STAT

HEALTH

Called ‘hogwash,’ a gene test for addiction risk exploits opioid fears

KENDRICK BRINSON FOR STAT Proove Biosciences, based in Irvine, Calif., markets an unproven “opioid risk” test.

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When the federal government reversed course last month, deciding not to regulate many genetic tests, one big winner was Proove Biosciences, a Southern California company that markets an unproven “opioid risk” test.

Proove claims its test can predict, with 93 percent accuracy, which patients will become addicted to or misuse prescribed opioid pain pills. That’s been an irresistible sales pitch for many physicians, who struggle to treat pain patients compassionately but fear adding to the national epidemic of opioid addiction. The Irvine, Calif., company has recruited

400 doctors, who have used the test to guide their treatment of more than 100,000 patients in the last five years.

But STAT has found that the opioid risk test lacks a firm scientific basis. Genetics and addiction experts — including one of Proove's medical advisers — said genetic testing isn't able to predict addiction, and questioned the evidence used to back up the company's accuracy claim. Erroneous results could misinform doctors and lead them to unnecessarily refuse opioids to patients suffering severe pain, the experts warned.

Tests represented as authoritative and scientific without convincing evidence smack of "opportunism" and exploit understandable alarm about opioid addiction, said Leigh Turner, a bioethicist at the University of Minnesota. "If the company says 'trust us,' and provides no peer-reviewed data, it's important to be wary."

Rockefeller University's Dr. Mary Jeanne Kreek, a leading researcher on genetic links to addiction, said Proove's test — which combines a standard patient questionnaire with genetic data — was "hogwash." Other experts described company studies to validate the test's effectiveness in similar terms.

That hasn't kept Proove, which is paid an average of $300 for each test, from taking in an estimated $28 million in revenue this year for that genetic test and others, most of them related to pain drugs or pain perception. It has been ranked among the nation's fastest growing firms by Deloitte Consulting and Inc. magazine.

Proove is one of an expanding number of players in the multibillion-dollar genetic testing market that promote tests unsupported by hard data to doctors and consumers — and because of a regulatory loophole, it's all legal. These tests have proliferated with the emergence of personalized medicine and its promise to tailor treatments to patients, and the rapid drop in the price of sequencing genes.

The Food and Drug Administration has warned that inaccurate results can lead to botched diagnoses and improper treatments, but last month it withdrewproposed guidelines for "laboratory-developed tests," which, like those from Proove, are created and used within a single corporate or hospital lab.

FDA puts off closing lab-test 'loophole,' leaving decision to Congress and Trump

The FDA guidelines languished for years amid fierce lobbying, and now it will be up to the newly elected Congress and President-elect Donald J. Trump to decide what, if anything, to do. Experts regard the likelihood of strong regulation on laboratory-developed tests as less likely since the election, given Trump's and Republican lawmakers'

anti-regulation rhetoric. For the foreseeable future, companies like Proove can operate without any oversight on whether or not their products work as advertised.

"People expect that if they are offered a test in a doctor's office or in a health care setting, that it has gone through a fairly significant level of screening and that it will do what it says," Dr. Margaret Hamburg, the former FDA commissioner who presided over the drafting of the guidelines during the Obama administration, said in an interview. "At a minimum, there needs to be a lot more transparency about the available data to support these tests."

Proove CEO Brian Meshkin defended the opioid risk test, saying it helps doctors detect addicted patients who lie to obtain opioids. In addition to that flagship test, the company offers genetic analyses that it says show "good vs. poor responders" to specific opioids, such as hydrocodone, oxycodone, and morphine, and to medicines often used to treat addiction. It also sells tests for susceptibility to abuse of alcohol, nicotine, methamphetamines, and other drugs.

"We take away all that subjectivity, and we analyze genetic information around how my brain feels pain," then back it with "big data" analysis and patient interviews, Meshkin said in an interview. "That's what makes the precision medicine [approach] so accurate." Meshkin said Proove data to be published in scholarly journals next year would persuade the doubters about the opioid risk test's validity.

Beyond the immediate impact on patient care, unreliable predictions based on inherited addictive traits, once entered in a patient's electronic medical record, might cause future problems, said Wayne Hall, an addiction ethics expert at Queensland University in Australia.

"If patients are hospitalized with severe pain after something like a [heart attack], and are being treated for post-operative pain, physicians might be reluctant to prescribe opioids that they really need," said Hall. "If a family member was diagnosed by this test as being at a high risk of opioid dependence, then physicians may well be reluctant to prescribe to other family members, to children."

Spurious test results could also undermine confidence in promising personalized treatments for cancer and other diseases, said Jon Retzlaff, who directs scientific and government affairs for the American Association for Cancer Research, a leading scientific publisher and trade association for researchers and physicians from academia and industry.

"If precision medicine is going to advance and flourish, we really need to get this right," Retzlaff said. "If we don't … the wheels are going to come off on our ability to talk about precision medicine in a transformative way."

JED CONKLIN FOR STAT Dr. Robert Rust, who practices family medicine in Sandpoint, Idaho, was dissatisfied with the two Proove tests he ordered to treat his patients.

Research that's 'a marketing effort'

Dr. Robert Rust understands the appeal of Proove's promise to remove the guesswork from pain care for physicians on the front lines. The Sandpoint, Idaho, family medicine doctor treats many patients addicted to opioids — often victims of car crashes or other accidents who fell into an abyss of chronic pain.

It's a common story around the country, after years of lax controls on the prescribing of pain medications. Easily obtained prescription painkillers fed a huge black market. When more cautious prescribing habits constrained the supply, many addicted patients turned to street drugs such as heroin and the powerful synthetic opioid fentanyl. The nation's resulting overdose crisis causes more than 28,000 deaths and costs nearly $79 billion annually, according to experts at the Centers for Disease Control and Prevention.

Dope Sick: A harrowing story of best friends, addiction — and a stealth killer

Rust ordered Proove's opioid risk test and a separate genetic test marketed as a way to predict a patient's response to buprenorphine — an opioid used to treat both pain and addiction. The tests involve a cheek swab to capture cells and a brief interview to determine personal, family, and environmental influences on patients.

Rust had hoped the tests would help him calibrate treatments for pain patients, but encountered a timing problem.

"A doctor has to make a decision about the medicine way before the test results are available," often weeks after the sample was obtained, he said. Proove promises to return some results in under five days — still too long for a patient urgently needing treatment.

When the genetic readings finally arrived, Rust said, they provided nothing beyond what he already knew from taking patient histories and using his clinical judgment to adjust dosages.

"If the company says 'trust us,' and provides no peer-reviewed data, it's important to be wary."

LEIGH TURNER, UNIVERSITY OF MINNESOTA BIOETHICIST

The opioid risk test and Proove's other drug-related genetic profiles emerged from an earlier Meshkin firm that sold genetic tests and dietary supplements — until it ran into a regulatory roadblock.

After an attempt to strike it rich with web marketing during the dot-com boom, then a stint in pharmaceutical marketing, in 2007 Meshkin started Salugen, a "nutrigenomics" company. It sold "GenoTrim" — a genetic test to customize weight-loss supplements — through Las Vegas spas and directly to consumers.

Salugen screened for what it called the "nervous eating" and "sweet tooth" genes. Its product line included "CraniYums," "the world's first functional candy product to improve mood and energy, as well as reduce stress and appetite," and "SpaGen," "for skin and mental well-being." Salugen said its "Haveos" package measured susceptibility to addictive tendencies and supported attenuation of the traits with "a DNA-customized blend of nutrients."

In 2008, California health authorities sent Salugen and other direct-to-consumer genomics firms a cease-and-desist letter for improper marketing. Salugen shifted to working with doctors who ordered tests for patients, and the company was later sold. Meshkin started Proove in 2009 based on the Haveos concept: Given the hazards of a pill-popping era, he thought personalized pain care could be the next big market.

The company has expanded partly by signing on doctors to enroll patients in studies to show the testing works. More than one-third of doctors who order Proove tests are paid $150 per hour to work on those studies — a strategy that critics said improperly blends business, scientific, and patient-care goals.

One observational study is recruiting 50,000 pain patients who will be provided Proove tests for a fee and monitored for adverse events and disabilities to examine how treatment decisions based on those tests affect how well patients do.

Rust, who operated one of the study sites, said Proove had requested only insured patients adding, "They signed me up to do a study, when really what they were wanting was to get more business. … I saw it as more of a marketing effort." Rust said Proove dropped him from the study for unstated reasons after it became clear that not all of his patients were insured.

Dr. Zainab Samaan, an addiction researcher at McMaster University in Canada, said the study lacks scientific rigor, including a controlled, randomized design or clearly defined variables.

Hall, the medical ethicist, questioned the adequacy of Proove's informed consent form signed by trial volunteers, because it fails to mention the risks of being judged genetically susceptible to opioid dependence.

He also questioned the integrity of research because of the financial incentives for clinicians and the trial sponsor. "There's all sorts of conflicts of interest and moral hazard in this sort of activity," he said, that "operate against them doing anything that looks like serious scientific research. … It should be done utterly independently by people who have no personal or financial interest in the outcome."

Meshkin did not reply to requests for the total amount Proove paid to physicians for conducting the research.

The trial's principal investigator, Dr. Daniel R. Kendall, a McLean, Va., osteopath, said in an email that Proove's payments for research are far less than what he earns for normal patient care, but worth the sacrifice for gaining new knowledge.

Kendall has never previously conducted a registered clinical study or published any scientific papers about pain or opioids, according to the National Library of Medicine. He works for the National Spine & Pain Centers, which operates private clinics. He did

not reply to questions about his qualifications for heading a massive study involving 21 trial sites, but said he had ordered Proove tests for hundreds of pain patients, resulting in "improvements in patient outcomes."

'Veneer of science'

Proove's opioid risk test incorporates a questionnaire similar to one widely used by clinicians who rely on patient histories and symptoms to guide their prescribing practices for pain patients. That widely used tool, developed by Dr. Lynn Webster, a member of Proove's medical advisory board and a past president of the American Academy of Pain Medicine, uses questions about a patient's personal and family history with drugs and mental health to help doctors identify patients at risk of possible misuse of drugs or addiction.

Meshkin discounted the value of such questionnaires by themselves, however, because drug-seekers often lie about their history, and patient reports about how opioids affect them can be hard to interpret. Proove sales materials describe clinical judgments as "no better than flipping a coin."

Webster strongly disagreed. "[M]ost physicians know, if a patient has a history of opioid abuse, they are at a much greater risk of abusing opioids when prescribed for pain," he said. "Their personal history, their family history of substance abuse, mental health disorders … all increase the risk. It is not a coin flip."

As revenue falls, a pioneer of cancer gene testing slams rivals with overblown claims

Proove's predictive abilities rely on a 12-gene profile. Preliminary studies, not conducted by Proove, have shown that some of the genes influence how a patient is affected by opioids, and might have associations with drug abuse, depression, and anxiety.

Meshkin said his DNA test delivers genetic ground truth.

Again, Webster disagreed, calling addiction a "biosocial disorder" with biological, genetic, and environmental components. "Genetic testing is informative. It can help. But we're not at a point where we can use genetic testing to predict addiction" or opioid abuse, he said.

Leading researchers said the science of predicting behavior involving opioids and other addictive substances is still in its infancy. "It's not time yet. We don't have enough information" to make accurate predictions about genetic causes for addiction, Rockefeller's Kreek told STAT. "We have identified 110 gene variants that are highly

significantly associated with severe opiate addiction," but even if a patient had all 110 — instead of just the 12 that Proove checks — it would not necessarily predict behavior, she said.

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>
> DR. LYNN WEBSTER, PROOVE MEDICAL ADVISER

Proove's opioid risk test sales brochure cited two posters summarizing results of studies and prepared for scientific meetings as validation for the claim of 93 percent accuracy identifying patients "at risk for abusing opioids." Neither had anything to do with genetics, however. When asked about the discrepancy, a surprised Meshkin called it a "freaking frustrating" mistake by a former marketing employee.

He then provided meeting posters that contained the relevant data.

STAT asked Samaan, Kreek, and Rockefeller University research professor Eduardo Butelman, an expert on opioids and addiction, to review the posters, and they cited serious methodological flaws that undermined Proove's claims. Butelman said in an email that Proove failed to account for the sharp ethnic differences in genetic links to drug abuse.

Samaan called Proove's evidence "very weak at best, or nonexistent." The provided statistics "can't be evaluated," she said in an email, because they leave out normal elements, such as the standard error. One poster, she said, merely noted the "clinical utility" of the Proove test based on subjective views of clinicians, some of whom said it provided "some benefit."

"Keep in mind the (Proove test) score included clinical history data that are useful for any clinician — such as 'did you have history of addiction?'" Samaan added. Another poster, she said, provided little support for sweeping conclusions, leaving the impression of "an advertisement rather than science."

Meshkin conceded that expert skepticism about Proove's claims was "very fair," given that the findings have not been peer-reviewed. He said convincing results will appear next year in peer-reviewed journals.

Turner, the bioethicist, said meager evidence paired with promises of more rigorous studies to come are a common refrain among companies trying to project a "veneer of science … without the proof."

Belief in precision medicine

With so little validation for the opioid risk test, some insurers and Medicare have refused to pay for it. "It's a fight every time," Meshkin said. But Specialty Health, a national managed-care provider focused on the workers' compensation market, recently signed a contract with Proove.

Specialty Health plans to sell a "spine bundle" to employers and insurers. CEO Jacqueline Cox described it as "a flat rate for spinal surgery, but only after somebody goes through a back program and is genetically tested through Proove to see which narcotics work best with them, and would they even succeed if they did have back surgery."

Depending on the results, she said, some patients would be steered into cognitive behavioral therapy rather than undergo surgeries that are "driving up the cost for the employer." Patients might still be approved for surgery or other treatments if they refuse the Proove tests, Cox added.

She discounted concerns about the reliability of the tests as "dueling experts," and said she will rely on her own experience: "Until we use this, until we determine whether it's true or false, I'm going to believe [Meshkin's] done a pretty good job."

Alan Gurvey, a California attorney who represents workers in compensation cases, said he was troubled by the use of unverified genetic tests. He said via email that employers and insurers often describe cost containment justified by unproven diagnostics, such as some genetic tests, as in "the best interests of the injured worker."

Proove has attracted financial backing from a major figure in health policy. Former Utah Governor and Health and Human Services Secretary Mike Leavitt — an adviser to Trump on the presidential transition (and formerly to the Hillary Clinton campaign

transition team) — sits on Proove's board. Last year his investment firm, Leavitt Equity Partners, bet $3.5 million on Proove, and promised another $3.5 million, Meshkin said.

At HHS, Leavitt appointed a blue-ribbon panel to assess regulation for genetic tests. Many of its 2008 ideas were reflected in the recently withdrawn FDA guidance.

Former FDA official Susan Winckler directs risk management at the former secretary's health care consulting firm, called Leavitt Partners. She said Leavitt was and is a strong advocate "to clarify and strengthen the role of FDA in the regulatory regime" for laboratory developed tests like Proove's. His investment "was made based on a belief in precision medicine" and on Proove's commitment to meet future regulatory requirements, Winckler said.

Meshkin said Leavitt provided a convertible note — a loan that can be changed into stock, rather than an outright ownership stake.

This investment approach seems to reflect Leavitt's wait-and-see attitude about Proove's claims. Given concerns raised by leading geneticists, Winckler said, Leavitt was pressing Proove to "have the scientific rigor to continue to evaluate and to validate" its offerings, "… to determine which side is accurate, the advocates or the skeptics."

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