FUNDING

Parallel Discovery of Alzheimer's Therapeutics

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As the prevalence of Alzheimer's disease (AD) grows, so do the costs it imposes on society. Scientific, clinical, and financial interests have focused current drug discovery efforts largely on the single biological pathway that leads to amyloid deposition. This effort has resulted in slow progress and disappointing outcomes. Here, we describe a "portfolio approach" in which multiple distinct drug development projects are undertaken simultaneously. Although a greater upfront investment is required, the probability of at least one success should be higher with "multiple shots on goal," increasing the efficiency of this undertaking. However, our portfolio simulations show that the risk-adjusted return on investment of parallel discovery is insufficient to attract private-sector funding. Nevertheless, the future cost savings of an effective AD therapy to Medicare and Medicaid far exceed this investment, suggesting that government funding is both essential and financially beneficial.

Despite the rapidly growing prevalence of Alzheimer's disease (AD) and its related costs—which are expected to dominate medical care by 2030—progress in the development of AD therapeutics has been unacceptably slow. More than 5 million Americans now suffer from AD, and that number is expected to more than double by 2050 (*1*). Between 1998 and 2011, there were 101 unsuccessful AD drugs in development and only three approvals (none since 2003) (*2*). The U.S. Food and Drug Administration (FDA) has approved only five AD drugs, and these treat the symptoms of the disease without altering its course. Substantial resources have focused on the build-up of β-amyloid protein in AD brains. Half a dozen costly phase 3 trials designed around the so-called amyloid hypothesis have failed to meet their primary end points, including the high-profile bapineuzumab and solanezumab trials completed in 2012 (*3*, *4*). Although focus has shifted to exploring anti-amyloid treatments at earlier stages of the disease, the ultimate outcome of such therapies remains unclear. Thus, it is essential to explore other aspects of AD pathophysiology, which could provide additional therapeutic targets (Table 1).

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The cost and complexity of AD clinical trials implies that any single drug-development program represents an enormous financial risk to its investors. Here, we describe a portfolio approach—the "megafund" model set forth by Fernandez *et al.* (*5*)—in which multiple distinct AD drug development projects ready for testing are undertaken in parallel. Although this approach requires greater upfront investment than does a single-target approach, the probability of at least one success will be considerably higher with "multiple shots on goal," mitigating the risk and increasing the attractiveness of this undertaking to—and the amount of funding provided by—the private sector. More importantly, conducting parallel clinical trials reduces the expected waiting time for a success, substantially reducing the enormous taxpayer burden of caring for AD patients. If a single drug-development program takes 13 years from beginning to end and has a 5% probability of success, the expected waiting time for the next approved AD drug is 260 years if each trial is independently and identically distributed and conducted sequentially (fig. S1). In comparison, a portfolio approach is a more systematic, less risky, and thus economically more viable way of achieving the U.S. National Plan objective to "prevent and effectively treat Alzheimer's disease by 2025."

PARALLEL DISCOVERY

Parallel drug discovery begins with delineating and prioritizing the most compelling scientific hypotheses about disease mechanisms and pathophysiology. Until recently, most AD hypotheses emerged from analysis of post-mortem AD brains, in which prominent amyloid plaques and neurofibrillary tangles implicated the amyloid and tau pathways (*6*). Converging biochemical and genetic data supporting the importance of amyloid has largely overshadowed other compelling targets; additional basic science insights could catapult these targets into therapeutic development. For example, agents that target tau-derived neurofibrillary tangles and neuroinflammation are leading alternatives to anti-amyloid therapeutics but are the subject of far fewer research projects and clinical trials. In addition, a wealth of attractive starting points for drug discovery is now emerging from genomic data sets (*7*), gene expression data (*8*), and statistical genetics (*9*) that assess large AD populations for genes that point to dysregulated biological pathways and confer risk.

A systematic and strategic effort to identify, prioritize, and categorize preclinical pathways that culminates with lead compounds for each hypothesis category could generate a portfolio with sufficient depth and broad scientific support to justify multiple simultaneous clinical trials. Furthermore, emerging scientific data will be used to continue to refine the preclinical leads in the AD portfolio.

PUBLIC-PRIVATE COLLABORATION

Although the megafund model requires substantial upfront investment (an estimated $38.4 billion over the next decade), the higher probability of success relative to a single-target approach mitigates risk and increases the attractiveness of this undertaking to—and the amount of funding available from—the private sector. But investing in multiple shots on goal is challenging from both scientific and financial perspectives. The required number of shots depends on the probability of success of each shot. With a 5% success rate among independent trials, 100 or more shots may be needed to yield an attractive investment; this requires $50 billion and the identification of nearly twice as many potential therapeutic targets than we currently have. Therefore, despite its enormous societal value, the economic incentives for developing an effective AD therapy in the private sector are considerably lower than for cancer, diabetes, and heart disease, each of which has successful drugs that target more than one disease pathway. Accordingly, we need new creative methods for financing translational medicine research in the AD arena.

Governments have an additional economic incentive to support AD translational research: cost savings. In 2014, AD-related Medicare and Medicaid (M&M) expenses

Table 1. Potential AD projects. Proposed projects for an AD megafund portfolio and the estimated "degree of validation" for each. Uppercase entries indicate hypotheses, boldface entries indicate categories, and remaining entries indicate projects. In cases in which hypotheses and categories are more speculative, they may constitute single projects. Entries containing numbers in parentheses indicate multiple projects.

Projects	Degree of validation
AMYLOID	
Aβ passive immunotherapy	
Aβ antibodies (6)	High
Pyro Aβ antibodies (3)	High
Antibodies against soluble oligomers (3)	High
Aβ synthesis	
β-secretase inhibitors (6)	Medium
γ-secretase inhibitors and modulators (3)	Low
α-secretase agonism	Low
Aβ antiaggregation inhibitors/beta-sheet breakers	Low
Aβ clearance	
Neprilsyn and plasmin	Low
Insulin-degrading enzyme	Low
Low-density lipoprotein receptor overexpression	Low
TAU PATHWAY	
Phosphorlyation inhibitors	
CDK5	Low
GSK3β	Low
MARK/par1	Low
PKC	Low
MAPK	Low
PKA	Low
p70S6K	Low
Antiaggregants (TRx0237)	Low
Microtubule stabilizing agents (BMS 241027)	Low
Reduction of tau levels (Tau antibodies and antisense oligonucleotides)	Low
APOE4/LIPID METABOLISM	
Activated receptor gamma and liver X receptors in coordination with RXR's	Low
SIRT1, sirtuin	Low
GIVA-PLA2	Low

Projects	Degree of validation
NEUROINFLAMMATION	
Complement receptor 1	Low
TREM 2	Low
PPAR agonists	Low
IL-1, IL-6, IL-12, IL-23	Low
TNFR	Low
P2X7R	Low
Monoacylglycerol lipase	Low
AUTOPHAGY/PROTEASOME/UNFOLDED PROTEIN RESPONSE	
Nilotinib	Low
Proteasome pathways	Low
Unfolded protein response	Low
HORMONES/GROWTH FACTORS	
Inactivation of gonadotropin-releasing hormone (GnRH)	Low
Allopregnanolone	Low
CERE-110: Adeno-associated virus delivery of nerve growth factor	Low
DYSREGULATION OF CALCIUM HOMEOSTASIS	
InsP3R	Low
CALHM1	Low
HEAVY METALS	
Copper	Low
Zinc	Low
MITOCHONDRIAL CASCADE/MITOCHONDRIAL UNCOUPLING/ANTIOXIDANTS (3)	Low
DISEASE-RISK GENES (3)	Low
HDAC INHIBITORS	Low
GLUCOSE METABOLISM	Low

alone are expected to be $150 billion (*1*). Taxpayers would enjoy substantial cost savings from therapies that delay AD onset or slow disease progression (*10*). Moreover, the U.S. government is in the singular position of being one of the most risk-tolerant and longest-horizon investors in the world and, currently, the investor with the lowest borrowing cost. Thus, large-scale government involvement is both essential and financially beneficial (from the taxpayer's perspective).

QUALIFYING PORTFOLIO PROJECTS

A prerequisite for large-scale private- or public-sector funding for AD therapeutics is a strategic approach to identifying and vetting leads for a megafund portfolio. AD has the potential to bankrupt the medical system, and if taxpayers assume the burden for drug discovery, the public's interests must be protected by prioritizing projects in a systematic manner.

What properties qualify a project for inclusion in the portfolio? Megafund projects should represent a diversity of disease hypotheses, meet defined thresholds for preclinical evidence, target well-characterized disease-pathway mediators that, when modulated, can modify disease outcomes, and have a newly discovered or repurposed drug in the pipeline, ready for clinical trials. Using these considerations, we identified 12 leading pathway hypotheses for developing AD therapeutics (Table 1). A well-devel-

oped hypothesis (for example, amyloid, tau, and neuroinflammation) typically contains multiple categories, which in turn may contain multiple projects, with each "project" defining the clinical development of an individual AD therapy. The extent to which one can develop multiple differentiated drug candidates within the context of a single disease hypothesis depends on how extensively the hypothesis has been characterized and the potential diversity of drug-development approaches to test the hypothesis. For example, amyloid-based therapeutics include antibodies to amyloid-β, small-molecule inhibitors of amyloid-β biosynthetic pathways, and protein-disaggregating agents. Each therapeutic antibody displays distinct affinities for amyloid-β oligomers and has different propensities for side effects such as amyloid-related imaging abnormalities–edema (ARIA-E) (*11*). Therefore, certain entries in Table 1 such as amyloid-β antibodies and both γ-secretase inhibitors and modulators can support multiple projects (6 and 3 projects, respectively, which is indicated in parentheses). However, for hypotheses that are still speculative (such as epigenetics-modifying HDAC inhibitors), we propose one project for each, with the expectation that as these speculations turn into hard scientific evidence, more projects will be generated.

The sources for these projects include the extensive AD literature, informal communication with scientists in the field, and a review of AD- and dementia-related clinical trials registered at clinicaltrials.gov. Some projects are more speculative than others, but all of the entries in Table 1 are either direct targets of an AD drug in development or display mechanisms of action consistent with a potential AD therapeutic. Therefore, all are plausible candidates for parallel discovery in the near term. Of course, all entries do not hold equal promise; we made an attempt to differentiate among them by specifying a "degree of validation" based on a subjective review of the evidence. Achieving success in modifying any given pathway would justify investing additional resources in prosecuting that pathway.

The identification of 64 projects may suggest an unintentional and false sense of precision in the candidate selection process. Depending on how broadly or narrowly a project is defined, the total number may be greater or fewer. For example, the number of targets within a project can multiply rapidly because pathology is the result of a complex cascade of molecular events with multiple control points. In fact, the amyloid-β pathway alone could generate a larger number of targets via its numerous collateral production and degradation pathways, as well as its many oligomeric forms. Thus Table 1 serves as a broad but concrete and actionable starting point for a dialogue among the scientific, clinical, and financial communities for developing a systematic approach to parallel discovery for AD therapeutics. Our hope is that this list will be continuously refined by the various stakeholders of the AD community over time and as clinical data accumulate.

A new business model will also be required to support the management of a complex portfolio. Pharmaceutical company portfolios are subject to shareholders and have strong economic incentives to reduce earnings volatility by shifting corporate assets away from risky early-stage R&D toward later-stage acquisitions and licensing deals. Small biotech companies must answer to venture capitalists looking for exits, and next-round financing opportunities often drive the scientific research agenda rather than the reverse. Neither of these business models is capable of supporting an AD megafund. We hypothesize that the ideal megafund business model will be a new hybrid of a drug-royalty investment company (for late-stage assets), a biotech venture-capital fund (for early-stage clinical assets), and a multiproject platform such as the NIH's National Center for Advancing Translational Sciences (NCATS). AD portfolio management must also implement innovative clinical trial designs; state-of-the-art patient enrollment criteria (such as patient stratification by biomarkers and genotype); expanded enrollment searches through community-based "brain shops" (*12*); Internet-based screening; and a national institutional review board for AD clinical trials (*13*). On the basis of recent and ongoing management research (*14*–*16*), we believe that a collective effort among biopharma stakeholders—venture capitalists, pharma industry leaders, financial engineers, patient advocacy groups, and philanthropists—is both necessary and sufficient to successfully launch and manage an AD megafund.

AD MEGAFUND SIMULATION

Fernandez *et al.* (*5*) have described a megafund financing structure that uses securitization, a common financial engineering technique in which bonds are issued and sold to investors, and the proceeds from those sales are used to purchase a portfolio of assets—in this case, drug targets and other therapeutics. The portfolio's assets serve as collateral for the bondholders and generate cash flows used to pay the bonds' interest and principal. Any remaining cash is paid to the megafund's equityholders. If the cash flows are insufficient to meet these obligations, megafund bonds will default, and the collateral will be transferred to bondholders through standard bankruptcy proceedings. Therefore, a megafund can only issue bonds if the underlying assets are sufficiently de-risked. In the specific context of oncology, the authors simulate the investment returns of a large portfolio of drug-development projects and conclude that funding multiple projects simultaneously can reduce risk to the point at which such megafunds can issue debt as well as equity. The ability to issue debt is critical because bonds markets have much larger capacity than those of venture capital, private equity, or public equity markets, and greater access to capital allows the megafund to reach its critical threshold of diversification.

We applied this portfolio approach to AD drug development by analyzing the hypothetical investment returns of a portfolio of 64 AD drug-development programs, each of which targets a different pathway or mechanism of action [see supplementary materials (SM)]. The analysis relied on several assumptions and parameters, including the cost of drug development, the length of time from phase 1 clinical trials to the filing of a new drug or biologics license application [New Drug Application (NDA) or Biologics License Application (BLA)], each project's probability of success, and pairwise correlations of success among the projects in the portfolio. Unlike oncology, which has many approved drugs and even more under development, there are currently only four approved AD drugs on the market, implying a paucity of data with which to calibrate our simulations. Therefore, our experimental design is more simplistic than that of (*5*). In setting our simulation parameters, we relied on generic information regarding the drug-development process and qualitative input from scientists with domain-specific expertise.

Specifically, the present value of out-of-pocket development costs for each of the 64 projects in the portfolio was set to $600 million, the sum of $100 million in ba-

sic research funding and $500 million for clinical development (*17*) over a 13-year period. The 13-year duration is supported by a recent study commissioned by the New York Academy of Sciences (*18*) focused on AD therapeutics. These figures assume trials with mild-to-moderate AD patients and standard progression from phase to phase; if earlier stages of AD are investigated or a trial must be repeated, costs and duration will increase and post-approval patent life will decrease. On the other hand, because we do not model the transition from one clinical phase to the next, the realized out-of-pocket cost of a typical project could be less than our assumed $600 million because of early termination of failed projects. For simplicity, we have chosen a value for out-of-pocket costs that falls between a range of higher (multiphase) and lower (early-phase failure) cost estimates, which is in line with industry estimates of the total development cost for a successful AD therapeutic (range, $500 million to $2 billion and beyond) (*17*).

At $600 million per project, the megafund of 64 projects requires $38.4 billion. To estimate the returns generated by such a portfolio, we assumed the annual profit of a successful AD therapy to be $2 billion for a 10-year period of exclusivity after FDA approval (at year 13) (Fig. 1). Although a 20-year patent life implies only 7 years of exclusivity after a 13-year therapeutic-development period, patent-protection extensions and data exclusivity provided by the Drug Price Competition and Patent Term Restoration Act of 1984 and the Orphan Drug Act of 1983 allow somewhat longer periods of exclusivity. Our assumption of $2 billion in annual profits is a plausible estimate based on net global sales for Namenda—the only approved AD drug still under patent—which is intended to treat moderate to severe stages of the disease. Despite its decline in sales volume due to changes in prescribing behavior in long-term care settings and its negligible effect on the course of the disease, Forest Laboratories reported Namenda's net sales for the year ending on 31 March 2013 to be greater than $1.5 billion (*19*). In addition, estimated peak sales of potential anti-amyloid biologics such as solanezumab are expected to reach major market sales of $5.5 billion in 2022, if approved (*20*). Using a 10% cost of capital for discounting these profits, we obtain a net present value of $12.3 billion upon approval in year 13.

If a $600 million investment in year 0 produces a drug worth $12.3 billion in year 13, this represents a compound annual rate of return of $(\$12.3/\$0.6)^{1/13} - 1 = 26.1\%$ over the 13-year development period. Of course, this attractive prospect is highly speculative and must be weighed against the possibility of a total loss if the project fails. Therefore, an assessment of the megafund's return requires estimates of the probability of success for each of the 64 portfolio projects and pairwise correlation of success among all 2016 different pairs. These parameter estimates were provided by two of the authors with domain-specific expertise (K.S.K. and C.H.). Our figures for the probabilities of success are based on estimates of the compounded probabilities of advancement from phase 1 to NDA or BLA filing. From recently reviewed industry data on neurology product phase transitions from 2003 to 2011 (largely composed of pain and psychiatric compounds), the probability of approval and the launch of a neurologically active drug at the start of a phase 1 study is 9%, and 15% at the start of phase 2, with the probability increasing to 50% at the start of phase 3 (*21*).

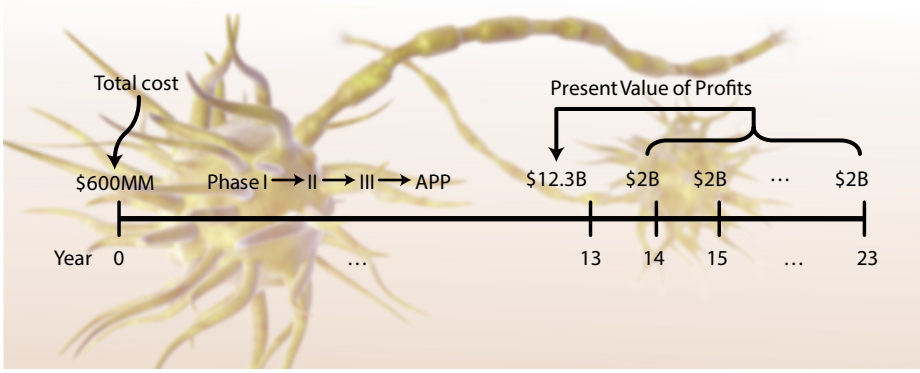

Fig. 1. Not on our side. Timeline of a hypothetical AD therapeutic–development program.

Given that the probability of success in pain and psychiatry may be higher than in neurodegeneration, we used lower probability estimates for AD targets in general. Probabilities of success were translated to high, medium, and low degrees of validation (Table 1), corresponding to probability estimates of 11 to 15%, 6 to 10%, and 1 to 5%, respectively. Pairwise correlations were qualitatively assessed as low, moderate, medium, or high, and these qualitative assessments were assigned numerical values of 10, 25, 50, and 90%, respectively. For example, we assumed the pairwise correlations of multiple projects within a single entry in Table 1 to be high. Figure 2 shows a heat map of these assumed correlations; the actual correlation matrix used in our analysis was the closest positive definite correlation matrix to the one shown Fig. 2 (see also fig. S2 and S3).

Unlike an oncology megafund (*5*) or a much smaller orphan-disease megafund (*22*), which yield attractive expected returns at tolerable risk levels, the simulated investment performance of an AD megafund is mixed, with negative-to-mediocre expected-returns for higher success probabilities and lower correlations, and highly negative expected-returns for lower success probabilities and higher correlations (tables S1 and S2). For example, with a 5% probability of success, even in the absence of pairwise correlation among the 64 drug development programs, the expected return is −4.2%, and the return standard deviation is 19.4%.

On the other hand, with a 15% probability of success and no correlation, the expected return is 8.6%, with a return standard deviation of only 2.8%, which is a risk-adjusted expected return that exceeds those of most professionally managed investment funds over the past decade. But even with such a high probability of success, as the pairwise correlation among the projects increases, the expected returns decline and the volatility increases. At 80% pairwise correlation, the expected return becomes −38.6% with a volatility of 48.4%, which is comparable to the worst-performing investment funds over the past decade. Yet the most sobering results involve parameters closest to reality (both in terms of individually calibrated probabilities of success and pairwise correlations); this case yields an expected return of −14.3%, a standard deviation of 33.4%, and a 13% probability that no project will reach NDA or BLA, implying that debt financing will be virtually impossible.

With such risk/reward profiles—which follow from our current understanding of AD translational research—a private-sector AD megafund is simply not economically

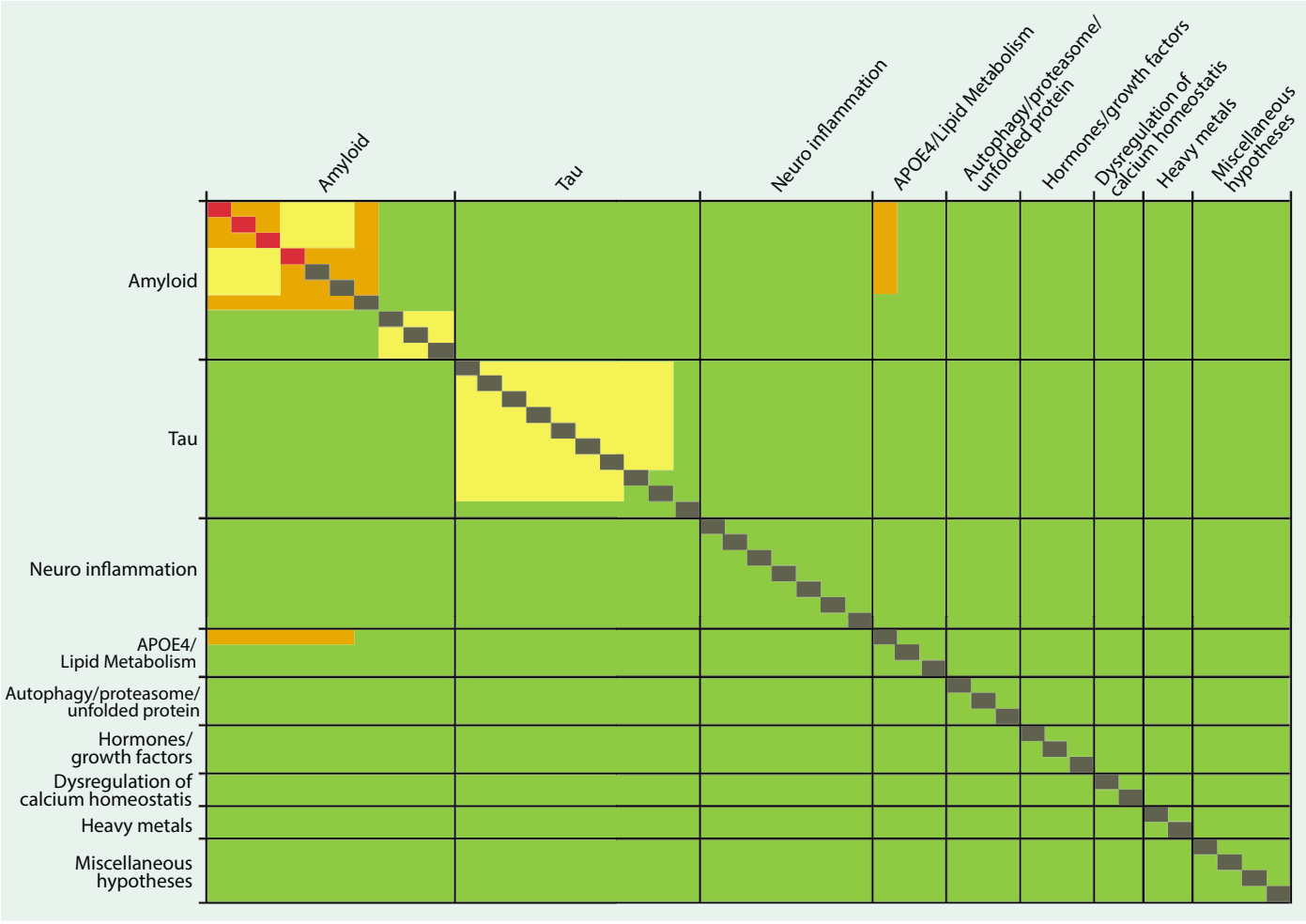

Fig. 2. Multiple shots are not independent. Heat-map representation of qualitatively determined pairwise correlation of success among 64 hypothetical AD therapeutics projects (as assessed by K.S.K. and C.H.), where 100% indicates perfect correlation (success and failure coincide for the pair), 0% indicates no correlation, and −100% indicates perfect negative correlation (success for one always implies failure for the other and vice versa). Red cells indicate estimated correlations of 90%, orange cells indicate 50%, yellow cells indicate 25%, and green cells indicate 10%.

viable. These results may well explain why no AD drug has been approved over the past decade: There has been an insufficient number of shots on goal because of a lack of economic incentives. The fact that AD therapeutics take so much longer to develop than do many other types of drugs implies that 20-year fixed patent terms are less valuable and pharma will be less motivated to invest (*23*).

COST-BENEFIT ANALYSIS

The mediocre investment returns of an AD megafund are counterintuitive given the prevalence of the disease and how much is currently being spent to address it. The explanation lies in the nature of the disease and its implications for the economics of drug discovery. Investigation of an AD target is expensive, lengthy, and risky, even by biopharmaceutical industry standards; hence, a $2 billion–a–year compound over a 13-year period of patent protection—a blockbuster drug by any other measure—is insufficient to recoup the costs of a sufficiently de-risked AD megafund. Unless more scientific progress is made so that the probability of success is higher, the correlation among projects is lower, and more shots on goal become available, the private sector seems unlikely to produce effective AD therapies over the next few decades.

Given the burden of AD on society, governments around the world have strong incentives to invest heavily in AD therapeutics. A common approach to such policy decisions is to weigh the costs and benefits of public spending on AD (see SM). Although the costs are fairly clear—$38.4 billion, for example—the benefits are considerably more difficult to estimate for a variety of reasons. For easily diagnosed terminal illnesses such as pancreatic cancer, the benefit of life-saving and life-extending therapeutics can be evaluated by using standard economic measures of the value of a statistical life (VSL). For example, the Environmental Protection Agency's (EPA) current VSL estimate used in its policy decisions is $7.4 million in 2006 dollars ($8.6 million in 2014 dollars). A 2009 estimate of the value of a single quality-adjusted life year (QALY) is $129,090 ($141,271 in 2014 dollars), which is similar in magnitude to the EPA figure given the current U.S. life expectancy estimate of 78.7 years.

Another standard measure of benefit in public health policy contexts is a consumer's "willingness to pay" (WTP) for a particular therapy or outcome. For example, a recent

evaluation of the economic return from the "War on Cancer" estimated that the average WTP for the 4-year survival gains that cancer patients achieved between 1988 and 2000 is $322,000 per patient, implying roughly $1.9 trillion of additional social value and an excellent return on investment, particularly from the patient perspective (*24*). Unfortunately, because much less is known about AD and because existing drugs treat only certain symptoms, eliciting a consumer's WTP for nonexistent therapies is highly speculative. Moreover, the burden of AD is not only imminent death but cognitive and functional impairment, loss of dignity and self-control, and the indirect toll—both emotional and financial—on family members and caregivers. Accordingly, survival rates and life-years are not the most relevant measures of benefit because the typical QALY scale implicitly assumes that there is nothing worse than death, which is not necessarily the case for diseases that cause extended periods of suffering such as AD (*25*). Moreover, the organic unawareness of deficits (anosognosia) renders AD patients unreliable reporters of their own conditions (*25*), including their WTP. Surveying presymptomatic subjects may not solve the problem because such subjects may underestimate their chances of being afflicted, and risk perception and risk tolerance can significantly bias WTP estimates (*26*).

For these reasons, WTP and related cost-efficiency studies of AD therapeutics are difficult to conduct and their findings are equally difficult to interpret. For example, one cost-benefit analysis of the early identification and treatment of AD reports net social benefits ranging from $10,000 to $172,000 for a 70-year-old patient, depending on the hypothetical drug's ability to reduce cognitive impairment (*27*). However, a more recent WTP study using retrospective Health and Retirement Survey data estimates the mean WTP to prevent AD altogether to be $155 per month, but these WTP estimates varied significantly with the respondents' household wealth and perceived risk of developing AD (*28*). An extensive prospective telephone survey of 1240 Swiss subjects was conducted to estimate WTP for three hypothetical AD intervention programs—easing the burden on caregivers, early detection of AD, and intensifying research to cure AD—using three different statistical techniques, yielding a matrix of nine measures (*29*). These measures range from $256 to $323 per year for caregiver relief, $184 to $202 for early detection, and $192 to $225 for research to cure AD (assuming an exchange rate of $1.12 per Swiss franc).

Given the challenges of WTP measures, we take a narrower and more practical approach by focusing on the potential impact of AD therapeutics on M&M expenditures because the U.S. government may have an incentive to invest heavily in AD therapeutics in the best interests of its taxpayers. Of course, cost savings do not necessarily translate into net benefits to society because they may come at the expense of other stakeholders (for example, reducing M&M expenditures on AD may increase unemployment among AD caregivers). However, potential cost savings may still serve as a useful measure of the first-order benefits of effective AD therapies, after which indirect effects can be calculated separately.

To estimate the potential cost savings realized by M&M from a new, effective AD therapy, we relied on the Alzheimer's Association's (AA's) (*10*) detailed projections of the current trajectory of AD-related expenditures (CT) assuming no new AD therapies and transition rates of 45% from mild to moderate AD and 28% from moderate to severe AD. These hypothetical trajectories are assumed to begin taking effect in 2015, and the AA model provides projections every 5 years through 2050. We compared AA's trajectories with those of two hypothetical scenarios: delaying the onset of AD by 5 years ("trajectory 2," or T2) or slowing down its progression ("trajectory 3," or T3) so that 10% of AD patients transition from mild to moderate stages of the disease each year and 5% transition from moderate to severe stages.

By assuming that these projected costs are constant each year until the next 5-year projection, we computed conservative present values of these annual expenditures over 10-, 20-, and 30-year horizons (Table 2). The potential cost savings of new AD therapeutics can then be computed by taking the difference of the present values of CT and each of the two counterfactual trajectories. The last two rows of Table 2 show that the potential cost savings to M&M are substantial (detailed calculations in SM; see also tables S3 and S4): $1.5 trillion for T2 and $813 billion for T3 over a 30-year period (both in 2010 dollars). Using the AD megafund's probability of at least one success as a proxy for the likelihood of T2 and T3, we computed the expected return and volatility that the cost savings (Table 2) represent relative to the initial investment of $38.4 billion in the megafund (or $35.9 billion in 2010 dollars) (Table 3). The results confirm the intuition that an effective AD therapy is of tremendous economic value when measured by the potential cost savings it can produce. For example, even with only a 5% probability of success and a 10% correlation among the megafund's 64 projects, the expected annualized return of T2 is 2.6, 13.8, and 19.5% over 10-, 20-, and 30-year horizons, respectively. With standard deviations of 35.0, 38.8, and 40.7%, respectively, for these three horizons, the risks are high but comparable with the stock-return volatilities of many publicly traded companies. The risk-reward profiles of T3 are qualitatively similar, although somewhat less attractive because of the less ambitious hypothesis of slowed progression.

However, the most practically relevant results are the performance statistics contained in the last row of Table 3, which corresponds to the most realistically calibrated parameter values. In this case, T2's expected annualized return of −0.4% and standard deviation of 38.5% for a 10-year horizon are unattractive; but for a 30-year horizon, the expected annualized return is 16.0%, and the standard deviation is 44.8%, which is

Table 2. Costs and savings. Present values (in billions of 2010 constant dollars) of annual AD-related M&M expenses and potential cost savings as estimated by Alzheimer's Association (*10*) over 10-, 20-, and 30-year horizons under the current trajectory (CT) and two hypothetical scenarios: a delayed-onset trajectory (T2) and a slowed-progression trajectory (T3). A 10% nominal cost of capital and a 5% inflation rate were used to discount the real cost estimates.

Trajectory	10-year 2015–2025	20-year 2015–2035	30-year 2015–2045
Current trajectory (CT)	1436	2766	4250
Delayed onset (T2)	1227	1961	2737
Slowed progression (T3)	1280	2298	3438
(CT – T2)	208	804	1513
(CT – T3)	156	468	813

Table 3. AD megafund risk and return to taxpayers. Investment returns and risks with respect to M&M cost savings from the AD megafund over a 13-year investment period for various combinations of probabilities of success (p), pairwise correlations (ρ), and probabilities of at least one hit (p_1) under the AA model (*10*) for the economic impact of new AD therapies that either delay the onset of AD (T2) or slow its progression (T3). The row labeled "KSK–CH" uses pairwise correlations and success probabilities calibrated qualitatively by K.S.K. and C.H. for each of the 64 hypothetical projects. E[R], expected return; SD[R], return standard deviation

			Horizon (years)											
			10	**20**	**30**	**10**	**20**	**30**	**10**	**20**	**30**	**10**	**20**	**30**
Parameters (%)														
p	ρ	p_1	E[R]: Delayed-onset (T2)			SD[R]: Delayed-onset (T2)			E[R]: Slowed-prog. (T3)			SD[R]: Slowed-prog. (T3)		
5	0	96	10.2	22.3	28.3	21.8	24.1	25.3	7.7	17.3	22.4	21.3	23.2	24.2
5	10	90	2.6	13.8	19.5	35.0	38.8	40.7	0.3	9.2	13.9	34.2	37.2	38.8
5	40	69	−21.5	−13.0	−8.6	53.2	59.0	61.9	−23.3	−16.5	−12.9	52.0	56.6	59.0
5	80	40	−54.0	−48.9	−46.4	56.1	62.3	65.4	−55.0	−51.0	−48.9	54.9	59.7	62.3
10	0	100	14.4	26.9	33.2	3.9	4.4	4.6	11.8	21.7	27.0	3.8	4.2	4.4
10	10	99	12.8	25.2	31.4	13.8	15.3	16.0	10.3	20.0	25.3	13.5	14.7	15.3
10	40	91	4.5	15.9	21.7	32.3	35.9	37.7	2.2	11.2	16.0	31.6	34.4	35.9
10	80	46	−46.8	−41.0	−38.0	57.1	63.4	66.5	−48.0	−43.4	−40.9	55.8	60.8	63.4
15	0	100	14.5	27.0	33.3	0.6	0.7	0.7	11.9	21.8	27.1	0.6	0.7	0.7
15	10	100	14.2	26.7	33.1	5.3	5.9	6.2	11.7	21.6	26.8	5.2	5.7	5.9
15	40	98	12.3	24.6	30.8	15.8	17.5	18.4	9.8	19.5	24.7	15.5	16.8	17.5
15	80	62	−29.1	−21.3	−17.4	55.6	61.7	64.7	−30.6	−24.5	−21.2	54.4	59.2	61.7
KSK-CH		87	−0.4	10.5	16.0	38.5	42.7	44.8	−2.6	6.0	10.6	37.6	41.0	42.8

considerably more compelling. For T3, the corresponding expected return and volatility are −2.6 and 37.6%, respectively, over a 10-year horizon, and 10.6 and 42.8% over a 30-year horizon. Given that the AA model's projections are based entirely on inflation-adjusted 2010 dollars, the expected returns (Table 3) are real returns; nominal returns would be even higher. The significant disparity in the expected returns of short- versus long-run horizons may be another reason why so few AD therapeutics have been developed in the past decade—and why government intervention may be beneficial.

ROLE OF GOVERNMENT

Our simulated investment performance statistics are highly speculative and based on hypotheses that are unavoidably imprecise, but they incorporate the most current information available on AD burden. We are spending more than $200 billion to care for the more than 5 million AD patients in the United States, of which an estimated 70% are covered by M&M. In addition, >15 million Americans currently provide unpaid care for people with AD and other dementias, valued at $220 billion (*1*). If no new drugs are discovered that alter the course of this disease, we are looking at greater than $1 trillion in costs of care and more than 13 million AD-afflicted Americans by 2050 (*10*). A $38.4 billion AD megafund could plausibly generate double-digit investment returns, but in the form of cost savings to U.S. taxpayers, who are now paying the $150 billion in AD-related M&M expenses for 2014 (*1*).

Because the government is uniquely positioned to invest in the very-long-term interests of its citizens, and because it is less risk sensitive than individual and institutional investors, it can greatly accelerate the development of AD therapeutics in at least three ways: (i) by providing guarantees for the debt of an AD megafund; (ii) by starting the patent clock upon commercialization rather than invention; (iii) by increasing the duration of patent protection from 20 to 30 years for AD therapeutics that meet a sufficiently high efficacy threshold; and (iv) by providing more funding for basic research on neurodegenerative diseases—a prerequisite for deciphering new disease pathways, pathophysiological mechanisms, and therapeutic targets to be translated by an AD megafund. The critical role of government support is underscored by the difficulty in earning reasonable financial rates of return on basic research; the output is too uncertain in timing and commercial value to justify private-sector investment. In economic terms, the "market failure" that necessitates the need for government intervention in this case is the outsized risk, cost, and lengthy horizon of developing AD therapeutics.

We have witnessed the impact that government involvement can have in catalyzing subsequent private-sector investment. President Nixon's declaration of the "war on cancer" in 1971 has spurred decades of invaluable basic research, a long-term investment that has only recently begun to bear fruit. With passage of the National Alzheimer's Project Act (NAPA) in January 2011 and the subsequent "National Plan to Address Alzheimer's Disease" (*30*), the war on Alzheimer's has only just begun. The National Plan contains a number of promising

strategies for achieving its number one goal "to prevent and effectively treat AD by 2025." But one key aspect is glaringly absent: specific funding commitments. For the fiscal year (FY) ending 30 September 2012 (FY12), NIH dedicated only $503 million for AD research (*31*), and the Obama administration invested only $50 million (*30*). NIH funding for cancer research in the same year was more than $5 billion (*31*). Before passage of the National Cancer Act of 1971, the annual budget of the NIH National Cancer Institute (NCI) was $270 million; by FY 1978, NCI's budget exceeded $770 million (*32*). The NAPA-established Advisory Council recommended a budget of $2 billion per year to achieve its 2025 goal, but there has been no mention of how this level of funding is to be achieved.

The scale and scope of current efforts for reducing the AD burden are insufficient to have material impact on the vast majority of AD patients within the next several decades. A government-sponsored initiative in parallel AD drug discovery—with active participation from the private sector—is both necessary and financially beneficial, but we must address the financing issues before these benefits can be realized (*33*).

SUPPLEMENTARY MATERIALS

www.sciencetranslationalmedicine.org/cgi/content/full/6/241/241cm5/DC1
Introduction
Computing expected returns and variances
IID Bernoulli Trials Correlated Trials
Fig. S1. Probability of success
Simulating correlated Bernoulli trials
Fig. S2. Heat map of pairwise correlations
Fig. S3. Heat map of positive-definite correlation matrix
Megafund investment performance
Table S1. AD projects and estimated probabilities of success
Table S2. Returns
Cost/benefit analysis
Table S3. Trajectories
Table S4. Medicare and Medicaid cost savings

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Acknowledgments: We thank M. Anderson, M. Baumgart, Z. Bozoky, M. Carillo, J. Cox, C. Duggan, A. Finkelstein, J. Franca-Koh, D. Knopman, M. Milken, S. Myers, E. Posner, D. Schmittlein, M. Stevens, R. Urban, D. van de Hoef, G. Vradenburg, and participants at the November 2013 CEOi/Fastercures Global Financing Mechanisms to Support Innovations in Alzheimer's Research and Care Salon Dinner and the 2013 G8 Summit on Dementia, for helpful comments and discussions.

10.1126/scitranslmed.3008228

Citation: A. W. Lo, C. Ho, J. Cummings, K. S. Kosik, Parallel discovery of Alzheimer's therapeutics. *Sci. Transl. Med.* **6**, 241cm5 (2014).