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Supplementary Materials for

Parallel Discovery of Alzheimer's Therapeutics

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1 Introduction

We present the details of our mathematical and simulation analysis of the expected return and volatility of a portfolio of 64 Alzheimer's disease (AD) projects. We begin with a discussion of how investment returns are defined and computed, which is straightforward when outcomes are known in advance but presents certain subtleties in the presence of randomness such as in the case of drug development. We then turn to the mathematics of independently and identically distributed (IID) Bernoulli trials and extend this model to the case of correlated Bernoulli trials using multivariate normal latent variables. While the correlated case does not yield closed-form solutions for the portfolio's expected return and standard deviation, these values and the distribution of the total number of successes can easily be obtained by Monte Carlo simulation which we describe in detail. We apply these results to a cost/benefit analysis of the AD portfolio using the Alzheimer's Association model of the economic impact to Medicare and Medicaid expenditures of delaying the onset or slowing the progression of AD.

2 Computing expected returns and variances

The standard definition of an investment rate of return, R, in which an initial investment of I yields a single payoff of X is simply $R = (X/I) - 1$. If the duration of this investment is over a period of $T > 1$ years, the return is usually annualized so as to facilitate its comparison to other investments with different durations. The annualization is accomplished via geometric compounding as with a bank account since, by convention, interim interest payments are assumed to be re-deposited in the account; hence additional interest is paid on the interest earned, and so on. Therefore, the annualized return, R_a, is defined as:

$$R_a = \left(\frac{X}{I}\right)^{1/T} - 1 \ . \tag{S.1}$$

This definition of an investment's annualized return is uncontroversial when X is known. However, if X is a random variable, then R is random as well, and assessing the investment opportunity amounts to assessing the properties of this latter random variable. For example, if I = \$100 and X = \$0 or \$300 with equal probability p = 1/2, then the expected return and standard deviation of this investment are 50% and 150%, respectively. Much of modern portfolio theory is devoted to analyzing such random variables based on its first two moments: its expected return (E[R]) and return standard deviation (SD[R]). Rational investors are assumed to prefer higher expected returns and lower risk, where risk is measured by standard deviation, also called "volatility." Based on this behavioral assumption, it is often possible to construct "optimal" portfolios that maximize the expected return per unit of risk.

However, an important issue arises in the computation of expected returns and volatilities for multi-year returns which require annualization: should the two moments be computed before or after annualization? In the previous example where X = \$0 or \$300 with equal probability, suppose the duration of this investment was two years. In this case, we can compute the expected annualized return or annualize the expected two-year return:

$$\mathrm{E}\left[R_a\right] = p \times \left(\frac{\$300}{\$100}\right)^{\frac{1}{2}} + (1-p) \times \left(\frac{\$0}{\$100}\right)^{\frac{1}{2}} - 1 = 13.4\% \tag{S.2}$$

$$R_a\left(\mathrm{E}\left[X\right]\right) = \left(\frac{p \times \$300 + (1-p) \times \$0}{\$100}\right)^{\frac{1}{2}} = +22.5\% \tag{S.3}$$

where the expression R_a(E[X]) denotes the annualization of the expected two-year return of 150%. In this simple example, it is easy to see that the order of annualization and expectation yields wildly different measures of investment performance. It is a general mathematical relation that the expected annualized return is always less than the annualized expected return due to Jensen's Inequality. The difference between these two quantities is an increasing function of the duration T and the volatility of R.

Similarly, a difference arises with respect to the second moment or variance depending on whether annualization is applied before or after taking expectations of the squared return:

$$\mathrm{Var}\left[R_a\right] = p \times \left(\frac{\$300}{\$100}\right)^{\frac{2}{2}} + (1-p) \times \left(\frac{\$0}{\$100}\right)^{\frac{2}{2}} - \mathrm{E}^2\left[1-R_a\right] = 75.0\% \tag{S.4}$$

$$\mathrm{Ann.}\left(\mathrm{Var}\left[R\right]\right) = \frac{1}{2} \times \left(\mathrm{E}\left[\left(\frac{X}{I}\right)^2\right] - \mathrm{E}^2\left[\frac{X}{I}\right]\right) = 112.5\% \tag{S.5}$$

where we have made use of the fact that Var[1 + *Z*] = Var[*Z*]for any random variable *Z* to simplify the derivation. Note that the second relation implicitly assumes that variances scale linearly across time (hence the factor 1/2 to annualize the variance of the two-year return *R*).

There is no clear argument for using one method over the other in all contexts. With respect to the expected return, the second method (computing expected returns and then annualizing) is perhaps more common—it is the method used by venture capitalists in computing the "internal rate of return" (IRR) of their portfolio of investments, which are almost always multi-year investments. While this may seem deliberately optimistic because the IRR always exceeds the expected annualized return, it is a matter of necessity because IRR's are computed after the fact using realized payoffs, hence the annualization cannot be performed prospectively (assessing the probabilities of the payoffs of startup companies is exceedingly difficult and therefore almost never attempted).

By convention, we report the more traditional summary statistics (expected IRR and standard deviation of IRR) in the main manuscript, and provide both sets of performance statistics in this document for completeness.

3 IID Bernoulli trials

Denote by *Bi* a binary random variable taking on the value 0 or 1, depending on whether project *i* fails or succeeds. If the probabilities of success and failure are *p* and 1−*p*, respectively, then in *n* IID trials, the total number of successes, $B = \sum_{i=1}^{n} B_i$, is distributed as a binomial random variable with probability distribution:

$$\mathrm{Prob}\left(B = k\right) = \binom{n}{k} p^k \left(1-p\right)^{n-k}, k = 1,\ldots,n \ . \tag{S.6}$$

If a success garners a fixed and known net present value (NPV) of *X* at date *T*, then the total payoff of *n* IID trials at date *T* is simply *BX*. Given an initial investment of *I* at date 0, we can compute the compound annual rate of return of this investment *R* as:

$$R = \left(\frac{BX}{I}\right)^{1/n} - 1 \ . \tag{S.7}$$

Then its mean and variance can be computed in a straightforward manner using the binomial distribution:

$$\mathrm{E}\left[R_a\right] = \sum_{k=0}^{n} \left(\frac{kX}{I}\right)^{\frac{1}{n}} \mathrm{Prob}\left(B = k\right) - 1 \ , \tag{S.8}$$

$$\mathrm{Var}\left[R_a\right] = \sum_{k=0}^{n} \left(\frac{kX}{I}\right)^{\frac{2}{n}} \mathrm{Prob}\left(B = k\right) - \mathrm{E}^2\left[1 - R_a\right] \ , \tag{S.9}$$

where we have made use of the fact that $\mathrm{Var}[R_a] = \mathrm{Var}[1 + R_a]$ in the second equation to simplify the expression. The standard deviation of the return, $\mathrm{SD}[R_a]$, is simply the square root of the variance.

If we conduct the trials sequentially instead of simultaneously, an important statistic is the expected waiting time before the first success. Denote by n^* the number of trials required to achieve the first success, hence

$$\mathrm{B}_1 = 0 \ , \mathrm{B}_2 = 0 \ , \ \ldots \ , \mathrm{B}_{n^*-1} = 0 \ , \mathrm{B}_{n^*} = 1 \ .$$

Then we have:

$$\mathrm{Prob}\left(B_{n^*} = k\right) = \left(1 - p\right)^{k-1} \, p \tag{S.10}$$

$$\mathrm{Prob}\left(B_{n^*} - 1 = k\right) = \left(1 - p\right)^{k} \, p \ \sim \ \text{Geometric } (p) \tag{S.11}$$

$$\mathrm{E}\left[B_{n^*}\right] = 1 + \frac{1-p}{p} \ . \tag{S.12}$$

For $p = 0.05$, the expected waiting time for the first success is 20 trials or 260 years if each trial takes 13 years, and the cumulative distribution of $n^* \times 13$ years is given in Figure S.1.

4 Correlated trials

There are a number of methods for allowing the outcomes of Bernoulli trials to be correlated and this is particularly important when modeling the outcome of clinical trials that have certain scientific elements in common. The most general approach is to allow arbitrary sets of $\{B_i\}$ to be dependent, but such generality is impossible to analyze or even develop meaningful intuition with which to calibrate the nature of the dependence. Instead, we allow for pairwise dependence between B_i and B_j in the following manner. Suppose that associated with each Bernoulli variable B_i is a continuous random variable Z_i that is normally distributed with mean 0 and variance 1 which is related to B_i in the following way:

$$B_i = \begin{cases} 0 \ \text{ if } \ Z_i < \alpha_i \\ 1 \ \text{ if } \ Z_i \geq \alpha_i \end{cases} \ . \tag{S.13}$$

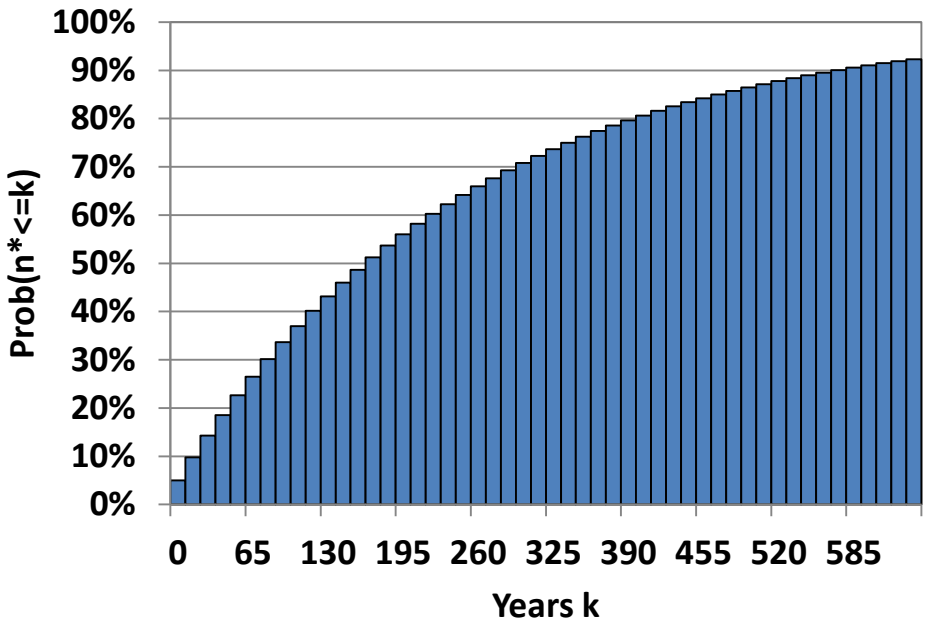

Fig. S1. Probability of success. Cumulative distribution of the probability (Prob) that the first success in consecutive sequences of 13-year AD clinical trials occurs in less than or equal to k years, assuming a 5% probability of success for each clinical trial.

We define $\alpha_i = \Phi^{-1}(1-p_i)$, where $\Phi^{-1}(\cdot)$ is the inverse of the standard normal cumulative distribution function. If we now let $\{Z_1, Z_2,\ldots,Z_n\}$ be distributed according to a multivariate standard normal distribution with covariance matrix $\mathbf{\Sigma}$, then pairwise correlation among the Bernoulli trials is captured by the off-diagonal elements of $\mathbf{\Sigma}$, i.e., pairwise correlation among the Z_i's.

In the special case where the B_i's are identically distributed with probability p and all pairwise correlations of the corresponding Z_i's are identical and equal to ρ, we can derive a simple expression for the distribution of B:

$$\text{Prob}(B=k) = \binom{n}{k} q \ , \ k = 1,\ldots,n \tag{S.14}$$

$$q = \text{Prob}(Z_1 > \alpha,\ldots,Z_k > \alpha, Z_{k+1} \le \alpha,\ldots,Z_n \le 0) \tag{S.15}$$

where q is computed with respect to the multivariate standard normal distribution function with a covariance matrix given by 1's on the diagonal and ρ's for all the off-diagonal elements:

$$\sum = \begin{pmatrix} 1 & \cdots & \rho \\ \vdots & \ddots & \vdots \\ \rho & \cdots & 1 \end{pmatrix}. \tag{S.16}$$

Observe that if the Z_i's are independent, then q reduces to the familiar expression $p^k(1-p)^{n-k}$.

5 Simulating correlated Bernoulli trials

In practical applications, equi-correlated outcomes are rare; hence the simple expression derived above is useful mainly for developing intuition, not for computation. Although closed-form expressions are unavailable for the probability distribution of the pairwise correlated Bernoulli trials we have proposed, it is easy to compute this probability distribution numerically via Monte Carlo simulation.

Denote by $\epsilon \equiv [\ \epsilon_1\ \ \epsilon_2\ \cdots\ \epsilon_n\ ]'$ a column-vector of random multivariate standard normal variables. Then for any positive-definite matrix $\mathbf{\Sigma}$, the new vector of random variables $Z = \mathbf{\Sigma}^{1/2}\epsilon$ is multivariate normal with covariance matrix $\mathbf{\Sigma}$, where $\mathbf{\Sigma}^{1/2}$ denotes the Cholesky factorization or matrix square root of $\mathbf{\Sigma}$. Once the success probability p_i for each Bernoulli variable B_i is defined, the α_i associated with each Z_i is determined and realizations of correlated Bernoulli trials can be simulated by:

1. Generating a realization of column-vector of ϵ IID normal random variables
2. Pre-multiplying this column-vector by $\mathbf{\Sigma}^{1/2}$ to generate $\mathbf{Z}$
3. Computing a column-vector of 0's and 1's: 0's for Z_i's less than α_i and 1's for Z_i's greater than or equal to α_i

If this process is repeated a large number of time, the relative frequency of the realizations of the sums of the $\mathbf{Z}$'s will approximate the distribution of B.

The only subtlety in this simulation exercise involves the specification of $\mathbf{\Sigma}$. For our purposes, pairwise correlations are meant to capture commonalities among translational medical programs so that success or failure in one program has predictive power for the success or failure of another program. Specifying values for each entry in $\mathbf{\Sigma}$ that are based on domain-specific knowledge of the underlying science is both necessary and fraught with difficulty because an arbitrarily specified matrix need not satisfy a critical property of bona fide correlation matrices known as positive-definiteness. Although this may seem like a technical point, a non-positive-definite correlation matrix implies that certain weighted averages of the $\mathbf{Z}$'s may be assigned negative variances, which clearly violates the definition of variance. Therefore, entries in $\mathbf{\Sigma}$ cannot be arbitrarily set.

In our simulations, we adopt a three-step process in which all pairwise correlations between projects are first evaluated qualitatively as “low,” “moderate,” “medium,” or “high” by scientists with domain-specific expertise. This conjectured matrix is displayed in Figure S.2. These assessments are then translated into numerical values of 10% for “low,” 25% for “moderate,” 50% for “medium,” and 90% for “high.” The third step is to apply the numerical algorithm developed by Qi and Sun [1] to compute the closest positive-definite matrix to the one specified manually. Figure S.3 contains a heat-map display of the positive-definite correlation matrix constructed from the qualitatively determined matrix in Figure S.2, which confirms that they are virtually identical and that the Qi and Sun algorithm had minimal impact.

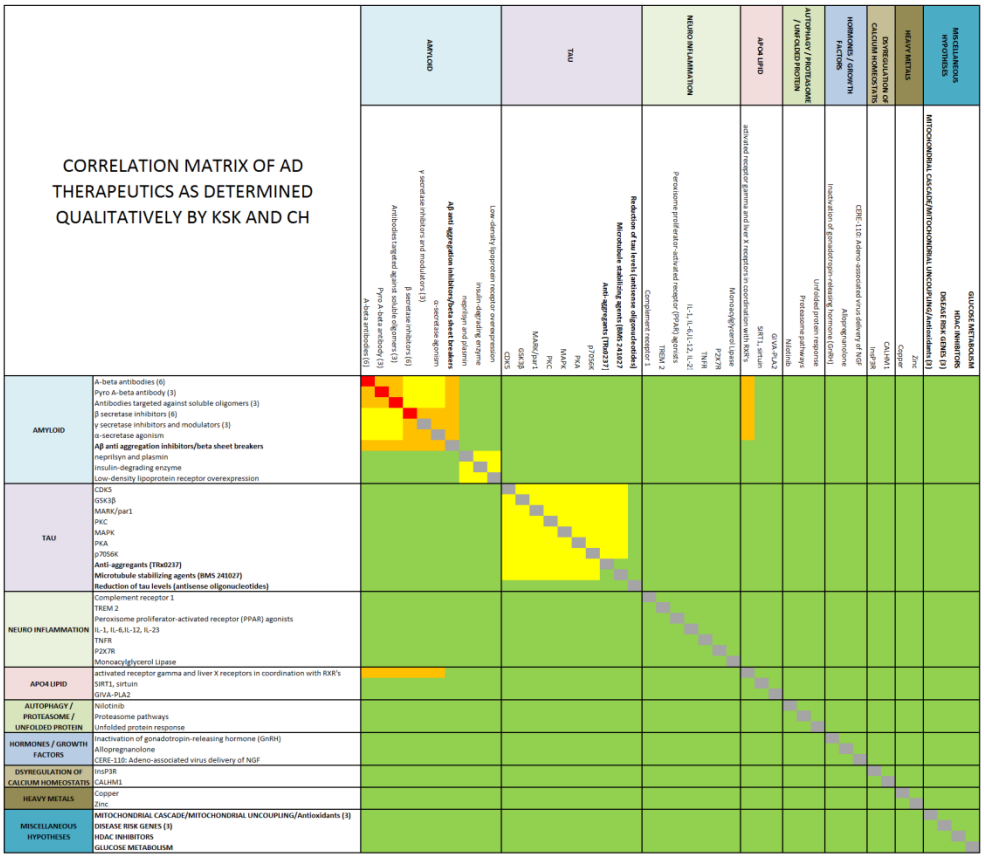

Fig. S2. Heat-map of conjectured pairwise correlations. Heat-map representation of conjectured pairwise correlations of success/failure of the 64 AD projects as determined by Dr. Kenneth S. Kosik (KSK) and Dr. Carole Ho (CH). Green, yellow, orange, and red entries indicate correlations that are 10%, 25%, 50%, and 90%, respectively.

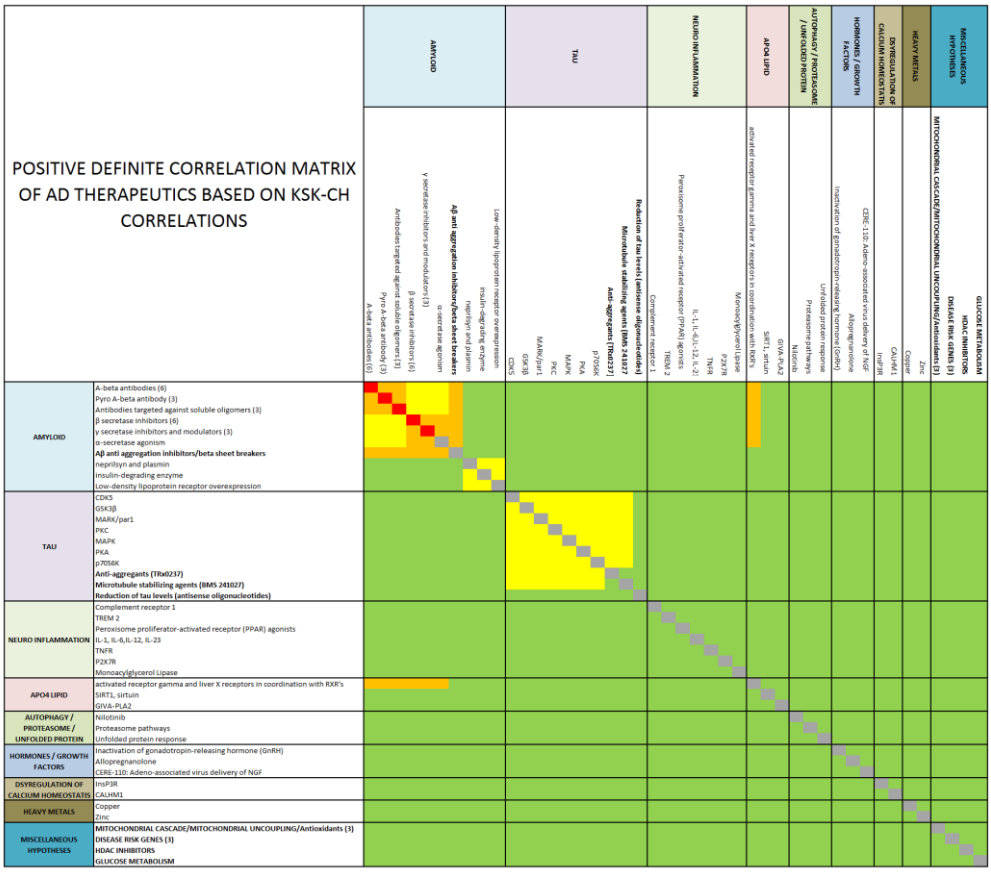

Fig. S3. Heat-map of positive-definite correlation matrix. Heat-map representation of positive-definite correlation matrix corresponds to the conjectured qualitative correlation matrix of pairwise correlations of success/failure of the 64 AD projects by Dr. Kenneth S. Kosik (KSK) and Dr. Carole Ho (CH). Green, yellow, orange, and red entries indicated correlations that are less than 25%, between 25% and 50%, between 50% and 75%, and greater than 75%, respectively.

6 Megafund investment performance

The final set of parameters required to compute the investment performance of the AD megafund is the probabilities of success for the 64 projects. Table S.1 contains the assigned probabilities in which high, medium, and low degrees of validation were assigned probabilities ranging from 11% to 15%, 6% to 10%, and 1% to 5%, respectively, by Drs. Kenneth S. Kosik and Carole Ho.

To illustrate the impact of annualization on expected returns, we report the performance statistics of the AD megafund in Table S.2 using both methods. The top subtable presents expected returns and standard deviations of annualized 13-year returns, and the bottom subtable presents the corresponding results for the reverse procedure. As expected, the bottom subtable has higher expected returns, in some cases much higher. For example, in the no-correlation case where $p = 5\%$, the first method yields an expected return of −4.2% whereas the second method yields +0.2%. Note that these two methods can yield values of different signs, which has significant implications for how these investments are perceived by investors and policymakers.

The difference between these two methods of reporting 13-year returns is even greater for the more realistic cases with success probabilities and correlations determined via expert judgment. Using the average of the two correlation matrices, the expected return from the first method is −14.3% and the expected return from the second method is −1.1%.

Projects	Estimated Prob. of Success
AMYLOID	
Aβ Passive Immunotherapy	
A-beta antibodies (6)	15%
Pyro A-beta antibodies (3)	15%
Antibodies targeted against soluble oligomers (3)	15%
Aβ Synthesis	
β secretase inhibitors (6)	10%
γ secretase inhibitors and modulators (3)	1%
α-secretase agonism	5%
Aβ anti aggregation inhibitors/beta sheet breakers	5%
Aβ clearance	
neprilsyn and plasmin	5%
insulin-degrading enzyme	5%
Low-density lipoprotein receptor overexpression	5%
TAU PATHWAY	
Phosphorlyation inhibitors	
CDK5	3%
GSK3β	3%
MARK/par1	3%
PKC	1%
MAPK	1%
PKA	1%
p70S6K	1%
Anti-aggregants (TRx0237)	3%
Microtubule stabilizing agents (BMS 241027)	3%
Reduction of tau levels (Tau antibodies and antisense oligonucleotides)	3%
APOE4 / LIPID METABOLISM	
activated receptor gamma and liver X receptors in coordination with RXR's	3%
SIRT1, sirtuin	3%
GIVA-PLA2	3%

Projects	Estimated Prob. of Success
NEUROINFLAMMATION	
Complement receptor 1	5%
TREM 2	5%
Peroxisome proliferator-activated receptor (PPAR) agonists	5%
IL-1, IL-6,IL-12, IL-23	3%
TNFR	3%
P2X7R	3%
Monoacylglycerol Lipase	3%
AUTOPHAGY/PROTEASOME/UNFOLDED PROTEIN RESPONSE	
Nilotinib	5%
Proteasome pathways	5%
Unfolded protein response	5%
HORMONES/GROWTH FACTORS	
Inactivation of gonadotropin-releasing hormone (GnRH)	3%
Allopregnanolone	3%
CERE-110: Adeno-associated virus delivery of NGF	3%
DYSREGULATION OF CALCIUM HOMEOSTASIS	
InsP3R	5%
CALHM1	5%
HEAVY METALS	
Copper	1%
Zinc	1%
MITOCHONDRIAL CASCADE/MITOCHONDRIAL UNCOUPLING/Antioxidants (3)	1%
DISEASE RISK GENES (3)	1%
HDAC INHIBITORS	5%
GLUCOSE METABOLISM	5%

Table S1. AD projects and estimated probabilities success. Proposed projects for AD megafund portfolio and estimated probabilities of success for each. Upper case entries highlighted in gray indicate hypotheses, boldface entries indicate categories, and remaining entries indicate projects. In cases where hypotheses and categories are more speculative, they may constitute single projects. Entries containing numbers in parentheses indicate multiple projects.

p	ρ	p_1	E[R]	SD[R]	p	ρ	p_1	E[R]	SD[R]
Expectation and Standard Deviation of Annualized Returns (%)									
5	0	96.2	-4.2	19.4	15	0	100.0	8.6	2.8
5	10	89.6	-11.0	30.8	15	10	99.8	7.6	6.9
5	40	68.5	-32.5	46.0	15	40	98.1	3.2	15.8
5	80	40.2	-61.3	47.2	15	80	62.0	-38.6	48.4
10	0	99.9	5.0	5.0	KSK-CH		87.0	-14.3	33.4
10	10	98.5	2.8	13.6					
10	40	91.3	-7.2	29.4					
10	80	46.5	-54.5	49.0					
Annualized Expected Return and Standard Deviation (%)									
5	0	96.2	0.2	15.5	15	0	100.0	9.0	25.4
5	10	89.6	0.2	23.2	15	10	99.8	9.0	43.6
5	40	68.5	-2.0	26.2	15	40	98.1	7.1	49.2
5	80	40.2	-9.2	12.4	15	80	62.0	-2.3	25.8
10	0	99.9	5.7	21.3	KSK-CH		87.0	-1.1	19.4
10	10	98.5	5.6	34.7					
10	40	91.3	3.4	38.7					
10	80	46.5	-6.1	18.1					

Table S2. Returns. Expected returns and standard deviations of the AD megafund over its 13-year investment period for various combinations of probabilities of success (p), pairwise correlations (ρ), and probabilities of at least one hit (p_1). Expected returns and standard deviations are computed two ways: the top subpanel annualizes the returns before computing expectations and standard deviations, the bottom subpanel annualizes after computing these quantities. Rows labeled "KSK Corr.", "CH Corr.", and "Avg. Corr." employ correlations calibrated qualitatively by Dr. Kenneth S. Kosik, Dr. Carole Ho, and their average, respectively, and use individually calibrated success probabilities between 5% and 15% for each of the 64 projects.

7 Cost/Benefit Analysis

The cost of each of the 64 drug development programs is assumed to be $600 million in 2014 dollars, implying a total cost of $38.4 billion which is equivalent to $35.9 billion in 2010 dollars.

The benefits of a success in Alzheimer's drug development are harder to quantify, but we take advantage of the Alzheimer's Association's [2] (AA) economic model of two scenarios: a delayed-onset trajectory (T2) in which a new therapy delays the onset of AD by five years, and a slowed-progression trajectory (T3) in which a new therapy reduces the annual transition rate of patients from the mild to moderate stage of the disease to 10% and from the moderate to severe stage to 5% (current annual transition rates are 45% and 28%, respectively). They compare the economic consequences of these two trajectories to their projection of the status quo or current trajectory (CT) which assumes that no new therapies for Alzheimer's become available through

2050. Table S.3 presents a subset of these projected costs in constant 2010 dollars—those borne by Medicare and Medicaid only—under the status quo and the two hypothetical alternatives.

Trajectory	10-year 2015-2025	20-year 2015-2035	30-year 2015-2045
Current Trajectory (CT)	1,436	2,766	4,250
Delayed Onset (T2)	1,227	1,961	2,737
Slowed Progression (T3)	1,280	2,298	3,348
CT – T2	208	804	1,513
CT – T3	156	468	813

Table S3. Trajectories. Alzheimer's Association [2] estimated Medicare and Medicaid costs and potential cost savings (in billions of 2010 dollars) associated with Alzheimer's disease under three scenarios: the current trajectory (CT), a delayed-onset trajectory (T2), and a slowed-progression trajectory (T3).

Many assumptions and detailed computations underlie the AA model, but the most relevant for our cost/benefit computations are that:

- All cost estimates are in constant 2010 dollars and do not include the impact of general inflation (although they do reflect healthcare-related inflation), hence they must be discounted by real, not nominal, costs of capital.
- The new therapies implicit in trajectories T2 and T3 are assumed to start in 2015.
- The AA model includes many other costs beyond Medicare and Medicaid which we have ignored, hence our estimated return on investment (ROI) will be understated.

The starting point for the cost/benefit analysis is to compute the present values of the costs associated with each of the three trajectories, CT, T2, and T3. Because T2 and T3 are meant to reflect the benefits of new therapies for AD, they can serve as proxies for the economic impact of a success among the 64 projects proposed. Therefore, a crude cost/benefit calculation can be performed by comparing the cost of the 64 projects with the expectation of the present value of cost savings associated with T2 and T3, where the expectation is taken with respect to the binomial distribution of outcomes for the 64 projects. We make the following assumptions for these cost/benefit calculations:

1. Because the AA model only provides cost projections at 5-year intervals, we have to interpolate costs for the intervening years. For simplicity, we assume a "step function" for these costs so that the level remains the same until the next projection, i.e., annual costs for 2016 to 2019 are unchanged from 2015, changing only in 2020.

2. Since the AA model generates real cost projections, we discount them using a real rate of interest, currently assumed to be a 10% nominal rate of interest minus a projected inflation rate of 5%. The actual discount rate used is (1.10/1.05) −1 = 4.76%.

3. We compute present values over three different horizons: 10, 20, and 30 years. In principle, the cost savings of T2 and T3 should extend in perpetuity but we focus on a finite horizon to be conservative and to address the growing uncertainty in any economic forecast. Specifically, we focus on 2015 as the base year and discount all costs back to this year.

4. We assume that the AD therapies require a 13-year horizon to develop, and that the cost savings from a success (either in T2 or T3) begins to take effect in year 14. The present value of these cost savings, S_i, is assumed to be the difference between the present value of CT and T2 or T3, denoted by S_2 and S_3, respectively. Recall that 2015 is the base year for these calculations, but we are implicitly assuming that Si is realized in year 13 and computing the ROI of a $38.4 billion investment in year 0.

5. Because the AA model uses constant 2010 dollars, the initial investment of $38.4 billion must be converted from 2014 dollars to 2010 dollars. This conversion yields an initial investment of $35.9 billion.

6. The expected return of the investment is simply the probability of at least one hit, p_1—from the distribution provided by Drs. Kenneth S. Kosik (KSK) and Carole Ho (CH)—times the compound annual return of T2 or T3:

$$\mathrm{E}\left[R_{ia}\right] = p_1\left(\frac{S_i}{I}\right)^{\frac{1}{10}} - 1 \tag{S.17}$$

$$R_{ia}\left(\mathrm{E}\left[S_i\right]\right) = \left(\frac{p_1 S_i}{I}\right)^{\frac{1}{10}} - 1\ . \tag{S.18}$$

The standard deviation of the return follows readily from the Bernoulli-nature of this thought experiment:

$$\mathrm{SD}\left[R_{ia}\right] = \sqrt{\mathrm{Var}\left[R_{ia}\right]} = \sqrt{p_1\left(1-p_1\right)\left(\frac{S_i}{I}\right)^{\frac{2}{10}}} = \left(\frac{S_i}{I}\right)^{\frac{1}{10}}\sqrt{p_1\left(1-p_1\right)} \tag{S.19}$$

$$\mathrm{Ann.}\left(\mathrm{SD}\left[R_i\right]\right) = \sqrt{\frac{1}{10}\,p_1\left(1-p_1\right)\left(\frac{S_i}{I}\right)^{2}} = \left(\frac{S_i}{I\sqrt{10}}\right)\sqrt{p_1\left(1-p_1\right)}\ . \tag{S.20}$$

The results are reported in Table S.4 using both methods of annualization.

Parameters			Horizon (Years)											
			10	20	30	10	20	30	10	20	30	10	20	30
p (%)	ρ (%)	p_1 (%)	E[R]: Delayed-Onset (T2) (%)			SD[R]: Delayed-Onset (T2) (%)			E[R]: Slowed-Prog. (T3) (%)			SD[R]: Slowed-Prog. (T3) (%)		
Expectation and Standard Deviation of Annualized Return														
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
Annualized Expected Return and Standard Deviation														
5	0	96	14.2	26.6	33.0	30.6	118.1	222.2	11.6	21.5	26.8	22.9	68.7	119.4
5	10	90	13.5	26.0	32.2	49.2	189.8	357.1	11.0	20.8	26.1	36.7	110.4	191.8
5	40	69	11.2	23.4	29.5	74.8	288.7	543.1	8.7	18.3	23.5	55.9	167.9	291.7
5	80	40	6.7	18.4	24.3	79.0	304.8	573.4	4.4	13.6	18.5	59.0	177.3	308.0
10	0	100	14.5	27.0	33.3	5.5	21.3	40.1	11.9	21.8	27.1	4.1	12.4	21.6
10	10	99	14.4	26.9	33.2	19.4	74.8	140.6	11.8	21.7	27.0	14.5	43.5	75.5
10	40	91	13.7	26.1	32.4	45.5	175.5	330.3	11.2	21.0	26.2	34.0	102.1	177.4
10	80	46	7.9	19.8	25.7	80.4	310.0	583.3	5.5	14.9	19.8	60.0	180.3	313.3
15	0	100	14.5	27.0	33.4	0.9	3.4	6.4	11.9	21.8	27.1	0.7	2.0	3.5
15	10	100	14.5	27.0	33.3	7.5	29.0	54.6	11.9	21.8	27.1	5.6	16.9	29.3
15	40	98	14.3	26.8	33.1	22.2	85.8	161.4	11.8	21.7	26.9	16.6	49.9	86.7
15	80	62	10.4	22.4	28.5	78.2	301.8	567.8	7.9	17.4	22.5	58.4	175.5	304.9
KSK-CH		87	13.3	25.7	31.9	54.2	209.0	393.3	10.8	20.5	25.8	40.5	121.6	211.2

Table S4. Medicare and Medicaid cost savings. Annualized expected returns and standard deviations of Medicare and Medicaid cost savings, computed before and after annualization, from an AD megafund over its 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 Alzheimer's Association model [2] for the economic impact of new AD therapies that either delay the onset of AD (T2) or slow its progression (T3). Rows labeled "KSK Corr.", "CH Corr.", and "Avg. Corr." employ correlations calibrated qualitatively by Dr. Kenneth S. Kosik, Dr. Carole Ho, and their average, respectively, and use individually calibrated success probabilities between 5% and 15% for each of the 64 projects.