



## Medicine's Wild West — Unlicensed Stem-Cell Clinics in the United States

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In recent decades, there has been tremendous hope that stem-cell-based technologies would introduce a new era of regenerative medicine, revolutionizing the treatment of disease. These hopes have been

stoked by reports that often emphasize promising findings without adequately acknowledging the many remaining challenges. Although stem-cell therapy may hold great potential, the field is less advanced than the public has been led to believe. Stem-cell clinics in the United States and abroad have capitalized on this confusion by selling treatments that are not approved by the Food and Drug Administration (FDA), supported by clinical studies, or covered by insurers.

The FDA has approved few treatments involving stem cells. The approved therapies use hematopoietic stem cells to treat dis-

eases of the blood and immune system. But the majority of therapies offered by stem-cell clinics use adipose-derived stem cells packaged as a product called stromal vascular fraction (SVF). Procedures using SVF have become increasingly popular because of the relative ease of acquiring the cells. To produce SVF, clinics collect liposuction aspirate from a patient, separate the cells from the surrounding fat tissue, and administer the isolated cells back to the patient intravenously or by injection into the tissue to be treated. The stem cells found in SVF are multipotent, and proponents postulate that they may regener-

ate injured tissue or alter the immune system's inflammatory response. Although the FDA has not determined that SVF is safe or effective in treating any disease, U.S. clinics sell SVF-based procedures to patients with myriad conditions — from benign conditions such as hair loss to chronic and life-threatening diseases such as heart failure, muscular dystrophy, and Parkinson's disease.

These clinics neither claim their treatments are effective nor explicitly state that they're unfounded. Their websites frame their work as experimental — although none of the clinics are conducting FDA-approved clinical trials — and emphasize the potential regenerative capabilities of stem cells. Their language is intentionally imprecise and exploits the vulnerability of patients with debilitating diseases.

Since insurers don't cover unapproved stem-cell treatments, patients pay out of pocket for procedures that cost anywhere from \$5,000 to \$50,000.<sup>1</sup> According to the FDA, the procedures may cause complications including infections, emboli, and toxic effects of anesthesia. Although the complication rate for the liposuction procedure is low (0.7%),<sup>2</sup> the risks posed by SVF transplantation are largely unknown. Apart from directly harming patients, the activities of unlicensed clinics could hinder advances in the stem-cell field, if a tragedy resulting from unapproved treatment makes the public and regulators suspicious of stem-cell technologies in general.

Because FDA guidelines are ambiguous, stem-cell clinics have in effect been operating without regulation. The FDA classifies biologic products as either 351 products, such as cells that have been grown in culture or have undergone genetic manipulation, which are subject to strict regulatory oversight and cannot be used in patients without approval, or 361 products, such as vascular grafts, tendons, and semen, which can be used by licensed physicians as part of the "practice of medicine." The latter products must be "minimally manipulated"; they must be for homologous use, meaning the tissue must perform similar functions before and after transplantation; they may not be combined with other substances besides water, crystalloids (usually salts), and preserving agents; and they must be implanted into the patient from whom the tissue was taken.<sup>3</sup>

Unfortunately, the definition of a 361 product is too vague to deter clinics from offering unapproved stem-cell treatments. For

example, the FDA defines minimal manipulation as processing that "does not alter the relevant biological characteristics of cells or tissues." Stem-cell clinics have therefore defined the relevant biologic characteristic of SVF as incorporation of stem cells capable of regeneration, ignoring other characteristics of adipose tissue. The homologous-use requirement fails to consider that tissues commonly perform many functions in the body. Fat tissue, for example, provides cushioning underneath the skin and secretes many important hormones. The FDA guidelines do not clarify whether homologous use means the transplanted tissue must perform all its prior functions or only some of them.

Moreover, stem-cell clinics can often avoid having to prove that SVF qualifies as a 361 product altogether by citing an exception to the regulations. The guidelines say that if tissue is removed from a patient and implanted in that patient during the same surgical procedure, it can qualify as a 361 product without meeting the other criteria. So clinics have decided that a treatment that typically involves liposuction, processing fat tissue to produce SVF, and administration of the isolated cells can count as a single surgical procedure. Although the FDA probably didn't intend this application of the exception, its language has allowed clinics to interpret the rules broadly and claim legal standing.

To clarify its rules, the FDA recently published draft guidance for industry that addresses whether products derived from adipose tissue can qualify as 361 products.<sup>4</sup> The document concludes that separating cells from their

surrounding tissue represents more than minimal manipulation because it removes structural components that provide cushioning and support. In addition, the draft guidance clarifies that using SVF to treat bone and joint diseases would not qualify as homologous use because adipose tissue does not normally regenerate these tissues; this clarification, however, doesn't explain whether transplanted adipose tissue must retain all its prior functions. The document also makes it clear that since SVF production involves chemical digestion of noncellular components (using enzymes or detergents), the product comes into contact with substances other than water, crystalloids, and preserving agents. In addition, the FDA clarifies that the same-surgical-procedure exception applies only when the tissue undergoes minimal processing, such as rinsing, cleansing, or sizing,<sup>5</sup> and that such a procedure must be "a single operation performed at the same establishment."

In recent years, the FDA has issued warning letters and audited some stem-cell clinics to enforce the rules for stem-cell treatments that would probably be deemed 351 products. Although it's difficult to determine the number of unlicensed stem-cell clinics in the United States, there are strong indications that the FDA's actions to date are insufficient to enforce its regulations. A 2014 analysis of clinic websites found the United States has the world's highest density of online "stem-cell tourism" clinics.<sup>1</sup> New policies are clearly needed to prevent for-profit human experimentation and protect patients.

The FDA can address the proliferation of clinics selling unap-

proved treatments by first establishing clear guidelines defining what procedures physicians may not perform in the absence of regulatory oversight. Then the agency may need to change its procedures for identifying and penalizing clinics that are out of compliance.

The FDA might increase its enforcement capabilities by coordinating with state medical boards, which have authority to revoke the licenses of physicians performing these procedures. By sharing the results of its investigations, the FDA could make it easier for these boards to penalize doctors who are defrauding patients. The added risk of an audit by a medical board might even be enough to discourage many physicians from offering unapproved procedures in the first place.

The Federal Trade Commission (FTC) may also be able to help reduce the misinformation in stem-cell-clinic advertising. Although

clinic websites say the therapies are not FDA-approved and not proven to be effective, they suggest the procedures are based in scientific research and that there's hope for curative outcomes. In other health care areas, the FTC has worked in coordination with the FDA to combat such deceptive advertising — for example, filing complaints challenging claims made by the supplement industry. In regulating dietary supplements, the FTC has extensive guidelines regarding the amount and quality of evidence that must be collected before a claim can be advertised. It may be able to write similar guidelines requiring stem-cell clinics to consider the totality of the evidence, rather than individual studies, before making claims about a treatment's chances of success.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.


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 An audio interview with Dr. Taylor-Weiner is available at NEJM.org

## Medicare's Vision for Delivery-System Reform — The Role of ACOs

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Earlier this year, the Department of Health and Human Services announced the goals of tying 30% of Medicare payments to alternative payment models by the end of 2016 and 50% by the end of 2018.<sup>1</sup> That move was reinforced by the Medicare Access and CHIP Reauthorization Act of 2015, which replaced the sustainable growth rate formula

for calculating physician payments with a Merit-based Incentive Payment System (MIPS) that consolidates and incorporates key components of the Physician Quality Reporting System, the Physician Value-Based Payment Modifier, and the Medicare Electronic Health Records Incentive program for eligible professionals. The MIPS will adjust payment

rates on the basis of physicians' performance on quality measures, resource use, clinical practice improvement activities, and meaningful use of electronic health records.<sup>2</sup> Eligible professionals participating in eligible alternative payment models could receive a 5% lump-sum incentive payment each year from 2019 through 2024. If they meet pro-