Marketing of Unproven Stem Cell-Based Interventions: A Call to Action

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The growth of the industry engaged in direct-to-consumer marketing of unproven stem cell interventions online has become impossible to ignore[1, 2], and effective measures for regulating this sector at the national and international levels are urgently needed. Despite the lack of compelling evidence from well-designed studies to support their efficacy[3], or even in many cases of a plausible biological rationale, many providers aggressively promote the use of stem cells for a wide range of indications. Such practices first emerged in the peripheries of international biomedical research and development[4], but providers have been making inroads in some leading global markets, including Japan[5], Australia[2, 6], and the United States[1, 7]. Public warnings by scientific and medical groups[8, 9], government organizations[10], and the media[11] have not slowed the global expansion of stem cell marketing. The success of this industry has adverse implications for patients' health and the integrity of health care markets, as well as potential repercussions for legitimate biomedical endeavors. It also

provides an unsettling glimpse of what may lie ahead for other emerging biomedical technologies, such as mitochondrial replacement therapy and gene editing[12].

Efforts to ensure that stem cell-based interventions rest on a foundation of scientific evidence have not all been in vain. Authorities in Germany were successful in closing a private clinic that marketed primarily to overseas patients, but only after several reports of serious adverse events, including the death of an infant[13]. The Chinese Ministry of Health has made significant strides in curtailing an industry in which hundreds of clinics promoted purported stem cell therapeutics over the Internet[14]. More recently, the resolution of the Stamina Foundation controversy in Italy, provides an excellent example where academic researchers and regulatory officials successfully pushed back against a highly publicized provider of unproven stem cell treatments[15]. This was an important victory in the fight to ensure that unsupported therapeutic claims about stem cell therapies do not go unchallenged. The Stamina case in particular provides important insights into how many promoters of unproven stem cell treatments harness and manipulate popular sentiments and misconceptions, and how scientists and physicians can help inform both media representations and public policy[16]. By mobilizing support from international scientific organizations and engaging with the public through traditional and social media, scientists were able to exert a positive influence on national policies that initially appeared to be veering toward state support for pseudomedicine[17].

In this commentary, we draw on the mounting body of literature describing the growth and characteristics of direct-to-consumer marketing of stem cell-based therapies[1, 2, 18, 19] to highlight a number of key features and challenges for broad-based

efforts to ‘regulate’ this industry. We also examine how past successes in countering the premature commercialization of stem cell-based therapies in medicine can inform coordinated responses to this phenomenon at the national and international levels.

Defining the problem

The marketing of stem cells online takes place within a context of heightened direct-to-consumer (DTC) marketing activity in the health sector. DTC advertising of medical products and services reflects the increasingly commercialized and consumer-oriented nature of the health sector. The growth of the Internet and social media have provided new outlets for the marketing of both licensed and unlicensed therapeutics and offer sellers the ability to reach worldwide audiences, highlighting the difficulties of enforcing national laws in a global marketplace[20]. Critics have cautioned that such unmediated forms of drug advertising may evade regulatory oversight and provide unreliable or incomplete information regarding risks, efficacy, and treatment alternatives[21].

Numerous professional organizations, including the largest international academic societies in cell therapy[3] and stem cell research[22], have adopted a staged approach to determining what constitutes sufficient evidence of efficacy to justify routine clinical use. These approaches hold that such decisions should typically be based on results from independent randomized, controlled clinical trials (RCTs), a view broadly consistent with the norms of evidence-based medicine. Nevertheless, it is important to recognize that even within this paradigm, study designs and evidentiary standards continue to evolve, and there is a diversity of viewpoints on the nature and quality of evidence needed to support widespread clinical adoption. For this reason, there is

inevitably a ‘grey’ zone between the extremes of a strong scientific support and pure quackery[23]. Nonetheless, requiring novel stem cell-based interventions to be carefully evaluated for safety and efficacy prior to entering widespread clinical use is consistent with best practices in biomedical research and development, for which there is substantial agreement across many jurisdictions. The steps involved in conventional clinical translation of new therapies include: a compelling scientific rationale; well-defined and validated standards for *ex vivo* processing to achieve cellular product quality and potency; substantial evidence from rigorously designed independent clinical studies demonstrating safety and efficacy in the context of a specific medical indication; and the provision of information from such studies to inform clinical decision-making[24].

Stem cell-based interventions are classified under diverse and potentially incompatible national regulatory frameworks. Many countries, including the United States, have defined a wide spectrum of treatments using human cell and tissue as medical products under the oversight of the Food and Drug Administration (FDA) or equivalent national authority. Other countries, including Australia and Japan, allow physicians broad discretion in using autologous cells in the course of medical procedures[25]. In the majority of nations, however, clear rules governing the clinical use of stem cell-based interventions are absent. Cell-based interventions may be categorized as ‘products’, which are subject to oversight by national regulatory authorities, or as ‘procedures’ conducted within the scope of medical practice. These distinct regulatory philosophies have direct implications for how stem cells can be advertised in different jurisdictions, as evidence standards for advertising, market

authorization and standard of care, and the enforcement options available to national regulators, may vary considerably.

Inflated messages

Much of the coverage of stem cells in the popular press to date has been unjustifiably optimistic, both in terms of the potential clinical benefit and the timeframe in which such treatments would reach routine clinical application[26]. This positive messaging is leveraged by some providers to market unproven stem cell-based interventions. Indeed, the term 'stem cell' has been used broadly in promises of youth, rejuvenation and good health, as well as in the branding of cosmetics, dietary supplements, and sports products[27]. Such hyperbole carries with it not only an increased risk of exploitation of vulnerable families desperate for a cure, but also of significant damage to the health of those subjected to these unproven interventions. In the longer term, unfulfilled promises may bring regenerative medicine R&D into disrepute.

In parallel to the hyping of the clinical utility of stem cells, providers of unproven stem cell interventions often display tokens of scientific legitimacy, such as publications in journals with weak or non-existent peer review, and the registration of pay-to-participate clinical trials, in their marketing messages **[Fig 1]**. It can be difficult even for professionals, let alone patients, to determine whether these tokens demonstrate true compliance with the evidentiary standards for developing and testing stem cell therapies as outlined above.

Misrepresentations of the safety and efficacy of stem cell interventions by commercial providers may build on exaggerated accounts of the state of the science in popular

media and research publications. Media accounts may uncritically report statements about the efficacy of stem cell-based treatments. Such articles are then re-posted on clinic websites, cited in social media, and used in crowd-funding efforts, which may further consolidate public expectations and patients' curiosity. However, the presumption of the efficacy of stem cell-based interventions is not simply a media issue. The pressure to publish, patent, promote, and commercialize research results, as well as to secure funding for future research, are all contributors to the 'hyping' of stem cell science[28].

Regulatory turmoil

National regulatory authorities have been challenged in recent decades by calls for faster access to medical products, even in advance of the completion of rigorous clinical trials. This may reduce the willingness or ability of policy makers, patient groups, and regulators to take a stand against the commercial promotion of unproven stem cell interventions. In the United States, for example, in the face of a strong push for deregulation by providers and patient activists, the FDA is reviewing its regulations on human cell and tissue products. This comes at a time when so-called "right to try" laws designed to weaken federal oversight of the sale of products to terminally ill patients have been passed in the majority of U.S. States[29], and the newly enacted federal 21st Century Cures Act, has included provisions for accelerating approvals of cell biologics[30]. New laws passed in Japan to stimulate the regenerative medicine industry through the introduction of conditional approvals (effectively shifting efficacy testing to a post-market context)[31] have also had a major impact on discussions of how new stem cell-based products should be regulated.

Current trends toward ever greater ‘acceleration’ of medical approvals are a cause for concern given the limits they inevitably impose on premarket testing and the new ethical and legal questions they raise. While medical product deregulation may promote access to interventions via a market model, there are accompanying risks to the health and economic well-being of patients. In under-regulated markets or those in which direct-to-consumer marketing goes unchecked, patients are obliged to make healthcare decisions without access to reliable information. Furthermore, providers may not be held accountable for the validity of their therapeutic claims, thereby increasing physical, emotional and financial risks to patients and their families. When individuals spend their limited dollars on ineffective therapies, that expenditure comes at the cost of alternative effective therapies and other activities that could improve their quality of life; thus, patients purchasing inefficacious treatments might forego effective care. Further, under-regulated markets make it difficult for experts and non-experts to seek and evaluate information about competing claims. Even within regulated markets, health care is characterized by a high degree of information asymmetry, in which consumers must rely on providers’ expert knowledge. Under-regulated health markets in contrast permit a lack of reliable information on both sides of the equation (a ‘symmetry of ignorance’) that can be profitable to sellers without conferring utility to buyers. Such deficits severely limit both the opportunity for patients to make informed decisions and the incentives for investment in the development of definitive clinical evidence. Deregulation exacerbates these problems and thus increases the likelihood of the wasteful allocation of limited health care resources.

Time to act

What then is to be done? Clearly, mutual engagement across a broad range of stakeholders is needed to foster regulatory frameworks that facilitate progress in medical research and ultimately affordable clinical benefit. Uncontrolled advertising and delivery of stem cell interventions for which no evidence or proven rationale exists risks stem cell medicine becoming identified as just another instance of commercialization outpacing evidence. The situation is further complicated by jurisdictional limits on the ability to control cross-border trade in health services[32]. If the enormous public investment into stem cell research and development, and indeed its real therapeutic potential, is not to be squandered, it is important that healthcare systems are structured in ways that incentivize scientifically grounded, clinically meaningful and valuable innovation while curtailing exploitative practices.

Recent history provides several examples of successful responses against direct-to-consumer stem cell marketers. Journalistic pressure has in some cases been effective in exposing predatory stem cell clinics, leading to the closure of clinics in the United States[33] and Germany[13]. Medical specialties, such as plastic surgery[34]and respiratory medicine[35], have issued position statements highlighting the lack of sufficient evidence to justify routine use of stem cells in these fields, and state licensing boards have taken action in a small number of instances[36]. The Stamina incident, which involved dedicated efforts by biologists, physicians, social science scholars, lawmakers, regulators and the media over several years of often-heated public engagement is a case in point. Scientific experts worked with, and sometimes confronted, the media to get the facts straight on the actual state of the science with respect to the cells purportedly used by the clinic in question. This exposure was critical to successfully guiding the Italian government on how to handle what

appeared to be a surge in patient demand for unproven stem cell interventions. The commitment of experts to public engagement also helped to foster greater public skepticism about therapeutic claims made by the Stamina Foundation. Several leading scientists also made the critical decision to appeal to international colleagues to help them in taking a stand. After nearly five years, their advocacy efforts resulted in the closure of the clinic.

National efforts, while critically important, cannot alone succeed in countering the activities of a transnational industry. The effectively borderless nature of the Internet, the ease of international travel, and jurisdictional limits on extraterritorial enforcement all create windows of opportunities for clinics targeting patients across national boundaries. International research and medical organizations can play vital roles in supporting the work of local colleagues, but also in setting consensus regulatory and practice standards, driving evidence development, and facilitating the exchange of information among stakeholder groups. To date, organizations dedicated to stem cell and cell therapy research have taken the lead in global coordination, but recent surveys of the global stem cell marketing industry suggests that much work remains to be done. Proactive efforts should now be implemented by organizations with broad constituencies, such as the World Health Organization, in ways sketched out in Figure 1.

Standards-setting is as important in science regulation as it is in scientific research, but regulations over the use of stem cells in medicine appear to be diversifying at the global level. Approaches to international regulation need not only to develop consistent rules over the commercialization of medical practice and products, but to

give them teeth by developing cross-border partnerships for compliance. Consensus building and the inclusive consolidation of regulatory norms may best be facilitated by global agencies with the breadth of perspective and authority to coordinate and reconcile divergent interests. We note that international harmonization by professional, industry and other stakeholder groups has been broadly effective in the regulation of small-molecule drugs and biotechnologies, but this remains underdeveloped with respect to cellular therapeutics, which could similarly benefit from consensus medical practice standards, harmonization of market approval pathways, and resource-building for the development and enforcement of local regulations.

However, the need for global conformity should not preclude the option of local action where the opportunity arises. Given the time it takes to achieve consensus on regulatory issues, this would allow local jurisdictions to act to protect the interests of their citizens, while bringing them into line with a more globally harmonized framework subsequently. The globalization of health markets, and the specific tensions surrounding stem cell research and application have made this a difficult challenge. But the stakes are too high not to take a united stance.

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