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EDITORIAL

Disrupting Alzheimer's Disease Research

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Alzheimer's disease (AD) is a progressive neurodegenerative disorder that devastates the brain—affecting cognitive function, memory, visual spatial perception, abstract thinking, and eventually loss of bodily functions. Based on the latest Rand report on dementia and AD, the current costs in lives lost, families shattered, careers disrupted, and financial futures ruined is much too high. And with the projected increases in the number of individuals affected by AD and related dementias in coming years, the global costs become unendurable and insupportable.

Many pharmaceutical companies have dismantled their AD treatment discovery programs because of failed experimental therapeutics in costly Phase III clinical trials. Recently, a paradigm shift to focus earlier in the disease process to include preclinical populations with mild cognitive impairment (MCI) due to AD has emerged.[1–3] It is anticipated that at earlier stages, before functional impairments and severe neuronal damage has occurred, potential treatments might be more effective. But unless we take deliberate steps to disrupt the status quo, there is growing concern that AD research in this country will remain seriously underfunded.

A situation this complex requires novel approaches in at least three ways: (1) to accelerate research breakthroughs by fostering new thinking about neuroscience and AD by those currently not working in the area, (2) to incentivize computational researchers to mine public databases such as the Alzheimer's Disease Neuroimaging Initiative (ADNI), and (3) to focus on an aspect of the science that has the greatest potential to trigger a groundswell in advocacy, too long absent in the AD community.

As a benchmark, the history of heart disease research has demonstrated the importance and relevance of elucidating biologic sex differences for better-tailored detection, treatment, and prevention interventions. The research focus benefited both women and men and transformed the body politics. It is time for a concerted focus to do the same for AD.

What might AD research look like if science and advocacy coalesced to crowdsource such a challenge to a global network of millions of problem solvers and experts worldwide? This innovation model[4] supports the development of new ideas and paradigms, innovative tools from global investigators in multiple disciplines within medical science, but also in engineering, computer science, and mathematics. Why not apply it to elucidate the causes and consequences of male/female (sex) differences in the destructive physical changes and atrophy in the brain, how those changes translate into progression of physical symptoms, and the influence of genetics and hormones on the development of AD in both men and women?

The 2013 Geoffrey Beene Global NeuroDiscovery Challenge on male/female differences in the presymptomatic, early symptomatic, and late dementia stages of AD, with $100,000 in prize awards, attempts to leverage large sets of clinical data and novel analytical approaches. The challenge is seeking to encourage multidisciplinary teams to analyze public datasets from the National Institute on Aging and other research centers for differences between men and women in cognition, biomarkers, and progressive neurodegenerative decline due to AD. Figure 1 is a representative announcement for the challenge.

Women are disproportionally affected by AD; two-thirds of AD patients in the United States are women.[5] This disparity may be due in part to women's longer life spans, but recent research in MCI is beginning to point toward differences between men and women in the pathology and progression of this disease. Anatomical, molecular, functional, hormonal, and cognitive differences in the brain between males and females have been reported in many species including humans.[6–10] What biological sex differences in the brain mean for impairments in memory and progressive neurodegenerative diseases such as AD is not known. However, studies are accumulating that show a distinct male/female difference in the onset, course, and presentation of AD. For example, one study reported that women had more neurofibrillary tangles. Increased AD pathology was associated with a nearly 3-fold increase of clinical AD in men, compared with a more than 20-fold increase in women.[11] These and other data suggest that the same degree of cognitive impairment is associated with greater structural damage in men compared with women.[12]

In the ADNI, patients were grouped into three clinical categories—probable AD, amnestic mild cognitive impairment (aMCI), and healthy controls. Men and women in the AD and aMCI groups showed different patterns of decline through time.[13] In another ADNI study of brain atrophy rates, statistical mapping revealed significant age and sex differences, with rates of brain atrophy being about 1.0%–1.5% faster in women than in men.[14] The Mayo Clinic Study of

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FIG. 1. One of several announcements for the 2013 Geoffrey Beene Global NeuroDiscovery Challenge.

Aging reported that incidence rates for MCI were higher in men than women and suggested that risk factors for MCI should be investigated separately in men and women.[15] Also, the Australian Imaging Biomarker Lifestyle (AIBL) study of aging reported gender differences in β-amyloid levels, which was associated with worse episodic memory and visuospatial performance in females than in males.[16]

Genetic studies are also revealing AD differences between women and men. Female carriers of APOE ϵ4, a strong AD risk factor, have significantly more AD brain atrophy and memory disruption than men[17] and rates of atrophy are faster.[18] Additionally, differential risk for AD was associated with estrogen receptor ERα and ERβ genotypes.[19–21] Studies have reported evidence for greater inheritance of AD from the maternal lineage.[22,23]

The 2013 Geoffrey Beene NeuroDiscovery Challenge seeks to foster a disruptive approach to Alzheimer's by looking through the lens of male/female differences. We anticipate that any successful solution to the Challenge will be composed of two parts: (1) A clearly articulated novel hypothesis related to the causes or consequences of male/female differences (molecular, physiological, anatomical, hormonal, cognitive, genetic, etc.) in the pathogenesis and presentation of AD in its presymptomatic, early symptomatic, and late stages. The hypothesis needs to be accompanied by a solid scientific rationale and supported by analysis of data obtained separately for women and men. (2) A detailed research plan describing how to test the proposed hypothesis.

The Geoffrey Beene Foundation Alzheimer's Initiative envisions that up to five awards, with no single award being lower than $10,000, will be awarded to proposals that best meet the requirements of the challenge. Solutions will be evaluated by a panel of expert judges for their innovation and originality, the biological and clinical rationale for the hypothesis, and the technical rigor of the analyses or experimental design. One solution will be awarded an additional $50,000 to support additional database analysis or the proposed research plan. As of August 22, 2013, 65 countries* are represented with 750 multidisciplinary team project rooms opened on the Innocentive Challenge pavilion. (More information on the Challenge can be found at www.geoffreybeenechallenge.org or www.innocentive.com/ar/challenge/9933328).

Understanding and characterizing these biological sex-based variations, and others yet to be discovered, will provide new opportunities for the development of appropriate, tailored disease detection, treatment, and prevention modalities for both men and women. Matching a research challenge with an advocacy agenda both informs the science and energizes the mobilization of women against Alzheimer's. Challenging researchers to use existing big data as well as develop new methodologies to investigate any sex-based differences that may exist could ultimately affect how we treat—and, hopefully, one day prevent—this devastating disease. By any mindful measure, we are, indeed, a generation out of time.

*As of August 22, 2013, the countries represented in the Challenge included: Argentina, Armenia, Australia, Austria, Belarus, Belgium, Brazil, Bulgaria, Canada, China, Colombia, Croatia, Denmark, Egypt, Estonia, Finland, France, Germany, Greece, Hong Kong, Hungary, India, Indonesia, Ireland, Israel, Italy, Japan, Jordan, Kazakhstan, Kenya, Lithuania, Luxembourg, Macedonia, Madagascar, Malaysia, Mexico, Moldova, Morocco, Netherlands, Nigeria, Norway, Oman, Pakistan, Peru, Philippines, Poland, Portugal, Puerto Rico, Russian Federation, Serbia, Singapore, Slovakia, Slovenia, South Africa, Spain, Sweden, Taiwan (province of China), Trinidad and Tobago, Turkey, Ukraine, United Kingdom, United States, Uruguay, and Uzbekistan.

Background Information on Alzheimer's Disease

AD is the sixth leading cause of death in the United States and the only one in the top ten that cannot be prevented, cured, or even slowed. Scientists project that by 2050, the number of Alzheimer's dementia sufferers will rise to 13.8 million, with more than half aged 85 or older.[24] From 2000 to 2010, Alzheimer's deaths rose 68%.[25] The pervasive, destructive, and costly effects of this debilitating disease will become even more profound as Baby Boomers age, because the risk of developing AD doubles every five years after age 65. AD and related dementias affect as many as five million Americans and 36 million more people worldwide.[24,26]

In addition to the enormous physical and emotional burden on patients, families, and caregivers, the disease is also costly. In 2010, the costs of dementia care, which is often 24 hours a day, 7 days a week, were as much as $215 billion to the United States and $604 billion globally (1% of global GDP).[26] In the United States, around 70% of the cost of care—or $142 billion—is paid by Medicare and Medicaid. By 2050, the costs to Medicare and Medicaid are expected to increase more than 500%. This year more than 15 million Americans, mostly women, will provide unpaid care for AD patients valued at more than $216 billion.[27] Without disease-modifying therapy, AD is a pending epidemic for our aging population.

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