

VA conducting 'optimization study' of advanced prosthetic arm

Frederick Downs Jr., director of VA's Prosthetic and Sensory Aids Service, says he was "brought to tears" last summer when he first tried an advanced prosthetic arm developed by DEKA Integrated Solutions Corporation through funding from the Defense Advanced Research Projects Agency (DARPA).

Downs, who lost his left arm when he stepped on a land mine in Vietnam in 1968 and has been using a prosthetic hook ever since, was able to use the new prosthesis to bring a water bottle to his mouth and drink. The task may sound simple, but achieving the fine control that enables a user to grab a soft-plastic bottle firmly—without crushing it—and smoothly maneuver it is a major feat for prosthetics engineers.

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Milestone—Frederick Downs Jr. of VA tries the DEKA prosthetic arm for the first time at the company's New Hampshire headquarters.



Biomedical technician Weleetka Carter works with DNA samples at the Pharmacogenomics Analysis Lab at the Little Rock VA Medical Center.

Technology speeds hunt for disease-linked genes

Wanted: Information leading to the identification of genes that may put you at risk.

In a nutshell, that's the endgame of genomic research. Scientists are hunting for genes—or gene variants—that play a role in causing disease. New discoveries could improve screening and diagnosis or point toward more effective treatments. For instance, quieting a troublesome gene or activating a potentially helpful one may be a way to stop some cancers.

Genomic researchers also want to know which genetic variations affect how people respond to drugs. Such knowledge is already being applied: In some cases, for instance, doctors use a genetic test to predict how a patient will respond to the anti-clotting drug warfarin. Too much of the drug could result in bleeding; too little could allow dangerous clots to form. Knowing the patient's genetic profile makes it easier to set the right dose from the outset.

This type of "personalized medicine" is the fruit of genomic research. The more researchers learn about the effects of different

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Photo by Jeffrey Bowen

There's only a small portion of our DNA—less than one percent—that is of special interest to researchers.

Robotic precision—At left, a robotic liquid-handling machine injects DNA from research volunteers into trays holding “bead arrays” that contain snippets of test DNA. After further processing, scanning and analysis, the arrays will reveal which genetic variations are found in people with certain diseases or clinical traits.

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genetic variations, the greater the extent to which doctors will be able to tailor care for people based on their individual DNA.

There's only a small portion of our DNA—less than one percent—that's of special interest to researchers. That's where variations called SNPs (pronounced “snips”) occur. SNPs—short for single

nucleotide polymorphisms—are changes in one of the chemical bases that make up the DNA sequence, such as guanine or cytosine. They are what give us unique traits.

Searching for a million genetic variations at a time

Some of these changes might be of little consequence. Others might raise our risk for a serious disease. There are millions of these SNPs—among the three billion chemical base pairs that make up our DNA—so finding the critical ones is like finding the proverbial needle in the haystack. But thanks to futuristic robots, laser scanners and “bead array” technology, researchers are making progress.

“We can do in a few weeks what we couldn't do in years,” says Steven Schichman, MD, PhD, director of the Pharmacogenomics Analysis Lab at the Little Rock VA Medical Center. “We're using technology that enables you to simultaneously detect a million SNPs at a time in the genome [the entire genetic material] of a person.”

Detecting SNPs in an individual patient is one thing. Solving the mystery of which SNPs impact disease risk—or have other critical health effects—is another.

“That's a huge biological question,” says Anjanette Stone, a biomedical technician who helps run Schichman's lab. “You have to study hundreds of patients to see if there's a ‘phenotypic’ effect to a particular SNP. That polymorphism [SNP] may not do anything. It may not change a thing in your body. Or it could: What if it changes an amino acid sequence in a protein, and it totally changes the function of that protein? Once again, that may not do anything, or it may change how you metabolize a drug, for example. There could be many effects of a polymorphism, and the only way to understand them is to do these studies with huge numbers of patients.”

The studies Stone refers to are called genome-wide association studies. Here's how they work: DNA samples are obtained from large numbers of people with and without a particular disease. SNPs that show

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Photo by John Berth

Research volunteers share stories—Veteran Steve Beres (right) discusses his experiences as a VA research participant during a VA House Committee briefing that was held April 29 at the Cannon House Office Building in Washington, DC, as part of kickoff events for National VA Research Week. Seated with Beres are (from left) Penny Goree and her husband, research volunteer Timothy Goree; volunteer Sandra Bourget; and Dr. Joel Kupersmith, VA’s chief research and development officer. Also on the agenda was a demonstration of the DEKA prosthetic arm (see story on page 1).

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Downs was shown in a recent “60 Minutes” segment using the DEKA arm to grasp a soda bottle, pick up a screw and hold a PDA as he typed with his other hand. He said: “For the first time in 40 years, my left hand did this. It was such an amazing feeling. I was 23 years old the last time I did that.” In the interview, Downs spoke of the arm as if it were his own: “It felt like my arm. It was me.”

VA has launched a three-year “optimization study” of the DEKA arm at VA medical centers. In the study, participants with upper-limb amputation will be fitted with the arm, receive training and use the arm over two weeks. Their feedback—collected and analyzed by VA researchers—will help DEKA engineers refine the prototype. The first two study sites that were announced are in New York City and Tampa, Fla.

According to Michael E. Selzer, MD, PhD, VA’s director of Rehabilitation Research and Development, the VA-DARPA collaboration is the first time large-scale clinical testing will play

an integral part in the final design and development of a prosthetic device. “The design of the trial itself is groundbreaking,” he says. “We’ve got a prototype that is going to be redesigned and improved over the next three years. DEKA will use data from the VA study to tell them what changes need to be made to the arm to make it the best it can be.”

The effort resembles beta testing of software, whereby companies distribute early versions of software to a limited number of consumers who help work out the bugs. When the three-year clinical trial ends, notes Selzer, “The DEKA arm will have been optimized to the point where it can be manufactured and made available for routine prescription for our veterans.”

Study leader Linda Resnik, PhD, PT, of the Center for Restorative and Regenerative Medicine at the Providence VA

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Photo by Jeffrey Bowen

Gene pie—Weleetka Carter, a technician with the Pharmacogenomics Analysis Lab at the Little Rock VA, checks a pie chart representing data from a scan of DNA samples from research participants. For a slide show explaining the lab procedures involved in genomic research, visit www.research.va.gov.

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up more commonly in the affected population become prime suspects in the hunt for disease-related genes. The SNP could be in a gene—for example, patients with the disease might be more likely than healthy controls to have one or two copies of a gene variant—or the SNP could lie *near* a troublemaking gene in the genome. Either scenario can provide valuable clues for researchers.

Among other such studies now under way in VA, the Little Rock lab is part of research on Lou Gehrig’s disease, or amyotrophic lateral sclerosis (ALS). The team is helping genetic epidemiologists at the Durham, N.C., VA Medical Center learn which genes may contribute to ALS risk. DNA from veterans with ALS who have agreed to be part of a registry is being compared with DNA from patients without ALS.

“The people in Durham take all the data sets and compare them with one another to find SNPs associated with ALS,” says Schichman. “They’ll take a million SNPs and try to find a small subset, maybe less than 20, associated with the disease.”

The Durham group, led by Eugene Oddone, MD, is also looking at other environmental and health factors that may be part of the picture: diet, family and medical history, medications, exposures to toxins, and more. A similar approach is being used by other VA teams studying the genetic and environmental triggers of other diseases.

Survey of veterans shows most would support and take part in genomic research

A majority of veterans who have received health care through VA would support and participate in genomics research, according to a study by the Genetics and Public Policy Center at Johns Hopkins University. Results from the study are on the *Genetics in Medicine* website (www.geneticsinmedicine.org).

In 2006, VA created a Genomic Medicine Program to examine how veterans’ genetic information could be used to improve their health care. A 13-member advisory group was set up to guide the process. The agency is now considering creating a database of genetic information obtained from analyzing DNA from participants’ blood samples, combined with information extracted from their VA electronic health records. Such a database, with appropriate privacy

protections in place, would be a powerful tool for researchers seeking links between genes, environmental factors and health outcomes. Before deciding whether and how to undertake such a project, VA asked the Johns Hopkins center to find out whether veterans enrolled in VA would support a genomic database, and under what circumstances.

The authors first conducted nine focus groups in VA medical centers in Atlanta, the Bronx, Denver and San Antonio. The team used feedback from the focus groups to craft an 80-question online survey that was later administered to 931 veterans.

Eighty-three percent of respondents thought the database should “definitely”

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Such studies will become increasingly common in VA in the next few years. The agency already has a biorepository in Boston that stores frozen DNA samples from veterans who consented for their genetic material to be analyzed as part of clinical trials in which they took part. That facility may expand in the future as VA ramps up its genomics program. Based on an extensive survey of veterans (*see related story on pg. 4*), the agency is now exploring the best ways to widen efforts to collect DNA samples from consenting veterans in research and patient-care settings. The goal: Build a huge database of their genetic results. Such a storehouse of genetic information—combined with information extracted from the patients' VA electronic health records, a rich source of health and clinical data—would be the world's largest and could fast-forward the field of genomic research.

Long-term clinical relationships would enhance VA's genetic database

According to Ronald Przygodzki, MD, associate director of genomic medicine for VA, the long-term relationship that veterans have with the VA health care system would make the genetic database an especially valuable research tool.

“Our advantage is that we have a tremendously loyal, supportive group of veterans,” he says. “These people come to the VA medical center, to the CBOC [Community-Based Outpatient Clinic] and receive care there. They're long-standing patients. They're altruistic. They're willing to get involved to help themselves, their fellow veterans and the greater community. That's a plus that nobody out there has.”

Notwithstanding all the potential for progress, genomic researchers have their work cut out for them. Learning about the health effects of millions of SNPs and thousands of genes—itsself a mammoth task—is only the first step in unraveling a huge mystery.

Schichman: “Once the associations are pinpointed, the science needs to be done to show mechanistically how those associations may lead to, for example, higher susceptibility to a certain cancer.” Only then, he says, can the information be used to its full clinical potential.

Another hurdle to climb: figuring out how to weave veterans' genetic information into their electronic health records so it's helpful to clinicians.



DNA detective—Dr. Steven Schichman heads the Pharmacogenomics Analysis Lab at the Little Rock VA Medical Center.

“Even if we had the entire genome of each patient, just placing that information into the electronic medical record would have no meaning for doctors. It has to be translated into a usable format,” explains Schichman.

Every day, labs like his generate hundreds of gigabytes of raw data, including hefty image files, from DNA studies. After quality-control checks and preliminary analyses, reports get sent to other researchers who comb through the data on millions of SNPs and try to find answers.

Schichman says genomic researchers are undeterred by the vast amount of genetic information that is increasingly available to them, or by the equally vast challenge of learning how to use it to improve medical care.

“All the information we have may not make sense right now, but as it accumulates, and as we have bright people putting it

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Medical Center and Brown University, adds, “VA’s involvement will help to ensure that the arm is optimized to best suit the needs of veterans with amputation.”

Downs emphasizes that the DEKA arm will be made available to any veteran who can benefit from it, regardless of cost. “VA’s policy has always been to provide whatever is necessary to help veterans regain independence and mobility. The focus is on quality prescriptions, not price. The bottom line is, if a prosthetic is available in the marketplace, it is available to veterans.”

Strong need for new upper-limb technology

According to Resnik, as many as a quarter of people who have lost an arm or hand abandon their prostheses because existing models don’t restore enough function. Until recently, upper-limb amputees accounted for only a small percentage of prosthetics users, so investments in new technology were modest. DARPA’s ambitious “Revolutionizing Prosthetics Program,” which supports the DEKA arm and another model being developed by a consortium led by the Johns Hopkins Applied Physics Laboratory, was launched in the face of increasing numbers of troops returning home with upper-limb amputations.

“Twenty-two percent of new military amputees are upper-limb amputees,” notes Resnik. “And the majority of them will enter VA healthcare and VA will provide prosthetic care to them for the rest of their lives.”

The DEKA arm represents a huge leap forward in function. It has six pre-programmed grasps for the hand segment, and more grips can be programmed in. This will enable amputees to perform a range of tasks, from picking up a key to using a power drill. Current artificial hands basically only open and close.

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VA RESEARCHERS IN THE NEWS



Paradigm change—Infectious-disease researcher Dr. Dale Gerding of the Hines (Ill.) VA was quoted in a March 2 article in the Scottish newspaper *The Herald* about an international study he helped lead that yielded surprising results. See item below.

Kristin Yaffe, MD, of the San Francisco VA Medical Center and the University of California, was cited in a May 6 *U.S. News and World Report* article about research by her team and others showing that obesity, diabetes and heart disease may increase the risk of dementia. One study by Yaffe included nearly 5,000 older women and found a 23-percent-higher risk of dementia from each of three factors associated with metabolic syndrome: obesity, high blood pressure and low levels of HDL, the “good” form of cholesterol.

John Concato, MD, MPH, a physician-researcher with Yale School of Medicine and the VA Connecticut Healthcare System, was quoted in a May 5 *Forbes* article, based on a *HealthDay News* piece, about his research on biomarkers for prostate cancer. His recent study found three molecules that may help predict which prostate tumors are fast-growing and require aggressive treatment.

Suzanne Craft, PhD, of the University of Washington and the Geriatric Research, Education and Clinical Center at the Puget Sound VA, is among 25 leading scientists and physicians featured in HBO’s “The Alzheimer’s Project,” which involves films, a website and other materials. Craft’s research focuses on the connection between insulin resistance—the hallmark of type 2 diabetes—and Alzheimer’s disease.

Dale Gerding, MD, associate chief of staff for research at the Hines (Ill.) VA and a professor at Loyola University, was quoted in a March 2 article in the Scottish paper *The Herald* about a study he and other U.S. and Australian researchers conducted on *Clostridium difficile*, the leading cause of infectious diarrhea in hospitals worldwide. The study suggested that past research has focused on the wrong illness-causing toxin released by the bacteria. “For 20 years, we have been focusing on Toxin A. But it turns out the real culprit is Toxin B,” Gerding told the newspaper. “This is a major finding in how *C. difficile* causes disease in humans. It completely flips our whole concept of what the important toxin is with this disease.” —

“This will allow users of the DEKA arm to choose the right grip for the activity,” says Resnik. “We use a very different way of closing the hand when we want to hold a tennis ball than when we want to pick up a small object, such as a penny, or hold a pen or use a BlackBerry.”

The arm also has a “tactor”—a small device that sits on the user’s skin and vibrates to signal the strength of the hand grasp. A stronger grasp causes more vibration. This lets users fine-tune their grasp within each of the pre-programmed settings. One research participant said that for the first time in 26 years, he was able to “peel a banana without squishing it.”

Users can raise, twist and bend arm

Resnik adds that the DEKA arm has 10 powered degrees of freedom—far more than existing prosthetic models. This means users can raise, twist and bend the arm almost as they would their natural limb. The arm’s ability to reach overhead is a first for prosthetic arms. And though it contains an intricate network of microchips, wires, small motors and lithium batteries, the DEKA arm weighs no more than a natural arm—about eight pounds. Despite the relatively light weight of the DEKA system, the elbow is strong enough to lift 20 pounds—“more than two gallons of milk,” says Resnik, who will be studying how the arm performs in everyday situations.

DARPA program manager Col. Geoffrey Ling notes: “Our goal wasn’t to create a high-tech robotic arm. It was to restore function and to restore lives.”

Another unique feature of the DEKA arm is its control system, which can use a variety of inputs. In the VA trial, the arm will be equipped with “strap and go” controls that do not require any surgery—for example, noninvasive myoelectric sensors that pick up electrical impulses from residual nerves and muscles in the upper body, or sensors in a shoe insert that respond to pressure on different parts of the sole of the foot and send movement signals to the arm. The other DARPA arm now in development will offer high-level function to users who undergo surgical implants of electrode arrays into their neuromuscular system for control signals.

Veterans taking part in the VA trial will have their DEKA arm custom-assembled depending on how much of their natural arm remains. The system is modular so it can be customized for different levels of amputation. Specially trained VA prosthetists will also customize the DEKA arm for each study participant by programming in settings such as the speed of the motors that move the arm. ➔



Award recipient Dr. Thomas Starzl (left) shares a warm moment with Bob Phillips, for whom he performed a kidney transplant 46 years ago.

Organ-transplant pioneer honored at VA Research Week event

At a VA Research Week symposium held at the agency’s headquarters in Washington, DC, on April 30, Thomas Starzl, MD, PhD, received VA’s Diamond Award for his pioneering lifetime achievements in the field of transplantation medicine. Known as the “Father of Transplantation,” he spent nearly 50 years of his career as a transplant surgeon and scientist with VA.

In 1962, at the Denver VA Medical Center, Starzl conducted the first successful kidney transplant in humans. The survival of patients from his first series of kidney transplants has in some cases surpassed 45 years. His work on transplantation immunology and immunosuppressive drugs led to his discovery of methods to prevent rejection of transplanted organs and revolutionized the field of organ transplantation. His progress with kidney and liver transplantations became the foundation for successful transplants of other organs.

Starzl moved in 1980 to the Pittsburgh VA Medical Center. Now retired from VA, he continues his career at the University of Pittsburgh, where he directs the Thomas E. Starzl Transplantation Institute.

What happens to your DNA in a genomic study?

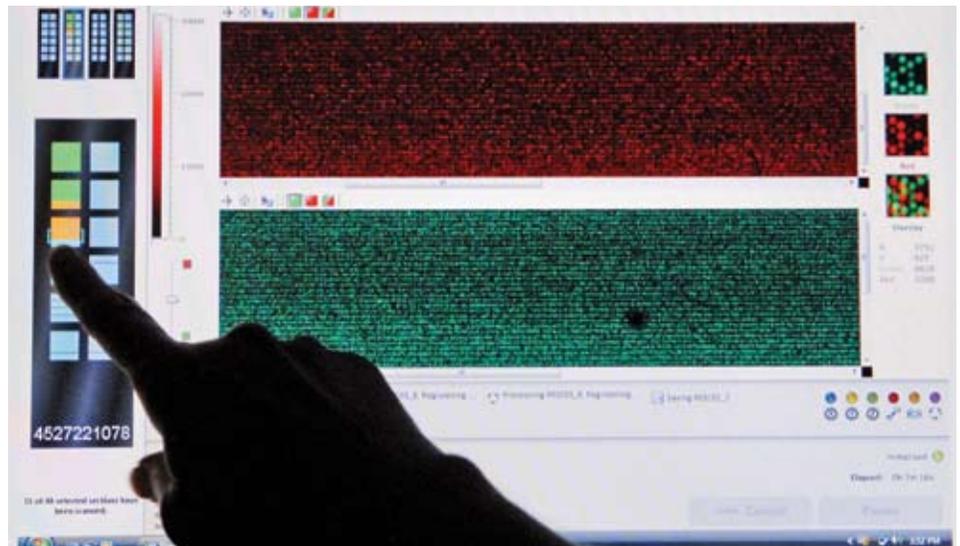
For an up-close look at how DNA is analyzed in genomic research,
visit www.research.va.gov

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or “probably” be created, and 71 percent said they would definitely or probably serve as a research participant if asked. Eighty-four percent believed the proposed database would “lead to improved treatments, cures, or lives saved for veterans,” and most respondents agreed with the statement that they were curious about the influence of genes on health.

Privacy protection was the greatest concern respondents expressed: Ninety-eight percent said it would be important for VA to develop safeguards to protect their information. Although researchers who used the database would not be given identifying information, a key would be needed if participants’ medical information were to be kept up-to-date in the database. Despite concerns about privacy, three in four thought a key should be kept.

The results of the survey are similar to those from another recent study by the Hopkins group. Funded by the National Human Genome Research Institute, that study examined public attitudes toward large, long-term genetics studies. It, too, found broad support and willingness to



DNA light show—A scanner display shows the million or so tiny dots of DNA on a bead array, each containing a different gene variant. Researchers analyze the light patterns to find matches between study volunteers’ DNA and the DNA probes on the array. (Photo by Jeffery Bowen)

participate in such research projects and strong desire for individual research results.

A slide presentation detailing VA’s Genomic Medicine Program and the results of the survey of veterans can be found on the VA research website at www.research.va.gov/programs/PRIDE/conferences/docs/accountability/Genomic-Overview.ppt. ➔

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together in new ways, we discover more and more,” he says.

“It’s like a huge jigsaw puzzle—you may not have any idea how all the pieces are related until the whole puzzle is assembled. We’re just assembling pieces of the puzzle, and we’re able to do it much faster now thanks to the technology.” ➔