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VA Research Currents

RESEARCH NEWS FROM THE U.S. DEPT. OF VETERANS AFFAIRS

Seeking genetic clues to schizophrenia, bipolar disorder

Major VA trial will analyze DNA, clinical information from up to 38,000 veterans

A new study funded by VA will probe the genetic basis of schizophrenia and bipolar disorder, which together affect some 170,000 patients in VA's health system.

The $33-million effort will involve up to 38,000 veterans at about 25 VA sites—one of the largest single studies of its kind to date worldwide. The study will include up to 9,000 people with schizophrenia, 9,000 with bipolar disorder, and another 20,000 without either disease, as controls.

"We've been hunting for genes of susceptibility for these two diseases, and you need a very large sample to establish genome-wide association," says Larry J. Siever, MD, of the Bronx VA and Mount Sinai School of Medicine, one of the study's chairs.

Siever says veterans' genetic results— as well as other information they provide to the study team—will be linked to their VA medical records. That way, researchers can tap into richly detailed medical histories—sometimes decades long—and reveal links between genes and health problems.

"The VA is unique among U.S. health-care systems in having a great electronic medical record and cohort of people who stay in the system," says Siever. He says information gained through the study may be useful in follow-up efforts, as well.

The study leaders say strict privacy safeguards will be in place. For example, databases will be password-protected and specimens will be bar-coded and "de-identified." This means they can be traced back to the individual veterans who supplied them, but only by researchers who go through a strict approval process.

Veterans who volunteer for the effort will provide a blood sample from which their DNA will be isolated. The researchers,

see **SCHIZOPHRENIA** on pg. 8

Deep freeze—Lab tech Christine Govans prepares to remove frozen biospecimens from a liquid-nitrogen "cryotank" at VA's Massachusetts Area Veterans Epidemiology Research and Information Center. The center's huge, secure biorepository will store blood and DNA samples from veterans in the schizophrenia and bipolar study.

TBI research featured in *JRRD*

The next issue of VA's *Journal of Rehabilitation Research and Development (JRRD)* will feature 19 timely scientific articles on traumatic brain injury, based on work by VA researchers and colleagues from a variety of disciplines. The papers were commissioned for a "state of the art" conference VA held last year to advance research in this area. The entire issue will be available online in November at *www.rehab.research.va.gov/jour/jourindx.html.*

Passion for 'building things' drives prosthetics career

Asked what drew him to prosthetics engineering, Richard Weir, PhD, goes back to his childhood in Ireland. "I have a twin sister who lost a hand when she was five. My father was a doctor, my uncle was an engineer, and I've always been interested in science fiction, robots and androids. I imagine it's an amalgam of all those things."

Today, as a scientist with VA, Northwestern University and the Rehabilitation Institute of Chicago, Weir is on the leading edge of prosthetics technology.

His group is part of an effort funded by the Defense Advanced Research Projects (DARPA) to build the world's most advanced prosthetic arm. They partnered with a private firm, Otto Bock, and the Applied Physics Lab at Johns Hopkins University to build a 15-motor hand for an arm system that was unveiled in 2007. The system is now being further developed. Weir also consulted on a different prosthesis—known as the DEKA arm—that was developed through the same overall DARPA initiative and is now being tested with veterans at several VA sites.

Building the initial DARPA hand was an engineering challenge, says Weir: "Weight is a huge issue, but it was also a question of robustness and speed. Could you meet the torque, speed and energy requirements and still do it at the correct weight? We showed it could be done." A natural hand has about 22 "degrees of freedom"—that's how many different ways it can move, bend, twist and turn. The DARPA model built by Weir's team and collaborators wasn't far behind; it had 18 degrees of freedom.

Weir's team is also exploring how to harness the body's natural movement impulses to control artificial limbs. Specifically, they are working on getting prosthesis control signals from all 18 forearm muscles through implantable myoelectric sensors (IMES).

The sensors are about a half-inch long and almost as thin as a grain of rice. They consist of a microchip, developed at the Illinois Institute of Technology, housed in a ceramic cylinder. At each end is a metal cap. The caps pick up the electrical impulses put out by muscles when they contract. The chip sends these myoelectric signals to a controller inside the prosthesis. There, the signals get translated into mechanical commands for the hand.

The sensor's outer casing was developed by the California-based Alfred Mann Foundation. The inner works are the product of Weir's lab.

see **PROSTHETICS** on next page

High-tech handyman—Dr. Richard Weir and his team design and build upper-limb prosthetics and control systems.

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PROSTHETICS *(from previous page)*

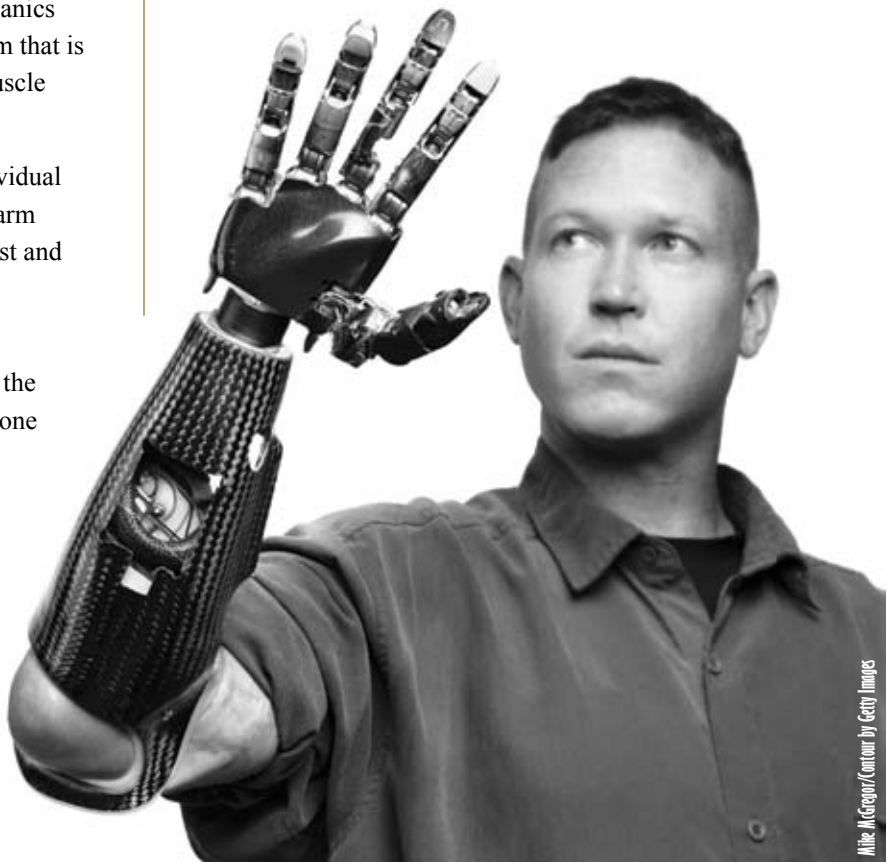
Weir's VA colleague Wendy Murray, PhD, a biomechanics expert, has created a 3-D musculoskeletal map of the arm that is guiding Weir's team as they learn how to convert the muscle signals into control signals.

Potentially, a user would think about bending an individual finger, say, and the impulse would go from brain to forearm muscles to sensor to prosthetic hand in an instant—as fast and smooth as nature itself, ideally. The greater the muscle contraction, the stronger the signal.

The IMES talk with the prosthesis controller through the skin via a radio link. "It's all wireless," says Weir. "The one thing the body really doesn't like is having wires pass through the skin."

The goal is to inject the tiny devices into the muscle with a hypodermic needle. "We want them to be injectable so we don't have to use surgery to put them into someone," remarks Weir. "A person who has undergone amputation surgery is usually reluctant to have more surgery."

Veteran Jon Kuniholm, who lost an arm in Iraq, took part in research at Weir's lab as part of a DARPA-funded prosthetics project.



Sensors would be stable in muscles 'for a lifetime'

So far, the sensors have performed well in animal studies. Weir says they "get encapsulated in fibrous tissue and get held in place in muscle." When they are ready for use in people, he notes, the goal will be "that they be rock-solid and stable in a person for their lifetime."

The next step for the IMES is a clinical trial in which they will be implanted in the forearms of volunteers. In a separate effort being planned with Hugh Herr, PhD, of the Providence (R.I.) VA and the Massachusetts Institute of Technology, the devices will be placed in patients' leg muscles.

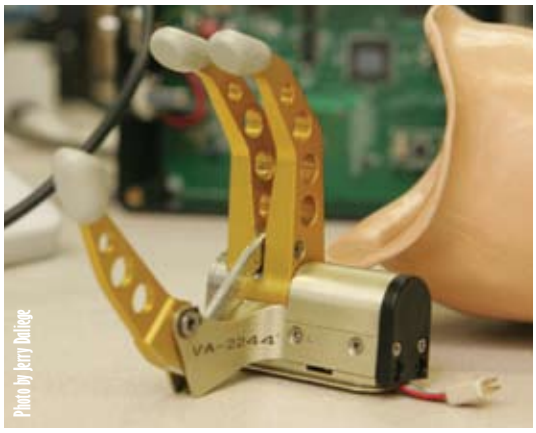
"Eventually, there'll be many applications for them," says Weir. "Anywhere you need to sense muscle signals. The IMES are a platform technology that has the potential to make a huge difference to people who use prostheses. It's fine and dandy to build [fancy devices], but if you can't control them, what's the point?"

Replicating the intricate workings of the human hand is a sort of Holy Grail for prosthetics researchers. But there's also a need—and market—for less elaborate devices. Weir's lab is active on this front as well. One of his VA-funded projects is a "partial" prosthetic hand for people with an intact wrist but no thumb or fingers. Weir demonstrated a prototype at a Senate hearing in 2006. The device opens and closes in response to electrical signals from residual muscles in the forearm. With two electrodes wired to his arm, a senator was able to control the hand and use it to hold a glass of water.

"It's a simple device that addresses a particular niche and will be of benefit to patients at that level," says Weir.

It seems the engineer is happy as long as he is building something that works well for the intended purpose—regardless of how simple or complex it may be. "That's what I believe I'm good at. I build things—I really don't mind what. Electrical circuits, mechanical pieces, cars, Legos—anything."

Weir's lab's partial prosthetic hand is for people with an intact wrist but no thumb or fingers.



Hot topic— Taking part in a panel discussion at a Sept. 23 symposium on comparative effectiveness research were (from left) Drs. David Atkins, Peter Peduzzi, John Concato, Grant Huang and Tricia Dorn, all with VA.

'Comparative effectiveness' event highlights VA role

"We need to know what works. We need to really understand what treatments make a difference, where we should put our best efforts, where we should put our resources."

With these words, Gerald Cross, MD, acting under secretary for health for VA, set the tone for a symposium held on Sept. 23 in Washington, DC, highlighting VA's 30-year track record in comparative effectiveness research. The event featured talks and panel discussions by leading researchers from VA, the National Institutes of Health and other federal agencies, and academic medical centers. The focus: What lessons could be learned from VA's experience?

Comparative effectiveness research (CER) compares medical treatments head-to-head to find out which ones work best for defined groups of patients. The topic has been in the news because of its potential role in health care reform. These types of clinical trials are by no means new, but increased federal funding may expand their number and scope.

VA's chief research and development officer, Joel Kupersmith, MD, is one of 15 members of the new Federal Coordinating Council for Comparative Effectiveness Research, created earlier this year to oversee $1.1 billion in research funds allocated through the American Recovery and Reinvestment Act of 2009.

At the symposium, Kupersmith gave an overview of current comparative effectiveness research in VA. Other presenters and panels addressed topics such as VA's unique role in CER; methodological challenges; the translation of study results into everyday clinical practice; and the best ways to use CER to save health care dollars.

One example of VA-sponsored CER cited at the meeting was a large clinical trial, conducted in collaboration with Canada's national health agency, that showed that a common heart treatment called percutaneous coronary intervention—also known as balloon angioplasty—does little to improve outcomes for patients with stable coronary artery disease who also receive optimal drug therapy and improve their diet and exercise habits.

Another focus was VA's Quality Enhancement Research Initiative, which helps apply study results to improve VA care.

To view all the slide presentations from the meeting, go to *www.research.va.gov/CEResearch/agenda.cfm.*

High blood pressure and combat deployment—A team with the Millennium Cohort Study, a joint effort between VA and the Department of Defense, tracked newly reported cases of hypertension among more than 36,000 service members who were surveyed in 2001 through 2003 and again three years later. Troops deployed in support of the wars in Iraq and Afghanistan generally had a lower incidence of hypertension than non-deployed troops. However, among deployed troops, those with multiple combat exposures were a third more likely to develop high blood pressure than those with no exposures. Overall, about 7 percent of the troops who responded to the survey developed hypertension. (*Hypertension,* online Sept. 14, 2009)

Fourth Infantry Regiment soldiers on patrol last month in Zabul province, Afghanistan.

Genetic link to rare bone cancer—VA, Duke University Medical Center and National Cancer Institute researchers discovered that people who inherit a second copy of a gene known simply as "T" are at greater risk for familial chordoma, a rare bone cancer. The investigators screened 65 people, 21 with chordoma, from seven families with a history of the disease. Guided by earlier studies, they specifically looked for changes in the T gene on chromosome 6. They found that all those with chordoma in four of the seven families had a second copy of the T gene. No such variation was found in 100 normal subjects. Curiously, though, the duplication did not appear among affected members of the three other families. "It is likely that other genes are at work here, or that some other mechanism we do not yet understand is in play," said senior author Michael Kelley, MD, chief of hematology and oncology at the Durham VA. (*Nature Genetics,* online Oct. 4, 2009)

Past violence tied to suicide risk—Among people seeking treatment for substance abuse, those with a history of violent behavior are more likely to think about suicide or actually attempt it, according to an Ann Arbor-based VA study of 6,233 patients. Those who had committed extreme violence—murder or rape, for example—were the most likely to have made multiple suicide attempts. The association between violence and suicidal ideas and attempts remained even after researchers adjusted for factors such as depression and childhood victimization. (*Addictive Behaviors,* online Sept. 10, 2009)

Racial, ethnic disparities in breast cancer care—Latinas who spoke little English were less likely to undergo reconstruction surgery after a mastectomy for breast cancer, according to a study led by a team with VA and the University of Michigan. The study included 806 white, African American, and Latina women in Detroit and Los Angeles. The Latinas were grouped accorded to their acculturation level—how well they had integrated into American society. Whether they mainly spoke English or Spanish was a key factor. The team found 41 percent of white women and 41 percent of highly acculturated Latinas had reconstruction, while only 34 percent of African Americans and 14 percent of less-acculturated Latinas did. The lower reconstruction rates were not due to a lack of interest: More than half of the less-acculturated Latinas, for example, said they would have liked more information about breast reconstruction. "We have good data that show reconstruction after mastectomy improves quality of life," said study leader Amy Alderman, MD, MPH. "This is a body part that affects women's self-esteem, body image, sexuality and social roles. Not all women should necessarily choose reconstruction—it's not right for everyone. But all women should be presented the option." (*Journal of Clinical Oncology,* online Oct. 5, 2009)

Nutrient tested—Dr. Joseph Quinn of VA and Oregon Health and Science University led a nationwide clinical trial of DHA to test it as a therapy for Alzheimer's disease. Millions of Americans take DHA supplements in softgels or other forms, from fish or vegetarian sources, because of the reported benefits for the heart and brain.

The Alzheimer's brain on fish oil: Mixed results in studies

If there were a Hall of Fame for good fats, DHA would be a shoo-in. DHA is the most widely known of the omega 3 fatty acids—one of several groups of essential fats people need in their diet to be healthy.

There are good food sources of the nutrient, but many people get extra DHA in their diet by taking supplements—usually in the form of fish oil. There's more than marketing hype here: Many studies have shown that DHA helps the heart and brain. But one key question has lingered unresolved: Can DHA stop—or at least slow—Alzheimer's disease?

A recent clinical trial funded by the National Institute on Aging and led by a VA researcher sheds light on the question. Results from the 18-month nationwide study were announced this summer at the 2009 international meeting of the Alzheimer's Association.

A team led by Joseph Quinn, MD, of the Portland VA and Oregon Health and Sciences University, compared DHA from algae-based supplements against placebo in 402 older people with mild to moderate Alzheimer's. The treatments boosted blood and brain levels of DHA but did not slow the rate of change on measures of Alzheimer's symptoms. The results "do not support the routine use of DHA for patients with Alzheimer's," Quinn said.

However, in a sub-analysis, participants who lacked a gene called ApoE-e4—shown in genetics studies to be a risk factor for Alzheimer's—benefited somewhat from DHA. They had a slower rate of decline on two tests of mental function.

DHA—the key nutrient in fish oil—may exert different effects based on people's genetic make-up.

Quinn called the finding "an intriguing exploratory result" that requires confirmation. He is now planning a trial of DHA for patients with mild cognitive impairment, an Alzheimer's precursor. His team will look closely at how DHA's effects differ by whether people have the ApoE-e4 gene.

In other research reported at the Alzheimer's Association meeting, Martek Biosciences Corporation—maker of the algae-based DHA supplements used in the trial led by Quinn—examined the effects of their product in 485 healthy older people with mild memory complaints. People who took the DHA capsules for six months performed better than those taking placebos.

According to William Thies, PhD, of the Alzheimer's Association, "These two studies—and other recent Alzheimer's therapy trials—raise the possibility that treatments for Alzheimer's must be given very early in the disease for them to be truly effective."


Suppes


O'Leary


Werner

Trisha Suppes, MD, PhD, director of the Bipolar Disorder Research Program at the Palo Alto VA, part of the site's War-Related Injury and Illness Study Center, received the 2009 Gerald L. Klerman Senior Investigator Award from the Depression and Bipolar Support Alliance for her research on mood disorders. Among Suppes' current studies is a clinical trial comparing three different drug treatments for mania, which can occur in either bipolar disorder or schizophrenia. The work is funded by the National Institute of Mental Health.

Timothy J. O'Leary, MD, PhD, deputy chief research and development officer for VA, will serve as editor-in-chief of the *Journal of Molecular Diagnostics.* His term begins in January 2010. Along with his leadership role in VA research, O'Leary is well-known for his work in molecular diagnostics. Prior to his VA service, he chaired the department of cellular pathology at the Armed Forces Institute of Pathology, where he expanded the use of molecular genetics and tissue magnetic resonance microscopy. His own research has focused on gastric tumors, detection of biological toxins, and the changes that occur in tissue specimens preserved in formaldehyde.

Rachel Werner, MD, PhD, a health economist with the University of Pennsylvania and VA's Center for Health Equity Research and Promotion, received the Alice S. Hersh New Investigator Award from AcademyHealth, the leading professional society for health services researchers and health policy analysts. Werner studies the effects of "pay for performance" and other quality-improvement initiatives on provider behavior, the organization and financing of health care, racial disparities in care, and overall health care quality.

Visionary research—Physician-researcher Glenn Cockerham, MD, seen here with Marine Cpl. Jason Poole, was the recipient, along with colleague Gregory Goodrich, PhD, of VA's 2009 Olin E. Teague Award. Both doctors are vision researchers at the VA Palo Alto Health Care System. Cockerham, chief of ophthalmology at the Palo Alto VA, has studied the anatomical and functional effects of traumatic brain injuries on the eye. Goodrich, a psychologist, has spearheaded research on diagnosing and treating the sometimes hard-to-detect effects of these brain injuries on vision. Through their research, they aim to develop innovative screening measures and therapies, as well as provide data to the Department of Defense to help guide preventive efforts to protect the vision of combat troops.

The Olin E. Teague Award is named after the late congressman from Texas, who served 32 years (1946 to 1978),18 of which were as chairman of the House Committee on Veterans' Affairs. Teague, known as "Tiger," was the second most decorated combat veteran of World War II, having been wounded six times. He participated in the D-Day invasion of Normandy and became a strong veterans' advocate in Congress.

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Inside: **Fish oil and Alzheimer's disease: What does the latest research show?**

SCHIZOPHRENIA *(from page 1)*

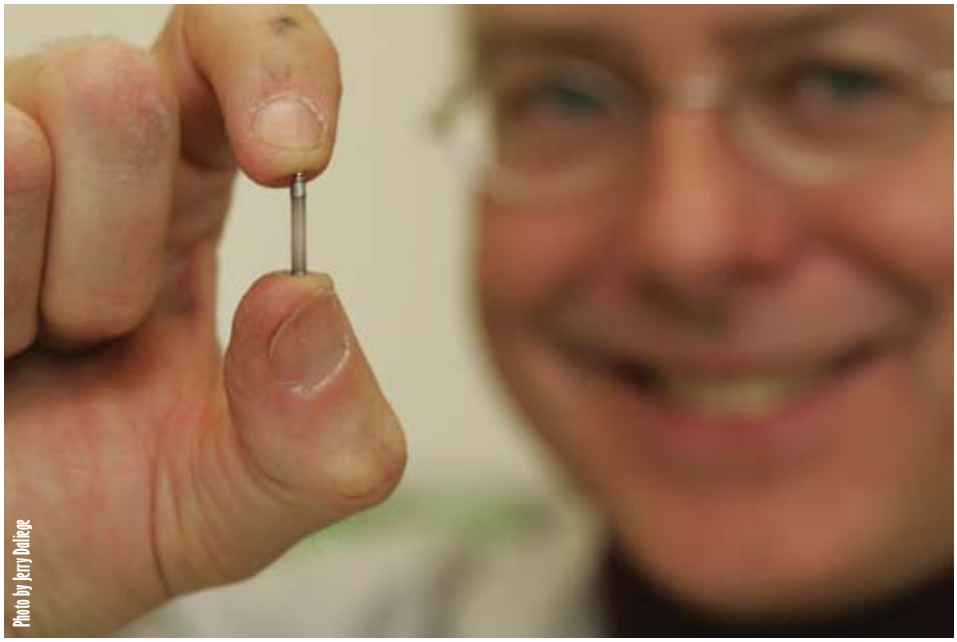
including a lab team at Yale University, will scan the DNA for hundreds of thousands of genetic variants. Those found in veterans with mental illness but not in "healthy" veterans will become suspects in the hunt for genetic risk factors. To date, a number of candidate genes have been linked to the two diseases, but none has yet led to concrete steps to boost care.

The researchers also hope to find genes tied to thinking problems and trouble with everyday tasks. Both types of symptoms are common in schizophrenia and bipolar disorder. Study volunteers will take pencil-and-paper tests that measure cognitive skills such as attention or memory. They'll also be observed writing checks, making telephone calls, and doing other everyday activities.

According to Siever, the ability to do such tasks—which can vary widely in people with serious mental illness—is a key predictor of overall function. He calls it "the great limiting factor determining whether people with schizophrenia or bipolar disorder can gain employment and function in society."

VA's chief deputy chief research and development officer, Timothy J. O'Leary, MD, PhD, says he expects the new study to have a major impact on care for the two diseases. "This research will be critical in helping us better understand the genetic basis of schizophrenia and bipolar disorder, which have such a huge impact within VA's health care system and in the nation at large. The knowledge gained through the study will no doubt lead to improvements in prevention, diagnosis and treatment."

Co-directing the study with Siever are Philip Harvey, PhD, with the Atlanta VA and Emory University; John Concato, MD, with Yale and VA's New Haven-based Clinical Epidemiology Research Center; and J. Michael Gaziano, MD, of VA's Massachusetts Area Veterans Epidemiology Research and Information Center. The study is funded by VA's Cooperative Studies Program.



Small wonder—VA prosthetics engineer Dr. Richard Weir displays an implantable myoelectric sensor. The devices, now in development, would be injected into muscles and pick up electrical signals to drive artificial limbs. Read more about Weir's leading-edge work inside.