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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 pathological 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 neuropathological side, there is a gradual accumulation of pathological 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 neuropathological 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. While 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 neuropathological 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, while 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-pathological 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 untangle these important questions regarding the development and progression of diseases of aging.

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

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behavioral indices[8]. With respect to the pathological 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 which incorporates support from industry and non-profit 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 (NEJM).

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 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 assessing 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 them. For example, the Mayo Clinic Study of Aging is a population-based longitudinal study of 2000 70–89-year-old subjects using neuroimaging measures and biomarkers as potential indices of cognitive aging (RR). However, even this study is limited to approximately 2000 participants due to 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.

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 may lead to optimal cognitive functioning over the lifespan.

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 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 may very well take an effort of this magnitude to validate many of the indices of plasma, serum, and neuroimaging. A subset of subjects may 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 employed with the ADNI and has been remarkably successful. This would serve as a tremendous resource for individual investigators as well as the pharmaceutical industry 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 as well as 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 may ultimately reflect a cooperative agreement among federal, private, academic, foundations and other not-for-profit entities. It may take an organization such as the Alzheimer's Association to broker this type of an effort. As a not-for-profit organization, they may be in position to oversee the administration of a project of this magnitude and may be able to use their chapter network to coordinate activities in various geographical locations. The Association may then solicit partnerships with the National Institute on Aging, the American Association of Retired Persons, the pharmaceutical industry, and various academic centers that may 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 Alzheimer's disease. The proposal for a national registry would be one step in the direction of developing predictors and, ultimately, prevention of cognitive impairment in aging. While 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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