# From Bench to Bedside: Bioethical Issues in the Clinical Implementation of Stem Cell Therapies

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On my honor as a University student, I have neither given nor received unauthorized aid on this assignment as defined by the Honor Guidelines for Thesis-Related Assignments.

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Since the 1960s, the discovery of adult stem cells has fueled an explosion in scientific studies on the use of such cells as therapeutics targeting degenerative diseases, cancer, or other conditions for which there are currently no or limited treatments (Herberts et al., 2011; Pean et al., 2019). In the US, the first company to sell stem cell treatments opened in 2002, and by May 2017, 432 US businesses sold stem cell-based interventions (SCBIs) (Sipp, 2013; Turner, 2018). Food and Drug Administration (FDA) regulations have not kept up with direct-to-consumer (DTC) stem cell innovations, leaving patients at risk from injury and financial exploitation (Knoepfler & Turner, 2018; Taylor-Weiner & Zivin, 2015; Turner & Knoepfler, 2016). Protecting patients involves understanding how various social groups involved in the US DTC adult stem cell industry advance their respective agendas. Participants in the DTC stem cell industry invoke the same set of principles of medical ethics to justify their respective agendas, but place emphasis on different principles to suit their needs. Strategies used include legal action by regulatory agencies, marketing appeals by DTC stem cell clinics, and guidelines publications, regulatory lobbying, and monetary support of institutions by advocacy groups and professional societies.

## Literature Review

The current landscape of the DTC stem cell industry has been shaped by a set of bioethical values that inform the laws, regulations, and agendas that participants in this industry abide by. These bioethical values trace their origin from early codes of modern medical ethics developed in the 1800s and have been used to justify the practice of DTC pharmaceutical advertising in the late 1900s and beyond. Today, these participants emphasize the relative

importance of some bioethical values over others to advance their agendas, illustrating how supposedly universal bioethical tenets can be used to simultaneously support differing agendas.

*The Development of Modern Medical Ethics*

One of the first codes of modern medical ethics was developed by Thomas Percival, an English physician, in the early 1800s to guide the professional conduct of physicians (Baker & Emanuel, 2000). In 1847, Thomas Percival's code was adopted by the American Medical Association (AMA), and violations of this code by member physicians can result in censure or expulsion (AMA, n.d.; Baker & Emanuel, 2000). In 1979, Beauchamp and Childress distilled values present in medical ethics into four tenets – respect for autonomy, beneficence, non-maleficence, and justice (Gillon, 1994). These tenets form a basic moral analytical framework for medical decision making and biomedical research in the US (Gillon, 1994).

The Belmont Report was written in 1978 by the National Commission for the Protection of Human Services of Biomedical and Behavioral Research as an ethical guide to human subjects research (National Commission, 1979). Tom Beauchamp was involved in the drafting of this report as well (Beauchamp & Childress, 2019). The three principles of research ethics identified in the Belmont Report – beneficence, justice, and respect for persons – share the same rhetoric as Beauchamp and Childress' four tenets and informed the development of ideas like informed consent, assessment of risks and benefits, and selection of subjects (Sims, 2010; Rothstein, 2009). The Belmont Report became the basis for federal regulation on human subjects research and established the first Institutional Review Boards (IRBs) (Sims, 2010). Overall, these biomedical ethical principles have been influential in the teaching and evaluation of medical ethical dilemmas and have led to the development of laws regulating research and medical conduct in the US (Rothstein, 2009).

*Patient Autonomy and the Development of Medical Marketing*

DTC pharmaceutical advertising is defined as an effort made by a pharmaceutical company to promote its prescription products directly to patients or providers via television and radio advertisements, print advertisements, or other forms of media (Abel et al., 2006; Ventola, 2011). Unlike most other high-income countries, the US is unique in that it allows DTC pharmaceutical advertising with claims about the safety and efficacy of the product (Ventola, 2011). DTC pharmaceutical advertising has been widespread in the US since the beginning of the sale of pharmaceuticals, and the FDA was first granted regulatory power over DTC pharmaceutical advertising in the 1962 Kefauver-Harris Amendments (Wang & Kesselheim, 2013). Regulations on advertising were loosened in the late 1990s and early 2000s and spending on DTC pharmaceutical advertising increased from less than $1 billion in 1997 to a peak of $5.4 billion in 2006 (Ventola, 2011; Wang & Kesselheim, 2013).

Supporters of DTC pharmaceutical advertising argue that it promotes patient autonomy and patients have a right to health care information (Kravitz & Halpern, 2006). DTC pharmaceutical advertising can educate patients, enable them to take a more active role in their healthcare, and reduce stigma with advertised diseases (Wang & Kesselheim, 2013). However, critics believe that DTC pharmaceutical advertising causes patients to seek unnecessary and expensive treatments and harms the doctor-patient relationship. Unnecessary drug prescribing can indirectly harm public health too (Kravitz & Halpern, 2006). In this debate, respect for patient autonomy conflicts with beneficence and non-maleficence, illustrating how the same general bioethical principles can be applied differently to support different participants' agendas. Pharmaceutical advertising is an important tool in the DTC stem cell industry, as it is frequently employed as a strategy for agenda advancement.

*Current Scientific Basis and Regulatory Status of Adult Stem Cell Therapies*

The primary function of adult stem cells, including mesenchymal/stromal cells (MSCs), endothelial progenitor cells (EPSs), and hematopoietic stem cells (HSCs), in differentiated tissues is to assist in the regeneration of aged or damaged tissues (Herberts et al., 2011). Adult stem cells are found in adipose tissue, neuronal tissue, and bone marrow (McCormick & Huso, 2010). Currently, HSCs are the most widely used type of stem cells in clinical trials and have been primarily used to treat hematologic and lymphoid cancers (Copelan, 2006; Trounson & McDonald, 2015). Clinical trials, the majority of which are in the early phase I/II stage, have also investigated the ability of neural stem cells to treat damaged areas in the central nervous system, EPSs to treat hypertension and heart conditions, and MSCs to treat a variety of conditions throughout the body (Trounson & McDonald, 2015). As of October 2019, the only stem cell products approved by the FDA are treatments for disorders related to blood production that "consist of blood-forming stem cells (hematopoietic progenitor cells) derived from cord blood" (Pean et al., 2019).

However, many stem cell clinics sell therapies using stem cells derived from adipose tissue that are converted to a product called stromal vascular fraction (SVF) (Taylor-Weiner & Zivin, 2015). SVF is produced by collecting lipoaspirate from a patient via liposuction, separating the cells from the surrounding fat, and administering the cells into the patient (Taylor-Weiner & Zivin, 2015). There are presently no FDA-approved devices for SVF production and administration (Turner, 2015). Regenerative medicine products including stem cell products and SVF have also not been approved by the FDA for the treatment of orthopedic conditions, neurologic disorders, cardiovascular or pulmonary diseases, autism, macular degeneration, blindness, fatigue, or chronic pain (FDA, 2020).

**Federal Agencies: Enforcing their Agendas through Regulatory Action**

The FDA protects "the public health by ensuring the safety, efficacy, and security of human and veterinary drugs, biological products, and medical devices" (FDA, 2018). Its core mission reflects concern for public safety through regulation of drugs, medical devices, and clinical trials (Fielder, 2006). Stem cell-based therapies fall under the jurisdiction of the FDA's Center for Biologics Evaluation and Research (CBER) as "human cells, tissues, and cellular and tissue-based products" (HCT/Ps) under the Code of Federal Regulations (CFR) Title 21 Parts 1270 and 1271 (Halme & Kessler, 2006; Reisman & Adams, 2014; FDA, 2021). Under 21 CFR Parts 1270 and 1271, tissue donors must be screened to prevent the spread of communicable disease, HCT/Ps must be registered with the FDA, and good tissue practices must be followed (FDA, 2021). To enforce compliance with its regulations, the FDA can send warning letters, issue injunctions, and pursue prosecution (FDA, 2017).

The FDA protects consumers through education and outreach to the public and legal actions against stem cell clinics that sell unapproved stem cell products. It warns consumers about unapproved stem cell therapies "to protect people from dishonest and unscrupulous stem cell clinics", and states that "unapproved stem cell therapies can be harmful and may be illegal and unproven" (FDA, 2019b). The FDA has also released consumer and public safety alerts on regenerative medicine products, including "stem cell products…or products derived from adipose tissue" (FDA, 2019a, 2020). In 2019, the FDA took judicial action against US Stem Cell Clinic LLC of Weston, Florida and US Stem Cell Inc. of Sunrise, Florida, to stop them from manufacturing or distributing any SVF products due to the two companies' failure to comply with the FDA regulations (Sharpless, 2019). The FDA also asserted that the defendants "adulterated and misbranded their cellular products" (Sharpless, 2019). By acting as a gatekeeper

and regulating consumers' access to safe therapeutics, the FDA promotes its agenda of beneficence and non-maleficence towards the public.

The Federal Trade Commission (FTC) is a federal agency that protects consumers by "stopping unfair, deceptive or fraudulent practices in the marketplace" and promoting competition (FTC, 2013). While the FTC is not explicitly involved in biomedical research and regulation of medical products, its pursuit of its agenda has brought it into conflict with DTC stem cell clinics. In October 2018, the FTC brought charges against Dr. Bryn Jarald Henderson, D.O. and the two companies he owned, Regenerative Medical Group and Telehealth Medical Group, for claiming without evidence that "amniotic stem cell therapy" can treat serious diseases such as Parkinson's disease, cerebral palsy, autism, macular degeneration, and heart attacks (FTC, 2018). In June 2020, the FTC issued warning letters to 35 companies, including Brexo Bio, a stem cell treatment company, for making "unsubstantiated claims that their products and therapies can treat or prevent COVID-19" (FTC, 2020). Like the FDA, the FTC takes legal action to enforce its agenda against direct-to-consumer stem cell companies that do not act in patients' best interests.

**Direct-to-Consumer Stem Cell Clinics: Creating the Appearance of Bioethical Conduct**

DTC stem cell clinics are for-profit enterprises that treat patients with a wide variety of medical conditions. On their websites, DTC stem cell clinics directly advertise to patients and attempt to establish trust through rhetorical language and appeals to scientific credibility. Regenexx is an international network of DTC stem cell clinics based in Colorado (Regenexx, 2021a). On the homepage of its website, Regenexx describes itself as "the trusted alternative to orthopedic surgery" and states that it has "published 44% of all orthopedic-stem-cell research worldwide and holds 15 patents on various Interventional-Orthopedic technologies and

protocols" (Regenexx, 2021b). Regenexx also has an outcome tracker on its website where it tracks joint function improvement, pain decrease, and overall improvement in its patients after stem cell treatment, although there are no clearly visible links to peer-reviewed scientific studies supporting this on the same page. Brexo Bio, another DTC stem cell clinic network in California, claims it is the "premier regenerative medicine resource company" and its slogan is "unlock your cellular potential" (Brexo Bio, 2018). Like Regenexx, Brexo Bio prominently displays links to published research on its website (Brexo Bio, 2018). Brexo Bio claims it helps patients get "access to customized stem cell therapies." In a disclaimer, however, it cautions: "this product is not intended to diagnose, treat, cure, or prevent any disease" (Brexo Bio, 2018). By appealing to scientific credibility, both companies attempt to convince patients of the beneficence of its stem cell therapies. Additionally, by using language like "the trusted alternative to orthopedic surgery" and "customized stem cell therapies", both clinics appeal to patient autonomy by presenting their product as a personalized alternative to invasive procedures.

Despite their outward appearance of credibility, the consistency of DTC stem cell clinic practices with regulatory standards is unclear. Regenexx claims its procedures are exempt from FDA regulation (Regenexx, 2021c). It justifies this with 21 CFR 1271, where "procedures involving minimally manipulated bone marrow for homologous use" and those "involving the removal of an [human cell, tissue, or cellular or tissue-based product (HCT/P)] … and implantation of that same HCT/P back into the same patient in the same surgical procedure are not subject to FDA regulation." The Regenexx-C cultured stem cell procedure is not exempt under 21 CFR 1271 and is not FDA approved, so it is only offered outside of the US in the Cayman Islands (Regenexx, 2021c). Brexo Bio's disclaimer explains its regulatory relationship with the FDA: "treatments are not conducted in our offices or in the US since these advanced

therapies are not yet approved" (Brexo Bio, 2018). Instead, Brexo Bio performs stem cell therapies in Mexico where its treatments are legal. A third DTC stem cell clinic network, Cell Surgical Network (CSN), also states that its stem cell procedures are not FDA approved but fall under "physician's practice of medicine, wherein the physician and patient are free to consider their chosen course of treatment" (CSN, 2018). Like Regenexx, CSN uses the loophole in 21 CFR 1271 to comply with FDA regulations. To work around lack of FDA approval, DTC stem cell clinics exploit regulatory loopholes or perform regulatory shopping, where clinics conduct actual procedures outside the US while recruiting patients from within the US (Sipp, 2013). Even while admitting to the lack of FDA approval and proven clinical efficacy of stem cell therapies, DTC stem cell clinics continue to highlight the cutting-edge nature of their technologies and appeal to patient autonomy while maintaining an appearance of scientific credibility.

Free eBooks are another medium through which DTC stem cell clinics convince and recruit patients. CSN has an eBook called *The Stem Cell Revolution* available for download on its website which does not have any publisher information (CSN, 2018). In this book, the mission of CSN is "to accelerate the quality of regenerative medicine and have safe and cost effective cell based therapies available soon to everyone in the world." Again, the authors reiterate that the therapies offered at CSN are outside the scope of FDA regulation and are completely legal. CSN is also careful to present its therapies as "patient funded research". To convince readers of its trustworthiness, CSN makes a distinction between itself and competing clinics, as other clinics "were located offshore and their quality was perceived as dodgy." CSN also sets itself apart from established medical institutions by disparaging the "million-dollar labs, inaccessible university programs…or bureaucratic obstacles" that standard clinical trials would involve. Through this eBook, CSN responds to critics of DTC stem cell clinics by highlighting

the drawbacks of conventional clinical research strategies and emphasizing how physicians at CSN, unlike physicians elsewhere, are fulfilling their Hippocratic oath through the ethical obligation of offering "a treatment that is apparently safe and effective."

Besides digital advertising, DTC stem cell clinics also use recruitment seminars to promote their agendas. Anecdotal evidence from a researcher attending one such seminar revealed that most attendees were elderly with serious medical conditions and were asked to fill out a personal information sheet with information like name, age, address, and preexisting medical conditions (Knoepfler, 2017). A credit application was included with the form. The presenters, mostly dressed in medical scrubs, made questionable medical claims about the ability of stem cells to fix many conditions and the lack of potential immune rejection in stem cell treatment. They also claimed that the treatment had no side effects and is FDA approved. The presenters used patient x-rays, MRIs, and testimonials to support their claims. While this evidence comes from only one stem cell educational seminar, it suggests that DTC stem cell clinics use similar strategies, such as appeals to scientific credibility and emphasis on positive treatment outcomes, both online and at seminars to convince patients to purchase treatments.

On the surface, DTC stem cell clinics portray themselves as ethical organizations with patient beneficence and autonomy in mind. Brexo Bio, Regenexx, and CSN use the appearance of scientific credibility to persuade patients. They display links to published research and use rhetorical language highlighting the cutting-edge nature of stem cell therapies. DTC stem cell clinics acknowledge that their therapies are clinically unproven and not FDA approved, but reassure patients that they are legal due to regulatory loopholes and regulatory shopping. While these clinics may indeed want the best for their patients, pursuit of profit likely motivates their actions too. Using "patient-funded research" and providing credit applications to prospective

patients ensures that DTC stem cell clinics will be profitable. The relative emphasis that DTC stem cell clinics put on patient autonomy as opposed to non-maleficence and the masking of adverse effects from stem cell therapies helps them achieve their agenda.

**Advocacy Groups and Professional Societies: Diverse Strategies for Diverse Agendas**

The International Society for Stem Cell Research (ISSCR) is a professional society composed of researchers and clinicians in academia and industry. It educates patients and develops guidelines for "an efficient, appropriate and sustainable research enterprise for stem cell research" (ISSCR, 2016). The ISSCR also organizes conferences and meetings on topics like computation stem cell biology and stem cell-based embryo models. The 2016 ISSCR Guidelines for Stem Cell Research and Clinical Translation states that the fundamental ethical principle of biomedical research is "to alleviate and prevent human suffering." These guidelines "build on a set of widely shared ethical principles in science, research with human subjects, and medicine" like the Nuremberg Code and Belmont Report (ISSCR, 2016). The ISSCR is also involved in advocacy too. In 2021, the ISSCR joined a coalition letter making recommendations for National Institutes of Health funding, led a coalition letter to President Biden on Human Fetal Tissue Research, and commented on Hong Kong's Guidance for Cell and Tissue Products (ISSCR, 2021a; ISSCR, 2021b; ISSCR, 2021c). The ISSCR advances its agenda of research safety by publishing guidelines to be adopted by researchers and organizations and lobbying regulatory agencies and government institutions.

The National Stem Cell Foundation (NCSF) is a nonprofit that funds adult stem cell research and connects children with rare diseases to clinical trials. The NCSF collaborates with partner institutions to "maximize donor dollars and speed research" (NCSF, 2020). The NCSF values justice and universal accessibility to treatment, as they help cover treatment costs for

children eligible for clinical trials (NCSF, 2020). To achieve their agenda, the NCSF directly funds chosen institutions and initiatives.

The International Cell Surgical Society (ICSS) is another nonprofit that seeks to advance "the safe and effective use of…SVF as part of the practice of medicine" (ICSS, 2019a). The ICSS promotes its agenda by managing an IRB registered with the Department of Health and Human Services to review proposed clinical studies involving stem cells (ICSS, 2019a). Three of the seven subpages displayed on the ICSS's webpage are titled "Patient Safety", "IRB Process", and "Belmont Report", emphasizing the ICSS's apparent focus on beneficence and non-maleficence. The CSN is a client of the ICSS and a short statement about a published paper by the CSN on the use of autologous SVF appears on the "Patient Safety" subpage of the ICSS's website (ICSS, 2019b). The relationship between the CSN and the ICSS raises doubts over whether the ICSS is an example of astroturfing by the DTC stem cell industry. The ICSS advances its agenda by promoting a DTC stem cell clinic, CSN, and operating its own IRB.

The various advocacy groups and professional societies involved in the DTC stem cell industry have a variety of agendas and strategies. Some like the ISSCR are cautious regarding the clinical translation of stem cell therapies while others like the ICSS are more aggressive. Some like the NCSF do not take a clear stance on the speed of clinical translation of stem cell therapies but advocate for its own specific interests. To accomplish these goals, advocacy groups and professional societies publish guidelines, lobby and fund institutions and organizations, and participate in the research pipeline through IRB review or organizing conferences.

## Conclusion

Within the framework of Beauchamp and Childress' four tenets, DTC stem cell clinics heavily promote respect for patient autonomy whereas regulatory agencies value proven

beneficence and non-maleficence of marketed therapies. Regulatory agencies have come into direct conflict with stem cell clinics over these values. The FDA and FTC have pursued legal action against several stem cell clinics for making false marketing claims about the efficacy and safety of their stem cell products. Advocacy groups and professional societies have a diverse range of agendas and strategies and their views appear to lie on a continuum between supporting regulatory agencies and supporting stem cell clinics. Even though these participant groups have competing agendas and strategies, they motivate their actions with the same four bioethical tenets. The use of the same ethical principles to motivate different courses of action highlights potential flaws of relying on overly generalized ethical or moral codes to guide behavior. When establishing codes of behavior, participants must weigh a balance between universality and specificity to best suit their aims. The DTC stem cell industry also exemplifies internal contradictions within codes of ethics that can undermine its effectiveness in governing behavior.

Establishing a more comprehensive list of DTC stem cell clinics, professional societies, and advocacy groups would be needed to determine whether the trends observed are generalizable. Other categories of participants not directly addressed in this discussion include patients, providers, and professional societies for physicians. Future studies may be directed at how these participant groups interact with regulatory agencies, DTC stem cell clinics, and other professional societies and advocacy groups. Other studies may be directed at examining the trajectory of clinical translation for other therapies, including vaccines or pharmaceutical drugs, and comparing those to the trajectory of stem cell therapies.

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