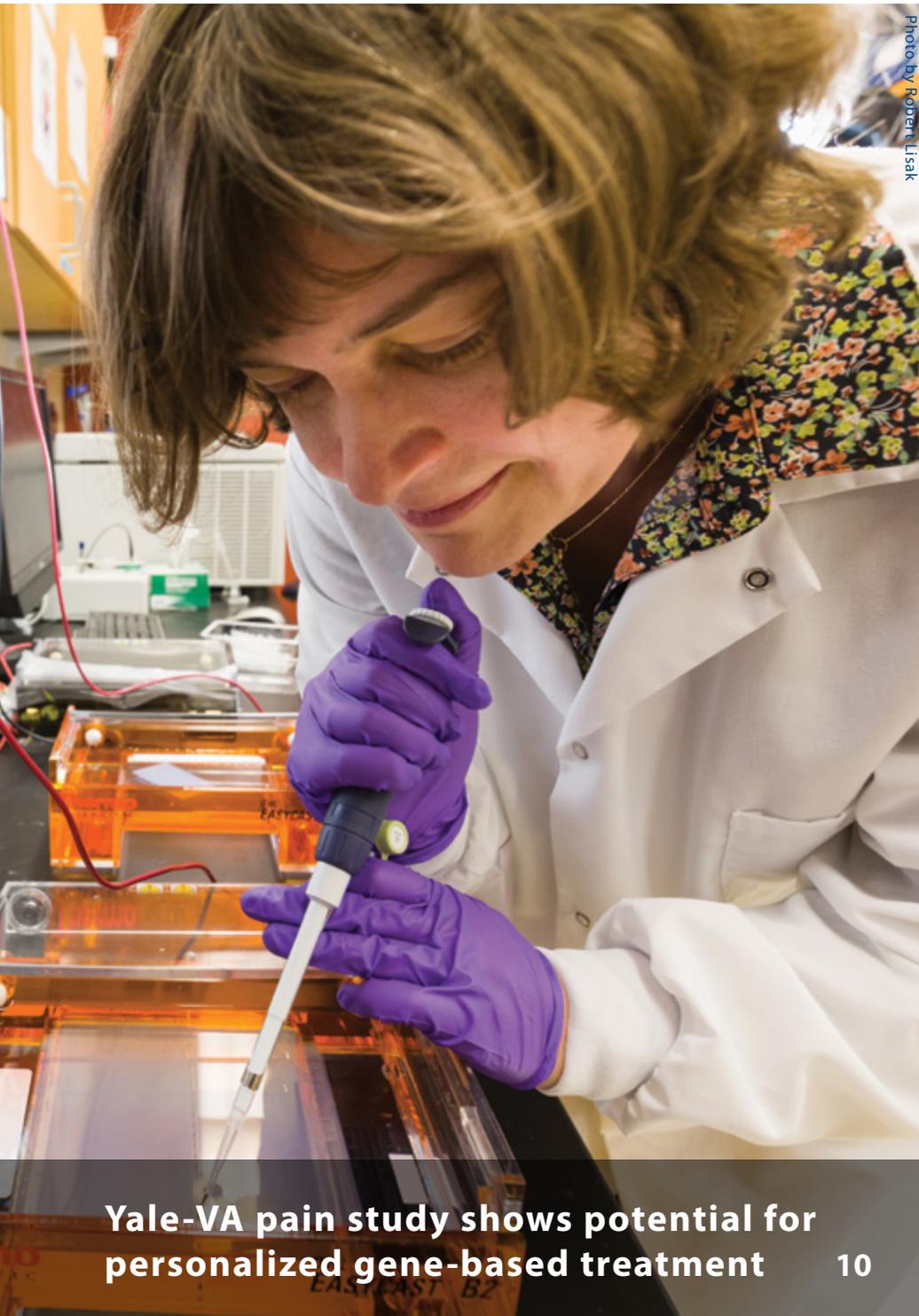


VA

RESEARCH CURRENTS

Research News from the U.S. Department of Veterans Affairs



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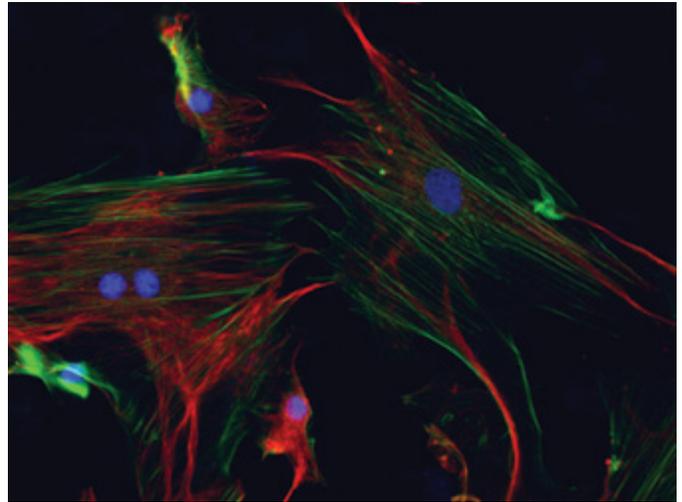
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This fluorescence image shows mesenchymal stem cells derived from bone marrow. The blue spots are nuclei, and the green and red filaments are different proteins.

Healing diabetic wounds with stem cells

A VA and Yale University team, with British and Chinese collaborators, has devised a new way to deliver stem cells for healing diabetic ulcers. They say the method, shown to work in diabetic mice, has a good chance of working in humans.

The experimental treatment uses mesenchymal stem cells, which are found mainly in bone marrow. They naturally turn into various cell types—bone, fat, muscle, cartilage—and in recent years researchers have been trying to learn how to harness them to regenerate tissue.

The VA-Yale team applied the cells to mouse wounds using a collagen scaffold designed to mimic the low-oxygen environment of bone marrow.

The researchers showed that this approach triggers the release of a protein called vascular endothelial growth factor, which spurs the stem cells to grow and differentiate. It also allows the cells to survive longer.

Mice that received the cell-infused scaffolds showed improved wound healing, compared with mice that were treated with the collagen scaffolds alone, or with straight injections of the stem cells alone. The mice that received the full treatment



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showed higher levels of macrophages—a type of white blood cell that eats cellular debris and harmful pathogens. They also had more new fibroblasts—proteins that act as building blocks for the “extracellular matrix” that supports cells—as well as more smooth muscle cells.

The experiment is described in the April 2016 issue of the journal *Regenerative Medicine*.

Read more at www.research.va.gov/currents

Study: Older age alone shouldn't rule out knee replacements

A review and analysis of the existing literature by Iowa City VA Health System and University of Iowa researchers suggests that advanced age by itself should not disqualify people from getting knee replacements.

The findings appeared online Feb. 10, 2016, in the journal *BMC Geriatrics*.

Knee replacement, known medically as total knee arthroplasty, is a common and effective procedure to treat osteoarthritis of the knee. Knee replacement can relieve severe pain and allow people to carry out everyday actions like walking, climbing stairs, and getting out of chairs. More than 600,000 knee replacement surgeries are performed in the U.S. each year, according to the American Acad-



The rate of total knee replacement increased by 120 percent between 2000 and 2009, with much of the growth occurring among osteoarthritis patients ages 45 to 64. Here, Dr. Said Ibrahim examines Lawrence Woodson at the Philadelphia VA Medical Center.

emy of Orthopaedic Surgeons. Knee replacement surgery can cost as much as \$10,000 to \$20,000, most of which is usually covered by insurance.

Most patients who undergo knee replacement are older, with 75 percent of U.S. patients over the age of 65. The rate of total knee replacement increased by 120 percent between 2000 and 2009, with much of the growth occurring among those ages 45 to 64. Experts say the increase stems from growing acceptance of invasive surgery and recognition of the improvements in pain, function, and independence that

knee replacement can provide.

However, surgical risk and cost may increase with age, especially in older patients with other medical conditions, which may lead to fewer elective total knee replacements. Indeed, patients older than 85 are 41 percent less likely than those under 85 to receive knee replacement surgery, and their doctors may be less likely to even offer the procedure.

Read more at www.research.va.gov/currents



A Veteran competes in the 2015 National Veterans Wheelchair Games. Research shows that about a third of people with spinal cord injuries end up needing three or more hospitalizations during their lifetime for treatment of pressure sores.

Study suggests biomarkers could help ward off pressure ulcers for spinal cord injury patients

A team including a VA researcher pinpointed two proteins—one in the blood, the other in the urine—that appear to warn of the risk of pressure ulcers in patients with spinal cord injury. Testing for the biomarkers could help in efforts to prevent the sores, which affect about a third of SCI patients during their initial hospitalization.

The results need to be confirmed in a larger study, say the authors, with the University of Pittsburgh and the VA Pittsburgh Healthcare System.

The findings appeared online Jan. 25, 2016, in the *Archives of Physical Medicine and Rehabilitation*.

Pressure ulcers are a serious problem for spinal-cord-injured patients and others with limited mobility. The sores are caused by prolonged pressure on the skin. For wheelchair users, they occur most commonly on the buttocks. The ulcers form quickly and can be difficult to treat. Without prompt, effective treatment, they can turn into deep, open wounds.

Read more at www.research.va.gov/currents

Study finds uptick in lung disease in recent Veterans

Among VA patients who served in Iraq and Afghanistan, the prevalence of asthma nearly tripled between 2003 and 2011, from 1.1 percent to 3.1 percent.

The rate of chronic obstructive pulmonary disease (COPD) also increased, though not as sharply— from 0.31 percent to 0.55 percent.

Those are two of the findings from a study on chronic lung disease among the more than 760,000 Veterans who served in Iraq or Afghanistan and received VA health care during the study period.

The study appeared in the May

2016 issue of *Military Medicine*.

The authors, led by a team at the South Texas Veterans Health Care System, say the findings “may suggest a link between deployment exposures and increased diagnoses of chronic lung disease in [Iraq and Afghanistan Veterans].”

Mixed findings in past research

The new results add to other studies by VA and other institutions suggesting that recent deployments may have contributed to new lung disease. But the exact causes aren't clear.

Experts recognize burn pits, sand and dust storms, and other environmental hazards of the Mideast war zones as possible contributing factors. But relatively high rates of cigarette smoking among troops and Veterans also appear to play a significant role.

And in fact, some research that used rigorous clinical testing—such as lung function tests—did not find differences between deployed and non-deployed troops. The question continues to be studied.

Read more at www.research.va.gov/currents ★

A U.S. Army soldier braves a cloud of dust near the Iraq-Iran border in 2009. A new study found an increase in chronic lung disease between 2003 and 2011 among VA patients who served in Iraq or Afghanistan.



DoD photo



Study: Symptoms of 'chronic multisymptom illness' may be common in Iraq, Afghanistan Veterans

In a study of more than 300 soldiers who had deployed to Iraq or Afghanistan, a majority reported symptoms consistent with “chronic multisymptom illness”—a diagnosis that up till now has been associated mainly with Gulf War service.



Doc photo

In a VA study of more than 300 enlisted Army National Guard and Army Reserve members who had deployed to Iraq or Afghanistan, a majority reported symptoms consistent with a condition known as chronic multisymptom illness (CMI). The data were collected a year after the soldiers returned home.

The results suggest that deployment to these conflicts could trigger symptoms consistent with CMI. The ailment presents as a combination of medically unexplained chronic symptoms, such as fatigue, headache, joint pain, indigestion, insomnia, dizziness, breathing problems, and memory problems.

The study, by researchers with VA's War-Related Illness and Injury Study Center (WRIISC) in New Jersey, appeared online Feb. 22, 2016, in the *Journal of Rehabilitation Research and Development*.

"As a whole, CMI can be challenging to evaluate and manage," said lead author Dr. Lisa McAndrew. "CMI is distinct from PTSD or depression. It contributes to significant disability."

McAndrew is also with the University at Albany.

In the Veteran community, chronic multisymptom illness has previously been associated mainly with deployment to the Persian Gulf during operations

Army soldiers take part in a training exercise on Tactical Base Gamberi in eastern Afghanistan in 2015. Emerging research suggests a majority of Iraq and Afghanistan Veterans have symptoms consistent with a condition known as chronic multisymptom illness.

Desert Shield and Desert Storm in the early 1990s. As many as 4 in 10 of those Veterans may be affected, according to the most recent estimates.

Experts aren't sure, though, if that condition is the same one that has emerged among more recent Veterans, as documented in the newest WRIISC study and one or two earlier ones. Last year, for example, researchers with the Millennium Cohort Study reported that about a third of combat Veterans who served in Iraq and Afghanistan had CMI symptoms.

"This condition appears to be similar to that experienced by many Gulf War Veterans, in terms of the symptoms, but we don't really know if it's the same condition," says McAndrew. "That still requires study."

Rates of CMI higher after deployment

McAndrew and her colleagues surveyed 319 soldiers about their overall health before they deployed and one year after they returned. The VA team found there were 150 soldiers who did not report many symptoms before they deployed but who reported symptoms of CMI one year after deployment, suggesting a link between deployment to Iraq or Afghanistan and CMI.

In total, nearly 50 percent of the overall group met the criteria for mild to moderate CMI, and about 11 percent met the criteria for severe CMI, one year after deployment.

The most common symptoms reported were trouble sleeping, moodiness or irritability, joint pain, fatigue, difficulty remembering or concentrating, headaches, and sinus congestion.

Not surprisingly, the researchers found that Veterans who screened positive for CMI scored significantly lower on measures of physical and mental health function.

Strong link with chronic pain

Of the 319 Veterans in the study, 166 had chronic pain, lasting more than three months. Almost all of those with chronic pain—90 percent—also met the criteria for CMI. Similarly, 82 percent of those with CMI reported chronic pain.

The finding underscores the strong link between chronic pain and CMI, say the researchers.

The study also found that almost all Veterans with PTSD symptoms also showed signs of CMI—about 98 percent. Only seven patients had PTSD and did not meet the criteria for CMI. In contrast, though, about 44 percent of the Veterans with CMI did not have PTSD. In other words, the link between PTSD and CMI was not as robust as that between chronic pain and CMI.

The authors caution that the study looked only at pain and PTSD as factors tied in with CMI. It did not document other conditions that could possibly account for the symptoms of CMI, such as depression, traumatic brain injury, and substance abuse. At the same time, they say these other conditions are unlikely to completely account for the frequency of symptoms seen in the study.

By the same token, other conditions not examined in the study, such as arthritis or multiple sclerosis, could cause symptoms similar to those of CMI. More research is needed to tease out those variables.

Another limitation of the study: The research team used a definition of CMI, established by the Centers for Disease Control and Prevention (CDC), that is based on Gulf War Veterans. They say it might not exactly fit the symptoms of Veterans of the more recent conflicts.

Also, it's unclear whether the Guard and Reserve members surveyed in the study are representative of the larger Veteran or military cohort who deployed to Iraq and Afghanistan.

"As a whole, CMI can be challenging to evaluate and manage."

All in all, the research team advises that the results be interpreted with caution.

“We’re taking the approach that an abundance of caution is necessary in the clinical implications of the findings,” says McAndrew. “Respondents self-reported symptoms on pen and paper surveys. The symptoms were not confirmed or evaluated by a clinician. While the CDC case definition is fairly clear-cut, in clinical practice there is a lot of gray area around applying the label of CMI. We used the term ‘symptoms consistent with CMI’ to indicate the uncertainty due to the self-reported, clinician-unverified nature of the classification.”

Recommendation to clinicians: Consider CMI

Pending further research on the topic, McAndrew’s group says clinicians in VA or other settings should consider CMI when evaluating Iraq and Afghanistan Veterans, especially those with chronic pain. Once the condition is identified, clinicians in VA and the Department of Defense do have a clinical practice guideline for managing the condition.

“Acknowledging the presence of multiple symptoms and taking a holistic approach to achieving patient goals is critical in managing CMI,” says McAndrew. For example, pain management may need to be tailored to account for other symptoms of CMI.

The WRIISC study notwithstanding, McAndrew says not enough attention has been focused on the issue to date.

“There have been few studies of CMI among Iraq and Afghanistan Veterans. Our findings suggest this could be an overlooked problem.”

Senior researcher on the WRIISC study was Dr. Karen Quigley, now at the Edith Nourse Rogers Memorial Veterans Hospital and Northeastern University. ★

Cinnamon may be fragrant medicine for the brain

If Dr. Kalipada Pahan’s research pans out, the standard advice for failing students might one day be: Study harder and eat your cinnamon!

Pahan a researcher at Rush University and the Jesse Brown VA Medical Center in Chicago, has found that cinnamon turns poor learners into good ones—among mice, that is. He hopes the same will hold true for people.

His group published their latest findings in the *Journal of Neuroimmune Pharmacology*.

“The increase in learning in poor-learning mice after cinnamon treatment was significant,” says Pahan. “For example, poor-learning mice took about 150 seconds to find the right hole in the Barnes maze test. On the other hand, after one month of cinnamon treatment, poor-learning mice were finding the right hole within 60 seconds.”

Pahan’s research shows that the effect appears to be due mainly to sodium benzoate—a chemical produced as cinnamon is broken down in the body.

If that chemical sounds familiar, you may have noticed it on the ingredient labels of many processed foods. Food makers use a synthetic form of it as a preservative. It is also an FDA-approved drug used to treat hyperammonemia—too much ammonia in the blood.

Read more at www.research.va.gov/currents ★



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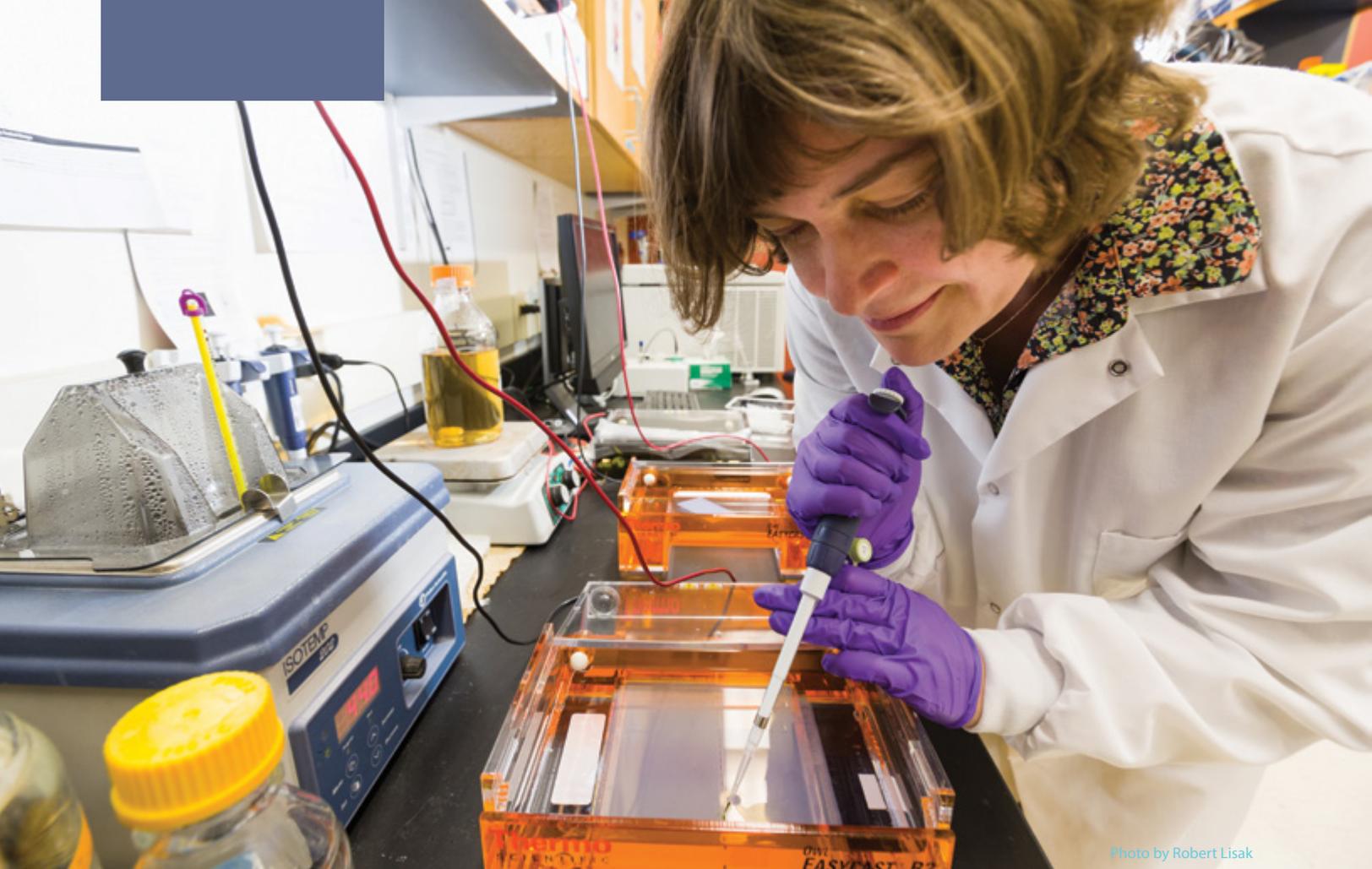


Photo by Robert Lisak

Yale-VA study yields promising results from genetically tailored pain treatment

A Yale-VA team used genetic information to tailor drug therapy for two patients with an inherited chronic pain syndrome. The researchers believe the approach may have wide potential for treating pain.

Researchers at the Yale School of Medicine and the VA Connecticut Healthcare System have successfully tailored a personalized treatment approach for chronic pain in a severe pain syndrome known as inherited erythromelalgia.

The findings appear in the June 2016 issue of *JAMA Neurology*.

Inherited erythromelalgia is also known as “Man on Fire” syndrome. It occurs when genetic mutations cause the body’s pain-sensing system to go into high gear. This leads to flare-ups of pain and burning sensations in response to seemingly benign triggers, such as warm temperature and mild exercise.

The Yale-VA team used molecular modeling and other techniques to find the most effective drug treatment plan for two patients, both from the same family. The search was guided by the exact location of the mutation in each patient’s genome.

The researchers then conducted a double-blind, placebo-controlled study in which they assessed the effect of a placebo or the drug carbamazepine on the two patients’ pain perception and brain activity. Compared with placebo, the drug led to significant improvements on several measures of pain.

Carbamazepine is a generic drug that has been around for decades. It is used mainly to treat neuro-

◀ Dr. Daria Sizova is with the Yale-VA Center for Neuroscience and Regeneration Research

pathic pain and epilepsy. It works on proteins called voltage-gated sodium channels.

In past studies on people with inherited erythromelalgia, the Yale-VA researchers had pinpointed the source of the problem as a mutation in a particular sodium channel, called Nav1.7.

Senior author Dr. Stephen Waxman said the new results offer an important proof of concept regarding pain therapy.

“While these results apply in the strictest sense only to the small number of patients carrying the S241T inherited erythromelalgia mutation, they demonstrate very clearly that it is possible to use genomics and molecular modeling to guide pain treatment,” said Waxman.

Waxman is a professor at Yale and director of the Center for Neuroscience and Regeneration Research, located on the campus of the West Haven VA.

The study also used functional magnetic resonance imaging to track changes in the patients’ brain activity following treatment.

“It was fascinating to see that reduction in pain, following treatment with carbamazepine, was paralleled by a shift in brain activity from areas involved in emotional processing to areas encoding accurate sensation,” said lead coauthor Dr. Paul Geha, an assistant professor of psychiatry at Yale.

Chronic pain affects an estimated 100 million people in the U.S. Current treatments often involve a long and frustrating trial-and-error approach with

drugs, including prescription opioids that carry the risk of abuse and addiction.

“I am hopeful that, some years from now, pain treatment will be transformed from trial-and-error to a precision medicine, first-time-around approach guided by the DNA of each individual patient,” Waxman said.

He said he hopes the work will lead to new therapies not only for neuropathic pain in inherited erythromelalgia, but also for neuropathic pain in multiple sclerosis, spinal cord injury, and related disorders.

In an accompanying editorial in *JAMA Neurology*, Dr. Juan Pascual of the University of Texas Southwestern Medical Center wrote that “the study provides an intelligent practical demonstration of the growing value of molecular neurological reasoning... There are relatively few examples in medicine where molecular reasoning is rewarded with a comparable degree of success.”

The research was funded in part by VA, the Erythromelalgia Association, the Kenneth Rainin Foundation, and the National Institutes of Health.

The Center for Neuroscience and Regeneration Research focuses on molecular and cell-based discoveries aimed at restoring and preserving nervous system function. The center involves support from and collaborations among VA, Yale, the Paralyzed Veterans of America, and United Spinal Association.

Adapted from an article by Lakshmi Bangalore, Center for Neuroscience and Regeneration Research. ★



Drs. Stephen Waxman (left), Mark Estacion (seated), and Sulayman Dib-Hajj are part of a Yale-VA team studying neuropathic pain.

Hot on the trail of PTSD genes

There's no definitive evidence yet for any single gene or set of genes. But scientists have promising leads and believe they are closing in on genetic factors that could inform treatment, prevention.

Nearly two decades ago, researchers with VA and other institutions reported on a gene that appeared to be linked to schizophrenia. Today, a number of drugs that target the alpha 7 nicotinic receptor are in clinical trials.

A similar process is underway for posttraumatic stress disorder.

Studies have pointed to several genes that appear to affect PTSD risk. Researchers caution there's still a long road to haul—as has been the case in schizophrenia—but they are confident they're moving in the right direction.

“There's a good chance” there'll be a payoff, notes Dr. Nathan Kimbrel, who stud-

ies PTSD genetics at the Durham VA Medical Center and Duke University, with support from VA Research's Career Development program. “It just takes a long time.”

His group has conducted a number of studies in the past few years in which Veterans give blood samples and take part in



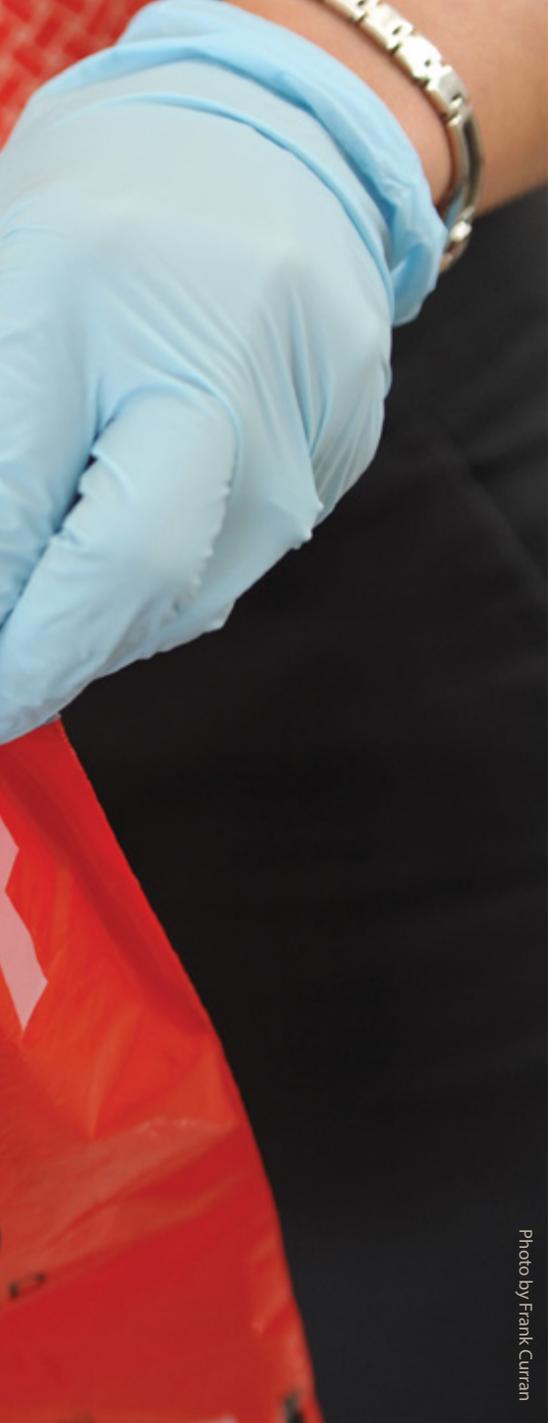


Photo by Frank Curran

◀ In most PTSD gene studies, participants provide blood samples from which DNA is extracted.

than 1,600 Iraq and Afghanistan Veterans, Kimbrel and colleagues homed in on a genetic variant called APOE4—known mainly for its links to Alzheimer’s disease. APOE4 is present in about 1 in 5 people. Interestingly, in the study, it appeared to heighten PTSD risk only in those Veterans who had been in heavy combat. Among those with low exposure to combat, it didn’t seem to matter whether they carried the APOE4 allele or not.

Another gene, SLC6A4, which affects levels of the neurotransmitter serotonin in the brain—essential for mood—figured in another 2015 report by Kimbrel’s team. Having a certain variant of the gene, known as 5-HTTLPR, increased the odds of a PTSD diagnosis by around 50 percent—but only in African American Veterans. No such effect was seen among whites in the sample of 1,105 Veterans. Unlike APOE4, though, this gene did not differ in its effects based on intensity of combat exposure.

Some findings replicated, others not

At least a dozen or so other genes have popped up in the PTSD genetics literature in the past couple of years. Some findings have been replicated

across studies by different groups; others haven’t. Trying to address how genetic risk might be affected by individual factors such as race, ethnicity, gender, and combat experience further complicates the equation.

On the one hand, there’s wide agreement that PTSD—like other mental illnesses—does have a genetic component. But some experts question whether that genetic influence might be too diffuse, too multifaceted, to allow for the identification of specific drug targets.

Dr. Mark Miller, with VA’s National Center for PTSD in Boston, says, “There are quite a few twin studies that have documented there’s a heritable influence on PTSD, as there is with all mental illnesses.” Much of that research has been based on VA’s Vietnam-Era Twin Registry.

“That’s what molecular geneticists are chasing after—they are trying to explain that heritability,” says Miller.

At the same time, he concedes that “there probably are skeptics of molecular geneticists’ ability to identify the genetic component.”

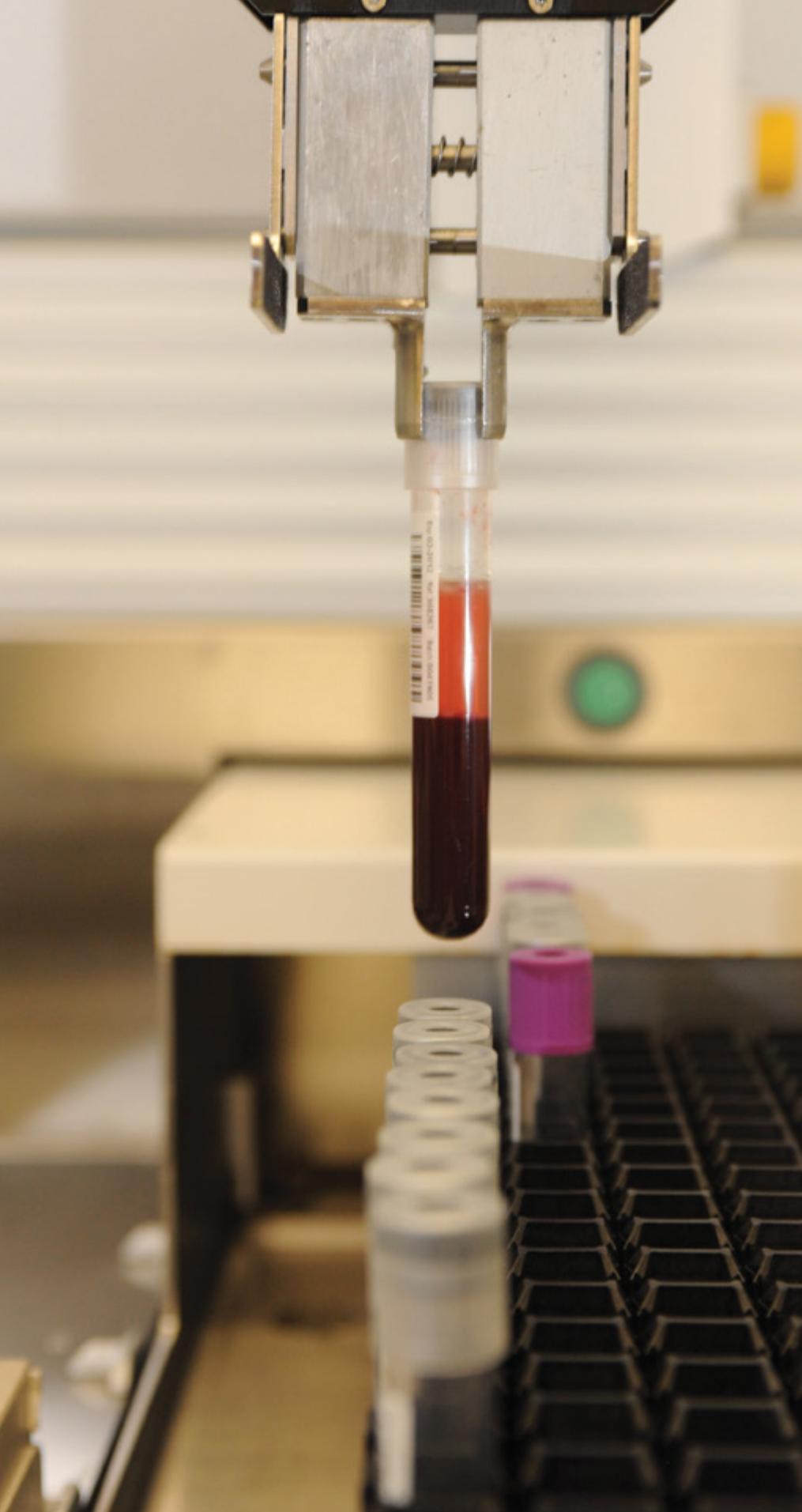
Dr. Murray Stein, with VA and the University of California, San Diego, is well-known in the field of PTSD and anxiety disorders. He too acknowledges that so far, the evidence for any single PTSD gene—or set of genes—is limited.

“I run into people who are not impressed with the size of

clinical interviews and surveys.

The group reported last fall, for example, on a possible link between PTSD and a gene called CHRNA5. A nicotine receptor gene, CHRNA5 has also been tied to an increased tendency to smoke cigarettes and become dependent on nicotine.

Prior to that, in a study of more



◀ VA's Million Veteran Program biorepository uses robotic equipment to process up to 2,500 or so incoming blood samples per week. Large numbers of research participants are crucial in studies aimed at identifying PTSD genes.

the effect, with the amount of variance that we can explain with molecular genetics at this point," says Stein. "I think everyone who works in this area is aware of that."

However, he points out that "this is a criticism you could probably level at a lot of molecular genetics research."

Kimbrel adds that the field of psychiatric genetics, in particular, is relatively young. "I think there's good reason to think that as it develops, we'll see more compelling results."

Gene hunters use two approaches

PTSD gene hunters use two main approaches. In one, they focus the search on specific "candidate genes" known to affect the body's response to stress.

A good example is the gene for CRH, a hormone involved in the HPA axis. This system involves the hypothalamus, the pituitary gland, and the adrenal glands, and the complex chemical interactions among them. The adrenals, for example, produce hormones called glucocorticoids—including

cortisol—in response to messages from the pituitary. Those hormones, in turn, act back on the pituitary and the hypothalamus in a negative feedback loop.

Miller: “It seems unequivocal that the HPA axis is involved. And we know an awful lot about that, and how it’s regulated, and how it may be dysregulated in PTSD.”

As a result, points out Stein, “it makes sense that people have gone in and looked at genes in this system.”

The other method is the genome-wide association study, in which researchers approach the question with no preconceived ideas, no target genes in mind. They simply scan the genomes of large groups of people—some with PTSD, others without—and check millions of possible variants, with the help of super-fast computers, to see which turn up in one group but not the other.

Stein was lead author on one such study that appeared online in *JAMA Psychiatry* in May 2016, based on the larger Army Study to Assess Risk and Resilience in Servicemembers (STARRS) study. The gene study included some 13,690 service members in all—some with PTSD, and some who had been exposed to similar traumas but did not develop PTSD.

As in the Durham-based study noted above, the results differed by race. Among African Americans, a gene called ANKRD55 was statistically associated with a higher PTSD risk. The gene is known to play in a role in several autoimmune and inflammatory disorders, including arthritis and multiple sclerosis. Interestingly, other research has looked at the role of inflammation in PTSD.

Among European-Americans in the study, the ZNF626 gene emerged. Its role in other health conditions is not well-established.

In neither case, though, was the effect of the gene variant particularly strong.

MVP-based study in the works

Stein points out that genome-wide association studies thrive on huge data sets. While the Army STARRS publication represents the largest such study on PTSD to date, results from an even larger effort, by the international Psychiatric Genomics Consortium, are now pending publication. The consortium, which involves Stein, Miller, and several other VA scientists, previously reported on a target enrollment of 40,000 people, including 10,000 with PTSD. But, says Stein, even those kinds of numbers may not be enough to guarantee replicable results.

“There are a handful of genome-wide association studies that have been replicated, and some that have not,” says Stein. “I think the bottom line is that until we get to very, very large samples, like those we’ve seen in schizophrenia, where some of the recent studies have had up to

200,000 or so people in them, we are going to see some findings replicated and others not. When we get enough statistical power, we should see more consistent results. We’re just not there yet.”

For his part, Stein is also co-leading, with Dr. Joel Gelernter, a genome-wide association study of PTSD in collaboration with VA’s Million Veteran Program. About 18 percent of the Veterans enrolled in the genomic research program have reported a diagnosis of PTSD. Ultimately, that may represent up to 180,000 or so Veterans with PTSD.

“MVP is a marvelous resource for the field,” says Stein. “It’s going to be a lot of help.”

Miller says that the two approaches—genome-wide association studies, and studies focused on candidate genes—“work best when they’re used to inform each other.”

Stein notes that with schizophrenia, it was genome-wide association studies that led scientists to discover genes they hadn’t thought of previously,

“When we get enough statistical power, we should see more consistent results. We’re just not there yet.”

and that are now driving drug development.

“Initially people were focused on dopamine genes and some others, because it was thought that’s where the biology was. But then these large genome-wide association studies pointed them in directions nobody would have thought of if those studies hadn’t been conducted. So science moves ahead by using both approaches. I think it’ll do that in PTSD eventually, too.”

Dr. Erika Wolf, who collaborates with Miller at the National Center for PTSD, points out that each approach has its own burden of proof. That might help explain why the findings from candidate-gene studies often appear to be more substantial and more promising than those from research focused on the whole genome.

“If you’re using a hypothesis-driven approach, and you know a specific biological system, like the HPA axis, that’s been shown to be related to PTSD, the empirical burden for showing an association is generally not as stringent as it would be if you were examining every SNP [pronounced “snip”—a type of genetic variant] that you have access to in the genome.”

Wolf, like Kimbrel, has been supported by VA’s Career Development program. One theme in her research has been identifying subtypes of PTSD, and, correspondingly, subtypes of genetic risk factors. This line of inquiry, she says, ties in to the wider “precision medicine” movement the White House has been promoting.

“It’s unlikely that there’s only one genetic variant,

Dr. Don Humphries, with the VA Boston Healthcare System, helps manage VA’s Million Veteran Program. MVP data will figure in a genome-wide association study of PTSD that is now in its early stages.

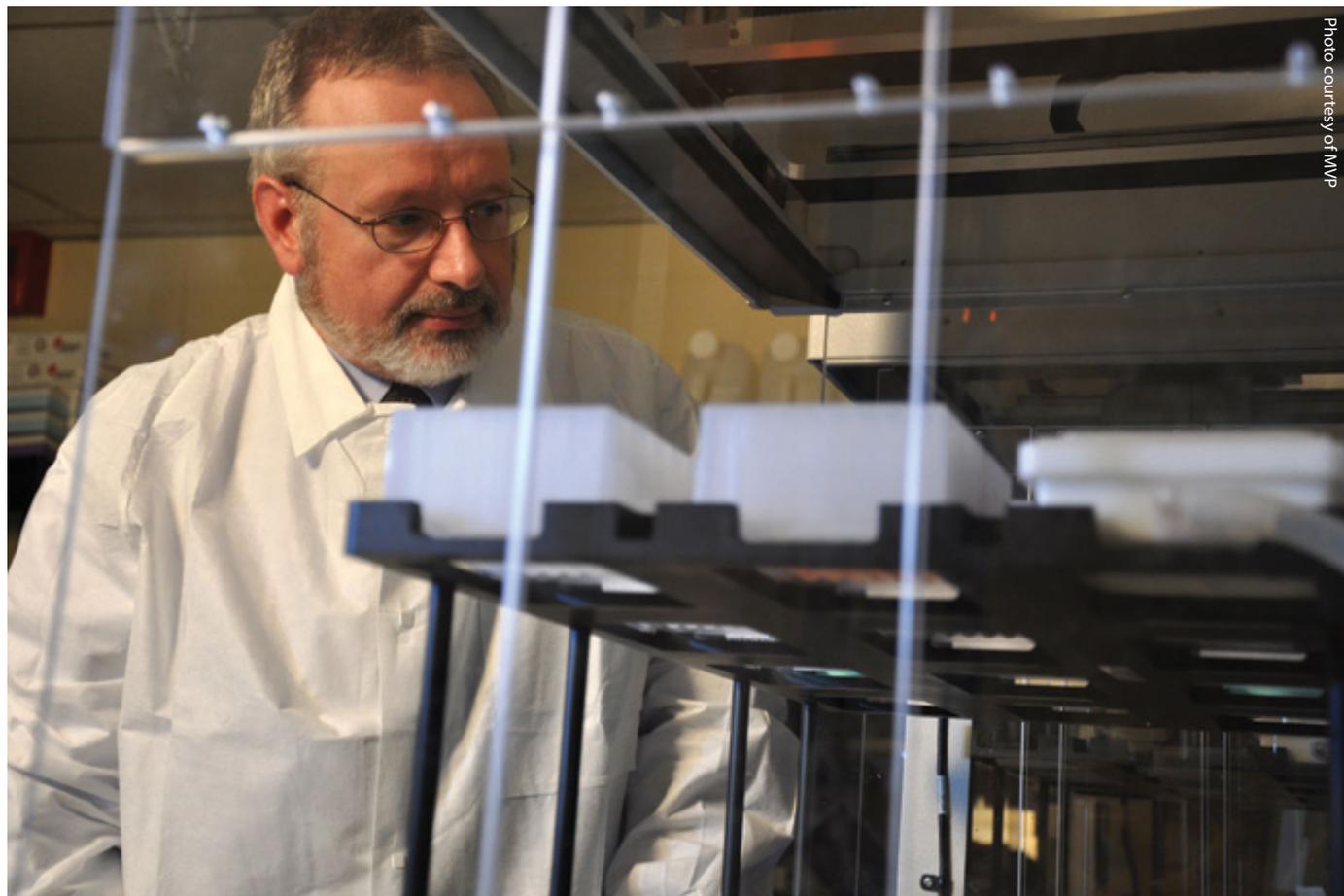


Photo courtesy of MVP

or even a handful, that are relevant for all cases of PTSD,” says Wolf. “There are probably subgroups of individuals who have different genetic risk factors that contribute to the disorder. So in the long run, there could be payoffs in that regard—identifying specific subgroups of people based on their genetic types, and tailoring treatment based on that.”

Research challenge: lack of precision in PTSD diagnosis

Another complicating factor in the search for PTSD genes is that diagnosing the disorder is not as cut and dried as diagnosing conditions such as diabetes or arthritis. If, say, 20 percent of the Veterans with a PTSD diagnosis in their medical record don't truly have the condition, that would seriously throw off the results of studies comparing these Veterans with non-PTSD controls and looking for gene variants found in one group but not the other.

Diagnostic fuzziness could also help explain the varying results seen across PTSD gene studies. Some studies, especially larger ones, rely on participants' self-reports of their condition. Others use diagnoses pulled from medical records. Still others use what is seen as the diagnostic gold standard—a clinical interview by a psychiatrist or psychologist. But even those diagnoses still rely, to an extent, on the professional's subjective opinion.

“The PTSD diagnosis ultimately comes down to the judgment of a clinician,” says Miller. “One of the big challenges is that relative to cancer or some other diagnosis where there's a clear biomarker of the disease, we don't have anything like that in PTSD. For that matter, we don't have it in any psychiatric condition.”

What would help, say the experts, is an objective biomarker, based on a blood test or brain scan. If hard-and-fast biological indicators of PTSD could be established, this would enable PTSD gene hunters to proceed in a more sure-footed manner.

Miller: “There are a lot of interesting biomarkers being studied, but I wouldn't say we're on the verge of a breakthrough. But there is a movement toward trying to get away from the DSM-based diagnostic system to other approaches. I think that's going to be part of the way forward in our getting a stronger understanding of the genetics and neurobiology of PTSD.”

The DSM, or Diagnostic and Statistical Manual of Mental Disorders, offers diagnostic criteria for PTSD. The criteria may change slightly with each edition, which further complicates things.

In the MVP-based genome-wide association study led by Stein and Gelernter, the team is not planning to rely solely on Veterans' self-reports of their PTSD diagnosis. Besides providing a blood sample from which DNA is obtained, MVP participants fill out extensive surveys about their health, lifestyle, and military experience, including topics such as PTSD and trauma exposure.

“The work that's gone on so far,” Stein explains, “is to develop and validate an algorithm that enables us to go into the VA electronic health record and pull out people who probably do have PTSD [based on their formal diagnosis, versus what they self-reported], and then take a look at the actual survey data they provided to MVP. We then should be able to determine, out of the total numbers of those who might have PTSD, how many are we fairly confident that they actually do. And we can also identify the people who have been exposed to trauma but don't have PTSD.”

What might it mean for the military?

Even if this MVP study, or the worldwide consortium efforts, do allow researchers to home in on specific genes, it still may be years before a safe, effective drug based on those biochemical pathways can be brought to market. In any case, improving treatment remains the primary goal of PTSD genetics.

Continued on next page »

Another outcome of the research, though, perhaps in the shorter term, might be some sort of screening tool for the Department of Defense. But this probably wouldn't play out in the way some might fear—as a way to exclude recruits with an unfavorable genetic profile.

Stein says that when his group presented genetics data from Army STARRS at the Pentagon, “the first thing the military psychiatrists said is that we'd never use this to exclude someone from being in the military, unless you told us they had a 100 percent chance of getting PTSD. And even then, we would probably still want them in the military, but perhaps not in combat.

“What we've been told by the military,” adds Stein, “is that they're unlikely to be in a position where they're going to want to turn away people who otherwise would be considered good soldiers. But, if we did have something that said, hey, there's a real high likelihood this person is going to have mental health problems if they're in combat, then they would try to come up with some way to make those individuals more resilient.”

Wolf points out that if the military really wanted strong predictors of PTSD risk, there are factors they could easily look to besides genetics.

“We have a lot of predictors of PTSD that are not genetic and that have much stronger effect,” she says. She cites three examples: prior PTSD, substance use, and certain psychological traits known as internalizing behaviors.

Miller suggests another perspective on what PTSD gene research might mean for the Pentagon:

rather than identifying the vulnerable ones and trying to keep them out of it.”

One might think these are simply two sides of the same coin, from a molecular genetics perspective—that one variant of a gene might increase PTSD risk, whereas another variant of the same gene might enhance resilience. It's not that simple, asserts Wolf.



Photo by Lance Cpl. Angelica I. Anastas/USMC

Marine Corps recruits go through training in San Diego in 2016. Experts say genetic tests for PTSD risk might eventually be used to help tailor military assignments, or to target some troops for extra resiliency training.

“A military application that might be more palatable to a lot of people is the flip side of the PTSD question, which is resilience. My guess is that the military would be better off spending time trying to identify highly resilient individuals and matching assignments to them,

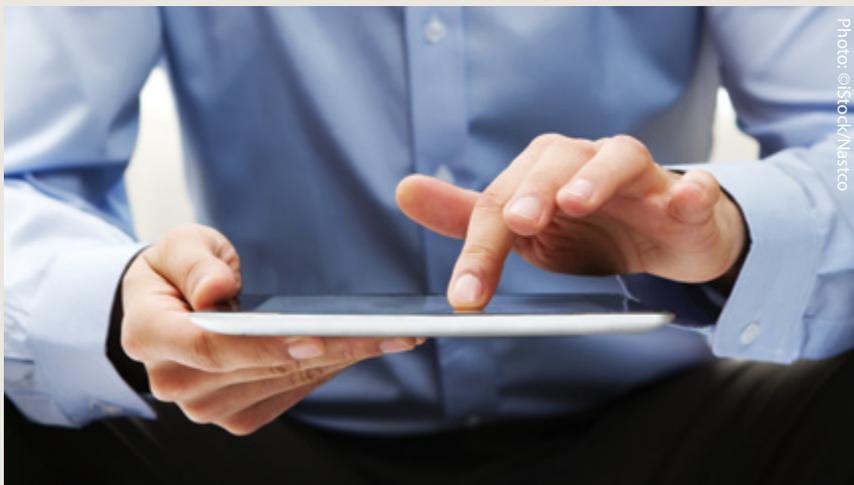
“There have been some studies that have tried to show that—for example, COMT as the ‘warrior-worrier gene.’ But I don't think that's been borne out. One of the issues is that resilience is not just the lack of psychopathology in response to trauma or other exposures.”

There are personality characteristics, such as hardiness, she says, that play a role in resilience, but their absence doesn't necessarily predispose a person to PTSD.

Notwithstanding those nuances, Miller contends that "the research on the neurobiology of PTSD crosses into an interesting scientific space where you may learn about what makes some people more resilient to adverse environments. If anything, I would think that would be the most useful information for the military. But of course, most of the funding gets directed toward the health problems—in this case, PTSD."

If that trend should change, and more interest builds toward resilience research, scientists like Miller stand ready to take up the challenge.

"It's typically the same people doing both types of studies," he says. "Presumably there's a spectrum of individual differences [including genetic variants] that confer risk or resilience. And there are a lot of researchers interested in trying to map out that whole spectrum." ★



Patients in a VA study used tablets to complete a new computerized-adaptive test for PTSD. The test, pending further validation, may offer clinicians a new tool for fast, accurate PTSD assessment.

New computer-based test aims to make PTSD screening faster, more accurate

VA researchers are developing a new tool to assess symptoms of posttraumatic stress disorder. Known as a computerized-adaptive test (CAT), the new system uses a computer algorithm to adapt questions in real time based on the patient's answers to the previous items. This allows the test to determine symptom levels faster and more accurately than many pen-and-paper assessments. The tool needs further validation, but the researchers hope it will become a new option for clinicians.

The researchers reported on the test in the journal *Psychiatric Services*.

According to VA's National Center for PTSD, clinicians should consider many factors when choosing a PTSD assessment tool, such as how long it takes to administer and whether it assesses the areas the clinician wants to examine. The CAT could be a valuable addition to the PTSD screens already available, say the researchers.

The new test showed strong validity and required only eight items to accurately and reliably identify low PTSD symptom severity. To identify high symptom severity, it needed only six items. Pen-and-paper PTSD screens often require as many as 35 items.

Clinicians already use CATs for conditions such as anxiety, depression, and community integration. The authors hope the new CAT can lead to accurate and fast clinical screening for PTSD as well.

Read more at www.research.va.gov/currents ★

How to engage Iraq, Afghanistan Veterans in health research: Lessons from focus groups

VA's Seattle Epidemiologic Research and Information Center conducted 10 focus groups in five U.S. cities in late 2015 to gain insight into how to involve Iraq and Afghanistan Veterans in VA research.



Photo by Sgt. Eddie Siquenza

Altruism is alive and well—at least among 89 Iraq and Afghanistan Veterans who took part in focus groups held by VA's Seattle Epidemiologic Research and Information Center (ERIC).

The ERIC, part of VA's Cooperative Studies Program, conducted 10 focus groups in five U.S. cities in late 2015 to gain insight into how to involve Veterans of this cohort in VA research. Individuals were compensated \$150 to participate in the focus groups, which took about three hours, including travel time.

Most of the Veterans who took part said they wanted to benefit others, in addition to possibly finding solutions for their own health challenges.

“The findings suggested Veterans are interested in joining research to help find ways to improve their own health, as well as help their fellow service

◀ U.S. soldiers from the Guam Army National Guard prepare to board a CH-47 Chinook from Camp Phoenix in Kabul, Afghanistan, in 2013, before heading home.

members and future generations,” said project coordinator Emily Ashmore.

The focus groups covered a wide range of topics related to research participation. The Veterans—average age 38, nearly a third of whom were women—talked about factors that would motivate them to get involved; what type of compensation they thought would be fair; and issues relating to privacy, and the interface between research and their VA benefits. (In short, there is no impact on benefits.)

Focus groups part of a broader effort

The lessons gleaned from the sessions add to the ERIC’s existing knowledge about recruiting and retaining Veterans in research.

“We’ve gained a vast amount of knowledge that could improve recruitment strategies for studies,” says Ashmore. Her group has been sharing that

Most of the Veterans who took part said they wanted to benefit others, as well as possibly find solutions for their own health challenges.

wisdom with other VA researchers through a variety of vehicles, including a recent webinar.

The project is part of a broader effort among VA researchers to learn more about the best ways to engage Veterans in research, and to share those lessons with other researchers. The Cooperative Studies Program Epidemiology Center in Durham, N.C., has some projects in that vein as well.

VA Health Services Research and Development convened a Veteran Engagement Workgroup in early 2015 to address the topic, and has since held two cyberseminars to share the group’s recommendations and to further explore the topic.

Ashmore says such efforts across the VA research community “allow researchers to skip some of the trial and error process typically found during the beginning stages of constructing a study.”

Here are more of the lessons that her team learned from the recent focus groups:

- Participants said they would be motivated to participate in studies if they felt their time was well-compensated. Feedback suggested that around \$50 per hour for an in-person visit and a minimum of \$25 for completing a questionnaire at home would be viewed as fair.
- If an in-person study visit of two hours or more is needed, provide an agenda so participants know their time will not be wasted waiting to be seen.
- Plan to share information about what the study found, so Veterans can see how their participation had an impact.
- Reassure Veterans that the information they provide in a study will not affect their benefits.
- The Veterans in the focus groups preferred being contacted first via a mailed letter, followed by a phone call. They did not want to be initially recruited by email. Consider sending study information in a large, non-standard envelope with an official VA logo. Many Veterans noted that the large envelope grabbed their attention.
- Generally, Veterans reported being willing to drive about an hour for a study-related visit, but this was contingent on the timing working with their work and family obligations, and the compensation and intangible benefits being sufficient to outweigh the burden.

Ashmore notes that the findings may not reflect the attitudes of other cohorts of Veterans. She said her team and others in the Cooperative Studies Program are now doing similar focus groups with Veterans from the Vietnam and Gulf War eras. ★

Study yields potential blood biomarkers for Gulf War Illness

Based on a study of 85 Gulf War Veterans, VA researchers in Minneapolis have developed a tentative panel of blood markers they say can verify a diagnosis of Gulf War Illness with 90 percent accuracy.

The method now needs validation in larger groups of patients, say the researchers.

The findings appeared June 28, 2016, in the journal *PLOS One*. Lead author was Dr. Gerhard Johnson, with VA and the University of Minnesota.

As many as 300,000 Veterans—about 4 in 10

fog, memory problems, headaches, insomnia, and gastrointestinal problems.

Chronic inflammation in the body may be the chief underlying culprit, or at least one of the key factors driving the illness, suggests the new study.

Biomarkers point to inflammation as culprit

The study found that several commonly used blood tests—all indicating inflammation—tended to yield different results between Veterans who reported symptoms consistent with Gulf War Illness, and those who did not.

The researchers suggest that a panel of such markers, once validated in further research, could serve as an objective biomarker for the condition. This could help clinicians diagnose the illness. It could aid further research as well. As of now, different research groups use different criteria for determining who has the condition, and that may hamper progress.

The study involved 57 Gulf War Veterans who met the current diagnostic criteria for the illness, and 28 who did not. They

were mostly white, male, and middle-aged.

The researchers tested the volunteers' blood samples for red, white, and platelet counts, and for more than 60 different proteins.

Three types of white blood cells—lymphocytes, monocytes, and neutrophils—were all higher in the Gulf War Illness group. Platelets—small cells that form clots to heal injured blood vessels—were also elevated.

Along with these changes, six different proteins



Troops from the 82nd Airborne Division wear protective gear as they try to acclimate to the heat of the Saudi summer during Operation Desert Shield.

of those who deployed to the Persian Gulf during operations Desert Shield and Desert Storm in the early 1990s—are now estimated to have Gulf War Illness, more than 25 years later. That figure comes from a VA survey, based on Veterans' self-reported symptoms, published earlier this year.

But the illness is still difficult to define and diagnose, and there is no broad agreement on the diagnostic criteria, let alone an exact cause. Commonly reported symptoms include pain, fatigue, mental

'Biggest losers' over time

Average weight loss after
30-week competition

129 lbs.

Average weight regained after
6 years

90 lbs.

Source: "Persistent metabolic adaption 6 years after 'The Biggest Loser' competition," *Obesity*, online May 2, 2016. By researchers with NIH, VA, and Towson University.

Infographic by Michael Escalante, VA Research Communications (June 2016)

found in the blood showed significantly different values between the two groups. Levels of C-reactive protein, leptin, BDNF, and MMP-9 were higher in the Gulf War Illness group. Levels of two other proteins—MMP-2 and H-FABP—were lower.

Three of the markers used together—lymphocytes, monocytes, and C-reactive protein—yielded a predictive value of 90 percent for those Veterans whose probability of Gulf War Illness was 70 percent or more based on clinical interviews. In other words, the test indicated the presence of Gulf War Illness in 90 percent of those who appeared to have the condition based on conventional diagnostic criteria.

Taken together, write the researchers, the results "support the hypothesis that chronic inflammation is a component of the pathophysiology of [Gulf War Illness]."

Dr. Ronald Bach, the senior author on the study, said, "The fact that so many significant blood biomarker differences were detected in a relatively small study supports the conclusion that we are

seeing a strong signal of a well-defined chronic inflammatory disease."

Clinical trial now underway

His group is already putting their theory about inflammation to the test. A clinical trial is now underway at the Minneapolis VA Healthcare System to test whether an anti-inflammatory drug—a new delayed-release form of the corticosteroid prednisone—improves health-related quality of life in Veterans with Gulf War Illness. The study, projected to be completed in 2020, will involve 100 Veterans in all.

"We are trying to translate the blood biomarker fingerprint into an effective evidence-based treatment for Gulf War Illness," said Bach.

Both the study of biomarkers and the clinical trial are supported by the Department of Defense Congressionally Directed Medical Research Program.





RESEARCH CURRENTS

Research News from the U.S. Department of Veterans Affairs



CONFIRM co-leader Dr. Jason Dornitz

Did you know?

A VA study on preventing colon cancer deaths has now become the largest VA clinical trial in history, with enrollment approaching 39,000 Veterans, out of an overall target of 50,000. The study, known by the acronym CONFIRM (for Colonoscopy versus Fecal Immunochemical Testing in Reducing Mortality from Colorectal Cancer), surpassed the Shingles Prevention Study, completed in 2011, in which VA and collaborators had enrolled 38,546 participants. Large numbers of participants help trials achieve clinically meaningful results. VA's Cooperative Studies Program, sponsor of both clinical trials, has a long history of conducting large-scale trials that have strongly influenced medical practice in the U.S. and worldwide.



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