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Title: Who Gets to Decide on What It Means to Have Alzheimer's Disease?

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Alzheimer's has historically been defined as a progressive neurodegenerative disease impacting memory and cognitive functions, where the presence of abnormal β-amyloid is considered a key pathological feature. However, there is a current movement, led by a workgroup created by the Alzheimer's Association, to revise this definition. The proposed change seeks to redefine Alzheimer's as an abnormal accumulation of amyloid, regardless of current or future cognitive function.[1] This new definition and the workgroup behind it raise a rarely asked question in medicine: Who gets to decide how to redefine a disease?

The process used to change the definition of Alzheimer's disease serves as an exemplar of the insidious nature of how industry, including pharmaceutical and diagnostics corporations, influences the re-drawing of disease boundaries. If one looks at the Alzheimer's Association workgroup, a third of the members are directly employed by industry, and another third have significant conflicts of interest (Figure 1).[2] What may have been a reasonable workgroup for setting a research agenda is now just another example of a longstanding practice that industry is the "who" in who gets to define the nature of disease in routine clinical care. For example, a study from 2013 found that diagnostic thresholds for what defines a disease are lowered by expert panels composed of those with financial ties to multiple companies that may benefit directly from those decisions. Furthermore, these expert panels widened disease definitions without considering the potential risks of increasing the number of people living with the disease.[3]

The changes proposed by the heavily conflicted Alzheimer's Association workgroup, while framed as a gradual evolution from a research framework to one that should now be used in the clinical setting, will have effects that will be far from subtle and will undoubtedly be marketed as a new "Alzheimer's epidemic." There are currently an estimated 6 million Americans age 65 and older living with Alzheimer's dementia, with the majority being over the age of 75. The proposed changes will move what is a feared but far from universal disease of aging, Alzheimer's dementia, to a largely silent, asymptomatic disease affecting a much larger population, as most people with positive amyloid biomarkers have no cognitive issues. Current estimates suggest that around 40 million cognitively normal adults in the US would test positive for amyloid.[4] A cognitively normal 50-year-old would have a 1 in 10 chance of being amyloid positive.[5] Furthermore, it would be a stretch to call this new definition of Alzheimer's disease a progressive disease as most of these individuals will never progress to either MCI or dementia during their lifetimes.[4,6]

The benefits of redefining Alzheimer's would be more apparent if there were evidence that treating cognitively normal individuals who are biomarker-positive reduces the risk of developing Alzheimer's. However, there is no such evidence that the presence of amyloid in a cognitively normal individual should lead to the initiation of any clinical intervention, let alone that removing amyloid helps these individuals. Furthermore, current evidence suggests that amyloid is far from the only factor that contributes to Alzheimer's disease progression. One only needs to look at the trial data for lecanemab and donanemab, both of which have an

exceptional ability to remove amyloid but only a rather subtle effect on the rate of decline in cognitive and functional measures.[7]

This is not to say that we should not pursue current or future changes to the definition of Alzheimer's disease. What is defined as disease is not an immutable fact but something always in flux.[8,9] Nor is it to say the industry is inherently bad. We, though, must acknowledge that corporations have a duty to maximize shareholder value and create firewalls to ensure that any redefinition of disease is not primarily a tactic to expand markets for existing commercial products.

There is a clear path forward to protect individuals from diagnostic creep when modifying disease definitions. A Guidelines International Network (G-I-N) workgroup developed an 8-item checklist to aid in decision-making regarding the uncertainties and trade-offs when modifying disease definitions.[10] Importantly for the current Alzheimer's Association workgroup, key recommendations are missing, including discussions of the potential harms of their proposals to expand the definition of Alzheimer's disease. However, this checklist does not explicitly address the "who" gets to be at the table when redefining disease and the considerable financial conflicts of interest involved in most expert committees. Any modification of disease definitions should also follow similar guidance for developing guidelines. Institute of Medicine of the National Academies of Science and the Council of Medical Specialty Societies (CMSS) have each published recommendations that recommend that the majority of clinical guideline panels be comprised of members who are free of conflicts and that there be a process for

identifying and resolving any potential conflicts.[11, 12] Disease-modifying workgroups that do not follow these standards to minimize conflicts of interest, including the current Alzheimer's Association workgroup, should not be considered legitimate by the medical community. Furthermore, governmental organizations, including the National Institute for Health (NIH), which is represented by a steering committee member in the current workgroup, and the National Institute on Aging (NIA), which until recently co-sponsored the workgroup and now acts only as "advisors," should have a zero-tolerance approach in participating in conflicted workgroups even as advisors.

The Alzheimer's Association draft criteria should serve as a caution of how a confluence of interests can lead to a slow creep of diagnostic thresholds that pushes a narrative that life itself is only a collection of disease states—raising the hopes of newly defined sufferers that, with the power of modern medicine, their illness can now be treated and managed, although never truly cured. Pharmaceutical corporations, laboratory companies, and patient advocacy organizations benefit from market growth. Academics benefit from new papers to write and new grants to get funded. There is no resistance, as there are no patient advocacy groups for those healthy individuals who do not want to be diagnosed with a disease that more than likely will never truly affect them.

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Figure 1: Industry Influence in the draft Alzheimer's Association Workgroup for the Revised Criteria for Diagnosis and Staging of Alzheimer's Disease