Establishing a Biomarker Model of Alzheimer’s Disease

Diagnosis of Alzheimer’s Disease

Alzheimer’s disease (AD) pathology is defined by the presence of amyloid plaques and neurofibrillary tangles in the brain. While studies in the last ten years have sought to develop tools that can confirm the presence of AD pathology in a living patient, diagnosis is traditionally only confirmed by autopsy. Typically, AD pathology in the brain corresponds to dementia in the final years of a patient’s life. However, it is not uncommon to find these hallmarks of Alzheimer’s disease at autopsy in people who showed no evidence of dementia in life. This has led researchers to attempt to better define the relationship between AD pathology and dementia.

Alzheimer’s Disease Neuroimaging Initiative (ADNI)

The Alzheimer’s Disease Neuroimaging Initiative (ADNI) is a nationwide collaboration of over 55 research centers that seeks to use different biomarker tools (MRI, PET, lumbar puncture, etc.) to detect Alzheimer’s pathology in its earliest stages and track its progression over time. Due to the contributions of over 1500 research participants, a massive wealth of data has been collected that has led to the development of models of AD progression. While there is plenty of discussion amongst researchers as to the details of such a model, data suggest three general stages: a preclinical phase during which little or no cognitive decline can be detected, a period of mild cognitive impairment, and finally dementia. A patient is considered to progress from mild cognitive impairment to dementia when the cognitive symptoms begin to significantly interfere with the patient’s daily living and independent functioning. Due to the failure of recent drug trials on patients with dementia, researchers have hypothesized that applying therapeutic strategies to patients with symptoms of AD dementia may be too late for certain treatments to be effective. Consequently, research has refocused on understanding the earliest stages of AD pathology, when drug therapies might prove more effective.

The Amyloid Model

Dr. Clifford Jack, the head of the MRI portion of ADNI, and other ADNI collaborators have recently proposed an exciting new biomarker model of the early stages of Alzheimer’s disease. Detection of decreased brain amyloid load using lumbar puncture and/or PET imaging is the first step in Dr. Jack’s biomarker model, occurring 10-20 years or more before dementia onset. The lumbar puncture involves the removal via syringe of cerebrospinal fluid from the lower back, allowing the levels of both the amyloid and tau protein in the brain to be quantified. Currently, the lumbar puncture is the only tool that allows researchers to measure levels of the amyloid and tau proteins that correspond to AD. Other less invasive tools have been developed in recent years that allow the visualization of the amyloid protein using a brain scan. Amyloid PET imaging involves injecting a radioactive compound...
There are issues unique to individuals with memory changes and to their family members. We are trying to learn how to better address these issues by developing new services and providing support groups that meet the needs of individuals with memory problems and their families. We are involved in ongoing development of support groups to achieve these goals. Currently the following groups are available at our center:

Caregivers Support Group
This is a small group designed to support and guide caregivers who are dealing with challenges in caring for their loved ones. It will address their questions and concerns and provide them with ways to handle day-to-day issues. Also, the group will help caregivers to care for themselves better, as well as provide them with an opportunity to meet a network of people in similar situations. The group meets twice a month, on the second and fourth Wednesdays, from 1:30 pm to 2:30 pm. You are welcome to come to both dates, or to just one.

Mild Cognitive Impairment (MCI) Group:
This group is designed for individuals with a diagnosis of mild cognitive impairment (symptoms not meeting criteria for dementia) and their family members or friends. This group focuses on 1) education, 2) communication, 3) management, and 4) psychosocial concerns. The group meets on the 2nd and 4th Wednesdays of the month from 11 a.m. to 12:30 p.m.

Educational Seminars
These are monthly informational/educational seminars given by professional staff addressing a variety of topics pertinent to memory loss and caregiver issues. These seminars are open to all participants and their caregivers and will include a question-and-answer session. Seminars meet on the fourth Wednesday of each month from 10-11 a.m.

All groups meet at the
VA Palo Alto Health Care System 
3801 Miranda Ave., Bldg. 6, 
2nd floor Conference Room (C-258) 
Palo Alto, CA 94304

If you are interested in the support groups or would like additional information, please contact Virginia Dao at (650) 493-5000 ext. 66121.

Website: http://svalz.stanford.edu/groups.html

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that binds to amyloid and emits a signal that when scanned allows researchers to observe whether amyloid deposits can be found in the brain. Data from ADNI and other studies have clearly established that increased levels of the beta amyloid protein (the main component of the plaques observed at autopsy in AD brains) can be observed in healthy older adults. Because no cognitive impairment is usually observed at this stage, whether the increased amyloid deposition is indicative of early AD pathology is a major source of contention amongst Alzheimer’s researchers. However, researchers have consistently shown that levels of the amyloid protein are clearly related to age and genetic factors related to Alzheimer’s disease (such as apolipoprotein E). Further research in healthy older adults with and without increased amyloid levels will hopefully resolve this issue.

As an individual moves along the time course of the proposed biomarker model, the next observed abnormality in healthy older persons is increased tau levels in the cerebrospinal fluid. Unlike the amyloid protein, increases in tau protein are not usually observed until just before the onset of cognitive symptoms, and increases in tau appear to correlate with severity of cognitive impairment. While researchers are seeking to develop tools similar to the amyloid PET scan, lumbar puncture is currently the only direct measure of the tau protein. Thus, the lumbar puncture remains essential to research concerning the diagnosis and early detection of Alzheimer’s disease. However, the tau protein is not unique to Alzheimer’s disease. It is present in many other dementing disorders, and is believed to be indicative of brain cell injury and dysfunction. Such injury and dysfunction can be detected using FDG-PET brain imaging, and is the next step in Jack’s model. This brain scan involves the injection of a radioactive sugar molecule that when scanned emits a signal that indicates the level of metabolic activity in different parts of the brain. Abnormal levels of activity are often indicators of dysfunction and injury in the brain. Thus this biomarker tool allows researchers to assess the level of...
Spotlight: Michelle Farrell

Mental Illness Research, Education, and Clinical Center (MIRECC),
VA Palo Alto Health Care System;
Michelle Farrell graduated from the University of California, Berkeley in 2007 with a B.A. in Molecular and Cell Biology with an emphasis in Neuroscience. At Berkeley, she did undergraduate research on the impact of sleep on memory consolidation and reward-learning in older adults. She joined the Stanford/VA Aging Clinical Research Center in 2009.

Michelle is the study coordinator for the Stanford chapter of the Alzheimer’s Disease Neuroimaging Initiative (ADNI), a nationwide study that seeks to use different biomarker tools to detect Alzheimer’s pathology in its earliest stages and track its progression over time. She is also a research assistant with the Aviator MRI Study, which tracks changes in structural MRI and cognitive performance over time in older pilots. More recently, she has become involved with the War-Related Injury and Illness Study Center and the Memory Clinic.

Michelle is currently applying for graduate school to pursue a PhD in Neuroscience. She is interested in continuing to study Alzheimer’s and healthy aging. She is particularly interested in continuing to study the early detection of Alzheimer’s, especially insofar as it can help shed light upon the differences between healthy aging and the earliest stages of Alzheimer’s and how best to prevent Alzheimer’s and other aging-related diseases. She very much appreciates the generous contributions of volunteers to Alzheimer’s disease and healthy aging studies at the ACRC, and hopes to continue to do research that serves the aging population. In her free time, Michelle enjoys hiking, going to the beach, camping and traveling as much as possible.

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dysfunction and injury in the brain, which the model suggests occurs early in the progression of AD pathology and continues to cause impairment of cognition.

Contributing Factors

According to Dr. Jack’s biomarker model, as injury and dysfunction accumulate and worsen, brain cells lose their connections then start to die and shrinkage can be detected in certain areas of the brain using MRI methods. MRI allows researchers to measure the size and shape of different brain structures and subsequent MRIs allow the observation of very small changes in size and shape over time. Early in the disease process, shrinkage is most commonly observed in specific areas of the brain that are known to be essential for memory formation and retrieval. Soon after changes can be observed using MRI, mild memory and cognitive symptoms start to appear. Over the next several years, memory and cognitive function continue to worsen as AD pathology spreads to other areas of the brain. Eventually these symptoms begin to interfere with the individual’s ability to function normally and care for themselves, and dementia is diagnosed.

It must be noted that this model does not fit all published data. Individual variability results in many cases that do not fit this model, especially when other dementing disorders like vascular dementia are present. It is therefore extremely important that researchers continue to collect data to evaluate the accuracy of this model and adapt and expand the model to better fit all cases.

The local chapter of ADNI is recruiting participants with memory problems across the spectrum, from those with mild but not incapacitating memory problems to those with severe problems that interfere with daily living. Individuals with diagnoses of mild cognitive impairment or mild dementia of the Alzheimer’s type are particularly encouraged to consider participation. If interested, see the research opportunities listing on page 4 or call Michelle Farrell (650-849-0491) for more details.

By: Michelle Farrell

Reference:
Alzheimer’s Disease Neuroimaging Initiative (ADNI)

The Alzheimer’s Disease Neuroimaging Initiative (ADNI) is a nationwide study with the goal of determining whether imaging of the brain (through MRI, PET and amyloid imaging scans) and collection of blood and cerebrospinal fluid (via lumbar puncture) can help predict and monitor the progression of mild cognitive impairment (MCI) and Alzheimer’s disease.

Participants should be:
- 55-90 years of age with some memory problems or a diagnosis of mild cognitive impairment or Alzheimer’s disease
- Have a study partner - a friend or relative who can accompany the volunteer to some clinic visits.
- Available for 5-10 clinic visits per year for 5 years

To sign up for this study
Contact: Michelle Farrell
(650) 849-0491

Citalopram for Agitation in Alzheimer’s Disease (CitAD)

The goal of the CitAD study is to see if a medication called Citalopram (Celexa) is helpful for people experiencing memory problems and anxiety. Benefits include a review of current medications by the study physicians, psycho-social support from a gero-psychologist for the care partner, and a 24-hour help line.

You may be able to participate in the CitAD study if:
- You are over 50 years old
- You have a diagnosis of probable Alzheimer’s disease, and are experiencing some anxiety
- You have a study partner - a friend or relative who can accompany you to all clinic visits

To sign up for this study
Contact: Jeff Newell
(650) 493-5000, ext. 65275

Computer Games and Well-being Study

Are you feeling anxious or down most of the time? Are you interested in how computer games can improve your concentration and well-being?

The study consists of several laboratory visits during which you will complete computerized exercises and questionnaires, and daily homework completed either from home or in our laboratory.

You may be eligible to participate if:
- You have anxiety or depression
- You have internet access and a computer at home

To sign up for this study
Contact: Etkin Lab at (650) 725-9510
(please leave a voicemail) or stanfordpsychiatry@gmail.com
RESEARCH OPPORTUNITIES

Are you distressed by memories of a traumatic event?
This study takes brain scans before and after people with Post-traumatic Stress Disorder (PTSD) receive the gold standard psychotherapy treatment for PTSD. The goal is to identify changes that occur in the brains of people with post-traumatic stress disorder during psychotherapy and help guide the development of new treatments.

You may be eligible to participate if:
• You have experienced a traumatic event
• Your life is affected negatively by unwanted memories of that event

To sign up for this study
Contact: Etkin Lab at (650) 725-9510
(please leave a voicemail) or stanfordpsychiatry@gmail.com

This project is developing an approach to screen for memory problems in group sessions.
Each screening session:
• Begins with a brief talk on memory & aging
• Involves simple memory games many enjoy
• Reviews your results and concerns with staff

Please call for the next Memory Screening session.

To sign up for this study
Contact: Elena Marinelli
(650) 493-5000 ext. 67729

The Stanford/VA Alzheimer’s Research Center provides no-cost, comprehensive memory evaluations and follow-ups for patients with memory concerns or complaints. A physician’s referral is not necessary. Patients may be eligible to participate whether or not they have previously been diagnosed with memory problems. The memory evaluation consists of a meeting with a clinician, a brief neurological exam, and neuropsychological testing. Upon completion of the evaluation, the patient and family will meet with a clinician to review the diagnosis and any recommendations or referrals to community resources, and to discuss other issues or concerns.

You may be able to participate if:
• You have memory concerns or complaints
• You are community-dwelling (i.e., not residing in a nursing home)
• You have a study partner (friend or relative) who is willing to provide information for a baseline visit and possibly for subsequent semi-annual or annual visits

To sign up for this study
Contact: (650) 852-3287

Memory Evaluations

Psychotherapy for PTSD

For dates of Memory Screening sessions,
Contact: (650) 852-3287

Memory Screening

The Stanford/VA Alzheimer’s Research Center provides no-cost, comprehensive memory evaluations and follow-ups for patients with memory concerns or complaints. A physician’s referral is not necessary. Patients may be eligible to participate whether or not they have previously been diagnosed with memory problems. The memory evaluation consists of a meeting with a clinician, a brief neurological exam, and neuropsychological testing. Upon completion of the evaluation, the patient and family will meet with a clinician to review the diagnosis and any recommendations or referrals to community resources, and to discuss other issues or concerns.

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• You have a study partner (friend or relative) who is willing to provide information for a baseline visit and possibly for subsequent semi-annual or annual visits

To sign up for this study
Contact: Elena Marinelli
(650) 493-5000 1, 1, ext. 67729
Memory and Sleep Study

Are you a healthy male VETERAN interested in research on sleep, memory, and aging? VA Researchers are studying how sleep disordered breathing, age, and genetics may affect memory in older veterans WITHOUT Post Traumatic Stress Disorder.

You may be eligible to participate if you are:

• A healthy male VETERAN
• 55 years old or older
• NOT experiencing Post Traumatic Stress Disorder
• Willing to travel to the Palo Alto VA for yearly testing
• Willing to have yearly sleep apnea screening overnight at the VA

To sign up for this study
Contact: Emily Luther
(650) 849-0482

The End of Alzheimer’s Disease Starts with You

For the 5 million Americans living with Alzheimer’s Disease (AD) and the nearly 11 million people who provide their care, the end to Alzheimer’s Disease cannot come soon enough. Each day, individuals and families struggle to cope with the many changes AD brings to their lives, while scientists and physicians strive to improve the understanding and treatment of AD. On Saturday, October 15th, we join forces to take a stand against this terrible disease at the Walk to End Alzheimer’s in San Jose.

The Walk to End Alzheimer’s is organized by the Alzheimer’s Association, the nation’s premier voluntary health organization dedicated to raising awareness and improving the lives of those with AD. Staff and friends of the Stanford/VA Aging Clinical Research Center (ACRC) participate each year as a team to walk and raise funds. Formerly known as Memory Walk, this year’s Walk begins at 10am at the Arena Green Park in downtown San Jose. Walkers may choose a 1-mile or 3-mile route.

We welcome everyone to join our team and be a part of this special event. You can sign up to walk and raise funds, or donate without walking. It’s easy to join our team, and it only takes a couple of minutes. Funds raised through our team benefit both the Alzheimer’s Association, and the Stanford/VA ACRC as its non-profit partner. This has been an important source of funds for our Center in the past, and is more important as Federal and State funds become more scarce.

• Call us at (650) 852-3287 to request a paper registration or donation form.
• OR Register online to join the Stanford/VA Aging Clinical Research Center at http://walktoendalz.kintera.org/sv11/acrc and click on ‘Join Our Team’ at the top of the page.

The Alzheimer’s Association funds more Alzheimer’s research than any other private, nonprofit organization in the world. Their support, care and educational services help hundreds of thousands of people each year. It also is the leading voice for Alzheimer’s advocacy in the US, working to pass legislation at the local, state and federal levels. The Walk to End Alzheimer’s is the major source of funds for the Alzheimer’s Association to provide these crucial services and continue the fight against AD. Held in nearly 600 communities across the US, this event unites families and friends, researchers and health care providers as they walk to bring an end to Alzheimer’s.

More information on the local chapter of the Alzheimer’s Association and the Walk to End Alzheimer’s is available at http://www.alz.org/norcal or call them at 650-962-8211.
Screening for Memory Disorders in the Community

The initial symptom of Alzheimer’s disease typically involves increased difficulty in remembering new information. However, mild memory problems are also common in healthy adults, especially as they age. For this reason, seniors are frequently unsure about whether minor lapses in their memory are the early signs of something serious such as dementia.

One solution to this problem is to provide routine memory screening in the community in much the same way that other tests are used to detect medical problems such as high blood pressure, diabetes, or high cholesterol. Unlike these, screens for memory problems can be time-consuming and expensive and consequently are not routinely used. A suitable screen for memory disorders would be a boost as many potentially reversible factors can contribute to mild memory problems that are worse than would be expected due to aging alone, such as medical illness, depression, medication side-effects, or cardiovascular factors.

To address this issue, a team of researchers at the Stanford/VA Aging Clinical Research Center has developed a screening test for memory. Unlike other memory screening tests, this test was developed for screening large numbers of people simultaneously. Audiences were given a 5-minute slide-show in which 50 photographs of everyday items such as buildings, kitchen utensils and articles of clothing were presented, of which 25 were repeated. Audience members responded by recording on a score sheet if an image was a repetition. The memory test was given to audiences at community events, senior citizen centers and retirement living communities in the San Francisco Bay Area during talks about Alzheimer’s disease and the signs of dementia. Over 1000 participants were screened in this way, and audience members ranged in age from 40 to 97 years old.

As expected, results showed that memory performance declined with age. More tellingly, there was a three-fold increase in test score variability from younger to older adults. This pattern of greater variability in memory across individuals is consistent with the increased frequency of memory problems, including dementia, in the elderly. The study did not use any other test of memory or thinking. Further studies are needed to establish the reliability, validity, and utility of this test in well-defined populations. However, the test has many features that make it potentially suitable as a memory screen: it can be administered to a large number of individuals simultaneously in an audience setting; it is brief and easy to administer; and it is actually fun for many audiences. For this reason, it shows considerable promise to serve the important needs of a memory screen. Such memory tests represent a practical and novel approach to screen for the signs of early dementia.

Reference

Relationship between Apathy and Sleep Disturbance

Apathy is the most frequently reported neuropsychiatric symptom across all stages of Alzheimer’s disease (AD). Both apathy and sleep disorders are known to have independent negative effects on the quality of life in individuals with AD. The aim of this study was to assess the relationship between apathy and sleep/wake patterns in individuals with AD using wrist actigraphs (a device worn on the wrist which measures arm movement). One hundred and three non-institutionalized individuals with AD wore a wrist actigraph continuously for one week. Apathy continued on next page
was assessed using the Neuropsychiatric Inventory. Among the 103 study participants, those with apathy had significantly lower nighttime activity, increased wake time after sleep onset, and spent more time in bed during the night than those without apathy. Sleep latency, nighttime motor activity and time in bed did not differ significantly between the two subgroups. To our knowledge, this study is the first to identify a relationship between apathy and sleep disturbance in those with mild or moderate AD: apathy was associated with increased time in bed during the night and more wake time after sleep onset. These results suggest that AD patients with apathy have less consolidated nocturnal sleep than those without apathy.

Reference

From the Stanford/VA Alzheimer’s Research Center:

Impact of dementia and mild memory impairment on spousal relationships

This study used focus groups to compare relationship issues between caregivers of patients with dementia and Mild Memory Impairment (MMI). Five key themes emerged: communication, cohesiveness of the relationship, affectional expression, caregiver burden, and ambiguity concerning the future of the marital relationship. Dementia caregivers reported more difficulties with communication, cohesion, and perceptions of increased burden than their MMI counterparts. Both groups indicated reduced sexual expression due to physical limitations; substitute activities including hand-holding, massaging, and hugging were noted. Both groups also reported difficulty anticipating the future of the relationship due to present stressors. While dementia caregivers could consider future romantic relationships with others, MMI caregivers were primarily able to consider future relationships only for companionship and emotional intimacy.

Our findings suggest that early therapeutic interventions may assist couples in modifying activities, behaviors, and expectations about the future of the relationship. Such modifications may help maintain relationship satisfaction, decrease burden, preserve quality of life, and delay time-to-placement.

Reference

Gender differences in intimacy in marital relations in AD patients and spouses

This study evaluated the impact of gender differences on intimacy and sexual satisfaction in marital relationships in which one partner has AD. Our study found that the majority of couples dealing with AD reported engaging in some form of intimacy, suggesting its importance in the relationship. Our results also show that: 1) female caregivers reported higher levels of stress and depressive symptoms than male caregivers, 2) female caregivers who reported less sexual satisfaction reported more frequent stress and depressive symptoms, and 3) caregiver gender, satisfaction with intimacy, and the AD patient’s level of cognitive functioning significantly contributed to caregiver well-being.

Our findings indicate that gender-specific therapies to address patient sexual difficulties and caregiver well-being could potentially maintain or improve the marital relationship.

Reference
Memory Maintenance Program: Top 10 Recommendations

1) Maximize and continue your education and mental exercise. Take classes in subjects that interest you. Do mentally stimulating activities, including puzzles.

2) Have a regular exercise program; include both aerobic and strengthening exercises. Stretching improves flexibility.

3) Maximize your social network and spiritual interactions. Stay active with your friends and in your community. Focus on interdependence with others.

4) Continually monitor and improve your diet. Take your vitamins daily. *(discuss your vitamin intake with your clinician).* Maximize your fruits and vegetables. Eat more fish, less red meat.

5) Keep your Body Mass Index (BMI) in the optimal range (19-25). To optimize your BMI, control your food intake and exercise. *(BMI = 703 * weight (pounds) / height (inches) squared)*

6) Physically protect your brain: Wear your car seat belt. Wear a helmet when you are riding a bicycle. Decrease your fall risk through physical exercise; improve your balance.

7) Know your body and your health risks. Check blood pressure, cholesterol, fasting blood sugar, B12, BMI. Review your health habits, diet, sleep, avoidance of tobacco and smoke. Keep your hormones stable. Visit your clinician on a regular basis.

8) Optimize your cardiovascular health: Take your blood pressure regularly; (systolic pressure should be less than 130, diastolic blood pressure less than 85). If your cholesterol is elevated (above 200), talk to your clinician about appropriate treatment.


10) Optimize your cognitive health: If you think that you have significant difficulty with your memory, talk to your clinician about further evaluation and therapy.

Make a difference: Help end Alzheimer’s Disease!

A contribution to the Aging Clinical Research Center is a gift to future generations in our quest to cure Alzheimer’s disease. Your generous support ensures that the Center continues to conduct top-quality clinical research to improve treatment options and to provide education and support for patients and families. With your help, our clinical researchers investigate the causes of memory loss and neurodegeneration, develop and test better treatments for Alzheimer’s disease, and share these discoveries with the local community and with scientists around the world.

Tax-deductible contributions can be made by check, payable to: Stanford University

Please indicate Stanford/VA Aging Clinical Research Center in the memo line.

Mail your contributions to:

Jerome Yesavage, MD, Director
Stanford/VA Aging Clinical Research Center
3801 Miranda Avenue (151Y)
Palo Alto, CA 94304

Gifts may be made in honor of someone’s special occasion or in memory of someone who has passed away. Please provide the name of the person you wish to honor, as well as the name and address of anyone whom you wish to receive an acknowledgement of the gift.

For additional information about the Stanford/VA Aging Clinical Research Center, or to contribute, call (650) 852-3287. All donations are tax-deductible.
UPCOMING EVENTS

Walk to End Alzheimer’s

When: Saturday, October 15, 2011, Check-in opens at 8:30am, Walk begins at 10:00am

Where: Arena Green Park, Downtown San Jose, CA

Register at: http://walktoendalz.kintera.org/sv11/acrc
and click on ‘Join Our Team’ at the top of the page. OR
Call (650) 852-3287 to request a paper registration or donation form.

Walk to End Alzheimer’s is a great opportunity to participate in the movement to end Alzheimer’s disease. Thousands of walkers come out to support the cause at walks throughout Northern California and Northern Nevada. Join our team at our local walk.

7th Annual Alzheimer’s Disease Circle of Care Conference

When: Saturday, November 12, 2011

Where: Crowne Plaza Hotel, 1221 Chess Drive, Foster City, CA


This annual education conference is designed to fit the needs of families caring for a loved one with Alzheimer’s disease or related dementia. It is also for professionals who would like to learn more about Alzheimer’s disease, the challenges and hope for the future.

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Visit us on the web:
Sierra-Pacific MIRECC: http://www.mirecc.va.gov/visn21/
Aging Clinical Research Center (ACRC): http://alzheimer.stanford.edu
Stanford/VA Alzheimer’s Research Center: http://svalz.stanford.edu

To add or remove your name from our mailing list, call (650) 852-3287 or visit the ACRC web site.

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