Returns to investing in the health of Californians

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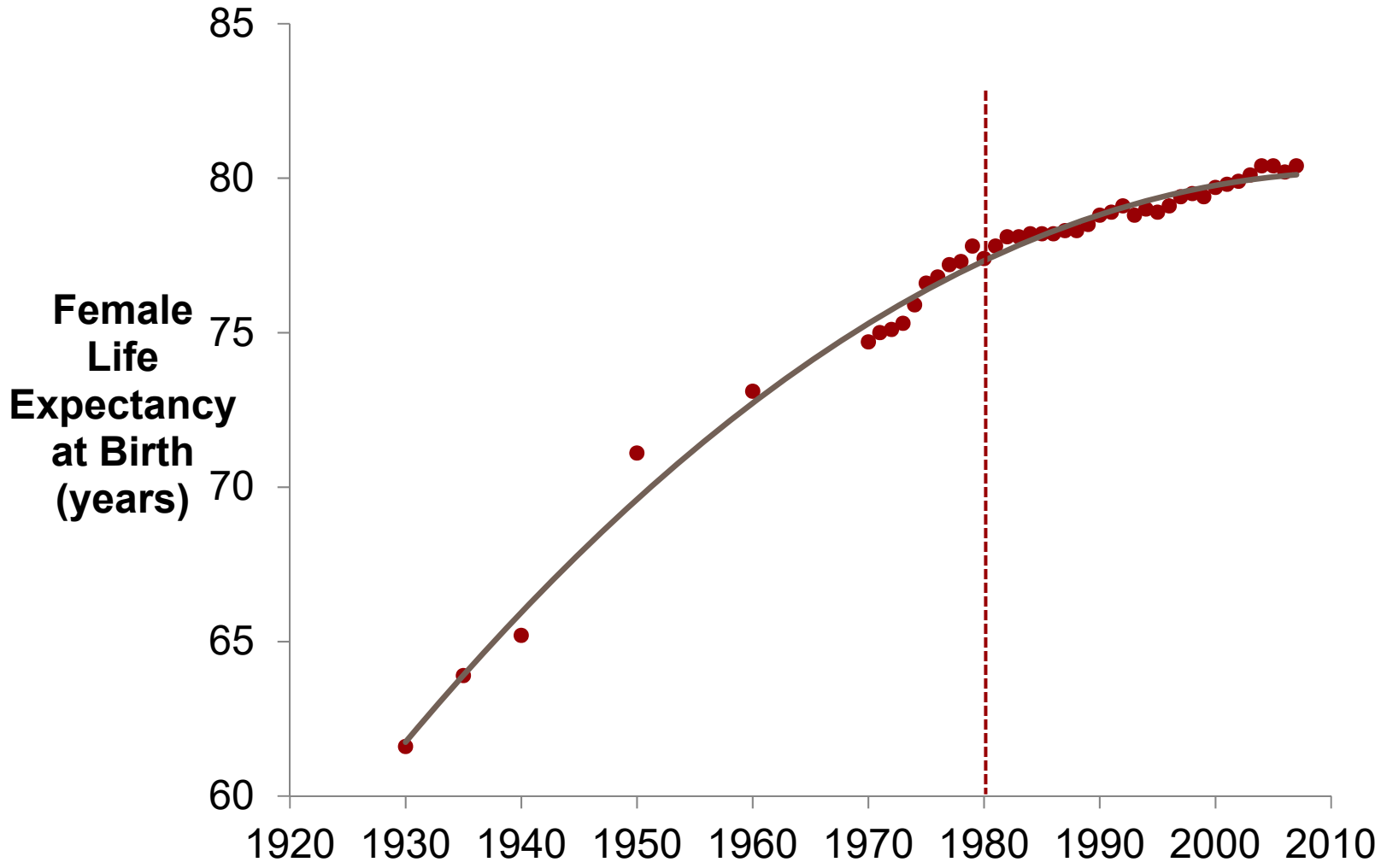
California needs a new approach to fight disease and disability

- **Demography**
- **Science**
- **Economics**

Until about 1982, we made rapid progress fighting illnesses earlier in the life course



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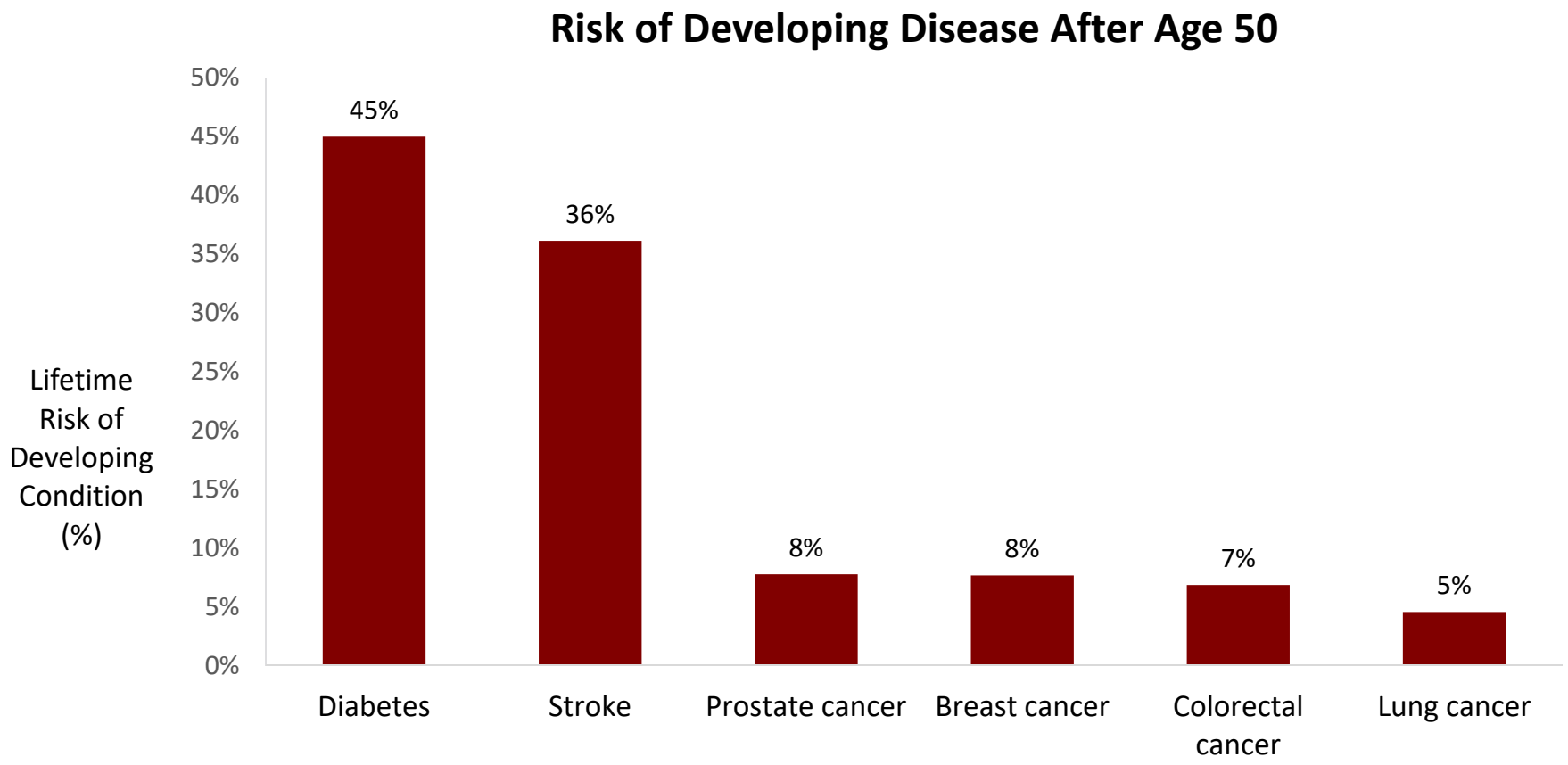
Source: National Center for Health Statistics, *National Vital Statistics Reports.*

We have become victims of our own success



Source: Authors' calculations using the Future Elderly Model.

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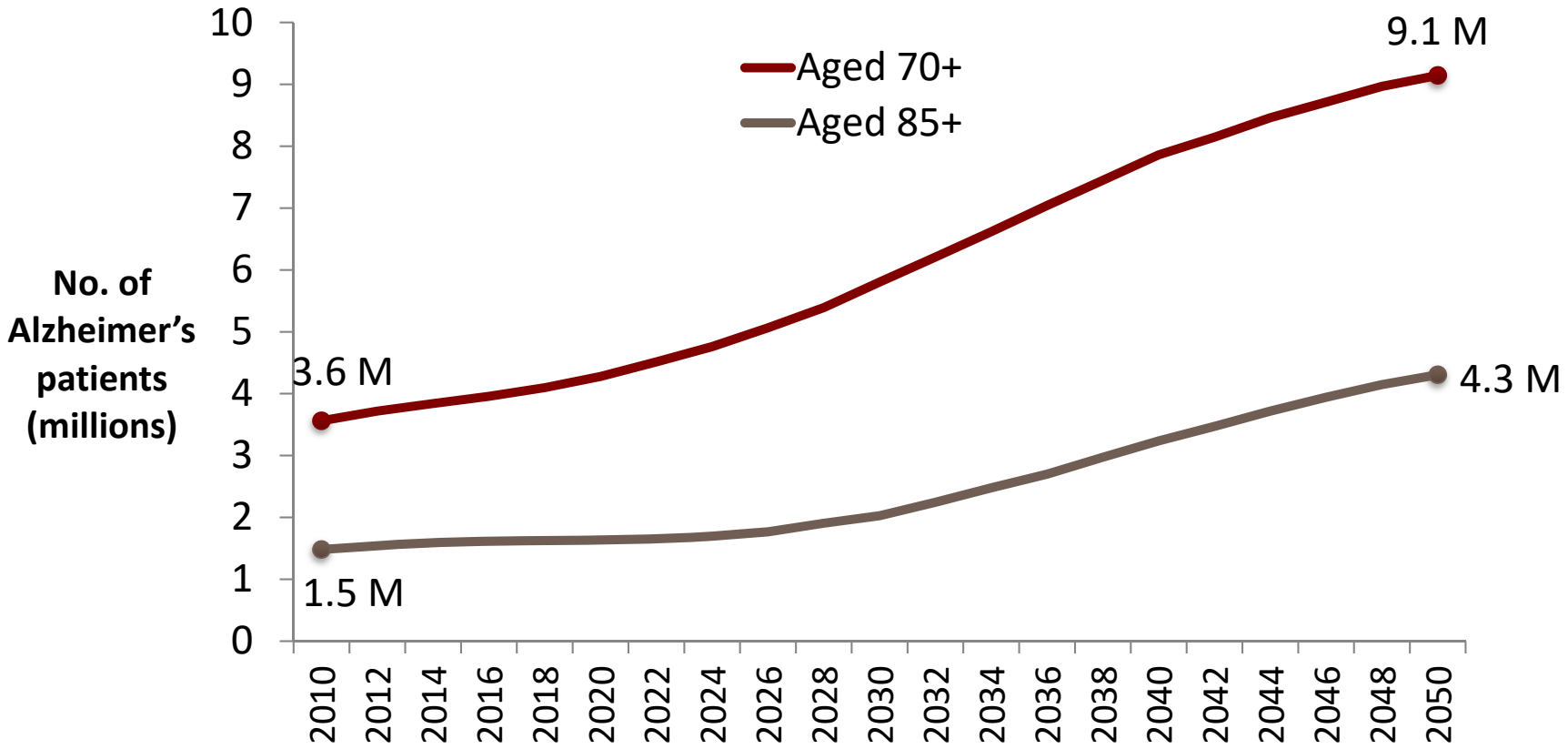
The number of Americans with Alzheimer's disease will double over the next several decades



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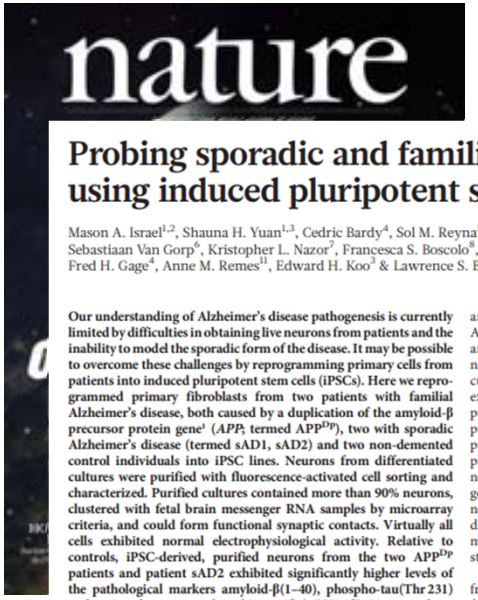
California needs a new approach to fight disease and disability

1. Demographic progress fighting other diseases
2. Scientific promise
3. Economic (dis)incentives

Regenerative medicine show tremendous promise



nature

Probing sporadic and familial Alzheimer's disease using induced pluripotent stem cells

Mason A. Israel[1,2], Shauna H. Yuan[1,3], Cedric Bardy[4], Sol M. Reyna[1,2], Yangling Mu[4], Cheryl Herrera[1], Michael P. Hefferan[5], Sebastiaan Van Gorp[6], Kristopher L. Nazor[7], Francesca S. Boscolo[8], Christian T. Carson[9], Louise C. Laurent[8], Martin Marsala[5,10], Fred H. Gage[4], Anne M. Remes[11], Edward H. Koo[3] & Lawrence S. B. Goldstein[1,3]

Our understanding of Alzheimer's disease pathogenesis is currently limited by difficulties in obtaining live neurons from patients and the inability to model the sporadic form of the disease. It may be possible to overcome these challenges by reprogramming primary cells from patients into induced pluripotent stem cells (iPSCs). Here we reprogrammed primary fibroblasts from two patients with familial Alzheimer's disease, both caused by a duplication of the amyloid-β precursor protein gene[1] (*APP*; termed APP^{Dp}), two with sporadic Alzheimer's disease (termed sAD1, sAD2) and two non-demented control individuals into iPSC lines. Neurons from differentiated cultures were purified with fluorescence-activated cell sorting and characterized. Purified cultures contained more than 90% neurons, clustered with fetal brain messenger RNA samples by microarray criteria, and could form functional synaptic contacts. Virtually all cells exhibited normal electrophysiological activity. Relative to controls, iPSC-derived, purified neurons from the two APP^{Dp} patients and patient sAD2 exhibited significantly higher levels of the pathological markers amyloid-β(1–40), phospho-tau(Thr 231) and active glycogen synthase kinase-3β (aGSK-3β). Neurons from APP^{Dp} and sAD2 patients also accumulated large RAB5-positive early endosomes compared to controls. Treatment of purified neurons with β-secretase inhibitors, but not γ-secretase inhibitors, caused significant reductions in phospho-Tau(Thr 231) and aGSK-3β levels. These results suggest a direct relationship between APP proteolytic processing, but not amyloid-β, in GSK-3β activation and tau phosphorylation in human neurons. Additionally, we observed that neurons with the genome of one sAD patient exhibited the phenotypes seen in familial Alzheimer's disease samples. More generally, we demonstrate that iPSC technology can be used to observe phenotypes relevant to Alzheimer's disease, even though it can take decades for overt disease to manifest in patients.

Alzheimer's disease is a common neurodegenerative disorder, defined post mortem by the increased presence of amyloid plaques and neurofibrillary tangles in the brain[2]. Amyloid plaques are extracellular deposits consisting primarily of amyloid-β peptides, and neurofibrillary tangles are intraneuronal aggregations of hyperphosphorylated tau, a microtubule-associated protein involved in microtubule stabilization[3]. The causative relationship between amyloid plaque/amyloid-β and tau pathologies is unclear in humans. Although the vast majority of Alzheimer's disease is apparently sporadic with significant non-Mendelian genetic contributions[4], analyses of cellular and animal and other fragments. Mouse models that overexpress familial Alzheimer's disease mutations develop extensive plaque deposition and amyloid-associated pathology, but neurofibrillary tangles and significant neuronal loss are conspicuously absent[5,6]. Fetal human cortical cultures have also been used to study the APP–tau relationship. For example, cortical cultures treated with 20 μM amyloid-β have elevated phosphorylated tau (p-tau)[7]. However, it is still unclear whether physiologically relevant levels of amyloid-β directly cause elevated p-tau and which kinases are directly involved in this aberrant phosphorylation. Additionally, experimental approaches using fetal human neurons are hindered by limited availability of samples and unknown genetic backgrounds. The recent developments in iPSCs and induced neurons have allowed investigation of phenotypes of neurological diseases *in vitro*[8,9,10]. However, not all diseases have been successfully modelled using iPSCs[11], and it is unclear whether iPSCs can be used to study sporadic forms of disease.

Here we report the derivation and neuronal differentiation of iPSCs from patients with familial and sporadic Alzheimer's disease, as well as from non-demented, age-matched controls. Using purified human neurons we probe three key questions concerning Alzheimer's disease: (1) can iPSC technology be used to observe phenotypes of patients with Alzheimer's disease, even though it can take decades for overt disease to manifest; (2) is there a causative relationship between APP processing and tau phosphorylation; and (3) can neurons with the genome of a sAD patient exhibit phenotypes seen in familial Alzheimer's disease samples? Supplementary Fig. 1 summarizes the experimental approach and findings.

We characterized *APP* metabolism in fibroblasts before reprogramming to iPSCs (Supplementary Fig. 2). *APP* expression and amyloid-β secretion were quantified in early-passage primary fibroblasts from two non-demented control (NDC) individuals, two sAD patients and two APP^{Dp} patients (Table 1). The presence of the genomic duplication was confirmed in fibroblasts. Relative to NDC and sAD cells, APP^{Dp} fibroblasts expressed higher levels of *APP* mRNA and secreted 1.5- to twofold higher amounts of amyloid-β(1–40) peptides into culture media compared to NDC cells. We did not detect significant increases in amyloid-β(1–42/1–40) or amyloid-β(1–38/1–40) in patient samples versus controls.

We generated iPSC lines by transducing fibroblasts with retroviruses encoding *OCT4, SOX2, KLF4, c-MYC* and, in one-third of cultures, *EGFP*. Each of the six individuals was represented by three

CIRM 2018 Annual Report
Every Moment Counts. Don't Stop Now

2018 Industry Support

Disease	Grantee	Investment/Industry Partner	2018 Funding
Kidney Failure	Humacyte, Inc.	Series C	$75 million
Multiple Myeloma	Poseida Therapeutics, Inc.	Series B	$31 million
Adenosine Deaminase-Deficient Severe Combined Immunodeficiency	Orchard Therapeutics	GlaxoSmithKline	Undisclosed
Acute Myeloid Leukemia	Nohla Therapeutics	Series B	$56 million
Acute Myeloid Leukemia and Advanced Colorectal Cancer	Forty Seven, Inc.	Initial Public Offering	$113 million
Kidney Failure	Humacyte, Inc.	Fresenius Medical Care	$150 million
Adenosine Deaminase-Deficient Severe Combined Immunodeficiency	Orchard Therapeutics	Series C	$150 million
X-Linked Severe Combined Immunodeficiency	Dr. Sorrentino (St. Jude's)	Mustang Bio	Undisclosed
Type 1 Diabetes	ViaCyte, Inc.	CRISPR Therapeutics	$25 million
Type 1 Diabetes	ViaCyte, Inc.	W.L. Gore & Associates, Inc.	$10 million
Advanced Solid Tumors	Fate Therapeutics	Follow-on Public Offering	$144 million
Adenosine Deaminase-Deficient Severe Combined Immunodeficiency	Orchard Therapeutics	Initial Public Offering	$226 million
Spinal Cord Injury	Asterias Biotherapeutics	BioTime, Inc.	Undisclosed
Type 1 Diabetes	ViaCyte, Inc.	Series D	$80 million

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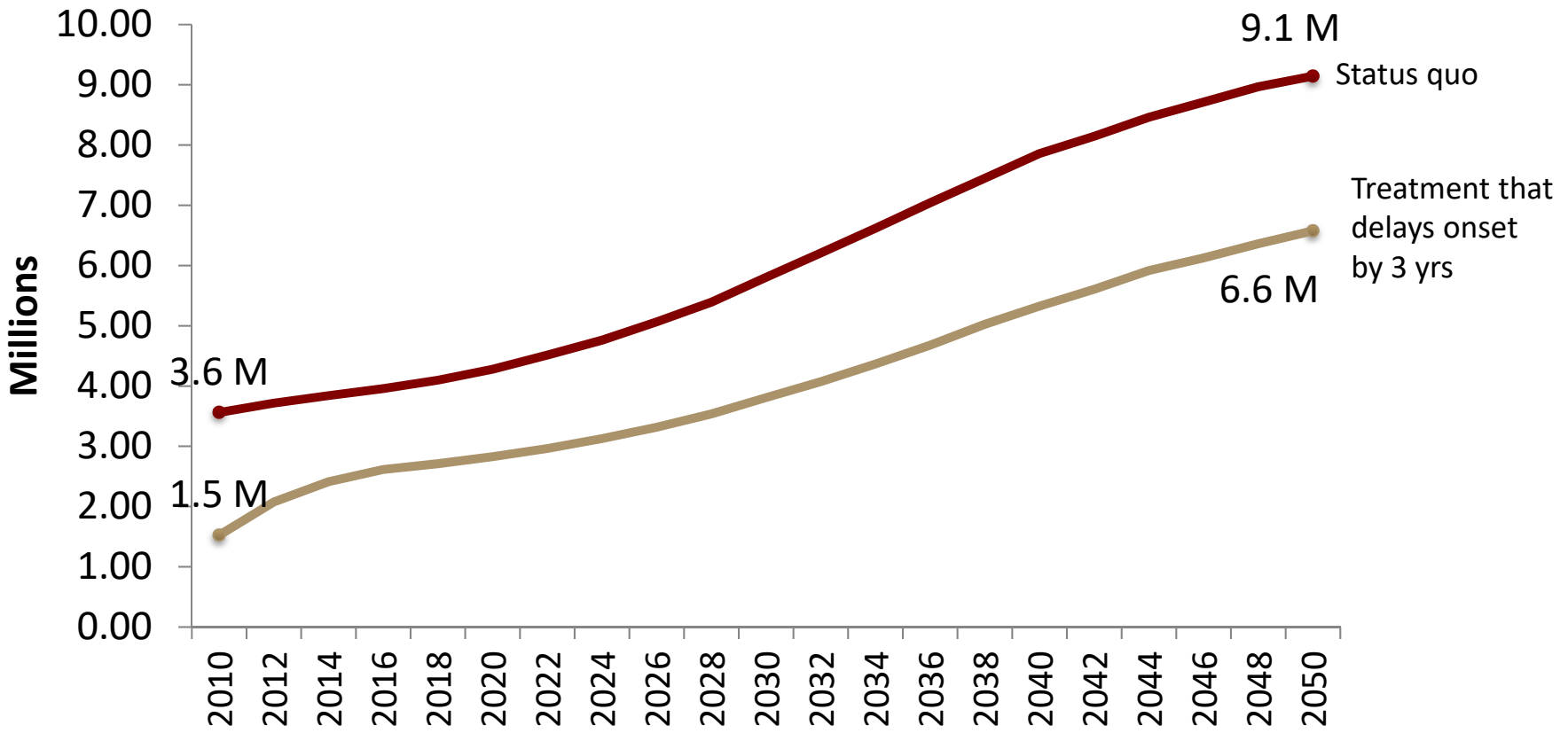
Population with Alzheimer's Disease



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Source: Authors' calculations using Future Elderly Model.

Why is this important now?

1. Demographic progress fighting other diseases
2. Scientific promise of stem cell therapies
3. Economic (dis)incentives

Our health care system tilts the playing field against regenerative medicine

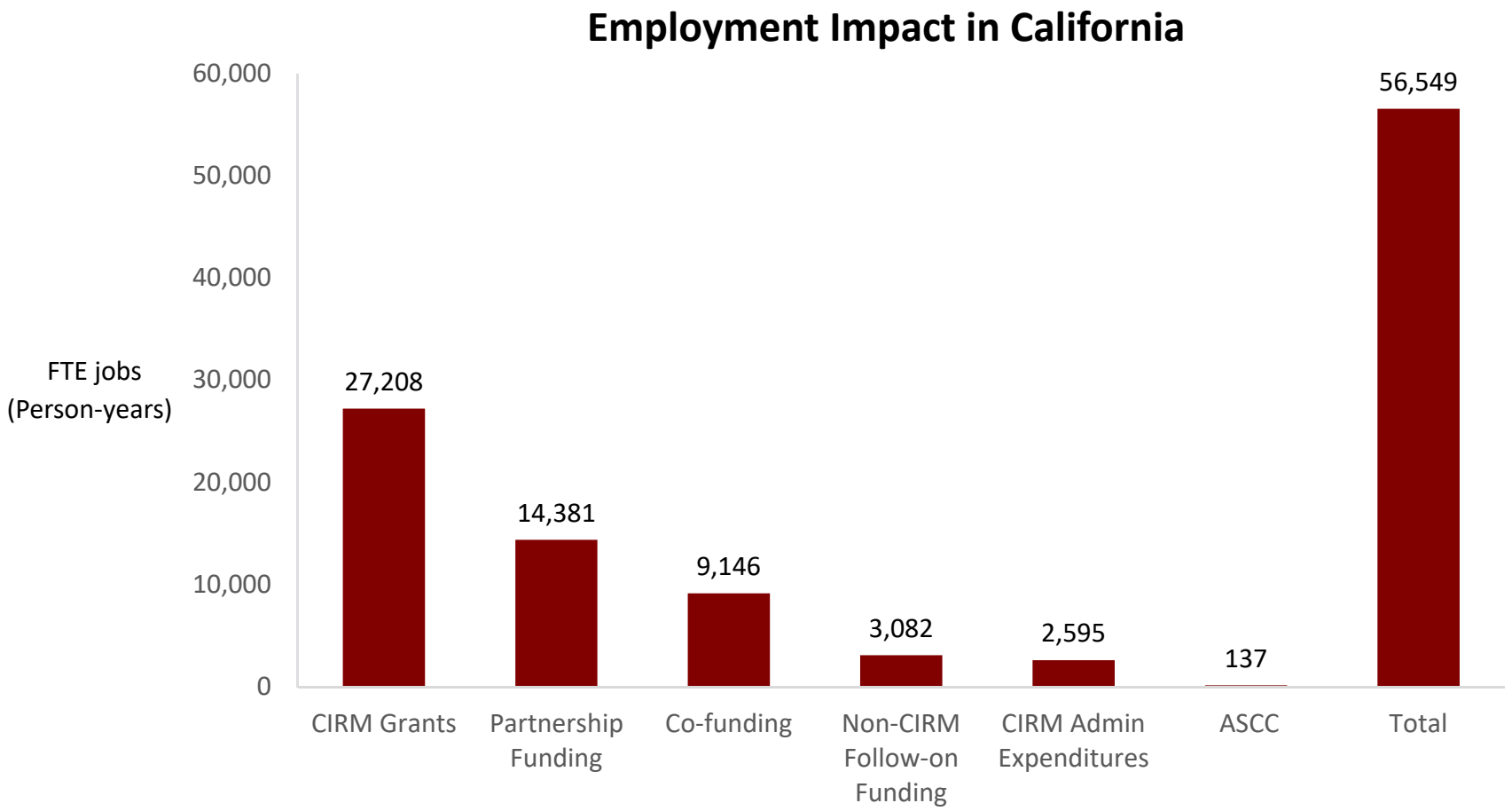
- Current reimbursement model rewards treatment over prevention or cures
  - Most coverage is still fee-for-service (even if managed)
  - Higher return to managing chronic illness, rather than eliminating it or preventing it in the first place
- Regulatory approval process reinforces the reimbursement incentives

⇒ Regenerative medicine R&D is at a significant disadvantage

We estimated the benefits of additional investment in regenerative medicine in California

1. **Direct stimulus to the economy**
2. **Potential health benefits to California:**
   - **Addressing high prevalence conditions (cancers, diabetes and stroke)**
   - **Treating severe disease (dAMD)**

CIRM added 56,000+ jobs to the California economy from 2006 to 2023



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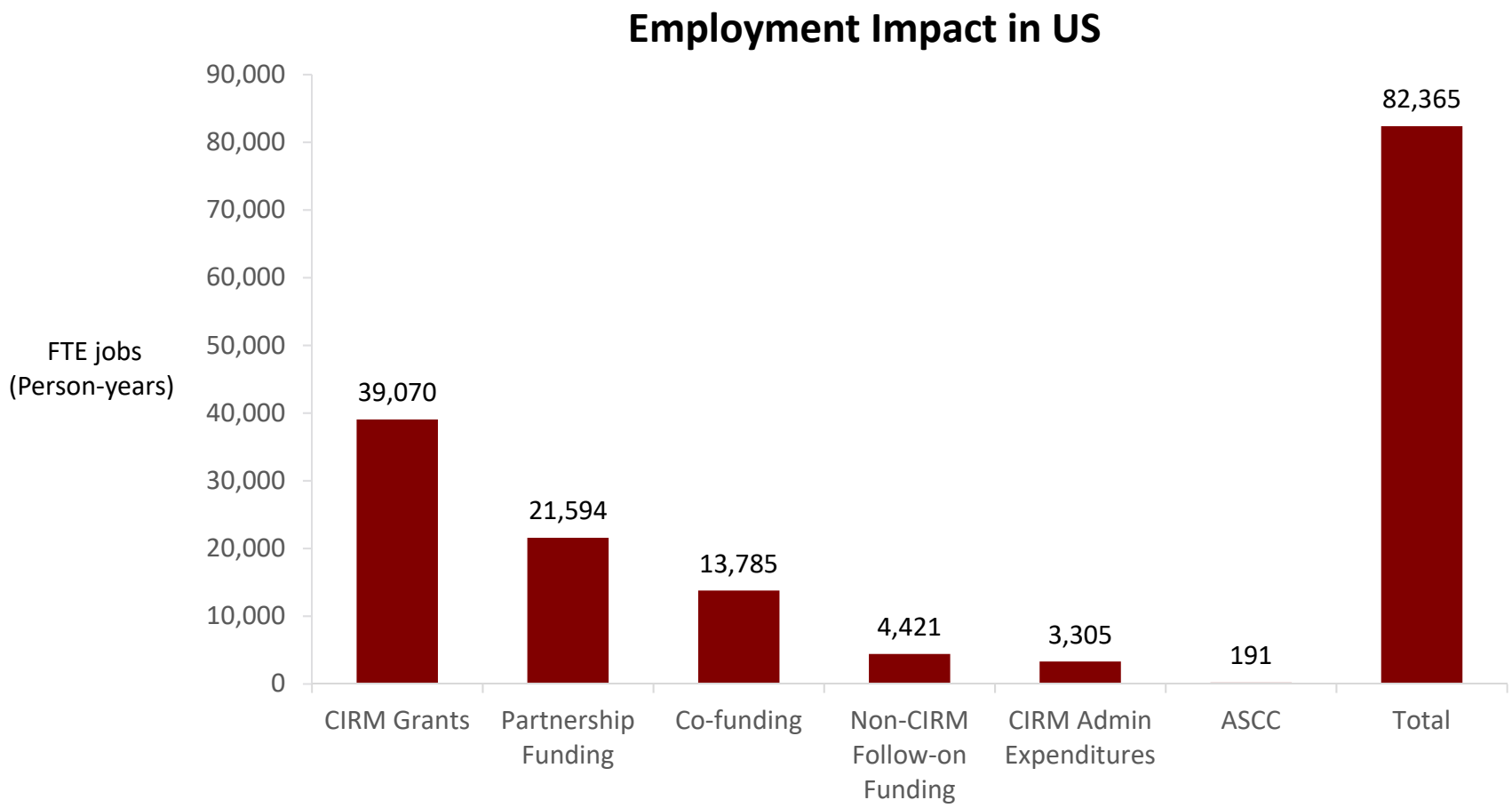
…and 82,000+ jobs nationwide



Note: Impacts include both those on the California economy and on the rest of the US

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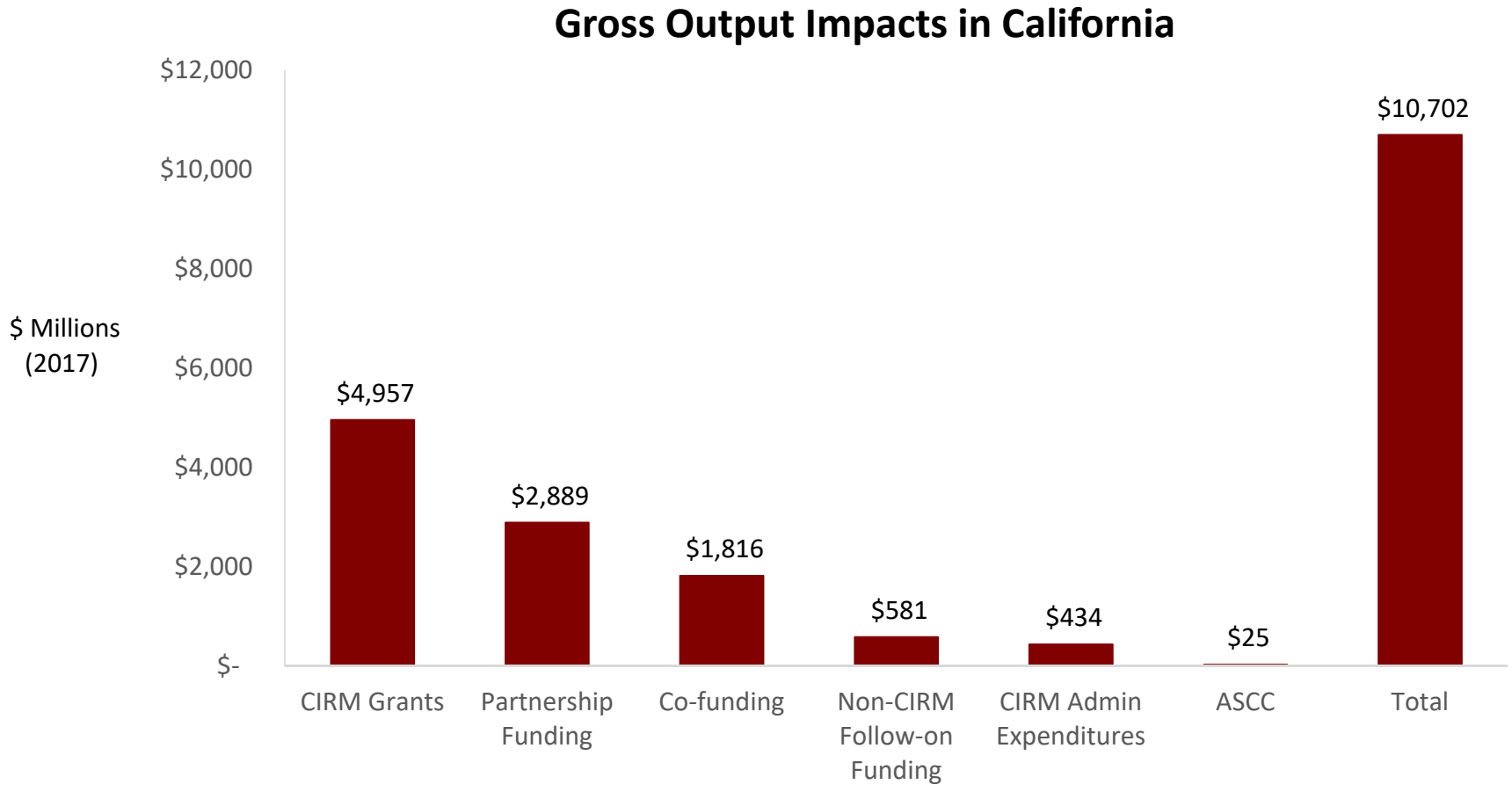
With an economic advantage in CA of $10 billion



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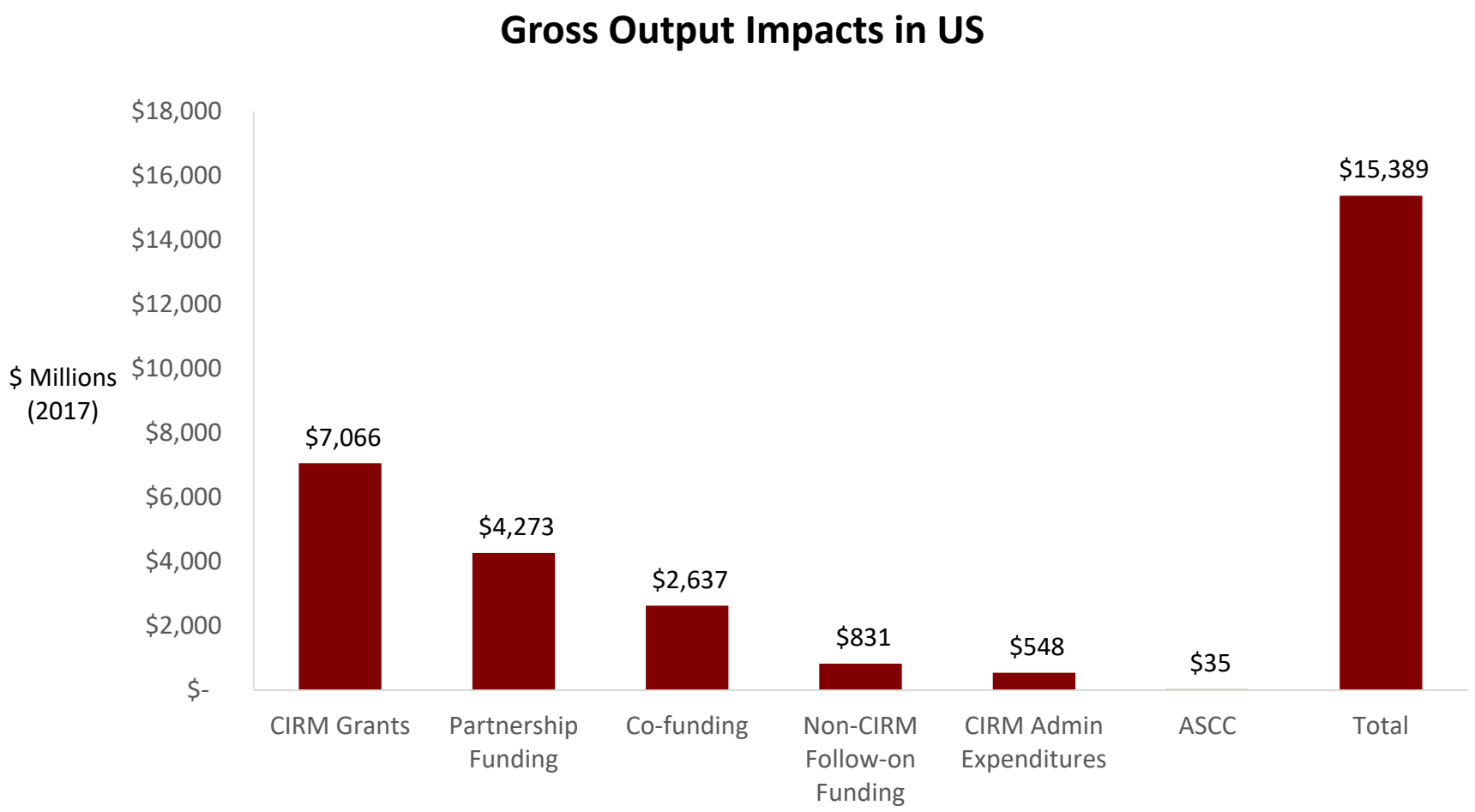
…and $15 billion nationwide



Note: Impacts include both those on the California economy and on the rest of the U.S.

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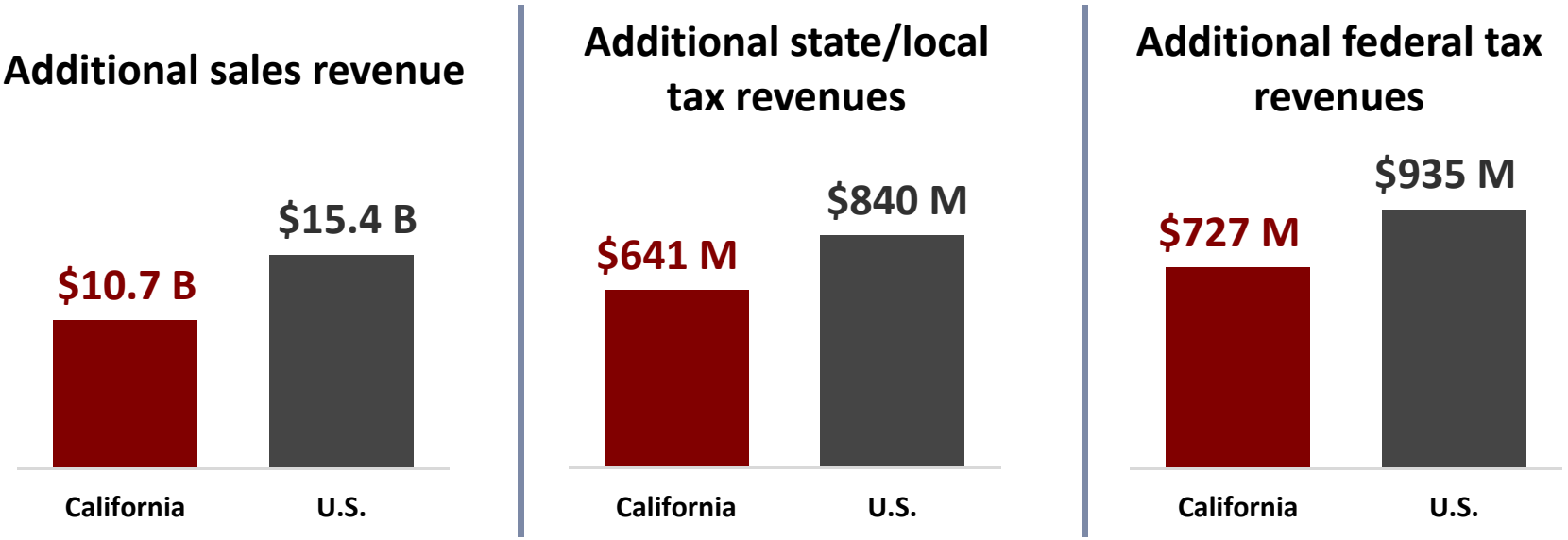
CIRM also generated additional tax dollars for federal, state, and local use



CIRM's impact created additional jobs

82,365 **Additional jobs in U.S. (total)**

56,549 **Additional jobs in California**

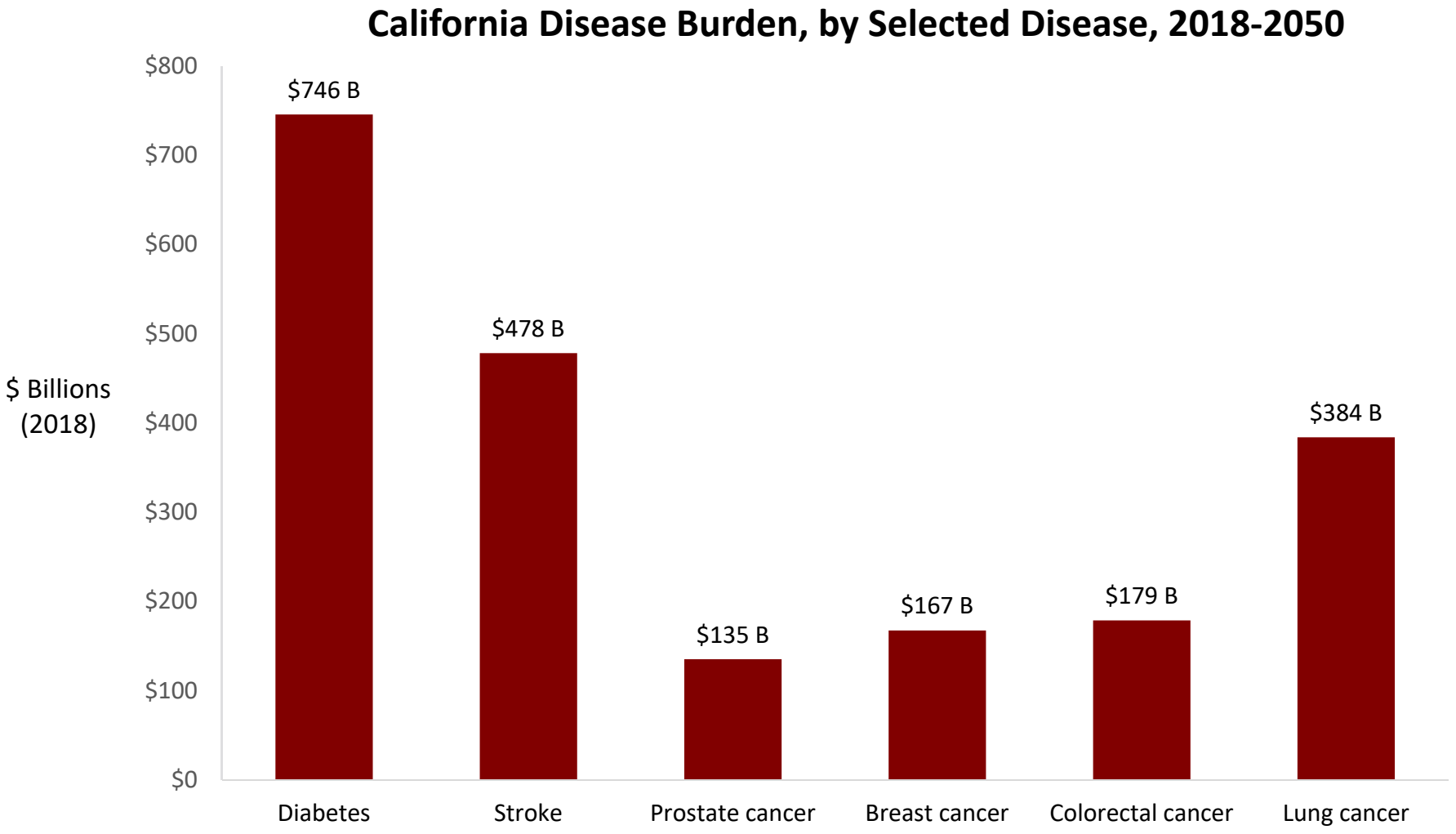
High quality jobs

- **Half at salaries considerably higher than state average**; **50.2%** of the gross output increase and **46.4%** of jobs created are concentrated in **medical and health-related research, manufacturing, and service sectors in California**
- **38.4%** of the gross output increase and **36.0%** of jobs created are concentrated in **medical and health related research, manufacturing, and service sectors in U.S.**

We estimated the benefits of additional investment in regenerative medicine in California

1. Direct stimulus to the economy
2. Potential health benefits to California:
   - Addressing high prevalence conditions (cancers, diabetes and stroke)
   - Treating severe disease (dAMD)

These conditions impose a hidden, but substantial, burden on the state



Note: Disease burden measured as reduced quality-adjusted life-years, expressed in dollars using $150,000 per QALY.

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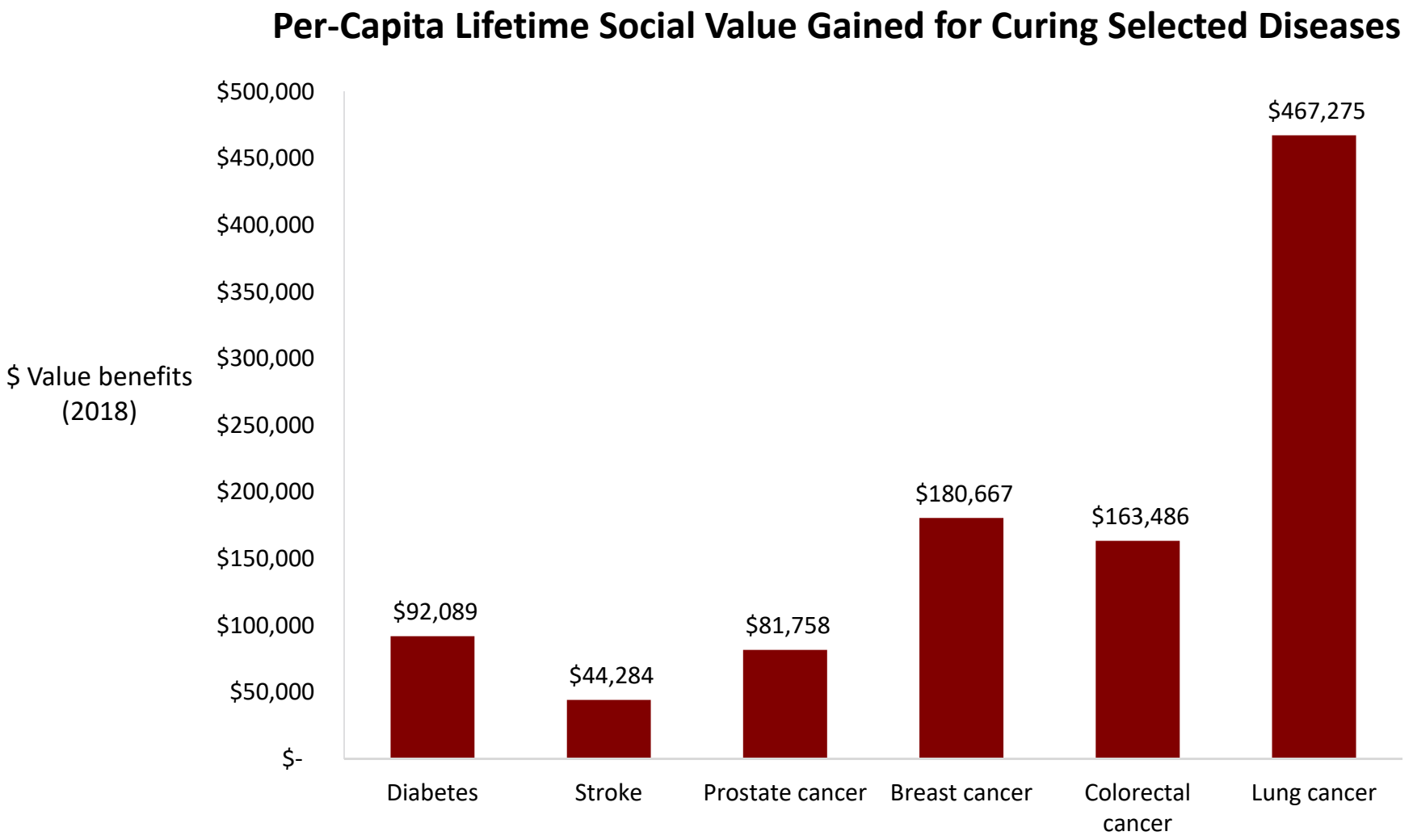
The potential gains to each person are substantial



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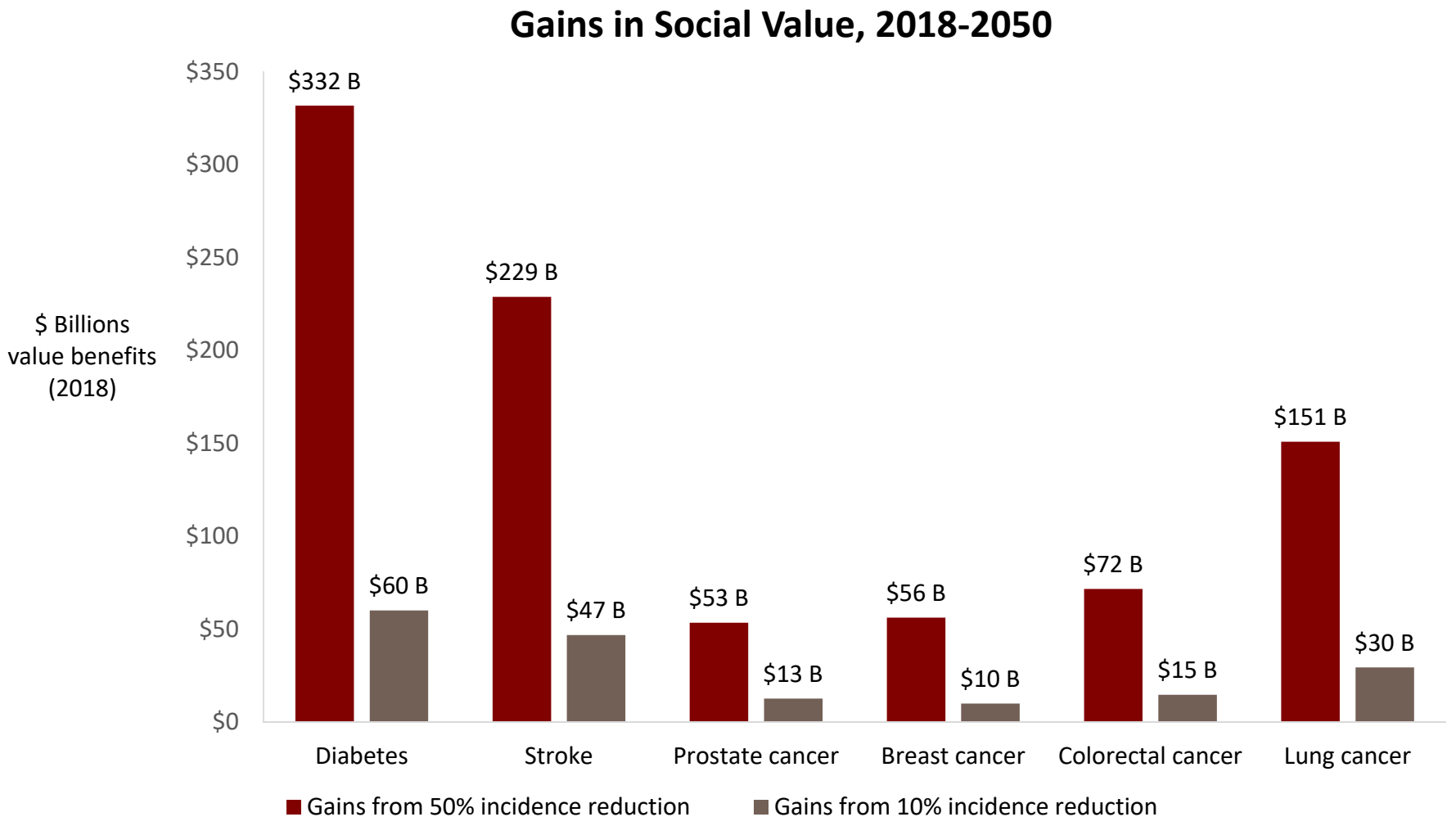
Source: Authors' calculations using Future Elderly Model.

The cumulative value to making progress is enormous



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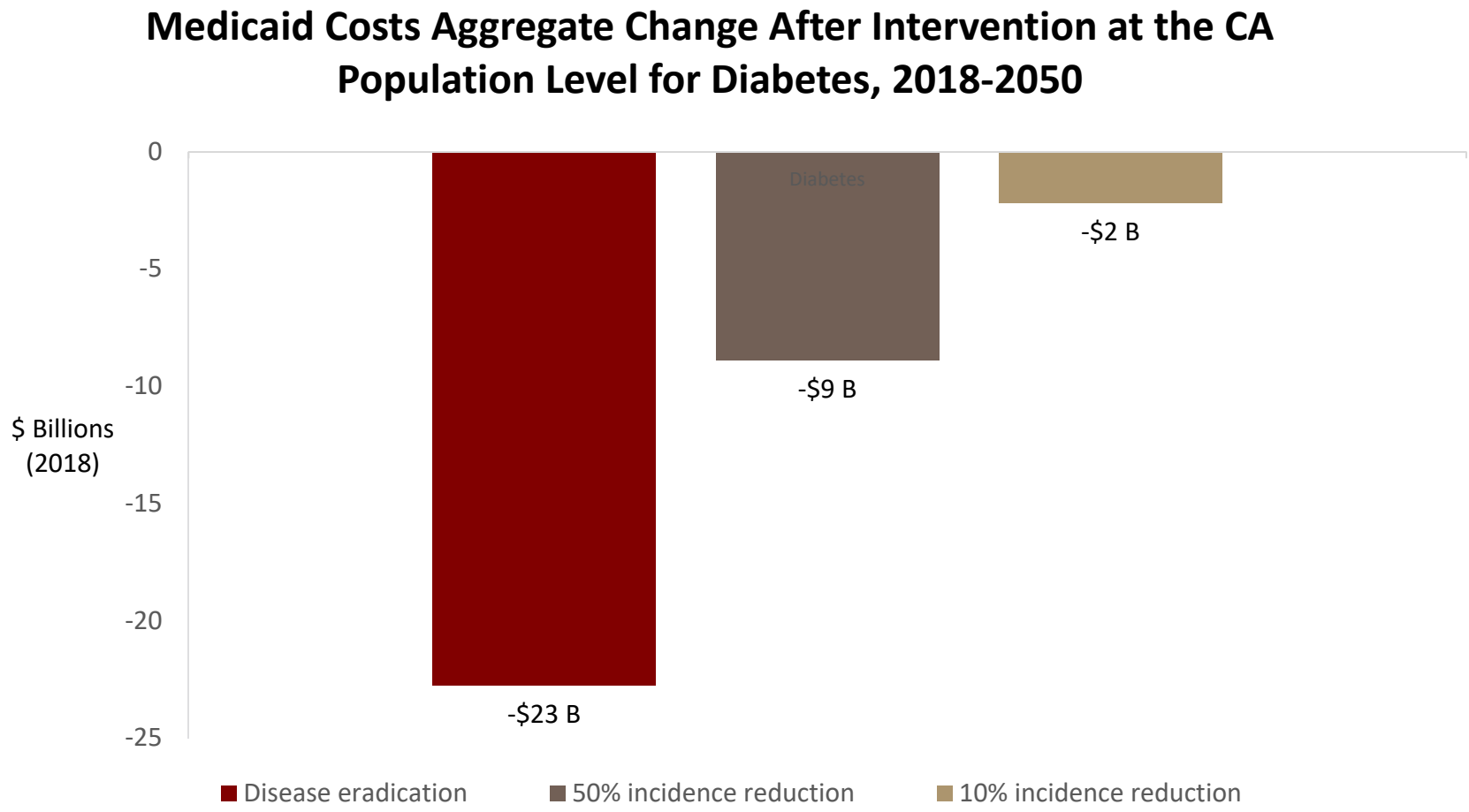
Note: Disease burden measured as reduced quality-adjusted life-years, expressed in dollars using $150,000 per QALY

Improvements in diseases would generate savings for CA Medicaid



Notes: Future value discounted 3% annually. About 38.5% of Medicaid spending paid by California.

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Why is preventing and curing disease in CA so important?

- **The potential value of reducing the incidence of common diseases—for example, breast, colorectal, lung, and prostate cancer and diabetes and stroke—in California is large.**
- **A relatively small investment in research to find new treatments or cures potentially can return great value at the individual and societal levels by reducing disease burden.**

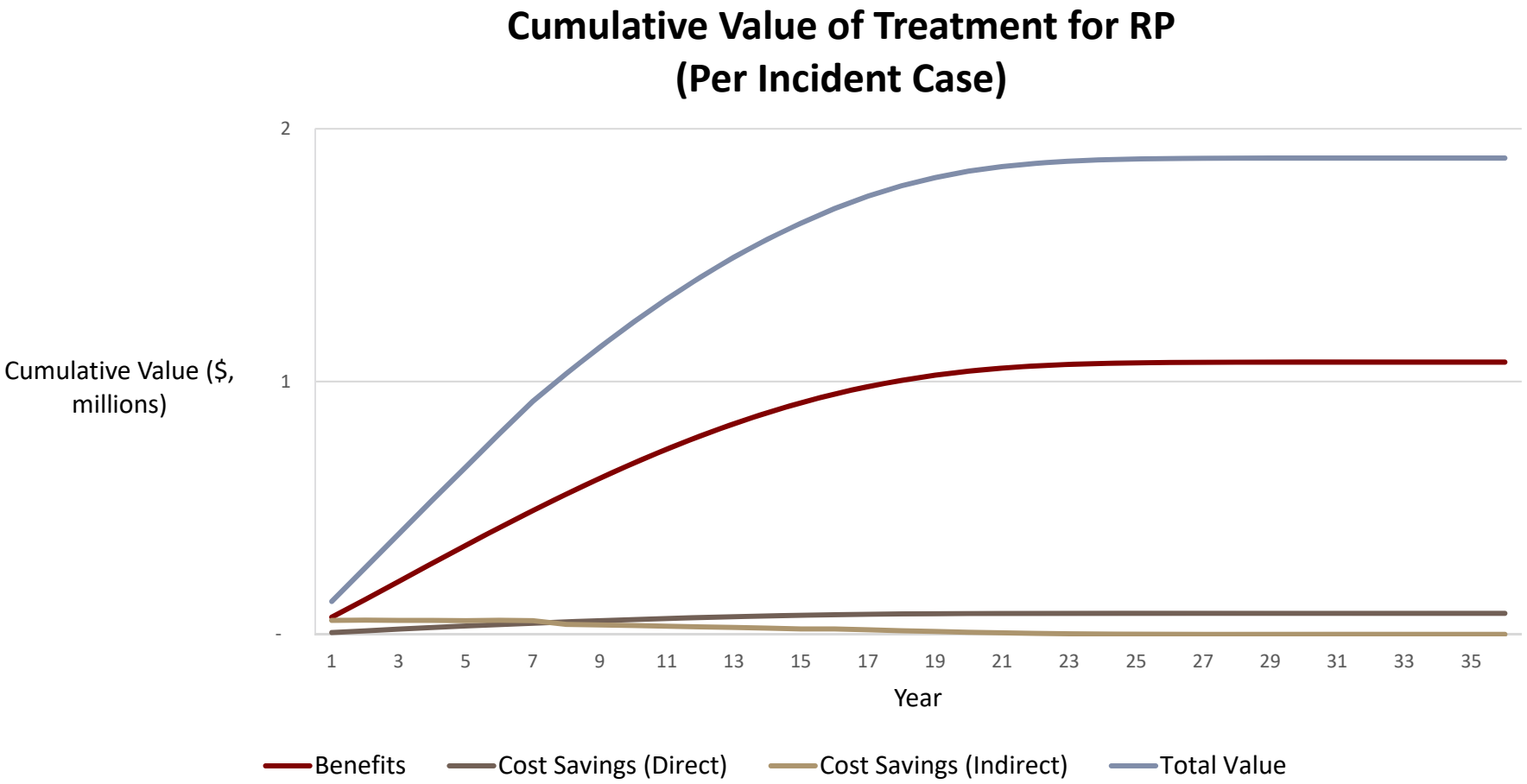
We estimated the benefits of additional investment in regenerative medicine in California

1. Direct stimulus to the economy
2. Potential health benefits to California:
   - Addressing high prevalence conditions (cancers, diabetes and stroke)
   - Treating severe disease (dAMD and RP)

Eye Diseases: Severe and Prevalent

- **Dry age-related macular degeneration (dAMD)**
  - **Leading cause of severe central vision loss for Americans ages 60+**
  - **Irreversible; develops as eye ages**
  - **Over time vision worsens, affects basic tasks (driving, reading, face recognition)**
  - **11 million people in US affected**
- **Retinosis pigmentosa (RP)**
  - **Causes vision loss over time due to dysfunctional photoreceptors in retina**
  - **Genetic**
  - **Many become legally blind**
  - **Affects 1 in 4,000**

Treatment for RP would generate $1.8 million in total value per incident case



Notes: Starting model year normalized to 1. Incident population for RP is 217; starting cohort is aged 51-52. Total value calculated as benefits minus costs. All future values are discounted at a rate of 3%. Direct costs include medical expenditures, vision services, and devices. Indirect costs include employment (earnings) and productivity, nursing home costs, and caregiver burden.

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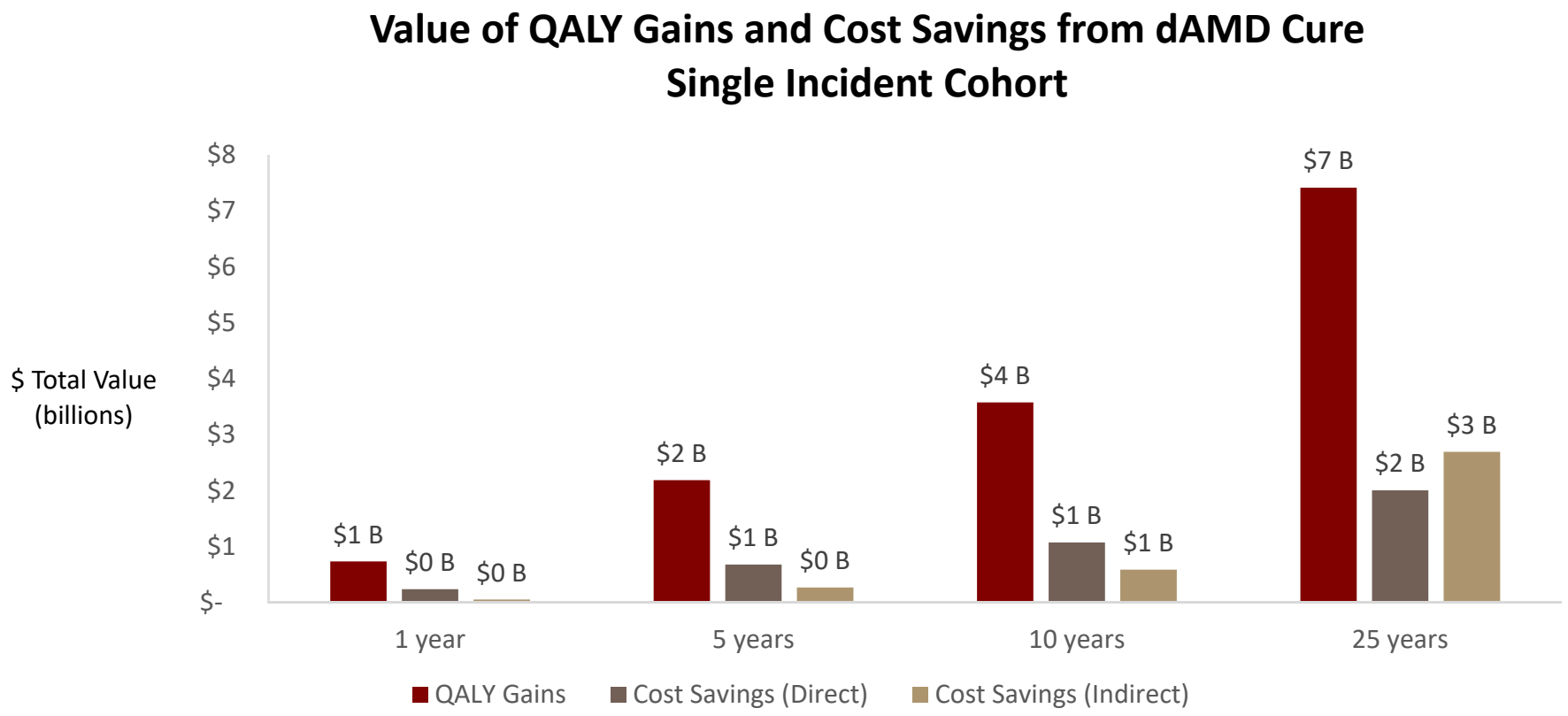
Treatment for dAMD would generate $2.7 billion for a single cohort over 25 years



Notes: Incident population for dAMD is 22,155; starting cohort is aged 65-66. All future values are discounted at a rate of 3%. Direct costs include medical expenditures, vision services, and devices. Indirect costs include employment (earnings) and productivity, nursing home costs, and caregiver burden.

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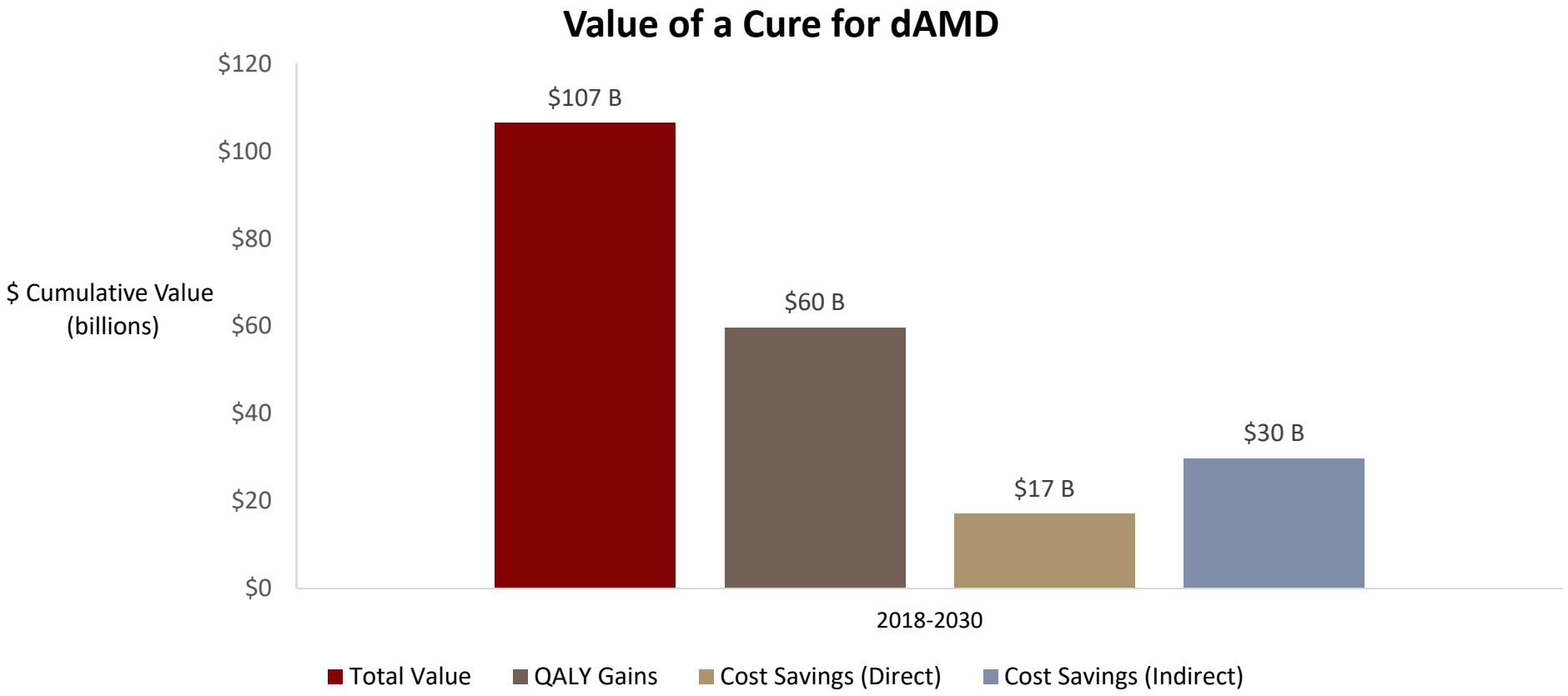
Treatment for dAMD would generate $107 billion between 2018-2030



Notes: Estimates include all prevalent dAMD cases in 2018, plus new incident cases each year thereafter. Incident population for dAMD is 22,155, and new cases are diagnosed in a cohort aged 65-66. All future values are discounted at a rate of 3%. Direct costs include medical expenditures, vision services, and devices. Indirect costs include employment (earnings) and productivity, nursing home costs, and caregiver burden.

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Summary of Findings

- As a society, we underinvest in health
- CIRM had substantial economic benefits in California
- The greatest value to California lies in the future promise of ameliorating disease
  - A 10% chance of progress in preventing stroke alone would justify CIRM's entire R&D portfolio
  - Investments in cures for rare diseases also will pay substantial dividends

Disclosure

Throughout his career, Dr. Goldman has received research support, speaker fees, travel assistance, equity, or consulting income from the following sources: Abbott, AbbVie, ACADIA Pharmaceuticals, Alkermes, Allergan, Alphabet, American Dental Association, American Medical Association, Amgen, Aspen Institute, Avanir, BIO, Biogen, Blue Cross Blue Shield of Massachusetts, Blue Cross Blue Shield of Arizona, Bristol Myers-Squibb, California Institute for Regenerative Medicine, Celgene, California Hospital Association, Cambia Health Solutions, Cedars-Sinai Medical Center, Centers for Medicare & Medicaid Services, Claremont College, Commonwealth Fund, Columbia University, Congressional Budget Office, Dignity Health, Edwards Lifesciences, Eli Lilly, EMD Sorono, FAIR Health, Gemvax, Genentech, General Electric, Gilead Sciences, GRAIL, GSK, Intuitive Surgical, Johnson & Johnson, Kaiser Family Foundation, LA Biomed, Lockheed Martin, MacArthur Foundation, Merck, National Cancer Institute, National Institute on Aging, National Institutes of Health, National Pharmaceutical Council, National Science Foundation, National Railway Labor Conference, Novartis, Novo Nordisk, Otonomy, Otsuka Pharmaceuticals, Pfizer, PhRMA, Precision Health Economics, Providence St Joseph Health, RAND Corporation, Roche, Sanofi, Stanford University, Takeda, University of Arizona, University of California, University of Chicago, Walgreen Boots Alliance, West Coast Healthcare, and Western University College of Pharmacy.

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