Medical News & Perspectives

# Unproven but Profitable: The Boom in US Stem Cell Clinics

Rita Rubin, MA

Stanford orthopedic surgeon Jason Dragoo, MD, is conducting 4 randomized clinical trials of the use of autologous stem cells to treat knee osteoarthritis.

Interest in the trials seems high—nearly 100 people inquire about them daily, Dragoo says—but he recognizes that some patients might not volunteer for a study in which they could get a placebo instead of stem cells. "We're trying to do good science," he explained, but "the patients could easily say, 'why would I take a risk of being in the control group? I could just go down the street and have it [stem cell therapy].'"

These days it seems like there's a stem cell clinic on almost every corner, especially in urban areas in Dragoo's home state of California and in Florida. They market treatments, typically using patients' adipose tissue, for arthritis and a host of other conditions. Despite the proliferation of these clinics, however, the science to support their claims isn't there yet, Dragoo said. Not even close.

"There's a lot of good in this," he said of the potential of stem cells for treating musculoskeletal problems. But with the proliferation of stem cell clinics offering unproven therapies that might not actually even contain living stem cells, Dragoo said, "it's just gone haywire."

Stem cell clinics market their treatments as "natural" alternatives to major surgery, such as joint replacement. As one clinic's website puts it, stem cell therapies "work by harnessing the body's innate ability to grow and heal itself."

But instead of randomized controlled trials, these clinics base their claims on patient testimonials. Instead of peer-reviewed publications, the clinics depend on the placebo effect to prove that their treatments work, critics say. "Those are the things that make us completely cringe," Dragoo said.


According to a recent report, the number of US clinics offering unproven stem cell therapies at least doubled annually from 2009 to 2014, and from 2014 to 2016, approximately 90 to 100 new stem cell business websites appeared yearly, the authors wrote. In 2016, they found, 351 US companies were marketing stem cell interventions at 570 clinics. Today, said coauthor Paul Knoepfler, PhD, professor of cell biology and human anatomy at the University of California, Davis, School of Medicine, "there might be 700 to 750 of these clinics out there."

Relief of orthopedic problems and pain are by far the clinics' most common claims, Knoepfler and his coauthor, Leigh Turner, PhD, found, but they also market stem cells for conditions ranging from Alzheimer disease to erectile dysfunction to Parkinson disease.

"The lack of action on the part of the FDA [US Food and Drug Administration] has been a kind of green light," said Turner, an associate professor at the University of Minnesota Center for Bioethics, School of Public Health, and College of Pharmacy.

In August 2017, though, FDA Commissioner Scott Gottlieb, MD, announced the agency would step up enforcement activity in the area of stem cells "to make sure the agency is separating the promise from the unscrupulous hype."

Shortly before Gottlieb's announcement, US marshals on behalf of the FDA seized 5 vials of live vaccinia virus vaccine, containing 100 doses each, from StemImmune Inc in San Diego. The vaccine,

which is reserved only for people at high risk of smallpox (mainly military) and not commercially available, was being used by California Stem Cell Treatment Centers in Rancho Mirage and Beverly Hills to create an unapproved stem cell cancer treatment.

In November, the FDA rolled out a "comprehensive policy framework" for the development and oversight of regenerative medicine products, including novel stem cell therapies. And in May, the US Department of Justice (DOJ), on behalf of the FDA, filed complaints in federal court seeking permanent injunctions against 2 stem cell clinics, US Stem Cell Clinic of Sunrise, Florida, and the California Stem Cell Treatment Center.

The company in Florida made headlines after 3 customers treated in 2015 and 2016 for age-related macular degeneration developed severe bilateral vision loss, as noted in the DOJ's complaint. The California company has more than 100 for-profit affiliates that have treated more than 6000 patients, according to the complaint. Both companies have argued that treating people with their own stem cells does not fall under the FDA's bailiwick.

"I think the FDA is doing more than it was doing several years ago," Turner acknowledged. "The problem is the marketplace is accelerating at a really fast rate."

## A Tale of 2 Parkinson Disease Studies

Jeanne Loring, PhD, says that when fellow party guests learn that she studies stem cells, they often respond, "I had stem cell therapy!"

"It really does kill conversations," said Loring, a professor at the Center for Regenerative Medicine at the Scripps Research Institute in La Jolla, California, and a vocal critic of the stem cell clinics that have popped up near her campus and beyond.

Loring has been working with the FDA to launch a clinical trial to test the therapeutic potential of transplanting dopamine neurons derived from induced pluripotent stem cells (iPSCs) into patients with Parkinson disease. To generate iPSCs, Loring and her collaborators reprogram patients' skin cells in vitro into a pluripotent, embryonic stem cell–like state. The FDA approval process could take up to 2 more years, she said. "We're ready for it. We've done all the work."

The trial will recruit patients who would qualify for deep brain stimulation. Instead of electrodes, though, they will receive stem cell–derived dopamine neurons through a magnetic resonance imaging–guided catheter. "We're transplanting a person's cells to their own brain, and that way we don't have to worry about rejection," Loring said.

Just a 5-mile drive from her laboratory on Scripps' 35-acre campus, a company called StemGenex is planning its own study of stem cell therapy in patients with Parkinson disease, using "a cellular concentrate derived from an individual's own fat," according to its description on ClinicalTrials.gov.

The StemGenex study is designed to evaluate changes in such factors as self-image and sexuality, urinary function, and independence, as measured by the Parkinson's Disease Quality of Life scale, for up to 12 months following treatment, its description states. StemGenex's studies—it has a total of 5 registered on ClinicalTrials.gov—entail looking at subjective outcomes of customers who pay for its therapies. The last line of a disclaimer on the StemGenex website states: "Any decision to participate in our patient-funded clinical stem cell studies is completely voluntary."

An observational study can't prove effectiveness, noted Larry Goldstein, PhD, director of the Sanford Stem Cell Clinical Center and scientific director of the Sanford Consortium for Regenerative Medicine, both at the University of California, San Diego. "These companies hide their lack of proof in the fine print, and that's not right."

In fine print at the bottom of its home page, beneath links to testimonials from satisfied customers, StemGenex states, "Stem cell therapy is not FDA approved and is not a cure for any medical condition."

## Using ClinicalTrials.gov as a Marketing Tool

StemGenex is not alone in registering pay-to-participate studies on ClinicalTrials.gov, according to a commentary Turner and colleagues published online in June.

Studies charging $7500 to $20 000 have been registered in the database, raising the specter of ClinicalTrials.gov "being repurposed as a marketing platform by businesses selling unproven stem cell interventions," Turner and his coauthors noted.

Although ClinicalTrials.gov states that registered research must conform to "any applicable regulations of the national or regional health authority," the California Stem Cell Treatment Center, which the FDA is trying to shut down, managed in 2013 to register a study that planned to look at the safety and effectiveness of its stem cell treatments in 3000 paying customers with any of a host of conditions.

"Patients kind of see that [a listing on ClinicalTrials.gov] as validation, that it's done with government oversight," said Sunir Garg, MD, a retina specialist at Philadelphia's Wills Eye Hospital and a spokesman for the American Academy of Ophthalmology. But, Garg noted, trials posted on ClinicalTrials.gov don't go through a vetting process. "Even a lot of physicians don't appreciate that nuance."

Pamela Robey, PhD, chief of the skeleton biology section at the National Institute of Dental and Craniofacial Research, which, like ClinicalTrials.gov, is part of the NIH, said, "There are many of us who have been begging the webmaster to post very clearly that listing in ClinialTrials.gov does not mean NIH (National Institutes of Health) approval, IRB (institutional review board) approval, or FDA approval."

ClinicalTrials.gov did eventually post a disclaimer on its home page—"Listing a study does not mean it has been evaluated by the U.S. Federal Government"—but, Robey said, "it's not very prominent." Besides, she said, many people don't understand the significance of a clinical study conducted without regulatory approval.

## Status by Association?

The Miami-based American Association of Stem Cell Physicians (AASCP) invited several University of Miami faculty members as well as Mark Berman, MD, co-founder of the aforementioned California Stem Cell Treatment Center, to speak in August at its first-ever meeting. The meeting also offered 2-hour workshops, costing $2000 apiece, on such topics as "stem cell eye drops" and "neuroregenesis."

A. J. Farshchian, MD, AASCP board secretary and spokesman, ran the workshops, and his clinic, the Center for Regenerative Medicine, which has the same address as the AASCP, markets the treatments. The neuroregenesis Facebook page, which links to Farshchian's clinic, describes it as "effective cutting-edge therapy" for healthy individuals older than 50 years "who seek brain function enhancement."

In February, Farshchian blogged about "Neuroregenesis as an Alternative Option for the Treatment of Neurological Diseases,"

in which he described treating a patient with Alzheimer disease with intranasal injections of stem cells. She scored higher on the clock drawing test, a widely used dementia screening tool, after treatment than before, Farshchian wrote, leading him to conclude that neuroregenesis was an effective treatment for Alzheimer disease.

However, Loring said she'd never heard of this type of treatment. "It's another example of people making up things in order to charge people money," she said.

"Hocus-pocus" is how Garg described the notion that stem cell eye drops could improve vision, as Farshchian claims. "You can make any claim that you want," Garg said, "because there are no data to refute it, and there are no data to support it."

In an interview with *JAMA*, Farshchian acknowledged that "people have different thoughts about it [stem cell therapy], but the ones who are practicing it and are seeing results with their patients are physicians who … are able to harness the power of the stem cells. They are getting great results with their patients." He provided a statement outlining AASCP's goals, which include "[making] available to physicians the benefit of stem cell therapeutics, to share ideas and technique, to make stem cells the standard of care in [the] near future…."

One conference speaker, Lee Kaplan, MD, director of the University of Miami Sports Medicine Institute, conceded that he had questions about the AASCP's mission.

"I have a big concern, living in South Florida, with a lot of billboards up" that promote unproven stem cell therapies, Kaplan said. However, he said, his school's compliance office approved his talk at the AASCP meeting, for which he received no payment.

Perhaps it is especially important for credible stem cell researchers to speak to such groups, Kaplan said. "My point is you really should have some people talking about where we really are. What we know and don't know." However, he said, his participation in the meeting "shouldn't be used as an endorsement" of the AASCP.

But it could be, and that is why academic stem cell scientists and physicians need to be cautious when accepting invitations to speak, Knoepfler said.

"The problem is doctors who want to market stem cell treatments will just go ahead and create new professional organizations to serve as front groups," Turner added.

### "Looking for Miracles"

If there's no solid evidence to back up the claims made by the stem cell clinics, why do some customers swear by them?

"Many of the conditions that are being treated [osteoarthritis and multiple sclerosis, for example] are conditions that wax and wane," explained Robey. "There are good days, and there are bad days. If they have a good day, they think it's because of the treatment. There's also the placebo effect, and I think there's a bit of denial, too."

Some clinics "mix a bunch of stuff together" in their stem cell injections, such as corticosteroids and hyaluronic acid (the FDA in May approved a device that injects a substance similar to hyaluronic acid into the knee to treat osteoarthritis pain), Dragoo said. "Who knows what the stem cell part of this is? Of course they feel better after a corticosteroid injection."

News reports about professional athletes getting stem cell injections probably help attract weekend athletes. But, Goldstein noted, "These top athletes also have the best physical therapy. They're dedicated. You don't know whether the stem cell injection made a difference or not."

Wishful thinking might be the main reason for the stem cell clinics' appeal, Loring suggested. "I think the problem is people are looking for miracles," she said, "and when they don't see one, they invent one." ■

**Note:** Source references are available through embedded hyperlinks in the article text online.

The JAMA Forum

# The Surprising Resiliency of the Affordable Care Act

Gail Wilensky, PhD

Ever since the passage of the Affordable Care Act (ACA) in 2010, Republicans (and, more recently, President Trump) have made their opposition to the ACA a rallying cry. The focus on "repeal and replace" during the 2014 Congressional election and again in the November 2016 full election led many Republicans to expect a rapid replacement of this key Obama administration legislative victory. House Republicans had even proposed a general legislative strategy before the 2016 election called "A Better Way," which included changes in several areas of public policy, including health care.

However, the reality of getting replacement legislation through the Republican Congress proved to be much more challenging than many had anticipated. Republican House leadership had to work very hard to get their version of a replacement bill passed in May of 2017, despite the substantial Republican majority (240-194) in the House. The bill that was ultimately passed frustrated both conservatives who thought it was not conservative enough and moderates who were concerned about the Congressional Budget Office's estimate that an additional 22 million people would be uninsured as a result of the legislation. Given the House's unsuccessful experience in attempting to replace the ACA, it was not surprising that the Senate, with its very narrow majority of 52-48 and no prior history of an agreed-upon replacement bill, was unable to pass its own version of replacement legislation.

### Limited Bipartisan Efforts

The more logical strategy would have been to structure a bipartisan approach—primarily because of the increased likelihood of sustainability with legislation that has received support by both parties. Previous examples of such legislation include the Medicare and Medicaid bills passed at the beginning of the Johnson Administration