Parallel Discovery of Alzheimer Therapeutics: Supplementary Information

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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 49 Alzheimer's disease (AD) targets. 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:

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

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 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 ($\mathrm{E}[R]$) and return standard deviation ($\mathrm{SD}[R]$). 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:

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

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

where the expression $R_a\left(\mathrm{E}[X]\right)$ 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:

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

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

where we have made use of the fact that $\text{Var}[1+Z] = \text{Var}[Z]$ 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).

For our purposes, we shall report the expected annualized return in the main manuscript so as to be more conservative in assessing the investment performance of an AD megafund, but we provide the corresponding annualized expected returns in Table 1 below for completeness.

3 IID Bernoulli Trials

Denote by B_i a binary random variable taking on the value 0 or 1, depending on whether target 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:

$$\text{Prob}(B=k) \;=\; \binom{n}{k} p^k (1-p)^{n-k} \;,\; k=1,\ldots,n \;. \tag{6}$$

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:

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

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

$$\begin{aligned} \mathrm{E}\left[R_a\right] &= \sum_{k=0}^{n} \left(\tfrac{kX}{I}\right)^{\frac{1}{n}} \mathrm{Prob}(B=k) - 1 \ , & (8) \\ \mathrm{Var}\left[R_a\right] &= \sum_{k=0}^{n} \left(\tfrac{kX}{I}\right)^{\frac{2}{n}} \mathrm{Prob}(B=k) - \ \mathrm{E}^2[1+R_a] \quad , & (9) \end{aligned}$$

where we have made use of the fact that $\mathrm{Var}\left[R_a\right] = \mathrm{Var}[1+R_a]$ 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 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

$$B_1 \ = \ 0 \ , \ B_2 \ = \ 0 \ , \ \ldots , \ B_{n^*-1} \ = \ 0 \ , \ B_{n^*} \ = \ 1 \ .$$

Then we have:

$$\begin{aligned} \mathrm{Prob}(B_{n^*} = k) &= (1-p)^{k-1} p & (10) \\ \mathrm{Prob}(B_{n^*} - 1 = k) &= (1-p)^{k} p \ \sim \ \text{Geometric}(p) & (11) \\ \mathrm{E}[B_{n^*}] &= 1 \ + \frac{1-p}{p} & (12) \end{aligned}$$

For $p = 0.05$, the expected waiting time for the first success is 20 trials or 200 years if each trial takes 10 years, and the cumulative distribution of $n^* \times 10 \ \mathrm{years}$ is given in Figure 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

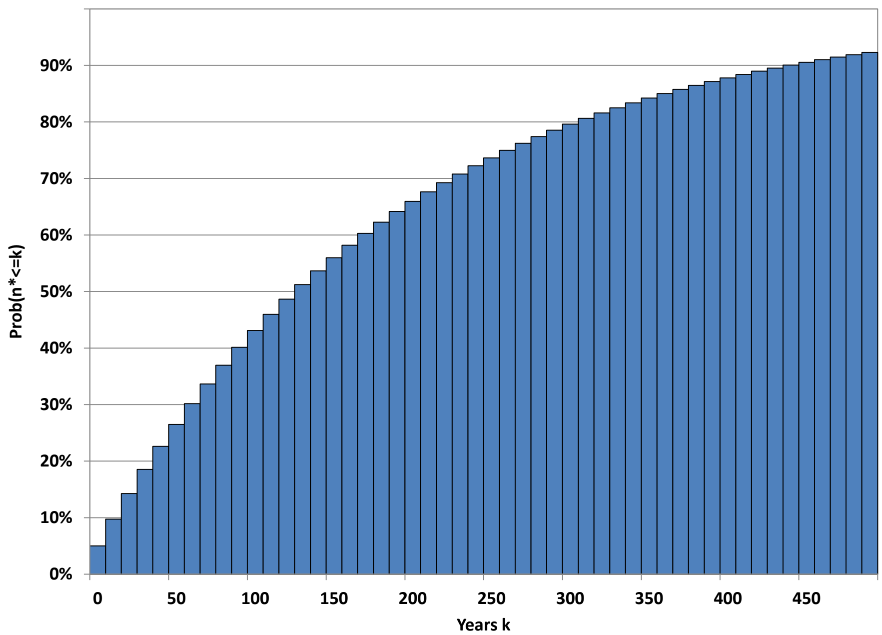


Figure 1: Cumulative distribution of the probability that the first success in consecutive sequences of 10-year AD clinical trials occurs in less than or equal to k years, assuming a 5% probability of success for each clinical trial.

is related to B_i in the following way:

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

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:

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

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

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:

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

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 $\boldsymbol{\epsilon} \equiv [\ \epsilon_1 \ \ \epsilon_2 \ \cdots \ \epsilon_n \ ]'$ a column-vector of random multivariate standard normal variables. Then for any positive-definite matrix $\boldsymbol{\Sigma}$, the new vector of random variables $Z = \boldsymbol{\Sigma}^{1/2}\boldsymbol{\epsilon}$ is multivariate normal with covariance matrix $\boldsymbol{\Sigma}$, where $\boldsymbol{\Sigma}^{1/2}$ denotes the Cholesky factorization or matrix square root of $\boldsymbol{\Sigma}$. 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 a column-vector $\boldsymbol{\epsilon}$ of IID normal random variables
2. Pre-multiplying this column-vector by $\boldsymbol{\Sigma}^{1/2}$ to generate $\mathbf{Z}$
3. Computing a column-vector of 0's and 1's: 0's for Z_i's less 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 times, the relative frequency of the realizations of the sums of $\mathbf{Z}$'s will approximate the distribution of B.

The only subtlety in this simulation exercise involves the specification of $\boldsymbol{\Sigma}$. 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 $\boldsymbol{\Sigma}$ 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 $\boldsymbol{\Sigma}$ cannot be arbitrarily set.

In our simulations, we adopt a three-step process in which all pairwise correlations between targets are first evaluated qualitatively as "low", "medium", or "high" by scientists with domain-specific expertise. These two conjectured matrices are displayed in Figure 2. These assessments are then translated into numerical values of 10% for "low", 40% for "medium", and 80% for "high" (in some cases, a qualitative evaluation of "low-medium" was given, which was assigned a numerical value of 25%). 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 3 contains a heat-map display of the positive-definite correlation matrix constructed from the average of the two conjectured matrices in Figure 2.

6 Megafund Investment Performance

To illustrate the impact of annualization on expected returns, we report the performance statistics of the AD megafund in Table 1 using both methods. The top subtable presents expected returns and standard deviations of annualized 10-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 -6.6% whereas the second method yields $+2.1\%$.

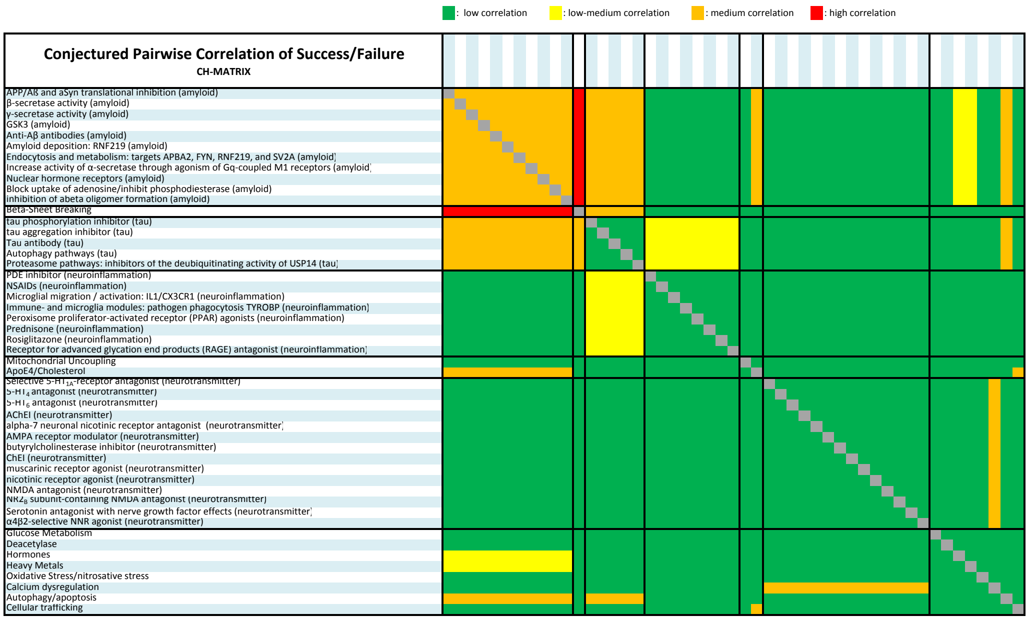
The difference between these two methods of reporting 10-year returns is even greater for the more realistic cases with success probabilities and correlations determined via expert judgment. Using the average of the two correlation matrices, the expected return from the first method is -6.0% and the expected return from the second method is $+4.2\%$. This is not only a large numerical difference but also involves a sign change, which has significant implications for how these investments are perceived by investors and policymakers.

7 Cost/Benefit Analysis

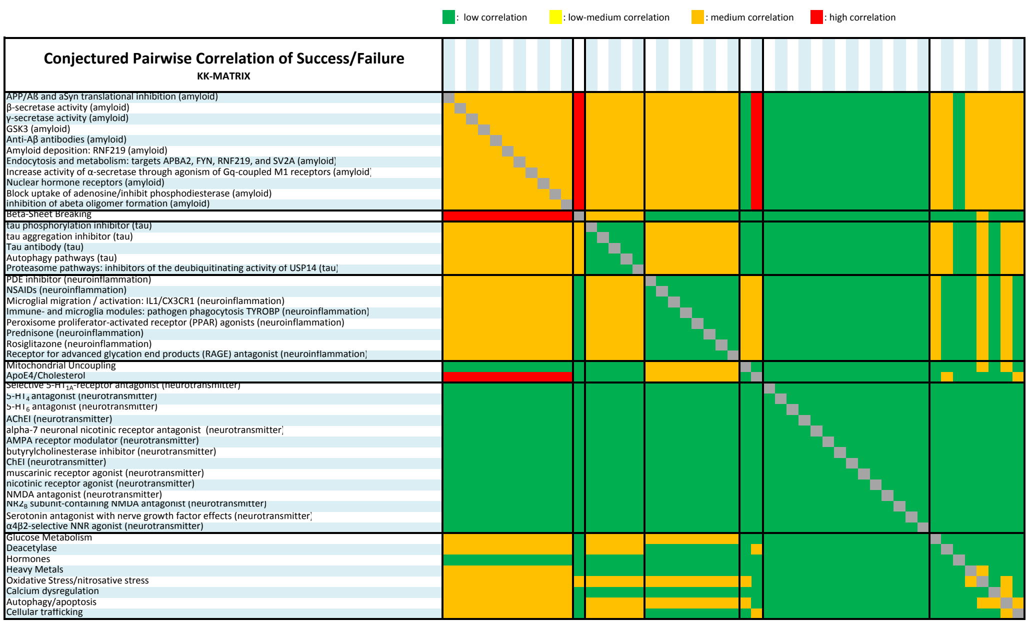
The cost of each of the 49 drug development programs is assumed to be $500 million in 2013 dollars, implying a total cost of $24.5 billion which is equivalent to $22.9 billion in 2010 dollars.

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 2 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.

Many assumptions and detailed computations underlie the AA model, but the most relevant



(a) CH matrix



(b) KSK matrix

Figure 2: Heat-map representation of conjectured pairwise correlations of success/failure of the 49 AD targets as determined by: (a) Dr. Kenneth S. Kosik, and (b) Dr. Carole Ho. Green, yellow, orange, and red entries indicate correlations that are less than 20%, between 20% and 40%, between 40% and 60%, and greater than 60%, respectively.

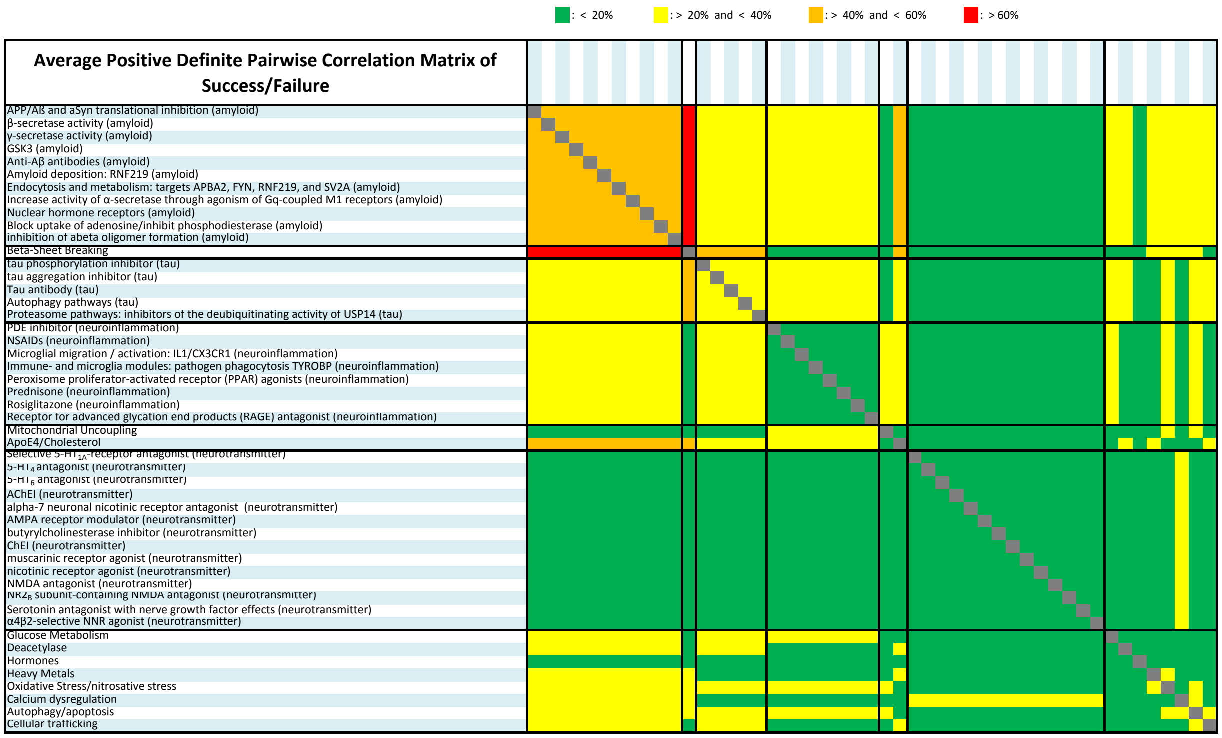


Figure 3: Heat-map representation of positive-definite correlation matrix corresponding to the average of the two conjectured qualitative correlation matrices of pairwise correlations of success/failure of the 49 AD targets by Dr. Kenneth S. Kosik and Dr. Carole Ho. Green, yellow, orange, and red entries indicate correlations that are less than 20%, between 20% and 40%, between 40% and 60%, and greater than 60%, respectively.

p	ρ	p_1	E[R]	SD[R]	p	ρ	p_1	E[R]	SD[R]
Expectation and SD of Annualized Returns									
5%	0%	92%	-6.6%	28.2%	15%	0%	100%	13.2%	4.7%
5%	10%	84%	-14.9%	38.3%	15%	10%	99%	11.5%	11.7%
5%	40%	62%	-37.2%	49.8%	15%	40%	96%	4.3%	24.1%
5%	80%	39%	-61.8%	48.1%	15%	80%	57%	-41.0%	51.2%
10%	0%	99%	7.9%	9.6%	KK Corr.		88%	-8.9%	33.7%
10%	10%	97%	4.1%	20.7%	CH Corr.		91%	-6.2%	30.9%
10%	40%	86%	-9.6%	37.5%	Avg. Corr.		91%	-6.0%	30.2%
10%	80%	45%	-55.0%	50.4%					
Annualized Expected Return and SD									
5%	0%	92%	2.1%	24.2%	15%	0%	100%	13.9%	39.6%
5%	10%	84%	2.0%	34.2%	15%	10%	99%	13.9%	64.0%
5%	40%	62%	-0.4%	39.6%	15%	40%	96%	11.6%	74.0%
5%	80%	39%	-9.1%	19.5%	15%	80%	57%	-0.3%	40.0%
10%	0%	99%	9.4%	33.3%	KSK Corr.		88%	4.0%	37.7%
10%	10%	97%	9.4%	51.1%	CH Corr.		91%	4.6%	38.2%
10%	40%	86%	6.7%	58.4%	Avg. Corr.		91%	4.2%	36.5%
10%	80%	45%	-5.1%	28.2%					

Table 1: Expected returns and standard deviations of the AD megafund over its 10-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 49 targets.

Trajectory	5-year 2015-2020	10-year 2015-2025	15-year 2015-2030	20-year 2015-2035
Current Trajectory (CT)	804	1,436	2,080	2,766
Delayed Onset (T2)	771	1,227	1,601	1,961
Slowed Progression (T3)	778	1,280	1,774	2,298
CT – T2	33	208	480	804
CT – T3	27	156	307	468

Table 2: Alzheimer's Association [2] estimated Medicare and Medicaid costs (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).

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 49 targets proposed. Therefore, a crude cost/benefit calculation can be performed by comparing the cost of the 49 targets 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 49 targets. 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 two different horizons: 10 and 20 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 10-year horizon to develop, and that the cost savings from a success (either in T2 or T3) begins to take effect in year 11. 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 S_i is realized in year 10 and computing the ROI of a $24.5 billion investment in year 0.

5. Because the AA model uses constant 2010 dollars, the initial investment of $24.5 billion must be converted from 2013 dollars to 2010 dollars. This conversion yields an initial investment of $22.9 billion.

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

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

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

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

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

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

The results are reported in Table 3 using both methods of annualization.

Parameters			10-Year	20-Year	10-Year	20-Year	10-Year	20-Year	10-Year	20-Year
p	ρ	p_1	E[R]: Delayed-Onset (T2)		SD[R]: Delayed-Onset (T2)		E[R]: Slowed-Progression (T3)		SD[R]: Slowed-Progression (T3)	
Expected Return and SD of Annualized Return										
5%	0%	92%	14.7%	31.2%	34.0%	38.9%	11.4%	24.3%	33.0%	36.8%
5%	10%	84%	4.2%	19.2%	46.3%	52.9%	1.2%	12.9%	44.9%	50.2%
5%	40%	62%	-23.0%	-11.9%	60.6%	69.4%	-25.2%	-16.5%	58.9%	65.7%
5%	80%	39%	-51.7%	-44.7%	60.8%	69.5%	-53.1%	-47.6%	59.0%	65.9%
10%	0%	99%	24.0%	41.9%	9.3%	10.7%	20.4%	34.5%	9.0%	10.1%
10%	10%	97%	20.5%	37.9%	22.6%	25.8%	17.0%	30.6%	21.9%	24.5%
10%	40%	86%	7.1%	22.6%	43.5%	49.7%	4.0%	16.1%	42.2%	47.1%
10%	80%	45%	-44.4%	-36.3%	62.0%	71.0%	-46.0%	-39.7%	60.2%	67.2%
15%	0%	100%	24.7%	42.7%	2.3%	2.6%	21.1%	35.2%	2.2%	2.4%
15%	10%	99%	23.8%	41.7%	10.7%	12.2%	20.2%	34.2%	10.4%	11.6%
15%	40%	96%	19.2%	36.4%	25.8%	29.5%	15.7%	29.2%	25.0%	27.9%
15%	80%	57%	-28.4%	-18.1%	61.7%	70.6%	-30.5%	-22.4%	59.9%	66.9%
KSK Corr.		88%	10.2%	26.1%	40.0%	45.8%	7.0%	19.5%	38.9%	43.4%
CH Corr.		91%	13.0%	29.4%	36.3%	41.6%	9.8%	22.6%	35.3%	39.4%
Avg. Corr.		91%	13.6%	30.0%	35.6%	40.8%	10.3%	23.1%	34.6%	38.6%
Annualized Expected Return and Standard Deviation										
5%	0%	92%	23.7%	41.5%	78.4%	302.5%	20.1%	34.1%	58.6%	176.0%
5%	10%	84%	22.5%	40.2%	106.8%	412.0%	19.0%	32.8%	79.7%	239.6%
5%	40%	62%	18.8%	36.0%	139.9%	539.8%	15.4%	28.9%	104.5%	314.0%
5%	80%	39%	13.4%	29.8%	140.3%	541.1%	10.2%	23.0%	104.7%	314.8%
10%	0%	99%	24.6%	42.7%	21.5%	83.0%	21.1%	35.1%	16.1%	48.3%
10%	10%	97%	24.3%	42.3%	52.1%	200.8%	20.7%	34.8%	38.9%	116.8%
10%	40%	86%	22.8%	40.6%	100.3%	387.0%	19.3%	33.2%	74.9%	225.1%
10%	80%	45%	15.0%	31.7%	143.1%	552.1%	11.7%	24.7%	106.9%	321.2%
15%	0%	100%	24.7%	42.7%	5.2%	20.1%	21.1%	35.2%	3.9%	11.7%
15%	10%	99%	24.6%	42.6%	24.6%	94.9%	21.0%	35.1%	18.4%	55.2%
15%	40%	96%	24.1%	42.1%	59.5%	229.3%	20.6%	34.6%	44.4%	133.4%
15%	80%	57%	18.0%	35.0%	142.4%	549.3%	14.6%	27.9%	106.3%	319.5%
KSK Corr.		88%	23.2%	41.0%	92.4%	356.3%	19.6%	33.6%	69.0%	207.3%
CH Corr.		91%	23.5%	41.3%	83.9%	323.6%	19.9%	33.9%	62.6%	188.3%
Avg. Corr.		91%	23.6%	41.4%	82.2%	317.1%	20.0%	34.0%	61.4%	184.5%

Table 3: Expected returns and standard deviations of Medicare and Medicaid cost savings, computed before and after annualization, from an AD megafund over its 10-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 49 targets.

References

[1] Qi, H. and Sun, D., 2006, “A Quadratically Convergent Newton Method for Computing the Nearest Correlation Matrix,” *SIAM J. Matrix Anal. Appl.* 28, 360–385.

[2] Alzheimer’s Association, 2010, *Changing the Trajectory of Alzheimer’s Disease: A National Imperative*. Chicago, IL: Alzheimer’s Association.