Drug Discovery & Development

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CNS Disorders

- More than 1 billion people worldwide suffer from diseases of the central nervous system (CNS)

- One in five Americans currently takes at least one psychiatric drug and mental disorders are recognized worldwide

- In the United States and European Union, the economic burden of CNS diseases—including direct medical costs, direct nonmedical costs, and costs of informal (family) care—is estimated at more than $2 trillion, a number expected to triple to $6 trillion by 2030

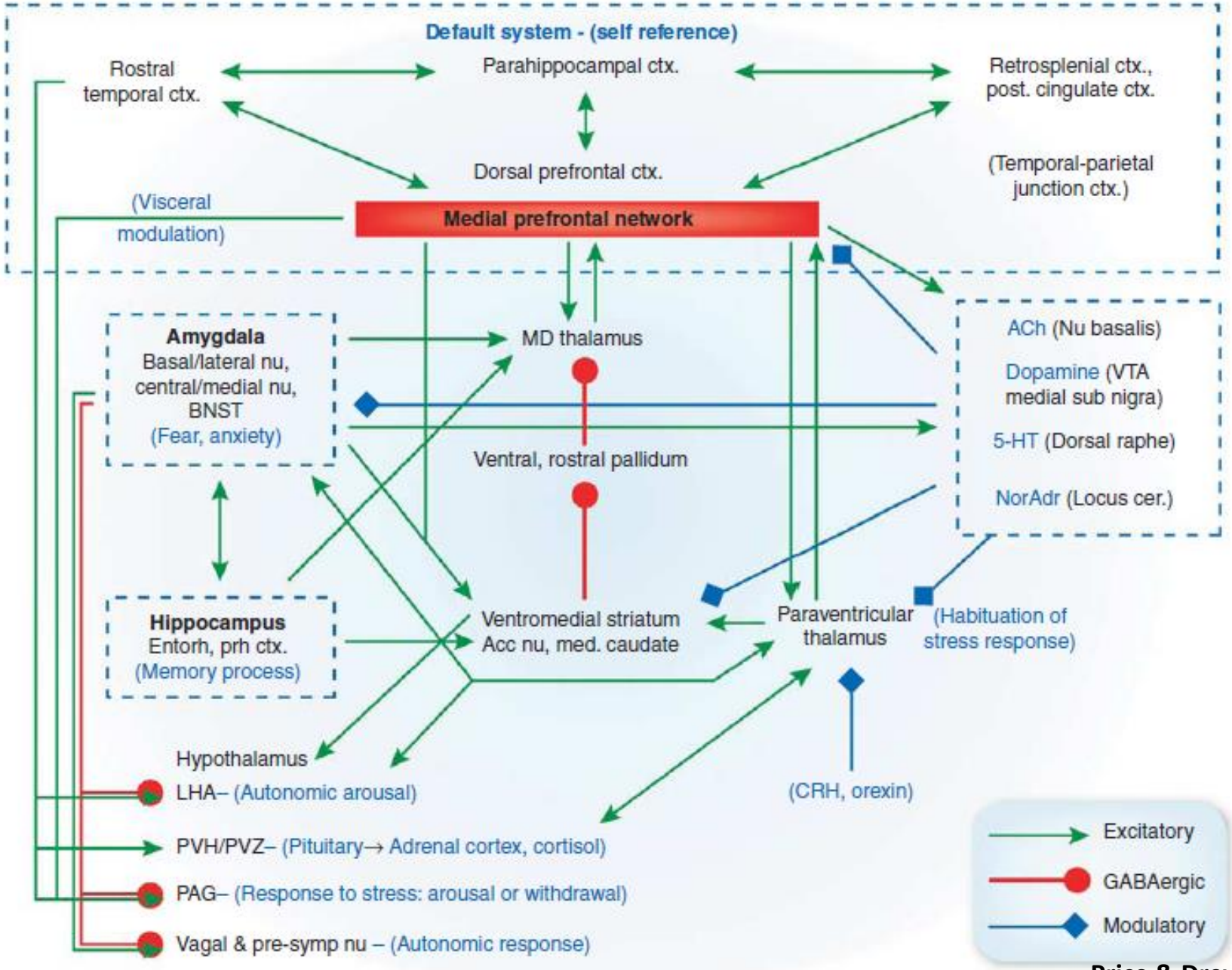
Ereshefsky et al, 2017

Serendipity or Good Science: Building Opportunity

Hoffman

Osterloh

Mood Disorders: Medial Prefrontal Network & Amygdala



Price & Drevets (2010)

Outline

I. Time & Risk

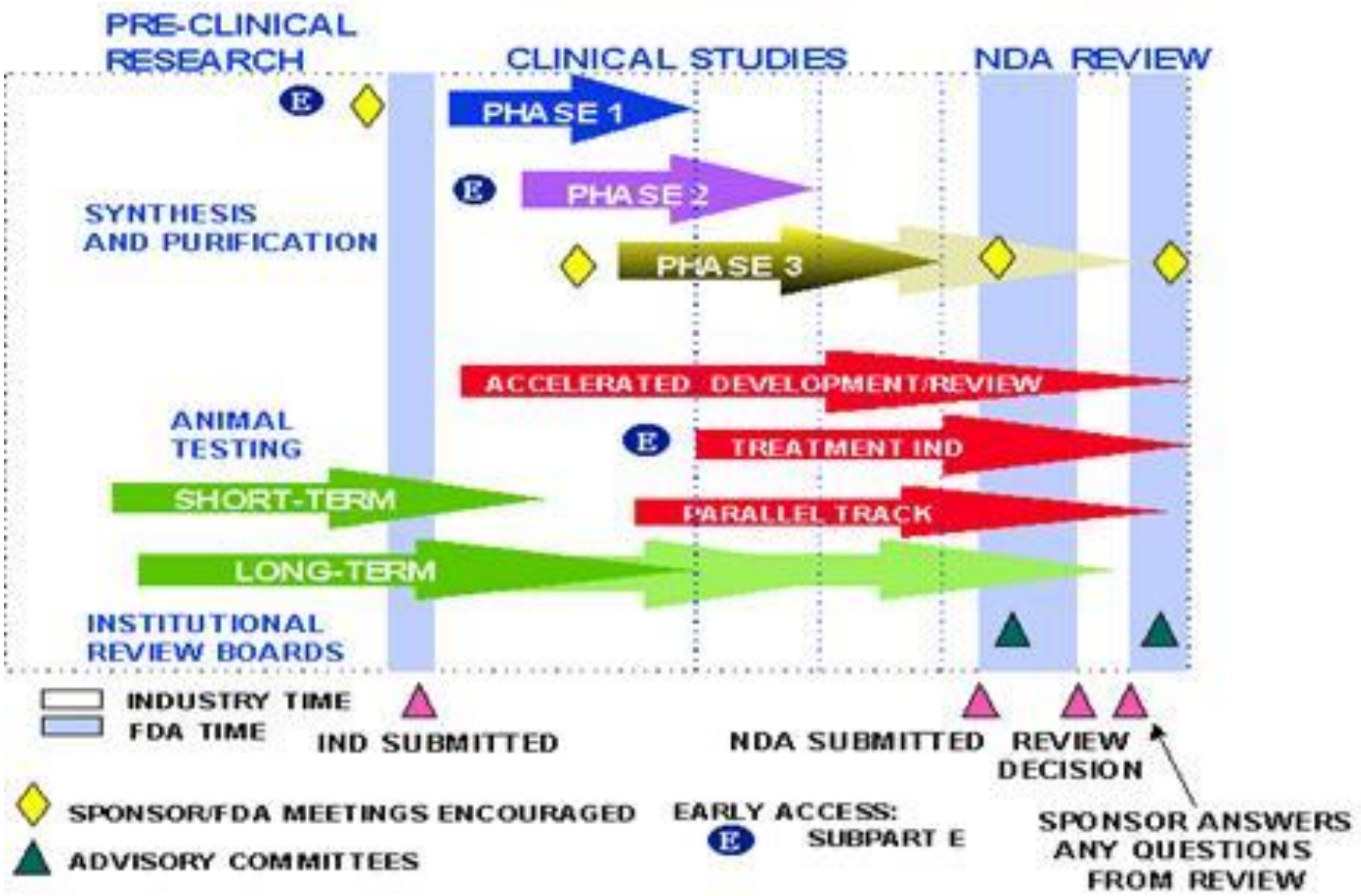
II. The R&D Landscape: Cost

III. Innovation and Transformation

IV. Designing Drug Development Trials: Alzheimer's Disease

1. Time and Risk

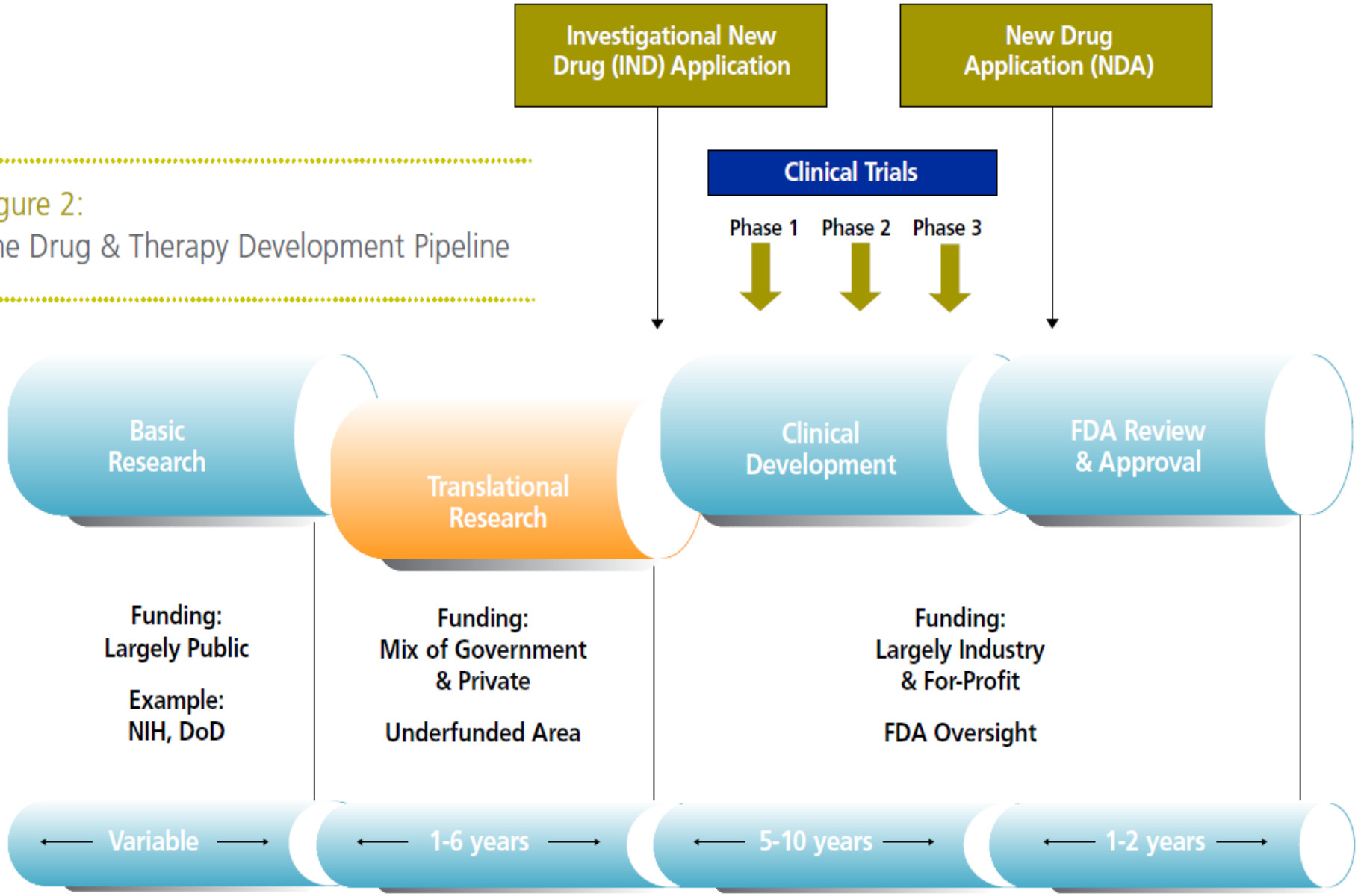
Drug Development Process



US FDA

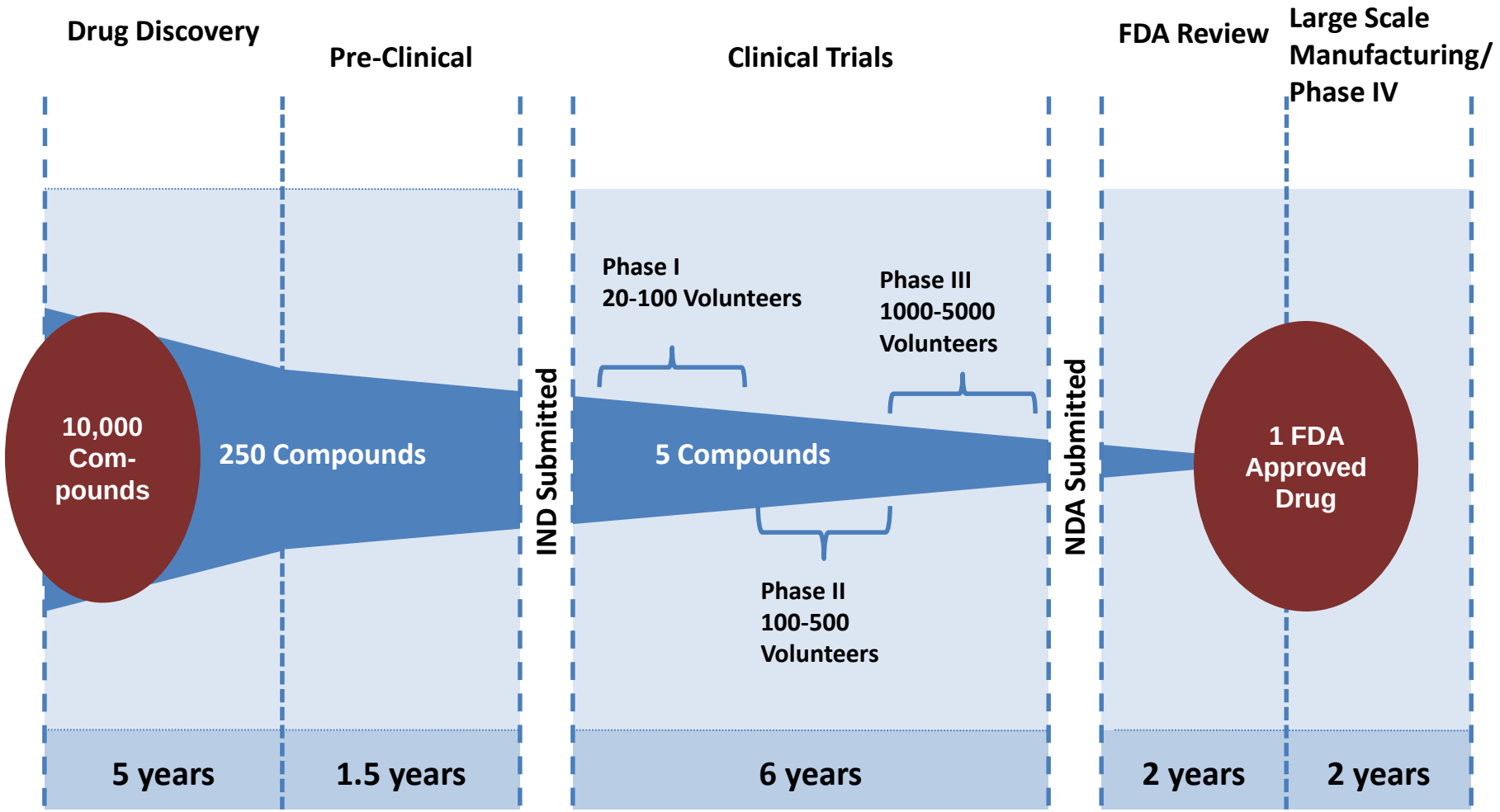
Drug Development Process: The Path to New Medicines

Figure 2:
The Drug & Therapy Development Pipeline



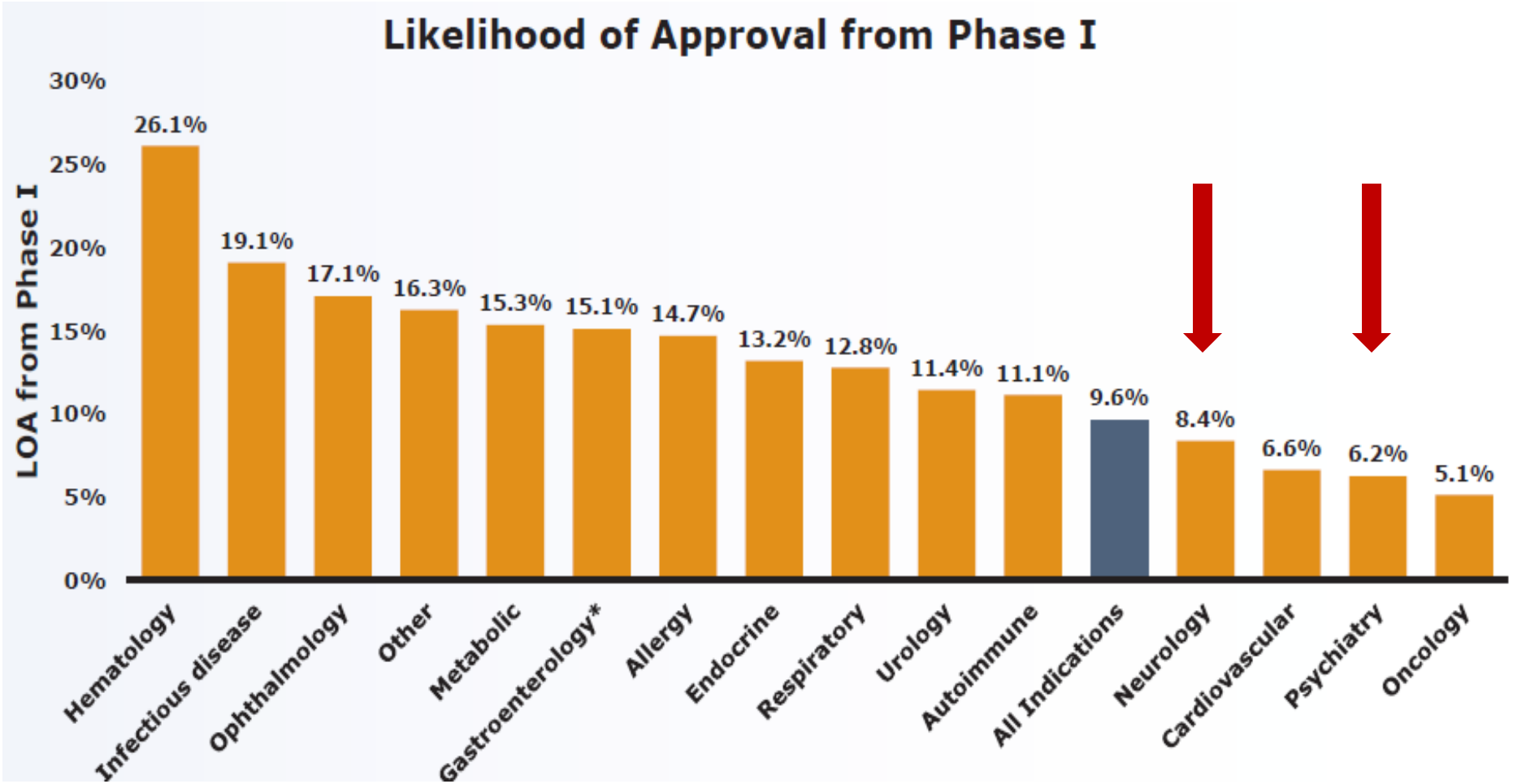
Source: Parkinson's Action Network

Biopharmaceutical Drug Development: Attrition



Quelle: Burrell Report Biotechnology Industry 2006

Approvals from Phase 1 by Disease Area

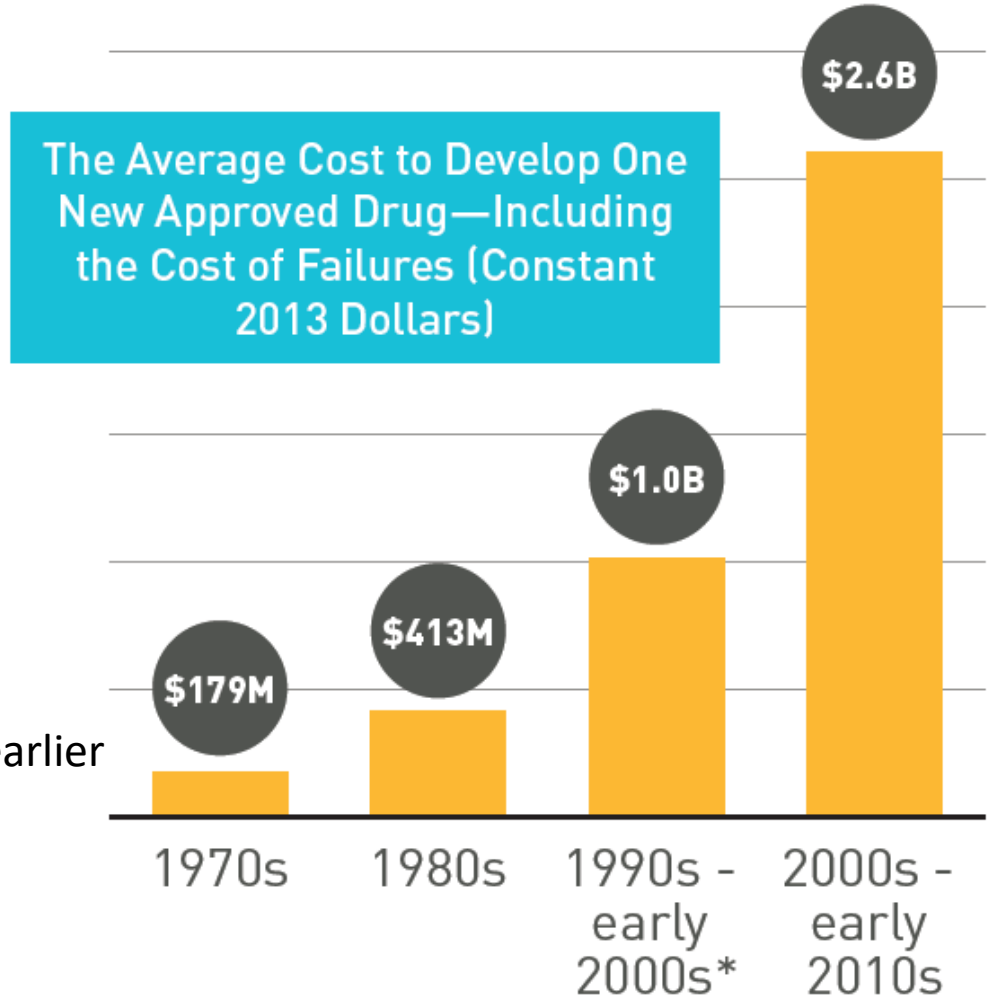


Thomas et al (2016) BIO.

II. The Research & Development Landscape

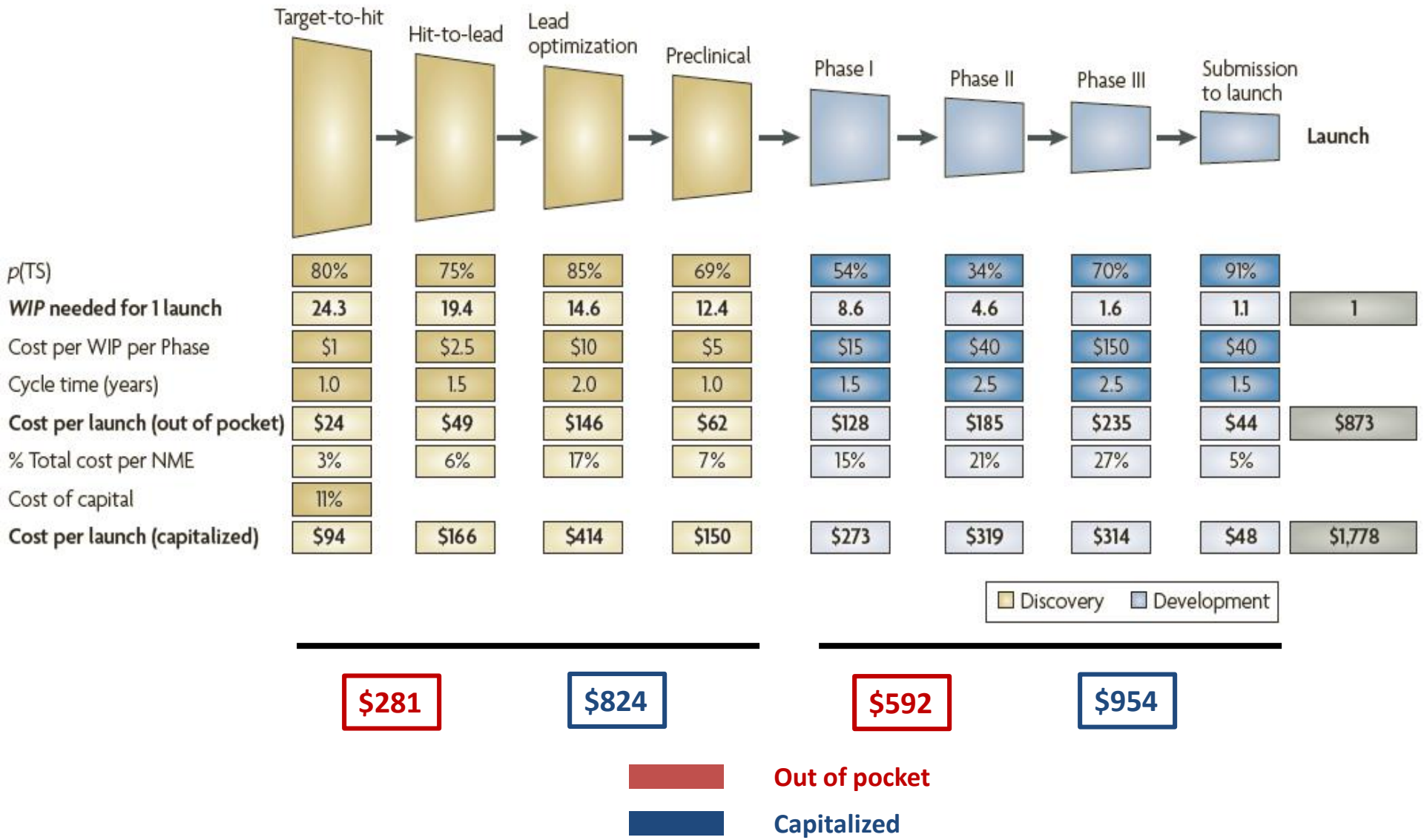
Cost Drivers

- Increased clinical trial complexity
- Larger clinical trial sizes
- Greater focus on targeting chronic and degenerative diseases
- Higher failure rates for drugs tested in earlier phase clinical studies

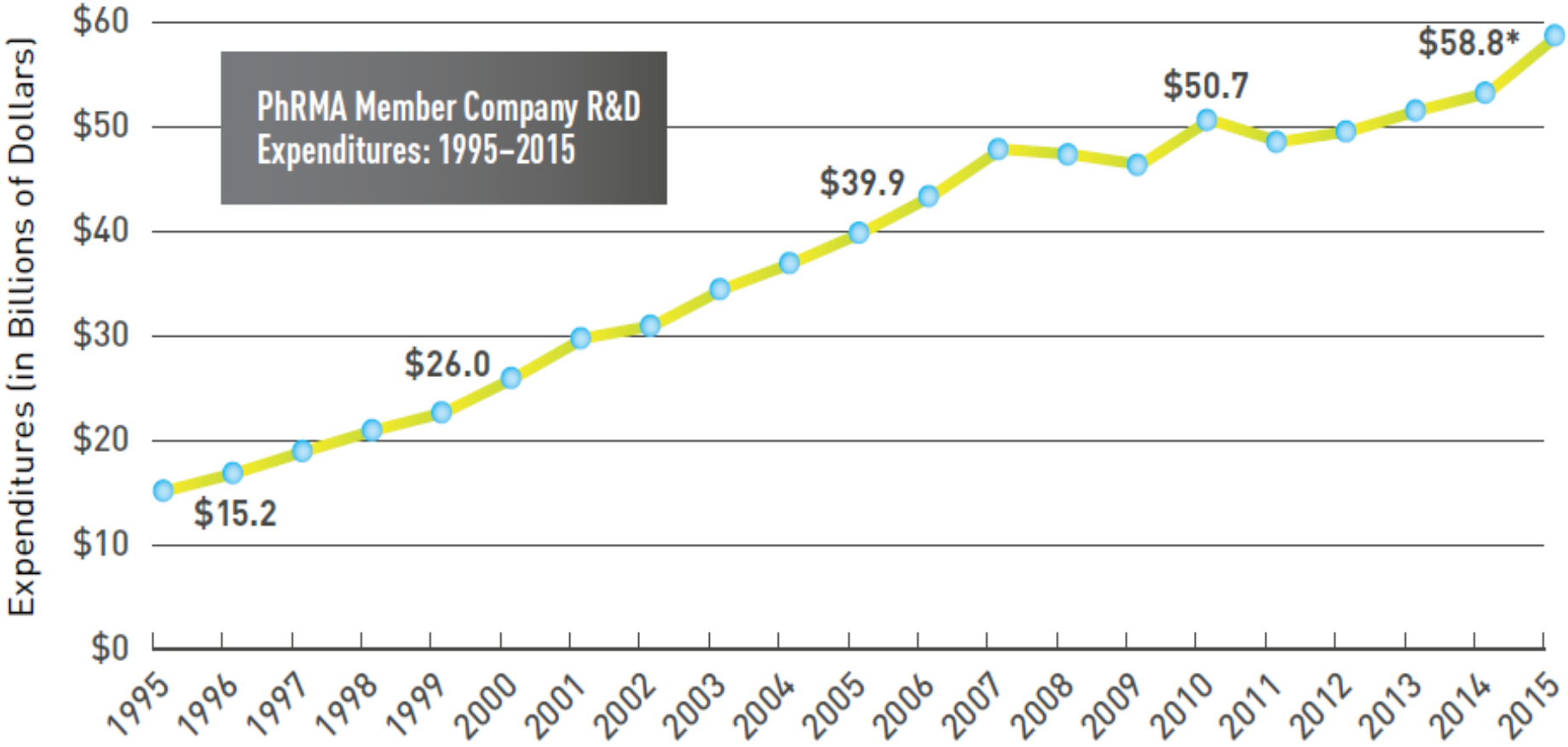


Source: Tufts Center for the Study of Drug Development (CSDD). Cost of developing a new drug. Briefing. Boston, Mass.: CSDD. Published November 2014. Accessed March 2015.

R&D Cost Model per New Medical Entity



Paul et al (2010). Nature Rev Drug Discovery



Sources: Congressional Budget Office (CBO). Research and development in the pharmaceutical industry. www.cbo.gov/sites/default/files/cbofiles/ftpdocs/76xx/doc7615/10-02-drugr-d.pdf. Washington, DC: CBO; October 2006. Accessed April 2016. Pharmaceutical Research and Manufacturers of America (PhRMA). PhRMA annual membership survey, 1996-2014. Washington, DC: PhRMA; 2016

TABLE 1: Domestic R&D and R&D Abroad,* PhRMA Member Companies: 1980–2018

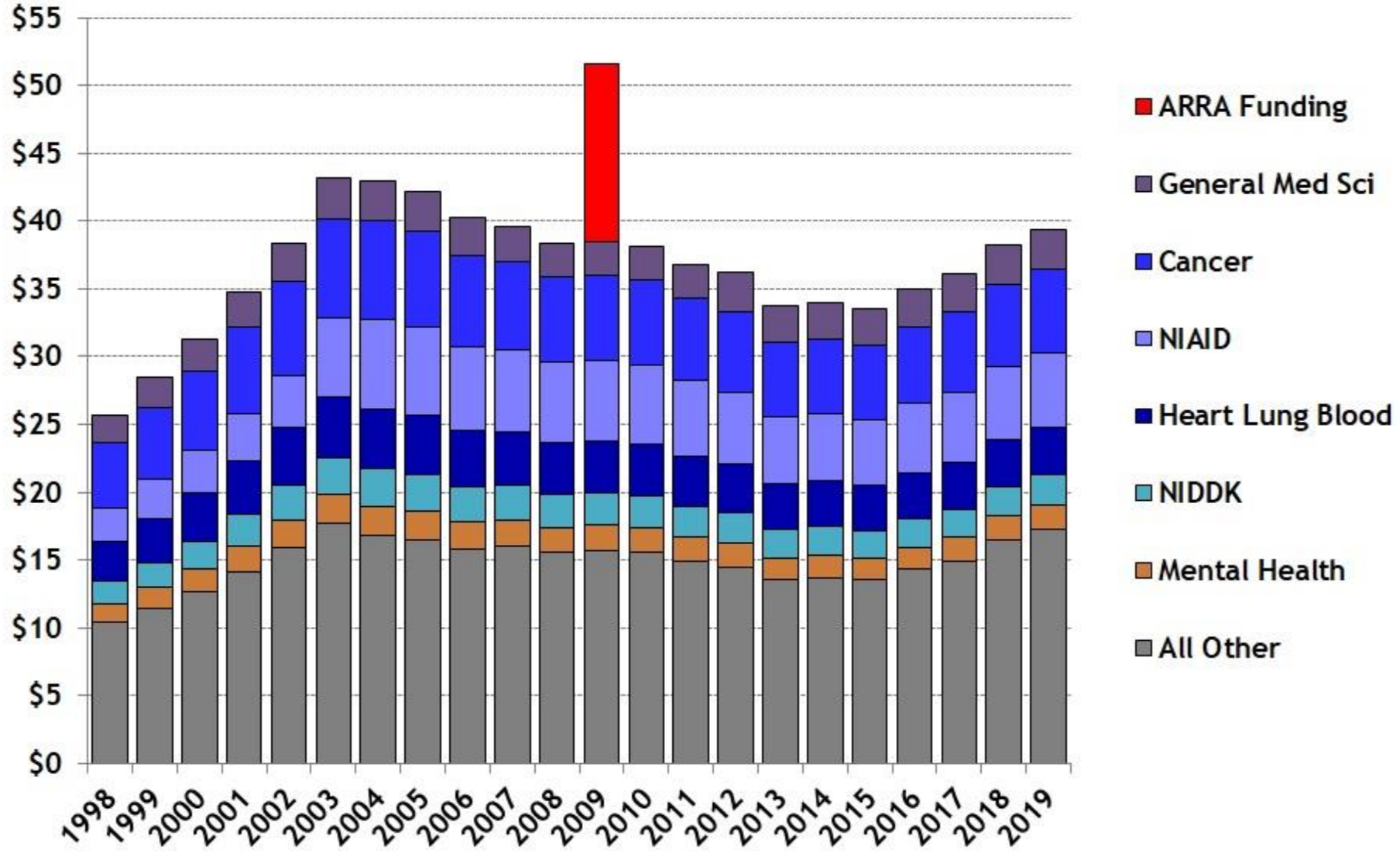
(dollar figures in millions)

Year	Domestic R&D	Annual Percentage Change	R&D Abroad*	Annual Percentage Change	Total R&D	Annual Percentage Change
2018	$62,219.7	11.6%	$17,383.1	11.1%	$79,602.8	11.5%
2017	$55,755.0	6.4%	$15,644.4	19.2%	$71,399.4	8.9%
2016	$52,418.2	9.0%	$13,120.1	13.8%	$65,538.3	9.9%
2015	$48,110.5	18.1%	$11,531.9	-7.9%	$59,642.4	12.0%
2014	$40,737.3	0.8%	$12,515.9	11.6%	$53,253.2	3.2%
2013	$40,396.0	7.7%	$11,217.6	-7.1%	$51,613.6	4.1%
2012	$37,510.2	3.1%	$12,077.4	-1.6%	$49,587.6	1.9%
2011	$36,373.6	-10.6%	$12,271.4	22.4%	$48,645.0	-4.1%
2010	$40,688.1	15.1%	$10,021.7	-9.6%	$50,709.8	9.2%
2009	$35,356.0	-0.6%	$11,085.6	-6.1%	$46,441.6	-2.0%

* R&D Abroad includes expenditures outside the United States by U.S.-owned PhRMA member companies, and R&D conducted abroad by the U.S. divisions of foreign-owned PhRMA member companies. R&D performed abroad by the foreign divisions of foreign-owned PhRMA member companies are excluded. Domestic R&D, however, includes R&D expenditures within the United States by all PhRMA member companies.

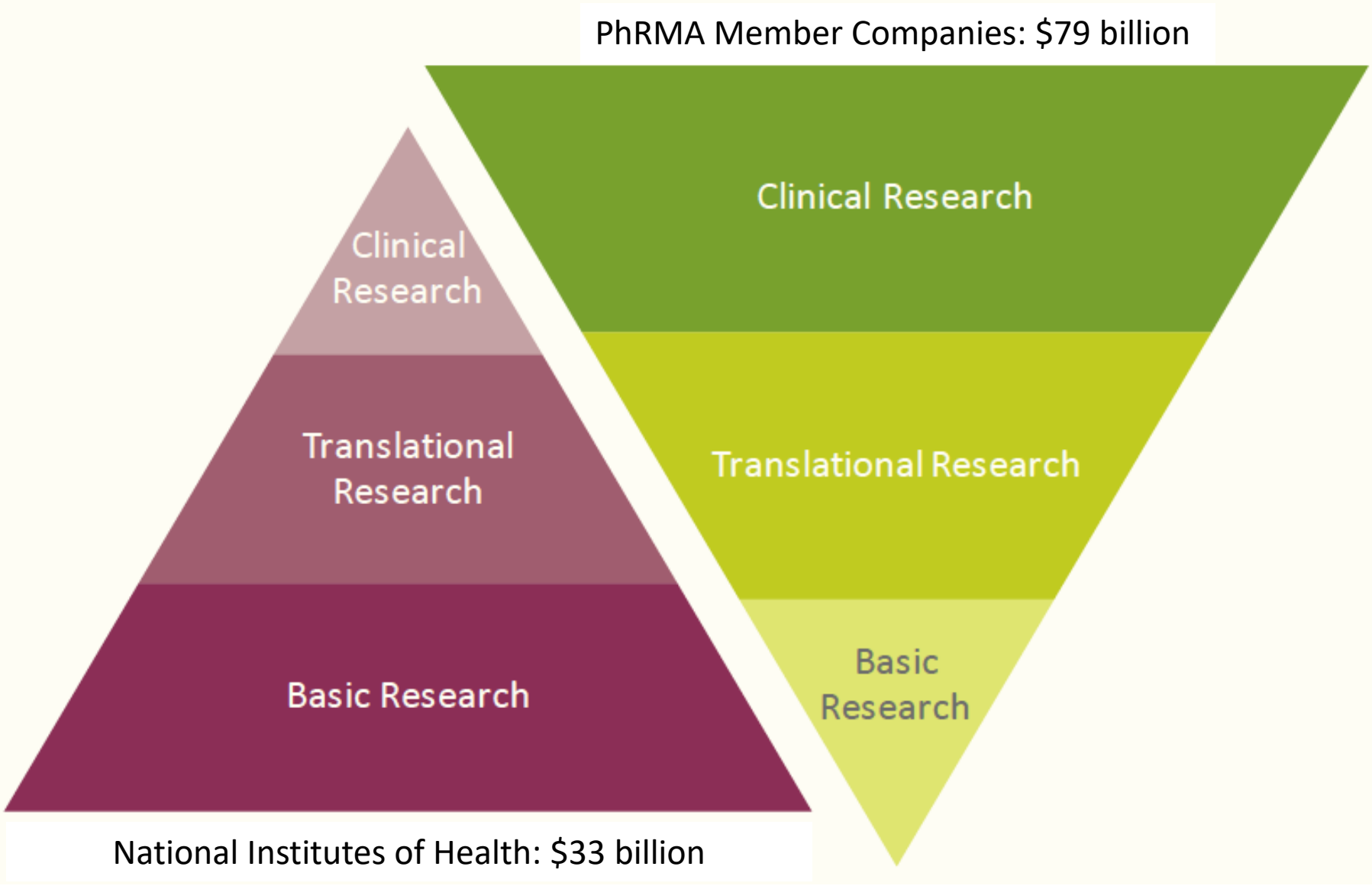
National Institutes of Health Budget, 1998-2019

budget authority in billions of constant FY 2019 dollars

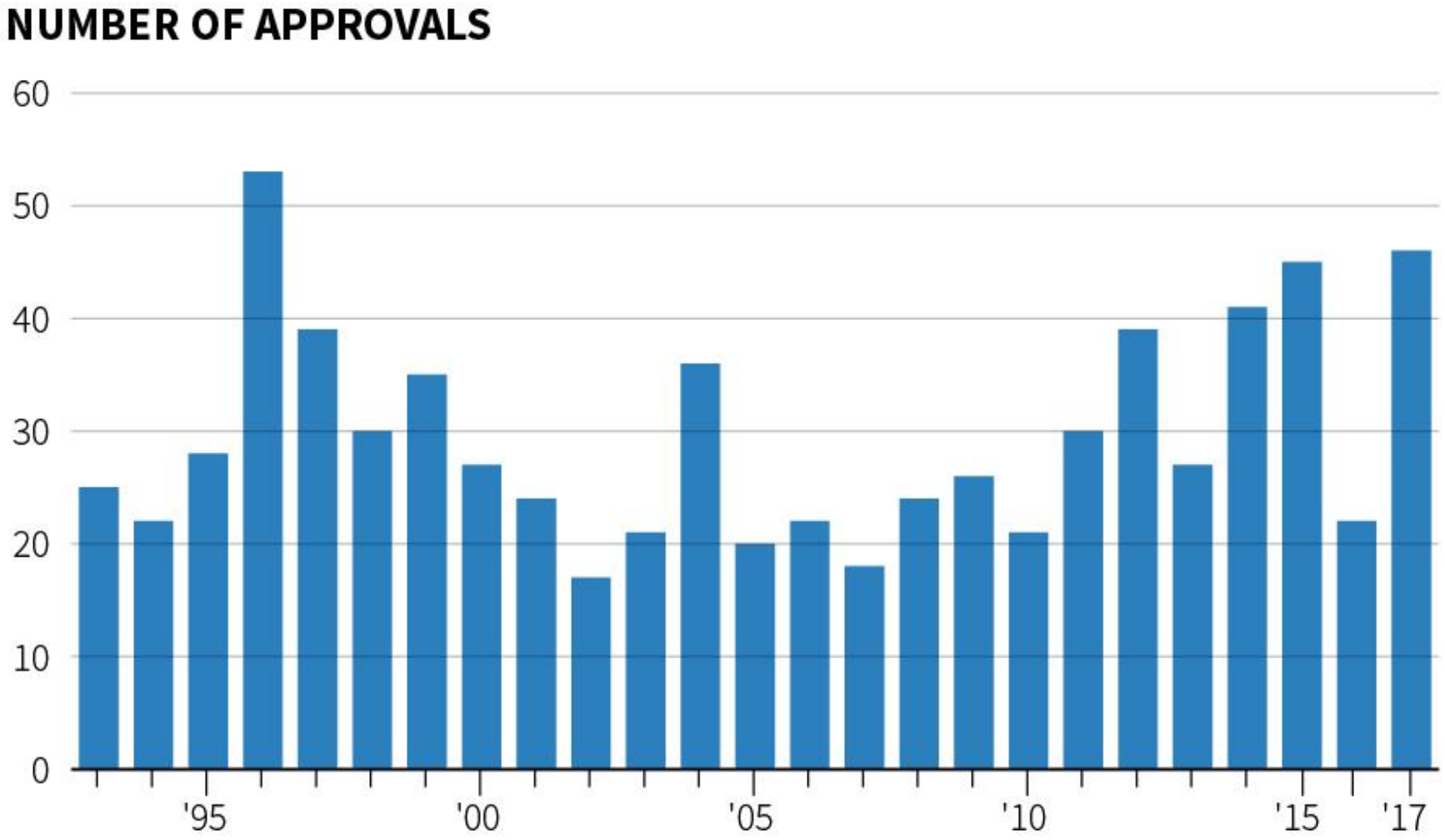


Source: AAAS data, agency budget documents, and appropriations. Adjusted for biomedical R&D inflation rate (BRDPI). Excludes supplemental FY 2017 Zika proposal and FY 2015 Ebola funding.

Private & Public R&D Spending: Is There a Partnership



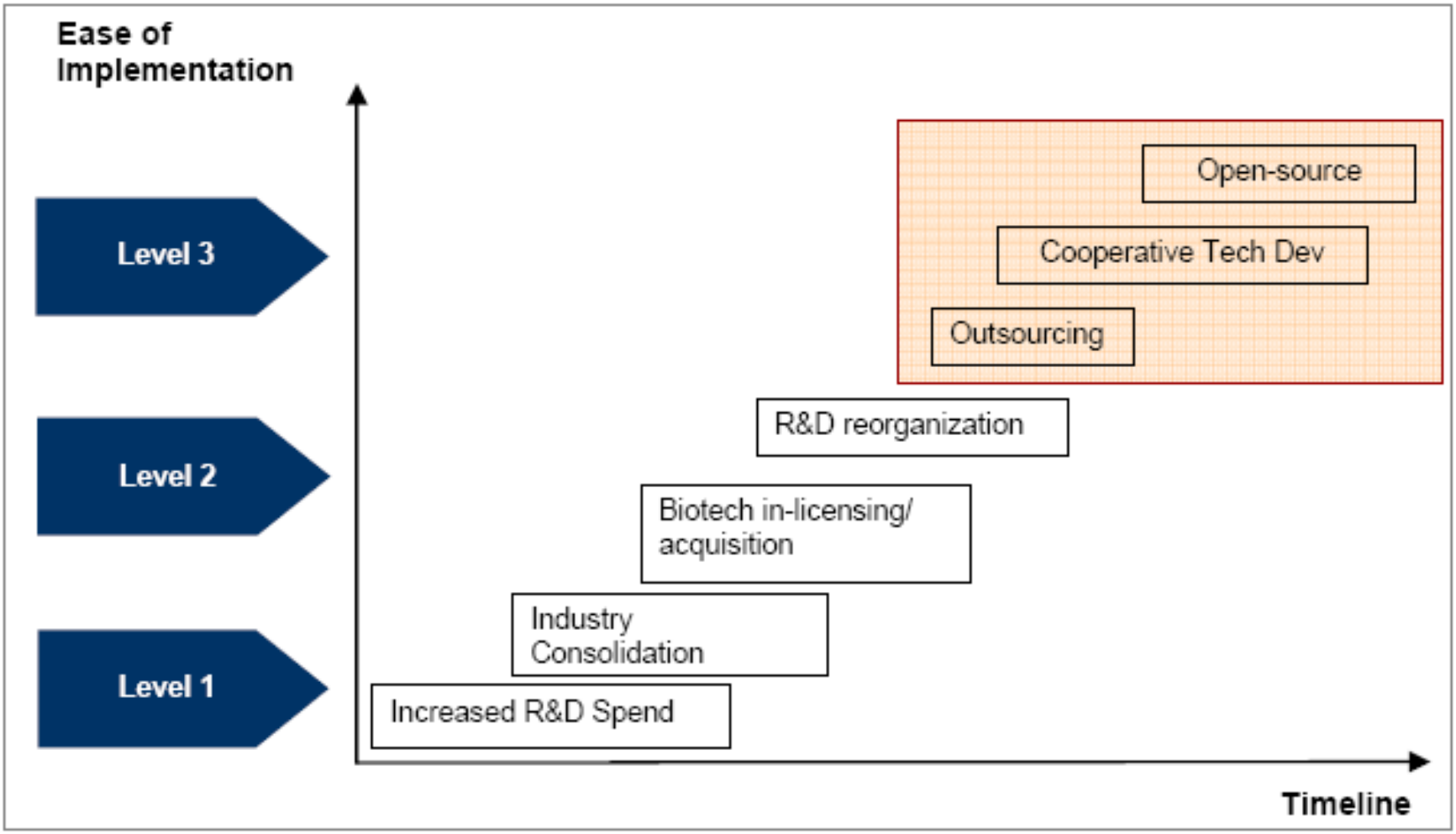
U.S. FDA drug approvals



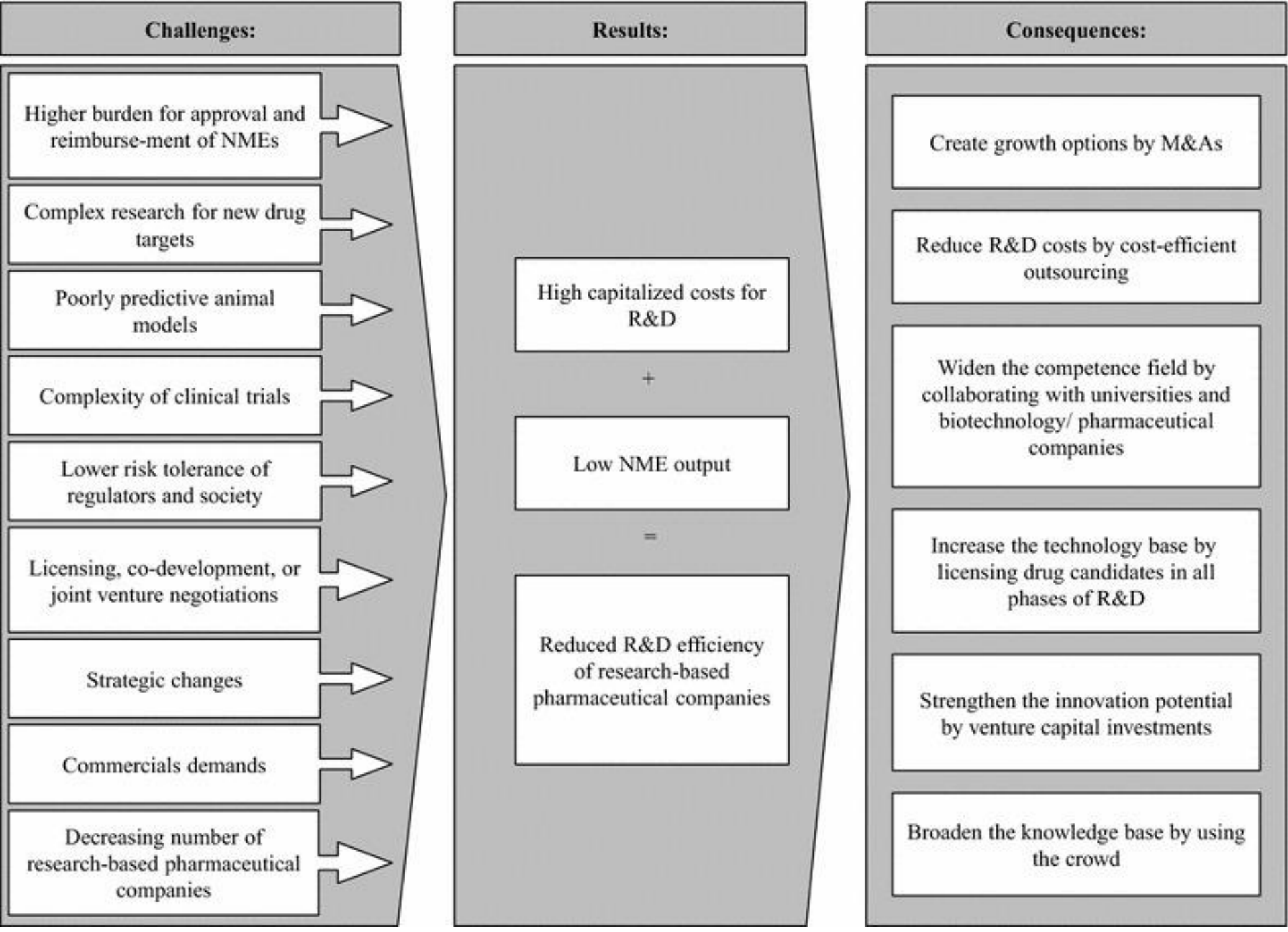
Source: U.S. Food and Drug Administration

III. Innovation and Transformation

Innovation and Transformation Models



Hu et al (2007)



Schumaker et al, 2016

Me Too Drugs: Antidepressants (Anti-Innovation?)

1986	Fluvoxamine	(Luvox; Solvay) SSRI
1987	Fluoxetine	(Prozac; Lilly) SSRI
1992	Sertraline	(Zoloft; Pfizer) SSRI/NRI
1993	Venlafaxine	(Effexor; Wyeth) SSRI/NRI
1996	Buproprion	(Wellbutrin; Wyeth) SNRI/DRI
2002	Escitalopram	(Lexapro; Forrest) SSRI
2004	Duloxetine	(Cymbalta; Lilly) SSRI/NRI
2008	Devenlafaxine	(Pristiq; Wyeth/Pfizer) SNRI
2011	Vilazidone	(Vybrid; Forest Labs) SSRI/5HT1a

IV. Designing Drug Development Trials: Alzheimer's Disease

Alzheimer's Disease

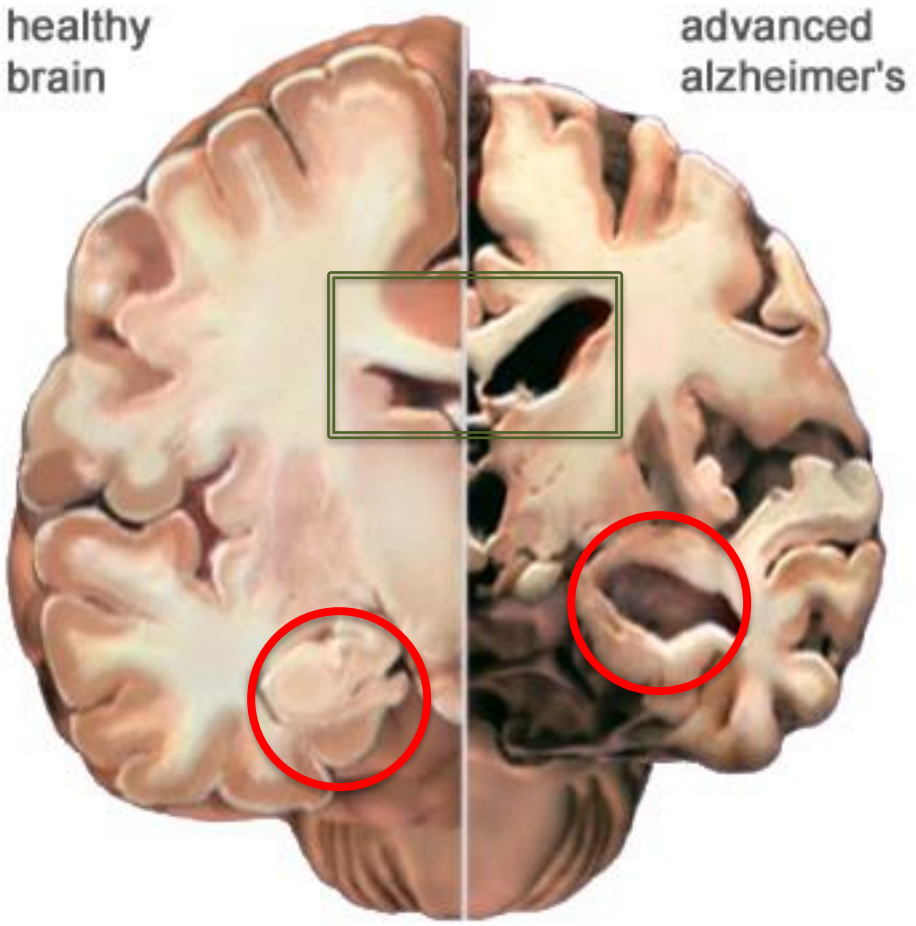
- **An estimated 5.7 million Americans have Alzheimer's Disease**
- **6th leading cause of death in the United States**
- **$232 billion: the direct costs of care in the United States in 2017**
- **In 2050: 14 million people will have AD**
- **In 2050: $1.1 trillion in direct costs (2018 dollars)**

Desperate need for Treatment

Alzheimer's Disease: Symptoms

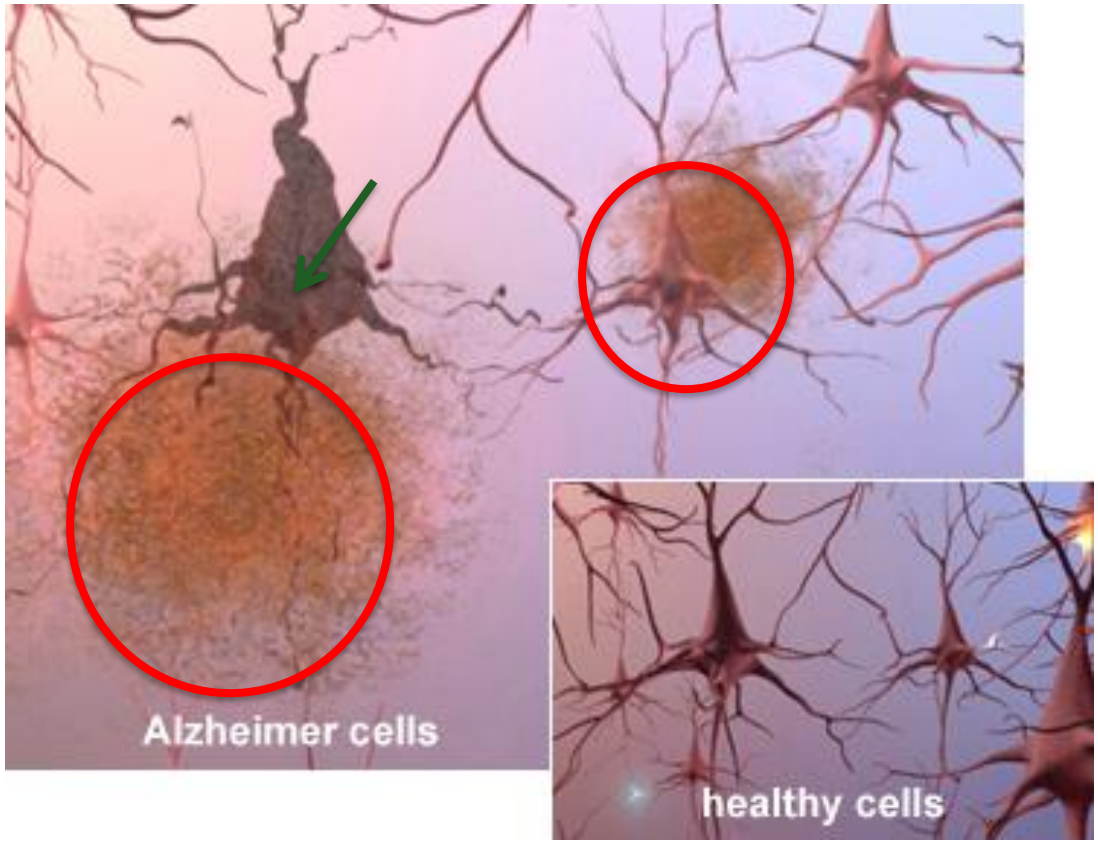
- **Memory loss that disrupts daily life**
- **Challenges in planning or problem solving**
- **Difficulty completing familiar tasks**
- **Confusion with time or place**
- **Trouble with visual images and spatial relationships**
- **New problems with words when speaking or writing**
- **Mood and personality changes**

The Alzheimer's Brain: Gross Anatomical Changes



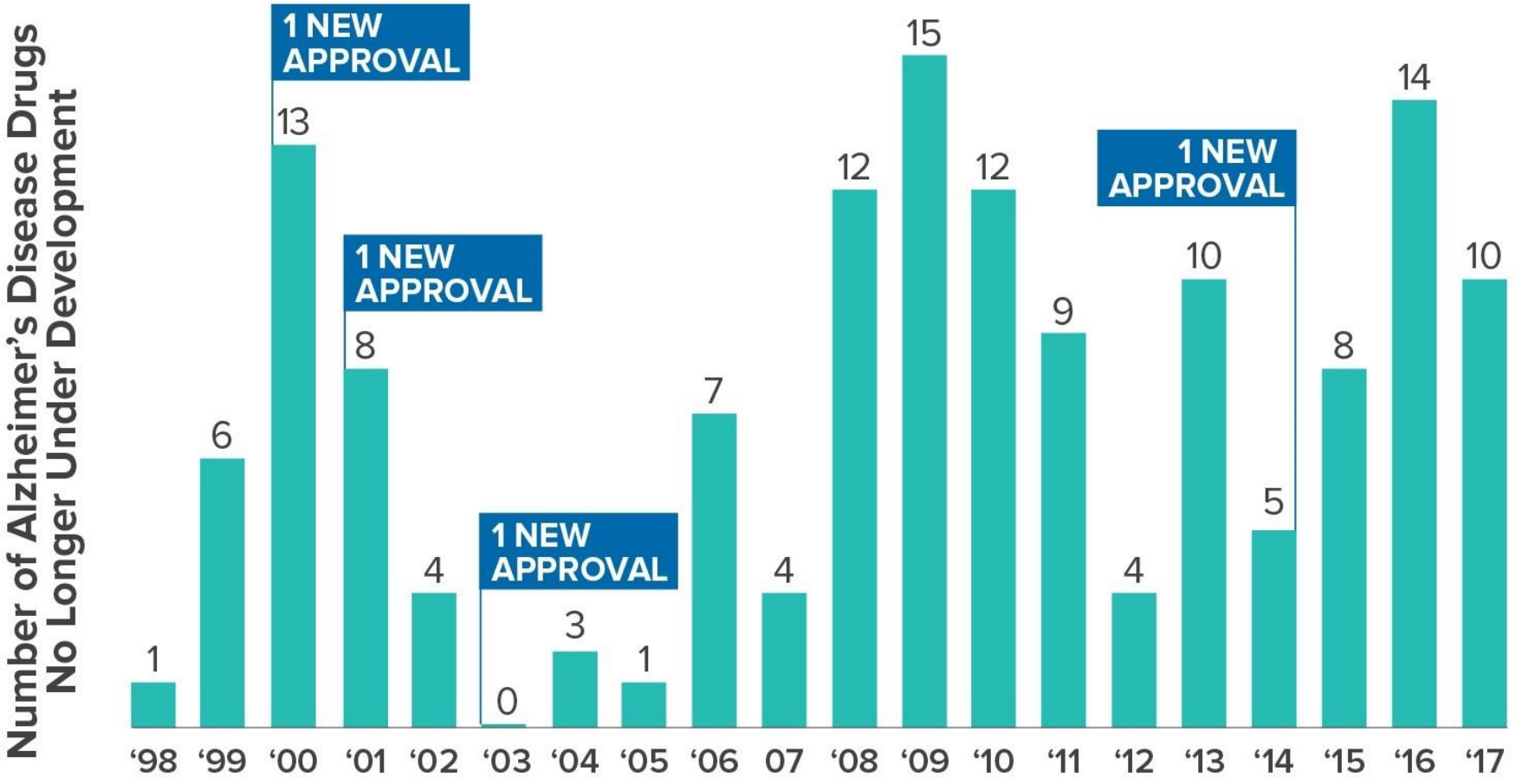
- The **cortex** shrivels up, damaging areas involved in thinking, planning and remembering.
- Shrinkage is especially severe in the **hippocampus**, an area of the cortex that plays a key role in formation of new memories.
- **Ventricles** (fluid-filled spaces within the brain) grow larger.

The Alzheimer's Brain: Microscopic Changes



- Alzheimer's tissue has many fewer nerve cells and synapses than a healthy brain.
- **PLAQUES**, abnormal clusters of protein fragments, build up between nerve cells.
- Dead and dying nerve cells contain **TANGLES**, which are made up of twisted strands of another protein.

Unsuccessful Investigational Drugs for Alzheimer's Disease (1998-2017)



146 Total Unsuccessful Drugs I **4** Total Approved Medicines

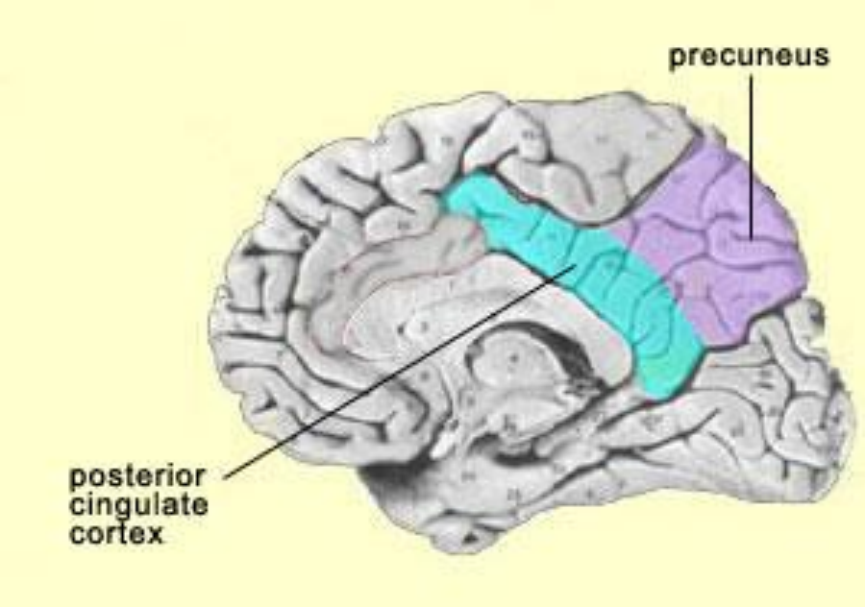
Bateman et al (2012)
Clinical and Biomarker Changes in Dominantly Inherited Alzheimer's Disease

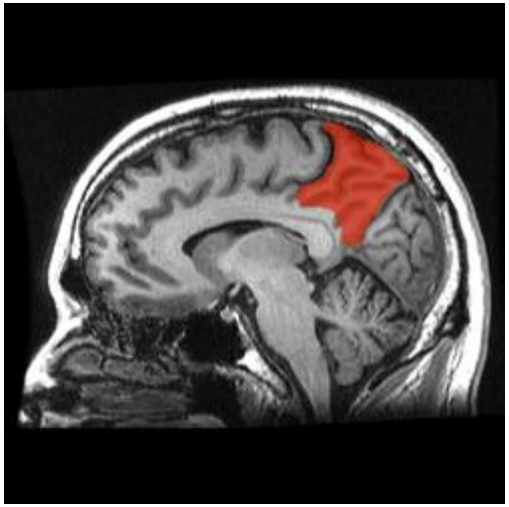
- **Autosomal dominant AD**
- **128 patients**
- **Baseline clinical and cognitive assessments, brain imaging, and cerebrospinal fluid (CSF) and blood tests**
- **Participant's age at baseline assessment and the parent's age at the onset of symptoms of Alzheimer's disease to calculate the estimated years from expected symptom onset**
- **Autosomal dominant Alzheimer's disease was associated with a series of pathophysiological changes over decades in CSF biochemical markers of Alzheimer's disease, brain amyloid deposition, and brain metabolism as well as progressive cognitive impairment**

Bateman et al., 2012

Precuneus:

- Episodic memory, visual-spatial abilities, and motor activity coordination strategies. self perception, consciousness, and the executive and working memory.
- At rest it has the highest metabolic rates, consuming more glucose than any other cortex
- Part of Default Mode Network





PUTATIVE BIOMARKERS I

Variable	Estimated Years from Expected Symptom Onset					
	−25	−20	−15	−10	−5	0
Aβ deposition in the precuneus (SUVR ratio)††						
Noncarriers	0.69	0.69	0.69	0.70	0.70	0.69
Carriers	0.71	0.76	0.9	1.08	1.24	1.36
Difference	0.02±0.28	0.07±0.17	0.21±0.15‡	0.38±0.13§	0.54±0.12§	0.67±0.15§
Glucose metabolism in the precuneus (SUVR ratio)‡‡						
Noncarriers	2.06	2.04	2.01	1.99	1.97	1.95
Carriers	2.16	2.05	1.94	1.83	1.72	1.61
Difference	0.10±0.16	0.01±0.13	−0.07±0.11	−0.16±0.09§	−0.25±0.08§	−0.34±0.09§
Total hippocampal volume (mm^3)						
Noncarriers	8999	8874	8748	8622	8497	8371
Carriers	8767	8511	8255	7999	7743	7486
Difference	−232±675	−363±548	−493±442**	−623±370‡	−754±356§	−885±406§

†† Deposition of amyloid-beta (Aβ) in the precuneus was measured by positron-emission tomography (PET) with the use of Pittsburgh compound B (PIB). A higher SUVR indicates greater binding of PIB to fibrillar amyloid.

‡‡ Glucose metabolism in the precuneus was measured by PET with the use of fluorodeoxyglucose. A lower SUVR indicates lower metabolism.

§ P<0.001. ** P<0.05. ‡ P<0.01

COGNITIVE MARKERS

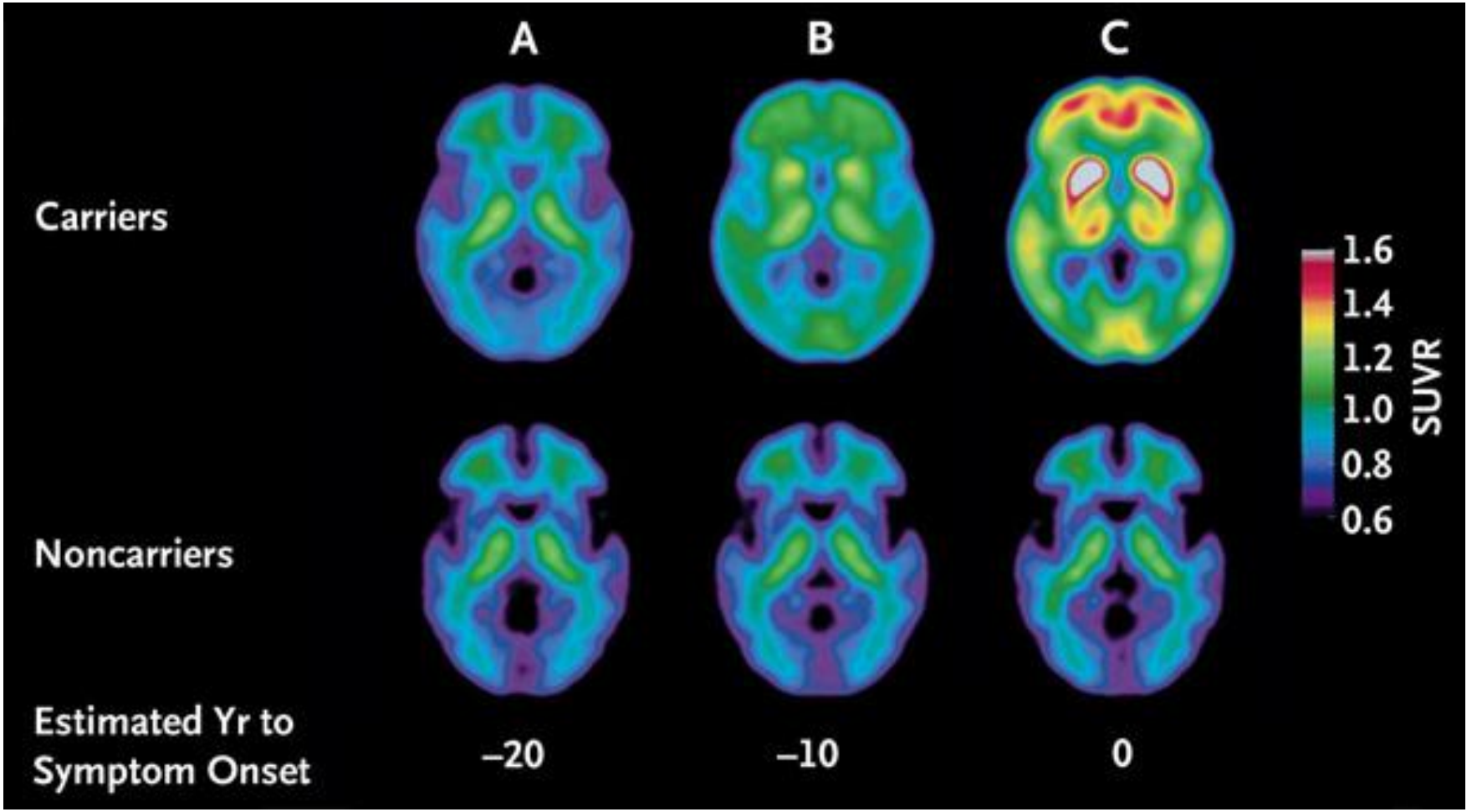
Table 2. Clinical, Cognitive, Imaging, and Biochemical Estimates in Mutation Carriers and Noncarriers.*

Variable	Estimated Years from Expected Symptom Onset					
	−25	−20	−15	−10	−5	0
CDR-SOB score (no.)†						
Noncarriers	0	0	0	0	0	0
Carriers	0	0	0.2	0.7	1.5	2.6
Difference	0±2.2	0±1.4	0.2±1.1	0.7±1.1	1.5±1.1‡	2.6±1.1§
MMSE score (no.)¶						
Noncarriers	29.4	29.5	29.5	29.5	29.6	29.6
Carriers	29.9	29.7	29.1	28.1	26.5	24.6
Difference	0.5±4.0	0.2±2.5	−0.4±1.9	−1.4±1.9	−3.1±2.0‡	−5.0±2.0§
Logical Memory score (no.)‖						
Noncarriers	14.7	15.6	15.1	13.9	12.5	11.3
Carriers	16.3	15.9	14.1	11.4	8.3	5.2
Difference	1.6±4.2	0.3±2.7	−1.0±2.0	−2.5±2.0**	−4.2±2.2§	−6.1±2.2§

† Scores on the CDR-SOB range from 0 (cognitive normality) to 18 (maximal cognitive impairment).‡ P<0.01. § P<0.001. ¶ Scores on the Mini–Mental State Examination (MMSE) range from 0 (severe impairment) to 30 (no impairment). A score higher than 27 is considered normal. Scores on the Logical Memory subtest of the Wechsler Memory Scale–Revised range from 0 (no recall) to 25 (complete recall). ** P<0.05.

Bateman et al., 2012

Predicting Alzheimer's Disease: Biomarkers



Brain scans show evidence of Alzheimer's disease 20 years before symptoms arise (far left), 10 years before (middle), and after the onset of symptoms (right). Beta amyloid, a protein associated with the disease, is more visible in people who develop the disease (top row) than in those who don't. The more color in the scan, the more beta amyloid is present in the brain.

Bateman et al (2012)

Serendipity or Good Science: Building Opportunity

Hoffman

Osterloh

Thank you for your time and attention