Original article

Ethical issues in early diagnosis and prevention of Alzheimer disease

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This paper considers ethical issues related to early diagnosis and all forms of prevention of Alzheimer disease and related conditions. It offers a critical view of the current state of scientific, clinical, and social responses to the growing number of older people with cognitive challenges, and suggests how priorities going forward should be different from those receiving most attention today. We begin with a review of global policy efforts, consider the fundamental goals of prevention, examine issues surrounding early diagnosis, explore more deeply values associated with efforts to prevent age associated cognitive decline, and conclude by considering often unexplored ethical issues that contextualize the field and should influence our approaches to the future.

Current policy development priorities and issues

One manifestation of the growing concern about the impact of age-related cognitive challenges in the world is the development of national and global strategies to address dementia. International organizations such as Alzheimer’s Disease International and the World Health Organization, as well as a growing number of countries, have developed comprehensive plans. Virtually all strategies advocate early diagnosis, education of the public, improving care, and research to develop more effective treatments for AD and related conditions. Increasing attention is also being paid in policy statements to the public health aspects of dementia and on prevention, rather than just focusing on finding a medical cure. Many plans and policies are focusing broadly on dementia rather than just AD. This is in part because AD is now being seen as a heterogeneous spectrum of conditions, and there is a growing recognition that public responses need to address the wide range of persons with cognitive...
impairment who often have similar needs regardless of specific diagnosis. Often forgotten in policy efforts (like Dementia Friendly Community efforts) is that dementia affects people of all ages, not just adults.

These policies are emerging in concert with other scientific and social trends relevant to addressing the challenges of dementia. First, despite billions of dollars being invested in finding cures and other biological interventions, no new therapies have been found or seem to be emerging, and the field is in some degree of disarray regarding future directions. Major pharmaceutical companies are beginning to disinvest, as evidenced most recently by Pfizer discontinuing its research and development in AD and Parkinson disease. Second, psychological interventions (so-called “nonpharmacological” approaches) are being demonstrated to be valuable in improving quality of life for those affected by dementia. Finally, evidence is emerging that community and public health interventions (eg, increased access to education and health care, removal of lead from gasoline, etc) may actually be reducing rates of dementia over time. So how is policy development tracking these trends?

What are some of the ethical presumptions in these policies? The first presumption is that we understand enough about the conditions themselves to prioritize our approaches to addressing the challenges. What are we researching, and what are we telling people about what we know and do not know? For example, AD, which receives much of the attention as the most common cause of dementia, has been found genetically, pathologically, and clinically to be quite heterogeneous. Is it a single condition? With this unfounded assumption of diagnostic clarity, a challenge to corollary emerges that early diagnosis is preferable to a delayed diagnosis. The various different forms of AD likely have important clinical differences such as rates of progression and prognosis. By using a single label, AD, which receives much of the attention as the most common cause of dem entia, has been found genetically, pathologically, and clinically to be quite heterogeneous. Is it a single condition? With this unfounded assumption of diagnostic clarity, a challenge emerges that early diagnosis is preferable to a delayed diagnosis. The various different forms of AD likely have important clinical differences such as rates of progression and prognosis. By using a single label, AD, which receives much of the attention as the most common cause of dementia, has been found genetically, pathologically, and clinically to be quite heterogeneous. Is it a single condition? With this unfounded assumption of diagnostic clarity, a challenge emerges that early diagnosis is preferable to a delayed diagnosis. The various different forms of AD likely have important clinical differences such as rates of progression and prognosis.

The second major presumption is that more medical research will lead to more effective therapies and that these imagined medications will save money. For example, the Alzheimer’s Association issued a report that claimed that such a medication could save trillions of dollars over the decades to come. However, they assumed in their model that the promised drug would have a cost of “zero.” Such claims are irresponsible in my view. Public health interventions are likely to be more effective, including cost effective, than drugs and will improve the health of people with various other conditions, besides dementia.

The final assumption is that the approaches advocated for in the international and national plans represent a reasonable use of social resources given other huge competing health and social problems, such as environmental deterioration and social injustice. What are the opportunity costs of investing so much in dementia, particularly in biomedical approaches? Climate change and poverty, through the intervening variables of environmental and social determinants of health, are existential threats to our communities and even civilizations and species.

**Goals of prevention and related ethical issues**

Prevention is often described as primary, secondary, or tertiary depending on when the intervention is offered during the course of the illness and what the expected outcome is. In primary prevention, the intention is to stop the condition from appearing in the first place. In secondary and tertiary, the condition will have manifested but the aim is to delay or arrest the condition (secondary) or any other health and functional consequences that might be associated with the main illness (tertiary).

Fundamentally, the goal of prevention is to improve length, but particularly quality of life. Here, a challenge is that the cognitive difficulties of a person with dementia may limit their ability to report the subjective aspects of quality of life that are critical in this measurement domain. As a result, clinical trials often focus on activities of daily living or mood as important components of quality of life, although most believe that quality of life encompasses more than function and mental health, including one’s own personal interpretation of the quality of one’s own life. These issues link to surrogate decision-making. When someone becomes cognitively impaired enough to impact their judgment about their own health, they will need someone else to make or assist in decisions. Should the patient’s repre-
sentative make their decision and assessment of quality of life using substituted judgment based on a sense of the likely choice of the person with dementia (perhaps guided by an advanced directive) or best interests as perceived by the surrogate? People with any degree of cognitive impairment (and even those with normal intelligence) have difficulty making decisions about clinical issues and research participation. Who fully understands genetic risks or the likelihood of the success or dangers associated with medicines in early or even late stages of development? Quite clearly the experts do not, and worryingly they have an intrinsic bias towards encouraging people to participate in trials. In general, the best ethical standard is to reflect the voice of the affected person in the decision-making conversation space, realizing that people's views of cognitive impairment change as their symptoms progress. Open and appropriate communication strategies sensitive to levels of education and degree of intellectual impairment are key.

In addition to the effects of individuals directly impacted by the diagnosis, others in society may also be affected. Given that social resources employed to address one particular condition, like dementia, might not be available for other health priorities, like vaccination or eradicating lead poisoning in children, the allocation of resources in one domain of medicine will potentially affect the quality of life of people with other conditions. Balancing priorities is key, as well as looking for win-win situations. Eliminating the brain damage associated with lead poisoning would help children, and, from a long-term perspective, help them become brain healthier elders. Allocations to social programs such as dementia and age-friendly community development could actually make communities friendlier for children and in fact all of us, for instance by creating better signage, safer and healthier public spaces, and easier to navigate public transportation systems. Currently however, it is not clear that synergies will emerge because of the narrow foci of groups and lack of coordination involved in community transformation. Moreover, most such efforts ignore the deteriorating natural environments due, for example, to climate change or land misuse (e.g., fracking, urban sprawl).

Scientists and clinicians often ask for more resources to support their own activities. Researchers almost invariably conclude papers with a statement such as “more research is needed.” Often ignored is that interventions in non-health domains may have longer enduring effects. For example, artists and musicians are frequently ignored in advocacy and funding efforts, even though evidence suggests that people with dementia can benefit from their approaches. And besides, if we wish to “normalize” people with dementia and reengage them in the community as fellow human beings, how much evidence do we need that people with dementia—who have spent lifetimes enjoying aesthetic experiences—are stimulated by such activities just as the rest of us are? The spectrum of cognitive impairment from subjective cognitive impairment (SCI), though mild cognitive impairment (MCI) to activities-of-daily living impairing dementia also challenges this idea that one day you are just enjoying art and music and then you become eligible for art and music therapy and special programs.

The nature of evidence to change clinical practice and policy is a central challenge. Medical professions assert the value of basic medical research such as animal models and randomized controlled trials (RCTs). Animal models have had limited predictive value about the effects of biological interventions, and it has often been the case that drugs that cure so-called “Mouse-heimer’s” fail to make an impact in human beings. Billions of dollars have been spent trying to prove the value of drugs and biologics through RCTs. Yet the epistemological and practical limitations of this dominant epistemology are often neglected; for example, limits in the generalizability of the results of RCTs, the small clinical value of some research outcomes, and the relative neglect of long-term safety. Data does not “speak for itself,” as is sometimes asserted, and those who produced or stand to benefit from positive data are often biased in their interpretation, even as they promote “scientific objectivity.” Trials supported by industry are more likely to favor their potential product.

More complex interventions, such as educational programs and community day programs, are often more difficult to evaluate using RCTs. The blinding protocol and choice of control group can be challenging. And unlike drugs where usually each participant takes a uniform pill, specific clinical protocols in activities such as the arts are often intensely personalized. There is, in fact, a danger that we study interventions that are easy...
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to study but ultimately less worthwhile, while ignoring those that do not have the resources or even appropriate methodologies to assess and which, like art and music, might prove ultimately highly impactful.

Diagnosis of what and how early is early?

In early diagnosis, the question of what specific conditions one is trying to diagnose becomes critical. Lack of clarity can lead to misunderstanding and longer periods of potential anguish over any misapplied label. Moreover, not often asked is how a label affects the person so diagnosed in terms of providing information (or not) that might lead to changes in perception of and action in one’s life. Those who favor the early diagnosis of AD are commonly confused by changing disease concepts and terminology themselves. For example, genetic, pathological, and clinical research of the last several decades have shown considerable heterogeneity in what we continue to singularly label as “Alzheimer disease,” as well as great difficulty in differentiating “normal” aging from pathological conditions. The grand quest for subtypes that might respond differently to different therapies has mostly been a failure. Mixed-cause dementia, which features not only plaques and tangles, but other pathologic features such as vascular changes and Lewy bodies, is the most common form. Personalized medicine based on genetics seems an elusive goal and may in fact dehumanize people through its biological determinism. Was it a political success, but ultimately a clinical and scientific problem, to label senile dementia (after age 65) as “Alzheimer disease” when this classification was originally reserved for the rare early onset (before 65) dementia that was frequently caused by autosomal dominant genes? This decision in the 1970s has effectively created an epidemic of AD and fostered expectations of a single cure.

And if we are to diagnose early, how early should we test? Should we test fetuses for the presence of autosomal dominant mutations? Should we inform those over 18 who carry a determinist mutation or even a susceptibility gene like APOE4? The latter is a risk factor relevant to every human being since we all carry genes for APOE, as a protein involved in normal cholesterol metabolism. Moreover, APOE4 is pleiotropic, meaning it alters risk for a variety of neurological and cardiovascular conditions in addition to so-called AD. Research has shown that people find genetic risk information difficult to understand and often revert to their perceived risk prior to testing, throwing into question the utility of genetic tests in the clinical setting.

The lessons from another autosomal dominant dementia, Huntington disease, have taught us that even diagnostic disclosure of causative genes are fraught with challenges. People sometimes do not want to know their gene status. And discrimination against asymptomatic people on the basis of their genetic is still possible despite legislative efforts to protect such information from disclosure to others such as employers or long-term care insurance vendors.

Other forms of degenerative diseases that are mistaken for AD clinically are less well-known, such as hippocampal sclerosis. As noted above, considerable overlap occurs among different forms of degenerative diseases including Parkinson disease, frontal lobe dementia, and AD. Our understanding of the relationships between vascular dementia and degenerative dementias are now less clear than we thought 25 years ago.

Even when symptoms become manifest how early should we push our diagnostic labels? SCI requires only the complaint that one’s memory or other intellectual abilities are getting worse over time. Aging Associated Memory Impairment (AAMI) and Age Associated Cognitive Decline (AACD) were invented concepts representing earlier stages of loss where some cognitive impairment can be found on neuropsychological testing. Finally, we get to the most common pre-dementia label—early and late MCI. Depending on how one defines them statistically in relationship to so-called norm ality, the label MCI could be applied to millions more people. Yet studies have shown considerable variability in how experts use the term, how people respond to this statistically precise but conceptually vague term, and how they progress once labeled. MCI is said to affect function not at all or only a little. But to what degree is still controversial? Does early diagnosis mean using all these labels?

The word “timely” diagnosis is often used to replace “early” in discussing the diagnostic process. Timely means occurring at a favorable or useful time. But whose favor or usefulness is being considered here—the doc-
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Diagnosis is often linked to conversations about existing or promised future therapies. All patients should get advice about lifestyle regardless of diagnosis or not. It is possible that people with a diagnostic label are more likely to actually implement lifestyle changes, but this is not certain. Moreover, do we have to label people as sick before we encourage healthy prevention-oriented strategies like changes in diet, exercise, and so on? It is often said that we diagnose early to encourage people to enroll in trials. But is this ethical? Clinical and research domains should remain separate. Controversy about whether amyloid plaques or tau tangles are the essential pathological features leads to considerable confusion about what the therapeutic target really ought to be and in the end to failure in clinical trials. 

Ethical issues in prevention

The biomedical orientation towards precise and specific diagnosis steers us towards targeted drug and biologic therapies, for treatment and prevention. However, there is much we can do to promote health that does not require specifically identifying diseases. Brain health has become a popular term that focuses people’s attention on what they can do to prevent cognitive decline, not to mention motoric and other functional neurological and psychological declines. This form of health practice based around diet, physical exercise, social engagement, cognitive stimulation, as well as treating medical risk factors, is not really specific to the brain. General body health can be supported through these activities as well.

Experts would like to have more biomarkers to employ, like blood, CSF, or imaging measurements. In fact, they surmise that a panel of biological tests will eventually be needed for diagnosis in the future. Clinical diagnostic assessment such as memory testing is seen as too insensitive and variable. Biological measures are often believed on faith to be more objective, reliable, and real. Various CSF markers and neuroimaging techniques are already being used in research. It is ethically unfortunate, however, that research tools are often brought into clinical practice before their validity and utility have been demonstrated. Amyloid imaging in the United States is a case in point; yet the scans are of unclear benefit. Scans are reported as “positive or negative,” even though more quantitative information is available than just a report of “yes or no” suggests. This method of feedback creates considerable confusion amongst those who receive the label of having a positive amyloid scan and are thus placed at elevated risk for dementia. (How increased is elevated, one wonders). Recent research diagnostic criteria go even so far as to make a diagnosis of AD possible without any clinical features being present, based exclusively on biomarkers. This approach may create easier drug targets for the pharmaceutical industry, but will it benefit patients to acquire a stigmatizing “disease” label in the absence of any symptoms? And we must remember there is growing considerable controversy about whether the amyloid therapeutic strategy makes sense in the face of uncertain science and failed trials.

Lifestyle variables, such as lack of exercise and poor diet, have been relatively easy to identify but harder to modify. We need more research on how to modify individual behaviors and how cognitive impairment affects such approaches. However, it may be more effective to change communities and culture through educating groups of people rather than focusing on individuals. Safe green spaces in which families can walk together may be better investments of resources than personal exercise programs, for example.

The one area of health enhancement that could be said to be specific to “brain” is cognitive and social activity. Here we find another vast space of commercial and scientific interest in prevention, namely the brain fitness and neurotechnology space. Proponents of these approaches argue for keeping one’s mind active by using digital devices such as computer games or mobile apps. The literature here is large and of variable quality. There is some evidence that one can improve performance on the specific task featured in the game itself, but evidence for generalizability beyond the specific fitness game task to overall cognitive abilities and especially to slowing decline is just not there, despite the lofty claims made by marketing departments.
Of course, the traditional way that we have kept ourselves cognitively active is through learning, both in formal and informal settings. The two main consistently identified factors that relate to preventing dementia include age and level of education. Level of education is a complex variable because of covariates, such as income, diet, and environmental factors like quality of the community. It is unclear whether people who are born with brains that are more resistant to cognitive aging get more education, or whether education through schooling and work and other activities itself builds so-called brain or cognitive reserve. Cognitive reserve is a poorly understood concept that tries to capture the variability in how people with similar degrees of brain pathology function more or less well. Education and exposure to lifelong intellectual challenges are said to build so-called cognitive or brain reserve.

Measuring the impact of educational interventions is difficult. That said, there is some evidence that keeping cognitively active improves quality of life. One such study involved observing the effects of people with mild to moderate dementia volunteering in a public intergenerational school in which elders worked one-on-one with young students on tasks such as reminiscence and reading. It is reasonable to think that purposeful and meaningful activities that create a legacy of having contributed to the lives of children might have a profound effect on people’s lives including their brains.

We have known for some time that brains can change because people can learn. Yet, neuroscientists have aggressively promoted neuroplasticity as a major discovery. Yes, the newfound mechanisms, such as new neuronal growth in the adult brain, are exciting but are of limited value in actually fostering psycho or social plasticity, i.e., behavior and cultural change. We need broader models of health such as ecopsychosocial approaches in order to ask how relevant are specific diagnoses and what the best ways of approaching brain and cognitive health are.

The prefix “eco” turns us towards the issues of preventing dementia by examining environmental effects on cognitive health. Unfortunately, long-standing examples exist in the case of pollution with heavy metals such as lead, mercury, and arsenic. Yet perhaps the greatest threat to the quality of life of people with dementia, and in fact all of us, is ultimately global climate change. Drought, floods, fires, and other environmental disasters affect individuals with cognitive impairment more than others because they cannot plan for the disasters and avoid the danger and as well as those who are cognitively intact. My own belief is that educating people together across the life course about our responsibilities for future generations and about what we can all do to address climate change may be the best long-term way of preventing cognitive impairment. And in that process we might all recognize that we ourselves have difficulties with remembering the past, planning for the future and with our basic and instrumental activities of the living, such as finding healthy food and dealing with our biological and industrial waste products. We need to learn to appreciate limits to our individual and collective behavior. Perhaps a degree of wisdom might be achieved if we recognize some “dementia” in all of us.

Deeper ethical issues

Ethics is not monolithic. Some bioethicists focus on principles like autonomy, beneficence, and justice, others on analysis of narrative, some on empirical findings, and more rarely, others emphasize virtue and the character of individuals and groups, such as organizations of professions. Even more rarely, bioethicists will question their own roles and moral standards.

However, most ethicists would agree that the field has a responsibility to surface value-related issues for discussion and assist in their analysis and action. Traditional biomedical ethical issues well represented in the literature relate to early diagnosis and prevention and include topics such as informed consent, which in turn includes research issues like assessment of likely risk and benefit, and clinical issues related to care, for example surrogate decision-making and end-of-life care. But there are deeper bioethical issues that also require examination.

One particular prominent issue today is the role of science in society and the potential dangers of unbridled faith in science, so-called scientism. Alzheimer experts have been saying for decades that the cure or at least more effective therapies will be available shortly. Yet this has not happened. Is this excited messaging largely to promote professional fame and fortune allied with the pharmaceutical industry or is it a characteristic
and justifiable zeal for the potential of scientific and technological breakthroughs? Despite many changes in rules and regulations to govern the relationships between professional and industry, conflicts of interest still abound between clinical scientists as detached experts with a moral responsibility to guide the public and as private individuals enhancing their own financial interest (often not fully disclosed) that bring personal and/or organizational gain.26

Moreover, increasing attention is being paid in science to the problem of replication of results.23 The pressure to publish has increased for career advancement, as has the encouragement from media relations offices in universities to promote academic discoveries very early in their development. The Alzheimer’s field is full of unreplicated results and unfulfilled promises.2,46 We have had many triumphantly announced “breakthroughs” in the press that lead to little or nothing of clinical or social value. Maybe so many unfulfilled breakthroughs represent a breakdown in scientific process and public trust. For example, the Alzheimer’s Association in the United States claims that we could save trillions of dollars over the next few decades if we develop an effective medicine by 2025 that they predict will occur if we invest enough in research. One might imagine that they might include some estimate of the cost of the drug. However in their pharmacoeconomic model, the cost of such a promised (but as yet undelivered drug) was set at zero, ie, a free drug. Is this a responsible way to try to influence policy?24 Science has come to be dominated by market capitalism, that will either enhance or destroy future life on this our only planet. It is time to rethink what it means to be a caring human being who ages and dies, perhaps with cognitive impairment at the end, but leaves a legacy that will either enhance or destroy future life on this our only planet.

Dementia and AD as social phenomena are much more important cultural issues than just the challenges faced by these clinical conditions.44 If we were to address dementia through appropriate community and environmental approaches, we could address the overall health of the human population, as well as other living creatures. If we could truly see the limitations of our current molecular reductionist obsession with cure and rise above our self-serving values to a sense of responsibility for investing and innovating for the future, we might actually survive and flourish as a species. We are living in a time of great derangements in our collective thinking and distortions in our values. Dementia is one such domain in which our promises and expectations are mismatched with our actual deliveries and the real constraints of the world in which we live. It is time to rethink what it means to be a caring human being who ages and dies, perhaps with cognitive impairment at the end, but leaves a legacy both as an individual and as a member of a generation that will either enhance or destroy future life on this our only planet.

Disclosure/Acknowledgements: The author thanks Danny George for his collaboration and for his comments on the manuscript and Spitz Foundation and the Shigeo and Megumi Takayama Foundation for financial support.

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