



Board of Directors

Executive Committee

Kathryn G. Schubert, MPP
President and CEO
Society for Women's Health Research

Shontelle Dodson, PharmD
Board Chair
Senior Vice President, Health Systems
Astellas Pharma Inc.

Gretta Stone
Board Secretary-Treasurer
Director
Reservoir Communications Group

Roberta L. Gartside, MD
Immediate Past Board Chair
New Image Plastic Surgery Associates

Dawn Halkuff, MBA
Chief Commercial Officer
TherapeuticsMD

Jenelle S. Krishnamoorthy, PhD
Associate Vice President, Global Policy
Merck & Co. Inc.

—

Anne B. Cropp, PharmD
Chief Scientific Officer
Early Access Care LLC

Nieca Goldberg, MD
Medical Director
Joan H. Tisch Center for Women's
Health, NYU Langone Health

Linda G. Griffith, PhD
Professor of Biological Engineering
Massachusetts Institute of Technology

David C. Page, MD
Director, Whitehead Institute
Massachusetts Institute of Technology

Alan T. Wright, MD
Chief Medical Officer
Roche Diagnostics Corporation

Michael Ybarra, MD
Vice President,
Medical Affairs and Strategic Alliances
PhRMA

—

Florence Haseltine, PhD
Founding Honorary Board Director
Executive Director of Health Research,
University of Texas at Arlington

October 16, 2020

Submitted electronically to: publiccomments@icer-review.org

Dr. Steven D. Pearson, MD, MSc, President
Institute for Clinical and Economic Review
Two Liberty Square, Ninth Floor
Boston, MA 02109

Re: Institute for Clinical and Economic Review (ICER) Alzheimer's Disease Update: Open Input

Dear Dr. Pearson:

The Society for Women's Health Research (SWHR) appreciates the opportunity to provide open input to the Institute for Clinical and Economic Review (ICER) as it begins a new assessment on Alzheimer's disease (AD).¹

SWHR is a 30-year-old national nonprofit dedicated to promoting research on biological sex differences in disease. We work to improve women's health through science, policy and education. We are pleased to serve as a resource to ICER on key aspects of value assessment that have implications for women and their health. SWHR has a network of interdisciplinary experts² that works to raise awareness about biological sex disparities in AD and create recommendations for future research and policies in this field.

In October 2019, we shared with ICER a set of principles³ that SWHR conceived to help ensure value frameworks and value assessments 1) account for patient population diversity, including sex and gender and 2) have the infrastructure and analytic capability to evaluate data that matters to women. Grounded by these principles, SWHR is pleased to provide the following information and guidance to inform ICER's AD value assessment:

ICER's AD research protocol should analyze data on AD sex and gender differences and account for them in its model analysis plan.

In line with SWHR's Health Care Value Assessment Principles, value assessments should account for diversity among patients (including sex and gender) for a given disease state by analyzing data that represent relevant patient populations and subgroups.



This principle is especially important to consider for conditions such as AD, which predominantly impact women. Of the 5.8 million American adults diagnosed with AD, about two-thirds are women. AD is the 5th leading cause of death for women.⁴

While age is the major risk factor for AD, women live longer than men, so more women than men will develop AD over their lifetime. Women in their 60s are more than twice as likely to develop AD over the rest of their lives as they are to develop breast cancer.⁵

The strongest genetic risk factor for late-onset AD is the $\epsilon 4$ allele of the APOE gene. Women with APOE $\epsilon 4$ have an increased risk of developing AD compared to women without APOE $\epsilon 4$ and men both with and without APOE $\epsilon 4$.⁶ However, researchers are now questioning whether the risk of Alzheimer's could actually be higher for women at any given age due to biological or genetic variations or differences in life experiences.⁷

Women and men may differ with respect to AD etiology and presentation. Men show more aggressive behaviors, more comorbidity, and higher mortality than women, whereas women tend to have more affective symptoms and disability but longer survival times. These presentations may indicate neuropathological differences that necessitate different management strategies to serve men and women with dementia.⁸ For example, at early stages of neurofibrillary tangle development, women exhibit greater senile plaque deposition than men. AD pathology has shown to be more strongly associated with clinical dementia in women than in men.⁹

ICER's AD research protocol should carefully consider the role of sex and gender differences in regards to etiology, symptom presentation, and disease course, and should attempt to account for these topics in its model analysis plan. Given that women are disproportionately affected by AD, ICER should highlight women as a subpopulation in its report section on patient heterogeneity.

When conducting value assessment for AD, ICER should consider for comparison all available evidence-based options, including behavioral therapies and lifestyle interventions.

Researchers and innovators around the globe are striving to stop, slow, and prevent AD. Until there is a therapy that can prevent the disease or reverse disease course, the goal for effective AD management is to develop effective treatments to better manage debilitating cognitive and behavioral symptoms. Regimens must also provide realistic expectations for patients and caregivers throughout the course of the disease. Factors that may influence the effectiveness of therapy include early and efficient diagnosis, behavioral or lifestyle modifications, patient compliance, and sequential or combinatorial therapeutic approaches with available drugs.¹⁰

SWHR's Health Care Value Assessment Principles indicate value assessments should acknowledge the full spectrum of treatment options for a given medical condition. Therefore, we strongly recommend that ICER consider all available evidence-based options within the health care system including behavioral therapies and lifestyle interventions.



To comprehensively assess the value of any new treatment, ICER should quantitatively account for the public health burden of AD in its cost-effectiveness methodologies. Burden of illness factors that impact women disproportionately (e.g., caregiver burden) should be included in ICER's model analysis plan.

The public health impact of AD is huge and growing. As the population of the United States ages, AD is becoming a more common cause of death. Presently, AD is the only top 10 cause of death that cannot be prevented, cured or even slowed. The long duration of illness contributes significantly to public health impact because much of that time is spent in a state of dependence and disability. The total lifetime cost of care (including Medicare, Medicaid, out-of-pocket expenditures, and the value of unpaid care) for someone with dementia was estimated at \$341,840 in 2017 dollars.¹¹

Nearly half of all caregivers (48 percent) who provide help to older adults do so for someone with AD or another dementia. In 2017, caregivers of people AD or other dementias provided an estimated 18.4 billion hours of unpaid assistance, a contribution to the nation valued at \$232.1 billion. The costs associated with family care are 70 percent of the lifetime dementia care costs stated above (\$143,735 in the value of informal care and \$95,441 in out-of-pocket expenses related to care in 2017 dollars).¹²

The responsibilities of caring for someone with dementia frequently fall to women, with daughters comprising over one-third of dementia caregivers. Female caregivers report a twofold higher level of caregiver burden compared to male caregivers. While men also provide assistance, women tend to spend more time providing care than men (21.9 vs. 17.4 hours per week). Further, women are likely to assist with more difficult caregiving tasks, such as toileting and bathing, while men are more likely to assist with finances or arrange for other care.¹³

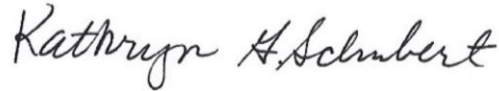
Caregiving generally is associated with elevated levels of cortisol and impaired attention and executive function. Dementia caregivers in particular are broadly at risk for a variety of health difficulties, including increased rates of chronic conditions, more frequent interactions with the health care system, decreased engagement in healthy preventative behaviors, and increased behavioral health concerns, such as smoking. Caregivers also demonstrate poorer immune responses to vaccines, slowed healing time, and reduced overall immunity to diseases. It has been hypothesized that spousal caregivers may be at higher risk of cognitive impairment or dementia than non-caregiver spouses in response to several psychosocial (e.g., depression, social isolation, and sleep problems), behavioral (e.g., exercise and diet), and physiological (e.g., metabolic syndrome and inflammation) variables.¹⁴

In addition to measuring clinical outcomes, value assessment frameworks should account for what matters most to patients, caregivers and society. Therefore, to assess the value of any new AD treatment comprehensively, ICER should quantitatively account for the public health burden of AD in cost-effectiveness methodologies. Burden of illness factors that impact women disproportionately (e.g., caregiver burden) should be included in ICER's model analysis plan.



Thank you for the opportunity to provide open input to ICER for its value assessment of AD. Please do not hesitate to contact SWHR's Vice President of Public Policy, Sarah Wells Kocsis, at swellskocsis@swhr.org or 202-496-5003 with any questions or concerns.

Sincerely,



Kathryn G. Schubert, MPP
President and Chief Executive Officer
Society for Women's Health Research

¹ Institute for Clinical and Economic Review. Assessments. Retrieved from: <https://icer-review.org/topic/alzheimers-disease/>

² Society for Women's Health Research. Science Networks: Alzheimer's Disease. Retrieved from: <https://swhr.org/science/networks/alzheimers-disease/>

³ Society for Women's Health Research. Health Care Value Assessment Principles. Retrieved from: https://swhr.org/swhr_resource/swhrs-health-care-value-assessment-principles/

⁴ Centers for Disease Control and Prevention. National Center for Health Statistics: Alzheimer's Disease. Retrieved from: <https://www.cdc.gov/nchs/fastats/alzheimers.htm>

⁵ Alzheimer's Association. Women & Alzheimer's. Retrieved from: <https://www.alz.org/alzheimers-dementia/what-is-alzheimers/women-and-alzheimer-s>

⁶ Nebel, RA., et al. Understanding the impact of sex and gender in Alzheimer's disease: A call to action. *Alzheimer's & Dementia*. 2018 1-13.

⁷ <https://www.alz.org/alzheimers-dementia/what-is-alzheimers/women-and-alzheimer-s>

⁸ Mazure, C., & Swendsen, J., Sex differences in Alzheimer's disease and other dementias. *Lancet Neurol*. 2016 April 15(5): 451-452. doi:10.1016/S1474-4422(16)00067-3.

⁹ Carroll, JC, Rosario ER, Kreimer S, et al. Sex differences in β -amyloid accumulation in 3xTg-AD mice: role of neonatal sex steroid hormone exposure. *Brain Res*. 2010;1366:233-245. doi:10.1016/j.brainres.2010.10.009.

¹⁰ Farlow, M. et al. Treatment Options in Alzheimer's disease: Maximizing Benefit, Managing Expectations. *Dement Geriatr Cogn Disord* 2008;25:408-422. DOI: 10.1159/000122962.

¹¹ Alzheimer's Association. 2018 Alzheimer's disease Facts and Figures. *Alzheimer's Dement* 2018;14(3):367-429.

¹² Alzheimer's Association. 2018 Alzheimer's disease Facts and Figures. *Alzheimer's Dement* 2018;14(3):367-429.

¹³ Family Caregiving Alliance. Family Caregiving and Transitional Care: A Critical Review. 2012. Retrieved from: <https://www.caregiver.org/family-caregiving-and-transitional-care-critical-review-2012>.

¹⁴ Brodaty, H., & Donkin, M. (2009). Family caregivers of people with dementia. *Dialogues of Clinical Neuroscience*, 11(2), 217-28. Retrieved from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3181916/>.