



The stem cell market and policy options: a call for clarity

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INTRODUCTION

The field of regenerative medicine is widely viewed as having the potential to improve treatment options for a broad range of conditions. Stem cell research in particular has been celebrated for its considerable clinical promise. Although measured enthusiasm surrounding this area of research is warranted, it must be balanced by patience and set in the context of a long-term perspective that is cognizant of the many steps required to bring safe and efficacious therapies to market. Creating therapeutic applications of stem cell technologies is an intricate process involving complex biology. It will require careful scientific investigation and evaluation under responsible ethical frameworks and regulatory standards in order to safely maximize their potential. Alongside the many

promising avenues of responsible research currently underway in countries throughout the world, a global market has emerged where a wide range of putative stem cell-based interventions are sold on a direct-to-consumer basis and marketed over the internet.^{1,2,3,4}

In this paper, we discuss a number of concerns associated with this market that stem from a lack of clarity in several key areas, and propose approaches for how they might be remedied. Although we are not the first to identify many of these concerns, their persistence demonstrates the need for clear and concise actions. The market for unproven stem cell-based interventions engages varied interests and crosses different regulatory, research, and clinical domains. We draw on the considerable body of work in this area to highlight the contributing factors to this problem and to facilitate actions to ameliorate some of the most concerning issues. Engaging the different groups and entities that are involved in this space, and clarifying and coordinating their actions, will be critical to the success of policy efforts aimed at mitigating the risks of this market while promoting responsible progress in stem cell research.⁵

Numerous issues and concerns with the market for unproven stem cell-based interventions have been identified. Many for-profit clinics selling unproven stem cell-based interventions directly to patients take advantage of the hyperbole surrounding stem cell research^{6,7,8} to advertise their products and services. In many cases, interventions are sold that have no established biomedical or scientific basis (eg stem cell-based treatments for autism). In other instances, the interventions offered may be rooted in basic scientific findings and preliminary clinical experience, but currently have insufficient formal clinical testing to justify widespread clinical use (eg adipose derived stem cells for treatment of orthopedic injuries). At times, it appears that uncontrolled and non-standardized products are being administered, without credible evidence that the products contain active stem cells or have demonstrated any regenerative effects. In addition to other concerns (eg potential fraud and financial loss), when these unproven interventions are advertised and administered without an adequate evidence base, they risk

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- ¹ Darren Lau et al., *Stem Cell Clinics Online: The Direct-to-Consumer Portrayal of Stem Cell Medicine*, 3 CELL STEM CELL 591–94 (2008).
 - ² Alan C. Regenberget al., *Medicine on the Fringe: Stem Cell-Based Interventions in Advance of Evidence*, 27 STEM CELLS 2312–19 (2009).
 - ³ Ruairi Connolly, Timothy O'Brien & Gerard Flaherty, *Stem Cell Tourism – A Web-Based Analysis of Clinical Services Available to International Travelers*, 12 TRAVEL MED. INFECT. DIS. 695–701 (2014).
 - ⁴ Israel Berger et al., *Global Distribution of Businesses Marketing Stem Cell-Based Intervention*, 19 CELL STEM CELL 158–62 (2016).
 - ⁵ Judy Illes & Fabio Rossi, *Seeking Evidence for Efficacy of Stem Cell Interventions - A Collaborative Conference among Researchers, Ethicists, Clinicians, and Providers*, Sept. 26, 2018, University of British Columbia.
 - ⁶ Timothy Caulfield et al., *Confronting Stem Cell Hype*, 352 SCIENCE 776–77 (2016).
 - ⁷ Kalina Kamenova & Timothy Caulfield, *Stem Cell Hype: Media Portrayal of Therapy Translation*, 7 SCI. TRANSL. MED. 278ps4 (2015).
 - ⁸ National Health Service (NHS), *Hope and Hype; An Analysis of Stem Cells in the Media. A Behind the Headlines Special Report* (2011), https://www.nhs.uk/news/2011/11November/Documents/hope_and_hype_1.0.pdf (accessed Feb. 28, 2018).

causing serious injury to patients and violating professional and legal standards.^{9,10,11} For example, recent reports of adverse results include lesions of the spinal cord¹² and retinal detachments following intraocular injection of adipose-derived stem cells.¹³ A comprehensive analysis of reported adverse events from patients who received unproven stem cell-based interventions published in 2018 details 35 cases of acute or chronic complications or death, emphasizing the potentially serious consequences of these unproven interventions.¹⁴

Early research investigating this global online direct-to-consumer marketplace for purported stem cell interventions revealed a preponderance of clinics in China, India, and Mexico.^{15,16} More recent research documents a growth of the market in such countries as the United States, Canada, Australia, and Japan.^{17,18,19,20} For example, one empirical study of the US direct-to-consumer marketplace for unproven stem cell interventions found over 350 businesses marketing putative ‘stem cell treatments’ for a wide range of diseases and injuries, and a recent update describes 716 clinics operating in 45 of the 50 US states.²¹ The risks associated with different supposed stem cell-based interventions available on the private market vary tremendously and depend on numerous factors including the source and type of cells used; the quality of harvesting and processing procedures and facilities; levels of procedural reproducibility and quality control; the manner and site of cell administration; the training and expertise of the health care team and the degree and quality of post-procedure care and follow-up.

Leading scientific bodies such as the International Society for Stem Cell Research (ISSCR) have made important strides in developing voluntary guidelines for stem cell research and clinical translation pathways.²² However, as the global market for stem cell interventions continues to expand and diversify, it is increasingly difficult to draw sharp

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- ⁹ George Q. Daley, *Polar Extremes in the Clinical Use of Stem Cells*, 376 NEW ENG. J. MED. 1075–77 (2017).
- ¹⁰ International Society for Stem Cell Research, *Guidelines for Stem Cell Research and Clinical Translation*, <http://www.isscr.org/docs/default-source/all-isscr-guidelines/guidelines-2016/isscr-guidelines-for-stem-cell-research-and-clinical-translation.pdf?sfvrsn=4> (accessed Jan. 3, 2018).
- ¹¹ Claire Horner et al., *Can Civil Lawsuits Stem the Tide Of Direct-To-Consumer Marketing of Unproven Stem Cell Interventions*, 3 REGEN. MED. 5 (2018).
- ¹² Aaron L. Berkowitz et al., *Glioproliferative Lesion of the Spinal Cord as a Complication of “Stem Cell Tourism”*, 375 NEW ENG. J. MED. 196–98 (2016).
- ¹³ Steven S. Saraf et al., *Bilateral Retinal Detachments After Intravitreal Injection of Adipose-Derived ‘Stem Cells’ in a Patient With Exudative Macular Degeneration*, 48 OPHTHALMIC SURG. LASERS IMAGING RETINA 772–75 (2017).
- ¹⁴ Gerhard Bauer, Magdi Elsallab & Mohamed Abou-El-Enein, *Concise Review: A Comprehensive Analysis of Reported Adverse Events in Patients Receiving Unproven Stem Cell-Based Interventions*, 7 STEM CELLS TRANSL. MED. 676–85 (2018).
- ¹⁵ Lau et al., *supra* note 1, at 6 (Supp).
- ¹⁶ Regenberget al., *supra* note 2, at 2313.
- ¹⁷ Berger et al., *supra* note 4.
- ¹⁸ Megan Munsie et al., *Open for Business: A Comparative Study of Websites Selling Autologous Stem Cells in Australia and Japan*, 12 REGEN. MED. 777–90 (2017).
- ¹⁹ Alison K McLean, Cameron Stewart & Ian Kerridge, *Untested, Unproven, and Unethical: The Promotion and Provision of Autologous Stem Cell Therapies in Australia*, 6 STEM CELL RES. THER. 12 (2015).
- ²⁰ Misao Fujita et al., *The Current Status of Clinics Providing Private Practice Cell Therapy in Japan*, 11 REGEN. MED. 23–32 (2016).
- ²¹ Leigh Turner & Paul Knoepfler, *Selling Stem Cells in the USA: Assessing the Direct-to-Consumer Industry*, 19 CELL STEM CELL 154–57 (2016); see also Leigh Turner, *The US Direct-to-Consumer Marketplace for Autologous Stem Cell Interventions*, 61 PERSP. BIOL. & MED. 7–24 (2018).
- ²² International Society for Stem Cell Research, *supra* note 10, at 1922.

lines between what may constitute responsible and ethical instances of medical innovation,^{23,24} and activities that are clearly unethical because of the inappropriate personal financial burden they may create for the patient, the risks they pose, the uncertainties about their risks, or the lack of any potential benefits. This murkiness and the growing difficulties associated with identifying clear ‘red flags’ of problematic commercial activity creates challenges for prospective patients, health care providers, and regulators alike.

We suggest that there is a need for policy makers and stakeholders to focus on achieving informational clarity about stem cell interventions in three key and interconnected areas, each of which carries different responsibilities for those involved: (i) with regulation that is clear and comprehensive, as well as consistently and robustly enforced; (ii) with scientific and clinical transparency, and (iii) with patient communication and engagement strategies that prioritize informed decision-making, accurate representations, and realistic expectations. Improvements in each of these domains depends on progress in the others. Effective regulation requires scientific and clinical precision. Similarly, truly informed decision-making by patients demands a clear understanding of scientific and clinical realities, while responsible scientific and clinical progress is facilitated by clear and consistent regulation that oversees the production of a high-quality product, thus improving reliability, patient confidence, and decision-making. We situate our analysis and recommendations largely in the Canadian and US contexts. In both countries, we see opportunity for timely, strategic interventions to restrict proliferation of the most egregious and concerning forms of this market. We also note however that the global nature of this market demands an important role for international cooperation and coordination.

I. REGULATORY CLARITY AND SPECIFICITY

First and foremost, it is imperative that regulatory bodies maintain clear, comprehensive, and transparent governance frameworks for therapeutic cell-based interventions, and enforce those frameworks in a robust and consistent manner. Gaps in oversight and ambiguity regarding how regulations should be interpreted and applied can create regulatory gray zones. These gray zones then create space for the spread of potentially risky and/or ineffective interventions. We will address three key areas of regulatory authority and identify where there are opportunities to clarify how existing rules apply to unproven stem cell-based interventions. This clarification will be a critical component of regulatory certainty and effective enforcement.

National regulators such as the US Food and Drug Administration (FDA) and Health Canada have a central role to play in governing drugs, biologics, and medical devices, including human cells and tissues.²⁵ However, gaps have been noted regarding how current frameworks apply to some types of cell-based therapies. For example, in Canada there is ambiguity surrounding permissible applications of minimally

²³ Olle Lindvall & Insoo Hyun, *Medical Innovation Versus Stem Cell Tourism*, 324 *SCIENCE* 1664–65 (2009).

²⁴ Margaret Elizabeth Sleeboom-Faulkner, *The Large Grey Area Between ‘Bona Fide’ and ‘Rogue’ Stem Cell Interventions — Ethical Acceptability and the Need to Include Local Variability*, 109 *TECHNOL. FORECAST. SOC. CHANGE* 76–86 (2016).

²⁵ Sowmya Viswanathan & Tania Bubela, *Current Practices and Reform Proposals for the Regulation of Advanced Medicinal Products in Canada*, 10 *REGEN. MED.* 647–63 (2015).

manipulated autologous cell therapies for homologous use—a common application advertised in the private stem cell market—and how existing frameworks are monitored and enforced.²⁶ In the USA, the FDA has been fairly public with its struggle to facilitate innovation while constraining high-risk interventions.^{27,28} It has recently released guidance on how minimal manipulation and homologous use²⁹ and the same surgical procedure exceptions³⁰ should be interpreted. Punctuated by reports of enforcement,^{31,32} including the FDA's May 2018 decision to seek injunctions against two stem cell clinics,³³ these efforts are promising and may provide much needed clarity. Nonetheless, their impact on the growing commercial marketplace for stem cell-based interventions in the US remains to be seen. Health Canada has yet to release any similar official policy on this issue, but is reportedly taking steps to investigate potentially problematic clinics.³⁴

Although the fast-moving nature of this field may present regulatory challenges—including resource limitations that may influence regulators to focus enforcement efforts on particularly high-risk activities—such challenges are not unique to the stem cell context. Regulation by agencies such as the FDA and Health Canada is often rightly described as a means of protecting patients from unsafe or ineffective interventions. But it is important to note that such regulation is also a crucial framework for encouraging high-value innovation by requiring that rigorous research be conducted to study the effects of technologies.³⁵ Although such research

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- ²⁶ Jolene Chisholm et al., *Workshop to Address Gaps in Regulation of Minimally Manipulated Autologous Cell Therapies for Homologous Use in Canada*, 19 CYTOTHERAPY 1400–11 (2017).
- ²⁷ Food and Drug Administration (FDA), *Statement from FDA Commissioner Scott Gottlieb, M.D. on the FDA's New Policy Steps and Enforcement Efforts to Ensure Proper Oversight of Stem Cell Therapies and Regenerative Medicine*, <https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm573443.htm> (accessed Jan. 3, 2018).
- ²⁸ Peter Marks & Scott Gottlieb, *Balancing Safety and Innovation for Cell-Based Regenerative Medicine*, 378 NEW ENG. J. MED. 954–59 (2018).
- ²⁹ Food and Drug Administration (FDA), *Regulatory Considerations for Human Cells, Tissues, and Cellular and Tissue-Based Products: Minimal Manipulation and Homologous Use - Guidance for Industry and Food and Drug Administration Staff*, <https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/UCMS85403.pdf> (accessed Jan. 3, 2018).
- ³⁰ Food and Drug Administration (FDA), *Same Surgical Procedure Exception under 21 CFR 1271.15(b): Questions and Answers Regarding the Scope of the Exception - Guidance for Industry*, <https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-bio-gen/documents/document/ucm419926.pdf> (accessed Jan. 3, 2018).
- ³¹ Food and Drug Administration (FDA), *FDA News Release: FDA Warns US Stem Cell Clinic of Significant Deviations*, <https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm573431.htm> (accessed Feb. 28, 2018).
- ³² Food and Drug Administration (FDA), *Warning Letter: American CryoStem Corporation 1/3/18*, <https://www.fda.gov/ICECI/EnforcementActions/WarningLetters/ucm591225.htm> (accessed Feb. 28, 2018).
- ³³ Food and Drug Administration (FDA), *FDA News Release: FDA Seeks Permanent Injunctions Against Two Stem Cell Clinics*, <https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm607257.htm> (accessed Aug. 22, 2018).
- ³⁴ CBC News, *Health Canada Investigates Canadian Stem Cell Clinics* (2017), <http://www.cbc.ca/news/health/second-opinion170909-1.4281703> (accessed Jan. 3, 2018).
- ³⁵ Rebecca S. Eisenberg, *The Role of the FDA In Innovation Policy*, 13 MICH. TELECOMM. & TECH. L. REV. 345–88 (2007). See also DANIEL CARPENTER, REPUTATION AND POWER: ORGANIZATIONAL IMAGE AND PHARMACEUTICAL REGULATION AT THE FDA (2010).

takes time, federal regulators have considerable expertise and experience in addressing questions of access to novel therapeutics and in facilitating patient access to promising unapproved products outside of clinical trials.³⁶ Ideally, these expert regulators will accept the challenge of providing clear and unequivocal leadership in this field, helping to encourage the creation of truly beneficial therapies as the field continues to develop. Even with such efforts, national agencies such as the FDA and Health Canada cannot solve this issue alone. Additional regulatory support is needed.

For example, professional regulatory bodies such as the colleges of physicians and surgeons across Canada and state medical boards in the USA are of central importance when it comes to setting and enforcing standards of practice for medical professionals and providing policy advice to their members. Given that physicians licensed by these bodies are major participants in this market,³⁷ there is a need for these authorities to provide guidance to their members regarding what is and is not acceptable practice when it comes to stem cell-based interventions, and to sanction members who demonstrate unprofessional conduct.³⁸ Such disciplinary action could include fines, restrictions, suspensions, or revocation of licenses, depending on the extent to which standards of practice have been violated and the specific rules of the particular jurisdiction.

In general, professional regulatory bodies in Canada and the USA have yet to take a proactive approach to addressing the potentially problematic conduct of their members who are advertising and/or providing unproven stem cell-based interventions. We also have yet to see them take a leadership role in terms of providing advice or setting policy in relation to this specific issue.³⁹ In some cases, policies developed to govern the integration of complementary and alternative medicine into traditional medical practice may serve as useful precedent for policy development in this area, particularly where they focus on rigor in practice and professional responsibility. For example, the College of Physicians and Surgeons of Ontario's Policy Statement addressing complementary and alternative medicine confirms that physicians' practice must be informed by science and evidence, prohibits exploitation of patients, requires physicians to practice within the limits of their knowledge, skill, and judgement and in the scope of their clinical competence, and states that 'Physicians must never inflate or exaggerate the potential therapeutic outcome that can be achieved ... or make claims regarding therapeutic efficacy that are not substantiated by evidence'.⁴⁰ Setting out similar requirements with respect to stem cell-based interventions could provide helpful clarity to physicians engaging in these practices.

³⁶ Patricia Zettler, *Compassionate Use of Experimental Therapies: Who Should Decide?*, 7 EMBO MOL. MED. 1248–50 (2015).

³⁷ Blake Murdoch, Amy Zarzeczny & Timothy Caulfield, *Exploiting Science? A Systematic Analysis of Complementary and Alternative Medicine Clinic Websites' Marketing of Stem Cell Therapies*, 8 BMJ OPEN e019414 (2018).

³⁸ Amy Zarzeczny et al., *Professional Regulation: A Potentially Valuable Tool in Responding to "Stem Cell Tourism"*, 9 STEM CELL REP. 379–84 (2014).

³⁹ This inaction lays in contrast, for example, to the leadership a number of professional regulatory bodies in Canada demonstrated in relation to the so-called 'Liberation Therapy' or 'CCSVI' treatment for multiple sclerosis by providing guidance to their members. For example, see The College of Family Physicians of Canada, *Advisory to Members Regarding CCSVI and MS*, June 29, 2011, https://www.cfpc.ca/Advisory_to_members_regarding_CCSVI_and_MS/ (accessed Aug. 22, 2018).

⁴⁰ For example, see College of Physicians and Surgeons of Ontario (CPSO), *Complementary and Alternative Medicine - Policy #3-11*, https://www.cpso.on.ca/uploadedFiles/policies/policies/policyitems/complementary_med.pdf, at 5 (accessed Jan. 3, 2018).

In an example of promising developments along these lines, the Federation of State Medical Boards in the USA recently created the Workgroup to Study Regenerative and Stem Cell Therapy Practices which has developed several recommendations for state medical boards. Among these, state medical boards are encouraged to better inform licensees of existing and pending laws and policies governing clinical stem cell research and treatment, and to proactively monitor FDA warnings and investigate such practices including the review of marketing materials and claims about stem cell therapies.⁴¹ It remains to be seen how far state medical boards will go in terms of operationalizing these recommendations, but they nonetheless mark encouraging progress.

Consumer protection and advertising standards are another, as-yet underutilized, avenue of enforcement with considerable potential.^{42,43,44} Many countries, including Canada and the USA, have existing laws and policies that set standards regarding how products and services can be advertised to consumers. For example, in Canada, claims that are false or misleading in a material respect can lead to criminal or civil liability.⁴⁵ While there may admittedly be enforcement challenges associated with the cross-border and online nature of much of the advertising of stem cell-based interventions available on the private market, coordinated efforts (such as Operation Pangea which is coordinated by INTERPOL to target online sales of illegal medicines: <https://www.interpol.int/Crime-areas/Pharmaceutical-crime/Operations/Operation-Pangea>) and vigorous enforcement of existing standards could play a meaningful role in challenging potentially problematic marketing practices in this field. Where claims made on the websites of clinics operating in Canada⁴⁶ run afoul of consumer protection legislation (eg because their claims of effectiveness or of being risk-free are scientifically inaccurate, exaggerated, false, and/or misleading), authorities can require they be removed and impose additional penalties. This type of active enforcement would not only remove problematic advertising from the public realm but perhaps serve as a deterrent to other similar practices.

Unfortunately, we still await robust enforcement from either the Competition Bureau in Canada or the Federal Trade Commission in the USA. Recognizing the realities of limited resources, it may be that advocacy from invested stakeholders including medical professionals will be required to help make this issue a priority area. As a valuable first step the Competition Bureau could, for example, issue a Bulletin to provide clarity about the legal requirements for advertisements of stem cell products and services, focusing on what may be considered false or misleading advertising with particular emphasis on online communications, and noting potential sanctions. An official statement

⁴¹ Federation of State Medical Boards, *Regenerative and Stem Cell Therapy Practices; Report and Recommendations of the Workgroup to Study Regenerative and Stem Cell Therapy Practices*, Apr. 2018, <http://www.fsb.org/globalassets/advocacy/policies/fsmb-stem-cell-workgroup-report.pdf> (accessed June 5, 2018).

⁴² Barbara von Tigerstrom, *Regulating the Advertising and Promotion of Stem Cell Therapies*, 12 *REGEN. MED.* 815–26 (2017).

⁴³ Ubaka Ogbogu, *Combatting Unlicensed Stem Cell Interventions Through Truthful Advertising Law: A Survey of Regulatory Trends*, 9 *MCGILL L. J.* 311–35 (2016).

⁴⁴ Murdoch et al., *supra* note 37, at 8.

⁴⁵ Competition Act, R.S.C., c. C-34 (1985).

⁴⁶ Ubaka Ogbogu, Jenny Du & Yonida Koukio, *The Involvement of Canadian Physicians in Promoting and Providing Unproven and Unapproved Stem Cell Interventions*, 19 *BMC MED. ETHICS* 32 (2018).

of this nature could encourage those already engaged in this kind of marketing to modify their behavior and perhaps serve as a deterrent to others. Even if not, it may serve as a useful resource for health care providers and others seeking to provide accurate information to support informed decision-making by their patients, as discussed more in Section III.

II. SCIENTIFIC AND CLINICAL SPECIFICITY AND TRANSPARENCY

The development and application of reasonable, evidence-based policy and regulatory instruments for any field requires a clear and broadly shared understanding of what, precisely, is being governed. As we will address below, specificity and transparency must be promoted within scientific and clinical communities, and facilitated via use of consistent terminology and meaningful reporting processes, robust peer review, and appropriate identification and oversight of clinical research. These demands have both internal implications for individual practice and external demands for how those practices are communicated to broader scientific and regulatory communities.

First, it is essential that stem cell researchers and those engaged in responsible clinical translation develop and use accurate terminology that describes, specifies, and distinguishes the active cellular components and products that are used.⁴⁷ An example would be the terminology (eg HPC, Apheresis and HPC, Marrow) developed by the Foundation for the Accreditation of Cellular Therapy (FACT) and the Joint Accreditation Committee ISCT-EBMT (JACIE) to describe products containing hematopoietic stem and precursor cells used for marrow regeneration.⁴⁸ While the biologically relevant active cellular component is similar in both products, other cellular components in the grafts differ and this results in different outcomes after transplantation.⁴⁹ Unfortunately, although naming conventions provide important detail that furthers scientific and clinical understanding and consistency, in some instances they are also highly complex and still evolving, with gaps in definition and lack of coordinated application.⁵⁰ It is important that those engaged in providing stem cell interventions in a clinical context are as transparent as possible with the details of their treatment protocols and results,⁵¹ and that they comply with the relevant naming conventions.

Separate from disclosure obligations to patients which are discussed in the next section, this transparency within scientific and clinical communities, and with regulatory bodies, is critical both for ensuring compliance with appropriate regulatory standards and for contributing to advancing knowledge and practice in this field. Nonetheless, at present this degree of specificity and transparency is not common practice among private market providers. Many of the products used, such as adipose-derived cell products

⁴⁷ Chisholm et al., *supra* note 26.

⁴⁸ Foundation for the Accreditation of Cellular Therapy, *Establishing Global Standards in Cellular Therapies*, <http://www.factwebsite.org/Standards/> (accessed Aug. 29, 2018); see also ISBT, *Standard Terminology for Medical Products of Human Origin*, <https://www.iccbba.org/tech-library/iccbba-documents/standard-terminology> (accessed Aug. 29, 2018).

⁴⁹ Udo Holtick et al., *Comparison of Bone Marrow Versus Peripheral Blood Allogeneic Hematopoietic Stem Cell Transplantation for Hematological Malignancies in Adults - A Systematic Review and Meta-analysis*, 94 CRIT. REV. ONCOL. HEMATOL. 179–88 (2015).

⁵⁰ For example, see C. Fred LeMaistre et al., *Standardization of Terminology for Episodes of Hematopoietic Stem Cell Patient Transplant Care*, 19 BIOL. BLOOD MARROW TRANSPLANT 851–57 (2013).

⁵¹ International Society for Stem Cell Research, *supra* note 10, at 18, 24.

from liposuction, are complex mixtures of cells with potential variation and uncertainty regarding whether and to what degree the products actually contain active stem cells. Increasing the reproducibility (such that products can routinely and reliably be replicated) and the efficacy of such interventions requires that providers be able to identify the active cells and quantify the activity of functional components, as well as evaluate and standardize the optimal dose necessary to achieve the intended results. It is incumbent upon any provider who purports to be engaged in responsible, ethical practice to meet these standards. Recognizing that there may be no inherent incentive for businesses that profit from the sale of stem cell interventions to modify their current practices and enhance transparency, it is also the responsibility of regulators to exercise their powers of oversight to ensure compliance. For example, private market providers may be encouraged to comply if their medical licenses were at risk, or if they faced fines or other sanctions pursuant to federal regulatory oversight such as from Health Canada or the FDA. Governments also have a direct role to play by ensuring regulatory bodies are appropriately resourced so that they can fulfill their mandates and provide this necessary oversight.

Second, though admittedly not without its flaws and limitations,⁵² publishing in high-quality, peer-reviewed journals is perhaps the most well-established and broadly accepted avenue in scientific fields for promoting transparency and enabling reproducibility of study methods. One challenge to achieving transparency via publication in reputable academic journals is the emergence of journals (sometimes referred to as 'predatory journals') that do not provide legitimate peer review or editorial oversight, among other deficiencies in quality control.^{53,54,55} Unfortunately, these publication venues can be used as 'tokens of scientific legitimacy' by providers of unproven interventions seeking to artificially enhance the credibility of their products and services.⁵⁶ Publications which lack robust quality control standards are a threat to transparency and trust in the scientific process.⁵⁷ Although this challenge cuts across various disciplines, in this context the primary concern relates to the potential that patients (and perhaps others including health care providers) will be misled about the actual state of the science and its readiness for routine clinical application. As such, members of scientific and clinical communities must do their part to control this risk by being vigilant about their own publication practices and by being prepared to explain the implications of deficient practices to non-experts seeking information or advice, perhaps in addition to drawing attention to misleading articles. Recent enforcement activities by the US Federal Trade Commission alleging deceptive practices by several publishing groups⁵⁸

⁵² David Robert Grimes, Chris T. Bauch & John P.A. Ioannidis, *Modeling Science Trustworthiness Under Publish or Perish Pressure*, 5 R. SOC. OPEN SCI. 171511 (2017).

⁵³ Robert E Bartholomew, *Science for Sale: The Rise of Predatory Journals*, 107 J. R. SOC. MED. 384–85 (2014).

⁵⁴ Jeffrey Beall, *Criteria for Determining Predatory Open-Access Publishers* (3rd ed. 2015), <https://beallist.weebly.com/uploads/3/0/9/5/30958339/criteria-2015.pdf> (last visited Feb. 22, 2018).

⁵⁵ David Moher et al., *Stop This Waste of People, Animals and Money*, 549 NATURE 23–25 (2017).

⁵⁶ Douglas Sipp et al., *Marketing of Unproven Stem Cell-Based Interventions: A Call to Action*, 9 SCI. TRANSL. MED. eaag0426 (2011).

⁵⁷ John Bohannon, *Who's Afraid of Peer Review?*, 342 SCIENCE 60–65 (2013).

⁵⁸ Federal Trade Commission, *FTC Halts the Deceptive Practices of Academic Journal Publishers*, <https://www.ftc.gov/news-events/press-releases/2017/11/ftc-halts-deceptive-practices-academic-journal-publishers> (accessed Aug. 22, 2018).

are a promising step towards curtailing this growing problem and protecting the authority of academic publishing such that it can be a reliable resource for health care providers, patients, and their extended networks.

Third, there is a need for greater quality control standards around registering clinical studies and reporting trial results. The public value and utility of the widely used database ClinicalTrials.gov, a resource maintained by the US National Library of Medicine and the National Institutes of Health (NIH), is increasingly compromised by the inclusion of ‘pay-to-participate’ studies, the successful registration of studies of questionable scientific rigor, the listing of studies that do not appear to comply with applicable regulatory standards, and undisclosed conflicts of interest on the part of study investigators.⁵⁹ Once assumed to be a trusted public resource that could be used to distinguish credible clinical trials from other commercial activities, companies engaged in direct-to-consumer advertising of unproven stem cell-based interventions are increasingly using ClinicalTrials.gov to register ‘pay-to-participate’ clinical studies of questionable ethical, scientific, and legal standing.⁶⁰ Because the US National Library of Medicine (NLM) does not carefully screen clinical studies before they are registered and publicly listed on ClinicalTrials.gov, some businesses are using clinical trials as marketing devices and attempting to use ClinicalTrials.gov as an advertising platform to draw prospective clients to their clinics. While ClinicalTrials.gov has increased the visibility of a disclaimer that the NLM does not carefully scrutinize and evaluate studies registered on the database, the inclusion of ‘studies’ of questionable ethical and scientific status makes it increasingly difficult for ill or injured persons, their loved ones, and their health care providers to distinguish facilities providing access to evidence-based stem cell interventions from businesses marketing unlicensed and unproven stem cell products.

Finally, clearer lines need to be drawn around activities that are most appropriately characterized as clinical research, and those falling in the routine standard of care for clinical practice. The drawing of these lines is a shared responsibility between national regulators such as the FDA and Health Canada, professional regulatory bodies such as the colleges of physicians and surgeons in Canada or the state medical boards in the USA, and research ethics oversight. It will require coordination and consistent enforcement. These actions are necessary because in some cases, private market stem cell providers use the experimental or early-stage nature of their work to explain why they do not have approval from the FDA or comparable regulatory bodies. At the same time, others appear to take the position that they are not engaged in research, and therefore do not require research ethics oversight, but rather are selling established interventions—even in the absence of robust evidence of safety and efficacy.

Research involving human participants must be subject to independent oversight, including via Research Ethics Boards, Institutional Review Boards, and ethics committees.⁶¹ It is important these bodies provide truly independent scientific and ethical review of proposed clinical studies and avoid ‘rubber-stamping’ approval of studies of

⁵⁹ Leigh Turner, *ClinicalTrials.gov, Stem Cells and ‘Pay-to-Participate’ Clinical Studies*, 12 *REGEN. MED.* 705–19 (2017).

⁶⁰ Darcy Wagner et al., *Co-opting of ClinicalTrials.Gov by Patient-Funded Studies*, 6 *LANCET RESPIR. MED.* 579–81 (2018).

⁶¹ International Society for Stem Cell Research, *supra* note 10, at 19–22.

questionable scientific and ethical standing. Apart from the research enterprise, new treatments and procedures introduced in clinical practice, including stem cell-based interventions, should meet the standards of professionally regulated accreditation bodies (such as FACT) that use experts involved in the field as inspectors. Similarly, the outcomes of these treatments and procedures should be reported to clinical registries so that ongoing systematic evaluations of short and long-term outcomes are available as quality and safety measures tools—much like the cell therapy and transplant outcome registries⁶²—to ensure that cell-based medical products are still safe and beneficial when used in a broader population. As yet, this does not appear to be common practice among providers of unproven stem cell-based interventions.

III. CLEAR EXPECTATIONS FOR PATIENTS

The complex regulatory, scientific, and clinical challenges described above contribute to what has become a deeply confusing and conflicting pool of information from which individual patients have to make very difficult decisions about their health. Much of the concern surrounding an unchecked market for stem cell-based interventions focuses on the risks such commercial activity poses to the patient community. Indeed, there are concerns relating to physical harm following reports of adverse events^{63,64} and financial risks, given the high reported costs of treatment,⁶⁵ among others (eg emotional, psychological, and familial risks related to anxiety and false hopes). It is often argued that individuals with capacity to make relevant health care decisions have the right to accept such risks, on the condition that they have accurate information and have provided informed consent. However, the ability of patients to exercise autonomy in this sphere can be compromised by misleading, insufficient, or inadequate information. For patients to make autonomous decisions and form realistic expectations, they need appropriate disclosure from providers of stem cell-based interventions, adequate support from their regular physicians, and the tools to evaluate the morass of information available online, including patient testimonials. We address each of these in turn, with accompanying recommendations including guiding strategies for communication and engagement efforts.

The requirement for informed consent plays a central role in health care decision-making in the USA and Canada. However, the ability to provide informed consent requires that competent individuals have access to accurate information to inform their decision. It is particularly important that individuals are informed about the risks and benefits of any intervention, which also requires some understanding of what remains unknown (eg due to lack of evidence). Whether the information provided by clinics selling unproven stem cell interventions meets the requirements for informed consent is questionable. Certainly the extremely positive nature of portrayals on clinic

⁶² For example, the Stem Cell Therapeutic Outcomes Database (SCTOD) which collects data on allogeneic hematopoietic transplants performed in the USA, <https://www.cibmtr.org/About/WhatWeDo/SCTOD/Pages/index.aspx> (accessed Aug. 29, 2018).

⁶³ D. Thirabanasak, K. Tantiwongse & P.S. Thorner, *Angiomyeloproliferative Lesions Following Autologous Stem Cell Therapy*, 21 J. AM. SOC. NEPHROL. 1218–22 (2010).

⁶⁴ Ajay E. Kuriyan et al., *Vision Loss after Intravitreal Injection of Autologous “Stem Cells” for AMD*, 376 NEW ENG. J. MED. 1047–53 (2017).

⁶⁵ Alan Petersen, Kate Seear & Megan Munsie, *Therapeutic Journeys: The Hopeful Travails of Stem Cell Tourists*, 36 SOC.HEALTH ILLN. 670–85 (2013).

websites^{66,67} gives rise to doubt. California, which Turner and Knoepfler's study⁶⁸ identified as a stem cell clinic 'hot spot', enacted a law explicitly requiring health care providers to inform patients when the stem cell interventions they offer are not approved by the FDA and imposing fines for failures to comply.⁶⁹ Although the California law and a similar law passed in Washington⁷⁰ could face First Amendment challenges on the ground that they impermissibly regulate the speech of clinics, the laws may be able to survive such challenges because they require relatively non-controversial, factual, and low-burden disclosures.⁷¹ Moreover, regardless of their ultimate fate, these laws are an encouraging effort to improve the depth and quality of information available to prospective patients, but also suggest current deficiencies in the disclosure practices of at least some stem cell clinics.

While the primary disclosure obligations lie with health care professionals providing stem cell interventions, other health care providers (eg family physicians and specialists who have long-standing care relationships with patients) have important roles and responsibilities here as well. Hope can be an important motivating factor underlying patients' interest in pursuing unproven stem cell-based interventions, particularly where people suffer from life-threatening or chronic conditions for which effective cures and treatments do not exist.^{72,73} Unfortunately, hope can be manipulated and even commodified by those who may profit from desperation. It is important that health care providers do not avoid difficult but realistic conversations about the consequences of unproven therapies out of concern about the potentially damaging effects of destroyed or betrayed hope. Indeed, it is vital that physicians working with patients interested in unproven interventions continue to meet their legal and ethical duties, including beneficence,⁷⁴ by providing accurate, evidence-informed information about the risks and

⁶⁶ Lau et al., *supra* note 1, at 594.

⁶⁷ Ubaka Ogbogu, Christen Rachul & Timothy Caulfield, *Reassessing Direct-to-Consumer Portrayals of Unproven Stem Cell Therapies: Is It Getting Better?*, 8 *REGEN. MED.* 361–69 (2013).

⁶⁸ Turner & Knoepfler, *supra* note 21, at 154.

⁶⁹ Senate Bill (SB) No. 512, *An act to add Section 684 to the Business and Professions Code, Relating to Healing Arts*, ch. 428 Legislative Council's Digest (2017), http://leginfo.legislature.ca.gov/faces/billNavClient.xhtml?bill_id=2017201805B512 (accessed Jan. 3, 2018).

⁷⁰ Stem Cell Therapies – Informed Consent, Engrossed Substitute House Bill 2356, ch. 216, laws of 2018, <http://lawfilesex.leg.wa.gov/biennium/2017-18/Pdf/Bills/Session%20Laws/House/2356-S.SL.pdf> (accessed Aug. 22, 2018).

⁷¹ This may be true even after the US Supreme Court's recent decision in *National Institute of Family and Life Advocates v. Becerra*, striking down a California law that required pregnancy-crisis centers to make certain disclosures about their licensing status and the availability of abortion services elsewhere. 138 S. Ct. 2361 (2018). See also Wendy Parmet et al., *The Supreme Court's Pregnancy Crisis Center Case—Implications for Health Law*, *NEW ENG. J. MED.* (2018), doi: 10.1056/NEJMp1809488 (analysing the implications of *National Institute of Family and Life Advocates* for health-related disclosure laws). For example, the stem cell disclosure laws require clinics to provide information that is far less controversial than the disclosures about abortion services at issue in *Becerra*—meaning the laws may receive deferential review—and the disclosures are less burdensome than the disclosures about crisis centers' licensing status at issue in *Becerra*—meaning the laws may be more likely survive that deferential review.

⁷² Petersen et al, *supra* note 66.

⁷³ Charles E. Murdoch & Christopher Thomas Scott, *Stem Cell Tourism and the Power of Hope*, 10 *AM. J. BIOETHICS* 16–23 (2010).

⁷⁴ Michelle Bowman et al., *Responsibilities of Health Care Professionals in Counseling and Educating Patients With Incurable Neurological Diseases Regarding "Stem Cell Tourism"*, 72 *JAMA NEUROL.* 1342 (2015).

scientific uncertainties of unproven stem cell-based interventions. Any desire physicians may feel to preserve patients' hope does not override the obligation of informed consent, even where meeting that obligation involves providing a patient with information they may not want to hear. Greater guidance from professional and medical associations may be of considerable assistance in clarifying expectations in these contexts.⁷⁵

Clinicians, professional medical societies, patient support communities, and advocacy organizations also have a valuable role to play in helping individuals make informed decisions and in promoting realistic hope, based on credible expectations, rather than hope generated by inaccurate representations about the therapeutic promise of stem cell interventions. Supporting patients in their decision-making process will require—at minimum—better information about what is available as part of the standard of care for their condition(s), about what alternatives there are—including for improving quality of life (respecting differences in values around priorities and perspectives of risk and benefit),⁷⁶ and about what is offered on the private market. Information should be clear and reliable, easy to access and understand, and tailored to the needs and priorities of patients. Given that internet-based recruitment strategies are so common in this market, enhancing the availability of quality information online is critical.

Although some excellent work has been done in this field, research examining online educational content about clinical translation of stem cells suggests that for the most part, accurate, comprehensive information is lacking.⁷⁷ Stem cells feature in online discussions, including on social media,⁷⁸ but there too information is of widely varying quality. For example, patient narratives and testimonials have long played a prominent role in the marketing of stem cell-based interventions and in news stories,⁷⁹ which is concerning given they are often more trusted than other, perhaps more objective sources of information.⁸⁰ Increasingly, patients are turning to crowd funding campaigns to seek financial support in aid of their pursuit of an unproven stem cell-based intervention. These campaigns, which often include compelling personal stories from the prospective patients, demonstrate that direct-to-consumer marketing messages including suspect claims about the efficacy and safety of stem cell interventions are being internalized by individuals seeking care, and in turn they are propagated to larger audiences as these requests for funding are shared on social media.⁸¹ As a powerful marketing tool,

⁷⁵ Jeremy Snyder et al., *Navigating Physicians' Ethical and Legal Duties to Patients Seeking Unproven Interventions Abroad*, 61 CAN. FAM. PHYSICIAN 584–86 (2015).

⁷⁶ Judy Illes et al., *A Blueprint for the Next Generation of ELSI Research, Training, and Outreach in Regenerative Medicine*, 2 REGEN. MED. 21 (2017).

⁷⁷ Zubin Master et al., *Stem Cell tourism and Public Education: The Missing Elements*, 15 CELL STEM CELL 267–70 (2014).

⁷⁸ Julie M. Robillard et al., *Fueling Hope: Stem Cells in Social Media*, 11 STEM CELL REV. 540–46 (2015).

⁷⁹ Amy Zarzeczny et al., *Stem Cell Clinics in the News*, 28 NAT. BIOTECHNOL. 1243–46 (2010).

⁸⁰ Kimberly Sharpe et al., *A Dichotomy of Information-Seeking and Information-Trusting: Stem Cell Interventions and Children With Neurodevelopmental Disorders*, 12 STEM CELL REV. 438–47 (2016).

⁸¹ Jeremy Snyder, Leigh Turner & Valorie A. Crooks, *Crowdfunding for Unproven Stem Cell Procedures Wastes Money and Spreads Misinformation*, STAT NEWS Aug. 6, 2018, <https://www.statnews.com/2018/08/06/crowdfunding-for-unproven-stem-cell-procedures-wastes-money-and-spreads-misinformation/> (accessed Aug. 22, 2018).

testimonials tend to be highly emotive and persuasive,⁸² without necessarily presenting a balanced or entirely accurate picture. Recent research examining crowdfunding campaigns for unproven stem cell interventions reveals these campaigns often underemphasize risks while exaggerating efficacy, and suggests the use of personal narratives may make such claims more forceful.⁸³ They also tend to draw on the marketing tactics of the stem cell businesses that use purported connections to research and leverage the names and reputations of regulatory bodies such as the FDA and the NIH in the USA, in order to enhance the legitimacy and scientific credibility of the stem cell interventions.⁸⁴

These and other examples of inaccurate, exaggerated, or incomplete representations about the state of stem cell research and its clinical applications can mislead the public, raise unreasonable expectations and risk being exploited for financial gain by purveyors of unproven stem cell-based interventions.⁸⁵ An additional element of any communication plan aimed at supporting informed decision-making by patients needs to include practical guidance for critically evaluating the quality and reliability of different kinds and sources of information, including testimonials. Several tools have been developed with this goal in mind, and through sets of quantitative or qualitative criteria, empower Internet users to evaluate the quality of online health information. Examples include the Health on the Net (HON) Code, QUEST, DISCERN, and LIDA tools, to name a few. Health care providers, advocacy groups, patients, and their caregivers may benefit from becoming familiar with and applying these resources. Indeed, health care providers—including primary care providers and specialists—have an important role in assisting their patients who may be considering unproven stem cell-based interventions to critically evaluate information so that they are able to make an informed decision.

In parallel, the research community should continue to closely monitor the emergence of new platforms for information exchange, including social media tools, to understand how they are harnessed by the private market to disseminate both information and misinformation about stem cells, and to examine their role in health decision-making. In addition to measures that focus on informed consent and communication strategies, awareness of and realistic expectations towards stem cell interventions can be improved through engaging patients in legitimate, evidence-based stem cell research. Including patients in all stages of research, from study design to dissemination, may increase their understanding of the research process and of the current state of the science, and facilitate more nuanced evaluation of interventions and information sources.

CONCLUSION

The direct-to-consumer market for unproven stem cell-based interventions and the diverse concerns it raises are now well recognized and have been the subject of considerable attention within the scientific, clinical, academic, and policy spheres. Despite

⁸² Michael D. Slater et al., *A Test of Conversational and Testimonial Messages versus Didactic Presentations of Nutrition Information*, 25 J. NUTR. EDUC. BEHAV. 255–59 (2003).

⁸³ Jeremy Snyder, Leigh Turner & Valorie A. Crooks, *Crowdfunding for Unproven Stem Cell-Based Interventions*, 319 JAMA 1935–36 (2018).

⁸⁴ Jeremy Snyder & Leigh Turner, *Selling Stem Cell ‘Treatments’ as Research: Prospective Customer Perspectives From Crowdfunding Campaigns*, 13 REGEN. MED. 375–84 (2018).

⁸⁵ International Society for Stem Cell Research, *supra* note 10.

varied efforts to limit detrimental effects, the continued expansion of this market indicates more needs to be done. We suggest that many of the most significant challenges and risks associated with this market are propagated by uncertainty, ambiguity, and misinformation. We have argued that there is a pressing need for enhanced clarity on at least three interconnected fronts—regulatory action, scientific and clinical precision, and information-based communication strategies. Confusion, ambiguity, or inaction in any of these areas will impair progress in the others. In our view, enhanced clarity in all of these domains is necessary for the success of future policy efforts targeted at controlling the spread of potentially harmful and/or deceptive practices, while encouraging successful—and responsible—clinical translation of promising avenues of stem cell research.

We also recognize the importance of national and international cooperation.⁸⁶ A global strategy, potentially with the leadership of bodies such as the World Health Organization,⁸⁷ will be necessary for the long-term success of efforts to curtail high risk and problematic private market practices while promoting the enduring health of the field of stem cell research and its social license to operate.⁸⁸ However, the value of pursuing these large-scale goals does not diminish the importance of proactive policy and governance work focused at the local, regional, and national levels. For example, the relatively early stage of the market developing in Canada presents an important and valuable opportunity to take a deliberate, proactive, and informed approach to its oversight and governance.⁸⁹ Such efforts could ultimately serve as useful examples for other jurisdictions to draw upon. Likewise, the US regulatory system is currently being put to the test with increasing pressure on it to respond to the rapidly growing market within its borders. If it rises successfully to the challenge, it could establish important precedent and contribute to setting global standards in this field.

Our call for enhanced clarity and pre-emptive efforts at a number of levels cannot be answered by any one entity in isolation. Rather, it has implications for governments, regulatory bodies, professionals engaged in relevant practice areas including health care providers and scientists, and patient advocacy groups, among others. It is within the power, and responsibility, of those with interests and influence in stem cell research to engage in this important issue and take steps necessary to safeguard the well-being of individual patients, the public more broadly, and the long-term clinical potential of this promising field.

Disclaimers

Zubin Master was part of the Federation of State Medical Boards' Workgroup to Study Regenerative and Stem Cell Therapy Practices. Leigh Turner has submitted an expert

⁸⁶ Douglas Sipp et al, *supra* note 56.

⁸⁷ Tsung-Line Lee et al, *Regulating the Stem Cell Industry: Needs and Responsibilities*, 95 BULL WORLD HEALTH ORGAN 663–64 (2017).

⁸⁸ Giulio Cossu et al, *Lancet Commission: Stem Cells and Regenerative Medicine*, 391 THE LANCET 883–910 (2017).

⁸⁹ For example, see the proposal made by Fabio Rossi & Judy Illes, *A consensus is building on how to move forward on stem cells*, Vancouver Sun Oct. 10, 2018, <https://vancouversun.com/opinion/op-ed/dr-fabio-rossi-and-dr-judy-illes-a-consensus-is-building-on-how-to-move-forward-on-stem-cells> (accessed Oct. 29, 2018).

opinion report, on a pro bono basis, supporting claims of plaintiffs in litigation filed against a stem cell clinic.

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In addition to those listed as authors on this piece, workshop participants included Sarah Benedict; Cécile Bensimon (Canadian Medical Association); Janetta Bilj (Stem Cell Network); Marjorie Bowman (Ottawa Hospital); William Brock (Maryse and William Brock Chair in Applied Research into Stem Cell Transplantation); Benjamin Davis (Multiple Sclerosis Society of Canada); Jo-Anne Kershaw (Local Health Integration Network); Christen Rachul (University of Manitoba); Ian Sadin-sky (stem cell trial participant); Maureen Taylor (Michael Garron Hospital); Lisa Willemse (Ontario Institute for Regenerative Medicine); Terrence Yau (University of Toronto).

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