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Perspectives

Commentary on ''A roadmap for the prevention of dementia II: Leon Thal Symposium 2008.'' A national registry on aging

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As the field of aging and dementia evolves, it becomes apparent that there are likely multiple underlying continua of clinical and pathologic substrates that characterize progression. On the clinical side, there is a natural progression from normal cognition through mild cognitive impairment (MCI) to dementia. Correspondingly, on the neuropathologic side, there is a gradual accumulation of pathologic markers that likely develop over years and probably decades. The challenge is to develop reliable and valid correspondences between the clinical features and the underlying neuropathologic markers that are consistent and meaningful. Numerous studies have demonstrated that clinically normal individuals late in life can harbor significant pathology in the brain, and, conversely, some individuals who are demented have relatively little demonstrable pathology [1–3]. The correlations are imperfect.

Currently, we make arbitrary distinctions among clinical categories such as normal aging, MCI, and dementia. Although we all recognize the artificiality of dividing a continuum into discrete categories, the exercise does serve a purpose in allowing us to communicate the clinical significance of findings to patients and also promotes interactions among physicians and scientists [4–6]. Similarly, from a neuropathologic perspective, we make arbitrary distinctions regarding the meaningfulness of the development of amyloid deposits in the brain and the spread of neurofibrillary tangles throughout the brain [7]. Again, although certain demarcations are necessary for communication, the clinical significance of the development and spread of these markers needs to be clarified. As mentioned, the clinical-pathologic correspondence between these two continua is variable.

This type of discussion begs for the development of a collection of persons across the age spectrum on whom extensive demographic, clinical, imaging, and biomarker data would be available. It is only through the longitudinal study of all of these measures in concert that we will be able to disentangle these important questions regarding the development and progression of diseases of aging.

1. Challenge

As these continua become investigated in greater depth, it becomes necessary to develop markers of progression along the underlying dimensions. To a large extent, the clinical indicators are available and are being refined, consisting of cognitive, functional, and other behavioral indices [8]. With respect to the pathologic spectrum, serial imaging and chemical biomarkers are being developed to tap into the underlying status of the brain and central nervous system [9]. One of the largest efforts on this topic is the Alzheimer's Disease Neuroimaging Initiative (ADNI) sponsored by the National Institute on Aging, the Foundation for the National Institutes of Health that incorporates support from industry and nonprofit organizations [10]. This study involves 58 centers in the United States and Canada and is designed to evaluate the utility of imaging and chemical biomarkers at tracking disease progression from normal to MCI and ultimately to Alzheimer's disease (AD), with the anticipation of developing surrogates for use in clinical trials. The ADNI project has recruited a selective group of participants that closely match clinical trials' populations [11].

In a somewhat similar vein, the National Institute on Aging Alzheimer's Disease Centers Program recruits and tracks individuals characterized as normal, MCI, and AD, and through the National Alzheimer's Coordinating Center it has developed a national database of subjects enrolled in these research centers. These subjects are also being studied with a variety of neuroimaging techniques and biomarkers.

Finally, several population-based projects are underway to assess a decidedly different set of subjects. These studies randomly recruit elderly subjects from a given population and follow them longitudinally. Many of these projects also have neuroimaging studies and biomarkers embedded within

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them. For example, the Mayo Clinic Study of Aging is a population-based longitudinal study of 2000 70- to 89-year-old subjects that uses neuroimaging measures and biomarkers as potential indices of cognitive aging [12]. However, even this study is limited to approximately 2,000 participants because of expense, and consequently, the ultimate utility of the measures must be evaluated on a larger scale. What is needed is a longitudinal nationally representative registry on aging to serve these purposes.

2. National registry

It is timely to consider the development of a national registry on aging to provide a substrate for validating the clinical, imaging, and chemical biomarkers that are forthcoming from the smaller types of studies discussed above. This type of registry could serve as a study of all cognitive aging: successful aging, typical aging, and impaired aging including MCI and dementia. A registry such as this could be distributed geographically to include all regions of the country, ethnic groups, urban and rural populations. By including all aspects of cognitive aging, successful, typical, and impaired aging, there would be no stigma of an Alzheimer's Disease Registry. Rather, cognitively healthy subjects could be studied to elicit factors that might lead to optimal cognitive functioning over the life span.

A national registry could establish a large cohort of subjects with certain baseline characteristics. At a minimum, basic demographic, cognitive assessments and perhaps biospecimens for DNA, plasma, and serum could be obtained on all subjects. More in-depth evaluations could be conducted on subsets of participants, depending on specific questions and protocols. Subjects could then be reevaluated longitudinally to characterize their status and change over time. An effort of this magnitude would likely be conducted by using the Internet to capture and store clinical data.

A repository of this scope could serve several purposes. Initially, it could provide valuable cross-sectional data on aging as well as an opportunity to determine the frequency of various cognitive and biospecimen profiles. These individuals could be considered for large-scale intervention protocols on lifestyle modifications, clinical trials, or assessments of the natural history of cognitive aging, imaging measures, and biomarkers. It might very well take an effort of this magnitude to validate many of the indices of plasma, serum, and neuroimaging. A subset of subjects might submit to cerebrospinal fluid analyses if the research center–based studies discussed above indicate that these measures might be useful on a broader population-wide basis.

A significant advantage of national registries would include the provision of well-characterized subjects who would be available for validating surrogates and evaluating therapeutic interventions. With appropriate safeguards for confidentiality, the data from this registry could be made available on the Internet. This strategy has been used with the ADNI and has been remarkably successful. This would serve as a tremendous resource for individual investigators as well as the pharmaceutical industry in planning to undertake therapeutic interventions. An effort of this magnitude would have to be initiated on a limited basis, but the systems and infrastructure could be designed to rapidly expand to encompass a true nationwide sampling of the population. This type of registry would be useful for public policymakers, the National Institutes of Health, academic centers, and industry for multiple investigations of national importance in an aging society. The value of an enterprise such as this would be limited only by the imaginations of potential users.

Issues concerning the oversight of such an effort would be challenging. It might ultimately reflect a cooperative agreement among federal, private, academic, foundations, and other not-for-profit entities. It might take an organization such as the Alzheimer's Association to broker this type of an effort. As a not-for-profit organization, they might be in position to oversee the administration of a project of this magnitude and might be able to use their chapter network to coordinate activities in various geographical locations. The Association might then solicit partnerships with the National Institute on Aging, the American Association of Retired Persons, the pharmaceutical industry, and various academic centers that might benefit from the establishment of this type of registry. The Alzheimer's Association is not bound by ''grant cycles'' in the same fashion as government agencies and consequently might have the latitude for true longitudinal planning. An effort such as this would require unconventional planning and foresight.

The Second Leon Thal Symposium sponsored by the Lou Ruvo Brain Institute served as a forum for the discussion of new initiatives in aging and AD. The proposal for a national registry would be one step in the direction of developing predictors and, ultimately, prevention of cognitive impairment in aging. Although the specific details of a proposal such as this would need to be considered very carefully, the potential benefit to society is likely well worth it.

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