Businesses marketing putative stem cell interventions have proliferated across the U.S. This commercial activity generates a host of serious ethical, scientific, legal, regulatory, and policy concerns. Perhaps the most obvious regulatory question is whether businesses advertising nonhomologous autologous, allogeneic, “induced pluripotent,” or xenogeneic “stem cell therapies” are exposing their clients to noncompliant cell-based interventions. Such practices also prompt ethical concerns about the safety and efficacy of marketed interventions, accuracy in advertising, the quality of informed consent, and the exposure of vulnerable individuals to unjustifiable risks.

Prior analyses of companies engaged in direct-to-consumer marketing of stem cell interventions have not explicitly focused on attempting to comprehensively locate and examine U.S. businesses (Lau et al., 2008; Ogbogu et al., 2013; Regenberg et al., 2009), although recent scholarship has identified some U.S. businesses engaged in such activity (Connolly et al., 2014). While such companies have attracted some scrutiny from researchers and journalists, these businesses have not yet been examined in a comprehensive manner (Perrone, 2015; Turner 2015a). This gap in scholarship has contributed to misunderstandings that need to be corrected.

For example, health researchers, policy-makers, patient advocacy groups, and reporters often use the phrase “stem cell tourism” when addressing the subject of unapproved cell-based interventions and even in 2016 assume that U.S. citizens must travel to such destinations as China, India, Mexico, and the Caribbean if they wish to access businesses promoting stem cell procedures for a wide range of clinical indications. While travel from the U.S. to international “stem cell clinics” continues, the rhetoric of “stem cell tourism” often fails to acknowledge the hundreds of U.S. businesses engaged in direct-to-consumer advertising of stem cell interventions.

To address the urgent need for better information concerning the U.S. marketplace for such businesses, we used Internet key word searches, text mining, and content analysis of company websites to investigate and analyze this arena. We used key words and phrases such as “stem cell treatment” and “stem cell therapy” to find putative stem cell businesses and then evaluated the text on each given site to refine our analysis. Here we discuss the variety and prevalence of different kinds of stem cell interventions currently advertised and the breadth of marketing claims that U.S. businesses make. Our analysis should be useful to health researchers, policy-makers, regulators, patients and their advocates, and other parties.

Geographic Locations and Distribution of U.S. Businesses Marketing Stem Cell Interventions

Using rigorous Internet-based key word searches (see Supplemental Information for details), we found 351 U.S. businesses engaged in direct-to-consumer marketing of stem cell interventions offered at 570 clinics. For each business, we collected the company name, location(s), website address, advertised stem cell types, and diseases, injuries, and other conditions that clinics claim to treat with stem cell interventions. (Table S1 lists and describes all of the businesses we identified).

Figure 1 shows the geographic distribution of such businesses across the U.S. Many stem cell companies employ multiple physicians and advertise interventions available at numerous clinics. Although such businesses are widely distributed all over the county, we found that clinics tend to cluster in particular states. For example, we found 113 clinics in California, 104 in Florida, 71 in Texas, 37 in Colorado, 36 in Arizona, and 21 in New York. “Hotspot” cities including Beverly Hills (18), New York (14), San Antonio (13), Los Angeles (12), Austin (11), Scottsdale (11), and Phoenix (10) are designated with stars on the map. Some metropolitan areas, including Southern California around Los Angeles and San Diego, the South Florida region surrounding Miami, the greater Denver area, and the Dallas-Fort Worth metro region, have a relatively high number of clinics even if not all such facilities are technically in one city (Figure S1). While our analyses here do not explain why these businesses cluster in particular areas, we plan to investigate this question further. Possible factors include a relationship between number of clinics and population density, regional variations in use of “alternative” medical interventions, aging population demographics, and regulatory orientation of state medical boards and consumer protection agencies.
Types of Advertised Stem Cell Interventions
We also analyzed the particular stem cell types that businesses advertise (Figure 2A). Most of the businesses we identified market autologous cell-based interventions, with an estimated one in five advertising allogeneic stem cell interventions sourced from amniotic material (17%), placental tissue (3.4%), and umbilical cords (0.6%). Some clinics market both autologous and allogeneic stem cells.

Of the businesses advertising autologous stem cell procedures, 61% market autologous adipose-derived stem cell-based interventions, 48% market what they describe as autologous stem cells obtained from bone marrow, and 4% market stem cells reportedly obtained from peripheral blood. Adipose stem cells were most often referred to using the adjective “adipose,” but some companies used phrases such as “fat stem cells” and other businesses advertised that they use “stromal vascular fraction” or “SVF.” Bone marrow stem cells were also sometimes referred to as “bone marrow aspirate concentrate” or “BMAC.” Combinations of stem cell types were also promoted. We found that a mixture of autologous adipose and bone marrow stem cells is the most commonly advertised “combination stem cell therapy.”

Clinics marketing amniotic stem cells, amniotic stem cell allografts, or amniotic stem cell fluid also sometimes used such terms as “placenta” or “placental stem cells.” The relative abundance of U.S. businesses marketing “amniotic” and “placental” stem cells was notable. The precise source of these products is not clear in all cases, particularly for allogeneic products such as amniotic stem cells.

One business promotes access to what it claims are induced pluripotent stem cells. This company did not indicate the purported source of induced pluripotent stem cells or address whether they are derived on a patient-by-patient basis for autologous therapy. Another business markets access to what it describes as “embryonic stem cell” interventions. In addition, we identified two clinics that marketed “bovine amniotic cells,” a xenogeneic product, for use in humans. Approximately 3% of businesses marketed stem cell interventions without mentioning a particular type of stem cells.

One unanticipated interpretive challenge we encountered is that many businesses advertise both stem cell interventions and platelet rich plasma (PRP) procedures either as the basis for separate treatments or as combination “cell therapies.” Though not an actual stem cell product, PRP is sometimes marketed as an autologous “stem cell treatment” derived from peripheral blood. In such cases, the rhetoric of “stem cells” is presumably used as a marketing hook intended to attract potential customers (Turner, 2015b). For the purpose of our analysis, clinics marketing putative stem cell interventions derived from peripheral blood were included within the scope of our inquiry but clinics only marketing PRP interventions were excluded.

Marketing Claims about Clinical Indications
U.S. businesses promoting stem cell interventions claim to treat a wide range of...
diseases and injuries, as well as advertising stem cells for cosmetic applications, “anti-aging,” and other purposes (Figure 2B). Some clinics occupy relatively specialized marketplace niches. For example, many cosmetic surgery clinics advertise such procedures as “stem cell facelifts” and “stem cell breast augmentation” as well as sexual enhancement procedures. Orthopedic and sports medicine clinics often promote stem cell interventions for joints and soft tissue injuries. Other clinics take a much broader approach and list stem cell interventions for 30 or more diseases and injuries. Such businesses commonly market treatments for neurological disorders and other degenerative conditions, spinal cord injuries, immunological conditions, cardiac diseases, pulmonary disorders, ophthalmological diseases and injuries, and urological diseases as well as cosmetic indications. Many of these marketing claims raise significant ethical issues given the lack of peer-reviewed evidence that advertised stem cell interventions are safe and efficacious for the treatment of particular diseases. Such promotional claims also generate regulatory concerns due to apparent noncompliance with federal regulations.

We also examined the prevalence of stem cell marketing claims targeted at parents or guardians of minors. We found nine clinics each promoting stem cells for autism and for cerebral palsy. We also identified 33 marketing claims for muscular dystrophy (MD), a disease that primarily though not exclusively afflicts children. This kind of advertising reveals another tangled knot of ethical and legal concerns, as the apparent target audience for such marketed interventions is not adults with decision-making capacity but rather the parents or guardians of children. A comparable kind of marketing situation may exist for Alzheimer’s disease (27 promoted claims) and other neurodegenerative illnesses where in at least some cases patients themselves are not necessarily the primary targets of online advertising.

### Ethical, Regulatory, and Policy Concerns

Our investigation was in part motivated by ethical, scientific, and regulatory concerns related to the proliferation of U.S. businesses engaged in direct-to-consumer marketing of stem cell interventions. However, it was not our intention to make evaluative statements concerning whether particular companies are marketing stem cell interventions in compliance with federal and state regulations as well as contemporary ethical standards for medical practice. Nor was it our intention to make ethical or legal assertions about specific marketing claims. We also did not address whether contemporary ethical, scientific, and legal standards are being met by individual businesses. However, at a broader level we recognize the importance of these ethical issues and regulatory concerns (Knoepfler, 2015).

Given that many of the businesses we identified market autologous interventions that do not appear to fit FDA criteria for homologous use and minimal manipulation of cells and tissues, allogeneic products, combination products, or “xenograftic stem cells,” there are clear grounds for concern that some of the companies we found are not compliant with federal regulations. There are related ethical concerns about information provided to prospective clients and the veracity of marketing claims, the safety and efficacy of advertised procedures, and the risk of physical, emotional, and financial harm to already ill or injured and vulnerable individuals. Recent draft guidelines issued by the FDA provide increased clarity concerning how the FDA interprets federal regulations applicable to the use, sale, and distribution of stem cell products. These draft guidance documents suggest to some observers that the FDA is preparing to take increased regulatory action (https://www.statnews.com/2016/02/08/fda-crackdown-stem-cell-clinics/) in response to businesses selling stem cell interventions in a manner that some critics have described as exhibiting a “Cowboy Culture” (http://www.nature.com/news/stem-cells-in-texas-cowboy-culture-1.12404).

Some proponents of deregulation argue that current federal regulations governing the advertising, processing, and administration of autologous stem cells are too onerous and have resulted in few approved stem cell therapies reaching the American marketplace (Chirba and Garfield, 2011; McAllister et al., 2012). The REGRROW Act is an example of the current push from some political quarters and even from some
individual stem cell researchers for lowering safety and efficacy standards for adult stem cell-based interventions. However, we found that hundreds of U.S. businesses are already promoting stem cell interventions for an extraordinary range of clinical indications. Advocates of deregulation will perhaps be pleased by our findings that many putative stem cell interventions are currently available for sale in the U.S. In contrast, proponents of a marketplace in which cell-based therapies have traditionally been tested for safety and efficacy and subject to pre-marketing review by the FDA will likely be concerned by how many U.S. businesses are currently marketing stem cell interventions. We are particularly concerned that we found many advertising claims related to ALS, Alzheimer’s disease, Parkinson’s disease, and many other conditions for which there is no established scientific consensus that proven safe and efficacious stem cell treatments now exist.

Given that we identified 351 businesses actively advertising stem cell products in the U.S., it is fair to ask whether regulatory inaction has emboldened entrepreneurial physicians and other market participants. We place a high value on the imperative to provide patients with safe and efficacious interventions and see a need for more effective regulation of the U.S. marketplace for stem cell interventions. Our analysis should serve as a valuable resource for contemporary debate concerning whether the U.S. marketplace for stem cell interventions is adequately monitored and regulated by the FDA, the Federal Trade Commission, state medical boards, and other agencies tasked with promoting patient safety and accurate advertising (https://www.federalregister.gov/articles/2015/10/30/2015-27703/draft-guidances-relating-to-the-regulation-of-human-cells-tissues-or-cellular-or-tissue-based).

Weighing Risks and Benefits Associated with Identifying Marketing Stem Cell Interventions

While examining the U.S. marketplace for direct-to-consumer advertising of stem cell interventions, we gave careful consideration to possible risks associated with and documenting specific businesses engaged in such commercial activity. We acknowledge that a public record containing locations and websites of businesses marketing stem cell interventions could be misappropriated and misused for marketing purposes, be used as a search tool by patients seeking particular procedures, or even be used to claim that, with so many businesses already operating in the U.S., de facto deregulation has occurred and it is too late for the FDA and other agencies to provide more robust regulatory oversight of this marketplace. While we recognize these risks, we argue that the benefits associated with a detailed examination of U.S. businesses marketing stem cell interventions outweigh potential risks. We also want to emphasize that we analyzed businesses that are already readily identifiable and take multiple steps to market their products. Patients have little difficulty finding stem cell clinics and comparable businesses on the Internet. The best way to address ethical, legal, and scientific issues related to such businesses is to acknowledge their existence, examine and evaluate their marketing claims, and conduct public debates and policy discussions in the most evidence-based manner possible.

SUPPLEMENTAL INFORMATION

Supplemental Information for this article includes investigation methods, one figure, and one table and can be found with this article online at http://dx.doi.org/10.1016/j.stem.2016.06.007.

WEB RESOURCES

