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Trail of a Killer
**A Fitness Mogul,
 Stricken by Illness,
 Hunts for Genes**

Study of Lou Gehrig's Disease
 Pinpoints DNA Variations
 Common to Its Sufferers

Entrepreneur's Latest Pursuit

By **GAUTAM NAIK** and **ANTONIO REGALADO**
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While water-skiing in Vietnam's Mekong Delta about two years ago, Augie Nieto fell several times. His muscular arms suddenly went slack and he couldn't haul himself up.



Augie Nieto

Mr. Nieto was diagnosed with amyotrophic lateral sclerosis, or ALS. About 30,000 Americans have the ailment, also known as Lou Gehrig's disease. They progressively lose control of limbs, speech and the ability to breathe. Most die within five years.


The diagnosis was a shock to Mr. Nieto, who had built his life around exercise. As a young man he had founded what became one of the world's biggest makers of exercise equipment for gyms. "I remember wondering what I had done to deserve this death sentence," says

Mr. Nieto, now 48 years old.

After an initial bout of despair, he decided to fight. He assembled a team of doctors, geneticists and ALS experts and gave them a mission: Identify the genetic basis of the disease in order to seek a treatment.

In just nine months, the effort has yielded some clues to a better understanding of ALS. Its findings will be released at an ALS conference in Japan today. Though the chances of halting Mr.

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Privately bankrolled gene-hunting efforts are under way in a number of maladies such as Amyotrophic Lateral Sclerosis, or Lou Gehrig's Disease. However, it's still too early to tell whether a new approach, known as a whole-genome scanning, will pay off. [Jean Lee of Dow Jones Online reports](#)¹.

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Nieto's deteriorating condition are slim, researchers are already using the new understanding to study existing drugs, to see if any might help him and others.

Mr. Nieto is one of a wave of wealthy patients bankrolling a new technology to jump-start the search for a cure: machines that sift through DNA at lightning speed. They identify tiny genetic differences that show up more often in people with an intractable illness than in others. Finding these differences is a first step toward understanding what underpins a disease, which can pave the way for new treatments.

Using the new machines is costly, and government funding is scarce. Now, privately funded gene quests are under way in a number of maladies, including autism, Parkinson's disease and Alzheimer's. The Cure Alzheimer's Fund, sparked by three families touched by the disease, raised \$3 million for a gene search conducted by Rudolph Tanzi, a geneticist at Harvard Medical School. Today, says Dr. Tanzi, science has "the ability to find the key genetic players in a disease. It's expensive, and families are stepping up to the plate." In the case of ALS, at least two other privately funded studies besides Mr. Nieto's are in progress, at Harvard and Johns Hopkins University.

It's too soon to tell whether the gene approach will pay off. Some efforts have been disappointments. The Michael J. Fox Foundation for Parkinson's Research paid close to \$3 million to scan genes of Parkinson's patients. An initial report identified 13 gene suspects, but follow-on studies didn't confirm a role for them.

Some doctors worry that the research is too rushed and could even harm patients -- such as by prompting hopes that any discoveries will rapidly translate to treatments. Others say an approach focused on genes may overlook environmental and lifestyle factors that can also play a role.



Dietrich Stephan

Like Mr. Nieto's search for ALS genes, his quest to build a fitness business began with a personal problem: He was a chubby teenager. To keep the weight off and help others do the same, he opened a gym while he was in college in California.

Soon he learned about a stationary exercise bike developed as a medical device, which could crudely record the user's heart rate. He sold his gym after college, bought marketing rights to the bike, and drove 5,000 miles cross-country in a motor home trying to get health clubs to buy the yellow "Lifecycle." In nine months he sold just 11.

Unfazed, in 1980 he teamed up with the bike's developer, and they sent bikes free to 50 big health clubs. The clubs installed them, they proved popular, and Life Fitness of Chicago grew rapidly. In 1997 Mr. Nieto, who then co-owned the business with an investment fund, sold it for \$310 million. He traveled the world indulging his taste for physical adventure -- fast cars, scuba diving and Arctic snowmobiling.

In mid-2004, he found himself struggling to lift his usual weights. After he had more trouble during the water-skiing trip months later, doctors diagnosed ALS. "Your first reaction is denial, then anger," he says. "Then you get ready to fight."

Mr. Nieto met with a several doctors and researchers in ALS, who had varying theories about it. He was given an antibiotic, which caused sun exposure to turn his skin several shades darker. He

was prescribed the breast-cancer drug Tamoxifen, which gave him hot flashes. Neither seemed to help him.

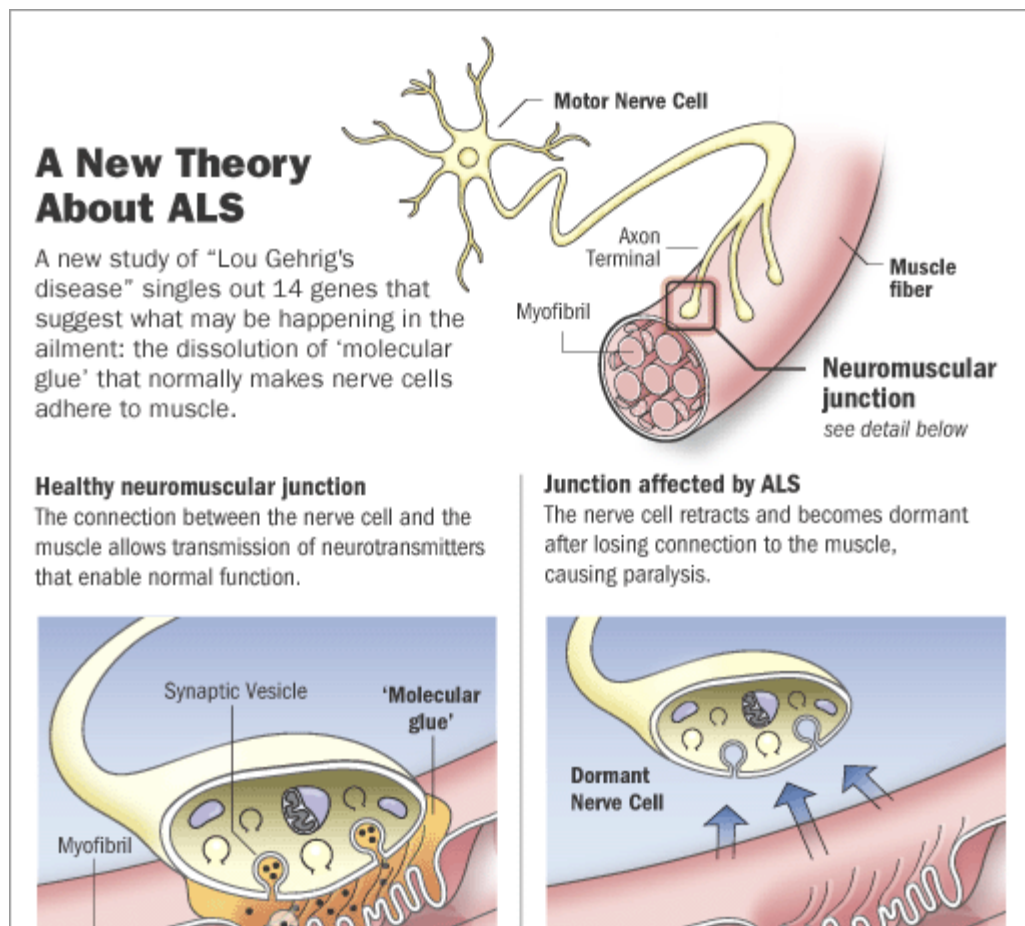
Taking matters in his own hands, Mr. Nieto drew up plans for an ALS foundation, Augie's Quest, that he and his wife's family put money into. To raise funds for a study, he turned to the Muscular Dystrophy Association, or MDA, a group involved in more than 40 neuromuscular diseases and one of the biggest funders of ALS research. He wanted the project to have the attributes of an entrepreneurial business -- speed, efficiency and focus. His doctor, Tahseen Mozaffar, from the University of California, Irvine, worried that the 50-year-old MDA was "a top-heavy, centralized organization" that might not buy into a proposal from an entrepreneur.

Mr. Nieto traveled to the MDA's offices in Tucson, Ariz., in mid-2005 to present his case. "You've got to put a human face on ALS," he recalls saying. "I'm a brand guy." To attract funding, "you have to let me go through the transformation as an ALS patient in public, not in private."

The MDA agreed to help but didn't buy into everything Mr. Nieto had in mind, such as special access to research findings for big donors. "We have defined ways of doing things," said an MDA vice president, Sharon Hesterlee. "Augie wants us to do things very quickly. He's blown things apart" in speeding up the research.

A year ago, Mr. Nieto visited Translation Genomics Research Institute, or TGen, a nonprofit group in Phoenix that uses gene screening to seek targets for various diseases. A TGen senior researcher, Dietrich Stephan, told Mr. Nieto a screen could be done quickly. "After banging your head against the doors of academics, it was like a breath of fresh air," Mr. Nieto says.

A short time later, he was at a Las Vegas trade show getting an award for his role in the fitness industry. He persuaded the organizers to turn the dinner and reception into an ALS fundraiser, and the evening ended up bringing in more than \$1 million for ALS research. His foundation, through the MDA, offered \$650,000 of that to TGen for a hunt for ALS-



related genes.

TGen matched the amount, and the three groups agreed to a deal in March 2006.

For the gene search, the team needed DNA from more than a thousand ALS patients. Doctors and medical centers with stored blood samples didn't give them up easily. Some worried about patient confidentiality, and others wanted a financial cut. Pressed by Mr. Nieto's constant urging for speed, the TGen team paid clinics \$400 per DNA sample. In three months, it had 1,250 of them.

Human cells contain around six billion DNA "letters," dubbed A, G, C and T. The letters spell out genes, each of which tells the body to produce a particular protein. Although any two people's DNA is more than 99% identical, there are millions of sites along the DNA chain where variations regularly occur -- where, for instance, most people have a letter C but some people have a T. Some variations influence what a person looks like; others may make someone either more or less likely to develop a particular disease someday.

Machines now can check DNA from a blood sample for hundreds of thousands of these genetic variations in a matter of hours. Even as the speed of doing so has increased, the cost has fallen, thanks to competition between the machines' makers, **Affymetrix Inc.** and **Illumina Inc.**

TGen scientists put a sample from each ALS patient on a tiny "gene chip" and an Affymetrix laser scanner read it. The scanner also read the samples from people without ALS. The next step was to compare the results for any differences that stood out among the ALS patients. By crunching large amounts of data from the gene screens in a computer, the team initially pinpointed variations in about 50 genes that seemed to have some association with ALS.

In late September, a dozen members of the team met at the MDA's Tucson headquarters to study these. Using their laptops, with each scientist initially looking at just one of the 50 genes, they spent two days scouring scientific literature for clues. "We turned the cellphones off and really tried to figure this out," says Dr. Stephan. The effort narrowed the 50 down to about 25 genes that appeared to play a bigger role.

The research points to a novel theory of ALS. Fourteen of the 50 suspect genes are involved in making "adhesion" molecules that help cells stick to one another. It could be that one big problem in ALS is that nerves aren't anchoring correctly to muscle. Scientists already know that some cells become dormant if they aren't attached to another cell. They call it *anoikis*, the Greek word for homeless.

However, ALS is a complex disease, which may be caused by overlapping genetic malfunctions. For example, TGen says its search also pinpointed a gene called Nox4, long suspected of having a role in ALS. It codes for a toxin that the immune system uses against invaders, but in ALS patients, the gene seems to produce too much of this substance and ends up damaging nerve cells. Another set of genes TGen identified is linked to the degeneration of a part of the skeletal structure found inside motor nerves.

The team hopes the data released today in Yokohama, Japan, will help spur the search for ALS drugs. At the same meeting, a competing team from Johns Hopkins University and the National Institutes of Health will present the result of its own study, and its own list of suspect genes. "What will be interesting is for both of us to see if we come up with the same hits, because if we did, that means they are real," says John Hardy, an NIH researcher who led that effort. Dr. Hardy says so far his genes point a different direction, toward molecules that help the foot-long nerves

that connect to muscles to keep their shape. But the groups haven't yet shared their data.

TGen is releasing the results of the gene screen before publishing them in a peer-reviewed journal. Mr. Nieto, at a planning meeting in Phoenix two weeks ago, said, "We have time pressure, so we need to get this information out." He spoke in a slow, slurred voice typical of ALS sufferers, who, because of reduced motor function, can't easily control their tongue and jaw.

Mr. Nieto takes the only U.S.-approved ALS drug, Rilutek, which can prolong survival for several months, and also a drug that can reduce mood swings in patients with ALS or MS. His wife, Lynne, says of the recent TGen findings: "It's the first time I've had hope."

Mr. Nieto's doctor asked TGen to retrieve Mr. Nieto's genetic data after the gene screen. Dr. Stephan did so, but here a problem cropped up. Dr. Stephan soon realized that federal law requires keeping the identity of samples in such research secret. "I thought we could just flip him his [gene data] but we can't do that," he says.

Mr. Nieto and his physician persisted, Dr. Stephan says, so TGen is trying to help them out by having the same gene test done on Mr. Nieto's blood again, in another lab. "We are trying to accommodate [him] as best we can," Dr. Stephan says. "We want to give something he can sink his teeth into."

Mr. Nieto sold his silver Ferrari after he was diagnosed with ALS. To avoid stairs, he recently had an elevator installed in his cliff-side house in Corona del Mar, Calif. He still exercises an hour a day but can no longer play golf or feed himself.

Mr. Nieto says his mind is as sharp as ever and he isn't stopping. His latest project: to financially kick-start a new institute that focuses on cutting-edge ALS research. "The business of ALS is a blast," Mr. Nieto says. "The disease sucks."

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