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Global Distribution of Businesses Marketing Stem Cell-Based Interventions

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A structured search reveals that online marketing of stem-cell-based interventions is skewed toward developed economies including the United States, Ireland, Australia, and Germany. Websites made broad, imprecise therapeutic claims and frequently failed to detail procedures. Widespread marketing poses challenges to regulators, bioethicists, and those seeking realistic hope from therapies.

The direct-to-consumer marketing of unproven stem cell-based interventions has developed into an international industry that has been the focus of extensive commentary and criticism (Connolly, O'Brien, and Flaherty, 2014; Taylor-Weiner and Graff Zivin, 2015). Some stem cell clinics make an extraordinary and implausible range of claims for their offerings. These are not only medical in nature but can include aesthetic and quality of life claims; anti-aging, tissue rejuvenation, and cosmetic surgery are major industry niches (Sipp, 2011). Such claims are typically made without supporting evidence from randomized, controlled, independent clinical trials and lack market authorization from a regulatory authority. While some clinics that engage in the marketing of unproven stem cell-based interventions have sought to register clinical trials, the reporting of study results has been rare (Bianco and Sipp, 2014). Such clinics not only pre-emptively proceed to marketing in advance of reporting, review, and approval, they often claim broader clinical benefits than can be justified by the specific indications they purport to have tested (Bianco and Sipp, 2014).

In the early days of this under-regulated industry, clinics were typically located in developing economies, in which weak laws or lax enforcement enabled such businesses to operate with relative impunity (Lau et al., 2008). More recently, richer countries such as Australia, Germany, Italy, Japan, and the United States have seen clinics take advantage of real or imagined gaps in regulation (McLean et al., 2015; Fujita et al., 2016; Taylor-Weiner and Graff Zivin, 2015). Consequently, overseas clinics targeting inbound medical travelers now compete directly with those located domestically within major markets.

Despite the rapid growth of this unorthodox medical sector, the full scope and diversity of the businesses engaged in marketing unproven stem cell-based interventions globally remain poorly documented. This deficit in basic quantitative knowledge of the size and activities of the industry worldwide has serious policy implications. Regulatory authorities may be hesitant to prioritize enforcement actions without a clear understanding of the scale of the suspected problem. This, in turn, may facilitate further development of the market in an environment of continued under-regulation. In the present analysis, we sought to document the state of direct-to-consumer marketing of stem-cell-based therapies through a detailed content analysis of clinic websites.

Global Distribution of Stem Cell Clinics

We conducted a series of structured English-language online searches (see Supplemental Information) supplemented by a hand-curated dataset and identified 417 unique websites advertising stem cell-based therapies. The distribution of clinics was highly concentrated, with the largest fraction located in the United States. This is consistent with the accompanying findings of Turner and Knoepfler (2016) in their analysis of online direct-to-consumer marketing activity in the US and may suggest growth in the domestic industry. We identified 187 unique websites in the US offering interventions at 215 clinics (Figures 1A and 1C), while Turner and Knoepfler found 351 distinct businesses offering interventions at 570 physical locations. Due to differences in search strategy stringency, inclusion and exclusion criteria, and search engines used, it is not possible to make direct comparisons between these analyses, but the implication is that growth of the industry in the US has been rapid and pronounced. This may reflect uncertainties over the interpretation of existing federal laws governing the manufacture and distribution of human cell and tissue products, or the consequence of a lack of substantive enforcement activity.

We also found that Australia is home to a very high concentration of stem cell businesses advertising clinical services online (Table S1). With 19 unique clinic locations offering stem-cell-based interventions for a population of 23.5 million, Australia has a higher number of clinics per capita than the United States, which had the greatest total number of such sites in the world in our search (187 clinics for 310 million people) (Figure 1B). While Ireland had relatively few clinics, it had an unexpectedly large number per capita (five clinics for 4.5 million people), third only to the Cayman Islands and Bahamas (Table S2).

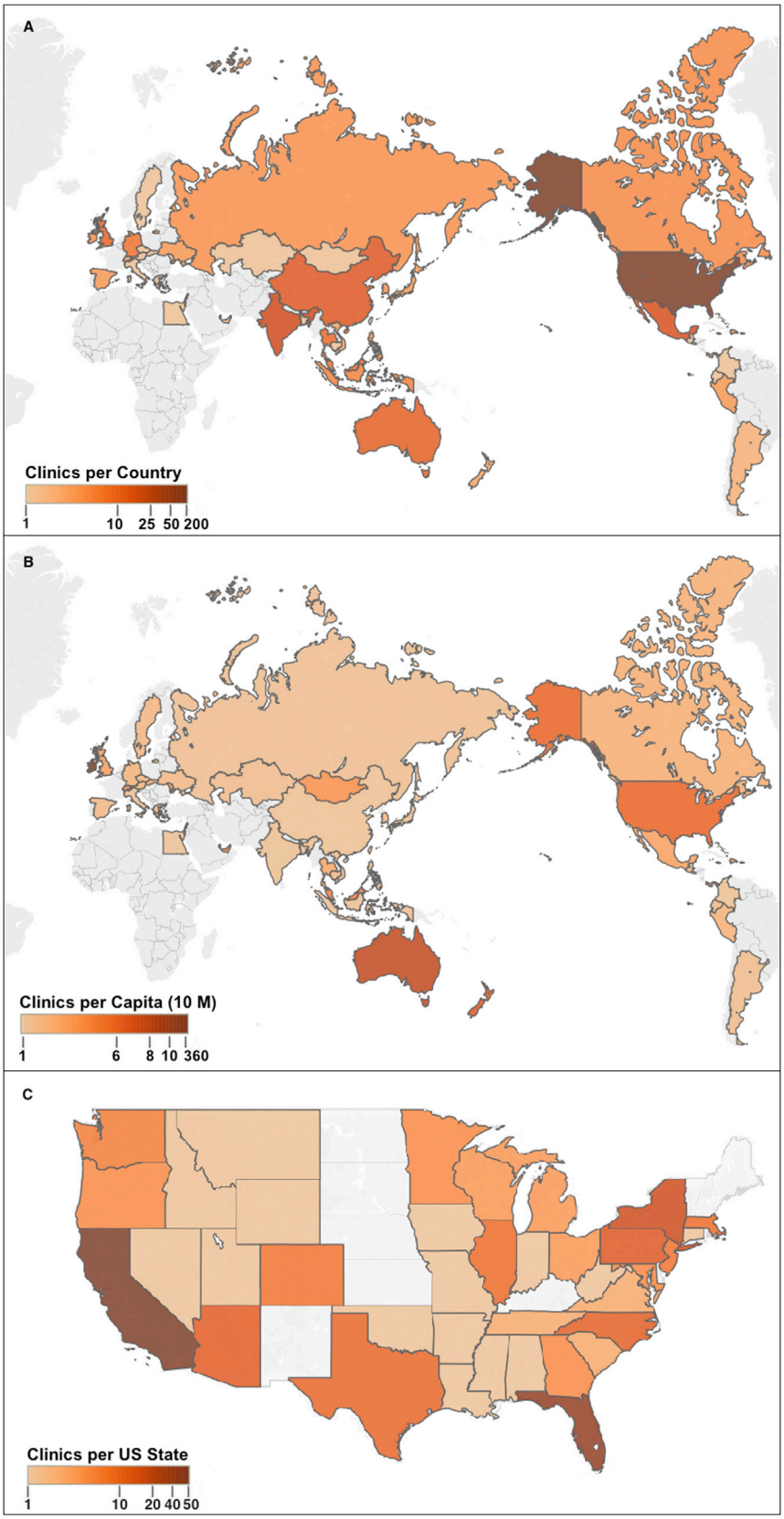

Figure 1. Locations of Stem-Cell-Based Clinics

(A) Clinics per country, top ten countries by number of clinics: USA (187 clinics), India (35), Mexico (28), China (23), Australia (19), UK (16), Thailand (14), Malaysia (12), Germany (11), and Indonesia (7).

(B) Clinics per capita (10 M), top ten concentrations of clinics in countries per capita (in descending order): Cayman Islands (364.4), Bahamas (86.7), Ireland (11.2), Singapore (10.0), Australia (8.1), New Zealand (6.8), USA (6.0), Qatar (5.9), United Arab Emirates (4.2), and Malaysia (4.2).

(C) Clinics per US state. Top five states: CA (49), FL (35), NY (15), PA (11), and AZ (10). No sites were recorded in HI and AK, not shown.

Grey indicates no clinics recorded.

Cell Types and Indications

We conducted a content analysis of all websites captured in our search to evaluate their claims about cell types used and medical conditions treated. This analysis was complicated by the lack of specificity and standardized terminology across websites. The majority of websites (n = 347, 83.2%) offered adult stem cells, followed by stem cells of unspecified type (n = 53, 12.7%). The remainder offered embryonic, induced pluripotent, or fetal stem cells (n = 33, 7.9%) or amniotic stem cells (n = 4, 1.0%). Approximately half the sites (n = 217, 52%) did not indicate the donor source of cells. In sites that did provide such information, those offering autologous stem cells were the most common (n = 164, 39.3%), while about half this number offered allogenic stem cells (n = 76, 18.2%). This may reflect the weaker oversight of autologous cell-based interventions in countries such as the United States and Australia, or market response to patient preferences for autologous cells. Interestingly, 4.1% (n = 17) of sites advertised the clinical use of non-human cells.

We compared the cell types and donor sources of cells being offered in the top ten countries to the USA, representing the largest total number of clinics (Table S1). All four amniotic stem cell offers were in the USA or India. Compared to the USA (n = 10, 5.3%), relatively more embryonic, induced pluripotent, and/or fetal stem cells were offered in India (n = 6, 17.1%), χ^2 (2, N = 222) = 6.13, p = 0.01). There were no significant associations between countries and unspecified cell types or adult stem cells, although there was a non-significant trend toward Indonesia offering fewer adult stem cells (n = 4, 57.1%, p = 0.07). We observed a

wide variation in donor cell sources of autologous stem cells and donor cells from unspecified sources. There were no significant associations between the frequency of autologous cells offered and countries when compared with the USA (n = 71, 38.0%). However, there was a significant difference when comparing Australia (with the largest proportion of autologous cells offered, n = 12, 63.2%) and the UK (with the smallest proportion, n = 4, 25.0%), χ^2 (2, N = 35) = 5.10, p = 0.02. The USA (n = 108, 57.8%) was much more likely to offer cells from unspecified sources compared to related economies such as Australia (n = 5, 26.3%, χ^2 (2, N = 206) = 6.88, p = 0.009) and Germany (n = 2, 18.2%, χ^2 (2, N = 198) = 6.59, p = 0.01). Clinics in Mexico (n = 10, 35.7%) were more likely to offer allogenic cells than the USA (n = 33, 17.6%), χ^2 (2, N = 215) = 4.97, p = 0.03). Clinics in Malaysia (n = 2, 16.7%, χ^2 (2, N = 199) = 6.50, p = 0.01) and Germany (n = 4, 36.4%, χ^2 (2, N = 198) = 27.18, p < 0.001) were more likely to offer xenogenic cells than US clinics (n = 5, 2.7%).

Websites were frequently imprecise on the medical conditions for which they offered interventions (Table S2). As with our analysis of cell types used, we did not find consistent use of terminology or categorization of diseases across sites. The most common indication we identified overall was anti-aging/skincare (n = 178, 47.2%), suggesting that a considerable fraction of stem cell providers market interventions for lifestyle or aesthetic, rather than strictly medical, concerns (Table S2). Clinics in Thailand (n = 10, 71.4%, χ^2 (2, N = 201) = 12.85, p < 0.001) and Malaysia (n = 7, 58.3%, χ^2 (2, N = 199) = 5.76, p = 0.02) were more likely to offer anti-aging/skincare interventions than US clinics (n = 49, 26.2%). The most common medical conditions were diabetes, orthopedic injuries, multiple sclerosis, and Parkinson's disease (Figure 2A). Many sites promoted interventions for multiple unrelated medical and/or cosmetic indications.

The lack of specificity we found in both therapeutic claims and information on cell types and sources presents a challenge to more detailed analyses and may be a source of confusion for patients and consumers. Commercial websites have a clear interest in using language that is familiar to their customers, which may account for some of the ambiguity in claims. The absence of fundamentally important details in a high number of the sites we evaluated, however, raises important questions about the verifiability of claims being made by online entities regarding putative stem cell-based interventions.

Blurring of Lines

We were interested in determining how stem cell marketing websites project an image of scientific validity or authority to their users and evaluated diverse claims that might suggest such legitimacy. Nearly 40% of sites (n = 162) listed affiliations with a professional society or network, and nearly one-third claimed partnerships with academic institutions (n = 137). A small number of sites stated that they had received FDA approval (n = 34, 8.2%), whereas some explicitly mentioned exemption from FDA oversight (n = 23, 5.5%). Most sites that stated they had received some kind of official endorsement cited approval from a local authority (n = 202, 48.4%), approval from another authority (n = 183, 43.9%) or professional accreditation (n = 148, 35.5%). Some sites stated that they had received a patent (n = 21, 5.0%) or had a patent pending (n = 16, 3.8%). Many sites stated that they were conducting clinical trials of investigational stem cell-based interventions (n = 141, 33.8%).

It is very difficult to distinguish between legitimate and unapproved applications of stem cell-based interventions without access to specific protocols used by clinics. The information provided by many websites was vague and clinics marketing unapproved stem cell-based interventions often operate in legislative gray zones within their respective jurisdictions. Thus it was not possible to obtain further information or make judgments about their legitimacy without potentially introducing sampling bias. Rather, our analysis aimed to document the extent and pattern of English-searchable websites' direct-to-consumer advertising of stem-cell-based interventions regardless of the value that may be placed on individual interventions or institutions. Interestingly, the results of our structured search identified 67 academic medical center websites (66 in the USA, 1 in India), as assessed by two independent reviewers, advertising stem cell-based interventions directly to the public. Academic sites were more likely than others to state that they were conducting a stem cell-related clinical trial, χ^2 (2, N = 417) = 88.35, p < 0.001. We note, however, that academic centers were relatively limited in the range of diseases they claimed to be treating or trialing using stem cells (Table S2). This reflects a preponderance of conventionally accepted stem cell-based interventions, such as those for hematological conditions, and relatively limited applications of novel stem-cell-based interventions (Figure 2B). While some of these novel applications were advertised as clinical trials, others were advertised simply as treatments. The higher amount of advertising for hematological therapies at academic centers (and to some extent private clinics) in the United States is likely to reflect both the fact that hematopoietic stem cells are regulated separately from most other cell and tissue products under relevant federal laws, and the degree of privatization of health care in the US compared to countries where these services are provided by publically funded hospitals.

Implications for Policy and Medical Ethics

In this analysis, we sought to assess direct-to-consumer marketing of stem-cell-based therapies through a content analysis of clinic websites. We identified significantly more clinics than previous surveys of international stem cell marketing (Lau et al., 2008; Ogbogu et al., 2013; Connolly et al., 2014), although an accompanying study of domestic activity in the United States (Turner and Knoepfler, 2016) suggests that growth of the US industry may be accelerating. Our investigation provides a new resource highlighting the scale and impact of this phenomenon both in the US and globally. We noted a number of websites with contact forms offering more information "on request" without making explicit therapeutic claims, but such sites were not captured using our inclusion criteria. Other clinics may only operate through referral services and medical tourism companies or otherwise do not maintain a website or social media page of their own. Even with our broadly inclusive approach, it is probable that we did not capture all stem cell marketing activity during the study period.

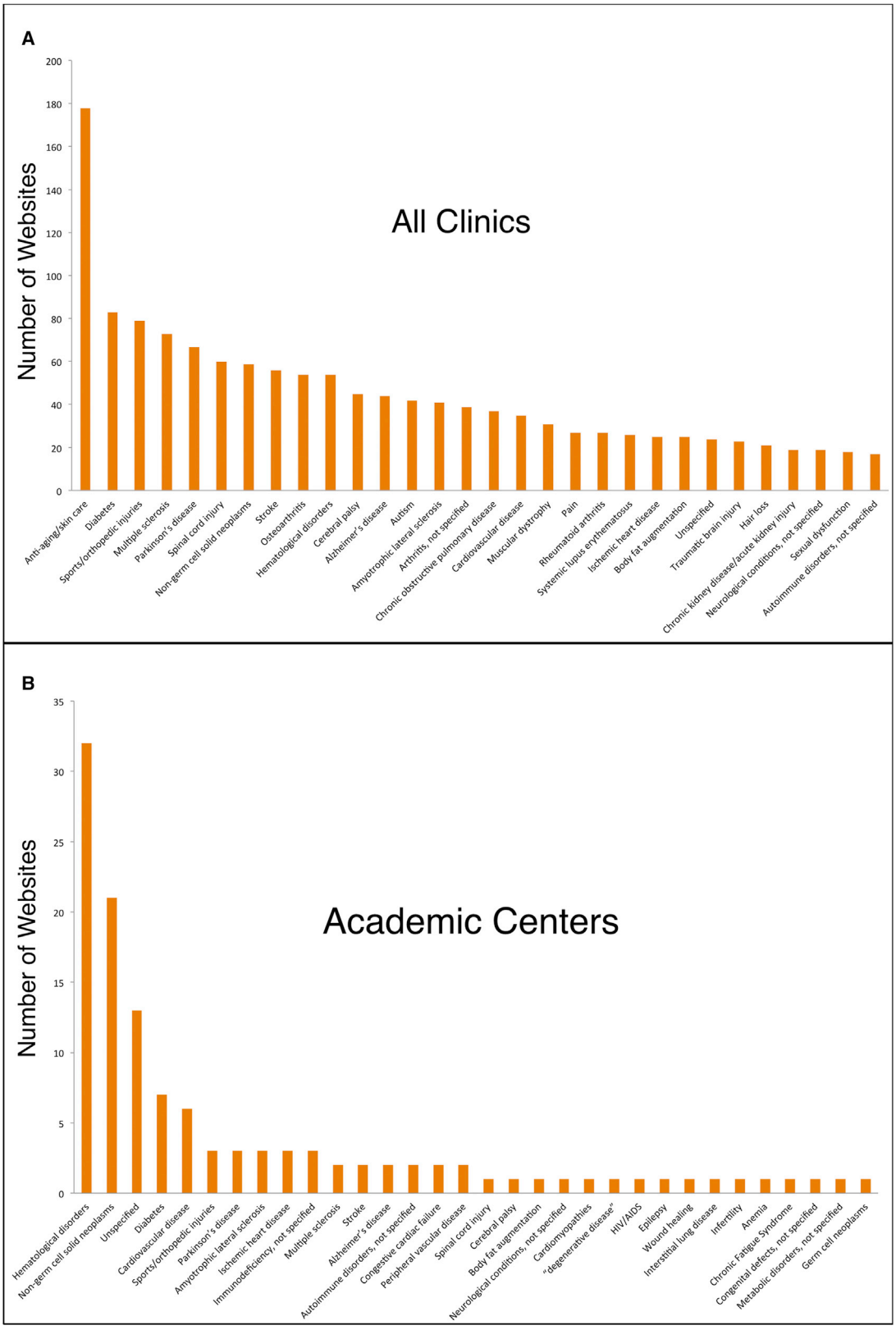

Figure 2. Top Conditions Treated by All Clinics and Academic Centers
(A) Top 30 conditions treated by all clinics.
(B) Conditions treated by academic centers.

It is surprising that we found businesses marketing stem-cell-based interventions were concentrated in countries that tend to have more stringent regulatory infrastructures governing health products and medical practice. For example, the Australian government does not consider some autologous cells to be medical products, so licensed physicians are currently relatively unrestricted in their ability to use such cells in medical procedures (McLean et al., 2015). Australia was 5th in total number of clinics (Figure 1A) and was also 5th in clinics per capita (Figure 1B). Similarly, use of adult stem cells is relatively unregulated in Ireland, which had the 3rd highest concentration of clinics per capita in the world (Figure 1B). India, which had the second highest number of clinics, has had national guidelines on clinical research and application of stem cells for nearly 10 years, but these are not legally binding. At the time of our search, China was in the top five countries for total number of clinics. China revised its regulatory framework governing clinical uses of stem cells in 2015 (Rosemann and Sleeboom-Faulkner, 2016), so the effects of these strengthened measures are therefore not reflected in our data. Future research should examine the relationship between health services regulation, stem cell regulation, and stem-cell-based interventions offered, as this is an important potential area for public health.

The provision of unproven stem cell-based interventions remains a concerning feature of the clinical landscape. We have conducted a census of websites advertising these services directly to consumers and found a number of features confirming those of earlier studies utilizing smaller samples and less exhaustive search strategies. Opacity, ambiguity, and lack of disclosure in marketing statements were prevalent in our sample. Vague descriptions of interventions, cell types, and donor sources, and extraordinarily broad, unsupported therapeutic claims were common.

Our findings of increased overall activity at the global level lend new quantitative support to the large body of media and scholarly reports that direct-to-consumer stem cell marketing remains widespread. We show that the global industry engaged in direct-to-consumer marketing of stem cell interventions in English shows geographic concentrations in highly developed countries, including the US. The ambiguity of claims made by private companies regarding cell type, cell source, conditions treated, and degrees of regulatory oversight and compliance are a source of concern. Access to accurate and precise information on therapeutic interventions is fundamental to informed decision-making by both patients and policymakers. Our analysis indicates that stem cell clinics often do not provide sufficiently detailed information about their interventions to support informed consent or evaluation of therapeutic options.

SUPPLEMENTAL INFORMATION

Supplemental Information includes two tables and Supplemental Experimental Procedures and can be found with this article online at http://dx.doi.org/10.1016/j.stem.2016.07.015.

AUTHOR CONTRIBUTIONS

Conceptualization, Writing, and Supervision, I.B., D.S., and J.E.J.R.; Methodology and Analysis, I.B., A.A., A.B., D.S., and J.E.J.R.; Software, T.K.; Visualization, A.B. and I.B.

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