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DESIGN OF COMPREHENSIVE ALZHEIMER'S DISEASE CENTERS TO ADDRESS UNMET NATIONAL NEEDS

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Abstract

The problem of Alzheimer's disease (AD) exemplifies the challenges of dealing with a broad range of aging related chronic disorders that require long-term, labor-intensive and expensive care. As the "baby-boom" generation ages and brain diseases become more prevalent, the need to confront the pending health care crisis is more urgent than ever before. Indeed, there is now a critical need to expand significantly the national effort to solve the problem of AD with special focus on prevention.

The "Prevent Alzheimer's Disease 2020" (PAD 2020) initiative aims to create a new paradigm for planning and supporting the organization of worldwide cooperative research networks to develop new technologies for early detection and treatments of aging related memory and motor impairments. PAD 2020 is developing an implementation plan to justify: a) increasing the federal budget for research; b) developing novel national resources to discover new interventions for memory and motor disorders; c) creating innovative and streamlined decision-making processes for selecting and supporting new ideas.

Since 1978, the National Institute on Aging (NIA/NIH) established an extensive national network of AD research facilities at academic institutions including: AD Centers (ADCs), Consortium to Establish a Registry for AD (CERAD), AD Cooperative Study (ADCS), AD Drug Discovery Program, National Alzheimer's Coordinating Center (NACC), National Cell Repository for AD (NCRAD), and AD Neuroimaging Initiative (ADNI). However, despite the success of these program and their critical contributions, they are no longer adequate to meet the challenges presented by AD.

PAD2020 is designed to address these changes by improving the efficiency and effectiveness of these programs. For example, the ADCs (P30s and P50s) can be enhanced by converting some into Comprehensive AD Centers (CADCs) to support not only research, but also by being demonstration projects on care/ treatment, clinical trials, and education as well as by seamlessly integrating multi-

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site collaborative studies (ADCS, ADNI, Patient Registries, Clinical Data Banks, etc.) into a cohesive structure that further enhances the original mission of the NIA ADCs.

Regional CADCs offer greater efficiency and cost savings while serving as coordinating hubs of existing ADCs thereby offering greater economies of scale and programmatic integration. The CADCs also broaden the scope of ADC activities to include research on interventions, diagnosis, imaging, prevention trials, and other longitudinal studies that require long-term support. Thus, CADCs can address the urgent need to identify subjects at high risk of AD for prevention trials and very early in the course of AD for clinical trials of disease modification. The enhanced CADCs will allow more flexibility among ADCs by supporting collaborative linkages with other institutions, and drawing upon a wider expertise from different locations.

This perspective paper describes the University of Pennsylvania (Penn) CADC Model as an illustrative example of how an existing ADC can be converted into a CADC by better utilization of Penn academic resources to address the wide range of problems concerning AD. The intent of this position paper is to stimulate thinking and foster the development of other or alternative models for a systems approach to the study of dementia and movement disorders.

BACKGROUND

On June 19th, 2009, a Planning Workshop was convened at the University of Pennsylvania (Penn) by Penn faculty¹ in conjunction with Zaven and Ara Khachaturian of Khachaturian, & Associates, Inc. The goals of this workshop were to: 1) Understand the concepts underlying the mission and deliverables of Comprehensive Alzheimer's Disease Centers (CADCs) formulated by a group of neurodegenerative disease research experts at the Leon Thal Symposium 2008 (1), and as proposed in the Alzheimer's Study Group (ASG) report (2) entitled "A National Alzheimer's Strategic Plan: The Report of the Alzheimer's Study Group" which was presented on 24 March, 2009 to the Senate Committee on Aging (<http://aging.senate.gov/>); 2) Determine how CADCs could be designed and implemented at a university or academic health center (AHC) in the near future, based on the ability of AHCs to provide clinical and basic neurodegenerative disease research programs, as well as active programs on health care policy, health services and economics of health care financing, all of which are essential elements for the success of effective and multi-disciplinary CADCs (1,2).

RATIONALE

As of January 1st, 2006, members of the "baby boomer" cohort in the United States (i.e. all those born between 1946 to 1964) began turning 60 years old – one every seven seconds. And, in 2011, they will begin to turn 65 years old, thereby entering the segment of the life span when Alzheimer's disease (AD) increases exponentially, with its prevalence doubling every 5 years after age 65 (3–8). Thus, in 2031, as each Baby Boomer begins to turn 85 years old, it is estimated that 50% of them at or beyond that age will have AD (3–8).

Due to the current global "longevity revolution", life expectancy in the United States continues to increase, and there continues to be emerging good news about the quality of health and functioning of the elderly population in the United States. For example, data from the 1982–

¹The Penn Faculty participants in this workshop have research interests in aging and aging related neurodegenerative diseases including Alzheimer's and Parkinson's disease, amyotrophic lateral sclerosis and frontotemporal lobar degeneration. Their research spans basic and clinical research as well as health care policy, health services and financing and they come from diverse schools at Penn including the School of Medicine, School of Nursing and the Wharton School. The workshop was organized by John Q. Trojanowski, Steven E. Arnold, Jason H. Karlawish and Virginia M.-Y. Lee from Penn and Ara Khachaturian and Zaven Khachaturian of Khachaturian & Associates, Inc. Penn faculty contributors to the workshop and this summary included: Kurt Brunden, Mark Cary, Christos Davatzikos, John Detre, Glen Gaulton, Murray Grossman, Howard Hurtig, Kathryn Jedrzewski, Leo McCluskey, Mary Naylor, Daniel Polsky, Gerard Schellenberg, Andrew Siderowf, Les Shaw, Viviana Van Deerlin, Li-San Wang, Rachel Werner and Sharon Xie.

2004 National Long-Term Care Survey suggest that chronic disability prevalence is decreasing at a rate of just over 2% per year for those over age 65 in the years between 1999 to 2004 (9). While many factors may contribute to this positive change, it is speculated to be due largely to the improving health of this population (9). This and other similarly positive news notwithstanding, there are increasing concerns about aging related diseases and especially aging related neurodegenerative disorders like AD (3–8). There are a range of estimates on the prevalence of AD in the United States, from 2.4 million to 5.2 million, based on differing methodologies and approaches to disease ascertainment (3–8). Regardless of these uncertainties, the number of people with AD is expected to explode soon as the global population ages, unless ways to prevent or treat the disease are found. Indeed, a new person develops AD in the United States approximately every 70 seconds, and AD has recently displaced diabetes as the 6th leading cause of death in the United States (3–8). By 2030, as many as 7.7 million people in the United States alone could have AD, and by 2050 this number could rise to around 11 to 16 million people (3–8). It is currently estimated that the cost of AD in the United States exceeds \$150 Billion annually, and AD will likely affect the economies of other countries to a similar extent, including developing nations. For example, the London-based Alzheimer's Disease International has determined that by 2040 the number of AD patients will more than triple in India, China and other countries in south Asia and the western Pacific (8).

With these projections in mind, a Planning Workshop was convened at the University of Pennsylvania (Penn) on June 19th, 2009 by Penn faculty to develop a Penn prototype model of a Comprehensive Alzheimer's Disease Center (CADC), i.e., the Penn CADC Model. This workshop was facilitated by Zaven Khachaturian, and the outcome of this workshop was the formulation of the Penn CADC Model summarized below.

THE PENN CADC MODEL

A description of CADCs in the ASG report and the Leon Thal Symposium 2008, as well as information provided during the Penn workshop were used as a springboard for formulating a plan for a university AHC-based Penn CADC Model. The Penn Workshop participants offer their CADC Model as a template for other AHCs that wish to establish these centers.

The design of the CADC proposed at the Penn workshop includes programs on AD as well as Parkinson's disease (PD), frontotemporal lobar degeneration (FTLD), amyotrophic lateral sclerosis (ALS) and vascular dementia (VaD) in research that spans the basic and clinical sciences, as well as health care policy, health services and the economics and financing of health care for patients with aging related neurodegenerative diseases, such as AD, FTLD, PD and ALS. Thus, while retaining the term CADC, the intent of the program proposed here is to include AD as well as PD, FTLD and ALS in the comprehensive neurodegenerative disease center because of the frequent overlap and co-occurrence of these disorders in patients, as well as growing evidence that they result from similar mechanisms of neurodegeneration, i.e. protein misfolding and aggregation. Further, taken together, PD, FTLD, ALS VaD present challenges to those of AD for health care policies, financing and services.

Each of the components of a university-based CADC are referred to in this document as a "Team" to distinguish them from the more familiar Cores and Projects of conventional National Institutes of Health (NIH) funded Program Project Grants (PPGs), which this CADC resembles to a certain extent. However, it also differs from conventional NIH PPGs in significant ways because of the more comprehensive mission of a CADC. Specifically, each Team will pursue activities typical of both Cores and Projects in traditional NIH PPGs. For example, the Genetics Team is envisioned to conduct routine Core-like genetic studies such as apolipoprotein E (APOE) genotyping as well as clinical genetic testing of known mutations using Clinical

Laboratory Improvement Amendments (CLIA) approved clinical testing methods. In addition, it will pursue Project-like discovery or hypothesis-driven research, and other types of genetic research as exemplified by the recent discovery by Van Deerlin et al of novel *TARDBP* mutations in familial ALS (11).

Below is a brief statement summarizing the mission of a university-based CADC, followed by short descriptions of each of the Teams and CADC deliverables based on the Penn CADC Model formulated at this Planning Workshop. Many but by no means all of the neurodegenerative disease research activities and programs referred to in this section have been summarized in a recent special issue of the journal *NeuroSignals* (12). Figure 1 schematically illustrates the pieces of the health care and research puzzle that ideally will be assembled into an effective and integrated program to achieve the mission of CADCs.

Mission Of A CADC

The mission of CADCs is to conduct multidisciplinary patient-oriented clinical and basic science research that improves understanding of and develops better treatments for AD, PD, FTLT, ALS, VaD and other aging-related neurodegenerative disorders. The overarching goal of this research is preventing these disorders (including the disability that stems from them such as memory, movement and mood impairments), and improving the care of patients now and in the future through well-resourced national health care delivery systems that are designed to serve the best interests of patients, families and society in the most cost-effective and efficient manner possible.

Administrative Team

The Administrative Team will oversee and coordinate the work of the CADC including all grant and financial oversight, Institutional Review Boards, Intellectual Property, corporate alliances and related matters. It also will promote communication between the university CADC and other CADCs as well as with existing NIA/NIH funded ADCs. It will be staffed and resourced to enable teleconference meetings with other CADCs and existing ADCs, as well as public/private agencies involved in the CADC mission. The CADC will be led by a director and an Executive Committee formed by the CADC Team Leaders. The CADC will be advised by an Internal Advisory Board comprised of campus-wide university faculty who have expertise relevant to the mission of the CADC, but are not members of the Center. Finally, the CADC also will benefit from the periodic review and advice provided by an External Advisory Board comprised of advisors beyond the university who have expertise relevant to the mission of the CADC, including non-scientists who represent patients, their families and patient advocacy groups.

Training Team

This Team will foster the development of the brightest MD, PhD, RN, OT, PT and other allied health trainees, as well as technical support people in areas to include clinical, health services and basic science research, as well as patient care. These trainees will ensure the long-term support and growth of care and research in neurodegenerative disease at the CADC. The emphasis by the Team will be to select and train “translationally oriented” clinicians, researchers and health care workers who will provide the seed-bed for CADC faculty and staff, thereby ensuring the longevity of this enterprise at and beyond CADCs.

Clinical Team

The charge of the CADC Clinical Team will be to discover, develop and promulgate models of accurate early diagnosis and excellent patient care, as well as to conduct clinical research, including evaluations of novel biomarkers and clinical trials. This will be accomplished by

expanding upon a well developed cohort of patients with AD, PD, FTLN, ALS, VaD and related disorders, as well as normal age matched controls with an emphasis on early onset or prodromal disease. Together with the Genetics Team, the Clinical Team will collect a detailed family history and assess these families as having definite, probable, possible and unknown risk for genetically-mediated disease. These subjects will be followed longitudinally by investigators in the Clinical Team who will have access to all relevant clinical, genetic, biomarker and neuroimaging capabilities and build upon existing infrastructure to develop a robust clinical trial program in the CADC.

Healthy Brain Aging Team

This Team will have faculty/staff (physicians, nurses, exercise physiologists, physical therapists/exercise trainers, dieticians/nutritionists, psychologists, life councilors/advisors) who work in partnership to design and implement evidenced-based best life styles or practices that are associated with a reduced risk for cognitive and motor decline. The Healthy Brain Aging Team will build on the work of the Clinical Team to study the effects of different life styles (e.g. exercise, diet, cognitive stimulating activities, social interactions or networks, avoidance of head trauma and metabolic syndrome, etc.) on cognition and other behaviors.

Genetics Team

This Team will implement genetic studies of all subjects followed in the CADC since all will be asked to consent to donating their DNA for research. Thus, the Genetics Team will conduct routine Core-like genetic studies, such as APOE genotyping, as well as clinical genetic testing of known mutations using CLIA approved clinical testing methods. In addition, it will pursue Project-like discovery research including genome-wide association studies and explore new technologies such as whole-genome sequencing.

Biomarker Team

This Team will implement biomarker studies of cerebral spinal fluid (CSF), plasma and other biofluids obtained from all subjects followed in the CADC since all will be asked to consent to donating biofluids for research. These studies will include efforts to standardize and validate CSF and plasma biomarkers for AD, PD, FTLN, ALS and VaD along the lines of the studies conducted by ADNI for AD biomarkers (13,14). In addition, the Biomarker Team also will pursue Project-like hypothesis driven research to identify novel biomarkers for these neurodegenerative disorders as well as for VaD and for healthy brain aging.

Neuropathology Team

This Team will implement postmortem studies of subjects followed in the CADC, and integrate postmortem data with clinical, neuroimaging, genetic and biomarker data in collaboration with other related CADC Teams. These studies will include efforts to standardize and validate diagnostic criteria for AD, PD, FTLN, ALS, VaD and other related disorders, but also pursue hypothesis driven research to elucidate mechanisms of neurodegeneration in these disorders, as well as resilience to aging-related neurodegenerative pathologies.

Neuroimaging Team

This Team will implement structural, functional, and molecular neuroimaging studies of subjects followed in the Clinical Team and the Healthy Brain Aging Team, using a diverse array of neuroimaging modalities. Similar to ADNI, this Team will develop and apply advanced image analysis and pattern recognition methods, building upon previous work on the development of early markers of AD, mild cognitive impairment (MCI) and normal cognitive status. However, it also will extend these methods to include integration of imaging and

chemical biomarkers in order to achieve higher specificity in identifying AD, PD, FTLN, ALS, VaD and related disorders at the very earliest stages of disease.

Data Management, Computational Modeling And Biostatistics Team

This Team will handle all data management and biostatistics needs for the CADC, as well as develop new algorithms for data integration and applications of these algorithms. State-of-the-art data mining and machine learning methods will be pursued to elucidate complex relationships between imaging and clinical phenotypes, chemical biomarkers, cognitive/motor performance and disease progression.

Drug Discovery Team

The Drug Discovery Team will develop disease-modifying therapies for AD, PD, FTLN, ALS, VaD and related disorders. This Team will advance compounds from hits identified by high throughput screening (HTS) to proof-of-concept studies in mouse models of these disorders, in order to discover and develop drugs that reverse or ameliorate neurodegeneration. The HTS efforts could be leveraged at individual CADCs through partnerships with commercial entities or with the NIH Center for Chemical Genomics (15). These potential drugs will then be carried forward to clinical trial in partnership with pharma/biotech or NIH-funded clinical trial programs such as the ADCS.

Integration Of Care Team

This Team will study and implement measures and policies that integrate care for patients and families affected by aging related disorders across the spectrum of health care delivery and wellness service institutions/providers as reviewed recently (16).

Healthy Policy/Comparative And Cost Effectiveness/Cost Effectiveness Team

This Team will implement and evaluate interventions that improve access to and delivery of diagnostic services and treatments for patients with neurodegenerative diseases, VaD and healthy individuals at risk for developing these disorders. Several approaches to take for this have been summarized recently (17,18).

CADC Outreach, Education and Dissemination Team

This Team will facilitate publication of CADC studies characterizing the cohort of patients and controls followed in the Clinical Team and Healthy Brain Aging Team, including data on clinical, biomarker, neuroimaging, genetic and life style practices. It will organize outreach efforts and annual “brain storming” meetings in concert with other CADCs and public/private entities involved in supporting the mission of the CADCs.

Structure Of The Penn CADC Model

Figure 2 schematically illustrates the organization of the Penn CADC formulated at the Planning Workshop to indicate how this CADC would be structured while Figure 3 depicts how the Penn CADC would reach out to and engage other CADCs, elements of the NIA funded ADC network and programs (19), other NIH components, public advocacy organizations and related entities that are relevant to the mission of the CADCs. It is anticipated that this organizational template could be exported readily to other university AHCs for the establishment of a network of CADCs.

CADC DELIVERABLES AT 10 YEARS

In keeping with the mission of this university-based CADC, the 10 year deliverables from this unique program will be to have an impact on preventing neurodegenerative diseases, such as

AD, PD, FTLN and ALS as well as VaD and optimizing successful/healthy brain aging through research. The costs of such CADCs would be significant, on the order of \$20 Million per year for each CADC, or \$100 Million for the first 5 years of a single CADC. Thus, we envision that 5 CADCs can be established in the US for a total cost of \$500 Million in the first 5 years of this program. However, we expect that the return on this substantial investment will be invaluable in terms of improved well-being of older adults, job creation, intellectual property generation, corporate alliances and of course significant savings in health care costs. Thus, the measurable 10-year deliverables of this program are projected to be delaying the 10% to 15% conversion rate/year for MCI subjects to AD or FTLN by half, or reducing by half the overall number of MCI converters to AD or FTLN over a 10 year period, while increasing significantly the numbers of MCI subjects who return to normal cognitive status during this time interval. In terms of health care cost savings, if successful, this CADC program could reduce by half the current \$150 Billion annual costs of AD, which are likely to double in the next 10 years. Thus, very conservatively, an investment of \$500 Million or less than 1% of the current annual costs of \$150 Billion for AD to the US economy could lead to savings of more than \$75 Billion in health care costs in ten years, and that is in addition to the impact CADCs can have on job creation and other effects CADCs will have on stimulating the US economy.

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FIGURE 1.

Figure 1 schematically illustrates the pieces of the health care and research puzzle that ideally will assemble into an effective and integrated team that can achieve the mission of CADCs.

FIGURE 2.

This figure schematically illustrates the internal organization of the Penn CADC with all the Teams needed for a successful program to achieve the mission of a CADC as described here.

FIGURE 3.

This figure schematically illustrates the how the Penn CADC will engage other CADCs, the NIA funded ADC network and programs (19), other NIH components, public advocacy organizations and related entities that are relevant to achieving the mission of the CADCs.