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COMMENTARY

The argument against crowdfunding Alzheimer's disease research

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Abstract: With pharmaceutical companies' repeated failures at finding effective interventions for Alzheimer's disease, together with an increasing reliance on the growing Federal funding for research, there is an emergent opportunity for financing alternate research through crowdfunding. Crowdfundingwhere funding is obtained from small donations from a large group of peoplehas become a new source of funding for medical research. By understanding how the research community has evolved to study Alzheimer's disease the pitfalls of this strategy can be highlighted. Alzheimer's disease research is complex. From its inception in the early 1900s, Alzheimer's disease has been at the center of movement within psychiatry to define the disease on the basis of its biology. Recent emphasisthrough the DSM (Diagnostic and Statistical Manual of Mental Disorders), RDoC (Research Diagnostic Criteria), RDoC (Research Domain Criteria) as well as the more recent Framework from the U.S. National Institute on Aginghave supported an exclusive emphasis on biology. But by excluding other aspects of the disease, such as its clinical expression, this research approach will be shown to be faulty and contradictory. So far this approach has resulted in 100% failures. By examining the historical and financial circumstances of the industry centered on Alzheimer's disease a strong warning is given to the public to mistrust crowdfunding Alzheimer's disease research. A broader and more inclusive approach is likely to generate a better understanding of the disease and therefore hold better promise for understanding the disease in the long term. Such a nuance approach competes badly with the more binary search for a cure and is less receptive to public support through crowdfunding.

Keywords: crowdfunding, Alzheimer's disease, DSM, RDoC

1 Introduction

The scientific method is based on two precepts. It must summarize past research by consolidating this body of knowledge into a theory, and it must be able to generate hypothesis (questions or predictions) from this theory that can be tested and which can be refuted. Observations within this scientific method ultimately improves theory and forms the primary distinction between science and metaphysics, myths or tautological.[1] Karl Popper in his book *Conjectures and Refutations* argued that by their function scientific theories must upset accepted views of the world. Scientists are necessarily radicals. They must work to overthrow accepted doctrines as part of their scientific purpose. If we know a phenomenon completely then science no longer has a function. Science is a method for acquiring knowledge (epistemology) that is accomplished through the development and then falsification of theories. Which is why we have an alternate hypothesis in scientific experiments since we can disprove a scientific theory (by accepting the null hypothesis) but we can never prove it (cannot accept the alternate hypothesis). Science, according to Karl Popper, evolves by observations eliminating weak theories by proving them as false

More than half a century ago, at the same time that Popper was writing about these percepts of scientific progress in the 1960s, Thomas Samuel Kuhn was writing about how science was being conducted and managed. In his 1962 book *The Structure of Scientific Revolutions*, Kuhn determined that the reason for the erratic progress of science was because of social factors.[2] Kuhn describes how even when hypothesis are falsified, there is enough invested interest in maintaining the given theory (i.e., the status quo) that this proof of falsification is ignored at best and disparaged at worse. Only when there is un-refutable and overwhelming evidence that a revolution takes place to overthrow the older theory in favor for the new one. The process of scientific progress mirrors not a linear progression but an organic social upheaval. Science is a political process as much as an epistemolog-

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ical method.

This paper attempts to understand the progress of Alzheimer's disease research over the last 70 years using these two metrics of scientific progress. The aim is to chart an alternate path for research and to understanding the social aspects of conducting research in Alzheimer's disease. The insights afforded by evaluating Alzheimer's disease research through these prisms will provide clearer understanding of the type of barriers that are still holding back the science. By identifying any barriers a clearer path might be exposed that should accelerate progress to understanding the disease. Alzheimer's disease research is at the breaking point of overthrowing the old theory and replacing it with a new broader theory. However continuing funding for the old theory with the possible inclusion of crowdfunding, will delay and impede this necessary transition.

Crowdfunding through sites such as Gofundme, Kickstarter, Indiegogo, Fundly, JustGiving, Rockethub and Facebook all have fundraisers for some aspects of Alzheimer's disease activity. Some even focus on research and promote trials on potential cures such as Petridish, #SciFund and Experiment.com (renamed from Microryza). Experiment.com is currently the largest dedicated platform for crowdfunding research.[3] In a 2018 review of crowdfunding in research[3] the authors reported that most of the activities involved scientific investigation (78%) and were mainly concentrated in the U.S. (89%) and the majority (80%) affiliated with universities and colleges. Which is not surprising since U.S. universities are adept at fundraising campaigns. Most of these research crowdfunding events were in the fields of social sciences and psychology and tended to promote undergraduate or master's students (30%) followed by PhD or MD students (25%). Overall through one website alone Experiment.com projects raised a total of $4.37 million, with the average project raising $6,425. Such numbers are miniscule compared to the $2.3 billion budget of the U.S. National Institute on Aging but it is a trend that shows incredible growth. Especially since crowdfunding is attracting junior faculty/researchers as their success rate for crowdfunding is higher than traditional sources of funding.

Crowdfunding complements other public participation in science especially "crowd science" or "citizen science" projects. These projects increase the permeability between scientists and the public who contribute their time (e.g., collecting samples or observing events), resources (e.g., computer power) and knowledge (e.g., experiences and feedback). But such participation is prescribed and relies on binary tasks that do not require complex chores or decisions. With a complex scientific problem, enticing public support would require making the problem seem far simpler than it is. Alzheimer's disease is now at that stage of simplification. Any federal source of information on Alzheimer's disease mimics the same interpretation as the 2018 Framework[4] which culminates a century of assumptions about the disease: that two misfolded proteins cause the disease. There remains great resistance from the status quo - a cabal of prominent researchers and administrators that have built their careers and business on this one specific hypothesis related to Alzheimer's disease - to change the dominant theory in research. Understanding this dominance provides an insight into how to untangle the political and the business from the science in Alzheimer's disease research.

2 The problem

Alzheimer's disease is one type of dementia - an umbrella term that encompasses many types of specific brain atrophy diseases - that also include the less common vascular dementia, Lewy bodies and Fronto-temporal dementia as well as other neurological brain diseases. There are other "comorbid neurological diseases" that affect the brain, more prevalent than Alzheimer's disease and had these conditions been known before their death would likely have affected their treatment before death.[5]

Alzheimer's disease was baptized in 1910 as a disease by Emil Kraepelin - Alois Alzheimer's supervisor - who included "Alzheimer's disease" as a new unique disease in the eighth edition of his book *Psychiatre*. Alois Alzheimer linked amyloid beta deposition and pathologic tau with dementia in a 45-year-old Auguste Deter who died six years later. While Alzheimer's disease continues attracting greater and greater interest there is a warning in this attraction of focusing on one disease. Auguste Deter died from infections from bedsores[6] a most painful death and one that is preventable. To this day we continue focusing on the disease while ignoring the patient.

Although there are many potential alternate approaches to developing research guidelines in Alzheimer's disease[7–12] in 2018 the NIA relapsed back to a much narrow definition of the disease. This new *Research Framework: Toward a biological definition of Alzheimer's disease* headed by Clifford Jack (referred to as the Framework)[4] embraces a piecemeal framework that focuses on two biological markers correlated with Alzheimer's disease while discounting the clinical expression of the disease.[4,13] For the first time the clinical aspect of the disease - what we

think of as Alzheimer's disease - how it is expressed through memory loss, changes in mental capacities and mood and personality changes - will be ignored. In contrast to the earlier 2011 guidelines[13] the new Research Framework favors three types of information: [A] amyloid beta deposition, [T] pathologic tau, and [N] neurodegeneration. This new AT(N) definition exclusively relies on the presence of biological markers to define the disease. It is a tautological argument, Alzheimer's disease is defined by its biology and the biology defines the disease. There is no way to refute this theory. Such a model, promoted by a U.S. Federal scientific agency, cannot be tested. Popper would argue that such arguments are not science but rather metaphysical. Exploring the reasons for promoting such pseudo-science leads to conflicts of interests among the primary authors of this new Framework. But a more insidious and pervasive argument is more nuanced and involves a historical predisposition to focus on biological determinism within psychiatry. Both these reasons highlight what Kuhn would call "development-by-accumulation" not for scientific but for political and economic purposes. Scientists are weakening the scientific process for political and/or economic gain.

3 Conflicts of interest

In a Supplemental Attachment to the Framework[14] a list of conflicts of interest activities can be indexed. From this list (Figure 1) we can see three main results.

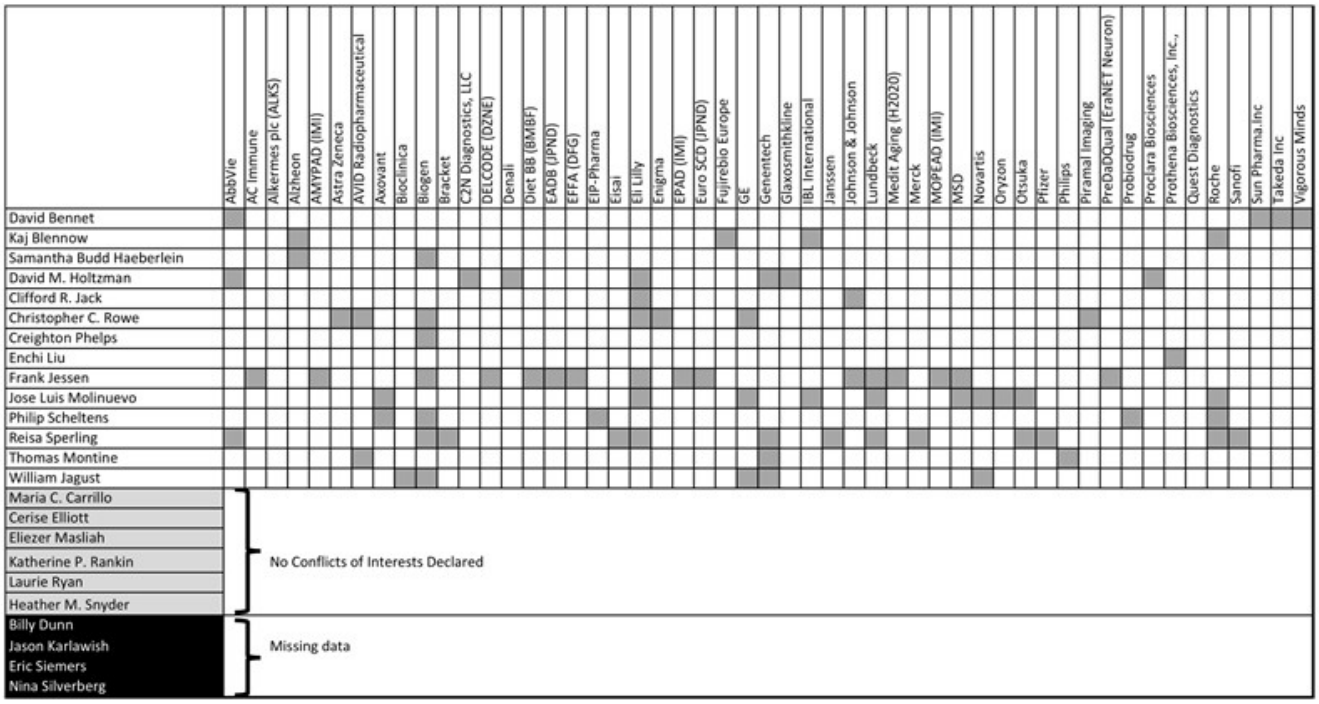
Out of 24 authors, only six report no conflicts of interests (25%) while four had no data or missing information from the source document (17%). For the majority 14 authors of the paper (58%) had multiple recent connections with pharmaceutical industry that benefit from Alzheimer's disease. These 14 authors reported 79 separate business or economic benefits with pharmaceutical companies (average of 5.6 per author.) In addition, three authors hold current patents that directly benefit from the approach being promoted by their manuscript. In contrast, in 2001 the highest French administrative court (Conseil d'Etat) requested the immediate withdrawal of guidelines on dementia elaborated by the French National Health Authority (Haute Autorit de Sant) owing to undisclosed serious conflict of interest for panel members.[15] The argument is if you disclose conflicts of interests does this disclosure diminish the conflict and reduce the interest in competing business?

The authors have argued that these federal declarations are Guidelines[13] or Frameworks[4] and therefore hold no binding influence. But this attitude conflicts with the reality of research. Because the Framework is published under the NIA auspices it forms the basis for NIA funding in Alzheimer's disease research. The majority of funding is allocated to studies that are within the dictates of these *de facto* theories. In reality, these are pseudo-science as they fund research that look for confirmation rather than refutation. Popper is more flippant when he writes "It is easy to obtain confirmations, or verifications, for nearly every theory - if we look for confirmations."[1] The foundation for such hubris goes much deeper. Especially with Alzheimer's disease there is a particular penchant to associate the disease purely with biological correlates. From its inception Alzheimer's disease was an important disease because it made such bold biological assertions from the start. The disease affects older people and has traditionally remained on the periphery of *avant garde* research. Alois Alzheimer's specialty was in fact syphilis, a bacterial infection that resulted in a terminal stage of neurosyphilis, a type of dementia. The attraction of Alzheimer's disease was that the same biological assertion could be made.

4 Biological determinism

Such scientific arrogance has been evolving for a century. At the turn of the 1900s academic disciplines were separating into distinct areas of study. In mental sciences, Emil Kraepelin, together with Eugen Bleuler, developed a more biological path for the nascent discipline of psychiatry through their work with schizophrenia and later Alzheimer's disease. This occurred at a time when much stronger forces - primarily the psychoanalysts championed by Sigmund Freund, and experimental psychologists championed by Wilhelm Wundt - were succeeding in redefining mental health as unresolved psychological trauma. Psychiatry was left with explaining mental illness as a chemical/biological imbalance. But at the time very little was known about such biological processes and as a result psychiatry was relegated to classifying diseases.

The 1880 U.S. Census only distinguished seven categories of mental illness: mania, melancholia, monomania, paresis, dementia, dipsomania, and epilepsy. Within this tangle of disorders, Kraeplein differentiated between premature (praecox) dementia (which we now called schizophrenia) and 'manic depression' as two separate forms of psychosis. Kraepelin was not the first to make such a distinction but he was the first to argue that schizophrenia is a biological illness caused by anatomical or toxic processes (as yet unknown.) Although Arnold Pick in 1891 defined schizophrenia as a psychotic disorder (hebephrenia) in 1911, Eugen Bleuler revised this idea, renaming 'dementia praecox' (premature



Source: Research Framework: Toward a biological definition of Alzheimer's disease Supplemental Materials. Accessed online at: https://www.alzheimersanddementia.com/cms/10.1016/j.jalz.2018.02.018/attachment/d08ee644-4512-4842-b0bc-6eeddb3ba300/mmc1.docx [13]

Figure 1. Authors of Framework [4] and their self-reported business interests with pharmaceutical companies (doesn't include privately held companies or patents that the authors declare)

dementia) as schizophrenia.[15] Together Kraepelin and Bleuler created a new emphasis of biological psychiatry - an emphasis that remains today. It marked a paradigm change in psychiatry, from a classification of diseases based on "symptoms" to one based on (assumed) neurological causes.

Throughout the history of nosology - the branch of science dealing with the classification of disease - the aim has been to define a more reliable and valid diagnosis. But the process was not linear as many diagnoses proved difficult. Our present nosology has been significantly influenced by the Diagnostic and Statistical Manual of Mental Disorders, or known by its acronym DSM. Most versions of the DSM aim at improving both the reliability and validity of categorizing specific disease to help with diagnosis. Other international classification systems exist including one coordinated by the United Nations, World Health Organization as the International Classification of Diseases (ICD). The DSM is not restricted to some clinical tool for diagnosticians. Emerging as the ultimate clinical reference manual the DSM also forms the foundation for residency training; it is used to define reimbursement by insurance companies; it is used to evaluate eligibility to accessing social and medical services; and it forms the basis for defining criminal culpability in courts of law.[17] The DSM is a veritable tool that defines significant aspect of our medical interaction.

First introduced in 1952, the DSM-I proved to be limited, ill applied and too broad. Although each subsequent version represented incremental improvements - up to the latest version V introduced in 2013 comprising 541 different diagnoses - the most radical change happened in 1980 with the DSM-III. The DSM-III established a more biological approach to diagnoses, elevating psychiatric disorders to neurological diseases and moved the focus of therapy from psychotherapy to medication.[18,19]

The reverberations from such change in emphasis are still felt today with the push to recognize schizophrenia as a neurological disorder - involving damage to and degeneration of the nervous systemrather than a psychiatric one.[20] Eventually the classification of both DSM - II and the ICD-8 became synchronized making a powerful testament of solidarity. However there was push-back. In particular two studies exposed their lack of reliability and validity. A 1971 paper comparing U.S. with British diagnostic practices reported a general carelessness among U.S. diagnostician in their application of the DSM-II.[21] This was followed by a study by David Rosenhan in 1973, where colleagues succeeded in being

admitted to a mental institution by pretending to hear a voice saying one word. These pseudo patients were later released with a diagnosis of "schizophrenia in remission."[23] In light of these damning evaluations, Robert Spitzer criticized these studies as pseudoscience, calling them "logic in remission."[23] Working with a Washington University group, Spitzer attempted to consolidate the diagnostic criteria through the Research Diagnostic Criteria (RDC).[24] RDC was initially a more reliable set of criterion that had both inclusion and exclusion criteria. Certain expressions excluded a patient from a diagnosis while other expressions increased the likelihood of a specific diagnosis. The DSM-III began to rely on RDC and started describing categories in more detail including demographic profile of patients, how to differentiate the target category from similar categories, and a brief discussion of what was known, if anything, about the course and onset of the disorder. This greater contextual detail was also supported by evaluations on a broader array of functionality of the patient. In addition, the DSM-III contained supplementary materials allowing clinicians to compare different diagnostic criteria between DSM and ICD and other details known about the disease. This permeability to input from practicing clinicians allowed the DSM to improve. But there were still problems with this classification system.

Clinicians were applying their own archetype of the disease in diagnosing patients. They were comparing their patient with a typical case rather than identifying unique features of the clinical expression in accordance with the DSM.[25] Although clinicians' evaluations proved consistent (reliable) they were not identical to either the DSM or ICD systems a practice that diminished their validity.[26,27] At the same time a more forceful external classification emerged that was again promoting a more aggressive biological determinism and influencing the DSM. Similar to the 1972 Research Diagnostic Criteria (RDC)[24] there was a new version of biological determinism championed by the then director of the U.S. National Institute of Mental Health (NIMH) Thomas Insel. The Research Domain Criteria (RDoC) baptism coincided with the publication of the DSM-5 in 2013, and heralds a radical diagnostic departure by relying exclusively on biomarkers - biological markers. The ambition of RDoC was to improve the reliability of classifying diseases. As such it was not a complete departure from the DSM, but it was a more forceful push for a biological definition of mental disorder. Although the DSM has incrementally inched its way to favor biological indicators of disease, with ICD similarly leaning towards this emphasis, RDoC was by birth exclusively focused on biological correlates of disease.

The implicit assumption being that behavioral/mental/clinical disorders are manifestations of biological/neurological disorders. Negative behavior is neural problems in the physical system. The argument proposed by RDoC is that by finding the bad circuits we will be able to fix the problem and to "yield new and better targets for treatment."[28] While explicitly demoting the importance of understanding the disease, it elevates the search for a cure. There are emerging criticism of this new nosology[8,29,30] but what remains untold is how RDoC is gaining legitimacy.

RDoC's biological determinism was promoted by the success of how easy it was for the public and scientists to believe that Alzheimer's disease was determined by biomarkers. The history of Alzheimer's disease laid the foundation for a new way of biological determinism that has not been seen since the height of the eugenics movement in 1923 when the American Eugenics Society was founded. But this emphasis on biology is unfounded. There is no evidence that biology exclusively determines the inception, progression and expression of Alzheimer's disease or many other mental disorders. But the illusion was made possible by the acceptance of such an association - that Alzheimer's disease is purely a neurological disease controlled by two "mis"-folded proteins.

5 Problems with biological determinism

Historically only tenuous evidence separated Alzheimer's disease from senile (old age) dementia. Alois Alzheimer's observation - shared by many of his contemporary researchers - was that the biomarkers were not unique either for Alzheimer's disease or among younger people. But the plaques and tangles found in the brain of Alzheimer's patients were elevated as a unique disease by Emil Kraepelin who was Alois Alzheimer's supervisor at the Munich clinic. From its inception, Alzheimer's disease was promoted as a unique disease because it promoted biological psychiatry. Alzheimer's disease supported the belief that genes and biology determine behavior - borrowing from eugenics - while old age invariably results in diminished capacity, a similar disease among young people is triggered by biology - borrowing from ageism. RDoC further supported the legitimacy of accepting that the plaques and tangles were indicators of Alzheimer's disease without providing any supporting evidence but providing a philosophy, a metaphysical belief of how disease is caused.

6 The causes of Alzheimer's disease

We continue to ignore our "...incomplete understanding of AD pathogenesis, the multifactorial etiol-

ogy and complex pathophysiology of the disease, the slowly progressive nature of AD [Alzheimer's disease], and the high level of comorbidity occurring in the elderly population."[31] Arnold Pick more than a century ago indicated that "a mosaic of circumscribed neuropsychological deficits" could cause dementia.[32] There are many events that we know cause dementia and/or Alzheimer's disease. Including: viral (HIV/AIDS, herpes simplex virus type I, varicella zoster virus, cytomegalovirus, Epstein-Barr virus), bacteria (syphilis and lyme-disease/borrelia), parasites (toxoplasmosis, cryptococcosis and neurocysticercosis), fungi (Candida collaborator), infections (possibly prions), and vascular (stroke, multiple-infarct dementia, hydrocephalus, injury and brain tumors).[11,33] There are other processes that either promote or delay the infection and the spread of infection, primarily through the Blood-Brain-Barrier[34] , inflammation, vascular, White Matter[35] and many other dynamic processes in the brain. Such models already exist.[36] In particular understanding how the brain protects itself from getting infected, and once infected has methods to cope with the infection is an important aspect of neuropathological development. Protective factors include cognitive reserve and the capacity of the brain to absorb trauma (maybe including education, multilingual, exercise, diet, enriched environment in infancy.)[37,38] While factors that worsen resilience possibly includes: behavior (alcohol, cigarette smoking, recreational drugs, concussion), environmental elements (possibly aluminum), and emotional trauma (divorce, death of a loved one, sexual, physical and emotional abuse and depression}[11] There are also cascading effects where one infection destroys or diminishes the ability of another system to protect the brain. For example, both amyloids and tangles diminish the blood-brain barrier and thereby expose the brain to outside infections.[39–41] Such complexity does not beckon simple interventions and does not easily translate to crowdfunding appeals.

7 The solution

Scientifically, the methodology for studying Alzheimer's disease requires a framework that establishes all parameters that impact the disease; including biological, chemical, neural, clinical, psychological, social and demographic. These parameters must then be examined to understand how they interact with each other and within the living environment (e.g., diet, exercise, stress, work etc.).[42] All these components must be summarized into a coherent theory (as much as is possible.) From this theory hypotheses can be generated and then tested that have the capacity to refute the theory.

More importantly the clinical expression of the disease needs to remain central, as dementia is first and foremost a clinical disease. If the neuropathology had no clinical outcomes (people do not express the disease and there is no change in their behavior) then there is no reason to cure the disease. Rather than focusing on neuroscience and the biological validity of diagnosis, emphasis needs to be redirected by recognizing clinicians as worthwhile and informative sources of information. Although complicated, it behooves us to appreciate that all psychiatric diagnostic tools are negotiated and malleable[43] and within this process it is imperative to acknowledge the role philosophical discourse plays in the development of a classification of disorders including Alzheimer's disease The lesson learned from the impressive clinical work of William Langston in understanding and ultimately developing interventions for Parkinson's disease provides an apt lesson.[44] In his review of the history of how he discovered part of the process of Parkinson's disease he writes: "Finally, I would like to conclude with some closing thoughts: If there is an overarching lesson from this story for clinicians, it is to never forget the power of clinical observation."[45] But in contrast to this wisdom, research on Alzheimer's disease, as dictated by the Framework[4] and by the U.S. federal funding mechanisms at least, is being pushed towards a more biological determinism discounting good clinical work. Both historical precedence as well as current conflicts of interests in Alzheimer's disease research has muted this lesson.[42]

8 Lack of clinical oversight

The lack of clinical oversight has created some disconnect in research. Although alternate theories exist, they remain ignored.[11,46,47] Research remains disorganized, clinicians remain confused, and the public has become increasingly worried[37,48]

That the biology contributes to and is part of the process of Alzheimer's disease is universally agreed upon. However no universal standards on biomarkers density and cutoff points have been defined and "...have not yet been established."[4] We do not know if a large concentration of these biological markers is needed to define a disease or just a few. Heiko Braak in 2011 after dissecting 2,332 brains ranging in age from 1 to 100 found that only 10 cases had complete absence of Alzheimer's disease related biology. Every person over 25 years of age had Alzheimer's disease biomarkers[49] therefore it is not logical to assume that these biological markers cause the

disease as some people have the biomarkers and not the disease. Such inconsistencies are reflected in unexpectedly high false positives and false negatives - missing identifying those with dementia and wrongly identifying unimpaired individuals as having dementia.

The authors of the Framework themselves highlight the unreliability of the definition: "Up to 60% of CU [cognitive unimpaired] individuals over age 80 years have AD [Alzheimer's disease] neuropathologic changes at autopsy or by biomarkers... Thus, using a clinical diagnosis of 'AD' to ascertain absence of disease is associated with an error rate exceeding 50% in the elderly."[4] And then there are false negatives, where the majority of people with Alzheimer's disease do not show any of the biomarkers. This observation by itself refutes the theory. Even the authors acknowledge these false negative cases "...using a clinical diagnosis of 'AD' to ascertain absence of disease is associated with an error rate exceeding 50% in the elderly."[4] There is no scientific precedence for adopting a definition of a disease that relies on the probability of a coin toss.[42]

The main motive for the framework was to develop strategies for a cure. "This approach also will enable a more precise approach to interventional trials where specific pathways can be targeted in the disease process and in the appropriate people."[4] Science is not beholden to outcomes. Science is a method of acquiring knowledge and a method cannot determine the outcome of the knowledge gathered. Engineering an outcome is not science but applied science or business application. Even in the pharmaceutical business, the industry itself acknowledges that there are other problems with Alzheimer's disease other than a cure. In the forward to the 2018 report on Alzheimer's disease research by the pharmaceutical industry George Vradenburg with UsAgainstAlzheimer's writes "...there is a shortage of geriatricians to care for the country's aging population, patients are commonly misdiagnosed, there continue to be long wait times to see neurologists, racial disparities persist, and many patients are never told of their diagnosis by their doctor."[50]

9 Federal funding

Despite that the 99% failure rate of Alzheimer's disease drug development[51] with a 100% failure rate of disease-modifying therapies for Alzheimer's disease[52] in 2014, the G8 - France, Germany, Italy, Japan, United Kingdom, United States, Canada and Russia - stated that dementia should be made a global priority with the aim of a cure or treatment by 2025.[53] In contrast, in 2018 Pfizer, the world's third largest drug maker announced that it is ending research in Alzheimer's disease. In the past 20 years, Pfizer has conducted over a hundred clinical trials, testing twenty-four potential Alzheimer's drugs resulting in only one drug, Aricept, being approved.

The reality is that Alzheimer's drugs are very expensive and so far proved ineffective. Estimates suggest that the cost of one new drug is now $5.7 billion.[54] Funding for such exuberant failures is primarily through federal finance which for Alzheimer's disease is through a network of federal agencies under the umbrella of the National Institutes of Health (NIH). These interagency funding includes the National Institute on Aging, National Institute of Mental Health, National Institute of General Medical Sciences, and National Center for Advancing Translational Science. In addition, other federal agencies such as the National Science Foundation, Veterans Administration, Food and Drug Administration, and the Center for Medicare and Medicaid Services all provide additional funding in Alzheimer's disease research. In 2018, the NIH's spending on Alzheimer's and related dementias research was estimated at $1.9 billion. With the 2019 budget targets including an additional $425 million,[55] and is now nearly equal to funding for cardiovascular disease the main killer in developed countries but still below funding for cancer. But there are other funds that go into this expanding research pot. Other inter-, and intra-agency collaborations have separate funding mechanisms for Alzheimer's disease beyond NIH, including private equity, research organizations, not-for-profit advocacy and philanthropic organizations, academic institutions, pharmaceutical companies and individual State funding sources.[52] New sources of funding are now being aimed at tapping public support through crowdfunding.[56] Sources of funding for Alzheimer's disease are similarly diverse in Europe. The United Kingdom has just funded a new initiative Dementia Discovery Fund with £250 million ($327 million) while the European Union funded three Alzheimer's Disease Research Platform projects from the Innovative Medicines Initiative with €138 million ($154 million).

Alzheimer's disease research is already one of the top medical research concerns worldwide, and funding is slated to grow. But as Leonard Hayflick comments on these budgetary successes, with all this money why not focus on the biology of aging rather than on piecemeal studies on Alzheimer's disease. He comments "What would be more important than a budget increase that favors research on Alzheimer's Disease and other age-related disease is to focus on research on the etiology of biological aging."[57]

10 What are we trying to cure?

Alzheimer's disease mainly afflicts older adults although the disease was initially diagnosed explicitly in younger people. The merger occurred when one of the founders of the National Institute on Aging, Robert Katzman - in an effort to gain funding for the establishment of the NIA in the 1970s - combined the rare Alzheimer's disease with the much higher prevalence of senile dementia. Katzman admitted that the numbers of "pure" Alzheimer's disease were so small that "Precise epidemiological information [on Alzheimer's disease] is not available..."[58] With this trick of combining Alzheimer's disease with senile (old-age) dementia Katzman announced in the title of his paper that Alzheimer's disease is a "major killer" in the USA. Such dramatic admissions hide some technical difficulties. Alzheimer's disease among older adults captures other diseases in the diagnosis. Older adults confront a cumulative number of diseases as they age. Some of these diseases have been found to contribute or at least accompany the development of Alzheimer's disease, such as hypertension, arteriosclerosis, depression, anxiety and a host of vascular diseases.[59] Alzheimer's disease in isolation from these other chronic diseases is rare, and among older adults unlikely and under-reported.[60] In one large study only 0.01 percent of patients had a diagnosis of dementia with no co-morbid conditions.[61] It is rare for older adults to have brain disease in isolation from other type of (non-cognitive) diseases such as depression[62] and anxiety.[63] Since individuals have multiple comorbidities, isolating the disease includes both a clinical problem as well as a neurological one.[64] As a result, among older people, many dementias are misdiagnosed.[65–67] This helps explain why multiple studies have shown that the correlation between plaques and tangles and Alzheimer's disease declines with age since there are other factors that are causing cognitive problems.[68] But such evidence remains what Kuhn calls incommensurable - this evidence cannot be acknowledged let alone accepted.

The primary theory in Alzheimer's disease is presented by the amyloid cascade hypothesis.[69] This theory proposes that active immunization against amyloid-β42 peptide (plaques), and neurotic tau (tangles) would cure the disease. So far, all types of immunization trials for both plaques and tangles continue to fail. The active amyloid immunization clinical trial by Elan Pharmaceuticals (AN1792) indicated that amyloid can be cleared from the brain. However cognition was not improved even after long-term follow-up.[70–73] This suggests that the plaques cannot be causing the disease.[74] The Framework now argues that the amyloids are precursors to the real disease that are the tau tangles, an argument made a century ago by Oskar Fischer[75] But this strategy adopts the same assumptions as for the amyloid hypothesis[76] and so far, the results have been predictably insignificant and diffuse.[77,78]

Older people have complex clinical issues. People will inevitably continue to die and as populations get older, older people will continue to die at higher numbers. If we eliminated the top diseases of older adults, such as cancer, diabetes, cardiovascular disease, stroke, influenza and pneumonia, and chronic obstructive lung disease older people will still die at a slightly older age. There will be a small extension of life. It seems counterintuitive that by eliminating one disease older people might experience slightly longer life with more disability. Since most older adults suffer from not just one but multiple health conditions it is only a matter of time that one disease will prove to be the exist disease. Statistically eliminating musculoskeletal conditions would result in an additional year of good health for women and under half a year for men.[79] But there are also negative outcomes of curing diseases. By eliminating cardiovascular disease or cancer a proportion of the years of life gained would be spent in poorer health and increased cost.[79] While in contrast, eliminating mental conditions (including depression and suicide) will result in fewer gains in life expectancy but with reduced periods of illness.[80] In the best-case scenario, by eliminating all major killer diseases, life expectancy at birth in 2019 will be expected to increase to 96 years.[81] But we will still die. The aging of population, by itself - with or without Alzheimer's disease - people will continue to die at increasing numbers since that population has succeeded at living longer. In support of Leonard Hayflick's argument, singling out one disease to cure is as illogical as conducting invasive surgery on moribund patients.

11 Quality of life

Although we are fearful of dementia, and this fear seems to be growing,[82, 83] reflecting our increasing fear of aging,[84] quality of life for people with dementia does not necessarily decrease as the dementia progresses.[85–87] Although studies show variable and inconsistent results, there is a common acceptance by social scientists that under certain circumstances people living with dementia are not necessarily less happy then they were before the diagnosis. Hannekeens Beerens and her colleagues report two studies that show that three months following admission to a long-term care facility only those with better cognitive abilities reported a decrease

in their quality of life (they were aware of their reduced capacity).[88,89] A general trend is that people with dementia living at home show more depressive symptoms compared to those living in long term care facilities. In fact, Jennifer Payne and her colleagues found that depression is reduced after entering a long-term care facility,[90] which may reflect on what Tom Kitwood terms as the negative interpersonal dynamics at home. Kitwood argues that some deterioration is the result of how the person with dementia is treated rather than by the disease itself[91] . He called this "malignant social psychology" where a caregiver's relationship, in some extreme cases, devalue, dehumanizes and diminishes the person with dementia by being stigmatized, infantilized, objectified or ignored. In less dramatic situations however, Alzheimer's disease is rarely experienced in isolation from a broader social context.

This interpersonal dynamic is an important component of life for people living with dementia. In a 2014 longitudinal study Linda Clare and her colleagues reported that over a 20-month period one-third of people living with dementia rated their quality of life higher. The determining factor was the negative quality of the relationship with their caregiver and taking acetylcholinesterase-inhibiting medication.[92] Caregivers want you to be the person that you used to be, which is why after 18 months in a long-term facility, even though self-rating of the quality of life did not change for the person with dementia their caregivers rated them as less happy.[93] Caregivers' base their judgment on the patient's cognitive and functional/physical decline, but for people living with dementia it was anxiety that mediated their rating. In most cases, anxiety is promoted by unreachable expectations from their caregivers. In most cases, by being away from their caregivers, people living with dementia expressed reduced anxiety and therefore reported better quality of life.[93]

Research indicates that there is no straightforward relationship between quality of life and dementia. There is much complexity in social contexts and quality for people for people with dementia varies consistently by country.[88] For those living in nursing homes, depression lowered their quality of life whereas for those living at home, falls reduced their quality of life. There are many confounding factors, but the evidence is consistent. A year after receiving the devastating diagnosis of dementia, most patients revert to their previous level of wellbeing.

It is caregivers that suffer the greatest loss of reported quality of life, both in terms of their interaction with the patient and their own health and wellbeing. Caregivers - whether they are still providing care, or those whose care-recipient died or became institutionalized - all expressed a great amount of psychological distress, including: depression, anxiety, interpersonal sensitivity and paranoid ideation and difficulty mental performance.[94] When compared with spouses who were caring for a spouse without dementia, caregivers of a spouse with dementia had higher psychological distress.[95] Caregivers' interaction with their care receiver determines the quality of life of both. It is the great sorrow that caregivers feel when their loved-one start to lose who they were. It is this angst that Crowdfunding appeals to.

12 Conclusion

The potential for crowdfunding in Alzheimer's disease is great. You have the perfect storm of anguished family members a disease that is being promoted as caused by simple biology of two misfolded proteins, affecting nearly everyone directly or indirectly, and there is great hype that a cure is around the corner. Combined with the difficulty for new researchers to get into the federal funding stream because of a cabal of researchers and their ever expanding research institutes, the constant failure rate of ongoing disease-modifying interventions and the increasing fear in the media all lead to the false impression that not enough funding is devoted to Alzheimer's disease research while at the same time a cure is just around the corner. Crowdfunding has the potential to fulfill a gap in this perceived funding gap. But using crowdfunding for research promotes pseudo-science.[96] Crowdfunding relies on emotional rather than scientific arguments. The fear of Alzheimer's disease will drive the urgency of such appeals. They are reliant on people's need for binary answers when, as discussed, there is great complexity in the disease. This is at a time when crowdfunding for science has become more attractive for younger researchers in academic institutions. More than 1,000 medical crowdfunding campaigns for 5 treatments that are unsupported by evidence or are potentially unsafe have raised more than $6.7 million.[97] While 408 campaigns raised more than $1 million for unproven stem cell interventions.[59]

While established researchers in Alzheimer's disease have an invested interest in maintaining adherence to a simplified but defunct theory, emerging researchers have very few options for funding. Although U.S. federal funding is increasing for Alzheimer's disease research, as are other sources of funding, there is a lack of diversity in funding recipients (especially for diverse approaches). Crowdfunding will seem as a solution. But given the nuances of a disease that interferes with the brain - one of the most complex organs ever encountered - translating

the problem into a venture capital issue dummies down the complexity and diminishes the likelihood that the right approach will be taken. The overall problem is that such nuanced approach to research requires strong federal support. Big science requires big funding support. However changing the direction within the U.S. federal health funding mechanism requires a revolution. Kuhn was right in highlighting the social aspect of science we now need to admit to this dimension in or work and address it before we waste another 70 years of research on a theory that has outlived its utility. Addressing dementia will require this level of political commitment.

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