

NCRAD Update

Newsletter of the National Cell Repository for Alzheimer's Disease

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The National Cell Repository

is a repository for families with Alzheimer's Disease or severe memory loss. Families having two or more living individuals with memory loss are encouraged to participate. We would like to thank the hundreds of families nationwide who are already participating in the National Cell Repository. Many family members have provided blood samples, which researchers use to study Alzheimer's disease (AD) and other related diseases. Our hope is that, through the efforts of our participants, we will one day unravel the mystery of devastating diseases, like AD. We are always eager to accept new families to help us move toward this goal.

National Cell Repository for Alzheimer's Disease Hereditary Genomics

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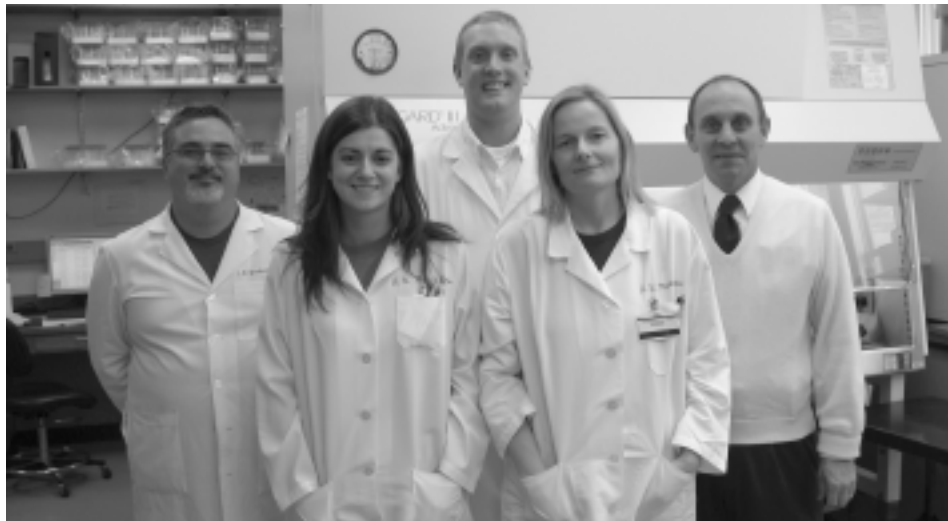
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In this picture from left to right back row: Michael Menke, Aaron Baker, Stephen Dlouhy
Front row: Lisa Beach, Katharina Sullen

THE NCRAD LABORATORY STAFF

We would like to take this opportunity to introduce the NCRAD laboratory staff. These individuals process the blood samples that participants donate to the study.

Stephen Dlouhy, Ph.D has been a faculty member in the Department of Medical and Molecular Genetics since 1987. His research focus is the identification of genes that cause a variety of different neurological disorders. He is the director of the NCRAD laboratory and the departmental DNA and cell repository.

Aaron Baker, MS joined the laboratory in 2003 and is now the supervisor of the NCRAD laboratory. He graduated from Purdue University with a Bachelor of Science in Engineering in 2001, and completed his Master of Science in Genetics at Indiana University in 2007. Aaron previously worked with various biomedical engineering related products including one for monitoring blood pressure in premature infants. In his

role as the laboratory supervisor Aaron is responsible for overseeing day to day activities in the lab, managing supply and sample inventory, as well as working in the lab with cell immortalizations and DNA extractions.

Katharina Sullen, BA grew up in Switzerland, was an exchange student in Indiana, and then went to Franklin College where she graduated with a B.A. in Biology. She has been working in the NCRAD laboratory for 16 years. Katharina is responsible for immortalizing and cryopreserving lymphocyte cell lines. She also extracts DNA and prepares the samples that will be sent to AD researchers.

Michael Menke, BS received a B.S. with honors from Indiana University in Microbiology in 1990. He then worked at what is now Dow Agrosiences as a Molecular Biologist from 1990-1992. He also worked at Eli Lilly from 1992-2001. Since 2001, he has worked at
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Responding to Your Debilitating Crisis: The

By Jeffery D. Stinson J.D.
Severns Associates, P.C.

Bob and his family had lived next to the Jones' for over twenty years. Tom and Mary Jones were a pleasant couple always inviting Bob and his family over for barbeques in the summer and hot tea and cookies in the winter. Bob had grown very close to Tom and Mary and considered them family. So, when Tom died a few years ago, it was only natural that Bob help Mary in whatever way he could. Unfortunately, Mary had shown signs of memory loss over the last few months. Even Mary herself admitted to Bob one day she knew something was wrong. A visit with Mary's physician confirmed everyone's suspicions; Mary was exhibiting symptoms of the first stages of Alzheimer's disease. Mary had no doubts on what she wanted. Later that day she said to Bob, "Bob, I have known you and your family for some time. I know you to be thoughtful and rational when making decisions and I want you to care for me if I become too sick to care for myself. Will you help me?" Bob honorably accepted this important role, but reminded Mary about her daughter in Florida. Although estranged for several years, Mary and her daughter, June, had recently reconciled. Mary replied that she loved June very much, but did not think she could trust her with her money and doubted she would make decisions conforming to Mary's own in regards to health care.

Mary clearly knows who she prefers to respond to a debilitating crisis. Unfortunately, Bob, as her unrelated friend and neighbor, has little legal authority to assist her without appropriate legal documents.

POWER OF ATTORNEY

If Mary intends for Bob to handle her finances once she no longer has the capacity to do so herself, she must provide him the legal authority to do so. Typically this authority is bestowed under a Power of Attorney. A Power of Attorney is a legal document in which the principal (Mary in this case) designates authority to an agent (Bob in this case) to handle certain transactions. Most needed authority can be derived from state statute; however, the principal is free to expand the scope of such statutory authority as he or she sees fit. A general power of attorney is one in which the agent has broad authority. A limited power of attorney declares that the agent has limited authority to manage a certain asset or conduct a certain transaction. A durable power of attorney is one that will remain in full force and effect after the incapacity of the principal. In Mary's case, she should consider arranging for the preparation of a General Durable Power of Attorney that would allow Bob to handle all her regular financial business upon her incapacity.

HEALTH CARE REPRESENTATIVE

A health care representative (may also be referred to as a health care power of attorney, health care proxy, or health care surrogate), at a minimum, is charged with consenting to health care for an individual whenever that individual is incapacitated. Most states have "default" appointments by statute if one fails to specifically name his or her health care representative in a legal document. Examples of a default appointment might be the individual's spouse, children, parents, or even his or her religious superior.

Although the health care representative is generally charged with consenting to another individual's health care when that individual is incapacitated, the individual may choose to broaden the role of the health care representative to other tasks whether the individual is incapacitated or not. For example, the health care representative may have the authority to employ or contract with caregivers or health care providers; admit or release the individual from facilities; access medical and other records regarding the individual's condition; make anatomical gifts on the principals behalf; request an autopsy; and make plans for the disposition of the individual's body.

Probably the most important function of the health care representative is the authority for the health care representative to instruct the withdrawal or withholding of care for the individual. If the individual is incapacitated, most state statutes permit the health care representative to withdraw or withhold care. However, many statutes require that the authority to withdraw or withhold care be specifically stated in writing. Without this specific statement, the health care representative has no authority to withdraw or withhold care.

An individual should appoint his or her health care representative in a document, rather than rely on the default provisions even if his or her representative is the same person as provided in the default provisions of the state statute. Not only can the document clearly indicate the authority of the health care representative, but also any ambiguity as to who should speak for the individual is clarified. Furthermore, if the individual desires that the health care representative have the authority to withdraw or withhold health care when he or she is incapacitated, then this must be in writing. Finally, the document will give the individual the opportunity to disqualify anyone under the default statute that the individual would not want to be making health care decisions for him or her. In Mary's case, she definitely will want to arrange for the preparation of a legal document appointing Bob as her health care representative. Since Bob is her unrelated neighbor, he will not have authority to speak for her in regards to health care without such documentation. The default appointments under most state statutes would not cover Bob. Furthermore,

Importance of Forming Your Response Team



since Mary knows that her own daughter's philosophies regarding health care conflicts with her own, she will want to specifically disqualify her from the health care decision making process. Finally, the process of putting her instructions into writing gives Mary the opportunity to discuss these important issues with Bob before he is faced with a circumstance where he must make a decision for her.

LIVING WILL

A living will is a legal document that indicates an individual's desires in regards to life prolonging treatment when he or she is in a terminal state. The circumstances in which a person's living will applies is determined by state law. The individual may make such instruction if he or she is incapacitated and suffering from a terminal disease or injury. He or she may also be permitted to make such instruction if he or she is in a persistent vegetative state or coma. Examples of the types of instructions that can be made is directing the withholding of artificially supplied hydration and nutrition, directing not to resuscitate, directing when and how pain medicine and antibiotics are used, directing the withholding of antibiotics, and directing whether organs should be donated.

The living will can either serve as a final instruction in regards to treatment or may serve as a baseline for the health care representative in making decisions for an individual. For example, Mary can instruct Bob to use the living will in making decisions for her as her health care representative. If Bob believes Mary's living will is too rigid in a particular circumstance, Bob may deviate from the terms of the living will (for example authorizing experimental treatment). On the other hand, Mary may not desire such flexibility and instruct that the living will shall be followed in strict compliance with its terms. In that situation, Bob's role will be to uphold its terms.

GUARDIANSHIP

The necessity for a guardianship is typically the result of

an individual failing to plan for a debilitating event. A guardian is appointed by a Court to oversee the affairs of an incapacitated person. In order for a person to be appointed guardian, the Court must find that the individual is incapacitated and that the person petitioning for guardianship is the most suitable person to serve as guardian. A hearing is usually held to make these determinations. After the guardian is appointed, the Court oversees the guardian's performance under the guardianship. Most Courts require the guardian report back to the Court periodically regarding his or her care of the incapacitated person. Transactions of substantial concern must also be approved by the Court before the transaction can be completed.

Due to the expense and extra time associated with a guardianship, it is to the individual's advantage to plan ahead for a debilitating event. Without such planning, the Court essentially writes the individual's estate plan for him or her. Most guardianship statutes provide an order of preference for who may serve as guardian. Consequently, the person who is appointed guardian may not be the one that the individual would have chosen. In Mary's case, if both Bob and June petitioned to be Mary's guardian, it is likely that June would be appointed guardian. As this is contrary to Mary's wishes, she should ensure that she prepares her own plan.

SUMMARY

Designating who should make decisions for an individual, especially health care, is one of the most important facets of estate planning. Unfortunately, few people take the opportunity to record their preferences in writing. The purpose of this article is to provide the basic knowledge regarding financial and health care decision making for another. A full review of each and every power an individual can give to an agent and what powers a particular individual should designate to an agent is beyond the scope of this article. It is recommended that an individual consult a knowledgeable attorney to further explain his or her options.

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The information provided herein is intended only to convey general information related to legal issues commonly encountered and is not intended to be legal advice. This information is not intended to create any legal relationship between Severns Associates, P.C. and the user. Although we strive to make certain that the information presented is accurate and useful, we strongly recommend you consult an attorney specializing in health care and elder law issues if you want professional assurance that our information, and your interpretation of it, is appropriate to your particular situation.

Impact of Gender on Dementia

By Dr. Martin Farlow
Indiana University School of Medicine
Department of Neurology



Dr. Martin Farlow

Estrogens, menopause, and other hormonal therapy may influence memory and cognitive functioning as well as the risk for Alzheimer's disease.

Menopause is the cessation of menstruation resulting from loss of ovarian function and is associated with a dramatic decline in estrogen levels in middle aged women. The mean age for natural menopause is 51 years. In the US, 46 million women are post menopausal and 2 million additional women become post-menopausal each year.

Estrogens have direct effects on the neurons (nerve cells) of the brain. Estrogens affect the neurons' actions on genes, receptors and interaction with proteins. Estrogens may act positively by stimulating higher levels of neurotransmitters including: acetylcholine, dopamine, and serotonin. Estrogen is also neuroprotective and may decrease levels of Beta-amyloid, a major protein associated with Alzheimer's disease.

Estrogens have long been thought to reduce risk of dementia and or delay its progression. Recently, the Women's Health Initiative looked prospectively at the use of estrogen versus placebo in 16,608 post-menopausal women who were followed for over 5 years and were also tested for memory function. Estrogen in this study did not improve memory but rather doubled the incidence of dementia. Therefore, estrogen is no longer recommended for prevention or treatment of Alzheimer's disease. However, a much smaller study

in younger women with suppressed estrogen levels after hysterectomy (with removal of their ovaries) had increased short term memory problems that were improved by taking conjugated estrogens. Thus, estrogen may help preserve memory in young women following surgically induced early menopause.

With regards to estrogen as a treatment for memory loss in women with established Alzheimer's disease, several small trials without controls suggested benefit; however, later, larger, longer trials have suggested estrogen has no effects in preserving memory in Alzheimer's disease. The overall evidence suggests that estrogen is not useful for symptomatic therapy or to delay biological progression of Alzheimer's disease. However, it does seem likely that some subgroups may benefit. In particular, several studies have suggested that short term (less than 2 years) use of estrogen is associated with decreased lifetime odds of developing dementia. In the large Multi-Institutional Research in Alzheimer's Genetic Epidemiology (MIRAGE) study, in the subgroup of women 50 to 63 years of age, estrogen use was associated with significantly lower risk for Alzheimer's disease than women who had never used estrogens or older women who were using estrogen.

Given the difficulties with using estrogen to prevent or treat Alzheimer's disease, their use for these indications has largely been abandoned. However, estrogens interact with literally dozens of proteins and receptors in the body and the brain, having both positive and negative actions. These actions involve regulating cholesterol, bone density, breast and uterine tissue, risk for stroke, as well as cognition and dementia. Drugs have been developed that are Selective Estrogen Receptor Modulators (SERMs), with major examples being tamoxifen and raloxifene. Tamoxifen has

been developed to suppress estrogen effects on the breast, delaying breast cancer recurrence in previously affected women. Raloxifene was originally developed to improve bone density, but also has breast cancer prevention effects. Raloxifene, within the brain, has a number of positive effects and may help preserve memory function in Alzheimer's disease and help improve mood in dementia patients. It can also reduce LDL cholesterol, and it does not seem to cause cardiovascular disease, which has been a concern with other estrogens.

Recently, a very large randomized placebo controlled trial, using raloxifene in 7,484 women with a mean age of 66 years and osteoporosis, was completed. No cognitive functioning differences were seen in women less than 70 years of age. However, in those over 70 years, verbal memory and attention were improved in women who took raloxifene. In another trial, lasting three years, of 5,386 post menopausal women who took raloxifene (120 mg/day) versus placebo appeared to have significant protective effects regarding reduced risk for developing mild cognitive impairment (MCI) or dementia in general. This suggests that raloxifene has promise as a treatment for Alzheimer's disease.

With the preliminary findings above, a recent 2-site trial of raloxifene versus placebo with a duration of 12 months in 72 post-menopausal women with mild to moderate Alzheimer's disease was organized. It was designed to determine whether raloxifene 120 mg/day would preserve or improve cognition, function in activities of daily living and behavior. In this trial, raloxifene or placebo will be given in addition to standard cholinesterase inhibitor therapy. Volunteers interested in participation may obtain further information by calling the Study Coordinator, Sheryl Lynch at (317) 278-8307.

Research Opportunities

Prevention of Alzheimer's Disease by Vitamin E and Selenium (PREADVISE)

- Purpose: As a prevention trial, PREADVISE is trying to find out if taking selenium and/or Vitamin E supplements can help to prevent memory loss and dementia such as Alzheimer's disease.
- Eligibility: Ages: 60 - 90, Male. Accepts Healthy Volunteers
- Locations: AL, AK, CA, CO, DC, FL, GA, IA, KS, KY, MD, MA, MI, MN, MS, MO, MT, NE, NV, NJ, NY, OH, OK, PA, SD, TN, TX, WA, WI, CANADA, PUERTO RICO
- Contact: Cecil R. Runyons
PH: 1-859-257-1412 Ext. 235
E-mail: preadvise@lsv.uky.edu

GIFT: Genetic Investigation in Frontotemporal Dementia and Alzheimer's Disease

- Purpose: To perform DNA studies to evaluate the genetic contribution to Alzheimer's Disease (AD) and Frontotemporal Dementia (FTD). Using a microarray-based approach, 80 genes related to neurodegeneration will be resequenced in order to identify rare mutations or risk-associated genetic variants.
- Eligibility: Subjects with clinical diagnosis of AD or FTD. Healthy volunteers.
- Locations: CA, GA
- Contact: <http://geschwindlab.neurology.ucla.edu/gift>

Anti-Oxidant Treatment of Alzheimer's Disease

- Purpose: To examine the safety and effectiveness of two anti-oxidant treatment regimens in patients with mild to moderate Alzheimer's disease. The anti-oxidant treatments include vitamin E+ C+ alpha-lipoic acid, and Coenzyme Q (CoQ).

- Eligibility: Ages 60-85, Both genders, Diagnosis of probable Alzheimer's Disease.
- Locations: AL, AZ, CA, FL, NY, OH, OR, PA, SC, WA
- Contact: ADCS Anti-Oxidant Study webpage http://adcs.ucsd.edu/Anti-Oxidant_protocol.htm or Linda Mandelco E-mail: linda.mandelco@med.va.gov

MIRAGE: Multi-Institutional Research in Alzheimer's Genetic Epidemiology

- Purpose: In the third phase of this study, researchers continue to evaluate genetic and non-genetic risk factors for Alzheimer's disease. There is a particular emphasis on exploring whether risk factors for vascular disease are also contributing risk factors for AD. It is hoped that by obtaining data from 1000 families, these associations can be better understood.
- Eligibility: Siblings (brothers and sisters) both of whom are at least 60 years of age, one of which has been diagnosed with Alzheimer's disease, willing to undergo a blood draw and a MRI scan along with answering questions regarding their family history.
- Contact: Contact: Michael Wake
E-mail: mirage@bu.edu

Depression in Alzheimer's Disease

- Purpose: To demonstrate whether the medication sertraline (Zoloft®) helps people with Alzheimer's disease. Through this study we hope to find out if treating depression can slow the progression of Alzheimer's disease.
- Eligibility: People who suffer from memory loss, Alzheimer's disease, and symptoms of depression. Participants must also be accompanied by their caregiver.
- Locations: CA, MD, NY, PA, SC
- Contact: Ann Morrison, PhD, RN
PH: 410-614-4605
E-mail: amorris7@jhmi.edu

The Genetics of Late Alzheimer's Disease (LOAD)

- Purpose: To identify families with multiple members diagnosed with late-onset Alzheimer's Disease. Families will be characterized clinically and blood samples will be collected to establish cell lines. If a blood sample is not available, autopsy samples will be collected for DNA extraction and storage. Our goal is to recruit 1,000 families over the course of the study. Clinical and demographic data from these families will be collected at the local site and coded data, without identifiers, will be sent and included in a national database of families with Alzheimer's Disease. This database, along with the biological samples, will be housed at the National Cell Repository for Alzheimer's Disease (NCRAD) at Indiana University.
- Eligibility: Two siblings (brothers or sisters) who developed AD after the age of 60 and another family member over 50 who may have memory loss or a family member over 60 who does not have any memory loss. Participants can live anywhere in the U.S. and can be of any racial or ethnic background.
- Locations: (sites in following states, but participation is open to subjects all over the United States) AL, CA, FL, IL, IN, KY, MA, MN, MO, NC, NY, OR, PA, TX, WA
- Contact: 1-800-526-2839

Sources for Information and Support

Alzheimer's Association

<http://www.alz.org>

Tel: 312-335-8700 or 800-272-3900

Alzheimer's Disease Education and Referral Center (ADEAR)

<http://www.nia.nih.gov/Alzheimers>

Tel: 301-495-3311 or 800-438-4380

** ADEAR lists all 29 Alzheimer's Disease Centers (ADCs) and their contact information.

Depression and Related Affective Disorders Association (DRADA)

www.drada.org

Tel: 703-610-9026

Family Caregiver Alliance

<http://www.caregiver.org>

Tel: 415-434-3388 or 800-445-8106

National Parkinson Foundation

<http://www.parkinson.org/>

Tel: 305-547-6666 or 800-327-4545

Parkinson's Disease Foundation (PDF)

www.pdf.org

Tel: 212-923-4700 or 800-457-6676

Society for Progressive Supranuclear Palsy

<http://www.psp.org>

Tel: 410-486-3330 or 800-457-4777

National Organization for Rare Disorders (NORD)

<http://www.rarediseases.org>

Tel: 203-746-6518 or 800-999-NORD (6673)

Center for Disease Control and Prevention (CDCP)

<http://www.cdc.gov>

Tel: 800-311-3435

Creutzfeldt- Jakob Foundation Inc.

<http://cjd.foundation.org>

10 Signs of AD

1. Memory loss.
2. Difficulty performing familiar tasks.
3. Problems with language.
4. Disorientation to time and place.
5. Poor or decreased judgment.
6. Problems with abstract thinking.
7. Misplacing things.
8. Changes in mood or behavior.
9. Changes in personality.
10. Loss of initiative.

If you recognize several of these warning signs in yourself or a loved one, the Alzheimer's Association recommends consulting a physician. Early diagnosis of Alzheimer's disease or other disorders causing dementia is an important step in getting appropriate treatment, care, and support services.

For more information, call the Alzheimer's Association at (800) 272-3900.

NCRAD Staff > continued from page one

IUPUI, first in the School of Dentistry, and now with NCRAD. In the NCRAD laboratory, he is responsible for DNA extractions, lymphocyte immortalization, cell culture, and completing requests for DNA samples. Mike is also responsible for operating the Biomek 3000, a new robot that was recently installed in the NCRAD laboratory, to help the staff more rapidly prepare samples for distribution to researchers.

Lisa Beach, BS joined the laboratory in 2004. She graduated from IUPUI with a Bachelor of Science in Biology in 2003. Her prior research experience includes studying the regulation of pituitary hormone genes involved in reproduction as well as the properties of transcription factors involved in limb regeneration. Her NCRAD lab responsibilities include DNA extractions and cell immortalizations.



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