

**PERSPECTIVE**

# On the horizon—the value and promise of the global pipeline of Alzheimer's disease therapeutics

Michael A. Cole<sup>1,2</sup> | Guy R. Seabrook<sup>3</sup>

<sup>1</sup>Clinical Science Program, University of California Berkeley, Berkeley, California, USA

<sup>2</sup>Global Neurohealth Ventures, San Francisco, California, USA

<sup>3</sup>Johnson & Johnson Innovation, South San Francisco, California, USA

**Correspondence**

Michael Cole, Clinical Science Program, University of California Berkeley, PO Box 842, Pacifica, CA 94044, USA.

Email: michaelcole@berkeley.edu

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G.R.S. is an employee at Janssen Pharmaceutical Companies of Johnson & Johnson and shareholder at Johnson & Johnson Inc.

## Abstract

**Introduction:** The recent failure of several late-stage Alzheimer's disease (AD) clinical trials focused on amyloid beta ( $A\beta$ ) highlights the challenges of finding effective disease-modifying therapeutics. Despite major advances in our understanding of the genetic risk factors of disease and the development of clinical biomarkers, and that not all  $A\beta$ -based approaches are equivalent, these failures may engender skepticism regarding the value of the AD pipeline.

**Methods:** To investigate these concerns, we compiled a database of current Phase 2 and 3 trials based on disease-modifying targets through a query of the National Institutes of Health's ClinicalTrials.gov. We then assessed the financial value of the pipeline. Financial modeling utilized risk-adjusted net present value (rNPV) measurements and included sensitivity analyses to help inform the drug development process.

**Results:** Results indicate that the preponderance of current Phase 3 trials were indeed targeting  $A\beta$ , with only 15% addressing other targets. In contrast, the pipeline of Phase 2 trials was more diverse. The estimated rNPV of Phase 2 and 3 therapeutics was estimated to be \$338 billion over 10 years. This figure increased to a theoretical cumulative value of \$788 billion when incorporating the assumption that diagnostics will be developed to identify individuals at high risk for developing AD. Results from model sensitivity analyses showed that speed of market penetration and patient access contributed the most weight to financial value. In contrast, decreasing drug development costs had minimal impact on rNPV.

**Discussion:** These findings argue in favor of conducting thorough biomarker-driven Phase 2 proof of concept studies to avoid prematurely advancing assets into Phase 3. Insights from these analyses are also discussed in the context of the financial ecosystem needed to maintain a healthy AD pipeline.

## KEYWORDS

AD, advocacy, Alzheimer's disease, biomarkers, biotechnology companies, clinical trials, dementia, disease-modifying therapy, pharmaceutical industry, Phase 1, Phase 2, Phase 3, prodromal AD

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## 1 | INTRODUCTION

The personal and societal burden of Alzheimer's disease (AD) is difficult to quantify, although the magnitude of effects of this disease can be appreciated on many levels. An individual diagnosed with AD experiences a slow erosion of their ability to remember daily activities that is accompanied by sleep and behavioral issues as well as major disruption of activities of daily living (ADLs). At a social systems level, there are few treatment options, which necessitates long-term care, a burden often left to family and loved ones. At an economic level, the effect of AD has a similarly severe toll, and it is increasing precipitously. Due to the aging population, the number of individuals with AD is expected to nearly triple by 2050.<sup>1</sup> The impact this will have to health care systems around the world emphasizes the critical need for investment, since the annual cost of care for patients with AD is expected to rise from \$290 billion in 2019 to \$1.1 trillion by 2050 in the United States alone.<sup>1</sup> The personal economic consequences for care of an individual with AD are more difficult to quantify, but they can often be substantial including a wide range of financial burdens such as paying for in-home health care, assisted living, and other health care-related costs in addition to many other considerations such as lost wages from caregiving. These as yet uncontrollable and high personal, societal, and financial costs of AD clearly establish it as a major unmet medical need.

Since the last drug approved for the treatment of AD symptoms was launched in 2003, memantine,<sup>2</sup> >500 clinical trials have been conducted for AD treatment. Approximately 50 compounds successfully passed Phase 2 clinical trials, but none have successfully passed through Phase 3.<sup>3</sup> There exist several critical challenges that impede progress in successfully developing novel therapeutic agents to treat AD. Until recently, challenges in developing appropriate biomarkers that have a definitive relationship with symptoms (eg, memory loss) have limited the ability to establish proof of relevance of candidate drugs without large-scale and expensive clinical trials. Furthermore, the insidious nature of AD results in diagnosis taking place long after appreciable progression of the disease has occurred, including extensive deposition of A $\beta$ , formation of neurofibrillary tangles, synapse loss, and cell death.<sup>4,5</sup> A $\beta$  deposition can start up to 17 years before the onset of symptoms, and an increase in astrocytes can appear 20 years before observed symptoms.<sup>6</sup> Thus, at the point of diagnosis and enrollment to conventional drug trials, the disease may have already progressed to a point at which the neurodegeneration is so widespread that it may be too difficult to reverse or sufficiently compensate for the damage. An additional challenge is the sheer complexity of the disease, since it involves multiple genes, cell types, and tissues that disrupt whole networks of neuronal circuitry.<sup>7</sup> These in turn can propagate further adaptive and/or destructive changes. Untangling the complexity of those interactions at genetic, cellular, neural circuit, and behavioral levels to determine valid points for therapeutic intervention is a daunting task, especially in advanced disease.<sup>8</sup> The analogy of a house fire is sometimes used to describe the disease process to help visualize the challenges to drug development. For example, once a house is engulfed by flames it is difficult to identify the root cause without the appropriate investigative tools (eg, biomarkers to disentangle the multifactorial

disease process and interactions). Likewise, it simply may not be possible to reverse the damage that has already occurred. Furthermore, despite the fact that charred wood can be found following a fire (A $\beta$  plaques?), this may not be relevant to the cause of the fire if it was the result of boiling oil left on the kitchen stove. Taken together, these factors raise an important question of whether the pipeline of drugs being developed for AD is, or has been, too weighted on one mechanism of action centered largely around A $\beta$  production?

Concern about AD drug development focus being overly dominated by a single hypothesis, the A $\beta$  cascade hypothesis, is not new<sup>9</sup> but also may be overlooking a significant number of non-amyloid-based approaches to disease modification by the field over the last several decades including M1 positive allosteric modulators, histamine H3 inverse agonists, peroxisome proliferator-activated receptors, nonsteroidal anti-inflammatory drugs, cyclooxygenase-2 inhibitors, statins, and growth hormone secretagogues, to name just a small sample of targets. Furthermore, not all approaches to targeting A $\beta$  are equivalent. For example, sequestration of A $\beta$  protein with antibodies that target specific epitopes and act largely upon extracellularly amyloid is not the same as blocking A $\beta$  production within neurons or alterations in cleavage of full-length amyloid precursor protein. Thus, it is also prudent to consider A $\beta$  as a potential by-product of the disease process and not necessarily as the sole driver.<sup>10</sup> Because the etiology of AD appears multifactorial, it is also logical to consider a range of other targets for potential therapeutic intervention. Likewise, even from a purely financial perspective, an investment in a diverse range of targets is prudent to spread risk and optimize potential return on investment rather than having "all the eggs in one basket." So, to what extent is the current drug development focus really only focused on a narrow range of potential pathological mechanisms (eg, A $\beta$  hypothesis) versus a range of therapeutic targets? To help understand the value and promise of therapeutics being developed for AD, this study investigated the diversity and financial value of the global late-stage drug development pipeline. We also examined the levers that are most important in helping drive portfolio value.

## 2 | METHODS

### 2.1 | Evaluating the diversity of the current late-stage AD drug development portfolio

An assessment of the current distribution of disease-modifying targets of AD Phase 2 and Phase 3 clinical trials was obtained by collecting data from clinicaltrials.gov. The "Final Rule" governing clinicaltrials.gov was updated in 2016,<sup>11,12</sup> mandating registration for all trials from sponsors with an Investigational New Drug or Investigational New Device. Submission of a new trial must be within 21 days of the enrollment of the first trial participant, and results must be provided within 12 months of completion of final data collection. Thus, clinicaltrials.gov entails a comprehensive list of clinical trials in AD that are targeting approval for use in the United States. However, potential limitations include sponsor noncompliance with rules of registration or

the timelines for submission of data. Data were extracted by entering “Alzheimer’s Disease (Incl Subtypes)” in the *Condition or disease* field, “Interventional Studies” for the *Study Type*, “Recruiting,” “Enrolling by invitation,” and “Active, not recruiting” boxes checked for the *Recruitment* field, and “Phase 2” and “Phase 3” boxes checked for the *Phase* field. The search was conducted from July 20 to 23, 2018. Trials were not included if they were listed as completed, terminated, suspended, or withdrawn. Drugs with only symptom-modifying targets as well as nonpharmacologic therapeutic approaches (eg, devices or behavioral/cognitive interventions) were excluded.

## 2.2 | Total value of the entire Phase 2 and Phase 3 disease-modifying AD therapeutics global portfolio

What is the total value of the current AD Phase 2 and Phase 3 disease-modifying drug portfolio? To answer this question, the combined value of current late-stage therapeutics was estimated. The risk adjusted net present value (rNPV) method described by Stewart and colleagues (2001) was applied to the therapeutics identified in the above-described data extraction from [clinicaltrials.gov](http://clinicaltrials.gov).<sup>13</sup> Modeling methods and assumptions are consistent with common industry practices for asset valuation. Table 1 provides a summary of the model assumptions that underlie final calculations. The total prevalence of the AD population worldwide was based on estimates for dementia provided by the *Alzheimer World Report*,<sup>14</sup> and then reduced by 30% to represent the proportion of total worldwide individuals with dementia who have likely AD.<sup>15</sup> The number of individuals with “pre-clinical” (or asymptomatic) AD, who are highly likely to proceed to develop AD, was

estimated in part from data derived from the Alzheimer’s Disease Neuroimaging Initiative (ADNI) project. Specifically, ADNI studies report first detecting neuropathological signs approximately 10 years prior to clinical progression to AD.<sup>16</sup> The assumption made for determining the number of pre-clinical AD individuals is that when effective biomarkers are developed with excellent sensitivity and specificity for predicting AD, they will likely detect meaningful neuropathological signal approximately 10 years prior to clinical AD diagnosis. Thus, the pre-clinical population estimate for a given year is the projected number of individuals diagnosed with AD in 10 years. For example, the estimated number for pre-clinical AD individuals in 2020 would be equal to the number of projected individuals with AD in 2030. Although there are many different approaches to generating this estimate, it is felt that this approach provided the best combination of being informed by data (ie, ADNI studies) and conservative so as to not overestimate the number of pre-clinical AD individuals.

Revenue generation modeling is based on an estimated 10 years remaining on the patent following initial market launch of the therapeutic. Extent of market penetration by geographic region (Table 1) was estimated in order to calculate the total projected revenue by region. The peak market penetration for each region (see Table 1) was multiplied by the proportion of population the region represents of the total world population, and the resulting percentage was used to estimate the total market captured by each region. Retail drug price was based on the average retail price for current disease-modifying treatments for multiple sclerosis<sup>17</sup> and includes a 3% annual inflation. The discounted price for each global region is estimated by averaging the regional price discount received for the top four selling drugs.<sup>18</sup> Cost of goods sold (COGS) is estimated to be 26% of sales<sup>19</sup> and is included in the final valuation estimate. Given the complexities of the likely first entrants into the AD disease-modifying market as it relates to timing, differing mechanism of actions, monotherapy versus combo-therapies, small molecule versus biologic, and so on, pricing estimates aggregate the first entrants to provide an average. To give an example of the final discounted value, the annual price in the United States is estimated at \$41,602. The pharmaceutical company proceeds retention from the retail value was estimated at 80%. The cost of the AD clinical trials was based on estimates reported by Cummings and colleagues (2018).<sup>20</sup>

Risk adjustment was based, in part, on historical data of the successful progression of neurological therapeutics advancing from one development stage to the next in the drug development processes as reported by Hay and colleagues.<sup>21</sup> However, this rate is considered an overestimation of the predicted rate of success for AD drug development. Therefore, the clinical trial rates were reduced by 75% to provide a conservative estimation of success at each stage. Specifically, the model estimates for the success rate for advancing from Phase 2 to Phase 3 utilized was 3.1%, the success rate for advancing from Phase 3 to NDA/BLA application was 15.1%, and New Drug Application/Biologic License Application (NDA/BLA) to FDA approval was 82.2%. Values for estimated success rate (ie, risk adjustment for the models) were used as an overall average risk for therapeutics in each stage. The risk for particular therapeutics would certainly differ, but analyses were conducted at the aggregate level for each phase of

**TABLE 1** Model assumptions for estimating the risk adjusted net present value (rNPV) of current Phase 2 and Phase 3 assets in development to treat AD

Model component (source/rationale)	Value
Total prevalence of dementia worldwide ( <i>Alzheimer World Report</i> <sup>14</sup> )	46.8 million in 2015; 131.5 million by 2050
Percent of total dementia cases that are AD <sup>15</sup>	70%
Revenue generating years (estimated 10 years remaining on patent following regulatory approval)	10
Estimated peak market penetration	Proportion world population × estimated peak market penetration = proportion worldwide market penetration
North America	$0.070 \times 0.600 = 0.045$
Latin America	$0.080 \times 0.120 = 0.010$
Japan	$0.020 \times 0.200 = 0.003$
Europe	$0.100 \times 0.430 = 0.041$
Asia, Africa, Australia	$0.730 \times 0.320 = 0.232$
Cost of capital <sup>23</sup>	8.55%

development so an averaged risk was utilized. In addition, it is important to note that applying the above-described risk adjustment values to the rNPV models produces comparable results to an approach that is derived from applying reported AD success rates by Cummings and colleagues for risk adjustment.<sup>22</sup>

Models were generated without cost of capital and also with cost of capital so that the total present value of the therapeutic could be assessed as well as the present value in the context of comparison to other investments in the pharmaceutical sector, respectively. Cost of capital refers to the required return to make an investment worthwhile when adjusting for what the anticipated average returns would be with another investment in the same sector. Thus, at least in theory when the model includes the cost of capital, any resulting net present valuation (NPV) of an investment above \$0 is worth pursuing because it is predicted to better what could have been achieved with another investment, on average, in that same sector. For example, the cost of capital for the pharmaceutical industry in 2018, as reported by the New York University Sterns Business School, was 8.55%.<sup>23</sup> This indicates that in order for investment in a therapeutic to outperform the sector, the risk adjusted net present value (or rNPV) must exceed \$0, which indicates that the investment performed better overall than the 8.55% returns anticipated for the pharmaceutical sector.

The total value of the current late-stage AD pipeline was determined by adding the value of each current Phase 2 and Phase 3 disease-modifying therapeutics together.

### 2.3 | Value estimate of individual Phase 2 and Phase 3 disease-modifying AD therapeutics

An individual therapeutic valuation was determined by the above-described modeling. Final values were determined for Phase 2 and Phase 3 disease-modifying AD therapeutics. Total value of a therapeutic was estimated (ie, no cost of capital) as well as value estimate when correcting for, or comparing to, investment in the pharmaceutical sector (ie, cost of capital included). It is important to note that valuations represent an averaged value at each respective stage of development. A wide range of variance in valuation exists for individual therapeutics given the potential for differences in magnitude of therapeutic benefit versus safety profile, their mechanism of action, whether small molecule versus a biologic, and level of target engagement, among many other factors.

An additional follow-up analysis determined how low the risk adjustment (or estimated success rate) could decrease and still maintain a positive rNPV value. In other words, what is the lowest value for the risk adjustment that still maintains a positive rNPV when cost of capital is considered. To perform this calculation, the rNPV value was set to \$1 and the model was set to solve for the estimated percent chance of success variable. Thus, the model was adjusted to solve for the lowest value for estimated success that still maintains a positive rNPV value and therefore is deemed a worthwhile investment when considered in a traditional finance approach.

### 2.4 | Sensitivity analysis of model assumptions

A sensitivity analysis was performed on model assumptions to test how sensitive the final therapeutic valuation is to assumptions made for the modeling. The sensitivity analysis was performed on primary model assumptions to determine the extent to which deviations from the model assumptions would affect the final model valuation estimate. Specifically, final model valuation estimates were generated after upward and downward modification of 25% increase and 25% decrease in the model assumption value. The sensitivity analysis also serves to highlight where variance in model components produces the most impact on the therapeutic value.

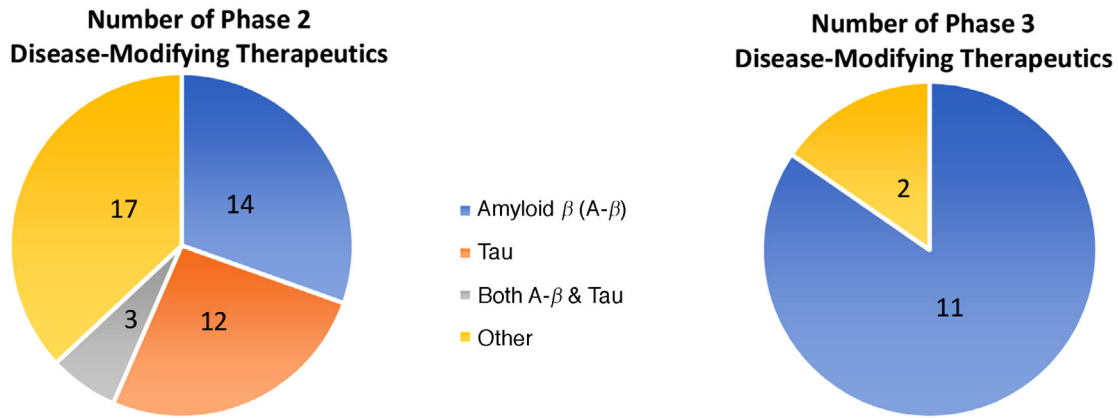
### 2.5 | Decision tree analysis

A decision tree analysis was generated to evaluate the drug development decision process from the point of view of expected individual therapeutic valuation at each step in development in the face of the uncertainty of success (ie, adjusted for risk). The total NPV of an AD disease-modifying therapeutic at market launch after receiving U.S. Food and Drug Administration (FDA) approval was calculated by the methods described earlier. The NPV value was not risk-adjusted, because each of the Phase and FDA approval hurdles would have been cleared at this point, and cost of capital was not included in the model. Then the rNPV for each prior stage was determined by multiplying the estimated probability of success by the estimated value, assuming the step was successfully completed. For example, the rNPV for Phase 3 would be calculated as follows; values are in millions): \$492,014 [value at beginning of NDA/BLA step] multiplied by 15.1% [probability of successfully completed Phase 3]—\$413 [estimated capitalized expenses of Phase 3 trial] = \$73,881 [rNPV beginning Phase 3] (see also Figure 2 for illustration). It should be noted that given the different methodology used to calculate the rNPV for the decision tree, these rNPV values are different than those calculated by the risk-adjusted methods described above.

## 3 | RESULTS

### 3.1 | Diversity of therapeutic targets

The extent to which the current late-stage AD pipeline is diversified was assessed (Figure 1). A limited diversity of targets for Phase 3 AD therapeutics exists as the vast majority (85%) target  $A\beta$  proteins. In contrast, a much greater diversity of disease-modifying targets exists for Phase 2 AD therapeutics.  $A\beta$ -related targets account for 37% of therapeutics in development, whereas non- $A\beta$  targets account for 63% of the therapeutics in development including 26% tau protein targets and 39% other potential disease-modifying targets (eg, metabolic, neuroprotective, regenerative, anti-inflammatory targets).



**FIGURE 1** Number of therapeutics for each category of therapeutic target (amyloid  $\beta$  [A $\beta$ ], tau, combined A $\beta$  and tau, other targets). Data were compiled for current Phase 2 and Phase 3 trials

**TABLE 2** Total value estimate of all late stage disease-modifying AD therapeutics combined

Model estimate	rNPV (in millions)
Risk adjusted net present value including cost of capital	
Treating diagnosed patients only	\$338,283
Treating diagnosed and pre-clinical patients	\$787,523
Risk adjusted net present value with no cost of capital	
Treating diagnosed patients only	\$832,619
Treating diagnosed and pre-clinical patients	\$1,931,753

rNPV = risk adjusted net present value.

### 3.2 | Value of the total late-stage AD disease-modifying therapeutic global portfolio

Results for models estimating the total global portfolio value for AD disease-modifying therapeutics are provided in Table 2. The total value of the current late-stage AD disease-modifying therapeutics global portfolio is estimated to be \$833 billion. This value more than doubles (\$1932 billion) when also considering the possible future ability to identify and subsequently treat pre-clinical individuals who are highly likely to develop AD. When including the cost of capital in the model, the portfolio continues to retain a high value: \$338 billion (rising to \$788 billion when able to identify and treat pre-clinical individuals). To reiterate the interpretation of the cost of capital model, a value >\$0 is traditionally interpreted as a better investment than that of the average pharmaceutical sector.

### 3.3 | Value of individual Phase 2 and Phase 3 AD disease-modifying therapeutics

Results for models estimating the Phase 2 individual value for AD disease-modifying therapeutics are provided in Table 3A. For Phase 2 therapeutics, the current estimated value for an individual therapeutic with potential for AD disease-modifying activity is \$9.1 billion. This

**TABLE 3** Value estimate of individual disease-modifying AD therapeutic

A. Model estimate for a Phase 2 disease-modifying therapeutic	rNPV (in millions)
Risk adjusted net present value including cost of capital	
Treating diagnosed patients only	\$3407
Treating diagnosed and pre-clinical patients	\$7884
Risk adjusted net present value with no cost of capital	
Treating diagnosed patients only	\$9,106
Treating diagnosed and pre-clinical patients	\$21,018
B. Model estimate for a Phase 3 disease-modifying therapeutic	rNPV (in millions)
Risk adjusted net present value including cost of capital	
Treating diagnosed patients only	\$13,967
Treating diagnosed and pre-clinical patients	\$32,683
Risk adjusted net present value with no cost of capital	
Treating diagnosed patients only	\$31,827
Treating diagnosed and pre-clinical patients	\$74,225

rNPV = risk adjusted net present value.

value more than doubles to \$21.0 billion when also considering the possible future ability to identify and subsequently treat pre-clinical individuals who are highly likely to develop AD. When including the cost of capital in the model, the Phase 2 therapeutic continues to retain a high value: \$3.4 billion (rising to \$7.9 billion when able to identify and treat pre-clinical individuals).

Results for models estimating the Phase 3 therapeutic valuations are provided in Table 3B. The current estimated value for a Phase 3 individual therapeutic with potential for AD disease-modifying activity is \$31.8 billion. This value more than doubles to \$74.2 billion when also considering the possible future ability to identify and subsequently treat pre-clinical individuals who are highly likely to develop AD. When including the cost of capital in the model, the Phase 3 therapeutic continues to retain a high value: \$14.0 billion (rising to \$32.7 billion when able to identify and treat pre-clinical individuals).



**TABLE 4** Testing key model assumptions with a sensitivity analysis

Model assumption for disease-modifying drug	-25% (\$ in millions)	+25% (\$ in millions)	Impact
Market penetration trajectory across each year on the market	\$-911	\$19,123	±110%
Peak market penetration	\$3916	\$14,296	±57%
Market penetration estimates by geographic regions	\$6738	\$11,474	±26%
Drug price	\$6921	\$11,291	±24%
Cost of capital	\$7285	\$10,927	±20%
Phase 2 → Phase 3 success rate	\$7467	\$10,745	±18%
AD and pre-clinical AD population estimate	\$7740	\$10,742	±15%
Percent drug price increase each year	\$8378	\$9834	±8%
Phase 3 → approval success rate	\$8469	\$9473	±7%
Drug development costs	\$9106	\$9106	±0%

An additional analysis was performed to determine the threshold point at which the risk adjustment value can reside while still maintaining a positive rNPV. In other words, how low can the estimated potential success rate be and still maintain a >\$0 rNPV, indicating a viable investment as compared to the pharmaceutical sector. Results indicate that for Phase 2 and Phase 3 disease-modifying AD therapeutics, the success rate (ie, risk adjustment) can drop to as low as 0.000000009% (or 9 in 100 billion chance of success) and still maintain a positive rNPV. In other words, the therapeutic can have an estimated extremely small fractional chance of success and still appear to be a viable investment, at least according to the traditional rNPV finance modeling approach. This finding may provide insight into the numerous recent AD Phase 3 failures as well as the applicability of this traditional finance modeling for decisions to pursue a therapeutic in development (which will be expanded upon further in the Discussion).

### 3.4 | Sensitivity analysis of model assumptions

We next performed a sensitivity analysis on primary model assumptions of the rNPV model for an individual AD therapeutic in order to determine the extent to which each of these factors influenced the potential value of the therapeutic. Each primary model assumption was adjusted by ±25% to determine the impact on the final therapeutic value. Results are summarized in Table 4. The variables with the most sensitivity to change are the three market penetration assumptions. Specifically, changes in the estimates for rate, peak, and geographic spread of the market penetration were the variables that had the most impact on the final valuation. In contrast, variation in the drug development costs had the least impact on the therapeutic valuation.

### 3.5 | Decision tree analysis

Figure 2 provides an overview of the drug development trajectory for a disease-modifying AD therapeutic. The risk-adjusted NPV for the hypothetical therapeutic is depicted at each stage of development proceeding from the Discovery stage to FDA approval. The ultimate estimated NPV of a therapeutic that successfully obtains FDA approval is \$598,582 million. The greatest inflections of therapeutic value are observed after successful completion of the Preclinical Phase (9-fold value increase) and after successful completion of Phase 2 (14-fold value increase). It is important to highlight that the Discovery stage valuation is negative, which has significant implications for the funding ecosystem that will be addressed in the Discussion section.

## 4 | DISCUSSION

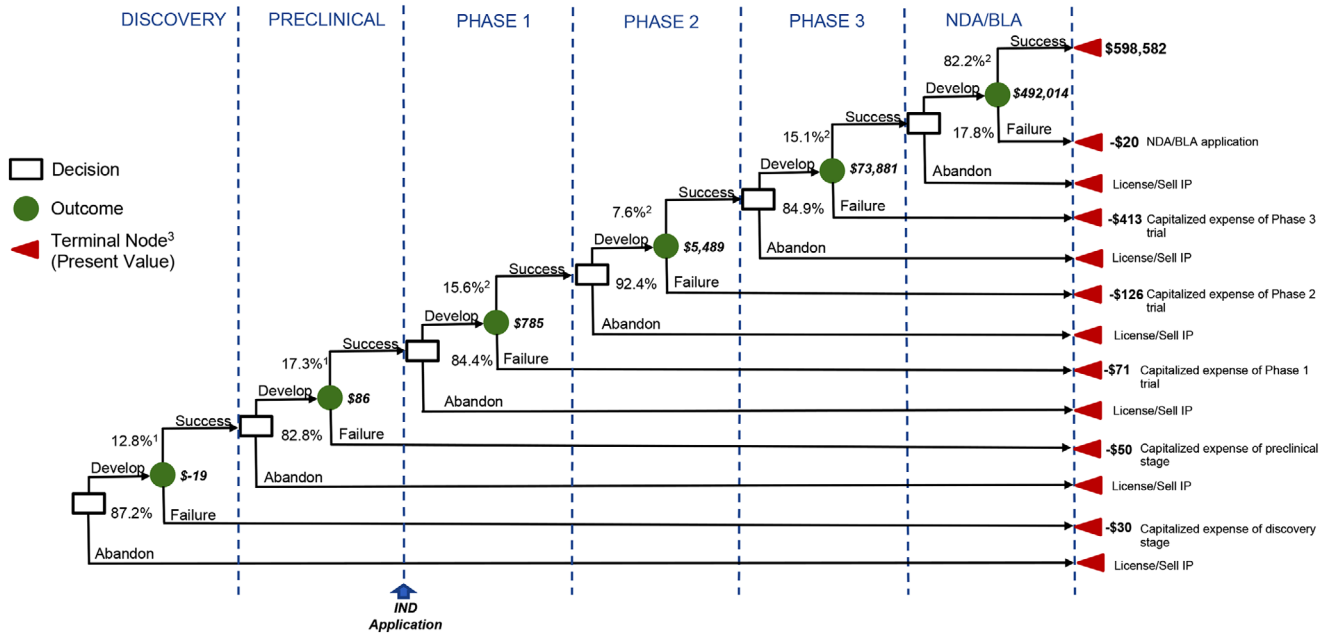
### 4.1 | Diversity of therapeutic targets

The Phase 3 pipeline for AD disease-modifying therapeutics is heavily focused on A $\beta$  with little heterogeneity of targets. Since the compilation of these data several notable additional A $\beta$ -related failures in the Phase 3 pipeline have been announced. It is important to note that not all A $\beta$ -related mechanisms of action are equivalent, and that they carry different risks as well as potential.<sup>10</sup> Greater diversity of disease-modifying targets is observed in the Phase 2 pipeline for AD. Although not the focus of the analysis, it is worth noting that a survey of Phase 1 and earlier stages of drug development and discovery reveal an even great diversity of targets. Given the complex etiology of AD, it is likely that addressing more than one neuropathological process will be necessary to effectively halt, and potentially reverse, AD. Thus, continued diversity of the global pipeline is not only critical to increase the probability of emergence of successful disease-modifying drugs, but also will likely result in multimodal treatments that will better tackle the disease.

### 4.2 | Value of the total late-stage AD disease-modifying therapeutic global portfolio

Given the numerous high publicity Phase 3 AD therapeutic failures that have occurred over the recent few years, some have come to question the value of the late-stage AD portfolio. Our estimate, which utilized conservative and widely accepted approaches to pharmaceutical asset valuation, suggests the late-stage AD disease-modifying global pipeline to be worth approximately \$833 billion. To date, other estimates have focused primarily on the AD drug market (rather than a valuation of the actual AD pipeline) and typically only measure a 1-year window (as opposed to the 10-year on-patent therapeutic future market window measured here). Examples of these estimates include the following: Zion Market Research estimated the global AD drug market will reach \$5.7 billion by 2024,<sup>24</sup> Transparency Market Research

**Alzheimer's Disease Drug Development Decision Tree Depicting Risk Adjusted Value for a Single Therapeutic<sup>3,4</sup> (\$ in millions)**  
-model valuations based on no cost of capital, a 10-year period on market before patent cliff, and ability to treat symptomatic and pre-symptomatic patients-



**FIGURE 2** <sup>1</sup>Paul SM et al. (2010). How to improve R&D productivity: the pharmaceutical industry's grand challenge. *Nature Reviews Drug Discovery*, 9(3):203-214, with 75% downward correction to account for AD therapeutic development context. <sup>2</sup>Hay M et al. (2014). Clinical development success rates for investigational drugs. *Nature Biotechnology*, 32(1): 40-51, with 75% downward correction to account for AD therapeutic development context. However, NDA/BLA step not corrected. <sup>3</sup>Important to note the following model assumptions: (1) cost of capital not considered; (2) the drug is the first AD disease-modifying therapeutic to market; (3) includes also treating asymptomatic individuals at high risk for developing AD, which assumes the availability of rapid and easy to use diagnostic biomarker(s) of risk and global access; and (4) each decision point considers previous capitalized expenses as sunk costs and are not factored into the decision economics. <sup>4</sup>Clinical trial expenses from Cummings and colleagues, 2018.<sup>20</sup> Discovery and preclinical stages are estimated to cost \$30 and \$50 million, respectively, and NDA/BLA is estimated at \$20 million

estimated the global AD drug market will reach \$6.4 billion by 2025,<sup>25</sup> and GlobalData estimated the global AD drug market will reach \$14.8 billion by 2026. These estimates are also constrained to only current symptom-modifying therapeutics being available and do not incorporate the potential future availability of disease-modifying therapeutics. In addition, these estimates do not include consideration of the eventual ability to hopefully be able to identify and treat pre-clinical AD. Assuming such diagnostics will be developed that allow for the treatment of pre-clinical AD patients, the previously noted \$833 billion estimated value of the late-stage global pipeline will more than double to an estimated \$1932 billion.

When including the cost of capital in the model, the global late-stage AD pipeline for disease-modifying focused therapeutics continues to retain a high value at \$338 billion. This finding suggests that the AD pipeline is a strong investment as compared to the pharmaceutical sector as a whole, upon which the 8.55% cost of capital was based.<sup>23</sup>

Taken together, these findings suggest that despite the recent high publicity spate of Phase 3 failures in AD and the subsequent reverberations of negative perception of AD drug development, the current late-stage AD pipeline consists of a moderately diverse portfolio (with strong diversity of targets for Phase 2 therapeutics) that is of substantial value.

### 4.3 | Value of individual Phase 2 and Phase 3 AD disease-modifying therapeutics

The value of Phase 2 and 3 AD disease-modifying therapeutics was estimated to be \$9 billion and \$32 billion, respectively. As noted previously, these represent an average value estimate for the respective phase in development, and a wide range of variance in valuation exists for respective individual therapeutics. Significant value is still retained when considering the cost of capital, which factors out returns that would be achieved by instead an average rate of return investment elsewhere in the pharmaceutical sector. Specifically, the Phase 2 value is \$3 billion and the Phase 3 value is \$14 billion when considering cost of capital. Of interest, the risk adjustment can be decreased to as low as a 9/100,000,000,000 chance of success and a positive rNPV is still retained, suggesting a worthwhile investment at least according to traditional rNPV financial modeling. To place this in perspective, this odds of success is equivalent to the odds someone residing in the United States has of being struck by lightning within their lifetime, twice.<sup>26</sup> This finding brings into question the utility of the traditional application and interpretation of the rNPV when evaluating a single therapeutic, particularly in the context of potential markets as large as is the case for AD disease-modifying therapeutics. Indeed, it is perhaps the high rNPV

for the late-stage AD therapeutics that led to the decisions to continue pursuit of  $A\beta$  therapeutics despite the mounting evidence against the efficacy of targeting  $A\beta$  after symptoms have already emerged and the numerous preceding failed trials. Thus, these findings suggest that the rNPV valuation approach should be applied within scientific context constraints when used to determine the estimated value of individual therapeutics. Unfortunately, the repercussions of these past decisions and the subsequent associated highly publicized AD failures is likely to generate deleterious reverberations into investment in AD, and perhaps clinical neuroscience more broadly as well.

#### 4.4 | Sensitivity analysis: implications for AD pipeline development

Findings from the sensitivity analysis provide insights into the drug development process highlighting areas of focus that can generate the most value from a therapeutic, and areas of focus where there might be less impact on total value generation. The ability to expand market penetration provides the most substantial increase in therapeutic valuation, which also importantly allows more individuals with AD to benefit from the therapeutic. Thus, increased focus and resources placed on greater market penetration for an approved therapeutic will substantially improve the therapeutic's value on multiple levels. Of interest, the variable with the least impact on the therapeutic valuation is cost of drug development, wherein shifting the costs upward or downward by 25% had nearly negligible impact on the ultimate valuation of the therapeutic. This is notable in the current climate of substantial focus on cutting drug development costs. These results suggest minimal ultimate gains in drug valuation when making significant drug development cost cuts. Moreover, the increasing trend for development shortcuts (eg, Phase 2 and 3 combination designs) may be overall more deleterious because necessary and important drug development steps (eg, efficacy, toxicity, pharmacokinetics, development of appropriate end points, dosing, and so on) are given short shrift and subsequently a greater price is paid when the drug then fails during later stages of development. Instead, a focus on quality trial design, better trial infrastructure, improved biomarkers for improved participant selection, and improved efficacy outcome measurements, and other factors<sup>22</sup> will be critical for efficient and effective AD drug development.

#### 4.5 | Implications of global portfolio analysis versus decision tree for single assets

The probability of global portfolio success is spread across hundreds of assets and across multiple mechanisms that mitigate risk at the global level. When one considers risk at the individual asset, it is critical to take into account the likelihood of success of each phase of the drug development process. Even after correcting with a 75% reduction in probability of success than the average neurological therapeutic in development at each respective stage, the estimated rNPV is positive after new molecular entity/investigational new drug (NME/IND) stage

of development despite the significant downstream costs and risks of development (see Figure 2). In contrast, at the Discovery phase, the business case is negative. This highlights the crucial interplay needed between multiple stakeholders across government, academia, philanthropy, and venture capital to support research in the medical innovation ecosystem to maintain the early stage pipeline.

#### 4.6 | On the horizon

The strength of the global pipeline is growing with the increased diversity of neuropathological targets observed for Phase 2 and earlier stages of development. In addition, the likelihood of a successful disease-modifying therapeutic being brought forward to patients in need is greatly facilitated by the rapidly expanding pace of scientific advances in AD research. Over the next decade it is to be expected that there will be major advances in the fields of clinical neuroscience, artificial intelligence, diagnostics, precision genomics, as well as accelerated digital health solutions, that can assist in both clinical trials and significantly improved patient outcomes. This analysis shows that the global AD pipeline, as well as the investment in individual AD disease-modifying therapeutics, is valuable. Taken together, a perceived negative bias for investing in AD research resulting from recent Phase 3 failures is unfounded. Additionally, traditional approaches to using risk adjusted net present value (or rNPV) in support of decision-making criteria need to be considered carefully.

Given the predicted and substantial increases in global AD prevalence, there is a critical need for sustained investment in this field. Achieving global patient access for developed therapeutics, as well as the development of better diagnostics and markers of patients at high risk for developing AD, will be highly valuable to address this major unmet medical need.

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