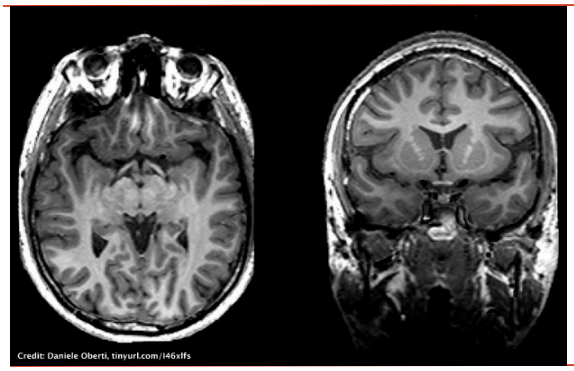

On the Road to 2025: The Global Dementia Deadline

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Modern medicine has enabled a drastic increase in the average lifespan of the global population. Recently, the WHO reported that between 2000 and 2015 the global average lifespan increased by 5 years, the largest growth since the 1960s [1]. Sadly, it is with a certain dark irony that this miraculous improvement of health has led mankind into the clutches of yet another malady: dementia. While the exact etiology of dementia is a contentious issue, a unifying risk factor for dementia in all its different forms is age [2]. The U.K. has already identified dementia, most prominently Alzheimer's disease, as the number one cause of death, overtaking heart disease for the first time due to an increasingly aged population [3]. Forecasts for Alzheimer's prevalence warn that this disease will only become more widespread, potentially quadrupling by 2050, with a global cost of care burden exceeding $2 trillion USD [4].

While dementia has only began capturing media headlines relatively recently, the scientific community has been tackling the issue for quite some time now, and a considerable amount of effort has been invested into basic research and drug development. Yet, despite this effort, to date there are only a handful of symptomatic treatments for Alzheimer's and not a single effective therapy ameliorating disease onset or progression. The paucity of effective therapies combined with the increasing burden of dementia on society has prompted global leaders to create a 2025 deadline for the development of a single therapy that can prevent or delay Alzheimer's [5]. While this deadline has been adopted by the field, the nature of drug development is full of pitfalls and once promising candidates have recently fallen by the wayside. Is 2025 still an achievable goal? And if so, how can government policies help achieve it?

This past autumn, the pharmaceutical giant Eli Lilly announced that their once touted Alzheimer's drug solanezumab has, alas, failed its third and final attempt to pass clinical trials [6]. This should be no surprise to a field that has witnessed over 400 failed therapies since 2003 [7], and, to most experts, it was not. However, gross over-statements of solanezumab's preliminary results by the media, with claims about renewed hope for Alzheimer's sufferers that a promising therapy was imminent, has no doubt left some people despondent about the possibility for a viable therapy to be developed on a relevant timescale [8]. Why did Eli Lilly's trial fail? Why has this road, in general, been so perilous? To try to answer these questions one has to look deep into the nature of the disease. As mentioned briefly above, the molecular origin of Alzheimer's and other dementias is still a debated issue. One of the most well-supported hypotheses, termed the amyloid hypothesis, posits that aggregation of certain misfolded proteins in parts of the brain is the causative agent of Alzheimer's and many other dementias. A plethora of

treatments based on this hypothesis have gone into trials attempting to target this pathogenic aggregation, including solanezumab, yet none have produced a significant clinical outcome. The lack of success of these candidate therapies has seriously called into question the validity of the amyloid hypothesis. However, the nature of this aggregation process is incredibly complex, with many stages of development, and the pathogenic phases of aggregation are only recently becoming well characterized [9]. This gap in the fundamental understanding of disease origins has created a poorly informed drug design process that has ultimately doomed some candidates from the outset.

Most diseases have sudden well-defined symptoms, but isn't forgetfulness just a part of ageing?

Another obstacle unique to dementia treatment that could have played a role in solanezumab's failure is the difficult diagnosis of these diseases. Most diseases have sudden well-defined symptoms, but isn't forgetfulness just a part of ageing? How do you know when you should be concerned? Determining if a family member is succumbing to Alzheimer's is perhaps the most difficult step in dealing with this disease. In fact, because aging is associated with the stereotype of becoming forgetful or lackadaisical, Alzheimer's was only recognized as a disease just over a century ago, due to the observation of an extremely early onset, heritable form of the disease. To be clear, dementia is absolutely not normal aging. But the generally slow progression of these diseases and the reliance on relatively insensitive cognitive tests at early stages makes their timely diagnosis incredibly difficult [4]. This challenge could have affected solanezumab's trial because the stage of the aggregation process that it is most likely to impact significantly, based on its reported target, occurs very early in disease progression, and some medical professionals believe it might have succeeded if Eli Lilly had attempted an earlier treatment [6]. However, this would necessitate a large pool of subjects who have been identified as high risk for the disease and yet be largely asymptomatic, which is very difficult for a disease that lacks early detection bio-markers.

These few reasons, along with many others, have contributed to the perilous nature of Alzheimer's drug development. So, what is the possibility that the field overcomes these hurdles and delivers on the 2025 deadline? For an accurate assessment, Cummings et al. [4] recently approached this question by working backwards from 2025. From development on through regulatory review, they claim an Alzheimer's drug would take over 9 years to gain Food and Drug Administration (FDA) approval, with most of that time spent in Phase 2 and 3 of clinical trials. That means that at the latest, a candidate must start Phase 3 trials by 2019. There is a precedent, however, for certain trials to get a "Breakthrough Therapy Designation" and receive an expedited track through trials, which could be appropriate if a promising AD therapy comes along later in the timeline. According to public records, there are only 38 amyloid-related therapies currently undergoing clinical trials and a similar number of trials targeting other entities within Alzheimer's such as inflammation [10]; if the notoriously high attrition rate of the past continues this may not be enough to ensure the deadline is met. That's not to say that some therapies currently in trials are not promising - Biogen has recently published a thorough scientific study showing their drug aducanumab significantly reduces aggregation in early clinical studies [11]. But if anything has been learned from Eli Lilly's failure, it's not to blow preliminary

results out of proportion; aducanumab is continuing on in phase 3 trials and it will be very interesting to see the outcome.

If the current cohort of trials proves fruitless, can researchers attempt to provide a treatment soon after 2025? After all, the deadline was not set strictly with the realities of drug development in mind, but rather as a hopeful goal decided by government officials based on prevalence forecasts. One attractive route is drug repurposing. This involves screening already FDA approved drugs for various diseases to see if they serendipitously also have an effect on Alzheimer's pathogenesis. Indeed, this approach has recently identified a small molecule that has significant effects on aggregation and is currently used as an anti-cancer treatment [12]. Since these drugs have already had their toxicity and long-term side effects evaluated in previous studies, they could potentially begin at phase 2 of clinical trials assessing efficacy for treating Alzheimer's, shortening their time to approval by years potentially [4]. However, a major issue with this approach, from the perspective of industry, is that these repurposed drugs may not be patentable, greatly lowering the incentive for their implementation from a fiscal standpoint.

The 2025 deadline is an ambitious goal, but the drive that comes from striving towards this date is exactly what is needed to keep the scourge of dementia at bay. Researchers are working very hard to unravel these complex diseases, but to meet this goal they need all the help and resources that can be mustered. One thing for certain is that the funding for dementia research is grossly out of proportion with its growing importance. To put this in perspective, in the U.K. cancer research receives approximately 5 times the amount of funding compared to dementia, even though dementia's cost of care burden on the country is already over double that of cancer [13]. If government officials are serious about the 2025 deadline, and want to aid in any way possible, this discrepancy in funding must be bridged if we are to truly rid the world of these diseases in an efficient manner.

At this point in time, 2025 is still an achievable goal for the development of a single effective Alzheimer's treatment; with promising drugs like aducanumab still in trials no one should give into despair. But, the memory of Eli Lilly's experience should be kept in mind. We also still must consider post-2025, even if this goal is met and a therapy arrives by then, that is by no means the end of the dementia story. Much work will still need to be invested in the treatment of other dementias besides Alzheimer's, and in other aspects such as developing bio-markers for early detection and advanced medical imaging techniques to assist with treatment decisions. All this and more can be assisted on the policy side if the resources available to dementia researchers match its indisputable importance to the future of global health. Age is just a number, and even though modern medicine has raised that number higher than ever before, it is meaningless if the increase is concomitant with a stark decrease in the quality of life. It is time for this discrepancy to be seriously dealt with and place dementia at the forefront of medical research.

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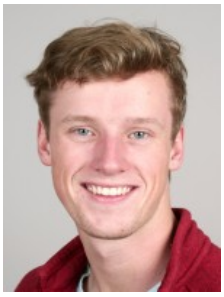

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