Costs and Capital Allocation in Drug Development for Alzheimer's Disease and Related Dementias

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Introduction

Alzheimer's disease is the leading cause of dementia and one of the most urgent public health challenges of our time. The global direct and indirect costs of dementia care are estimated at around a trillion dollars annually.[1] Despite decades of both publicly and privately funded scientific effort, treatment options for Alzheimer's disease and Alzheimer's disease-related dementias (AD/ADRD) remain limited. Between 2004 and 2020, the US Food and Drug Administration (FDA) approved no new therapeutic agents for Alzheimer's disease. Between 2021 and 2024, the FDA approved three new therapies, although their clinical benefits remain uncertain and they carry risks of potentially serious adverse effects. One of these therapies (aducanumab) has since been withdrawn from the market.

This study tries to understand the costs and risks of clinical development, and how research funding is allocated across therapeutic approaches in the context of AD/ADRD drug development. Findings can inform how policymakers design effective innovation policies that can increase the speed and decrease the expected cost of developing effective new AD/ADRD therapies.

This study has two aims. First, we quantified the risks and costs of AD/ADRD drug development. We estimated clinical development success rates. These estimates, along with data on trial size and duration, were then used to approximate the clinical investment required to bring one AD/ADRD drug to the US market, including expenditures on unsuccessful programs.

Second, in ongoing work, we are examining how public and private investments relate to the scientific maturity of therapeutic approaches. We are characterizing the maturity of AD/ADRD therapeutic approaches using publication-based measures of knowledge accumulation. We are then linking these measures to National Institutes of Health (NIH) funding and estimated industry clinical trial expenditures to examine the timing, concentration, and distribution of public versus private investment across therapeutic approaches.

Background and Literature Review

Alzheimer's Disease and Alzheimer's Disease-Related Dementias

Alzheimer's disease is the leading cause of dementia globally. Individuals with Alzheimer's experience progressive loss of memory, independence, and daily functioning, while caregivers face profound emotional and financial burdens. More than 50 million people worldwide are currently living with Alzheimer's, but they represent only a fraction of those at risk. Underlying biological processes unfold over decades, and hundreds of millions of people are currently accumulating plaques and tangles that, absent a therapeutic breakthrough, will ultimately lead to advanced dementia.

From 1995 to 2021, private firms spent an estimated $42.5 billion on clinical stage research and development (R&D) for Alzheimer's disease.[2] In 2019, the National Institutes of Health allocated $2.4 billion toward AD/ADRD research, more than spending on heart disease and hypertension ($1.7 billion), diabetes ($1.1 billion), and breast and prostate cancers ($972 million).[3]

Clinical Development and Costs

Several approaches have been used to estimate the probability of success in clinical development[4,5] and the costs of drug development.[6–8] However, to our knowledge, leading approaches from these two literatures have not been applied to AD/ADRD drug development. Given the small number of approved therapies relative to the prevalence and substantial social burden of AD/ADRD, drug development in this area may differ meaningfully from other therapeutic areas. AD/ADRD-specific estimates could therefore help inform policy targeting AD/ADRD development outcomes.

Scientific Maturity and Capital Allocation

Multiple factors may influence whether funding in AD/ADRD development translates into newly approved drugs. First, scientific maturity may affect clinical development success. Several studies have observed that cumulative publication counts (as a proxy for scientific knowledge) follow an S-shaped path: after an initial discovery, knowledge accumulates exponentially and eventually slows as the knowledge becomes established.[9] This growth cycle appears to be correlated with the success of clinical development, with better clinical development outcomes and new drug approvals occurring only after therapeutic approaches have matured, a phenomenon that has been documented across a range of areas including oncology and cardiovascular products.[9–11]

Second, R&D investments in certain therapeutic approaches may be socially suboptimal and driven by forces that operate independently from scientific knowledge. Private firms may

underinvest in the basic research that drives scientific maturation because they cannot fully capture its value. The empirical literature has documented instances in which firms exhibit risk aversion with respect to less established therapeutic approaches,[12] and the theoretical literature has explored how reputational concerns or other social forces lead to investment in a dominant paradigm becoming self-reinforcing, a type of "herding."[13,14]

Both concerns are potentially relevant for AD/ADRD development. While research has suggested that multiple prominent AD/ADRD therapeutic approaches have reached maturity, only amyloid-targeting therapies have received FDA approval in recent decades.[15] The literature also describes how AD/ADRD development is particularly concentrated in amyloid-targeting therapies.[16] The observed failures of the existing AD/ADRD development ecosystem have led to calls for alternative approaches, such as funding a diversified portfolio of approaches.[17]

No study has examined the relationship between scientific maturity and the allocation of R&D investments in AD/ADRD development, or systematically assessed how public and private investments differ in their timing relative to scientific maturation and their concentration across approaches.

Methods

Aim 1: Clinical Development and Costs

The two primary data sources for clinical development risks and costs are Citeline's Pharmaprojects and Trialtrove databases, both widely used in the academic literature to study pharmaceutical R&D.[5,18] Pharmaprojects contains information about drugs, including molecular target, mechanism of action, and firms involved in development. These data come from publicly available sources, including company press releases, patent filings, conference proceedings, regulatory reports, and the medical literature.

Trialtrove provides trial-level information, including trial phase, indication(s), primary intervention(s), start and end dates, enrollment, study endpoints, and sponsors. Its records combine daily feeds from registries such as ClinicalTrials.gov with company press releases, financial reports, study reports, and analyst reports. Trialtrove entries were linked to Pharmaprojects.

Clinical development outcomes were calculated at the path-level, where a development path is defined as a unique drug candidate-indication pair. The analytical sample includes all AD/ADRD paths with at least one clinical trial initiated between 1995 and 2025, as well as the one path that resulted in a 1993 FDA approval so that every approved drug was represented. Because the FDA rarely approves drugs based on clinical trial evidence generated exclusively outside the United

States, we only included paths with at least one clinical trial conducted within the United States. We excluded reformulations of previously approved drugs, as well as new combinations of existing drugs.

To calculate the probability of success from i to j ($POS_{i,j}$), we counted the number of paths observed in $i \in (Phase\ 1, Phase\ 2, Phase\ 3)$ that reached j, which represented either initiation of a later phase clinical trial or launch in the US market. We followed an existing approach to impute missing trial end dates and employed a right-censoring approach that distinguishes between paths plausibly still in-progress versus those likely discontinued due to development failure.[5] We calculated the probability of success for all immediate phase transitions and for each phase to market launch for all paths in the analysis sample: ($POS_{1,2}, POS_{2,3}, POS_{3,L}, POS_{1,L}, POS_{2,L}$). For each path-phase, we assumed that the earliest trial start date or initial US market launch represented the beginning of that phase of development.

We conducted a heterogeneity analysis by classifying development paths as disease-targeting therapies or symptom-targeting therapies, based on each drug's therapeutic target, mechanism of action, and the primary endpoints of linked clinical trials, following classification approaches used in the literature.[19] We calculated probabilities of success separately for disease-targeting therapies, symptom-targeting therapies, and unclassified paths.

We estimated development costs using trial-level data, with all results reported in 2025 USD based on the CPI-U index. For each trial included in our probability of success calculations, we estimated costs by multiplying the number of participants by a published estimate of the average per-patient cost for central nervous system agents.[8] For example, if a phase 3 trial enrolled 100 patients, at the estimated per-patient cost of $39,612 for phase 3 central nervous system agent trials, the trial's estimated cost would be $3,961,200. We then calculated mean cost per trial for each phase.

Next, we calculated the average number of trials per phase across development paths and multiplied those numbers by the mean cost per trial to get our estimated cost per phase. To account for expenditures on failed projects, we divided estimated cost per phase by the probability of success (from the phase to market launch), following prior studies on drug development costs.[6,7,20] For example, if estimated phase 1 costs were $1 million and the probability of success from phase 1 to market launch was 10%, the expected cost of phase 1 trials would be $10 million. Finally, we accounted for nonclinical costs (e.g., laboratory overhead costs) by scaling based on a published estimate of the ratio of clinical to total costs previously used in the literature.[6,8]

Aim 2: Scientific Maturity and Capital Allocation (in progress)

We used Pharmaprojects to compile a list of mechanisms of action and drug targets ("therapeutic approaches") represented among the paths included in Aim 1. For each approach, we searched PubMed using selected Medical Subject Headings (MeSH). We identified all publications related to each approach, constructing annual and cumulative publication counts by therapeutic approach from 1946 (the first year in which publications became searchable via MeSH terms) to 2025.

To characterize scientific maturity, we are using the Technology Innovation Maturation Evaluation framework, which fits an exponentiated logistic curve to cumulative publication counts.[9] The fitted curve identifies an initiation point and an establishment point, corresponding to maximum acceleration and maximum deceleration of log-cumulative publication growth. Ongoing work will validate search strategies, assess model fit and sensitivity to the observation window, and quantify uncertainty in the milestone estimates. Therapeutic approaches that cannot be adequately represented by a single curve will be identified as such.

Additionally, we will identify NIH-funded projects from 1985 (the first year in which RePORTER data is available) to 2025 using RePORTER/ExPORTER project records, publication links, and project text. Alongside the estimated clinical trial expenditures for private firm-sponsored paths observed in Aim 1, we can then construct a therapeutic approach-year panel that links scientific maturity measures to NIH and industry funding over time.

We will examine the timing, concentration, and distribution of public and private investment across therapeutic approaches. Exploratory analyses will relate maturity at clinical entry to subsequent progression, recognizing the limited number of launches and the retrospective nature of the maturity estimates.

Results

Aim 1: Clinical Development and Costs

Between 1995 and 2025, data were available for 498 AD/ADRD paths with products either in development or launched in the US. These paths included 478 unique drugs. The majority of paths (91%, 453/498) were products being developed for Alzheimer's disease; the remainder were for related dementias. Eight paths resulted in a new US drug approval during this time period.

Table 1 shows clinical trial success rates for AD/ADRD paths. The probability of advancing to the next phase of development was 78% for products in phase 1, 40% for products in phase 2, and 9% for products in phase 3. The overall probability of progressing from phase 1 to US market launch was 2%. For comparison, the table also shows the corresponding figures for neurological agents and agents in all therapeutic classes from an earlier study.[5]

Table 1: Probability of Success for AD/ADRD and Other Therapeutic Areas

Transition	Probability of Success		
		Wong et al. updated estimates[21]	
	AD/ADRD (1)	Overall (2a)	Neurological (2b)
Phase 1 to 2 ($POS_{1,2}$)	0.78	0.68	0.67
Phase 2 to 3 ($POS_{2,3}$)	0.40	0.44	0.44
Phase 3 to US launch ($POS_{3,L}$)	0.09	0.67	0.61
Phase 1 to US launch ($POS_{1,L}$)	**0.02**	**0.18**	**0.16**

53% of paths were classified as disease-targeting therapies, 24% as symptom-targeting therapies, and 6.4% as both disease- and symptom-targeting therapies; 16% of paths were ambiguous and remained unclassified.

Paths for disease- and symptom-targeting therapies had similar success rates across all phases (shown in Table 2). Ambiguous paths had lower success rates than classified paths at both phase 1 (76% versus 87%) and phase 2 (23% versus 41-42%). None of the products in ambiguous paths received marketing approval.

Table 2: Probability of Success for AD/ADRD, by clinical objective

Transition	Probability of Success			
	All AD/ADRD	Disease-targeting therapy	Symptom-targeting therapy	Ambiguous
Phase 1 to 2	0.78	0.87	0.87	0.76
Phase 2 to 3	0.40	0.42	0.41	0.23
Phase 3 to US launch	0.09	0.14	0.12	0
Phase 1 to US launch	**0.02**	**0.04**	**0.04**	**0**

Estimated clinical costs increase as drugs progress in development. Phase 1 trials cost an average of $5.7 million, phase 2 an average of $8.9 million, and phase 3 an average of $29.4 million

(Table 3, Column 1). The estimated cost per phase increases from $13.3 million in phase 1, to $15.7 million in phase 2, to $93.2 million in phase 3 (Table 3, Column 3).

After accounting for the likelihood of failure, the estimated clinical development cost was $590 million for phase 1, $507 million for phase 2, and $1.03 billion for phase 3 (Table 3, Column 4). This implies a total clinical cost needed to bring one AD/ADRD medicine to market of $2.1 billion (median $1.3 billion, numbers not shown). After scaling to account for preclinical costs, the estimated total cost becomes $3.8 billion. These estimates do not yet include the cost of capital, which will be applied in the next update of our analysis.

Table 3: Estimated AD/ADRD Development Costs (in millions of 2025 USD)

	Cost / trial	Trials / phase	Direct cost / phase	Probability-adjusted cost / phase
Phase 1	5.7	2.3	13.3	589.8
Phase 2	8.9	1.8	15.7	507.1
Phase 3	29.4	3.2	93.2	1,025.7
Clinical cost			**122.2**	**2,122.6**
Preclinical and clinical costs			**220.6**	**3,831.4**

Discussion and Forthcoming Results

The analysis of 498 AD/ADRD development paths identified substantial late-stage attrition. While probabilities of success in phases 1 and 2 were comparable to those observed across all therapeutic areas as well as all neurological products (Table 1), they were markedly lower in phase 3 (9% for AD/ADRD versus 67% for all therapeutic areas). Among AD/ADRD products entering phase 1 testing, 2% were ultimately approved by the FDA, compared with 18% of products across all therapeutic areas.

The lower phase 3 success rates contributed to a higher estimated development cost per approved drug than previously reported in the literature for samples consisting of drugs across therapeutic areas,[6–8] though these estimates are not yet directly comparable with published capitalized research and development estimates.

The concentration of failure in phase 3 raises a question about the organization of AD/ADRD innovation: why does so much uncertainty remain when developers commit to the most

expensive stage of clinical testing? Some failures may reflect scientific challenges, including limitations in patient selection or the ability of trial endpoints to detect benefit. Our forthcoming analyses focus on how the timing and direction of investment interact with those challenges. Clinical investment may arrive before an approach's scientific foundations are sufficiently developed to support successful translation. Alternatively, resources may remain concentrated in familiar approaches while other approaches attract limited support despite an increasingly established evidence base. Relating investment to scientific maturity will allow us to examine these patterns and identify where knowledge accumulation has, or has not, been followed by clinical development.

The comparison of public and private investment is central to this inquiry. Publicly funded research can generate knowledge whose benefits extend across firms and therapeutic approaches, creating opportunities for subsequent private development. We will examine whether NIH funding supports a broader range of approaches than industry, whether the two sectors concentrate on the same approaches, and how their respective roles change as the science matures. These comparisons will show how capital allocation has changed as the scientific opportunity set has evolved. Although they will not establish a socially optimal portfolio, they can identify potential gaps between the generation of knowledge and its translation into clinical programs.

Limitations

The analysis is limited by the following factors. First, estimates of AD/ADRD-specific clinical trial input costs do not exist, leading us to rely on estimates related to products in the broader central nervous system therapeutic area. Non-AD/ADRD estimates may not adequately account for expensive screening mechanisms of PET scans or other biomarker tests more typical of AD/ADRD than other conditions. The Trialtrove data also suggest that AD/ADRD trials last longer, on average, than trials of non-AD/ADRD central nervous system agents, meaning that using average per-participant cost for central nervous system agents as a whole may have led us to underestimate the costs of AD/ADRD trials. Second, missing data from Citeline, which is more common for older trials and for trials conducted outside the United States, bias estimates for probability of success and lead us to underestimate total development costs. Finally, our measure of scientific maturity is established based on bibliometric data that reflect trends in publication volume but do not directly measure the quality of science or validity of the therapeutic approach.

Conclusion

Effective therapies for AD/ADRD would have enormous social value, yet the private returns to developing them may be insufficient to sustain socially desirable investment. A central policy

question is whether the high cost of drug development is an unavoidable consequence of scientific difficulty or is compounded by misaligned incentives and suboptimal allocation of research funding. Combining estimates of development costs and risks with evidence on scientific maturity and capital allocation provides an empirical foundation for evaluating policies to narrow the gap between private returns and social value, alongside public funding strategies that advance foundational science and diversify the portfolio of therapeutic approaches.

If scientifically immature therapeutic approaches limit clinical success rates, increasing investment in basic and translational research can accelerate maturation. If firms' strategic decision-making has distorted the direction of innovation, then solutions could incentivize investments in relatively neglected approaches or pool risk across a diversified portfolio of approaches.

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