

II. AREAS OF FOCUS FOR THE 2012 INTERNATIONAL RESEARCH GRANT PROGRAM

Areas of focus are high-priority research areas in which the Association actively seeks proposals. The areas are defined broadly, and the examples cited are not intended to preclude or constrain other investigator-initiated projects or proposals. Potential applicants are strongly encouraged to submit proposals in their own areas of interest or formulate questions different from those presented in this announcement. Investigator-initiated research projects are the core of the Association's scientific program.

i. Research in Diverse Populations: Closing the Gap

Results of the 2000 census confirm that the overall population of the United States is rapidly becoming more diverse. However, the language and techniques often used to characterize diverse populations fail to reflect the true richness of origin, culture, and genetic variation represented in our society. This failure is well illustrated by the following excerpt: "Today, discussion of cultural diversity—ethnicity—most often identifies four major U.S. ethnic subgroups: African Americans (Blacks), Asian Americans and Pacific Islanders (or Pan Asian populations), American Indians and Alaska Natives, and Hispanics (or Latinos). Indeed, the term 'Asian Americans' represents more than 50 distinct linguistic groups. African Americans include persons who trace their roots to Africa, who were born in Africa, or who were born in the Caribbean Islands. Hispanics count more than 25 different countries of national origin. American Indians and Alaska Natives encompass over 500 federally recognized tribes and groups, with at least 30 different languages." (From *The Fourth Report of the Advisory Panel on Alzheimer's Disease, 1992: A Report to the U.S. Congress and the U.S. Department of Health and Human Services*; NIH Publication 03-3520.)

As the general population reflects a richer ethnic mix, subpopulations of older adults and those at risk for Alzheimer's disease are also growing more diverse. These extraordinarily rapid demographic changes are forcing organizations to re-evaluate whether they have sufficient knowledge of all groups within their potential clientele to deliver programs and services effectively. The Alzheimer's Association has concluded that there are significant information and data deficits about ethnic and cultural groups in most major research areas in Alzheimer's disease. These include screening and neuropsychological testing instruments; diagnostic procedures; recruitment and retention in research protocols and clinical trials; clinical and neuropathological correlative studies; caregiving and family studies; basic laboratory investigations; genetics projects; development of new models of long-term care and management of these services; epidemiological and health services research; and the economics of care.

Our understanding of Alzheimer's disease is limited by the characteristics of the people who have traditionally been included in investigations. There is a need for basic sociological and anthropological data about Alzheimer's disease, families and caregiving in specific cultural, social, and regional contexts to provide a working

platform for effective service, education and program delivery.

To fill these gaps in knowledge, projects must address the following issues:

Socioeconomic status: What is the effect of high or low socioeconomic status on Alzheimer's disease and its meaning in diverse populations? How can services for people with Alzheimer's disease and their families be developed most effectively to reach the range of socioeconomic levels of people and those from minority-groups. What level of importance do information and funds have on purchasing help and services? What is the best method to convey information about Alzheimer's disease to specific diverse groups?

Values and beliefs: How do values and beliefs shape receptivity to and perceptions about community-based and institutional services for Alzheimer's disease? How do values, beliefs, and perceptions vary among groups? How do the beliefs about Alzheimer's disease and normal aging encourage or prevent use of services? How must services and programs respond to be effective in the face of values and beliefs?

Role of the family and community: In specific diverse groups, how does the role of family differ in the long-term care of older members with dementia? How does the decision-making process differ in these groups? Is it necessary to understand family dynamics before planning interventions and services?

Geographical and regional variation: How do these factors affect the development and provision of services and programs? How do they interact with socioeconomic status and minority group membership in majority locales?

Interactions among factors: How do socioeconomic status, values and beliefs, the role of the family, and geographical and regional differences interact to influence care and service delivery to people with Alzheimer's disease and their families?

Incidence, prevalence and risk factors—key facts about the epidemiology of Alzheimer's disease—remain unknown in many defined ethnic and cultural groups. To better quantify the public health implications of Alzheimer's and support the development of necessary programs and services, reliable and valid data on the distribution of the disease in the U.S. population must be obtained.

Acquiring meaningful epidemiological data for diverse groups will require the ability to accurately detect and monitor Alzheimer's disease in the target population. In most cases, adequate tools for detection and monitoring do not exist. These research instrument deficits inhibit epidemiological investigations and limit the conduct of behavioral, social and clinical studies.

The following points outline some of the tools, instruments and strategies needed to address these deficiencies. Although very large population studies fall outside the funding scope of the Alzheimer's Association, smaller, well-designed studies can

effectively address a number of the information and instrument gaps that must be filled. This list is not exhaustive but is intended to highlight the types of research needed:

Screening and assessment instruments that are valid and reliable for specific age, gender, cultural, language, and ethnic groups, as well as for different levels of education and literacy, are needed as soon as possible. Expansion of epidemiological, behavioral, social and clinical research is hampered by the lack of these instruments.

Test norms standardized for age and gender for specific ethnic groups are also needed urgently. These norms must take into account language, education level, and literacy as well as educational equivalency between cultures and countries of origin. Norms derived from majority group data are often applied to minority groups and can result in misleading interpretations. This misapplication is especially serious for people with little or no formal education.

In research on Alzheimer's disease—especially in clinical drug trials— identification, recruitment, enrollment and retention of members of diverse cultural groups have lagged. Minority group members have been underrepresented in much of the research in Alzheimer's disease. The published literature on barriers to enrollment and retention has been largely descriptive and anecdotal. It is time to initiate a program of hypothesis-driven research to determine the efficacy of specific methods to enlist and retain ethnic minority and cultural group members in Alzheimer's disease research. Some of the issues of interest include:

Cross validation: Programs that are successful in the recruitment, enrollment, and retention of cultural group members must be cross-validated with other cultural groups and in different geographic areas to determine their broad-based usefulness in research.

Contacts: The differences in the effectiveness of recruitment approaches, and the mechanisms underlying these differences, must be explored. For example, under what circumstances are individual or local community-rooted approaches more effective than large mass media or marketing approaches? How do specific, clearly defined cultural groups differ from one another in the acceptability of various approaches and methods of contact?

Culturally competent investigators or investigators who are members of the cultural group: What difference does the cultural identity of the investigator make in successful identification, recruitment, enrollment and retention of specific cultural group members? Does it enhance long-term successful retention to have investigators who are of the same cultural group as the people to be recruited? Or, is it adequate that the investigator be culturally competent? And what, precisely, does it mean to be culturally competent for the purposes of Alzheimer's research?

Community barriers: What are the real and perceived barriers to participation in Alzheimer's disease research in specific cultural groups? How can these barriers be overcome?

ii. Social/Behavioral and Cognitive/Functional Focus: Evaluating Interventions and Translating Knowledge into Practice

Social and behavioral research has the potential to increase our understanding of the effects of Alzheimer's disease and other dementias on individuals with the disease, their families and other caregivers. At the same time, it can increase our knowledge about interventions that improve care practices, health, functional and emotional outcomes and quality of life, as well as prevent or reduce symptoms for millions of individuals and their families.

It is important to consider the influence of socioeconomic status, cultural and ethnic diversity, health/lifestyle practices, stigma and family attitudes about seeking care, availability of services and regional variation when proposing research about social and behavioral issues. Alzheimer's disease is heterogeneous, and the people with Alzheimer's disease are heterogeneous. Research into understanding these factors and how they might influence treatment outcomes (both in pharmacological and non-pharmacological trials) as well as the natural course of the disease are needed.

In addition, earlier detection and diagnosis are increasing the number of individuals identified with early-stage dementia. The characteristics and care needs of diagnosed individuals and their families in early, middle and late stages of Alzheimer's disease differ greatly. Social and behavioral research proposals should consider these differences in the design of proposed studies and the translation of findings from research into practice.

A wide range of questions in the social and behavioral arenas are ready for research. The answers to these questions, if broadly applied, would improve the quality of daily life for people with Alzheimer's disease and their families. The questions under each domain are provided as examples to facilitate the development of more specific research questions. Each investigator is encouraged to tailor his or her question to particular populations.

(1) Person with dementia: Over time, we have been able to gain an understanding of the experience of the person with dementia. This can be attributed to such things as people in the early stages speaking and writing about their experiences and the development of individualized approaches to care. Some questions include, but are not limited to:

- How can the experience of the person with dementia be characterized throughout the disease course to provide insight into areas such as decision-making capacity, quality of life and advance planning?

- How can the perspective of the person early in the disease process help shape decisions and care?
- Do personal or social factors influence the experience of the person with dementia in important and measurable ways?

(2) Physical and social environment: Environmental design for persons with dementia is a multi-dimensional construct that purports to satisfy the need for autonomy, dignity, safety, comfort and community as well as enhance one's mobility, cognition and memory. We need to gain a better understanding of the specific dimensions of the environment, as well as their interaction, and how they produce desired outcomes, such as:

- What characteristics of one's physical and social environment contribute to an individual's quality of life? How do these characteristics change through the course of illness?
- What are the components of a supportive environment in the home or residential care setting for someone with cognitive impairment? How do these components change through the course of illness?

(3) Family and household: The family of a person with dementia often plays a critical role in providing care and navigating the health and long-term care systems. Although caregiving has been studied intensively, there is still a need to understand how best to support the families that provide care and enhance (or ameliorate) the impact on the family. Research in this area may include, but is not limited to:

- What unique problems are encountered by families of persons with various types of dementia (e.g., early-onset dementia), and what interventions, services and policies are needed to mitigate those problems? How are these problems affected by the characteristics (e.g., socioeconomic status, culture and ethnicity, region of the country) of the families?
- What interventions can improve communication among family caregivers, persons with dementia and their health and long-term care providers and have a positive effect on care and outcomes?
- What effect do family attitudes about dementia have on the self-image and functioning of persons with dementia?

(4) Identification and evaluation of services and interventions: Researchers and care providers together must identify and evaluate the broad range of factors that can affect programmatic interventions. Examples include:

- What interventions or programs are most likely to have positive effects for people with Alzheimer's disease and/or their families in the community?
- What interventions or programs are most likely to have positive impact on people with Alzheimer's and the staff providing care in residential care settings?
- What characteristics of programs and services render them most acceptable to people with the illness and their families?

- What are the most effective strategies to motivate physicians and other health care providers to improve the quality of care they provide to people with dementia in clinical and long-term care settings?
- How can we translate programs developed in research settings to be effectively delivered in the community?
- What are the best strategies for effectively sustaining improved practices – either in the home or care setting?

(5) Health policy: Research can guide the adoption of policies that reshape systems of support in the home, community and health and long-term care settings. Researchers and policy makers together must ensure that public and private policies respond to the unique needs of those with dementia. Research may investigate questions like:

- What techniques should be used to determine consumer preferences for and satisfaction with their health and long-term care when the consumers have dementia?
- What techniques should publicly funded programs use to identify and properly care for people with dementia, including those with multiple chronic conditions?

(6) Maintaining cognitive function: Growing evidence suggests that lifestyle factors and behaviors interact with biological functions in maintaining cognitive function. It is important to find ways to effectively share information about prevention and about the potential benefits of changing behaviors.

(7) Implementation and dissemination of knowledge: With the development of novel interventions and the investigation of these interventions in scientifically valid ways, strategies for disseminating them must be established. Studies must bridge the gap between what has been demonstrated empirically and the daily care practices for people with Alzheimer's disease. Often, lack of knowledge about what constitutes a successful intervention hinders the transfer of the technique to everyday care settings. The research world is fragmented and disseminates its findings in ways that are not easily or routinely available to various audiences. Finding ways to meet this challenge and getting the information out to those who need it is essential.

- What strategies are effective for getting the science of prevention and treatment out to the general public?
- How can we measure and evaluate public response to (or acceptance of) such information?
- How can we measure and evaluate people's use of the information to change important behaviors? What help do people need to support important lifestyle changes?
- How can the effect of these strategies be measured in relation to their impact on cognitive decline?

(8) Cognitive/functional focus

By definition, dementia impacts cognitive function and day-to-day abilities. It is

important to understand the nature of these changes, as well as their biological basis. This can lead to better diagnoses, potential targets for treatment, and better understanding of the disease itself.

There are several themes that are considered important foci of potential proposals, including but not limited to:

1. Identification of cognitive/functional profiles:
 - Differentiation of cognitive/functional profiles in different forms of dementia
 - Identification of earliest cognitive/functional changes in the MCI or “predementia phase”
2. Development of better measures for diagnosis, testing, clinical trials
3. Identification of neural/biological correlates of cognition/function:
 - Identification of underpinnings of cognitive change
 - Correlation of imaging measures such as brain volume, cortical thickness, white matter hyperintensities, regional cerebral blood flow, brain amyloid with cognitive and functional changes
 - Correlation of biological measures from blood or CSF with cognitive and functional changes
4. Investigation of how cognitive and functional changes impact medical, legal, and day-to-day issues:
 - Relation of cognitive changes to the ability to consent
 - Exploring the impact of disease on medical or financial decision-making
 - Exploring metacognition, the recognition of deficit
5. Use the cognitive neuroscience approach to better understand and characterize cognitive/functional changes:
 - Use functional MRI, EEG, or other functional imaging measures to help identify functional brain changes underlying cognitive/functional change

iii. Biological Focus: Causes, Early Detection, Treatment, Models, Prevention and Risk Factors

Although vast advances have been made in Alzheimer's research, the field still faces a great number of serious impediments to progress in translating basic science discoveries into effective treatments and evidence-based clinical practices for dementia. Some of the many challenges that remain for investigators to address include:

Cause(s) of the Disease: How and why do specific sets of neurons in select brain structures become dysfunctional? Why do some neurons and not others die? What initiates these processes? What is the key step in the cascade of events leading to cell death? How do genetic factors interact with other factors to

influence these processes?

The primary neuropathological events in Alzheimer's disease involve abnormal expression and processing of proteins. Advances in molecular biology have provided the tools needed to begin to unravel the mechanisms of synthesis, trafficking and accumulation of these proteins in the brain. Research in this area has begun to produce promising leads about the role of these proteins in neural function, dysfunction, and cell death and to suggest strategies to correct this molecular damage. Although these insights into the neurobiology of the disease have generated a number of ideas, the precise etiology of the disease is still not known. While there are many theories on possible mechanisms of neural dysfunction and/or cell death, critical questions remain unanswered.

None of these theories has been validated by crucial experiments designed to demonstrate the functional relationship(s) between characteristic molecular aberrations and the clinical manifestations of the disease. One of the most difficult challenges for the field is to link the perspectives of investigators inhabiting two totally different worlds: those who view Alzheimer's disease through the prism of molecular/neuropathological events and those who know it through its behavioral and clinical manifestations.

The precise relationships between the clinical symptomatology and the neuropathology of the disease are not well defined. There is a critical need to understand not only the presumptive causal links between the neurobiology and clinical course of the disease but also the mechanisms for the heterogeneity of presentation. These mechanisms may vary widely and may influence differential diagnosis and differences in adverse events/responses to treatments.

Early and Accurate Detection and Diagnosis: What are the most sensitive, specific and cost-effective diagnostic procedures? What are the most sensitive, specific and cost-effective procedures for assessing change through the course of the disease?

Several converging lines of evidence suggest that the neurodegenerative processes associated with dementia begin several years before the first clinical features can be detected with current instruments. The precise duration of the preclinical period and the details of the early molecular events are not known. This uncertainty about symptom-free early stages of the disease stems from the lack of well-validated tools or technologies for detection.

Although clinical information can be gleaned from longitudinal studies, even these data are usually obtained in the middle to later stages of the disease when some of the cognitive and behavioral signs appear. As a result, there is little or no information on manifestations of the disease during its earliest preclinical stages or the very earliest behaviors of individuals at risk. These gaps result from the lack of appropriate technologies for noninvasive observation and early detection of the disease. Finding sensitive and specific markers will become even more important as pressure increases

to develop very early treatments, especially if these early interventions have the potential for harmful side effects, it is crucial that they be targeted appropriately. Thus, there is an urgent need to find accurate biological markers of the disease, including improved imaging techniques and more sensitive cognitive and behavioral assessment instruments.

Any effective biomarker must not only detect a fundamental biological process in the disease, but should also be validated in an adequately powered study with neuropathologically confirmed cases. The ideal marker should have sensitivity greater than 80 percent for detecting disease and specificity also greater than 80 percent for distinguishing Alzheimer's from other dementias. Testing for the marker should be reliable, reproducible, non-invasive, simple to perform and inexpensive. In addition, a putative biomarker should have confirmation by at least two independent studies conducted by qualified investigators. Currently, none of the putative biochemical markers have been validated in adequately powered investigations.

Well-tested biological markers for Alzheimer's disease are not the only critical need—it is also important for investigators to explore the observational and subjective perspective that family members, care providers and people with the illness can provide about the very earliest events. The observations of family members, nurses, social workers and other care providers have already provided some important insights about early cognitive and behavioral events.

Treatment: What are the most effective and safe pharmacological treatment strategies, behavioral management techniques, and combinations of therapies?

Research on interventions is poised for a revolution. The timing of the revolution is open to speculation—it may take two years, it may take ten—but it will happen. Dramatic advances in understanding the neurobiology of Alzheimer's—including elucidation of many genetic and molecular mechanisms involved in the disease—have provided numerous promising leads for drug development. It is now generally agreed that the most critical neurobiological events underlying the behavioral problems and clinical manifestations of the disease concern dysfunctions in nerve cell signal transduction, loss of synapses, and premature cell death. The primary scientific dispute revolves around theories concerning the precise cause or source of these destructive processes. Currently, the field of Alzheimer's therapy has a rich array of promising leads as therapeutic targets. If such potential treatments, using a variety of approaches, could be validated by well-powered clinical trials, they will have a profound effect on addressing the disease. The eventual utility/efficacy of any intervention can only be evaluated through clinical trials, which are expensive.

Until recently, strategies for developing interventions focused primarily on symptomatic treatments for middle and late stages of the disease. It is anticipated that as new therapeutic targets are discovered, it will be possible to improve the quality of signal transduction and the ability of nerve cells to communicate. As even more is learned about the neurobiology of Alzheimer's disease, there will be greater reliance on techniques to design specific molecules aimed at correcting a particular cellular

dysfunction. Some important therapeutic approaches should involve the discovery of interventions aimed at preventing premature cell death and restoring or prolonging the function of surviving damaged nerve cells.

Until effective pharmacological treatments are discovered, family and facility-based care providers must rely on a variety of behavioral and social interventions to assist in managing symptoms and maintaining the highest quality of life for people with Alzheimer's disease. The development and testing of new social and behavioral interventions, in the appropriate cultural context, is a priority and is discussed under Social/ Behavioral Research and Cognitive/Functional Focus.

Experimental Models of the Disease: Advances and Limitations

Considerable advances have been made in the development of animal models—especially transgenic mice carrying human genes for key Alzheimer proteins and variant forms of genes shown to be involved in dementia. Because these models make it possible to study the effects of specific factors such as A β , tau, and apolipoprotein E4 (apoE4) on memory and other cognitive functions, they have shed light on what each of these proteins may contribute to the development of Alzheimer's disease. For example, transgenic mice producing human amyloid precursor proteins have revealed that A β can cause neuronal dysfunction and memory problems even when it is not clumped together in large amyloid plaques, which can be visualized in live patients by radiological imaging. They have revealed similar dissociations between neurofibrillary tangles and memory problems and highlighted the disease-causing potential of smaller clusters of A β and tau that cannot yet be detected in brains of live patients. In addition, these models have helped unravel the intricate processes by which these poisonous aggregates impair brain functions.

However, a limitation of these models is that they do not capture the full complexity of the human condition, which is problematic if one wants to use them to predict the success of specific therapeutic interventions in patients with Alzheimer's disease. For example, anti-A β treatments may be effective if the only protein causing problems is A β , but it may not be enough to treat Alzheimer's disease in a patient who also has two apoE4 genes causing additional problems. To address these complexities, scientists are developing animal models that combine different factors. Determining whether these compound models can predict the success of therapeutic interventions for Alzheimer's disease will have to await the first truly effective drug trial in humans. This benchmark will prove or disprove these models.

To circumvent species differences that may complicate the use of rodent models for human disorders, investigators are now turning to new technologies that make it possible to turn a person's skin or blood cells back into stem cells and from there into mature neurons. Through this "induced pluripotent stem cell (iPSC)" approach, researchers can create patient- and disease-specific cell culture models that could have advantages over animal models. However, the full potential of this technology remains to be determined.

Prevention: What are the prospects and strategies for prevention?

One of the most important priorities is research on strategies to prevent Alzheimer's. The importance of prevention is rooted in the severe effects of the disease on individuals and their families, the very large number of people with the illness and the anticipated growth of these numbers with the aging of populations in the United States and other countries. Developing effective preventive strategies will bring significant benefit in reducing the economic and social costs, preserving the economic productivity of those who are or will be family caregivers, and lessening the impact on the health care system.

The most convincing argument, however, is the humanitarian one—effective prevention can spare future generations from one of the most feared and disabling infirmities associated with advancing age.

Research into basic disease mechanisms can have immense benefit for development of strategies for disease prevention, but there is not always a tight link between understanding the mechanisms of a disease and preventing it. In fact, highly successful prevention efforts have been designed and conducted under circumstances in which disease mechanisms were understood poorly, or not at all.

In general, it makes sense that intervening early in the process that causes a disease is easier and more effective than intervening at later stages when the disease has already taken its toll and has gained momentum. The prevention of cardiovascular disease by early and aggressive treatment of high blood pressure or high cholesterol levels is a good case in point. Besides genotyping for apoE4 and other risk genes, there is currently no measurement that can identify people at increased risk for Alzheimer's decades before the typical onset of the disease. Extensive efforts have been launched to change this situation. However, widespread genotyping for apoE4 is not currently recommended because of the lack of effective treatments for Alzheimer's disease.

Risk Factors: What are the characteristics, either genetic or acquired, that increase the risk of Alzheimer's disease or offer protection against or delay the onset? How do the risk factors vary among specific diverse populations? Are any risk factors modifiable?

Epidemiological studies reveal growing evidence that most cases of Alzheimer's disease likely involve a combination of genetic and environmental risk factors. Identifying and validating these risk factors remains one of the most critical scientific challenges. The main risk factors so far validated for late-onset disease are age, family history and certain susceptibility genes.

The potential link between cerebral blood vessel disease and Alzheimer's is one promising area of research. Vascular disease in the aged appears to have strong implications for neurodegeneration leading to dementia. Preliminary studies indicate that a broad spectrum of cerebrovascular lesions could lead to a decline in cognitive function. In addition, recent epidemiological studies have begun to implicate vascular conditions outside the central nervous system—such as heart disease and high blood

pressure—as potential risk factors for dementia. The broader implication is the hypothesis that systemic vascular factors are risk factors for developing Alzheimer's disease. This risk encompasses different forms of cardiovascular disease, including coronary artery disease, carotid atherosclerosis, history of hypertension or high cholesterol, Type II diabetes and stroke or transient ischemic attacks.

The e4 allele of the apolipoprotein E gene (apoe4)—which has been associated with increased risk of cardiovascular disease—is the best-validated susceptibility gene to date, with more widespread effects than any other genetic factor implicated in the late-onset, sporadic form of Alzheimer's. Several mechanisms have been identified by which apoe4 could increase the risk of developing Alzheimer's disease; most of them involve detrimental effects on brain cells rather than effects on the cardiovascular system.