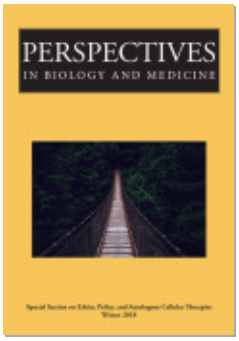
The US Direct-to-Consumer Marketplace for Autologous Stem Cell Interventions



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Perspectives in Biology and Medicine, Volume 61, Number 1, Winter 2018, pp. 7-24 (Article)

Published by Johns Hopkins University Press
DOI: https://doi.org/10.1353/pbm.2018.0024

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ABSTRACT Hundreds of businesses and clinics in the United States are engaged in direct-to-consumer marketing of unproven and unlicensed stem cell–based interventions. This essay provides an overview of this marketplace, examines advertising techniques companies use to draw clients and legitimate marketing claims, and summarizes the roles the Food and Drug Administration (FDA) and other agencies are supposed to play in regulating the direct-to-consumer marketplace for stem cell interventions. The essay also reviews federal regulations, describes how many businesses selling purported "stem cell treatments" appear to violate these standards, and considers ethical issues and harms associated with widespread promotion of unapproved stem cell products.

When journalists and health researchers address the subject of patients in the United States undergoing unproven stem cell–based interventions (SCBIs), they have historically crafted narratives about "stem cell tourism" to

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The paper was originally presented at a research symposium on "Autologous Cellular Therapies: Defining the Scope and Obligations of Clinical Innovation" in Singapore on May 24, 2017. This symposium was supported with funding from the National University of Singapore Office of the Deputy President (Research and Technology)–Humanities and Social Sciences Research Fund (WBS: R-171-000-055-646) and the Stem Cell Society, Singapore. Professor Alastair Campbell, National University of Singapore Centre for Biomedical Ethics, provided an oral commentary on the paper at the symposium, and the paper was revised following review from the guest editors and Professor Campbell.

Perspectives in Biology and Medicine, volume 61, number 1 (winter 2018): 7–24.

facilities located in such countries as China, India, Mexico, Panama, and Thailand (Bowman et al. 2015; Cohen and Cohen 2010a, 2010b; Ryan et al. 2010). These latter nations often are depicted as jurisdictions where clinics providing access to SCBIs operate without meaningful oversight, relevant regulations are nonexistent or have significant loopholes, and regulatory bodies are underfunded, understaffed, corrupt, or otherwise unable to provide effective oversight (Caulfield et al. 2009; Kiatpongsan and Sipp 2009). While travel from the U.S. to international "stem cell clinics" persists, hundreds of U.S. businesses now engage in direct-to-consumer marketing of putative "stem cell treatments" (Turner and Knoepfler 2016). The cellular products promoted by such companies are not typically supported by conclusive evidence of safety and efficacy and have not been approved by the Food and Drug Administration (FDA). Patients having stem cell procedures at such facilities have suffered serious injuries and even fatal outcomes (Kuriyan et al. 2017; McGinley 2017; Saraf et al. 2017). Other patients allege they were defrauded by businesses making false marketing claims (Marrero 2016; Martinho and Turner 2017; Wagner 2016).

Responding to the proliferation of U.S. businesses selling unproven SCBIs, I examine various features of this industry. First, I describe findings from an ongoing empirical study of this rapidly expanding marketplace. Second, I review advertising techniques companies use to attract patients and legitimize promotional claims and commercial activities. Third, I briefly sketch what roles the FDA and other oversight bodies are empowered by legislation to play in regulating the US marketplace for SCBIs. Fourth, I review federal regulations, summarize how the FDA interprets such standards, and address how companies market what in many cases appear to be noncompliant stem cell products. Finally, I identify various ethical issues related to direct-to-consumer marketing of SCBIs and review harms that can occur as a result of businesses selling unproven and unlicensed stem cell interventions.

Direct-to-Consumer Marketing of Stem Cell Interventions

In June 2016, Paul Knoepfler and I published a detailed empirical study of the US direct-to-consumer marketplace for stem cell interventions (Turner and Knoepfler 2016). In total, we found 351 US businesses and 570 clinics marketing SCBIs. Despite the striking number of businesses and clinics we identified, these findings underestimated the size of the US direct-to-consumer marketplace for stem cell interventions. Challenges inherent in efforts to identify such businesses resulted in overlooking some US companies and clinics selling purported stem cell therapies. In addition, many new businesses have entered the US marketplace since our findings were published. Drawing upon the search techniques and additional research methods used to create the database for the 2016 article, I have

expanded the dataset and developed an updated analysis of US companies selling unapproved stem cell products.

As of May 2017, 432 distinct US businesses sell SCBIs provided at 716 clinics. Such companies are particularly widespread in certain states: 125 such businesses operate in California, 116 are located in Florida, 100 are in Texas, 56 can be found in Arizona, and 45 are based in Colorado. In total, 442 of the 716 clinics (61.7%) are found in just these five states. Examining the US marketplace as a whole, 45 of 50 states, as well as the District of Columbia, have at least one clinic at which SCBIs are available.

Most US businesses engaging in direct-to-consumer marketing of SCBIs use autologous sources of stem cells, although allogeneic and xenogeneic products are also advertised. In total, 251 companies promote autologous SCBIs, reportedly sourced from adipose tissue, 214 market stem cells obtained from bone marrow aspirate, and 17 claim they use stem cells obtained from autologous peripheral blood. Five companies promote "combination" autologous stem cells obtained from both fat and bone marrow. Two companies market autologous "mesenchymal stem cell treatments" without identifying specific sources for these cells. The remaining businesses advertise allogeneic SCBIs reportedly sourced from amniotic material (80 companies), placental tissue (13 companies), or umbilical cord blood (five companies). Thirteen businesses do not clearly indicate the source of the stem cells they reportedly use, and one advertises a nonspecific allogeneic product. Two companies market xenogeneic stem cells, one promotes embryonic SCBIs, one advertises "very small embryo like" stem cells, and two claim to offer induced pluripotent stem cells. These figures provide insight into the prevalence of marketing claims about autologous adipose-derived stem cells and autologous bone marrow-derived stem cells. Total marketing claims for all cell types exceed the total number of businesses because it is common for companies to claim they use stem cells obtained from more than one source. For example, many businesses offer their clients a choice between autologous stem cells obtained from fat or bone marrow, or recommend one source of cells for particular kinds of treatments and another source for different health problems.

US companies advertise SCBIs for a wide range of indications. Of the 432 businesses engaged in direct-to-consumer marketing of SCBIs, companies promote stem cells for orthopaedic conditions (387), pain relief (240), sports injuries (110), neurological diseases and disorders (94), immunological diseases (88), respiratory diseases (80), cardiovascular diseases (61), cosmetic indications (60), urologic diseases and injuries (57), skin diseases (52), aging (47), diabetes (39), hair loss (38), Alzheimer's disease (34), vision loss (34), gastrointestinal disorders (33), spinal cord injuries (19), paediatric neurological diseases (14), kidney diseases (12), liver disease (9), cancer (4) fatigue (4), dental problems (3), and hearing loss (2). Of the many marketing claims made by such businesses, some promotional statements appear to be directed at parents or guardians of minors, with infants or

children the apparent intended recipients of stem cell injections or infusions. For example, 37 companies claim to treat individuals with muscular dystrophy, 13 purport to treat persons with autism, 11 market SCBIs for cerebral palsy, and one business advertises stem cells for juvenile diabetes. Targeting parents or guardians with promotional claims and then administering such stem cell–based interventions to minors who lack decision-making capacity raises numerous ethical and legal concerns (Zarzeczny and Caulfield 2010).

Empirical analysis of advertising claims provides valuable insight into the public representations businesses make about the cells they claim to use as therapies. However, analysis of promotional claims made on company websites does not answer the question of whether businesses actually administer the specific kinds of stem cells they advertise or even whether bona fide stem cells are provided to patients. Ongoing litigation filed by former clients of several US businesses draws attention to the possible gap between marketing assertions about stem cell treatments and the actual cells administered to patients (Marrero 2016; Wagner 2016).

Marketing Claims, Communications Media, and Credibility

The breadth of diseases and injuries US businesses claim to treat with stem cells resembles the expansive promotional claims made by international "stem cell clinics" (Berger et al. 2016; Kiatpongsan and Sipp 2009; Lau et al. 2008; Sipp 2011a, 2011b, 2013). The marketing techniques US companies use to promote stem cells are also similar to the commercial practices of international stem cell clinics (Sipp et al. 2017). For example, it is common for US businesses engaged in direct-to-consumer advertising of SCBIs to use Google ads, YouTube videos featuring patients or company representatives, Twitter feeds, Facebook pages, webinars, press releases, newspaper and television ads, sales pitches at hotels and conferences, brochures and flyers, and other marketing tactics for connecting with prospective clients (Knoepfler 2017).

US companies selling "stem cell treatments" use various promotional techniques, or "tokens of legitimacy," to make themselves seem credible and trustworthy (Sipp et al. 2017). Some businesses use before and after testimonials that feature dramatic narratives of patients self-reporting improved health following their SCBIs. Such videos can seem quite persuasive to prospective clients considering such interventions. It is also common to find businesses reassuring prospective clients by claiming to operate in compliance with federal regulations.

Some companies claim they administer stem cells within the context of clinical studies approved by institutional review boards (Turner 2017). While such businesses are in the minority, a number of US companies, as with various international "stem cell clinics," have registered for-profit, pay-to-participate clinical studies on ClinicalTrials.gov (Aldous 2017; Bazar 2016; Fung et al. 2017; Turner

2017). Such listings likely play a role in persuading prospective clients that businesses are legitimate and conducting credible stem cell research. Numerous businesses provide links to published preclinical studies or early-stage clinical trials conducted by researchers at academic institutions, even though such publications often do not provide scientific support for the SCBIs advertised by such businesses (Sipp et al. 2017). A few businesses involved in direct-to-consumer advertising of SCBIs have published case reports or case series that ostensibly describe "successful outcomes" following administration of stem cells (Lander, Berman, and See 2016; Weiss, Levy, and Malkin 2015; Weiss, Benes, and Levy 2016). It is common for such reports to appear in journals with weak or nonexistent peer review. The emergence of academic journals with low barriers to entry has facilitated efforts by companies to claim that their stem cell interventions are safe and effective and that they are contributing to peer-reviewed stem cell research (Sipp et al. 2017). Taken as a whole, the advertising techniques used by US businesses selling stem cell interventions make it difficult for patients to distinguish stem cell therapies for which substantial evidence of safety and efficacy exists from interventions that are not supported by such data (Sipp et al. 2017).

Federal Regulations and the FDA

Laws and regulations in the US create the appearance of meaningful regulatory oversight of stem cell therapies. The US Public Health Service Act and the Food, Drug, and Cosmetic Act provide the FDA with the regulatory authority required to oversee stem cell interventions marketed and administered to humans (Lysaght and Campbell 2011). The Code of Federal Regulations contains detailed regulations related to uses of stem cells and other cells and tissues in humans (21 CFR 1271).

The US has a risk-based federal regulatory framework for human cells, tissues, and cellular- and tissue-based products (HCT/Ps). Different regulatory tiers provide varying degrees of regulatory oversight and standards for review. These tiers are based on the degree of perceived risk specific types of HCT/Ps pose to public health and individual recipients. Depending upon various criteria, stem cell products can be classified as drugs, biologics, or medical devices that require premarketing approval by the FDA, as cells that are subject to regulations but do not require premarketing authorization, and as cells excluded from the detailed requirements specified in 21 CFR 1271.

When classified as drugs, biologics, or medical devices, the FDA is authorized to assess and determine whether sufficient preclinical evidence and clinical safety and efficacy data exist for particular stem cell products to receive premarketing approval. Safety and efficacy data must be provided to the FDA by study sponsors responsible for conducting clinical trials (Marks, Witten, and Califf 2016). Initiating and then conducting such studies requires submitting investigational

new drug (IND) applications to the FDA. Such studies also require institutional review board (IRB) approval. A similar regulatory pathway exists for medical devices used to produce cellular therapies, via applications for investigational device exemptions (IDEs).

In cases where cellular products fall outside the categories of drugs, biologics, and medical devices, premarketing approval by the FDA is not required. However, establishments marketing and providing such products must comply with the detailed regulatory requirements found in 21 CFR 1271. Many of these regulatory standards are intended to prevent the spread of communicable diseases by ensuring adequate screening and testing of donors and maintaining good tissue practices. Since it is not necessary to seek premarketing authorization from the FDA for such cells and tissues, the regulatory bar for such products is considered to be lower than for products requiring FDA approval.

The FDA is one of several federal agencies empowered by legislation to take action against businesses marketing stem cell products in violation of federal laws and regulations. The FDA's regulatory authority in this area is complemented by the Federal Trade Commission's (FTC) legal authority to investigate allegations of fraudulent marketing claims. While to date the FTC has not played an active role in challenging misrepresentations made by US businesses advertising unlicensed stem cell interventions, it has addressed other kinds of health fraud.

The Federal Bureau of Investigation (FBI), typically working in conjunction with the FDA's Office of Criminal Investigation and the Department of Justice, has an important role to play when possible violations of criminal law have occurred, such as when misbranded and adulterated drugs enter the marketplace and when companies are engaging in fraudulent commercial activity (Carroll 2011; DeMarco v. United States, No. 07-4249 (JHR) (2009); United States v. Sapse and Ralph M. Conti, No. 2:10-cr-00370-KJD-RJJ (D. Nev. 2012)). While there have been few criminal prosecutions of individuals selling and administering unproven SCBIs, targeting by law enforcement of particularly egregious marketing schemes involving stem cells has resulted in some convictions (Christie 2007a, 2007b; Nordli 2013; US Attorney's Office, Southern District of Texas 2014; US Dept. of Justice 2014).

State medical boards are empowered by state legislation to investigate and discipline physicians determined to be practicing outside the current standard of medical care. This authority provides them with the tools needed to discipline physicians and other health-care professionals marketing and administering SCBIs that fall outside the current standard of care (Zarzeczny and Clark 2014). Investigations and subsequent disciplinary proceedings can result in physicians having their licenses restricted, suspended, or revoked (Freeman 2015; Zarembo 2015). For example, Zannos Grekos, a cardiologist who ran Regenocyte, a Florida-based "stem cell clinic," provided an SCBI to a woman who suffered a stroke and was subsequently removed from life support before dying. The Florida med-

ical board concluded his conduct constituted medical malpractice and revoked his license (Freeman 2015). Emergency restrictions are sometimes imposed by state medical boards while they conduct investigations and decide whether formal disciplinary proceedings are warranted (Fitzpatrick and Griffin 2012).

The numerous federal and state regulatory bodies and law enforcement agencies legally empowered to engage in enforcement activities against businesses marketing unlicensed and unproven stem cell products can create the impression that stem cell products marketed and sold in the US are subject to strict oversight. Indeed, numerous critics of the FDA argue that the current regulatory bar for stem cell therapies is too high, and that more permissive standards are needed for adult SCBIs, if not for all regenerative medicine products (Aicher 2013; Caplan and West 2014). However, the appearance of a well-regulated and strictly overseen marketplace for stem cell products is misleading. Many US businesses currently advertising "stem cell treatments" appear to operate in violation of federal regulations, because they lack FDA approval for products that require premarketing authorization (Turner 2015a, 2015b). Despite apparent noncompliance, few such businesses have been subject to enforcement actions by the FDA or other agencies.

Federal Regulations and Direct-to-Consumer Marketing of Stem Cell Interventions

Most companies involved in direct-to-consumer marketing of stem cells claim they are selling access to procedures that do not require premarketing authorization by the FDA (Johnson et al. 2017; McFarling 2016; Turner 2015a, 2015b). Businesses make such assertions even when these statements do not appear to accurately reflect how the FDA interprets federal regulations.

Although not all such businesses provide explicit rationales for why they believe they can sell stem cell products that are not approved by the FDA, those companies that do provide justifications typically draw from a repertoire of four sets of assertions. First, 21 CFR 1271 contains a regulatory exclusion known as the "same surgical procedure" exception. According to 21 CFR 1271.15, cells or tissues obtained from and returned to the same individual during the same surgical procedure do not require a biologics license, need not be provided in the context of an IND or IDE clinical study, and do not have to comply with other requirements specified in 21 CFR 1271. Statements from the FDA's Tissue Reference Group, an FDA body that responds to questions about how particular types of cells and tissues are classified by the FDA, a draft guidance document, and a final guidance document issued by the FDA's Center for Biologics Evaluation and Research address what constitutes the "same surgical procedure" (FDA 2011, 2014a). According to the FDA guidance document, the exception is limited to such steps as rinsing, cleaning, sizing, or shaping (FDA 2014a, 2017a).

These actions are deemed to "raise no additional risks of contamination and communicable disease transmission beyond that typically associated with surgery." The exception is intended to enable such clinical procedures as "autologous skin grafting and coronary artery bypass surgery involving autologous vein or artery grafting." Although the same surgical procedure exception is narrowly interpreted by the FDA, many businesses use this regulatory exclusion to sell stem cells administered for a wide range of clinical indications, after first undergoing what the FDA classifies as manufacturing steps that place such cells beyond the scope of the regulatory exception and put them into the category of stem cells requiring premarketing authorization (Charo and Sipp 2018). For example, it is common for US businesses marketing stem cells obtained from adipose tissue to claim that such interventions fall within this regulatory exception and do not require FDA approval, even though the regulator has stated otherwise.

Second, 21 CFR 1271.10 specifies criteria that distinguish autologous stem cell products requiring FDA approval from cells that must comply with standards specified in 21 CFR 1271 but do not require FDA approval (Drabiak-Syed 2013; Lysaght and Campbell 2011; Lysaght et al. 2013). According to these criteria, autologous HCT/Ps that are minimally manipulated, intended for homologous use only, and either not combined with another article or combined only with such articles that do "not raise new clinical safety concerns with respect to the HCT/P" are "regulated solely under section 361 of the PHS Act" and the regulations in 21 CFR 1271.

In various documents, the FDA has defined what constitutes "minimal manipulation" of cells and tissues and has provided examples intended to clarify how it interprets this term (FDA 2006, 2014a, 2014b, 2014c, 2017b). According to these documents, the FDA does not consider the manufacturing steps required to obtain autologous adipose-derived stem cells to fall within the category of minimal manipulation.

The FDA has also addressed how it interprets and applies the criterion of homologous use. According to 21 CFR 1271, homologous use "means the repair, reconstruction, replacement, or supplementation of a recipient's cells or tissues with an HCT/P that performs the same basic function or functions in the recipient as in the donor." Non-homologous use of cells or tissues occurs when such HCT/Ps are utilized to perform a function other than what they typically have in the human body. Draft guidance documents, a final guidance document, determinations made by the Tissue Reference Group, and warning letters issued by the FDA to businesses that were found to be violating federal regulations make it apparent that the FDA is unpersuaded by claims that stem cells obtained from adipose tissue, bone marrow, peripheral blood, umbilical cords, amniotic tissue, and other sources can be provided on a homologous basis for dozens of diseases and injuries of diverse etiologies (FDA 2012a, 2012b, 2012c, 2015a, 2015b, 2017b). In particular, the FDA has addressed what it classifies as non-homolo-

gous uses of stem cells obtained from adipose tissue. Despite the FDA's position that autologous adipose-derived stem cells marketed for neurological diseases and many other conditions are provided on a non-homologous basis, many businesses challenge this assessment and claim that autologous adipose-derived stem cells are "panhomologous." Such companies typically claim that autologous adipose-derived stem cells can be used in a homologous manner to treat a wide range of diseases and injuries. On the basis of this assertion, businesses claim they are operating in compliance with federal regulations and need not obtain FDA approval for the stem cell products they market.

Third, many businesses marketing autologous bone marrow-derived stem cells assert that they do not require premarketing authorization from the FDA. Rather, they claim to use minimally manipulated bone marrow aspirate in a homologous manner. According to 21 CFR 1271.3, "minimally manipulated bone marrow for homologous use" that is not combined with other products (excluding acceptable combinations listed in 21 CFR 1271), is, for purpose of regulatory oversight, not classified as a human cell, tissue, or cell- and tissue-based medical product. 21 CFR 1271 and subsequent draft and final guidance documents do not directly address the question of what constitutes minimal manipulation of bone marrow or what marketing claims fall outside the scope of "homologous use" of minimally manipulated bone marrow. The decision not to classify minimally manipulated, homologous bone marrow transplants as regulated medical products was made to allow clinicians to continue administering such transplants for various cancers and blood related disorders. However, current marketing claims go far beyond the evidence base that exists for such hematopoietic stem cell transplants. Orthopedic clinics, sports medicine clinics, pain management facilities, and other businesses use this exclusion to claim that they can sell autologous bone marrow–derived stem cells for a wide range of conditions without requiring premarketing authorization from the FDA. Such marketing claims extend beyond orthopedic diseases and injuries to putative treatments of neurological disorders, diseases and injuries of the eye, heart failure, and immunological conditions. These claims raise questions about what falls within the scope of minimally manipulated bone marrow administered in a homologous manner, and they also point to the need for the FDA to more precisely address what constitutes non-homologous uses of stem cells obtained from bone marrow.

Fourth, "whole blood or blood components or blood derivative products subject to listing under parts 607 and 207 of this chapter" do not fall within the scope of 21 CFR 1271. This regulatory exclusion was made because transfusions of whole blood, blood components, and blood derivative therapeutic products were already subject to federal regulations and federal regulatory oversight. However, 21 CFR 1271 and subsequent guidance documents do not directly address the question of what constitutes compliant or noncompliant commercial activity when businesses make marketing claims about the therapeutic potential of stem

cells reportedly obtained from peripheral blood. As a result, some businesses marketing autologous stem cell treatments claim that they are not required to have a biologics license or to conduct clinical trials under an IND application because blood and blood-related products are excluded. Thus, an exclusion intended to facilitate transfusions of blood and blood components governed by a different section of federal regulations is now being used as a rationale for selling peripheral blood-derived stem cell transplants of unknown efficacy for lung-related disorders and other diseases and injuries.

The FDA is authorized by legislation to enforce laws and regulations and take action in response to businesses engaging in noncompliant practices. At present, hundreds of businesses are marketing stem cell products that appear to require premarketing authorization and yet are not FDA approved. Despite the proliferation of such businesses, the FDA has issued few warning letters to businesses marketing adipose-derived stem cell interventions and other stem cell products that require premarketing authorization (FDA 2012a, 2012b, 2012c, 2015b, 2017c, 2018). This limited regulatory activity has likely had a signalling effect, by suggesting that businesses violating the US Public Health Service Act, the Food, Drug, and Cosmetic Act, and 21 CFR 1271 are unlikely to attract scrutiny or become subject to enforcement action.

Ethical and Scientific Issues

Many US businesses advertise SCBIs that have not been tested in preclinical research and clinical trials. By selling stem cell products lacking conclusive evidence of safety and efficacy, these businesses expose their patients to various risks.

Some companies sell "stem cell therapies" in the context of what they describe as "patient-funded" or "patient-sponsored" studies that have been approved by IRBs (Aldous 2017; Blackwell 2015; Emanuel et al. 2015; Sipp 2012; Wenner, Kimmelman, and London 2015). Marketing stem cell interventions in this manner might suggest that some businesses are complying with federal regulations and ethical norms governing human subjects research. However, what at first glance might appear to be credible and compliant clinical research often is highly problematic, even if it has been approved by an IRB. In many instances, it appears that such studies should have been submitted to the FDA for review in addition to seeking IRB approval (Turner 2017). Numerous pay-to-participate stem cell studies also exhibit significant scientific and ethical shortcomings (Sipp 2012).

For example, one registered for-profit clinical study plans to recruit 3,000 research subjects for what is supposed to be a "safety" study involving administration of autologous adipose-derived stem cells (Cell Surgical Network 2013a, 2013b). This study will include thousands more individuals than are typical for phase I trials, which generally include only 20 to 80 subjects and patients (21 CFR 312). Whereas most clinical studies focus upon a well-defined study population, recruiting individuals who have a specific disease and meet strict inclu-

sion and exclusion criteria, this for-profit study involves individuals with a wide variety of diseases. It also involves various modes of administering cells to study subjects, and no meaningful description of what dose of stem cells study subjects will receive or whether the safety study will assess different doses. Another company charges patients to participate in "observational studies" (StemGenex 2014a, 2014b, 2014c). The business claims it is evaluating how its clients assess their health after undergoing an intervention with stem cells. While it is legitimate to ask study subjects about such self-assessments, in this case an "observational study" is being conducted without first conducting clinical studies that have well-defined endpoints and are intended to evaluate the safety of administered stem cell products.

Poor study designs, ill-defined study populations, inadequate inclusion and exclusion criteria, and other factors prompt troubling questions about the credibility of such businesses' claims that they are engaged in legitimate stem cell research. IRBs are implicated in such commercial practices (Turner 2017). The problematic design of numerous pay-to-participate "stem cell studies" suggests that patients visiting businesses selling SCBIs should be wary of marketing pitches that include references to pay-to-participate, IRB-approved clinical studies (Sipp 2012; Wenner et al. 2015). Similarly, the FDA should be more alert to businesses promoting clinical studies that have not been reviewed and permitted to proceed by the relevant FDA center. It should also increase its enforcement activity in response to studies that are not compliant with all applicable federal regulations governing HCT/Ps and the conduct of human subjects research.

Physicians and entrepreneurs associated with businesses engaged in direct-to-consumer advertising of unproven SCBIs argue that patients should be free to choose whether they wish to undergo such procedures. Such arguments in favor of patient autonomy and individual choice can fail to acknowledge that informed decision-making by patients requires companies and health-care providers to make honest and accurate assertions about risks and benefits associated with particular SCBIs. Businesses and physicians that make exaggerated claims about the promise of stem cell "treatments" are not providing prospective patients with accurate information (Berger et al. 2016; Kuriyan, Albini, and Flynn 2017). Hyperbolic marketing claims can also exaggerate the likelihood of benefits while failing to adequately disclose risks (Caulfield et al. 2016). Several ongoing lawsuits accuse businesses selling stem cell therapies of defrauding their clients by engaging in misrepresentations and unfair trade practices (Marrero 2016; Wagner 2016). This litigation points to the much broader problem of inaccurate advertising in the direct-to-consumer marketplace.

In addition to exaggerating benefits associated with advertised SCBIs and inadequately disclosing risks, some businesses disadvantage patients by insisting that they sign waivers of liability and nondisclosure agreements. Such documents can then be used against former clients who wish to publicly criticize the care they received.

Harms Caused by the Direct-to-Consumer Marketplace for Stem Cell Interventions

When discussing risks and ethical concerns associated with widespread direct-to-consumer marketing and delivery of unproven SCBIs, various harms need to be considered. Injuries and deaths following administration of SCBIs constitute one kind of harm. Published case reports and case series documenting physical harms suffered by patients who have undergone unproven SCBIs likely do not capture the full scope of injuries that have occurred at such clinics, since the businesses themselves typically do not publish such information or otherwise disclose details about serious adverse events. Nonetheless, even with the limited information that is publicly available in the form of peer-reviewed case reports and case series, it is evident that serious physical harms can occur when patients receive stem cells that have not been adequately tested. For example, published reports document the severe vision loss suffered by several women who had autologous adipose-derived stem cell interventions for age-related macular degeneration (Kuriyan et al. 2017; Saraf et al. 2017). These serious complications reveal the importance of administering stem cells within contexts in which risks to recipients are minimized.

Charging patients substantial fees without first establishing that advertised SCBIs are safe and efficacious exposes patients to another kind of harm. Not all individuals paying for such interventions can readily afford to pay for them. Medical crowdfunding websites provide insight into the significant fees stem cell clinics charge and the many individuals forced to seek financial support from friends, neighbors, and strangers (Wagner 2016). Unfortunately, many such donations find their way to businesses that do not have a credible basis for making claims about effective stem cell treatments.

While some scholars argue that businesses selling unproven SCBIs offer hope, preying upon hope and then dashing it by marketing interventions that prove to be ineffective or result in complications exposes patients to another kind of harm (Kemp 2017). Furthermore, this is a harm suffered by individuals who often are already dealing with serious health problems and other challenges. The psychological harms associated with undergoing SCBIs that do not provide therapeutic benefits merit further scholarly analysis.

Another kind of harm associated with this marketplace is the role it plays in steering individuals away from organizations that are conducting well-designed and carefully conducted clinical trials (Arnold 2012). Many individuals who pay for unproven stem cell interventions will not be able to subsequently participate in credible forms of clinical research, since exclusion criteria applied to individuals who have previously undergone cell-based procedures often precludes their enrollment in such trials. Thus, what some individuals experience as a source of personal disappointment can also be viewed as a collective loss to the development of scientific knowledge that in time might enable safe and efficacious stem cell therapies. This type of harm is not just a loss to the stem cell field, it is also

a loss to those patient communities that would benefit most from scientifically tested stem cell therapies.

Conclusion

US federal regulations governing stem cell therapies were developed with the understanding that most such therapies would be evaluated to generate evidence of safety and efficacy and then be subject to FDA premarketing approval before entering the US marketplace. This tiered, risk-based regulatory model is being challenged by businesses that claim their stem cell treatments do not require premarketing authorization. Such businesses argue that the SCBIs they promote fall within the practice of medicine. In many instances, these assertions do not appear to accord with how the FDA interprets federal laws and regulations.

Once depicted as a departure nation for patients seeking unproven stem cell interventions, the US now has a large and growing domestic direct-to-consumer marketplace for stem cell-based interventions. Given the paucity of credible safety and efficacy data supporting the marketing claims made by such businesses, it is unsurprising that this development has been accompanied by an increasing number of reports documenting injuries, as well as an expanding number of lawsuits alleging fraudulent advertising. To date, enforcement activity by the FDA and other regulatory bodies has been limited. Absent a significant increase in regulatory action by federal and state bodies, it seems likely that more businesses will enter this marketplace and advertise stem cell treatments without first generating evidence in clinical trials and seeking premarketing approval from the FDA.

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