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Commentary on “A roadmap for the prevention of dementia II: Leon Thal Symposium 2008.” “Big Asks”: What can be changed to increase and speed progress on Alzheimer's disease research and treatment?

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Abstract

The focus of the 2008 Leon Thal Symposium was to identify issues and changes that might be facilitated by government agencies, industry, or the academic research community that might move the field forward: “Big Asks” for fundamental shifts in the way we deal with Alzheimer's disease (AD) research. These items are therefore aimed at macro rather than molecular changes, but their impact will carry to the molecular level of research to increase our understanding of etiology and treatment of AD and associated disorders.

1. Easier access to Center for Medicaid and Medicare Services records for research purposes

The first thought that comes to mind when considering the use of Center for Medicaid and Medicare Services (CMS) lists is the possibility of determining disease burden: how many dementia subjects are there in the United States? Although the CMS records could be queried to provide some sort of prevalence estimate, that estimate is likely to be a rather soft one. Dementia is still rather poorly and incompletely diagnosed in the primary care setting, and there might be a number of practical reasons why, even if diagnosed, it would not be included or reported to Medicare for reimbursement, not the least of which is whether reimbursement for specific services could be obtained. Certainly, action could be taken to change and improve what would be reimbursed. Furthermore, initiatives could be launched among the primary care physician community to increase dementia diagnostic sensitivity: more completely recognize and more adequately diagnose AD and other forms of cognitive impairment. Both of these are big shifts in the status quo.

With the implementation of the Health Insurance Portability and Accountability Act (HIPAA), a wave of new restrictions on access to health care data was established. The HIPAA rules included safeguards so that personal information would not be available to those who did not have a need to know, with the hopes of avoiding potential discrimination by employers, insurance companies, and any number of other entities. The spirit of HIPAA was admirable and righteous, but because of variability of interpretation and the zeal for full compliance exhibited in some institutional review boards, it also seems to have had a chilling effect on the ability to accomplish descriptive and analytic observational research in the academic community. The HIPAA rules should be reexamined to determine whether

revisions could be made that would facilitate academic research without compromising patient welfare, especially with regard to CMS and other research databases.

Because the first and obvious thoughts regarding the CMS lists are of “case” determination, a much greater value that could be obtained through easier access is often overlooked. That greater value lies in the determination of and selection of “control” or comparison group subjects. Cases entered into CMS from primary care may be recognized, evaluated, and diagnosed differently and with different levels of understanding than would occur at Alzheimer's disease centers. Certainly, the potential for misclassification (false-negative diagnoses by default) exists in this group of presumptive controls, in the same general way as it would apply to complete identification cases, as noted above. However, the ability for research investigators to begin with presumptive lists of potential controls would greatly facilitate the progress of both descriptive and analytic observational research. At the aggregate level, for example, with available CMS data, such a comparison group might be able to provide important descriptive and hypothesis-generating results. The CMS controls could be compared with a “case series” of AD subjects available at a clinic or research institution, avoiding the potentially biased selection of “controls” who are only case spouses or perhaps are those hospitalized for reasons other than dementia. As is often said, what we observe as differences between disease cases and normal controls is not just a function of disease case characteristics but of the control/comparison group against whom they are evaluated. In that regard the increased availability of CMS lists to researchers, because of the broad, unselected, and inclusive character of these data, could facilitate research at many levels from data mining to hypothesis-driven analytic studies. This step would provide much greater value to research than, for example, post-study combination of clinical trial databases (which are essentially limited to cases anyway) for subsequent data mining because of the highly selective nature of the case enrollment into clinical trials.

2. Research criteria for the diagnosis of AD must be revisited and revised

The diagnosis of AD (and other dementias as well) has understandably, yet perhaps unfortunately, proceeded in reverse of how the disease occurs. The gold standard for disease diagnosis can only be obtained at autopsy many years after onset. Although this is faithful and hard evidence that the specific pathologic features consistent with AD description have actually occurred, it is unavailable for most and probably does not benefit the patient in question. The clinical diagnostic criteria (National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer's Disease and Related Disorders Association and Diagnostic and Statistical Manual [of Mental Disorders], Fourth Edition) were essentially formulated in the 1980s and have served well to characterize the clinical definition of AD (and dementia). The neuropathological definitions are also dependent on clinical expression of disease. So, those with severe enough pathology to be counted as “definite” or “high-likelihood” AD, but who are not yet clinically demented, would not be considered to have AD. This appears to need re-thinking if we are to identify disease pathology early, and correctly compare those with the disease and those without. By the time the clinical diagnostic criteria can be met it is quite likely that the patient might be too advanced to help by any current means. Certainly, work must continue to find appropriate treatments for those who reach this diagnostic level, but at the same time we must seek earlier means of disease recognition to increase the likelihood that new treatments might be effective at least in arresting the disease process if not to actually “cure” it.

A step in that direction was taken by defining mild cognitive impairment (MCI) [1]. Again, however, this clinical definition was based on symptomatic presentation, and it was also broad enough to include multiple etiologies, eg, AD, vascular, Lewy body disease, and frontotemporal lobar degeneration, among others. Possibly from among this overall MCI

classification an early AD subset could be reliably characterized, but still the disease process might have begun years before. Concurrent with progressing research on early AD and MCI, biomarkers have become a fashion statement. The various biomarkers are often evaluated against the clinical disease or even the autopsy gold standard for consistency, but for the most part they are taken cross-sectionally with clinical disease. Although this is likely a necessary step in the validation of a disease biomarker, it raises some concern as well. Effective secondary prevention efforts should be launched against targets before clinical symptoms of the actual disease (ie, cognitive impairment).

Newer neuroimaging modalities, including those that illuminate amyloid deposits or show metabolic changes as well as those registration techniques that might show changes in brain structures before clinical disease expression, might eventually allow us to reliably and validly determine those asymptomatic persons who have the pathologic disease process beginning. In a similar fashion, components with cerebrospinal fluid might also allow early identification of asymptomatic disease. At least in the research setting, determination of the existence of disease pathology or markers of that pathology in clinically asymptomatic subjects must be a goal we should work toward. We do not know with certainty at this point whether, for example, the amyloid seen in the imaging process is an appropriate measure of disease, but it is clear that substantial efforts need to be focused at the molecular level to bring about macro level changes in disease prevention, and the research criteria for disease must be revised to accommodate that as soon as we have the ability and understanding to do so.

Such early and asymptomatic diagnosis measures might carry with them many dangers and unanswered questions. For example, if we do not have available treatments, what would we offer persons presumptively identified as having the disease process; what would the likelihood of these persons be to develop clinical disease without any treatment; what would be the impact on their quality of life, family, social and occupational functioning, or insurance of such a determination? These potential negatives would force the asymptomatic diagnosis to be held confidential to the research studies unless and until effective treatments and other safeguards were in place. Nonetheless, continuing to focus our efforts to determine the cause of AD on the terminal end of the process will likely slow our progress and possibly also provide distracting and spurious clues concerning etiology.

3. The Alzheimer's Disease Centers program should seriously consider establishing a population-based design for subject enrollment at each Center, and each Center should be considered part of the aggregate, larger multicenter study

There is a great deal of misunderstanding about what comprises a population base, and partially because of that many would likely say this is impossible. Arguably, perhaps nothing has propelled observational research in cancer more than the underlying population-based design of the various cancer registries throughout the U.S. and the world. In its simplest sense, a population base might be limited to a specific set of persons who would be internally monitored for the occurrence and enrollment of all new cases of disease. This could take the form of a cohort study design, where a large disease-free group of individuals are followed longitudinally and new cases are diagnosed (according to whatever standard criteria) as they occur. It also could be as complex as establishing a surveillance network within a geographically defined area to identify and refer and/or collect data on all new cases of disease among residents of that geographic area as they are recognized by physicians in the community. This more geographic interpretation is consistent with the usual understanding of the term. The inclusive nature of this population-base description

ensures that subgroups (and probably risk factors) will be represented in the frequency of their usual occurrence in the defined population, and that will likely be similar in other population-bases of similar composition. Distributions of age, gender and ethnicity, for example in the population-base would be known and could inform the analysis of disease incidence and prevalence in those specific groups. In other words, the cases or control subjects so obtained would be representative of the underlying population. Such a population base would avoid drawing selection-influenced conclusions which might apply to an internally valid study based only on British doctors or confined to deceased mid-western clergymen. Internally valid studies can certainly be conducted within these cohorts and defined as “population-based”, in the strict and limited sense, but their findings may not generalize to the garden variety disease seen in communities. When characteristics related to subject selection begin to predominate over factors associated with disease, a crisis of inference occurs, true causes may be obscured and false causes exaggerated, misleading investigators. The key to determining the population-based nature of a study is the ability to enumerate, identify, and describe the underlying population that gave rise to the cases. The additional benefit of this approach is that all non-cases from the population base would form a reservoir from which to draw controls that would, by definition, be comparable to cases. For example, if our surveillance net of primary care physicians and neurologists would capture all new diagnoses of AD occurring in residents of a standard metropolitan statistical area, then the remaining residents would automatically become the reservoir of potential controls. Additional linking of these residents to CMS data might further facilitate and benefit analyses.

This shift in the status quo for the AD Centers program (ie, from samples of convenience) would require substantial change in thinking and understanding at the AD Centers as they currently exist. However, once implemented, it would not limit but would enhance the types of internal projects that could be done at centers. The population-based subjects would likely provide greater strength of inference to most clinical, basic, and translational studies that would be mounted. The aggregate of population-based subjects from all AD Centers nationwide would, of course, facilitate much better estimates of disease incidence and prevalence (regardless of the macro or molecular level of diagnosis chosen) than currently exist. Such a structure would also greatly facilitate and provide a more valid base from which to launch large center-wide studies such as genome-wide association studies. The basic AD Center structure is in place already, and the National Alzheimer's Coordinating Center could easily adapt the current data collection and database management system to form a population-based repository for access by researchers. Making the change at existing Centers would not only require the will and the goodwill of National Institute on Aging and of the Center Directors, but also additional funding of course.

References

1. Petersen RC. Mild cognitive impairment as a diagnostic entity. *J Intern Med.* 2004; 256:183–94. [PubMed: 15324362]