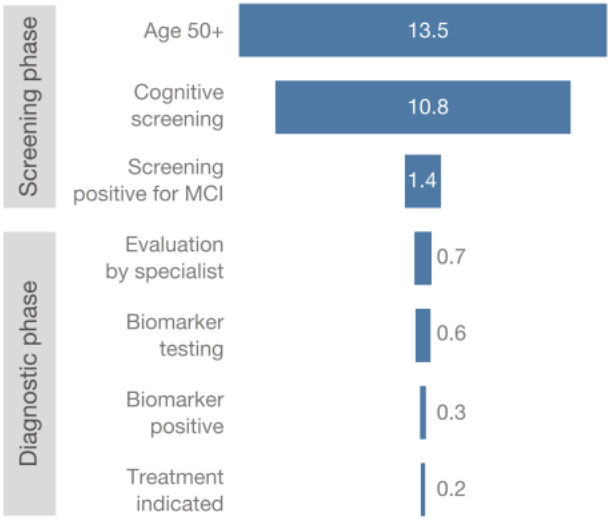
The RAND report

Liu et al., RAND Report 2019

Screening process and yearly estimates

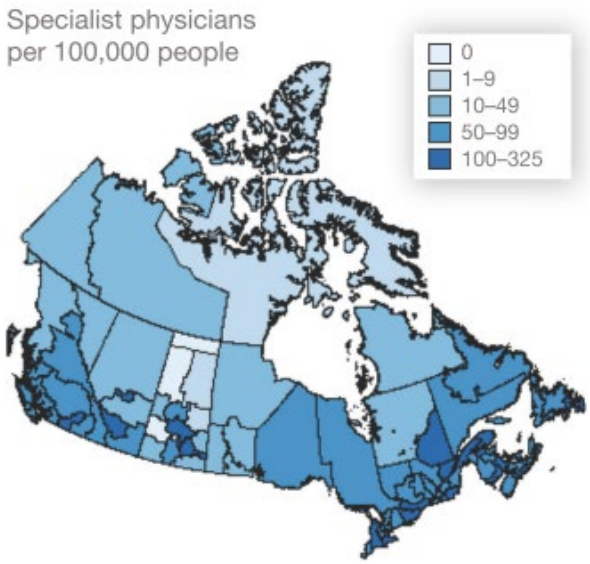


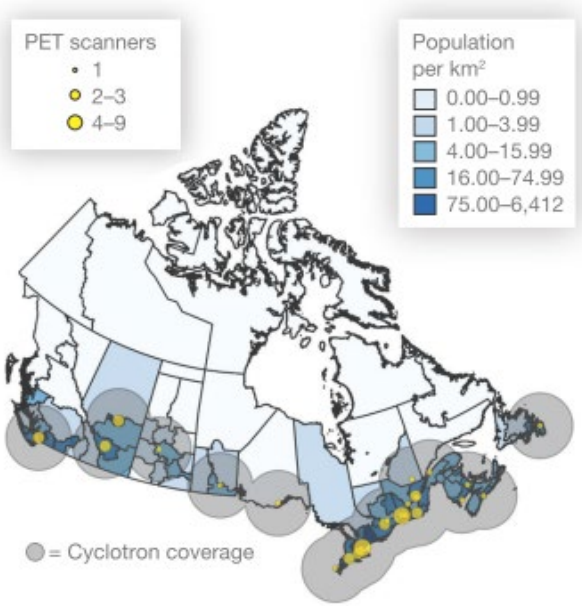
SOURCE: Liu et al., 2017.



Liu et al., RAND Report 2019

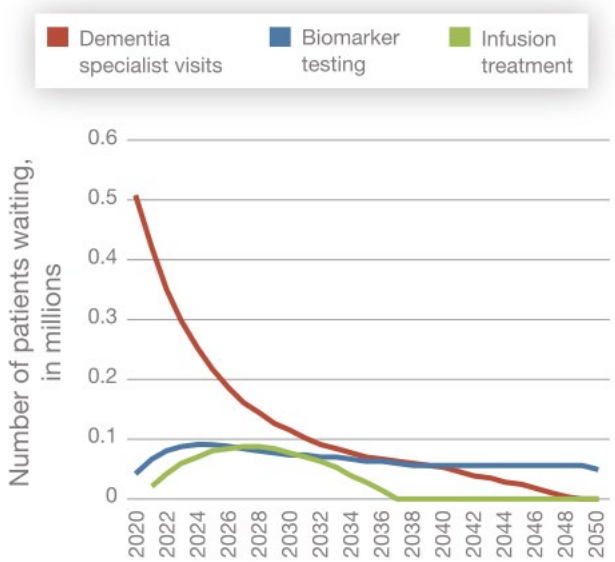
Existing bottlenecks



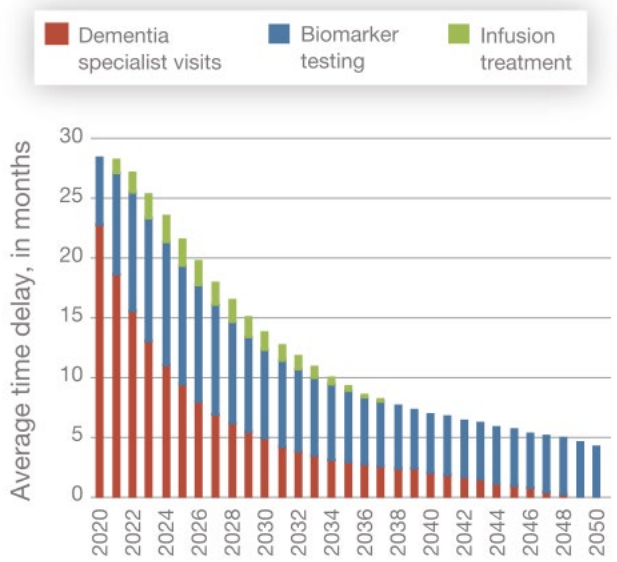


Liu et al., RAND Report 2019

Wait times for assessment and treatment



NOTE: Our base case scenario assumes 80 percent of biomarker testing conducted via PET and 20 percent via CSF.



NOTE: Our base case scenario assumes 80 percent of biomarker testing conducted via PET and 20 percent via CSF.

Liu et al., RAND Report 2019

RAND report / Key findings

• A simulation model to assess preparedness of the Canadian health care system infrastructure to diagnose and treat people with MCI due to AD.

• Average annual wait times for diagnosis and treatment in Canada could peak at 28 months and persist for decades.

• 166,000 to 485,000 Canadians could progress to AD dementia while on wait lists.

• Major constraints:
- Low capacity of dementia specialists
- Lack of facilities to perform PET and MRI brain imaging
- Large sparsely populated geographic areas with limited access to specialty care

• Need for coordinated efforts among multiple stakeholders to increase awareness and investment, and to implement policies that ensure adequate capacity.

National dementia strategy

Box 4. Canada's National Dementia Strategy

Canada became the 30th country to call for the development a national dementia strategy when the Canadian Parliament passed the National Strategy for Alzheimer's Disease and Other Dementias Act (Bill C-233) in June 2017 (Parliament of Canada, 2017). Key measures of the act include

- development of national objectives to improve patient situation and decrease the burden on Canadian society
- greater investment in research, including biomedical, clinical, and health services and systems
- international coordination in the fight against Alzheimer's and increased Canadian contribution
- assisting the provinces in developing and disseminating treatment guidelines and information on the prevention and management of early intervention
- making recommendations on national guidelines for standards of care based on evidence-based best practices.

Liu et al., RAND Report 2019

Conclusions

- We can expect almost one million people with dementia in Canada by 2030. A majority of them will have Alzheimer's disease.
- Current treatments do have effect, but only on the symptomatic level and do not interfere with the underlying disease process.
- The novel disease-modifying treatments have proven efficient to reduce central pathological features in brain.
- The novel treatments also show a modest clinical effect.
- The novel treatments can cause ARIA side effects, but only few of these are symptomatic.
- The novel treatments are currently very expensive and will, if used indiscriminately, overwhelm our social security systems.
- The Canadian health care system is currently not prepared to treat all eligible patients.
- An updated national dementia strategy is needed.

Thank you for your attention!
Questions?

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