Editorial

Uncertain Progress on the Fuzzy Boundaries of Alzheimer’s Disease: Reading Between the Guidelines

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Recently, the National Institute on Aging (NIA) and Alzheimer’s Association (AA) issued new guidelines for the diagnosis of Alzheimer’s disease (AD) and related conditions [1–4]. It is important to think deeply about the lessons learned from these new efforts both in terms of their actual content and the cultural context in which they were issued. We believe that these lessons about the state of AD research are more profound than the documents themselves, and speak to broad issues concerning the relationship between science and society, aging and disease, and efforts to improve the quality of life of older people affected by age associated cognitive challenges.

EXAMINING THE NEW GUIDELINES

The expressed motivation for the issuance of new recommendations 27 years after the original set offered by NINDS and ADRDA [5] is to incorporate the results of research conducted over the last quarter of a century. Perhaps most importantly, the guidelines are now divided into three papers addressing asymptomatic conditions, mild but pre-dementia states, and finally AD and dementia themselves. What are the new findings and politics that motivate these publications?

First, there seems to be recognition that memory failure was over-emphasized in the preceding 1984 guidelines as the initial symptom, less frequently, can be other cognitive problems. Moreover, the age range for diagnosis of AD proposed in the earlier guidelines was recognized for some time to be arbitrary, for example somewhat inexplicably ending at age 90. Most remarkably, the new recommendations assert that AD is now best considered a heterogeneous syndrome that bears complex relationships to other heterogeneous forms of dementia. The authors also argue that these conditions of brain aging occur on a continuum, although—as Zaven Khachaturian points out in his introductory editorial [6]—we do not know if and how the continuum of brain aging is different from the continuum of AD.

Further, and also critically, a disconnect between the clinical and neuropathological features has become apparent through research: AD as a clinical state is no longer to be definitively diagnosed (as it was in 1984) by the presence of plaques and tangles at autopsy. At present, we await the results of a fourth set of deliberations for the new proposed neuropathological criteria. As a biological replacement for autopsy, biomarkers—namely neuroimaging and cerebrospinal fluid measurements—are sprinkled liberally through all sets of guidelines. Finally, a specific model of pathogenesis beginning with amyloid and moving through nerve cell damage to clinical impairment is proposed. Expectations are created for promising new drug devel-
opment even though lack of progress in this area over the last several decades is recognized in the three articles.

Many of these pieces of “new” information have been known for many years. The clinical variability of AD, including symptoms beyond memory, has been quite evident since the description of Auguste D. in 1906. And if we are honest, we must admit that we have discovered much more overlap amongst dementia syndromes like vascular and Parkinsonism states. Our vaunted genetic and imaging approaches have exposed this overlap rather than helped sort out specific differences with greater accuracy. That a slowly progressive condition, be it aging or dementia, moves through different arbitrarily defined stages, some of which exist before clear symptoms are manifest, seems rather obvious. If one adds up all the stages of the pre-dementia conditions mentioned in the guidelines that address asymptomatic and mild cognitive impairment (MCI), many of which are defined by biomarker presence or absence, one comes up with a rather large proliferation of such arbitrary “stages” on the continuum. Are we just shuffling the semantic chairs on the Titanic boatload of existing conceptual errors created by presuming to have clinical pathological understanding that we actually lack? Despite considerable criticism in the field [7], including some mentioned in Khachaturian’s editorial, the papers are still based on an amyloid-centric model of pathogenesis.

STILL TRAPPED INSIDE THE AMYLOID BOX?

One can challenge the assertions behind the guidelines in the paper on both logical and empirical-scientific grounds. Ironically, while at the same time apparently abandoning the definite nature of the neuropathological changes found at autopsy and the clinical symptoms the authors are urging us to consider less well understood and more difficult to validate earlier biomarkers that are justified through their linkages to later pathological features. Why would we expect these clinical amyloid and neurodegenerative biomarkers to be any better predictors of clinical course or even therapeutic response than those found in the brains at autopsy? Perhaps the soluble forms are more toxic than the amyloid bound in plaques, but this is based on an unproven model of pathogenesis. Many of the comments in all three papers [8] emphasize that we do not have these markers well standardized, nor do we understand which are best for which purposes and how they relate to each other. Perhaps we should be thinking outside the amyloid box instead of repackaging it. We do not want our message to be that scientific progress is not possible and desirable, but rather that current research actually weakens the overly simplistic current dominant ways of thinking about “Alzheimer’s.”

Strangely, not much is said about genes in the guidelines, particularly susceptibility genes like apolipoprotein E, even though they confer some of its power by drawing the attention of researchers because of the original autosomal genetic mutations in the amyloid-β precursor protein. The highly pleiotrophic apolipoprotein E4 allele increases one’s risk for dementia, other neurological conditions, cardiovascular conditions, and perhaps is protective against some conditions such as macular degeneration. There is a whole sector of genetic risk assessment that is also clamoring for social resources, including rather irresponsible direct-to-consumer marketing of genetic tests. Yet this source of risk information is strikingly missing from the guidelines. In our view, that omission is actually quite appropriate given the lack of clear risk information associated with genes, but the same could be said of other biomarkers as well.

Lastly, there has been considerable confusion during the development of the guidelines as presented in early drafts and presentations as to whether these recommendations are designed for researchers or clinicians, or both. Final drafts of these papers make it clear that the asymptomatic guidelines are for researchers, the MCI in different forms for both, and the dementia ones more for clinical use. Yet the guidelines are not precise enough for researchers to be included in protocols, nor are researchers likely to accept the guidance of a small group of experts, as they may choose to study other markers in other ways. Healthcare professionals would wish to know much more about the clinical utility, public health, and economic implications of the recommended biomarkers. As mentioned, the papers are full of caveats about the fact that biomarkers are not standardized, perhaps not even reliable except in narrow research settings, and certainly not validated—so why recommend them for clinical use? And is doing so even ethical at this stage?

THE LARGER CULTURAL CONTEXT

Considering the broader social context of these guidelines generates many more questions about their purpose. The current dominant model of thinking man-
and frail elders with and without functionally disabling vulnerable citizens, including disadvantaged children challenges. Hence, we should focus more on developing towards a “cure”, health care systems and communities less of the progress in developing biological therapies that we could give to persons in the event that we developed predictive certainty. Surely late-life memory loss is common enough that physicians should recommend to older patients that they plan for that eventuality if they live long enough. To the extent that any evidence exists about current drugs, one might argue that their effects are greater later in the conditions than earlier; for example, no drugs have convincingly improved memory or other symptoms in so-called MCI.

The current dominant model also emphasizes the fear, terror, and despair surrounding the condition, using language that has been variously critiqued by social scientists as being marginalizing and dehumanizing towards aging persons [9, 10]. Our current labels and societal language patterns are thus freighted with ominous cultural meanings: we consider those with AD “disease victims”, “lost selves”, “bodies that have left the mind behind”, and even “zombies” [11], treating them as the living dead—walking corpses to be both pitied and feared, despite their obvious signs of life [9, 12]. As such, aging persons in our culture suffer not only from neurodegenerative processes, but also from the anxieties of a culture that is often dismissive, if not contemptuous, of those with more severe memory problems than the rest of us.

In this cultural context, the common assertion that we must find a cure now because otherwise our health-care systems will be bankrupted by bodes of demented older people acquires a tone of desperation and shortsightedness. Do we really think science can eradicate all cognitive impairment in the elderly, or is this science-fiction or fantasy? And further, what would a cure for AD actually look like? Would our bodies age while our cognition restored perfectly intact? Regardless of the progress in developing biological therapies towards a “cure”, health care systems and communities are going to need to care for older people with cognitive challenges. Hence, we should focus more on developing services and programs to foster quality of life for vulnerable citizens, including disadvantaged children and frail elders with and without functionally disabling cognitive impairment. The language and labels we use to describe the aging members of our society need to be imbued with shared humanity rather than the divisive fear generated by the medical model run amuck.

We find it peculiar that the guidelines give no consideration to any issues of an economic nature. It is impossible to know what the costs of the recommended panel of biomarkers would be if they were more widely introduced, as economies of scale might reduce current costs. And given that the guidelines do not actually recommend a single well-defined package, it is difficult to calculate the cost to society. However, using a modest and probably low estimate of $5,000 per person added to the number of people with various forms of MCI and dementia in the United States alone (perhaps 20 million) we come up with a projection of $100 billion dollars.

Even if we did spend this amount of money, what would we know and how would we use it to benefit individuals and society? Imagine a future in which some people would be told that their chances of late life dementia are probably somewhat greater than before they participated in the testing process. In reality, we would have little idea of how much the risk would be greater.

And how many people would be given erroneous information (i.e., false positives/false negatives) because of our incomplete understanding of biomarkers?

From an ethical perspective, we must think critically about who produced these guidelines and what conflicts of interest may exist. Both the NIA and the AA depend on funding from the public and private sectors based on the sense of urgency they can create around the conditions they study. Many of the authors of the guidelines are supported by drug companies, and the field itself is influenced strongly by the pharmaceutical model of health and its powerful industry. Being the case, these guidelines were not produced in an adequately unbiased and systematic way. Where was the representation of experts on guideline construction, or representation of people affected by the guidelines (caregivers and persons with dementia)? Any guidelines themselves should be the focus of a serious attempt to evaluate their reliability and utility before widespread introduction.

DEEPER LESSONS FROM THE GUIDELINES

We believe there are deeper lessons from these efforts at producing new guidelines and that these
lessons offer a major criticism of our Western, particularly American, approaches, to understanding aging and the brain. From a scientific viewpoint, we are perhaps more confused today about "AD" than we were 27 years ago. What has become apparent is that "Alzheimer’s" is a label that is in trouble. Far from being a singular disease, like polio, with a single cause and a powerful preventative strategy, it is a syndrome that likely includes many biological processes under the umbrella of that single eponym. Moreover, we have not established that AD is qualitatively different than the heterogeneous processes that characterize aging itself. Hence in our view, simple-to-produce, powerful molecular fixes liked those based on amyloid biology have become less likely since the first guidelines were issued in 1984. The fact that we do not know what the amyloid-related proteins do, and if and how they are damaging to neurons or play a protective role in the brain [13–15] despite billions of dollars and years of research is embarrassing. As Khachaturian points out, we need new approaches and theories rather than heavier investment in unsuccessful ones. AD probably represents a multitude of processes that cause in some people severe forms of brain aging and associated cognitive impairment. Is the field promising the neurological fountain of youth by claiming a universal "fix" for it?

In fact, the field appears a caricature of a distinctly American way of thinking about solving problems: if there is human suffering then there must be a scientific molecular biomedical fix that will be found if we just spend enough money. "Alzheimer’s" also represents an exaggeration of our already death-denying culture, and is promoted as a fate worse than death. Yet death is certain for all of us and perhaps some degree of cognitive impairment with aging is also inevitable if we live long enough. Further, maintaining quality of life is a real possibility if we can summon up compassion, empathy, and solidarity for aging persons in our communities rather than strategically sowing terror, sadness, and fear. Achieving that solidarity may well rely strongly on reframing AD not as a late-life disease event to be cured but rather as a lifelong process to be postponed; viewed in this way, the quality of life enjoyed by elders depends on how they have been taken care of and educated as children and across the lifespan. Brain health must be properly viewed as a lifelong endeavor that is relevant to all of us rather than just the very old. It must not be something we outsource to scientists and clinicians. With the increasing prevalence of dementia and the realization that disease-modifying drugs may not be available in the foreseeable future, it is the responsibility of science and other sectors of society to better communicate the worth of lifespan preventative healthcare measures to the public.

Ultimately, we hope to encourage critical reflection on the new guidelines so that others consider whether they may actually imperil genuine social progress. To that end, we would like to heed the contemplation words of the great German writer Johann Wolfgang von Goethe: "When a science appears to be slowing down and, despite the efforts of many energetic individuals, comes to a dead stop, the fault is often to be found in a certain basic concept that treats the subject too conventionally. Or the fault may lie in a terminology which, once introduced, is unconditionally approved and adopted by the great majority, and which is discredited with reluctance even by independent thinkers, and only as individuals in isolated cases."

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Authors’ disclosures available online (http://www-alz.com/disclosures/view.php?id=918).

REFERENCES


[11] As one AA representative put it at a National Institute of Health State-of-the-Science Conference: Preventing Alzheimer’s Disease and Cognitive Decline conference in 2010: “we are going to see in most of the cities in the world demented people wandering the streets because there is simply no place to put them, no way to prevent their dementia from occurring, and that’s going to be a public health disaster that we just can’t face up to.” - Bill Thies NIH State-of-the-Science Conference: Preventing Alzheimer’s Disease and Cognitive Decline - Day 3 (93:40 mark), http://videocast.nih.gov/summary.asp?Live=8412


