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Mario D Garrett and Ramón Valle

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What is This?
A methodological critique of the National Institute of Aging and Alzheimer’s Association Guidelines for Alzheimer’s disease, dementia, and mild cognitive impairments

Mario D Garrett
School of Social Work, San Diego State University, CA, USA

Ramón Valle
Alzheimer’s Cross-Cultural Research and Development [ACCORD]. San Diego, CA, USA

Abstract
In 2011, the U.S. National Institute on Aging published guidelines for clinical diagnostics for Alzheimer’s disease dementia. These guidelines define a continuum with three stages—an early, pre-clinical stage with no symptoms, followed by mild cognitive impairment, and a final stage of Alzheimer’s disease dementia. This methodological critique examines the validity of this continuum. No studies exist showing the progression of these biomarkers to Alzheimer’s disease. There is also a lack of empirical evidence showing how biomarkers determine mild cognitive impairment, which has multiple etiologies. The guidelines fail to explain anomalies where there are biomarkers but no expression of Alzheimer’s disease.

Keywords
dementia, guidelines, critique, methodology, validity, mild cognitive impairment, neuropathology, social intervention

Corresponding author:
Mario D Garrett, School of Social Work, San Diego State University, 5500 Campanile Drive, San Diego, CA 92182, USA.
Email: mariusgarrett@yahoo.com
Introduction

In 2011, the U.S. National Institute on Aging, in collaboration with the (United States) Alzheimer’s Association published new guidelines on Alzheimer’s disease (AD) (Jack et al., 2011). In doing so, the guidelines redefined the research agenda for AD. This paradigm change has received very little discussion. Although “These recommendations are solely intended for research purposes and do not have any clinical implications at this time” (Sperling et al., 2011, p. 280), the clinical implications are hard to dispel (Mattsson, Brax, & Zetterberg, 2010). This paper aims at contributing to an open discussion about the guidelines’ methodological validity before such clinical implications are adopted.

While the previous 1984 guidelines only recognized one stage—Alzheimer’s dementia—the new guidelines propose that AD progresses on a continuum with three stages (Jack et al., 2011). The first is an early, pre-clinical stage with no symptoms (Sperling et al., 2011), followed by a middle stage of mild cognitive impairment (MCI) (Albert et al., 2011), and a final stage of AD dementia (McKhann et al., 2011). An additional guideline updates the criteria for documenting and reporting Alzheimer’s-related changes observed at autopsy (Hyman et al., 2012).

The stated purpose for these new guidelines is to enable researchers to incorporate new neurological insights and technological advances, specifically in the area of biomarkers and techniques for the detection of neuronal damage. Some of the techniques that have been identified for AD biomarkers are brain-imaging studies using magnetic resonance imaging (MRI), positron emission tomography (PET), and proteins in cerebrospinal fluid (CSF). The advances in these techniques include not only hardware and software but also new methodologies for imaging such as with the functional MRI (fMRI), and for interpreting data as from volumetric MRI (vMRI).

By allowing these advances in science to be incorporated within a general framework of AD, these guidelines channel efforts to elucidate the early neurological basis of the disease. The ambition for the guidelines was to act as a consolidating force. Despite the intention of the guidelines to summarize a wealth of existing data, allowing the development of new hypotheses and predictions, and to establish a forum for sharing of ideas, it is not clear that these guidelines are more inclusive than their 1984 predecessor.

The new guidelines argue that when the neurological damage—as identified by the biomarkers—becomes severe, the disease turns first into MCI and then, with increasing severity of neuropathology, into AD. MCI refers to memory lapses that do not affect daily activities, while AD is the expression of memory loss and cognitive capacity that affect engaging in day-to-day activities. What was since 1984 a probability of association is now seen as a causal progression. Because finding a cure for AD has been illusive—mirroring the enigmatic behavior of cancer—there is a palpable yearning for such a linear system of causality. Except for one shortfall. At every stage in this proposed causal links, there is no definitive evidence that one stage causes the other. What the literature shows is that there is an increased probability that being in one stage increases the likelihood of experiencing subsequent stages. However, probability does not determine causality and there is no one study that reports causality in any stage of AD.

The guidelines assert to have been established to “improve current diagnosis, strengthen autopsy reporting of Alzheimer’s brain changes, and establish a research agenda for future progress in earlier detection and even greater diagnostic accuracy” (Alzheimer’s Association,
This critique similarly supports establishing a valid and comprehensive “...research agenda for future progress,” but one based on firmer science.

**Methodological shortfalls**

The guidelines both implicitly and explicitly suggest a causal pathway for AD. It is important to note that the refutation—rather than the acceptance—of a hypothesis is the basis of the scientific method (Popper, 2004).

One methodological design to test for causality would be to follow a randomly assigned group of young adults—one group with and one group without the biomarkers—and then see who develops AD. The guidelines do not report of such studies (Sperling et al., 2011). The assumption is that since AD is a neuropathological disease, biomarkers that identify early stages of this neuropathology can therefore act as proxies for the early stages of AD. Sperling et al. (2011) identify that there are empirical limitations in making these linear assumptions about the disease. The authors argue that it is important to note several potential confounding issues in the majority of pre-clinical dementia studies. One of these issues relate to the design being susceptible to “cohort biases” due to the convenience sampling methodology in all of these pre-clinical studies. It is very rare that people who have no memory or cognitive issues are ever studied. There might also be people who have the neuropathology but never become “symptomatic during their lifetime” (Sperling et al., 2011, p. 2).

**Biomarkers critique**

In the guidelines, the pre-clinical stage includes such biomarkers as hippocampal or whole brain atrophy, CSF Aβ42 levels, PiB imaging, genetic screening (ApoE e4 status), or behavioral deficits (Gauthier et al., 2006; Jack et al., 2010; Whitehair et al., 2010). The evidence that any one of these biomarkers causes dementia is correlational. Such associations lack external validity. As in the case of ApoE, where there are strong correlations, this correlation is diminished or disappears completely for different ethnic groups (Tang et al., 1998). There is also a symbiotic relationship between genes. In one study where AD-induced mice all developed plaques, only the ones with an a7Rs gene showed the impairments associated with AD (Dziewczapolski et al., 2009). Biomarkers are typically proxies for the disease and may not be the disease itself (as with the a7Rs gene). Despite the guidelines’ anchoring on the use of biomarkers, there are still other methodological issues with defining these biomarkers.

**Reliability of biomarkers**

The extent and quality of diagnostic biomarker data currently available is still in its infancy. Some biomarkers are difficult to identify while others are variable, depending on the patient. Mayeux (2004, p. 185) argues that “Reliability, validity, sensitivity, specificity, ascertainment bias, and interpretation of data using biomarkers should be reviewed just as carefully as any other variable.” Because of the unreliability of biomarkers, McShane, Noel Storr, Ritchie, and Flicker (2011) suggest that identifying specific biomarkers in diagnosing a specific disease is premature.
Validity of biomarkers

As acknowledged in the guidelines, biomarkers are not immutable. This might also be the outcome of disease rather than the disease itself. Moderating or mediating variables might influence biomarkers. The presence of the biomarkers does not determine the expression of the disease. In some cases, the underlying cause of dementia is environmental. One such environmental factor is the occurrence of concussions and other mild traumatic brain injuries (MTBI)—known colloquially as concussions. MTBI—incurred through falls, motor vehicle accidents, trauma from explosives, and sports-related activity—account for 75% of all traumatic brain injuries sustained in the United States (Faul, Xu, Wald, & Coronado, 2010). MTBI are seen at all ages from youth (Daniel, Rowson, & Duma, 2012; Guerriero, Proctor, Mannix, & Meehan, 2012; Stracciolini, Casciano, Friedman, Meehan, & Micheli, 2013) to adults (Kerr, Marshall, & Guskiewicz, 2012; Koerte, Ertl-Wagner, Resier, Zafonte, & Shenton, 2012), as well as military soldiers (Wilk et al., 2012). Sustaining only one or two concussions has permanent neurological repercussion (Johnson, Steward, & Smith, 2012; Theriault, De Beaumont, Tremblay, Lassonde, & Jolicoeur, 2011; Zhou et al., 2013) and are known to be risk factors for developing dementia later in life (Dams-O’Connor et al., 2013; Moretti et al., 2012; Wang et al., 2012). However, MTBI do not conform to the biomarkers within the guidelines.

There are 447 neurological diseases identified by the U.S. National Institute of Neurological Diseases and Stroke at the National Institutes of Health (NINDS, 2013). AD and dementia being just two of the diseases specified. Any biomarkers identified for AD might result in the expression of any—or many—of these neurological diseases, or none at all. To date, there is no empirical evidence showing that any biomarkers—including biomarkers associated with AD—cause any disease, or will specifically cause AD.

Even if there is evidence of the presence of selected biomarkers—severity of neuropathology in specific regions of the brain—this does not dictate the expression of AD. David Snowdon’s longitudinal study with nuns was the first to report such anomaly. Snowdon (1997) found that 8% of the nuns who behaved and acted free from dementia—when they died and had their brain examined—were found to have the most severe neuropathology—Braak and Braak stages five and six. These older nuns had high-functioning status despite having abundant and severe neurofibrillary tangles and senile plaques, the classic biomarkers of AD at the point of autopsy.

Numerous other studies even fail to find a correlation between the biomarkers and the expression of AD. Balasubramanian, Kawas, Peltz, Brookmeyer, and Corrada (2012) reported that all 58 individuals at autopsy, 90 years and older—who did not have any signs of dementia during three years prior to their death—nonetheless had evidence of biomarkers specifically associated with AD. It has become clear that this clinical-pathological correspondence is not consistent. Extensive neuropathology that is associated with AD, particularly diffuse amyloid plaques, can be present in the absence of any obvious symptoms (Davis, Schmitt, Wekstein, & Markesbery, 1999; Knopman et al., 2003; Price & Morris, 1999). These studies erode the direct linear link between the biomarkers and the expression of AD. There seems to be other mediating or moderating factors that future guidelines need to address.

More importantly for AD—because it is a disease that is correlated with older age—are those studies showing that the relationship between the biomarkers and AD becomes less reliable with older study sample (Brumback-Peltz, Balasubramanian, Corrada, & Kawas,
2011; Savva et al., 2009). Since cerebrovascular disease among older adults over 75 years of age is a prevalent condition—36% overall, 25% for coronary, 58% hypertension, and 11% for stroke (Schiller, Lucas, & Perego, 2012, Table 2, p. 19)—contemporary neuroscience still lacks a thorough understanding of exactly what contribution cerebrovascular disease makes to cognitive impairment and AD (Jellinger, 2008).

Contributing further to the complexities of diagnosis, current research suggests that dementia in the oldest-old, compared to younger people, is more likely to be related to mixed disease pathologies rather than to a singular morbiditry and therefore unlikely to be due to any single biomarker (Brumback-Peltz et al., 2011). As a result, the correlation between biomarkers, particularly AD neuropathology, and dementia declines with age (Savva et al., 2009). In part, this lack of association reflects increasing prevalence of biomarkers among all people as they age (Crystal et al., 1988; Imhof et al., 2007). Interestingly, approximately half of clinically diagnosed AD oldest-old have insufficient biomarkers to account for their dementia (Crystal et al., 2000; Polvikoski et al., 2001), while the other half who do not have AD have the biomarkers criteria for AD (Crystal et al., 1988; Katzman et al., 1988; Polvikoski et al., 2001). Esiri (2010, p. 2) succinctly summarizes that “…we delude ourselves if we think we can reach a molecular understanding of this still enigmatic disease without an opportunity to explore cellular and molecular changes in affected human brains.”

MCI critique

Before the new guidelines, MCI had a long history of research in psychology. MCI indicates difficulty with memory and thinking that are outside of what is considered as normal but still allow the individual to function independently. Before the 1990s, MCI was approached by researchers as a normal part of aging, but in 1991, Flicker, Ferris, and Reisberg reported results where they argued that most elderly subjects with MCI “…will manifest the progressive mental deterioration characteristic of dementia …” (p. 1006). Subsequently, MCI became a prodrome—an early sign—of AD (Petersen et al., 2001). Although there is growing application of a unified diagnosis for MCI, amnestic mild cognitive impairment (aMCI) as defined by Petersen et al. (1999, 2001) is often used in clinical and research practice as prodromal AD (Dubois et al, 2010).

Reliability of MCI

The guidelines fail to address the role that cultural variation plays in the diagnosis and treatment of MCI, despite acknowledging that much MCI “change can [exhibit itself] in a variety of cognitive domains” (Albert et al., 2011, p. 3). Low et al. (2012) reported that it is difficult to accurately diagnose MCI in persons from linguistically diverse groups, even when proficient in English. The fact that English language ability and level of acculturation need to be considered when assessing MCI erodes, in large part, the reliability of this measure in ethnically diverse cultures, as is the case in the USA and in most of Europe.

Among older adults, the prevalence of MCI and its subtypes varies greatly from one study to another, ranging from 3% to around 17% (DeCarli, 2003). The variance could be due to different diagnostic criteria or to different populations studied (Espinosa et al., 2013). Epidemiological studies suggest that the progression of MCI is also heterogeneous. MCI can be stable, might even be reversed, and in some people progress to dementia (DeCarli,
2003; Espinosa et al., 2013; Frisoni et al., 2000; Ganguli, Dodge, Shen, & DeKosky, 2004; Larrieu et al., 2002; Ritchie, Artero, & Touchon, 2001). There are no studies that elucidate what type of MCI leads to what type of outcome, and there are no studies that show that AD is caused by only one type of MCI.

The greatest methodological threat to asserting the link between MCI and AD is the fact that MCI is not a reliable measure in itself. In a review of the literature, Stephan et al. (2013) found large heterogeneity in the neuropsychological methods used to determine memory impairment with selective and unclear reporting of how each of the criteria was measured.

The reliability of MCI as prodromal dementia does not have strong evidence. In a review of the literature on intervention in MCI, Williams and Kemper (2011) looked at protecting factors for MCI. What they identified is that MCI can be prevented through cognitive activity, physical activity, as well as through social interventions. Having a healthy nourished brain reduces MCI (Correa-Leite, Nicolosi, Cristina, Hauser, & Nappi, 2001; Ojofeitimi et al., 2002). MCI is delayed through higher education (Kubzansky et al., 1998, Snowdon et al., 1996) having higher socioeconomic status, occupying cognitively demanding occupations (Salthouse, 2006), playing bridge and crosswords puzzles (Mireles & Charness, 2002), walking (Yaffe et al., 2001), and increased levels of activity (van Gelder et al., 2004; Weuve et al., 2004). Being socially engaged and having emotional support also has a protective factor (Beland, Zunzunegui, Alvarado, Otero, & del Ser, 2006; Holtzman et al., 2004).

There is also a substantial body of research showing the efficacy of cognitive interventions, which the guidelines fail to address. Memory training (McDougall, 2000), inductive reasoning and spatial games (Schaie, Willis, & Caskie, 2004), and specialized computer programs have all shown extensive improvement in cognition (Ball et al., 2002; Roenker et al., 2003; Willis et al., 2006; Wolinsky et al., 2006).

The possibility of delaying the progression of AD through social intervention—including computer aided programs—holds great potential in understanding the pathology of dementia and possible therapies. Cognitive training programs strengthen cognitive function and can provide a foundation for a therapy to restore sensory, cognitive, memory, and affect systems in aging, while delaying the onset of age-related cognitive diseases and improving quality of life (Manhcke, Bronstone, & Merzenich, 2006).

What these studies indicate is that MCI is not immutable, that memory is malleable. Because there are both protective as well as enhancing interventions that modify MCI, it is unlikely that biomarkers alone dictate MCI. Theoretically, there is a need for an intervening factor to explain these results which future guidelines need to address.

Validity of MCI

Some, but not all, people with MCI progress to AD (Espinosa et al., 2013). Longitudinal, population-based studies have shown that most people with MCI do not develop dementia even after eight years of follow-up (Busse, Bischkopf, Riedel-Heller, & Angermeyer, 2003; Fischer et al., 2007; Manly et al., 2005; Ritchie et al., 2001). Those studies that show greater predictability of conversion from MCI to AD also have a more stringent criteria for MCI (Teng, Tingus, Lu, & Cummings, 2009).

There are also some important causes of MCI, other than biomarkers linked to AD. Some of these causes of MCI include medications, stroke, depression, and alcoholism (Kirshner, 2008). Also some MCI, despite becoming more severe, does not result in AD. Mesulam
(1987) reported six patients with aphasia, with progressive word-finding and naming difficulties, worsened over the years, but who did not develop AD. AD is not a more severe MCI.

There are also situations where MCI is transient. The syndrome of transient global amnesia (TGA) first described by Morris Bender as early as 1956 is still not completely understood (Romero et al., 2013). Similar to MCI, TGA specifically affects memory function where patients can register information, but retentive memory ability is affected dramatically. Although studies show that TGA have age and risk factor profiles similar to those of patients with stroke (Shuping, Rollinson, & Toole, 1980), they have a low incidence of strokes on follow-up. In addition, TGA neurologic examination fails to demonstrate any pathology or biomarkers. Similarly, MCI studies show that 16% of subjects do not have any evidence for biomarkers associated with AD (Pettersen, 2013).

MCI conversion to AD is also moderated by gender. Men and women have different risk profiles both for a diagnosis of MCI and progression to dementia (Artero et al., 2008). As a result, intervention programs should focus principally on risk for stroke in men and depressive symptomatology and anticholinergic medication use in women (Artero et al., 2008). There are other inconsistencies in the logic that MCI causes or will ultimately result in AD. Specific studies show that MCI is a poor predictor of dementia. Ritchie et al. (2001) compared MCI with age-associated cognitive decline (AACD) during standardized neurologic examination in the general population. The authors found AACD to be more prevalent (19.3%) compared to MCI (3.2%), and that after three years follow-up MCI was a poor predictor of dementia with only 11.1% conversion rate compared to 28.6% conversion rate for AACD.

Empirical studies continue to erode the validity of MCI as a prodrome to AD. MCI is both an unreliable indicator as well as an invalid indicator of AD. There is also in the literature, great variance by what is meant by MCI and how clinicians and researchers differentially apply the term.

**Theoretical criticisms**

Overall the guidelines are prone to *theoretical isolation*. Studying AD in isolation to other neurological diseases or psychosocial processes assumes that AD is a neurologically specific disease. Studying the same or different biomarkers in other neurological diseases can contribute to identifying the uniqueness of AD, while including psychosocial studies will help explain some of the research anomalies that exist. Gaining a better understanding of how the brain accommodates neuropathology without any diminished cognitive affect should be a key feature of AD research which needs to be incorporated in future guidelines. Theoretical isolation is part of the biological determinism that is implicit in the old guidelines. The notion that specific neurological degradation will solely result in dementia might be logical but still untested. In contradiction to this biological determinism, numerous studies continue showing the importance of social intervention as mediating and moderating factors.

**Threats to construct validity**

There is variability in measuring the biomarkers, MCI, and AD. This variability poses a threat to the *construct validity*. If what we are measuring is not stable, then it is more difficult
to establish the relationship between two moving targets. The lack of reliability obscures the relationship being studied. There are numerous biomarkers competing for a role in AD formation. A coherent approach to identifying each of these biomarkers and how they could possibly interact among themselves is an important omission in the guidelines that erode the validity of these biomarkers as constructs. In addition, the lack of reliability in measuring MCI diminishes the soundness of using generic MCI as an indicator. One example for future guidelines is to focus on aMCI as defined by Petersen et al. (1999, 2001).

The guidelines fail to define the constructs primarily because we are still uncertain about what we are trying to measure. Is AD the neuropathology as defined by the biomarkers, or, as is assumed, the expression of the disease through loss of memory and change in capacity and personality? Therefore, there is an instrumentation issue in defining what AD is. Whether it is the neuropathology or whether it is the expression of the disease. Although AD was named because of the characteristic neuropathological progression associated with severe cognitive decline, the guidelines use any type of dementia as AD. In one example, Esiri (2010) indicates the likely confusion that might arise with respect to AD and AIDS-related dementia and also AD and other dementing illnesses. There are numerous types of dementia. AD is the most common form of dementia to be found in over 60% of cases followed by vascular dementia, dementia with Lewy bodies, fronto-temporal dementia, Korsakoff syndrome, Creutzfeldt–Jakob disease, and HIV-related cognitive impairment. The rare forms which occur in 5% of cases relate to corticobasal degeneration: Huntington’s disease, multiple sclerosis, Niemann–Pick disease type C, normal pressure hydrocephalus, Parkinson’s disease, posterior cortical atrophy, and progressive supranuclear palsy. Different types of dementia might have different and very specific causes. Focusing on a specific type of dementia will limit the variability in the dependent variable (Fratiglioni, De Ronchi, & Aguero-Torres, 1999). Up the chain of causality is the instrumentation issue with MCI. There is great variability in defining MCI, allowing researchers to select types of MCI that are more likely to be pre-dementia and then using that as the predictor, which makes for a tautological argument (Fratiglioni et al., 1999).

Since AD is mainly diagnosed behaviorally—and confirmed histologically—there is still the individual physician’s reliability in diagnosing AD. In a clinical setting, a physician’s ability to assess patients may improve over time. Some physicians are more competent at diagnosis than others, while some type of patients might be more likely to receive one diagnosis or severity of diagnosis then another patient (Christakis, 1999). Instrumentation issues in AD research are capricious and require new guidelines to provide some practical suggestions.

There are also threats to internal validity in establishing causality. Because these guidelines have sensitized people to associate MCI directly with dementia, patients might present themselves much later for diagnosis when AD is more likely to be a comorbidity. There will be a change in prevalence due to history as it relates to sensationalizing of MCI and AD (Metlife, 2011). There are also the ethical implications of early diagnosis (Mattsson et al., 2010) and legal implications of a diagnosis of AD on the individual, needs to be further considered in the literature.

Especially with much older older-adults, the confluence of morbidities means that not only is there selective sample attrition due to mortality, but there is increased confounding of variables. In cases of dementia in the oldest-old, when compared to younger people, it is more likely to be related to mixed disease pathologies (Brumback-Peltz et al., 2011).
Studies that are cited in support of the use of biomarkers for AD are based on people who initially present themselves as candidates for AD (Sperling et al., 2011). This methodology is not only based on convenience sample but is also self-selecting. Such non-representative sampling precludes generalization to a wider audience. Having mostly White patient base poses a non-representative research threat since minorities are unrepresentative in AD research and when they are included, show different outcomes (Tang et al., 1998). In the real world, a heavier toll and at earlier ages falls on minority populations (Clark et al., 2005; Haan et al., 2003; Valle et al., 2013). A homogenously White population explains the guidelines’ assertion to connect MCI with AD since with ethnically diverse groups MCI was found to be more unreliable (Low et al., 2012).

**Discussion**

There is ample evidence now showing that there are mediating and moderating factors in the expression of the disease. AD is mediated by education through a process Snowdon identifies as “...cognitive reserve—the capacity of the brain to resist the expression of symptoms in the face of existing neuropathology” (Snowdon, 2003, p. 453). These studies support the hypothesis that brain plasticity offers a possible mechanism through which the brain might be induced to repair itself (Gage, 2003). Overwhelming evidence exists that cognitive exercises have a positive influence on the neurology of the brain. Cognitive training programs have also been associated with delays in the onset of dementia and age-related cognitive diseases. Why the guidelines chose to exclude such burgeoning studies is unclear. What is relevant is to identify the importance of social factors in future guidelines and in any model of the etiology of AD. Non-cognitive variables such as SES, education, literacy, social class—might all have a mediating and/or moderating role in the etiology as well as in the expression of the disease.

In addition, there is evidence suggesting that some people do not conform to the statistical norm in terms of neurological shrinkage. It seems some people escape the correlates of aging. Evert, Lawler, Bogan, and Perls (2003) support this view when they examined death from heart disease, non-skin cancer, and stroke; 87% of male and 83% of female centenarians that they studied delayed or escaped these diseases. Similarly when Harrison, Weintaub, Mesulam, and Rogalski (2012) looked at two groups of older adults 80 years and older compared to 50 to 65 year olds, these exceptional older adults had a thicker outer layer of the brain important for memory, attention, and thicker anterior cingulate—which is responsible for attention. Exceptional people are the Popperian nemesis of these guidelines (den Dunnen et al., 2008).

If we apply the concept of escapers to the brain, then we can say that exceptional older adults escape from damaging their brain, and if they have neuropathology, they have enough reserve to cope with the day-to-day cognitive demands.

**Social impact**

These guidelines usher in a new era of fatalism. “Because no treatment is available for the condition...the prognosis significance of these tests eclipses their therapeutic utility” (Christakis, 1999, p. 12). The effect of these guidelines is to instill a lonely fear of declining cognitive ability: “On the one hand, the future course of an illness is actually for the patient to experience, and the experience indeed often takes place outside of the professional domain—removed from the doctor spatially, temporally, and physiologically”
(Christakis, 1999, p. 63). It is a lonely hopeless journey. Our task as scientists is to define a methodology that allow for an exploration of anomalies in order to fully understand the disease and provide preventing, mitigating, or moderating strategies. Unintended consequences of these new guidelines are stoking the fear of dementia, without hope of any forthcoming remediation.

**Conclusion**

The inductive method of observing the disease and then looking for biomarkers is a false syllogism (Fuller, 2011). Just because everyone with dementia might have neuropathology, we cannot assume that the neuropathology determined the dementia. The theoretical postulation that there is one linear causal pathway from a biomarker causing MCI which then matures into a dementing illness is not supported by a mounting body of evidence. These anomalies are pointing to the necessity of expanding the concept of biomarkers and showing that these biomarkers might be moderated or mediated by other, likely psychosocial, factors. Moderating variables are amiss in the these guidelines. Rather, any future guidelines need to include such variables as education, comorbidities, brain plasticity and neurogenesis, diet, exercise, and meditation (Ornish et al., 2008) and not to bypass culture and ethnicity (Clark et al., 2005; Haan et al., 2003; Valle et al., 2013). It is also amiss that there is no discussion of how epigenetics might modulate the genetic predisposition to AD. Are biomarkers the neuropathology of the disease, and is the “disease” the expression of dementia or the neuropathology? Dubois et al. (2010) recommend changing the lexicon “to consider AD solely as a clinical and symptomatic entity that encompasses both predementia and dementia phases” (Dubois et al., 2010, p. 1118) leading to potential situations where despite having normal memory and behavior you might still get diagnosed with dementia.

There is also a need to identify the type of MCI that leads to AD. The relationship between so-called Alzheimer’s changes and normal aging processes should be distinguished. One of the distinguishing features is the speed of attrition. Even though we still do not know enough about normal aging processes, sudden attrition might be indicative more of disease pathology. A longitudinal perspective is crucial for making such distinction. There are emerging tests that show promise in differentiating memory abilities affected by cognitive impairment from those affected by aging (Brainerd et al., 2013).

These are all important theoretical consideration that need to be part of an established “research agenda for future progress.” The only way to define a future agenda is to treat anomalies in the data not as errors but as shedding light on hidden and yet unknown dynamics. The NIA guidelines do not establish a research agenda for future progress. Instead the guidelines represent a dying proposition of biological determinism that exclude social and environmental factors as reflected in the emerging science of epigenetics and neuroplasticity.

**References**


**Author Biographies**

**Mario D Garrett**, PhD, is Professor of Gerontology at San Diego State University. Previously, he worked as deputy director with the United Nations International Institute on Aging where he was the team leader of a UNFPA-funded project in the People’s Republic of China. Professor Garrett has held research appointments at universities in Surrey/London School of Economics, Bath, Bristol, New Mexico, and North Texas. He is a visiting professor at Bogazici University, Istanbul, Turkey and at Onemda VicHealth Koori Health Unit, Centre for Health and Society, Melbourne School of Population and Global Health, University of Melbourne, Australia.

**Ramón Valle**, PhD, is a Professor Emeritus in Social Work and Gerontology from San Diego State University, specializing in cross cultural caregiver research in Alzheimer’s disease and associated dementias, as well as in minority mental health. He has served three terms on the National Board of the Alzheimer’s Association, the last one dating from 1999–2001. He has also served on numerous advisory Alzheimer’s Association committees and consultancies dating from 1984 to 2012.