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Commentary on "A roadmap for the prevention of dementia II. Leon Thal Symposium 2008." A National Registry to Identify a Cohort for Alzheimer's Disease Prevention Studies

Marwan N. Sabbagh, MD[1] and **Pierre N. Tariot, MD**[2]

[1] The Cleo Roberts Center, Banner Sun Health Research Institute, Sun City AZ 85351

[2] Banner Alzheimer's Institute, Phoenix AZ

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The Leon Thal Symposium in late 2008 was convened in conjunction with the Alzheimer's Study Group in an effort to help provide input into what will become the Alzheimer's Strategic Plan to be presented to legislators in 2009. There were many topics covered, including considerations of how to improve legislative funding, scientific review and ways to facilitate and accelerate scientific advancement. The proceedings of this are published in this issue[1].

One consideration discussed is the development of a national registry, which could serve a variety of purposes. For example, it could be used to capture incident cases of Alzheimer's disease, similar to disease tracking done by the Center for Disease Control (CDC) for infections (influenza, HIV, MMR), diabetes, allergies, and infant mortality. Another purpose of the registry could be to capture people who are interested in participating in clinical trials, specifically in prevention, biomarker or treatment studies. Such a registry could be used as a means of creating the large pool of potential subjects needed for prevention trials in the future. Such a registry could also be used to further develop risk stratification methods that might be used to enrich studies and identify non-demented people who are at higher risk for development of AD in their lifetimes.

Send Reprint Requests to: Marwan Sabbagh MD, FAAN, Cleo Roberts Center for Clinical Research, Sun Health Research Institute, 10515 W. Santa Fe Dr, Sun City, AZ 85351, Phone: (623) 876-5328, FAX: (623) 875-6504, Marwan.Sabbagh@bannerhealth.com.

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With respect to the last issue, the concept of risk stratification for AD has been proposed by others; some have developed scoring systems to develop aggregate scores of risk [2,3]. These stratification strategies involve a scoring system assigning points to approximate the hazard ratio identified through epidemiological studies[3]. For example, a family history with a first degree relative with Alzheimer's disease has a hazard ratio of ratio of about 3.0; in such a scoring system, a family history would result in a score of 3.0. Other factors that have been added to this cumulative risk include head injury with loss of consciousness; age; education < 7 years; female gender; hypertension with sustained systolic blood pressure >140 mm; Body Mass Index greater than 30 gms/m^2 and so on. Certain lifestyle variables might be shown to reduce risk, such as novel mental stimulation and/or aerobic exercise, or certain diets[4]. These putative protective factors would yield negative scores in a stratification system to offset contributing risk.

In addition to stratifying people at risk for developing Alzheimer's disease, others have proposed stratification of patients who have developed Alzheimer's disease as a means of identifying who would best be served by neuroprotective or disease-modifying drugs as they become available[5]. Iqbal and others have suggested that since there are subtypes of Alzheimer's disease, different treatment strategies might work according to the subtype. This approach might allow tailored treatment in the future. The possibility of differential treatment effects has already been suggested for the ApoE4 genotype[6].

There have been a variety of registry proposals focused on AD in the US. One of the first was CERAD, the Consortium to Establish a Registry for Alzheimer's Disease [Fillenbaum et al 2008], established in 1986 by a grant from the NIA to standardize procedures for evaluation and diagnosis of patients with Alzheimer's disease. AD subjects and non-demented, control subjects were recruited from 24 NIA sponsored Alzheimer Research programs and other university research programs in the US. All participants underwent standardized diagnostic evaluations and assessment instruments with similar diagnostic criteria applied to all. One of the intents was to delineate the natural progression of Alzheimer's disease. Autopsy conformation was included to confirm the clinical diagnosis. The net result was almost 1,100 carefully screened national participants with Alzheimer's disease and almost 500 non-demented controls [7,8]. CERAD served a useful purpose, but was not conceived as a means to accrue people into treatment or prevention studies.

We propose that the time has come to establish a national registry for people with AD, as well as those without who have a variety of risk factors for AD, for purposes of accelerating enrollment into treatment and prevention studies. This registry would serve as a primary resource for both treatment and prevention trials. It would allow for people who are interested about or concerned about their risk to voluntarily enroll and serve as a collective resource for investigator-initiated, federal and industry trials. A national registry would need to include many thousands of cognitively normal individuals depending upon the risk factor of interest. Enrichment could be on the basis of having a first-degree relative with AD, age, or genotype. A scoring system like the one mentioned above could be applied to all registrants to identify a high risk group. Using genotype as an example, if the risk factor of interest was E4/4 genotype in cognitively normal people aged 60-80, we performed an estimate of how many individuals would need to be available in order to yield a cohort of 200 people who were homozygous for ApOE4. Assuming 40% might not be eligible or willing to be genotyped, about 4M people would need to be available to achieve the ultimate sample size. Similar power analyses could be derived on the basis of the risk stratification scoring system to select an enriched population for a targeted trial.

A prototype of such a registry has been developed in Arizona under the auspices of the Arizona Alzheimer's Consortium. The Arizona Alzheimer's Registry serves as part of a larger process

to enhance participation in clinical research related to dementia, particularly treatment and prevention studies. The process includes efforts to promote awareness of the importance of research, a means of consenting and enrolling into the registry, and creation and maintenance of a database designed to match potential research participants available to research studies in Arizona. Information about the registry was distributed to media outlets with a “call to action” and a phone number and website address. Potential participants are sent a packet of information about the registry, HIPAA authorizations, consent form and a questionnaire regarding health, cognitive and functional status, particular research interests, and geographic preferences for research involvement. Following receipt and review of these forms by mail, enrolled participants undergo a telephone based cognitive and functional assessment[9,10]. Based on this screening process, enrollees are categorized as possibly demented, probably cognitively normal, or possibly cognitively impaired. A consortium physician then reviews the records of all the participants with probable dementia or possible cognitive impairment and authorizes referral to a Consortium site for evaluation and screening for a clinical trial. Those who appear to be cognitively intact are referred directly by registry staff. In cases where there is no study available, the referral is held pending availability of new studies. All data are held in a secure relational database.

It is possible that a process of this nature could be tailored to the needs and goals of a national registry to gather prospectively cases or people at risk or people who would be interested in research studies. Creation of a mechanism such as this might also attract the attention of sponsors or donors to a means to help accrue prospective subjects for research studies. The model lends itself to incorporation of stratification methods that might be used for prevention trials. A process of this nature could be conducted under the auspices of the CDC or through the Center for Medicare Services (CMS). Funding could conceivably come through a demonstration grant from CMS in conjunction with NIH.

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