A doctor retrieving bone marrow from a patient at the Nura Precision Pain Management clinic in Edina, Minn., for a stem cell procedure. The clinic is affiliated with Regenexx, which claims that many patients benefit from its treatments. Most researchers believe efforts to sell therapies involving adult stem cells have gotten way ahead of the science. Jenn Ackerman for The New York Times

Stem Cell Treatments Flourish With Little Evidence That They Work

The F.D.A. has taken an industry-friendly approach toward companies using unproven cell cocktails to treat people desperate for relief from aging or damaged joints.

By Denise Grady and Reed Abelson

May 13, 2019

Leer en español

A surgeon recommended a hip replacement, but Kenneth Cevoli said no thanks.

“They’re really quick to try to give you fake joints and make a bunch of money off you,” he said.

At 71, Mr. Cevoli, a high-school guidance counselor in Teterboro, N.J., coaches cross country, teaches mogul skiing, surfs and works summers as a lifeguard on Cape Cod. Despite pain in his left hip and knee, he questioned the need for major surgery, worrying it would sideline him for too long.

Instead, he tried an increasingly popular treatment, in which stem cells are extracted from a patient’s own bone marrow and injected

into worn or injured joints to promote healing.

Many people have become captivated by the idea of using stem cells to fix their damaged joints, and some claim to have been helped.

But there is no clear evidence that these treatments work, and their safety has yet to be established. Most researchers, including those at the National Institutes of Health, think that efforts to sell therapies involving adult stem cells, which can develop into different types of cells to replenish tissue, have gotten way ahead of the science.

Even so, hundreds of clinics have popped up around the country to meet the demand. Some of the clinics also inject joints with platelet-rich plasma, a solution of platelets extracted from the patient's own blood. A few employers have even agreed to provide insurance coverage for the treatments.

There is almost no regulatory oversight of orthopedic procedures using bone-marrow extracts or platelets, which are regarded as low risk. While the Food and Drug Administration insists that it does have the authority to regulate stem cell treatments, it adopted an industry-friendly approach in 2017 by giving companies a three-year grace period in which to describe their products or treatments so the agency can determine whether they meet the criteria of drugs that would require agency approval. So far, few companies have submitted any information.

In the meantime, rogue clinics offering other kinds of procedures have flourished, accused of blinding people by injecting cells into their eyes, mixing stem cells with smallpox vaccine to treat cancer or causing severe infections by administering contaminated blood from umbilical cords into patients' joints or spines. In some of the worst cases, patients had already been harmed before the agency took any action, and the patients took legal steps themselves, suing the clinics that injured them.

"We had our day job clearly cut out for us," said Dr. Scott Gottlieb, who was the F.D.A. commissioner until April. There is, he added, a lot of "really bad stuff."

Dr. Gottlieb spoke in an interview after leaving office. A spokeswoman for the agency said current officials declined to be interviewed. But she said the agency had taken about 45 enforcement actions against stem cell businesses in the past year, including two court cases and various types of warning letters.

Many scientists are skeptical about the treatments being offered, and have called for stricter oversight.

Jason Hellickson, chief executive officer of Regenexx. "Our procedures have been proven effective," he said.
Kathryn Gamble for The New York Times

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Mr. Cevoli was treated in December by a doctor in Wayne, N.J., affiliated with a company called Regenexx, one of the boldest players in the growing industry. Based in Des Moines, the company has dozens of affiliated clinics around the country, specializing in treating orthopedic problems with patients' own platelets or stem cells from their bone marrow. And Regenexx has persuaded some large, self-insured employers to cover its treatments.

The doctor in Wayne injected stem cells and platelets into Mr. Cevoli's knee, fitted him with a brace and sold him a vitamin supplement made by Regenexx to promote healing. The procedure cost $6,900, and was not covered by insurance.

Four months later, Mr. Cevoli said he thought the procedure was helping. He skied during the winter, and has begun running a few times a week.

"There was pain involved, and there is still swelling," he said. "The strength is starting to increase significantly in that left knee. I'm advised that there will be more of an improvement to come in the next couple of months."

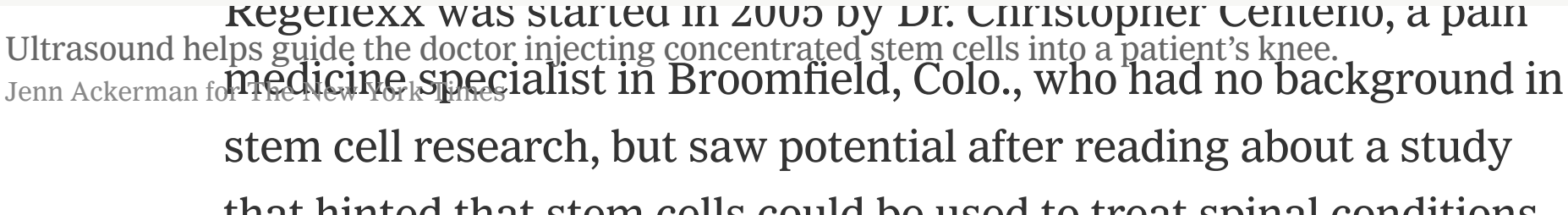
Although he's been told that the stem cell treatments are less successful in hips than in knees, he hopes to have his hip treated anyway, maybe in late summer or early fall.

Navigating the existing guidelines

Some stem cell businesses have carefully navigated F.D.A. rules to stay just inside the lines. The agency regulates cell and tissue products, but treatments that use a patient's own cells do not require the agency's approval if the cells are "minimally manipulated," meaning that they have not been cultured or multiplied in a lab, and no drugs or other substances have been added.

The agency also allows what is known as “homologous use,” deploying the cells in a way similar to their original function in the body.

Ultrasound helps guide the doctor injecting concentrated stem cells into a patient’s knee.
Jenn Ackerman for The New York Times



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Regenexx was started in 2005 by Dr. Christopher Centeno, a pain medicine specialist in Broomfield, Colo., who had no background in stem cell research, but saw potential after reading about a study that hinted that stem cells could be used to treat spinal conditions in rabbits.

The company is trying to commercialize stem cells and move them into mainstream medicine, while also seeking to distance itself from outfits that have injured patients and drawn fire from regulators.

Regenexx points to a registry it keeps of its results and says it has published nearly two dozen research papers. It also cites a 2016

study concluding that its procedures led to no more serious side effects than other injection-based therapies, and fewer side effects than more invasive procedures.

Regenexx claims 40,000 patients have been treated with its techniques. Of the 90,000 procedures the company says it has performed to date, 70,000 involved only platelets. Many patients pay thousands of dollars out of their own pockets. Although nearly all insurance companies have refused to cover the treatments, citing the lack of evidence that they work, some employers are covering the injections.

The company says six million people are now covered, and Regenexx hopes to increase that number to 20 million over the next year, Dr. Centeno said in an interview.

The company contends that employers can save hundreds of thousands of dollars by helping workers avoid more invasive, time-consuming and expensive remedies like joint replacements or other orthopedic surgery.

Regenexx is training doctors around the country to perform its procedures, and building a nationwide network of treatment centers that carry its brand.

Regenexx corporate headquarters in Des Moines.
Kathryn Gamble for The New York Times

“We have an extreme vetting,” said Jason Hellickson, the

and backs.

Regenexx corporate headquarters in Des Moines. Kathryn Gamble for The New York Times

Through the website, Dr. Centeno regularly criticizes other stem cell businesses, and has acted as an expert witness for injured patients suing his competitors.

The company did run afoul of the F.D.A. in 2008 over its use of cells cultured and multiplied in a lab to increase the stem cell count. After a protracted legal battle, Regenexx quit using that technique in the United States, but began offering it at a clinic on Grand Cayman.

“This has always been about creating a less invasive orthopedic

solution, what I call interventional orthopedics," Dr. Centeno said. He predicts a sea change in orthopedics similar to the revolution in cardiology, where much open-heart surgery was replaced by less invasive procedures.

While regulators may not consider them high risk, stem cell treatments involving bone marrow are not trivial. Collecting bone marrow involves forcefully puncturing the back of the hip bones in several spots, a painful process that requires local anesthesia. Then, pressure is applied to prevent bleeding, and the sites are bandaged to prevent infection.

Injecting the bone marrow or platelet extracts into the knee takes skill, even with X-rays to guide the needle. The injections can cause pain and irritation, and patients are usually sent home with leg braces that they will wear for a few weeks.

Sterile techniques are essential.

"Whenever injections are administered to the joint, there is always a risk of introducing infection," said Dr. Kiran M. Perkins, who has investigated such illnesses at the Centers for Disease Control and Prevention. With stem cell treatments, she added, "there are a lot of steps along the way where something could go wrong and you could have the introduction of microorganisms."

Needed: Real data

Scientists say that research on stem cells does hold tremendous promise for treating many diseases. But those goals are years

away.

“There’s not a whole lot you can say definitely about whether these therapies are efficacious,” said Scott Noggle, the senior vice president of research at the New York Stem Cell Foundation, a nonprofit scientific group. “Until you do well-controlled clinical trials showing it works in humans, the question is still up in the air.”

Bone marrow contains many different types of cells, and unless the extracts used to treat patients are analyzed, it is not clear which cells they are receiving, Dr. Noggle said.

Susan Solomon, head of the New York Stem Cell Foundation Research Institute, in her office in New York. “What if we find out it doesn’t work?” she said. “Then you’ve got a very large revenue stream that’s going to disappear.”
Demetrius Freeman for The New York Times

Susan Solomon, head of the New York Stem Cell Foundation Research Institute, in her office in New York. “What if we find out it doesn’t work?” she said. “Then you’ve got a very large revenue stream that’s going to disappear.”
Demetrius Freeman for The New York Times

“There’s great potential,” he said. “We are just not there yet. The marketing and use far outpace the science.”

Susan Solomon, chief executive officer of the New York Stem Cell Foundation, said that companies providing what she called “blood soup” treatments “are making a lot of money.”

She added: “We really need to have very significant clinical trials. That’s something we are in discussions with some large institutions about doing. But it’s hard to get funded, because there are a lot of doctors already doing it. What if we find out it doesn’t work? Then you’ve got a very large revenue stream that’s going to disappear.”

The lack of solid medical evidence has led health insurers to refuse to cover the treatments, said Dr. Elizabeth Burns, senior executive medical director for Regence BlueCross and BlueShield in Oregon. She is also concerned about patients’ safety. “There is potential for the cells to grow out of control,” Dr. Burns said.

Mr. Hellickson, Regenexx's chief executive, downplays the insurance companies' reluctance to cover the treatments. One of the main reasons insurers won't cover them, he argued, is that there aren't enough doctors to treat the potential customers. "People are trying to avoid invasive surgery," Mr. Hellickson said.

A former insurance brokerage executive in Des Moines, Mr. Hellickson came up with the idea of approaching area companies and 117 have agreed. Meredith, a media company that publishes People, Real Simple and other magazines, was among those signing up.

In reviewing the research, the company found "nothing in any shape or form that could be negative or create any sort of medical risk for our employees," said Steve Lacy, Meredith's chairman, who has gotten the treatment for a knee injury.

Eighty-five Meredith employees have chosen to get a Regenexx treatment over traditional care. The company estimates it would have spent $1.6 million if those individuals had knee replacements, compared with the roughly $400,000 it paid to cover the Regenexx treatments.

Dr. Nate Crider explaining a procedure at the Nura clinic in Edina, Minn., a Regenexx affiliate.
Jenn Ackerman for The New York Times

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“There isn’t anything that shows it’s harmful,” said Sheila Laing, an executive vice president. “Nothing says it makes you worse than it was.”

Dr. Centeno argues that the vast majority of orthopedic procedures performed today by mainstream physicians do not have any evidence that they work. Indeed, studies in recent years have challenged the value of many knee surgeries performed for torn cartilage.

By persuading employers to offer Regenexx, the Des Moines clinic became a billboard for Regenexx’s potential. Its procedure volume has soared to 1,234 in 2017 from 140 in 2014, according to the company.

Mr. Hellickson, who had invested in the clinic, eventually merged it with the company in 2017. He replaced Dr. Centeno as chief executive and raised $10 million from investors and expects to rapidly expand the company.

While Dr. Centeno emphasizes that the procedures taking place in the United States do not need F.D.A. approval, doctors and company executives tend to muddy the issue by claiming that competitors may need approval and could be operating illegally because they do not have it.

As for clinical trials, Regenexx says it is conducting them now. But only one small controlled study has been published, in December. Patients with arthritic knees got either exercise therapy, or stem cell treatment. After three months, the patients given stem cells were doing better. But all the patients in the exercise group later got stem cells, too, so the results are hard to interpret.

Most of the other studies Regenexx has listed on clinicaltrials.gov have either been abandoned or will not be completed until 2021 or later.

As a result, patients rely on testimonials and other informal evidence. But experts caution that word-of-mouth experiences are not a substitute for rigorous studies.

“The power of anecdotes is just amazing when it just catches on,” said Donna Messner, the president of the Center for Medical Technology Policy, a nonprofit research group. “This is how snake oil has been sold for generations.”

A version of this article appears in print on May 13, 2019, on Page D1 of the New York edition with the headline: An Unproven Cure. Order Reprints | Today’s Paper | Subscribe

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