DEC. 2011/JAN. 2012

VA Research Currents

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

Thinking big

Handling data from the Million Veteran Program is the health informatics challenge of an era

By now, most people who follow VA health care have heard of the Million Veteran Program.

Launched earlier this year, with some 15,000 Veterans enrolled already, MVP is on target to build the world's largest database of health and genetic information. The goal is to better understand the role of genes in disease risk and response to treatment, and to advance medical care that is personalized based on the patient's genetic makeup.

Few people, though, know anything about the infrastructure behind the effort. The amount of data collected through MVP will be massive. Creating order out of all of it, and enabling researchers to use it effectively over the coming years, is the challenge of an era for the relatively young field of bioinformatics.

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Photo by Frank Curran

Dr. Len D'Avolio, right, is associate director for bioinformatics at VA's Massachusetts Veterans Epidemiology Research and Information Center.

Brain studies sort out physical, emotional scars of war


Photo by April Ellers

Catching waves—Dr. Scott Sponheim (at computer) inspects EEG recordings of brain waves from former Marine and OEF/OIF Veteran Andrew Lisdahl at the Minneapolis VA Medical Center. Lab assistant Peter Lynn monitors electrode placement.

James Sperry, of Lebanon, Ill., considers himself lucky to be alive. In the fierce battle for Fallujah, Iraq, in 2004, a rocket-propelled grenade bounced off the Marine's Kevlar helmet.

Today, the 26-year-old Veteran is continuing to mend physically and emotionally. He is coping with mild traumatic brain injury and posttraumatic stress disorder—a dual diagnosis that affects many Veterans of the wars in Iraq and Afghanistan.

Many problems—such as lack of fatigue, trouble sleeping, irritability—occur in both conditions. The interplay between the two is highly complex. TBI damage to certain areas of the brain, for instance,

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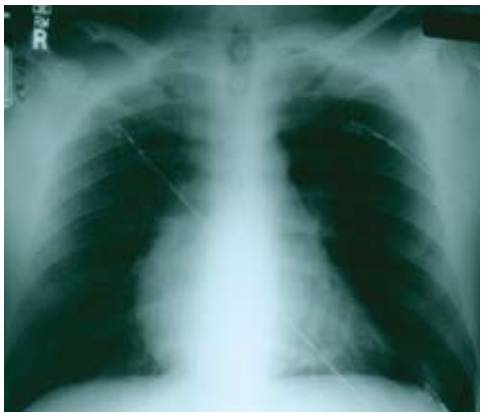
Shorter drug regimen could help eradicate TB

An international study that included six VA sites found that patients with latent tuberculosis—meaning they are infected with the TB germ but have no symptoms and are not contagious—can keep the disease from developing by taking a combination of drugs once a week for three months. The new drug combo appears to work just as well as the current standard of care, which calls for taking one of the drugs daily for nine months.

The researchers reported the findings in the Dec. 8 *New England Journal of Medicine,* and the Centers for Disease Control and Prevention, which sponsored the study, has since issued new clinical care guidelines based on the results.

Largely thanks to antibiotics, TB rates in the U.S. have fallen to all-time lows. Last year, there were only about 11,000 reported cases of TB illness. But there are some 11 million Americans with latent TB who "represent a ticking time bomb. They're the source of future TB cases," said Rear Admiral Kenneth Castro, MD, director of the CDC's Division of Tuberculosis Elimination.



Up to 10 percent of those with latent TB will develop the disease if they are not treated, but most don't know they are infected. Of the 300,000 to 400,000 Americans with latent TB who undergo preventive treatment each year, most learn of their infection through screening programs that target high-risk people, such as workers at hospitals, homeless shelters, drug rehab clinics, and prisons; or patients with HIV, diabetes, or head and neck cancers.

Nearly 8,000 high-risk individuals from Brazil, Canada, Spain, and the U.S. took part in the study. Of that number, about half received a combination of two drugs, rifapentine and isoniazid, once a week for 12 weeks, in the presence of clinic staff. Isoniazid alone was given to the other participants, who were told to take the drug daily for nine months, on their own at home.

After following patients for up to nearly three years after the medications were given, the researchers found that only seven (0.19 percent) of those who had taken the combination of drugs had developed TB. By contrast, 15 (0.43 percent) of those who had taken isoniazid alone developed the disease. In addition, 82 percent of those on the combination therapy completed the three-month course of treatment, whereas only 69 percent of those who took isoniazid for nine months completed their regimen.

"It's clear that the CDC now expects this [combination therapy] to immediately become the new norm for prevention of TB," said Fred Gordin, MD, chief of infectious diseases at the Washington, DC, VA Medical Center, and one of the study's authors.

Other VA sites participating in the trial were the VA medical centers in Little Rock, Chicago, Hines (Ill.), Houston, and San Antonio.

The study authors pointed out that more research is needed to see if people on the shorter, three-month regimen would take their medication even when not supervised in-person by medical personnel.

Reflections of history: VA TB trials in the 1940s

After World War II, VA, in conjunction with the Armed Forces, conducted a major study to test the effectiveness of the antibiotic streptomycin to treat tuberculosis. At the time, the potentially fatal disease was a huge public health problem.

The initial results in the hundreds of Veterans who took part were very favorable: The patients' fevers went down, their appetite and weight improved, and their overall sense of well-being improved.

Continued monitoring of the study participants, however, revealed two concerns about the streptomycin: It often caused inner ear damage that affected balance, and many patients developed resistance to the drug.

A follow-up trial in 1947 determined that a lower dose of streptomycin could achieve similar therapeutic results with less toxicity and less risk of drug resistance.

VA Research Currents

is published 10 times per year for the Office of Research and Development of the U.S. Dept. of Veterans Affairs by VA Research Communications

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Editor: Mitch Mirkin

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A team at the Boston VA Healthcare System has designed an ambitious, outsize system called GenISIS to meet the need. Backed by huge clusters of servers housed in two locations, the system links de-identified patient DNA samples and health information with a multitude of VA and non-VA databases, along with computer applications such as a call center and mail center to manage MVP enrollment, appointment-setting, and information-gathering.

"I think this is going to be a big deal not only in the world of informatics, but in the world of patient care," says Leonard D'Avolio, PhD, one of the visionaries and driving forces behind GenISIS. The acronym stands for "Genomic Information System for Integrated Science." D'Avolio is associate director for bioinformatics at VA's Massachusetts Veterans Epidemiology Research and Information Center. The center is home to the biorepository where bar-coded MVP blood samples are deep-frozen at minus 30 Celsius and robots help process and retrieve these and other research specimens. The biobank is now undergoing expansion and will eventually house up to four million samples, from MVP and other research.

If the biblical tale of Genesis recounts the creation of the first human—genome and all—VA's GenISIS promises to help scientists make sense of that genetic code. The system will allow for studies, many using MVP data, on any number of conditions that affect Veterans, from diabetes and depression to Parkinson's and PTSD. Experts hope the result will be a flow of genetic discoveries to help guide diagnosis and treatment.

Citing PTSD as an example, VA's chief research and development officer, Joel Kupersmith, MD, told *National Public Radio* in a recent interview, "We'll look at patients with PTSD and patients who don't have PTSD and … see if there's a gene that's there in the patients with PTSD that isn't there in the patients who don't have it."

Genetically speaking, each person's cells carry within them some 3.2 billion bits of data. That's how many pairs of nucleotides,

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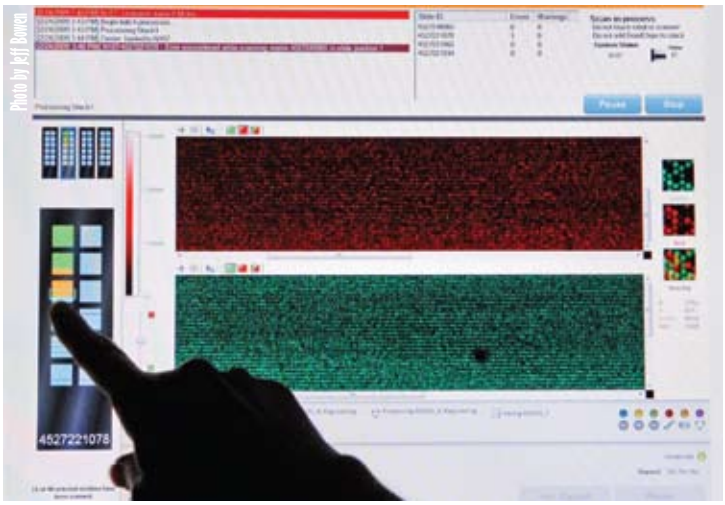
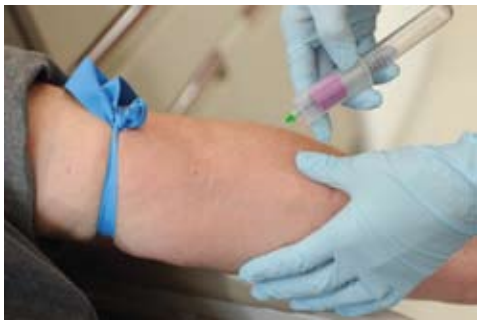
Dream team—Among the VA staff members working to turn the GenISIS vision into reality are (from left) project manager John Gargas; bioinformatics director Dr. Leonard D'Avolio; MVP project manager Jennifer Deen; IT manager Al Toby; and scientific director Dr. Saiju Pyarajan.

Photo by Frank Curran





DNA discoveries—Once a Veteran volunteers for MVP, reviews and signs an informed consent form, and donates a blood sample, his or her de-identified DNA becomes part of a sophisticated research and bioinformatics effort aimed at discovering how specific genes affect people's health and their responses to medical treatments.

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or chemical bases, are in the human genome. This represents tens of thousands of protein-coding genes, plus lots of other DNA. By and large, the precise role of one stretch of DNA versus another remains a vast unsolved mystery. There are countless possible variants that could affect health, and scientists have yet to learn about most of them.

"And it's not just the genome," points out D'Avolio. "Each patient also has hundreds if not thousands of other relevant pieces of information"—facts about his or her current and past medical conditions, lab values, prescriptions, family history, lifestyle, environmental exposures. Some Veterans who take part in MVP will have a VA electronic health record going back two decades.

Billions and quadrillions of variables

Multiply these billions of data points for each person by the million Veterans whom VA expects to take part in MVP, and you get a figure in the quadrillions. Not even the federal budget deficit is on that scale! These mind-boggling numbers reflect the amount of permutations researchers could potentially analyze using MVP data, in terms of how DNA interacts with other factors to affect health.

The good news is, the larger the numbers, the easier it is for meaningful patterns to emerge. With a study on 500 or 1,000 people, the association between a gene variant and a certain trait would have to be quite striking—a "strong signal," in genomic terms—to catch researchers' attention. This has happened with conditions in which a single gene or only a handful of genes plays a key role—such as the two BRCA genes in hereditary breast cancer.

With most diseases, however, researchers believe the genetic risk factors are spread across larger numbers of genes, with each gene playing only a modest role, subject to the effects of numerous non-genetic factors as well, such as diet. To detect these signals, researchers have to analyze samples that number at least in the tens of thousands. "These connections are going to be discovered only by looking across many data points," says D'Avolio, "which means you need huge data samples." He says MVP, with its projected million-Veteran patient sample, will "make that possible in a way that no one else can."

In the not-too-distant future, says D'Avolio, it could be that computers will automatically run searches in the background,

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Of mice and men

Lab scientists pay close attention to biological gaps between the species

The humble mouse has a lionlike reputation in medical research.

Mice are widely used in labs for a number of reasons. They share many genes and molecular pathways with humans, and they are easy and inexpensive to breed, handle, and genetically engineer. There are fewer ethical and practical concerns than with larger animal species.

One shining example of how mouse studies are relevant to human disease comes from Harvard researcher Pier Paolo Pandolfi, MD, PhD. His work led to a breakthrough in the treatment of a type of leukemia known as APL. Until recently, it was almost always fatal. Now, most patients are completely cured.

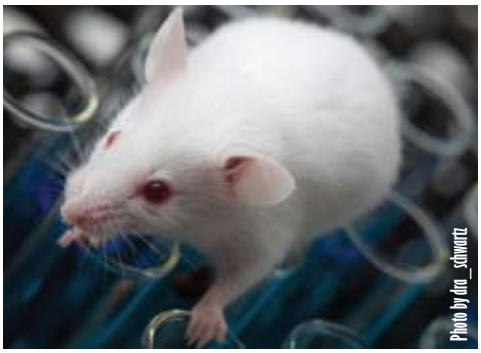
On the other hand, mice can often be poor predictors of medical outcomes in people. Scientists met last year at a European Commission workshop to discuss the issue. Their report noted the following: "Mice are not always reliable as preclinical models for human disease, and the scientific literature is littered with examples of drugs that worked well in animals but turned out to be ineffective in clinical trials on humans."

Insight on mouse-human divergence from VA study

A recent VA lab study, presented at the Gerontological Society of America annual meeting in Boston, offers an interesting example of how mouse and human biology can diverge.

David Canaday, MD, is associate director for research at the Geriatric Research, Education and Clinical Center at the Louis Stokes VA Medical Center in Cleveland. He's also an associate professor in the division of infectious diseases and HIV medicine at Case Western Reserve University.

Contagious curiosity—VA's Dr. David Canaday, who studies infectious diseases such as tuberculosis and influenza, says, "We want to get our clues from animals and then move to humans."



Super-sized role—Mice are huge in biomedical research, partly because they share many genes and molecular pathways with humans.

Among other topics, he studies why some vaccines don't work as well in older adults. What exactly is it about the aging immune system that thwarts a proper response?

His group studied cells from 20 older and 20 younger people. They looked for key differences among proteins that regulate the immune system. Among other findings, they learned that a molecule known as CTLA-4 (for Cytotoxic T-Lymphocyte Antigen 4) was six times more abundant in the cells from the older research volunteers. Another, called PD-1 (short for the cheery moniker Programmed Death 1), was only half as abundant in the older cells.

PD-1 helps dial down the immune response at the proper time by stanching the

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could result in symptoms identical to those typical of PTSD, or affect a Veteran's ability to recover from emotional stress.

Sorting out which symptoms stem from TBI versus PTSD could aid treatment. Psychotherapy indicated for PTSD might not work as well when TBI is also present. Drug indications might change depending on the mix of symptoms.

Brain scans help pinpoint TBI, PTSD effects

Identifying the precise effects of TBI and PTSD on brain structure and function has thus become an important goal for researchers in VA and the Department of Defense. One such effort is under way at the Minneapolis VA Medical Center. A team led by Scott Sponheim, PhD, is working with up to 180 Minnesota National Guard troops who have come home from Iraq with mild TBI, PTSD, both conditions, or neither. The four-year study is looking at both brain structure and function, using neuropsychological tests plus two types of brain scans.

In the EEG (electroencephalography) phase of the study, participants wear a thin red nylon cap with dozens of electrodes attached, as they sit in a resting state or perform tasks involving attention, memory, and processing of visual or verbal information. The researchers hope to be able to document key differences in the signals given off by TBI- versus PTSD-affected brains. For example, if their early data hold up, the investigators believe EEGs will consistently show less activity in the frontal lobes during memory tasks in those Veterans who have TBI, compared with those who have PTSD but no TBI.

To measure differences in brain structure, Sponheim's team is using a form of MRI called diffusion tensor imaging. It shows abnormalities in the brain's white matter, the pinkish, fatty tissue whose glial cells and insulated axons relay messages throughout the brain. Here too, the researchers believe TBI-affected brains will reveal a signature pattern not seen in PTSD.

Once reliable biomarkers emerge for each condition, clinicians will have more evidence on which to base their diagnoses and therapy recommendations.

In harm's way—An Army soldier patrols in Afghanistan in March 2011. Researchers are exploring how to distinguish between overlapping symptoms of PTSD and traumatic brain injury.

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comparing mountains of patient data against knowledge bases that store information on what is already known about certain genes, such as those of the National Center for Biotechnology Information. CPUs—not PhDs—will connect the dots and unearth links between gene variants and specific health traits or risks.

Informatics is not quite there, though. For now, researchers—mere humans—have to run specific queries. D'Avolio describes how the process works:

"Researchers can access GenISIS remotely and ask a question—for example, how many patients do we have consent and blood for, who have been seen in the last two years and who have diabetes? And then they can move that data, with appropriate permissions, into a secure environment with a big high-performance cluster, and huge amounts of storage. So we have a very sophisticated analysis environment."

MVP data updated through link to patient records

Already, a VA research team is planning to use MVP data for a study on serious mental illness, which affects some 170,000 Veterans who use VA care. While the study is recruiting thousands of Veterans who have schizophrenia or bipolar disorder, MVP would supply "healthy controls" for the sake of comparison. "It's no small thing to get up to 10,000 patients with schizophrenia or bipolar disorder," says D'Avolio. "But then you have to match that with another 10,000 who don't have either disease." He says this study is likely to be "the first scientific contribution of MVP."

Because the MVP database is linked to VA's electronic health records, it can be periodically refreshed to capture important changes in Veterans' health status, such as new diagnoses or prescriptions.

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flow of white blood cells once an infection threat has passed. It's like a military commander yelling, "Hold your fire!" If PD-1 levels sag, an immune response could go on too long. This, says Canady, can result in "pathology, such as scarring of lung tissue."

The researchers were somewhat surprised by the PD-1 finding. In their study abstract, they noted that the result was in "direct contrast to the aging mouse model data." They said the work underscored the "importance of generating data in aging human populations in addition to animal models." Otherwise, researchers could be misled and plan clinical trials that are not as well-founded as they seem.

At cellular level, 'parallels are really tight'

Canaday points to another area in which mice differ from people in ways that are critical for biomedical research: "Some pathogens don't infect mice very well, and tuberculosis is one of them," he says. "Mice don't get this disease in the wild. In the lab, we can make them get TB, but if you look at their tissues, they don't respond quite the same way. In people, you get granulomas," or nodules of inflamed tissue. "In the mouse, you don't. Most mice die of TB. Most humans recover. That's a huge difference right there."

While they may sometimes seem unpredictable, Canaday says the biological differences between mice and humans occur according to a scientific principle: "It depends on the level you're looking at. If you're looking at the fundamental biology of how DNA is synthesized, or protein signals in the cell, the parallels are really tight. But the further you go to the organism level, the more likely it is there will be variance. So it is important on that macro level to do human studies."

Christopher Austin, MD, senior adviser for translational research at the National Human Genome Research Institute, put it succinctly a few years ago when he told the *Associated Press:* "These mice are not going to tell us everything, and sometimes they tell us nothing. But as a starting point, mice play a central role."

Canaday couldn't agree more. "I've tried to do basic research mostly in humans"—for example, using human tissue samples from biopsies or swabs—"but there's a limit to what you can do. The animal studies are invaluable. We want to get our clues from animals and then move to humans."

Providing for a smoother, more predictable path from mouse to human studies is now a major goal of scientists worldwide. One key effort is the International Mouse Phenotyping Consortium, which aims to "knock out," or deactivate, one gene at a time in mice and describe what happens physically, biochemically, and behaviorally. Among the measures recommended at the European workshop mentioned above were more training for "mouse pathologists," and increased education for "human pathologists and clinicians to increase their understanding of the opportunities and limitations of mouse models."

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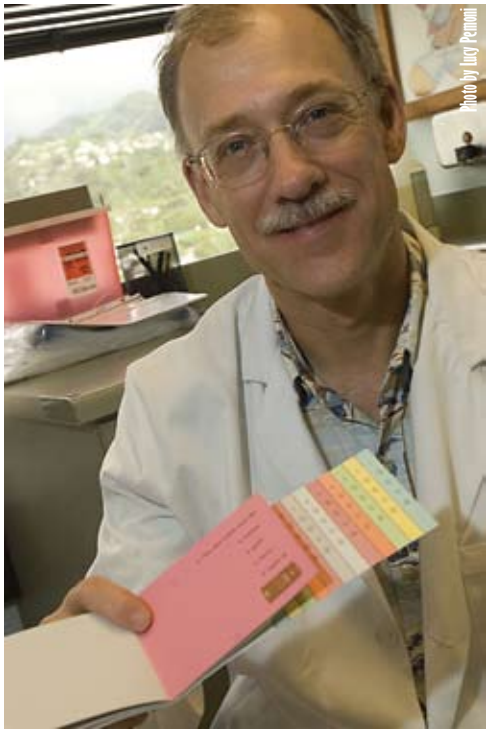
GenISIS, through its nexus with various VA and non VA databases, could also fetch specific data relevant to a researcher's question, even if those data are not being "brought over" to the MVP database on a routine basis. "Say you want to access specific lab results for your diabetes study, such as patients' hemoglobin A1C values," explains D'Avolio. "We have those 'hooks,' and we know which patients you want them for, so we bring back that data as well."

Veterans, researchers, clinicians, and others can learn more about the Million Veteran Program at ***www.research.va.gov/mvp.***



Scent science—Dr. G. Webster Ross displays a scratch-and-sniff booklet used to test patients' sense of smell, as a possible aid to early detection of Parkinson's disease.

Parkinson's precursors

A team led by G. Webster Ross, MD, at the Honolulu VA Medical Center found that impaired olfaction (sense of smell), constipation, slow reaction time, excessive daytime sleepiness, and faulty executive function may all warn of Parkinson's disease and increased likelihood of either Lewy bodies (abnormal protein clumps found in Parkinson's) or the loss of neurons. The study found that combinations of these signs—which could appear well before any movement-related symptoms—could predict up to a tenfold higher risk of the disease.

The results were presented at the recent World Congress on Parkinson's Disease and Related Disorders.

Ross and colleagues say that while tests of these functions would need to be used in conjunction with other measures, partly because of their low "specificity" (they could also predict any number of other conditions), "these methods may be useful for identifying a high risk group for participation in intervention trials aimed at preventing or slowing the progression of Parkinson's disease."

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VA-led study on police points to stress biomarker

Police recruits who showed the greatest rise in the stress hormone cortisol after waking up in the morning were more likely to show acute stress symptoms in response to trauma years later as police officers, according to a study by VA, the University of California, San Francisco, and New York University. The results were published in the December 2011 issue of *Biological Psychiatry.*

The researchers measured cortisol levels in 296 police recruits when they awakened, and then 30 minutes later. The difference between the two levels is known as cortisol awakening response, or CAR. After one, two, and three years of active service as police officers, the participants were then assessed for stress reactions in response to duty-related traumatic events.

"When we wake up in the morning, we all have a rise in cortisol as part of the normal awakening process that helps mobilize our body to start the day," says lead author Sabra Inslicht, PhD, a psychologist with VA and an assistant adjunct professor of psychiatry at UCSF. "In this study, the stronger a recruit's CAR, the greater the chance they would have stress symptoms years later in response to trauma."

Occupational stress—Studies on police, such as these officers at an "Occupy" protest in Los Angeles, may yield clues on acute stress response and PTSD, say VA researchers.

A stronger CAR predicted two specific stress responses: dissociation—a feeling of dreamlike unreality during the traumatic event; and acute stress disorder (ASD) soon after the event. ASD symptoms include intrusive memories of the event, increased heart rate, faster breathing, and avoidance of thoughts or feelings related to the event.

"These are symptoms of PTSD, but limited to a shorter time frame," says Inslicht. She notes that many people with ASD go on to develop PTSD. She adds that while more research is needed, the goal would be to "develop interventions to prevent and treat some of the stress responses that we see—or at least ways of identifying people who may be at higher risk of PTSD and would thus benefit from getting interventions earlier on."