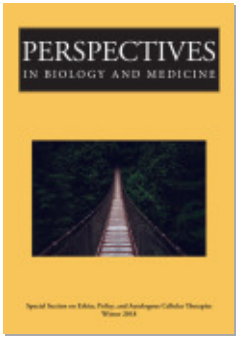
Challenges in the Regulation of Autologous Stem Cell Interventions in the United States



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ABSTRACT The direct-to-consumer marketing of stem cells for unproven therapeutic uses has grown rapidly in the United States in recent years. This development is surprising since the marketing and distribution of human cell-based medical products is stringently regulated in the US. This essay describes ambiguities, gaps, and inconsistencies in the current regulatory system that have enabled such businesses to thrive. In addition to directly challenging the authority of the Food and Drug Administration (FDA) over autologous cell-based products in the courts, stem cell marketing firms have also identified and exploited regulatory loopholes, such as the same surgical procedure exception, which exempts from FDA oversight human cell-based products that are harvested and reimplanted in a single procedure. Many businesses also advertise

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stem cell clinical studies on a pay-to-participate basis, which requires patients to pay large sums to enroll in clinical research. This business model not only shifts many of the cost and risks of medical experimentation from providers to patients but may also indemnify sellers from fraud litigation. Lastly, stem cell advertisers borrow heavily from the language and concepts of science-based medicine in their marketing. The inaccurate promotion of autologous stem cell injections as a form of "personalized" medicine lends a veneer of credibility and precision that may encourage patients to undergo procedures of uncertain effectiveness and to sympathize with stem cell businesses in their efforts to evade oversight.

THE GLOBAL INDUSTRY ENGAGED IN DIRECT-TO-CONSUMER marketing of unproven stem cell-based interventions (SCBIs) has undergone sweeping changes over the past decade. Two of the most striking developments in recent years have been the emergence of stem cell marketing businesses in highly developed nations, such as the United States, Japan, and Australia (Berger et al. 2016; Sipp 2014), and the industry's convergence on a much narrower range of supposedly therapeutic cell types than in the past. The greatest number of businesses advertising unproven uses of stem cells in English are now in the US, and the majority of those promote unproven therapeutic uses of autologous cells (see Supplementary Table S1 in Turner and Knoepfler 2016).

In this essay, I examine regulatory issues and marketing practices that have contributed to the rise of the autologous cell economy, as well as a number of ethical and scientific implications of the commercialization of self-derived cells. Through an analysis of the current regulatory framework and claims made by stem cell marketers, I highlight how variability and lack of clarity in the regulation of cell-based interventions in the US has enabled the growth of the domestic industry. I additionally outline some of the challenges confronting efforts to control unproven therapeutic claims surrounding the use of autologous cells in light of patient demand and understanding of the present-day evidence base and rationale supporting clinical uses of such cells.

Inconsistencies between how cell-based interventions are regulated as either *medical products* or *medical procedures* at the federal and state levels, respectively, have presented opportunities for businesses to market unproven SCBIs in ways that simultaneously exploit patients and indemnify the providers by taking advantage of these regulatory gaps. In this essay, I describe how stem cell businesses have broadly interpreted the "same surgical procedure" exception set forth in the federal rules governing the labeling and distribution of cellular biologics in ways apparently intended to shield them from oversight by the Food and Drug Administration (FDA). Next, I explain how some businesses market stem cell interventions in the form of clinical studies in which payment is required to enroll, an approach that of entails potential advantages to providers and disadvantages to patients. Lastly, I discuss how stem cell businesses have broadly coopted the concept of personalized medicine in ways that may inspire misunderstanding and false hope in patients and the general public.

Legal Challenges to the Regulation of Autologous Cell Interventions

Regulation of autologous SCBIs presents considerable challenges in the US and other countries (Eisenstein 2016; Lysaght et al. 2013, 2017). These challenges are due in no small part to maneuvers by industry seeking to minimize regulatory oversight and accountability. A key development in the evolution of the autologous stem cell marketing industry in the US was a 2009 lawsuit brought against the FDA in the Denver District Court by Regenerative Sciences, a Colorado company that had been issued a "black box" letter for misbranding an autologous human cell or tissue product (HCT/P) called Regenexx. This action triggered a countersuit by the FDA, which sought an injunction against the company. A legal battle that is described below continued until the US Court of Appeals for the District of Columbia Circuit upheld the FDA's authority to regulate HCT/Ps as defined under the relevant federal code.[1]

Part 1271 of the Code of Federal Regulations (21 CFR 1271), which sets forth the criteria by which human cell and tissue products, are designated as either "361 products" (which are, inter alia, only minimally manipulated and intended for homologous use and thus subject to less stringent testing and oversight by FDA), or "351 products" (which are more than minimally manipulated, intended for non-homologous or systemic use, or metabolically active and consequently subject to stricter regulation) (Sipp and Turner 2012). Regenerative Sciences challenged FDA jurisdiction on a number of grounds, including alleged breach of due process in the inclusion of autologous HCT/Ps within the scope of CFR 1271, the inapplicability of the federal rules to autologous products on safety grounds, and the exception of "intrastate" business activities from oversight by FDA, which has authority only over interstate commerce. The central argument, however, held that Regenexx was a medical procedure, not a medical product (or "drug"), and thus exempt from FDA regulation.

The FDA countered that CFR 1271 underwent the legally required public comment and review procedures prior to enactment, that even processes involving the reimplantation of autologous cells and tissues entail risks such as contamination and infection, and that its jurisdiction over interstate commerce encompasses even intrastate businesses that involve the use of components imported from other states. Based on these arguments and precedent, the Court of Appeals in 2014 rejected Regenerative Sciences' claims and upheld FDA authority, affirming "the district court's orders granting summary judgment to the government, dismissing appellants' counterclaims, and permanently enjoining appellants from committing future violations of the FDCA's [Food, Drug and Cosmetics Act] manufacturing and labeling provisions."

[1]United States v. Regenerative Sciences, LLC. 2014. US Court of Appeals for the District of Columbia Circuit. No. 12-5254 (D.C. Cir. 2014).

Marketing of Autologous Stem Cells Under the Same Surgical Procedure Exception

This legal victory over this purveyor of unproven clinical uses of autologous cells, while decisive, now appears to have been Pyrrhic. Prior even to the Court of Appeals' ruling, the company had offshored its business involving the use of cultured bone marrow-derived cells (Regenexx-C), and launched a domestic alternative (Regenexx-SD), which it claims is compliant with federal regulations. The important distinction between these two interventions is that the latter is described as being collected and delivered in the "same surgical procedure." Section 15(b) of CFR 1271 provides an exception for any "establishment that removes HCT/P's from an individual and implants such HCT/P's into the same individual during the same surgical procedure." According to the Regenerative Sciences website (http://regenexxdesmoines.com), over 50,000 Regenexx procedures have been performed since 2006, at the company's 44 affiliated sites. Regenerative Sciences merged with an Iowa orthopedic clinic and moved its headquarters to Des Moines in May 2017.

The use of the same surgical procedure exception by Regenerative Sciences, and subsequently other businesses, appears to have been a watershed for the industry (Turner 2015b). The Cell Surgical Network (CSN), the largest franchise of unproven stem cell marketers in the US with member businesses in at least 25 states), for example, notes in its informed consent document that:

> Processed adipose tissue can isolate large quantities of your cells that may in certain circumstances and under certain conditions be used *during the same surgical procedure* or stored in a deep freeze ("cryopreserved") for future use. The decision to use these cells immediately following the harvest procedure may be considered the "practice of medicine" and such use is a medical treatment decision solely between you and your physician. (CSN 2016, emphasis added)

Numerous other companies refer to their stem cell procedures as "same-day" or "outpatient," apparently also to invoke the CFR 1271.15(b) exception. For example, Bioscience Americas explains on its website that:

> The Bioscience High Performance procedures performed in the United States are compliant with CFR 21 Part 1271 and fall under the same surgery exemption discussed in 1271.15 (b). All of the procedures performed throughout our U.S. GIOSTAR Colombia/Bioscience High Performance Procedure Network are same-day procedures. This means that the patient's cells are harvested in the morning, isolated and processed, then re-injected into the patient's injured area—all within a period of a few hours. (Bioscience Americas 2017)

Similarly, US Stem Cell Clinic, a Florida business that received a warning letter from the FDA in August 2017, posted a response to the agency on its web-

site, stating the company's view that, "according to your current code of federal regulations, same surgical procedure is not subject to the rules for tissue banks which include minimal manipulation and homologous use" (US Stem Cell Clinic 2017). However, the breadth of the exception and its applicability to commercially marketed procedures have been the subject of extensive discussion in legal and professional reviews (Centeno and Bashir 2015; Chirba et al. 2015; Drabiak-Syed 2013; Freeman and Fuerst 2012).

The widespread citation of this exception by firms promoting unproven medical uses of autologous cells has not escaped FDA notice. In October 2014, the agency published a Draft Guidance for Industry on the "Same Surgical Procedure Exception under 21 CFR 1271.15(b): Questions and Answers Regarding the Scope of the Exception" (79 FR 63348) to provide "answers to common questions regarding the scope of the exception." In this draft document, the FDA indicated it would adopt a narrow interpretation of the exception, stating, "As a general matter, the establishment may qualify for the exception if the only processing steps taken are rinsing, cleansing, or sizing the tissue." In subsequent months, three additional draft guidances followed, suggesting further limitations on the definitions of minimal manipulation and homologous use, as well as clarifications of the FDA's views on the structure and function of adipose tissue (Turner 2015a). Some have surmised that these draft guidance documents are a signal of the FDA's intent to exercise increased oversight over a rapidly growing industry marketing medical interventions not supported by a solid evidence base. However, the agency's enforcement record to date has been poor (Sipp 2013; Turner and Knoepfler 2016), and its future under the Trump administration is uncertain. It remains to be seen whether the guidance documents published in late 2017, which set forth the FDA's position on the several key defining criteria for human cell and tissue products, will have an impact on its enforcement activities (Charo and Sipp, 2018).

Marketing of Autologous Cell Interventions as Pay-to-Participate Medical Experiments

A second feature of stem cell marketing in the US is the confused mixing of language indicative of therapeutic care with language indicating experimental intent. For example, in place of a "Conditions Treated" section on its website, CSN lists conditions it is "Currently Studying." This distinction comes with a significant difference, in that it may indemnify the business against accusations of making false therapeutic claims. In its online Frequently Asked Questions (FAQs) for prospective patients, CSN states: "All investigational data is being collected so that results will be published in peer review literature and ultimately used to promote the advancement of cellular based regenerative medicine. *Unless a technology has FDA approval, medical claims and advertising testimonials are not appropriate*"

(CSN 2017, emphasis added). A second entry in the same FAQs is more explicit in denying any liability, and indeed in avoiding any claims-making whatsoever, which is consistent with the "experimental" nature of interventions that are offered in the context of a trial, rather than explicitly as a therapy. Note the mixing of signifiers of care ("stem cell therapy," "cell based medicine") and experimentation ("IRB validated studies," "accumulate significant data") in the text below:

> What claims are currently made by CSN about what stem cell therapy can do for you?
>
> None. Our aim is to make cell based medicine available to patients who are interested and to provide ongoing research data under approved Institutional Review Board (IRB) validated studies. We will follow our stem cell treatment patients over their lifetimes. This will enable us to accumulate significant data about the various degenerative diseases we treat. Instead of providing simply anecdotal or testimonial information, our goal is to categorize the various conditions and follow the patient's progress through various objective (e.g. x-ray evidence or video displays) and subjective (e.g. patient and/or doctor surveys) criteria. *We are aware of a lot of stories about marked improvement of a variety of conditions, but we make no claims about the intended treatment*. (CSN 2017, emphasis added)

Other businesses, such as Stemgenex (California) and US Stem Cell (Florida), have registered open-label clinical studies on the National Institutes of Health (NIH) Clinicaltrials.gov database. Importantly, by compounding language suggestive of research with language suggestive of care, stem cell providers not only expose patients to risk, they do so in ways that minimize the oversight, protections, and avenues of legal recourse ordinarily associated with participation in clinical studies.

A 2017 report identified 18 clinical studies of experimental stem cell interventions registered on the NIH database, which were explicitly or apparently conducted on a charged basis (Turner 2017). Enrollment in such studies is typically conditional on payment of thousands of dollars, an approach that has been described variously as "pay-to-participate," "pay to play," or "patient-funded trials" (Emanuel et al. 2015; Sipp 2012; Wenner, Kimmelman, and London 2015). It is important to understand that the FDA allows sponsors to charge for investigational drugs under an investigational new drug (IND) application for the purpose of either clinical trials or expanded access for treatment use (21 CFR 312.8). However, there are strict limits to these provisions, including pre-approval and close supervision by FDA. Similarly, the 2016 Guidelines for Stem Cell Research and Clinical Translation published by the International Society for Stem Cell Research (ISSCR) also provide for patient-sponsored trials in exceptional circumstances and are conditional upon independent expert review (Daley et al. 2016). However, these Guidelines do emphasize several serious concerns over

how pay-to-participate research designs may "pose challenges for ensuring scientific merit, integrity, and priority as well as fairness" (ISSCR 2016).

The pay-to-participate business model has legal implications as well. A recent ruling in *Moorer v Stemgenex* (2017), a case involving allegations of false advertising, fraud and medical experimentation without informed consent brought by a patient who received an autologous cell transplant for the treatment of systemic lupus erythematosus, highlights the potential protective value of mixing the language of research with the language of care by stem cell marketers. The District Court for Southern California granted the company's motion to dismiss the plaintiff's claims of misrepresentation on the basis of multiple precedents that hold that *provable falsehood* is required to support an allegation of fraud. Simple lack of substantiation—in this case, the lack of dispositive evidence that SCBIs are efficacious in treating the medical conditions advertised on the company website—does not in itself constitute misrepresentation. The ruling notes that

> Plaintiffs further allege that at present, "no such therapy has shown its safety and efficacy in clinical trials." The closest Plaintiffs get to alleging falsity is when they state that "experts will testify that the generally accepted scientific consensus is that there is no treatment for degenerative diseases, or any disease, with a person's own adult adipose stem cells, that has been proven 'effective' at any level." However, the significance of this statement is unclear—is it currently the scientific consensus that no treatment exists because it has in fact been tested and disproven, or rather, is it because no study regarding its efficacy has been conducted yet, and thus, scientific literature is devoid of a conclusion?[2]

The court's decision to uphold the motion to dismiss the allegations of misrepresentation of efficacy is troubling. The court did allow the plaintiffs to proceed with the portions of their case alleging misrepresentation of customer satisfaction, as the company had claimed satisfaction rates of 100%, which the plaintiffs allege is demonstrably inaccurate. Nonetheless, the dismissal of the portions of the case focused on efficacy claims clearly sets a high bar for plaintiffs in civil courts, at least in the state of California, in that it imposes a burden on the consumer to show intentional falsehood on the part of the seller regarding statements made about the effectiveness of an advertised medical intervention.

Incidentally, the ruling also appears to present a significant disincentive for sellers of unproven medical interventions to conduct research studies capable of definitively showing that their treatments are ineffective. By remaining in a state of uncertainty regarding the efficacy of their offerings, businesses are able

[2]Moorer v Stemgenex, US District Court, Southern District of California. No. 3:16-cv-02816-AJB-NLS. See also ruling at: http://law.justia.com/cases/federal/district-courts/california/casdce/3:2016cv02816/517957/39/.

to avoid possessing the knowledge of ineffectiveness, and thereby insulate themselves against intentional deception. Thus, not only do companies acknowledge in their marketing materials that they are uncertain about the usefulness of the interventions they advertise (as seen on the CSN FAQs page cited above), but they are indemnified against claims of fraud to the extent that they remain in that state of uncertainty.

Ethical and Regulatory Issues Surrounding Pay-to-Participate Studies

While patient-funded "research" studies may insulate providers from litigation, they nonetheless involve a number of problematic features. Transactions in which patients must pay in order to join a clinical research study may have a fundamental impact on the study's scientific validity. Randomization between treatment and control groups and masking of group assignments, measures typically employed in clinical research to enhance integrity, may become difficult due to the fact that research participants have specifically paid to receive the investigational product or procedure. Other important features of study design, such as inclusion and exclusion criteria, also may be subject to significant bias due to differences in the ability of research subjects to pay, or in the willingness of the provider to turn away paying subjects. Pay-to-participate research has also been criticized as potentially harmful to the conduct of other clinical trials, as the availability of an investigational-stage product may attract patients who might otherwise opt to enroll in a research study better designed to yield generalizable knowledge (Emanuel et al. 2015; Sipp 2012).

The liability to scientific weakness of medical experiments in which patient-subjects must pay in order to enroll has serious ethical implications. There is a general consensus that badly designed clinical research is unethical, as it puts human subjects at unjustifiable risk (Emanuel, Wendler, and Grady 2000). This is encapsulated in a 2016 statement by the Council for International Organizations of Medical Sciences: "Scientific value refers to the ability of a study to produce reliable, valid information capable of realizing the stated objectives of the research. The requirement of scientific value applies to all health-related research with humans, regardless of funding source or degree of risk to participants" (CIOMS 2016). As further indicated by Emanuel and colleagues in a 2015 commentary, "Permitting patients to pay for participation in clinical research threatens the principles of social value and fair subject selection as well as robust clinical trial design" (Emanuel et al. 2015).

Note that these are not merely theoretical concerns. As described in a 2017 report by Turner, multiple US-based businesses have registered pay-to-participate stem cell clinical trials on the clinicaltrials.gov database maintained by the NIH (Turner 2017). The author of that analysis found that all such studies identified

involved open-label (unmasked), non-randomized, observational designs, and that in many cases the investigational product was tested against multiple unrelated medical conditions. The implementation of pay-to-participate studies was also a prominent complicating factor during the effort to resolve questions about the efficacy of high-dose chemotherapy plus autologous bone marrow transplant against late-stage breast cancer in the 1990s, as detailed in *False Hope* (Rettig et al. 2007).

As with the same surgical procedure exception described in the previous section, the marketing of pay-to-participate clinical "research studies" appears to rely in part on a generous interpretation of federal statute. As noted above, CFR 312.8 details the conditions under which a clinical trial sponsor may charge for an IND. Distinct from the reading of the provisions of CFR 1271.15(b), however, the terms of CFR312.8 explicitly apply only to clinical trials supervised by FDA and make any charge for an investigational product subject to FDA review and approval.

However, not all "clinical studies" registered on the NIH clinical trials database are under FDA supervision, a distinction that may not be clear to many prospective patient-subjects (see Turner 2017 for a more detailed discussion). Similarly, there can be crucial differences in the regulation of federally funded clinical research and that funded by other sources (including patient-funding) in the US. Federally funded clinical studies are governed by the Federal Policy for the Protection of Human Subjects (often referred to as the "Common Rule"). The Common Rule provides extensive protections for safety, consent, and respect for participants in human subjects research funded or supported by any of 18 federal agencies and departments (HHS 2009).

The Common Rule, however, does not necessarily apply to privately funded human subjects research. This asymmetry in the protections afforded to human research subjects in the US has been the subject of longstanding and intensive critique. A 2001 statement by the National Bioethics Advisory Commission (NBAC) exemplifies the troubling implications of differentially regulating human subjects research funded by the federal government and other sources:

> A comprehensive and effective oversight system is essential to uniformly protect the rights and welfare of participants while permitting ethically and scientifically responsible research to proceed without undue delay. A fundamental flaw in the current oversight system is the ethically indefensible difference in the protection afforded participants in federally sponsored research and those in privately sponsored research that falls outside the jurisdiction of the Food and Drug Administration (FDA). As a result, people have been subjected to experimentation without their knowledge or informed consent in fields as diverse as plastic surgery, psychology, and infertility treatment. This is wrong.

> *Participants should be protected from avoidable harm, whether the research is publicly or privately financed.* We have repeated this assertion throughout our deliberations, and recommendations in this regard appear in four previous reports . . . .
>
> In this report, we recommend that the protections of an oversight system extend to the entire private sector for both domestic and international research. A credible, effective oversight system must apply to all research, and all people are entitled to the dignity that comes with freely and knowingly choosing whether to participate in research, as well as to protection from undue research risks. This is consistent with our 1997 resolution that no one should be enrolled in research absent the twin protections of independent review and voluntary informed consent. (NBAC 2001, original emphasis)

In 2015, a set of proposed changes to the Common Rule was published in the Federal Register (Emanuel 2015). These included amendments that would "Extend the scope of the policy to cover all clinical trials, regardless of funding source, conducted at a U.S. institution that receives federal funding for non-exempt human subjects research," which would have thus closed the exemptions for privately funded research (FR 2015). However, the final rule published in January 2017, with most provisions scheduled to take effect in January 2018, "does not expand the policy to cover clinical trials that are not federally funded" (FR 2017). The consequences of this decision for the protection of human research subjects participating in non-federally funded studies remain to be seen, but clearly the lack of uniform standards will remain an issue in the US for some time to come.

The US thus has a form of "dual system," in which companies seeking to market cellular biologics engage with the FDA and undertake strictly supervised premarket testing in the form of multi-phase clinical trials designed to produce generalizable knowledge of the safety and efficacy of the product for a given indication. Notably, no stem cell product other than cord blood products intended for established uses in the treatment of hematological conditions has been approved in the US, due to termination or withdrawal of clinical trials for reasons of efficacy or cost (Eaton, Kwon, and Scott 2015; Weiss et al 2013).

In direct contrast to firms that comply with federal laws that mandate premarket testing, review, and approval, a minimally regulated private sector comprising hundreds of businesses has emerged, in which firms make sweeping marketing claims poised in the legally grey space between the (noncommittal) language of research and the language of therapeutic care. Thanks to the same surgical procedure exception (at least unless and until the current draft guidances are finalized and implemented) and assertions of physician discretion under the rubric of medical procedures (which are not federally regulated), such businesses now assert independence from FDA oversight, and thus the requirement to demonstrate safety and efficacy prior to marketing. Similarly, due to the continuing distinctions drawn between regulatory requirements for the protection of human subjects in

federally and non-federally funded research studies, "patient-funded studies" may be exempted from the Common Rule.

MARKETING OF AUTOLOGOUS CELL INTERVENTIONS AS "PERSONALIZED" CARE

A third feature in the strategies deployed by autologous stem cell businesses in the US is the suggestion that such interventions are "personalized" or made specific to the individual receiving the treatment. Given that the biological materials used are harvested from patients' own bodies, patients and the general public may tend to view treatments that use autologous cells as personalized and unique to the individual (as well as "safe" and "not subject to government regulation"). Stem cell companies frequently emphasize these aspects in their marketing materials, and they may additionally suggest that their offerings are a form of "personalized medicine" (a term that ordinarily refers to the use of genomic and other advanced techniques to stratify patients into groups sharing features such as disease susceptibility or response to a particular drug). The likening of "personalized" stem cell injections to personalized medicine appears to be another instance of co-optation of "tokens of scientific legitimacy," which is a common feature of the direct-to-consumer marketing of unproven SCBIs (Sipp, McCabe, and Rasko 2017).

Examples of the ambiguous use of signifiers of personalization can be found on many websites marketing stem cells for medical uses. On these sites, terms such as "personalization," "patient-centered," "customization," "tailored," and "individual/individualized" are used interchangeably, and injections of autologous stem cells are described as a form of "personalized medicine." A few representative examples are shown below:

> *Regenerative and Personalized Medicine using Genetics and Stem Cells*
> Regenerative medicine is a branch of medicine that deals with the process of replacing, engineering, and regenerating human cells, tissues, or organs to restore the body's normal function. As the practice of medicine moves into a "patient-centered" approach and non-invasive treatment of life-threatening disease and injury, the Mesenchymal Stem Cells (MSC) will play a central role in therapy for many diseases which now have no treatment.
>
> With personal medicine, stem cells can be utilized to decrease the body's inflammation, aid in bringing new blood vessels and repair the diseased area(s). (Texas Stem Cell 2017)

> *Personalized Medicine with Regeneris Medical*
> At Regeneris Medical, we take the time to sit with our patients to get the most accurate diagnosis. Before starting any sort of treatment plan, we will make sure that we create an individualized procedure that we think is best for your prog-

> nosis. Not only do we take a personalized medicine approach, but we also seek more natural alternatives so that there are no risks. Regeneris does this by using your very own body as a source of medicine. (Regeneris Medical 2017)

Personalization narratives such as these are apparent in the subsector of autologous cell banking services that market to adult patients seeking to use their own cells for therapeutic purposes either immediately after collection (often at a clinical affiliate of the cell bank), or as a kind of "insurance policy" for future medical needs (see for example"" BioEden 2016). However, some companies have also begun to advertise same-day procedures involving the harvesting, processing, and re-transplantation of autologous adipose stem cells under the rubric of personalization. In California, David Steenblock, who previously ran cross-border businesses marketing allogeneic cord blood treatments for US patients who traveled to affiliates in Mexico, has rebranded his business as "Personalized Regenerative Medicine" and relocated to southern California (Steenblock 2017). Stemgenex, also based in California, states on the home page of its website that "We believe the key to the most effective stem cell treatment is through treatment plan customization" (Stemgenex 2017).

Besides the marketing value of the "personalized" approach, there are implications for the scientific basis of and legal liabilities associated with therapeutic claims asserting that each intervention is uniquely tailored to the patient. As described in the previous section, it is common for stem cell marketing businesses to include disclaimers on their websites or to advertise their interventions in the guise of pay-to-participate clinical research. Claims of "personalization" or "customization" only further magnify the uncertainty, in that a truly individualized treatment would appear not to be testable by statistically based regimens, such as large-scale clinical trials. This represents a fundamental challenge to regulatory systems, such as that for medical products in the US, in which such testing is the norm.

Indeed, if we accept the stem cell marketers' argument at face value, the safety or efficacy of a "personalized" medical intervention based on a "customized treatment plan" may not be knowable at all. For if both the condition of the patient/research subject and the details of the treatment approach are unique, then the outcome will presumably also be unique to that particular pairing of patient and treatment and thus not generalizable to a broader population. Some advocates of personalized (or more recently, "precision") medicine have called for implementation of "$n = 1$ clinical trials" with novel study designs, based on the notion that improved scientific understanding of pathological mechanisms, increasingly reliable biomarkers, and broader uptake of "smart" medical devices, information technology and data mining will enable studies in individual patients to yield high-confidence results (Lillie et al. 2011). However, whatever the merits of the argument for $n = 1$ trials, the differences between the scenario described

by proponents of precision medicine and the practices of businesses marketing stem cell treatments indiscriminately over the internet are stark.

Proponents of stem cell deregulation commonly assert that clinical trials are unsuited to testing of cell-based interventions. In addition to the difficulties in statistically evaluating "unique" patient-treatment combinations, advocates of reducing testing and regulatory standards have also suggested that pre-market clinical trials impose such large burdens of time, money, and effort as to make even safe and efficacious products unviable from a business perspective, thus harming patients who might be helped by products kept off the market due by regulators. Some proposals have called for pre-market testing of stem cells to focus only on safety, and for efficacy to be determined on a post-market basis. Indeed, the government of Japan introduced a conditional approval system involving post-market efficacy testing of regenerative medicine products in 2015 (Konomi et al. 2015). The most extreme of such proposals effectively view market performance as a reliable indicator of a product's utility, the logic being that competitive pricing and free choice will work to sort out safe and effective medicines from ineffective or unsafe ones (Sipp, McCabe, and Rasko 2017). If claims about stem cell interventions being customized to each individual patient are accurate, however, the market mechanism would also presumably fail to sort the useful from the useless, as each buyer experience would be unique, and thus uninformative to the market at large. The atomizing effect of unmediated transactions between buyer (patient) and seller (stem cell business), each of which involves a bespoke treatment plan, is thus resistant to testing by both scientific and market-based means.

Discussion

The growth of the autologous stem cell marketing industry in the US has been rapid and sustained over the past decade. Irrespective of whether they deliver any therapeutic benefit to buyers, or indeed protect them from harm, the business models now being deployed are highly advantageous to the sellers. By evading federal oversight, indemnifying themselves against consumer claims of fraud and harm, inverting clinical research language in their promotion of pay-to-participate trials, and wording therapeutic claims in ways that make them appear simultaneously individualized and broadly inclusive, autologous stem cell businesses have insulated themselves well against both regulation and litigation.

The convergence on the use of autologous cells by the US stem cell marketing industry was prompted by a number of developments. Sellers first fought to define their interventions as medical procedures, rather than medical products, as procedures are generally immune to federal oversight. The use of the broad exemption of interventions delivered in the "same surgical procedure" under CFR 1271.15(b) permitted many businesses to enter the market through this exception, while bypassing federal oversight and the demand for pre-market testing

and review. The pay-to-participate clinical study model further enables sellers to portray their services as partly therapeutic and partly experimental, and thus enjoy both the marketing benefits of the former and the disclamatory protections of the latter. Claims of personalization similarly allow providers to suggest that their interventions (although advertised indiscriminately on sites accessible to anyone with an internet connection) are tailored to the individual patient's condition and needs, which has the convenient additional benefit of making the intervention unique, and thus difficult to test using the tools of evidence-based medicine.

The effectiveness of these business models is particularly acute within the highly privatized health care climate in the US, and against the background of hyperbolic claims and heightened media and public attention to the therapeutic potential of stem cells in particular (Caulfield et al. 2016). Patients are encouraged to take proactive interest in their health-care decisions, with the implicit understanding that the increased empowerment and freedom of choice comes with a greater responsibility to "own" the consequences of those decisions. In its extreme form, the market-based health care is depicted as a self-organizing system in which market outcomes themselves serve as proxies of efficacy (Sipp, McCabe, and Rasko 2017). This view, which has been embraced by many proponents of the deregulation of stem cell-based regenerative medicine, would replace mandatory pre-market efficacy tests by a poorly defined "wisdom of the crowd" (Bianco and Sipp 2014).

The FDA has made some effort to close, or at least narrow, the regulatory loopholes that have permitted sellers of unproven autologous stem cell interventions to thrive in the US. However, the response to the recent draft guidances at public hearing and online comment forums has been hostile (Sipp 2017). Whether this represents an actual snapshot of public opinion, or the result of a surreptitious advocacy campaign by the industry is uncertain, although there is some evidence of coordination (Sipp 2017). The total picture is reminiscent of past experience in the US of lobbying and indemnification of other alternative health product markets, such as the dietary supplements industry and homeopathy (Hurley 2006; Robins 2005). Despite the absence of compelling evidence to support their therapeutic claims, such unorthodox health practices are well-organized and prosperous in the US. The autologous stem cell marketing industry has learned from the successes of its predecessors in profiting from pseudo-medicine and is now well-equipped to resist efforts to rein in its excesses. Patients, advocates of science-based medicine, and other stakeholders must prepare themselves with an understanding of the industry's marketing and self-protective practices if they hope to prevail.

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