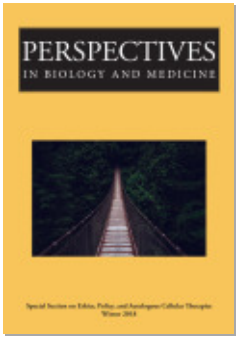
Editors' Introduction to the Special Section on Ethics, Policy, and Autologous Cellular Therapies



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Bioethical, legal, and professional discussions concerning human stem cell science have moved away from the contentious, and possibly irreconcilable, debates about human embryos to other sources of pluripotent stem cells. While there is an array of ethical and legal issues associated with all types of pluripotent stem cells (Sugarman 2008), in recent years complex issues have arisen with regard to the premature use of somatic or "adult" stem cells. Of particular concern is the global emergence of an industry selling products and services marketed as stem cells direct to the consumer, typically over the internet, for a range of serious medical conditions that lack credible evidence of safety and efficacy (Sipp et al. 2017). The worries are that such practices are placing patients at risk of unnecessary harms and are exploiting vulnerable populations with unsubstantiated claims of clinical benefit.

This industry has emerged over the last decade from the edges of medical tourism to penetrate the global marketplace (Regenberg et al. 2009). An international study published by Berger and colleagues (2016) identified 417 unique websites marketing stem cell products and services, with almost half (44.7%) of those being from the United States; the rest were distributed across countries as diverse as India (35), Mexico (28), China (23), Australia (19), the United Kingdom (16), Germany (11), and Japan (4). Other evaluations indicate that these figures are conservative and underestimate the size of the industry. Specifically, a concurrently published study identified 351 websites marketing putative stem cell ther-

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apies at 570 clinics across the United States (Turner and Knoepfler 2016). Both studies found that, where stated, the majority of those clinics are administering autologous stem cells. Unlike allogeneic cells, which come from another donor, autologous stem cells come from the patient who receives them. Furthermore, a comparative study of websites marketing autologous stem cells in Australia and Japan also identified higher numbers than previously reported, with 70 clinics in Australia and 88 in Japan (Berger et al. 2016; Fujita et al. 2016; McLean, Stewart, and Kerridge 2014; Munsie and Pera 2014; Munsie et al. 2017).

In addition to cosmetic applications, the industry is marketing autologous stem cells for serious medical conditions that vary widely, from muscle and tendon injuries and osteoarthritis to heart disease, diabetes, spinal cord injury, and neurological disorders, to name but a few (Berger et al. 2016; Munsie et al. 2017; Turner and Knoepfler 2016). Yet the efficacy and safety profile of many these approaches is not well supported by scientific evidence, nor is the assumption that explanted stem cells can home in and effectively repair tissue damage, which are important components of the rationale for using them (Marks, Witten, and Califf 2017). Even though autologous stem cells lack the safety issues typically associated with the immune-raising responses of allogeniec cells, their clinical use is not without serious risks. Indeed, reports of deaths and severe injuries attest to the need for effective regulation and oversight of this industry (Cyranoski 2010; Freeman 2014; Kuriyan et al. 2017; Lysaght et al. 2017; Tuffs 2010).

Globally, stem cells generally fall within regulatory frameworks for the marketing of biological and drug products. However, within these frameworks are mechanisms that exclude or exempt from regulation certain uses of autologous stem cells within the practice of medicine—for example, rescuing bone marrow function with stem cell transplantation following high-dose chemotherapy for the treatment of blood cancers. These mechanisms vary slightly across international jurisdictions, but in general they have enabled the industry to focus on providing autologous stem cells to patients primarily within the context of private clinical practices, where drug regulators lack authority (Lysaght et al. 2017). However, the clinical use of biological drugs, cells, and tissues, still falls under the governance frameworks that regulate the medical profession (Taylor 2010). And while professional governance bodies in some countries have taken action against practitioners for misleading or outright deceptive claims, the effects of these cases on the industry as a whole seems to be negligible (Lysaght et al. 2017).

Despite the potential impacts of this industry on patients, health-care systems, and public trust in science and medicine, many of the bioethical and regulatory issues related to autologous stem cells remain underexamined (Sipp et al. 2017). This gap prompted us to convene an international research symposium with scholars from multidisciplinary fields in bioethics, law, medicine, philosophy, sociology, and stem cell science. The symposium was held in Singapore in collaboration between the Centre for Biomedical Ethics at the National University

of Singapore, the Johns Hopkins Berman Institute of Bioethics, the Sydney Law School, and the Stem Cell Society, Singapore. We invited six speakers to present original research papers on the ethical, regulatory, and normative implications of the autologous stem cell industry, along with discussants who gave an oral commentary after each presentation. This collection of essays was peer-reviewed for publication in this special section of *Perspectives in Biology and Medicine*.

Innovation, Regulation, and Ethics

The first two essays in this special section focus on the market for autologous stem cells in the US. First, Leigh Turner builds upon the dataset published in Turner and Knoepfler (2016), showing that the number of clinics operating in this market has either grown from previous estimates or has been (and continues to be) underestimated. Turner deepens this anlaysis by drawing out some of the ethical and scientific issues associated with the marketing tactics that some clinics employ to establish credibility in the absence of carefully conducted, peer-reviewed clinical research to support claims of safety and efficacy. Turner also describes a complex regulatory environment in the US that erroneously creates an impression of strict oversight but in reality has many actors at both state and federal levels of governance failing to enforce laws and regulations that exist to protect consumers. These factors, he argues, are complicit in the proliferation of these clinics in the US and in the physical, financial, and psychological harms to which they are exposing patients.

Second, Douglas Sipp focuses on how specific regulations have encouraged the proliferation of clinics marketing autologous stem cells in the US. Sipp draws attention to lawsuits involving an unsuccessful challenge to the authority of the US Food and Drug Administration (FDA) over the sale and marketing of autologous stem cells in the context of medical practice. As the courts have affirmed the FDA's authority over such products that enter "interstate commerce," the industry has taken advantage of other mechanisms to avoid regulation under the FDA. The industry can be seen exploiting regulatory mechanisms such as the "same surgical procedure exemption" and the asymmetrical exclusion of some privately funded research from the "Common Rule" in order to market autologous stem cells direct to consumer with very little oversight, while charging patients to participate as subjects in research. Sipp also identifies the emergent practice of framing autologous stem cell therapies as "personalized" medicine in ways that differ radically from the intended purpose and nature of genomics-driven approaches to health care that use similarly terminology.

The next three essays consider regulatory contexts outside the US. Christine Hauskeller draws on the experience of clinician-researchers navigating the complex framework of the European Medicines Agency (EMA) for Advanced Therapy Medicinal Products (ATMP). Hauskeller reflects on the difficulties faced

by a consortium of clinician-researchers attempting to initiate a large-scale, multinational randomized controlled trial of autologous bone marrow–derived stem cells for acute myocardial infarction. When the framework came into effect, the proposed approach was classified as an ATMP, requiring higher and more costly standards of manufacturing and quality control processes than initial budget projections anticipated. Hauskeller argues that these requirements are undermining the intention of the framework to facilitate the development of innovative stem cell–based therapies, as clinician-led investigations are unable to procure the necessary funding and support without an industry partner. This situation, Hauskeller opines, is restricting clinical trials with promising stem cell–based approaches and pushing patients towards the market for unproven interventions with stem cells.

In the next essay, Tsung-Ling Lee and Tamra Lysaght focus on programs aimed at accelerating the regulatory approval process for novel therapeutics, including autologous stem cells, for patients with unmet medical needs. Drawing on the conditional market approval of two novel autologous stem cell–based products in Japan and Europe, Lee and Lysaght examine the potential benefits and burdens of these programs on patients and health-care systems. They argue that these programs may be inconsistent with the values and normative commitments of public health agencies that are responsible for protecting patients and promoting good health with safe and efficacious therapeutic products. In particular, they focus on how these programs may lower evidentiary standards of evidence for high-cost, novel therapeutics, and burden patients and health-care systems with the uncertainties of drug development without clear benefits for either, which raises important questions of justice. They suggest ways to reconfigure these programs to better align with the normative functions and institutional legitimacy of drug regulatory authorities.

Tereza Hendl's essay turns to Australia, where the regulatory framework allows medical practitioners to administer autologous stem cells to patients without oversight and in the absence of scientific evidence that demonstrates safety and efficacy. To understand the implications of this framework, Hendl applies an existing taxonomy of relational vulnerability that accounts for the social contexts shaping autonomy. She argues that this framework exacerbates the "inherent" vulnerabilities of illness and has generated other "situational" and "pathogenic" vulnerabilities that undermine patient autonomy. As Hendl argues, these vulnerabilities have arisen from a market that exploits patients through morally dysfunctional relationships with medical professionals who are selling potentially ineffective and unsafe stem cell–based interventions. This analysis leads Hendl to urge regulators to reform the current framework to reduce these vulnerabilities and promote patient autonomy.

In the final essay, Lipworth, Stewart, and Kerridge analyze the concept of *innovation*, a term that is sometimes deployed by those marketing autologous stem cell therapies as justification for selling products that lack evidence of safety and

efficacy. They argue that the definition of *innovation* that occurs within clinical contexts, or "clinical innovation," should be value-neutral and separated from moral justifications related to them. That is, the term "clinical innovation" is merely descriptive of activities or products that are new, experimental, unproven, or outside of accepted standards of care; additional justifications are needed to evaluate whether an innovation is ethically appropriate. To support their argument, they propose two normative principles that should be required to justify clinical innovations: beneficence and prudence. Applying these principles, an innovation would only be justifiable when there are commitments to providing benefit—either directly to patients or indirectly through more efficient, cost-effective health systems—as well as harm-minimization through a range of considerations. The authors then situate these and other applicable principles, such as autonomy, justice, and integrity, within a bioethical framework for the regulation and governance of responsible innovation.

From the information provided in this collection of essays, a sizable proportion of the autologous stem cell industry seems not to meet standards of responsible innovation. The collection also suggests that existing institutional and regulatory frameworks are not only failing to encourage responsible innovation with stem cells but may be enabling the growth of an industry that, at best, could be described as nonevidence-based and, at worst, exploitative of vulnerable people. Indeed, appeals to the rhetoric of innovation in the delivery of unproven autologous stem cells takes inappropriate advantage of the blurred boundaries between clinical research, practice, and innovation, and seems to be operating outside of accepted norms and standards for both biomedical research and evidence-based medicine, while charging services fees in accordance with whatever the market can bear. These market-based values treat medicine and health care as mere tradable commodities without moral worth.

Given the high stakes, this is an unfortunate and unjust state of affairs. Governments and other responsible authorities should work to ensure that unproven autologous stem cells are appropriately regulated and overseen. In addition, physicians and other health-care professionals must meet their professional ethical obligations that privilege the well-being of patients. After all, patients deserve medical interventions that are genuinely going to improve their health. With regard to autologous stem cell–based interventions, in clinical practice (outside of a handful of unusual situations), this generally includes having evidence of safety and efficacy or administration in a properly designed and conducted clinical trial.

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