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The American stem cell sell in 2021: U.S. businesses selling unlicensed and unproven stem cell interventions

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https://doi.org/10.1016/j.stem.2021.10.008

In March 2021, 1,480 U.S. businesses operating 2,754 clinics were found selling purported stem cell treatments for various indications. More than four times as many businesses than were identified 5 years ago are selling stem cell products that are not FDA-approved and lack convincing evidence of safety and efficacy.

Introduction

Nearly 1,500 U.S. businesses now advertise purported stem cell therapies for a wide range of diseases and injuries. Businesses make such claims despite lacking FDA approval for their stem cell products and absent convincing evidence from well-designed and appropriately powered controlled clinical trials that their interventions are safe and efficacious.

U.S. businesses began selling unlicensed and unproven stem cell products nearly two decades ago (as reported in 2007 by ABC News). What started as a trickle became a torrent as businesses poured into this space (Knoepfler and Turner, 2018). Marketplace expansion occurred even though the U.S. has comprehensive regulations related to cell-based interventions, guidance documents addressing how the FDA interprets and applies such regulations, and mechanisms that provide businesses with opportunities to determine the regulatory status of stem cell products they want to sell. Studies examining online advertising of unproven stem cell interventions have found that the U.S. has more facilities selling such products than any other country, including nations that were once leading destinations for "stem cell tourism" (Berger et al., 2016; Turner and Knoepfler, 2016).

To investigate the current state of the U.S. marketplace for putative stem cell treatments, repeated online queries using an array of search terms were conducted from 2016 to 2021. Additional scans for such businesses were conducted using Google Maps. Google Alerts were also used to find new businesses. Data mining of company websites and content analysis of online claims were used to document their marketing representations. Particular consideration was given to identifying how many such businesses and clinics exist and where they are located; what stem cell products these companies advertise; the types of diseases and injuries they purport to treat; the prices they charge; and what types of companies operate in this space. (See the supplemental information for additional details concerning this analysis.)

Geographic distribution of clinics selling unproven stem cell interventions

As of March 31, 2021, 1,480 U.S. businesses operating 2,754 clinics engage in direct-to-consumer marketing of purported stem cell therapies. The three states with the largest concentrations of such clinics are California with 347 clinics, Florida with 333, and Texas with 310. Clinics in these three states comprise more than one-third (990 of 2,754, or 35.94%) of all U.S. clinics. While the three most populous states have the greatest number of such clinics, Florida, with approximately seven million fewer inhabitants than Texas, has more clinics than the latter state. Similarly, Arizona, with 119 clinics, is tied with New Jersey in having the fourth largest number of clinics but is the fourteenth most populous state. Population does not appear to be the sole factor determining geographic distribution of clinics. Figure 1 documents the number of clinics identified per state.

Types of advertised stem cell products

Autologous stem cell-based products are the most commonly advertised interventions, with 671 U.S. businesses (45.33%) selling autologous bone-marrow-derived stem cell interventions, 437 (29.52%) marketing autologous adipose-derived stem cell products, and 42 businesses (2.83%) promoting autologous stem cell interventions reportedly obtained from peripheral blood. Seven companies (0.47%) sell combined administration of autologous stem cells derived from fat and bone marrow.

Allogeneic birth-tissue-derived stem cell products are widely promoted in the U.S., with 350 businesses (23.64%) selling umbilical-cord-blood- or tissue-derived stem cells, 260 (17.56%) advertising amniotic stem cell products, and 47 (3.17%) promoting placental stem cell products. Another 25 companies (1.68%) sell allogeneic stem cell products with no source specified.

Of the 1,480 businesses, 595 (40.2%) advertise mesenchymal stem cell (MSC) "treatments." The expansive breadth of claims peer-reviewed articles have made about the therapeutic potential of "MSCs" has perhaps contributed to popularization of this phrase in online advertising.

Most businesses promote the particular kinds of stem cells they purport to

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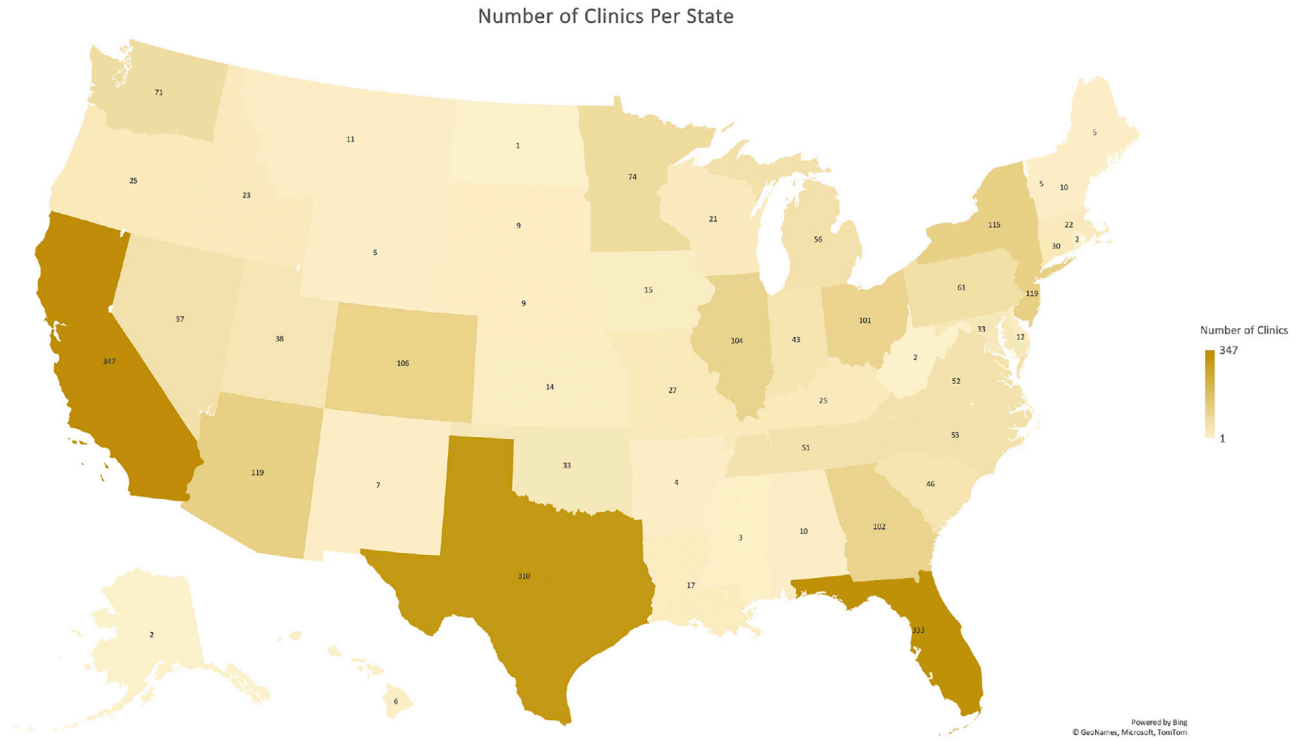

Figure 1. Map of number of clinics marketing stem cell interventions in each state
Data was collected on the number of businesses and clinics selling purported stem cell products in each state. The supplemental information provides additional information concerning how the map was developed.

administer. However, 220 companies (14.86%) advertise stem cell treatments without identifying the cell source or type of cells they purport to use.

A few businesses are marketplace outliers. For example, three companies sell xenogeneic stem cell products, three companies advertise embryonic stem cells, and one business promotes "Very Small Embryonic Like" stem cells. Unlike in 2016, in 2021 no businesses were found marketing induced pluripotent stem cell treatments.

One novel stem cell-related product has gained traction since 2016. Ninety-nine businesses (6.68%) now make therapeutic claims about the stem cell-derived exosome products they advertise. The promotion of this new product type suggests that other interventions could emerge in the marketplace for stem cell interventions. Figure 2A documents how many businesses sell particular types of stem cell products.

The contemporary U.S. marketplace is dominated by businesses marketing autologous stem cell-based interventions derived from bone marrow or fat and allogeneic birth-tissue-derived stem cell products. Particularly striking is the widespread promotion of products that appear to require FDA approval.

Diseases, injuries, and other conditions businesses claim to treat

U.S. businesses selling unlicensed and unproven stem cell interventions make an array of claims about the diseases and injuries they purport to treat. The most common marketing representation made by such companies is that their stem cell interventions relieve pain. Of 1,480 businesses, 1,262 (85.27%) claim to treat painful symptoms. The second most frequent claim relates to orthopedic diseases and injuries, with 689 businesses (46.55%) advertising stem cells to treat orthopedic conditions. Claims about treating sports injuries are widespread, with 339 businesses (22.90%) selling stem cell interventions for sports-related injuries.

Following these most common claims, 134 businesses (9.05%) claim to treat neurological diseases, 122 (8.24%) market stem cells for immunological conditions, 95 (6.41%) state they treat lung and respiratory conditions, 94 (6.35%) purport to treat erectile dysfunction and other sex-related conditions, 88 (5.94%) state they treat skin conditions and wounds, and 86 (5.81%) advertise using stem cells to treat cardiovascular diseases and conditions. Businesses promote stem cell interventions for additional disease and injury categories including diabetes (54 or 3.64%), urological (39 or 2.63%), spinal cord injury or paralysis (36 or 2.43%), and vision loss or impairment (29 or 1.95%).

Some businesses target minors as clients (23 or 1.55%) by marketing stem cell interventions for neurological indications such as autism spectrum disorder and cerebral palsy and by indicating they administer stem cells to children. Other companies (37 or 2.5%) promote purported stem cell therapies for adults suffering from Alzheimer's disease.

Beyond purporting to treat various diseases and injuries, businesses advertise stem cell interventions for cosmetic indications (123 or 8.31%), hair loss (109 or

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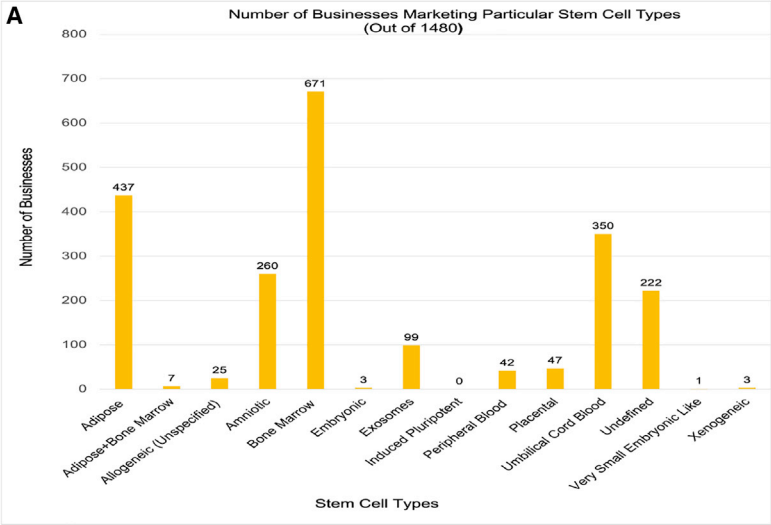

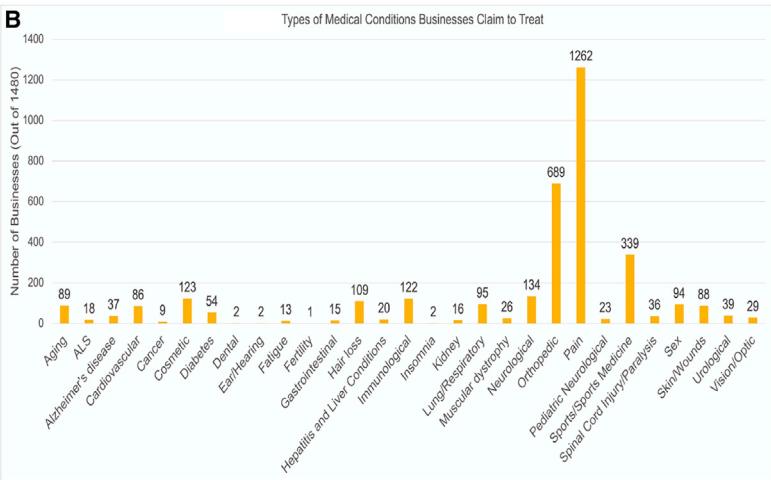

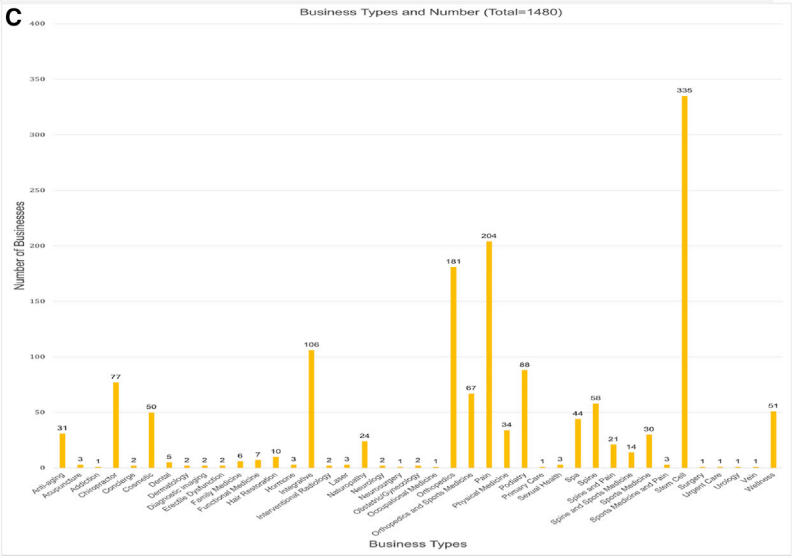

Figure 2. Types of stem cell products, types of diseases and injuries treated, and types of businesses marketing stem cell interventions

Company websites were mined and analyzed to determine (A) what kinds of stem cell products businesses purport to sell; (B) what diseases and injuries they claim to treat; and (C) how particular businesses brand and position themselves in the marketplace.

7.36%), and aging (89 or 6.01%). Figure 2B summarizes the diseases, injuries, and other indications businesses claim to treat with stem cell products.

Costs

Most companies do not disclose on their websites how much their stem cell products cost. Of 1,480 businesses, just 56 (3.78%) listed prices for such interventions. The lowest price advertised was $1,200, the highest listed fee was $28,000, the average rate was $5,118, and the median price was $4,000. For most patients, these stem cell interventions are out-of-pocket expenses.

Types of businesses

Of businesses marketing purported stem cell treatments, 335 of 1,480 (22.63%) represent themselves as stem cell clinics or stem cell and regenerative medicine facilities. However, most U.S. businesses selling purported stem cell interventions do not explicitly brand themselves as stem cell companies or clinics. Rather, stem cell interventions are advertised among a range of listed therapies, and other terms are used for corporate branding. While self-described stem cell businesses represent the largest share of this marketplace, other marketplace participants advertise themselves as operating clinics focused on the following: pain relief (204 or 13.78%), orthopedic care (181 or 12.22%), integrative medicine (106 or 7.16%), podiatry (88 or 5.94%), chiropractic care (77 or 5.20%), orthopedics and sports medicine (67 or 4.52%), the spine (58 or 3.91%), wellness (51 or 3.44%), and cosmetic surgery (50 or 3.37%). Additional businesses selling stem cell interventions brand themselves as spas, anti-aging clinics, naturopathy clinics, acupuncture clinics, laser clinics, or dental clinics. Three units within academic medical centers and two businesses operating clinics affiliated with academic institutions are among the

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facilities selling purported stem cell treatments for orthopedic indications, sports injuries, and pain relief. Figure 2C describes types of businesses marketing purported stem cell products.

FDA and businesses selling unlicensed stem cell products

The commercial and clinical activities of businesses selling putative stem cell treatments are problematic in part because they involve promoting and administering medical products that are not FDA-approved (Marks and Hahn, 2020). These interventions are not backed by convincing evidence of safety and efficacy generated in well-designed and adequately powered randomized controlled clinical trials (Marks et al., 2017).

There have been some encouraging results from early-stage clinical studies testing safety and efficacy of stem cell products for various orthopedic diseases, relief of pain caused by osteoarthritis, and some other indications (Rossi et al., 2020). These studies indicate the importance of proceeding from preliminary studies to pivotal clinical trials with robust research designs. The current state of stem cell research related to illnesses such as multiple sclerosis and Parkinson's disease provides grounds for cautious optimism that particular stem cell products will eventually emerge as safe and efficacious therapies approved for specific clinical applications (Miller et al., 2021). Such findings support further research. However, they do not justify commercializing stem cell products before convincing evidence emerges from controlled clinical trials.

Many U.S. businesses marketing unlicensed and unproven stem cell products claim their interventions do not require FDA approval. Regulations, guidance documents, and patient and consumer information issued by the FDA (most recently in 2021) make it apparent that such assertions often are incorrect (Marks et al., 2017). Acknowledging that some cell-based medical interventions such as products falling within the same surgical procedure exception and autologous, minimally manipulated cellular products used in a homologous manner do not require premarketing review and licensure by the FDA, most stem cell interventions are classified as biologics, drugs, or medical devices requiring safety and efficacy testing in clinical trials and FDA premarketing authorization.

Risks associated with business selling unlicensed and unproven stem cell products

Widespread promotion and administration of unlicensed and unproven stem cell products poses numerous risks to patients and has caused some individuals serious harm.

Published case reports and news media accounts document instances where patients suffered significant injuries after receiving unapproved stem cell products (as reported by Kuriyan et al., 2017 and The Pew Charitable Trusts). Allegations of such injuries have resulted in lawsuits being filed against businesses where patients were reportedly harmed. According to the FDA, adverse events resulting from the administration of unlicensed stem cell products are likely underreported to the agency (Marks and Hahn, 2020).

One of the most troubling features of this marketplace is that businesses selling unproven stem cell products often exploit the hope, suffering, fear, or desperation of patients. Many businesses use aggressive sales tactics and misleading claims to target vulnerable persons (as reported by the Washington Post in 2018). Alleged misrepresentations made by businesses selling stem cell products have resulted in two class action lawsuits and other civil lawsuits as well as actions by the Food and Drug Administration, Federal Trade Commission, and states' attorneys' general offices (Horner et al., 2018). Purportedly false advertising claims and other actions associated with selling unlicensed stem cell products have also resulted in criminal charges and convictions (see reports from the United States Department of Justice in 2014 and The Washington Post in 2021). Some patients report suffering substantial financial losses after purchasing stem cell interventions that were allegedly promoted with misleading claims.

This marketplace also poses threats to collective goods such as public health, the advancement of scientific knowledge, trust in public institutions, and the public understanding needed for citizens to be able to distinguish evidence-based stem cell interventions from products unsupported by convincing safety and efficacy data. Given how stem cell products are often advertised as safe and effective treatments even though data supporting such claims are lacking, it is possible that some patients have delayed or forgone receiving evidence-based medical interventions with legitimate prospects of providing therapeutic benefit after being administered what they believed to be "cutting-edge" stem cell procedures.

During the COVID-19 pandemic, some businesses have promoted stem cell products as "immune boosters" capable of protecting against the SARS-CoV-2 virus (Turner, 2020). It is unknown whether any patients have purchased such products and then, believing their immune systems to be better protected, reduced their use of masks and physical distancing or otherwise altered their behavior in a manner that increased their risk of being exposed to SARS-CoV-2. However, changed behavior could result from misleading representations and pose a public health threat.

The emergence of a large-scale marketplace composed of businesses selling unproven stem cell products has likely made it difficult for patients to separate evidence-based stem cell interventions from stem cell products for which data supporting safety and efficacy are lacking. It is possible the presence of 1,480 businesses promoting putative stem cell therapies via their websites, social media sites, and other platforms has helped make such interventions seem routine and credible. Various organizations have tried to alert patients to "red flags" associated with businesses selling unlicensed and unproven stem cell interventions. However, many patients likely find it challenging to distinguish facilities providing evidence-based stem cell therapies from businesses selling stem cell interventions unsupported by convincing scientific evidence. Given the scale of the marketplace for unproven stem cell products, urging patients to educate themselves and be alert to risks is a necessary but insufficient message. There is an urgent need for better oversight of this marketplace. Regrettably, marketing claims by some businesses also question the legitimacy and trustworthiness of regulatory bodies.

Another collective harm associated with this marketplace is the diversion of patients to facilities that have not made meaningful contributions to scientific research. While it is uncertain how many patients seek

care at U.S. clinics selling unlicensed stem cell products, the scale of this marketplace suggests that the number of individuals receiving such interventions is substantial. Some of these patients could have instead contributed to scientific research by serving as participants in well-designed clinical trials testing investigational stem cell products or other interventions. Loss of potential clinical trial participants is particularly significant in patient populations with rare diseases.

Conclusion

In 2016, 351 U.S. businesses and 570 clinics were found selling unlicensed and unproven stem cell products (Turner and Knoepfler, 2016). More than four times as many such businesses and clinics were identified in 2021. Expanded and refined search techniques likely played a role in identifying businesses and clinics that were not previously detected and locating recently established businesses that would not have been found using the approaches applied from the 2016 study. Nonetheless, the larger figures appear to be attributable in part to substantial marketplace expansion rather than improved detection strategies. Many new businesses were identified using internet searches and Google Alerts that captured when companies and clinics selling purported stem cell products announced they had commenced operations and were open for business. Other press releases noted that existing businesses had added stem cell interventions to their advertised services.

Much of the influx of new businesses and clinics occurred during a period of enforcement discretion, when the FDA was selective in enforcing federal regulations applicable to companies selling stem cell products. During this time, the FDA maintained its enforcement authority and acted against selected businesses posing risks to patients. For example, the FDA obtained a permanent injunction against U.S. Stem Cell Clinic; is seeking a permanent injunction against Cell Surgical Network, California Stem Cell Treatment Centers, and additional defendants; issued 14 warning letters and 24 untitled letters; and contacted an additional 400 businesses with letters stating that it had come to the FDA's attention that they were advertising purported stem cell treatments. Acknowledging these actions, the period of enforcement discretion was intended to provide time for businesses to determine whether their stem cell products require FDA premarketing approval. Businesses were supposed to comply with federal regulatory standards by obtaining premarketing authorization when required or ceasing the selling of noncompliant products. Few companies reportedly used this opportunity to obtain guidance concerning the regulatory status of their stem cell products and to come into regulatory compliance. Perhaps grasping that the period of enforcement discretion was a time when few companies would be subjected to significant enforcement actions, many businesses used this period to start selling unproven and unlicensed stem cell products. With the period of enforcement discretion concluded, the FDA faces many businesses marketing potentially noncompliant stem cell products.

The possibility of increased enforcement activity by the FDA does not appear to have deterred most of the businesses identified in this study from continuing to market purported stem cell therapies. Rather, a review of their activities following the end of enforcement discretion reveals that most of them are still selling such products. Furthermore, additional businesses and clinics are entering the marketplace. This trend seems likely to continue absent substantial increases in enforcement activity by FDA, FTC, and other regulatory bodies and law enforcement agencies. Whether such regulatory action will occur now that the FDA's era of enforcement discretion has ended is uncertain.

SUPPLEMENTAL INFORMATION

Supplemental information can be found online at https://doi.org/10.1016/j.stem.2021.10.008.

ACKNOWLEDGMENTS

Support for this project was provided by The Pew Charitable Trusts. The views expressed herein are those of the author and do not necessarily reflect the views of The Pew Charitable Trusts.

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Food and Drug Administration, https://www.fda.gov/vaccines-blood-biologics/consumers-biologics/important-patient-and-consumer-information-about-regenerative-medicine-therapies

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