Curbing the Harm of For-Profit Stem Cell Clinics

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Eirian Crocker
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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

Advisor
Joshua Earle, Department of Engineering and Society

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Introduction

The promises of stem cells for medical care range from a stem cell transplant that would restore the destroyed immune system of cancer patients (Morena & Gatti, 2011), to new organs made from a patient's own cells for a transplant that would not need immunosuppressants (Niklason & Langer, 2001), to stem cells, pulled from adipose tissue removed during liposuction, that could help heal wounds (Cherubino et al., 2011), regrow bone (Storti et al., 2019), or even cure macular degeneration (Leask, 2019). All of these are applications of stem cells that are either actively being researched, have been attempted in humans, or are currently used in patients.

Stem cells, which are cells that can both proliferate to make more of themselves and also differentiate into more specialized progeny, are critical in both the development and maintenance of the human body. Due to their ability to differentiate into many different cell types, the potential of stem cells for modern medicine has rarely been underemphasized. Some treatments, such as bone marrow transplants, have been well established and critical to patient health for decades (Morena & Gatti, 2011). Others are far more experimental. However, stem cell research has grown dramatically, far beyond simply academic research in university labs. In 2018, Paul Knoepfler mapped this changing stem cell ecosystem, as he termed it. Included in his network was a unique group that was also growing quickly: for-profit stem cells clinics selling unproven and improperly regulated stem cell treatments to patients.

I conducted a literature review on for-profit stem cell clinics, regulatory bodies such as the FDA and Institutional Review Boards, insurance companies, and primary care providers roles in misinformation mitigation. I primarily focused on exploring and expanding Paul Knoepfler's

stem cell ecosystem using Actor Network Theory to find ways to reduce the ability of for-profit stem cell clinics to manipulate patients.

Actor Network Theory (ANT) views systems as an interaction of human and non-human actors which each have their own interests. The actors form associations with other actors, and may work together in an alliance if their interests align, or oppose each other if their interests conflict in some way. Importantly, ANT fails to account for systematically excluded groups which have not been allowed to participate in the network and actors which are not central to the network (Sismondo, 2010). This weakness is one which will therefore be transmitted to this analysis as well. By analyzing which actors in the stem cell ecosystem are allies and which work against each other, a better understanding of the dynamics of this system can be achieved.

First, I give an overview of Paul Knoepfler's map of the stem cell ecosystem, with particular focus on his addition of for-profit stem cell clinics and the satellite entities that support them. I then delve deeper into stem cell clinics, noting the expansion of these entities, the danger to patients they represent, and the FDA loophole they frequently (and typically incorrectly) claim to avoid the expensive, lengthy process of acquiring FDA approval for their treatment. I then look at two of the satellite entities surrounding for-profit stem cell clinics: "iffy" IRBs and journals. I found that Knoepfler's network is missing a few key actors, so I then propose a modified model including insurance companies and doctors, describing how each fits into the network. Finally, I explore several solutions to reduce the harm of misinformation and unproven treatments at for-profit stem cell clinics both from a regulatory standpoint and from a patient-facing perspective.

Paul Knoepfler's work

Original Stem Cell Ecosystem

Paul Knoepfler, a researcher at the University of California, Davis School of Medicine, analyzed the groups and interactions involved in the stem cell product ecosystem in a 2018 paper (see figure 1). Originally, the stem cell ecosystem was mainly composed of academia (labs which published in scientific journals and organized in professional societies) and biotech companies, funded by the NIH or investors, and regulated by the FDA and lawmakers which conducted trials via clinicaltrials.gov that patients could become involved in and offered treatments that patients could receive. There was additionally the large presence of groups against embryonic stem cell research pressuring lawmakers, as well as the emergence of "stem cell tourism", where patients would travel to countries with fewer regulations to receive experimental stem cell treatments.

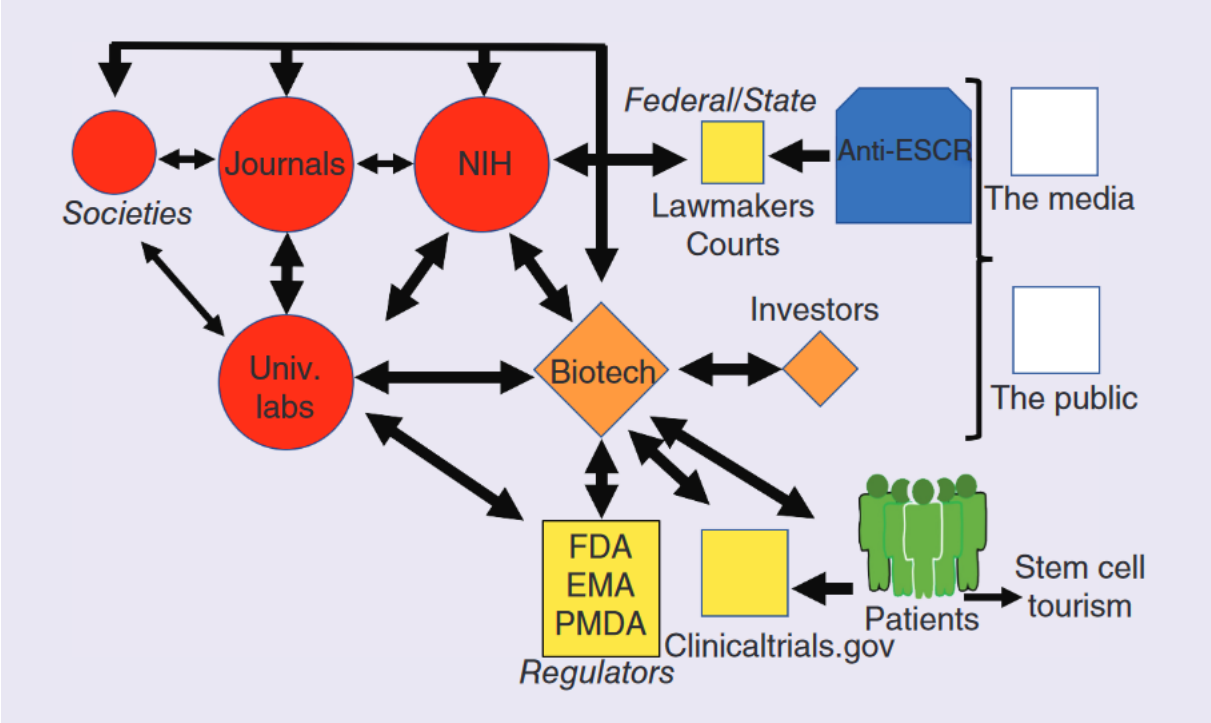

Figure 1: Paul Knoepfler's diagram of the stem cell ecosystem in 2005-2008 (Knoepfler, 2018).

The New Ecosystem

However, writing this paper in 2018, Knoepfler noted that the ecosystem had changed since 2008. It had grown much larger and more complex as the field developed. He found that now, "besides patients and their advocates, other key players in this system include academic labs, attorneys, biotech companies, funders including public and private funding agencies, investors, journals, physicians, politicians, regulators such as the US FDA in the USA and equivalents in other countries as well as additional governmental bodies, societies and foundations, and unfortunately, the mushrooming group of unproven, for-profit stem cell clinics" (Knoepfler, 2018). Among other changes, he has added lawyers, medical boards, funders for academic research, and notably, for-profit stem cell clinics and a halo of related groups – which I refer to as satellite entities – that enable the functioning and marketability of the clinics.

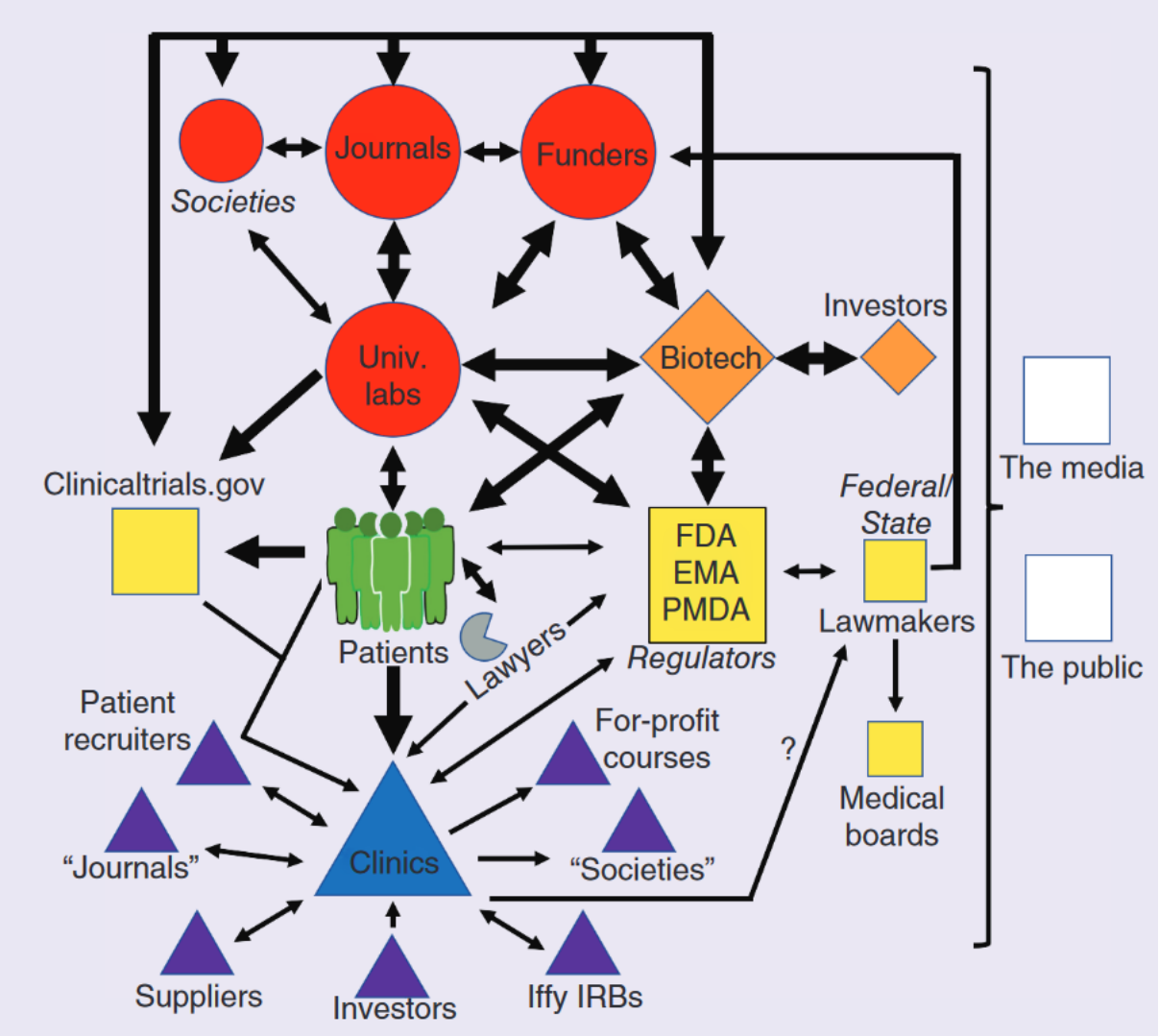

Figure 2: Paul Knoepfler's diagram of the stem cell ecosystem in 2018 (Knoepfler, 2018).

For-Profit Stem Cell Clinics

Number of Stem Cell Clinics Increasing

In 2018, Knoepfler published a paper with Leigh Turner, tracking the drastic increase in for-profit stem cell clinics, often involved in "stem cell tourism", which offer experimental, non-FDA approved, and often ineffective stem cell treatments to desperate patients. They tracked 351

businesses marketing stem cell procedures to consumers online in 2015-2016. 100 new stem cell clinics opened in 2015, up from only 2 in 2009. However, warning letters issued by the FDA's Center for Biologics Evaluation and Research (CBER) to stem cell clinics for failing to follow regulatory guidelines did not follow the same trend, peaking at 3 in 2013 and averaging less than one per year, disproportionate with the rapid growth of clinics and failing to adequately respond to the sale of unapproved stem cell products (Knoepfler & Turner, 2018).

For-profit stem cell clinics frequently list their products as part of studies on ClinicalTrials.gov, the US government database of clinical trials. However, unlike traditional clinical trials which are funded by a grant or the company who owns the rights to the treatment, these "clinical trials" often require the patients to pay to participate. This patient-funded system cloaks itself in the perceived legitimacy of ClinicalTrials.gov, possibly influencing patient trust in the clinics. Some of these have requested up to $7000-20,000 from patients to participate in the trial (Wagner et al., 2018). Patients not well versed in what is typical for clinical trials may not realize that this is abnormal, or they could be sick and desperate enough not to care.

Dangers of Stem Cell Clinics

A lack of FDA oversight and often unproven treatments can result in adverse effects for patients. A 2018 review by Gerhard Bauer and colleagues found 35 cases in the mass media or scientific literature of acute and chronic complications, 10 of which resulted in death, following stem cell treatments. However, there are likely far more cases, as this only included cases which were published. In 2019, Freya Leask contrasted the differences in outcomes between two treatments for macular degeneration. The first was a 2014 study led by Japanese scientist Masayo Takahashi using induced pluripotent stem cells (iPSCs) to create a retinal pigment epithelial sheet that was implanted in the eye of the patient. The second reported of three patients in

Florida left blind after adipose stem cells isolated from their adipose tissue were injected into their eyes, causing hemorrhaging and detached retinas (Leask, 2019).

FDA Approval Loopholes

Normal FDA Approval Protocols

In the United States, the Food and Drug Administration (FDA) regulates the sale of drugs, biologics, medical devices, radiation-emitting products, processed food, cosmetics and tobacco for both human and animal use (Commissioner, 2024). Acquiring approval for a new drug or biologic is a infamously long, arduous, and expensive process. Data from 2022 indicated that it takes more than 13.5 years and $1.784 billion on average to get a new drug through the FDA to the point where it is legal to market and sell it (Lim, 2022). Stem cell therapies would typically fall under the vaccines, blood products, and biologics category, therefore subject to review by the FDA's Center for Biologics Evaluation and Research (CBER). The requirements and costs for a biologic are nearly identical with that for drugs, so FDA approved stem cell treatment would similarly cost ~$1.5-2 billion and 13 years. This enormous expense and time sink makes the possibility of a drug or biologic being exempt from the FDA premarket approval process a lucrative deal.

Minimal Manipulation and Homologous Use

One of the most famous exemptions for biologics can be paraphrased as "minimal manipulation and homologous use". This is in fact the subtitle of CBER's guidance document *Regulatory Considerations for Human Cells, Tissues, and Cellular and Tissue-Based Products: Minimal Manipulation and Homologous Use*. A human cell, tissue, or cellular and tissue-based product (HCT/P) can be exempt from needing to go through the rigorous process of premarket approval if it meets those two criteria.

Minimal manipulation is defined by the FDA to mean that either "processing of the HCT/P does not alter the original relevant characteristics of the tissue relating to the tissue's utility for reconstruction, repair, or replacement" if the HCT/P is a structural tissue, or that "the processing of the HCT/P does not alter the relevant biological characteristics of cells or tissues" if it is a nonstructural tissue or cells (Food and Drug Administration, 2020). The FDA actually specifically states that processing adipose tissue into stromal vascular fraction to obtain adipose-derived stromal/stem cells, a very common process for stem cell clinics to obtain stem cells and one which they often claim the minimal manipulation and homologous use exemption for, is more than minimal manipulation due to the changing of the original characteristics of the adipose tissue.

Homologous use is defined by the FDA as "the repair, reconstruction, replacement, or supplementation of a recipient's cells or tissues with an HCT/P that performs the same basic function or functions in the recipient as in the donor" (Food and Drug Administration, 2020). They give specific guidance on hematopoietic stem/progenitor cells (HSCs), which are common products in for-profit stem cell clinics, particularly when derived from umbilical cord blood. Any intended use of HSCs apart from their natural role of replenishing the lymphatic and hematopoietic systems, including treating neural diseases such as cerebral palsy or remodeling the heart after a heart attack, is not homologous use and therefore would need to go through FDA premarket approval (Food and Drug Administration, 2020).

Satellite Entities

Iffy IRBs

Knoepfler describes the IRBs utilized by for-profit stem cell clinics as “iffy IRBs”. However, to understand why the quality of these regulatory bodies are called into question, first we must look at what IRBs are and why they exist in the first place.

History and Purpose of IRBs

Institutional Review Boards (IRBs) were established in response to several unethical scientific studies, including the infamous Tuskegee syphilis study and Nazi experiments during the Holocaust. The idea of having an impartial panel to review experiments involving human subjects was proposed in 1965 by US National Institute of Health (NIH) director James Shannon, MD. It was put into place for the US Public Health Service in 1966. The Department of Health and Human Services (DHHS) required review by a group ethics board, coining the term “Institutional Review Board”, 1974. In 1981, the FDA began requiring IRB approval, followed by 16 other government agencies in 1991 under the Common rule (Grady, 2015).

IRBs are registered with the DHHS Office of Human Research Protections. They are required to consist of 5 or more members with varying professions. At least one scientific member, one nonscientific member, and one unaffiliated member must be in the group. The IRB is tasked with reviewing and approving (or not) proposals for human subject research from the institution the IRB is tied to. They should ensure that risk (including risk of breaches of privacy) is minimal and the benefits in scientific knowledge sufficiently outweigh the risks. The IRB members must ensure informed consent of participants is obtained and documented with no

coercion, paying special attention to vulnerable populations such as prisoners, children, and the poor (Grady, 2015; Title 45, n.d.).

For-Profit IRBs

The IRBs used by many for-profit stem cell clinics are a type unlike the non-profit IRBs typically associated with universities. These IRBs are independent entities who review proposals from client companies who pay a fee for the review process. In a 2006 paper, Ezekiel J. Emanuel, Trudo Lemmens, and Carl Elliot debate whether for-profit IRBs are ethical. Emanuel contends that the notion that all non-profit entities are good, for-profit entities are bad. He argues that the focus should be on data showing different IRB's efficacy. However, as Adil Shamoo and Elizabeth Woeckner note in a paper responding to Emanuel et al., there is no good data on IRB efficacy, partially due to the "the lack of universal, legally codified human research protections discourages, if not prevents, collection of such information" (Shamoo & Woeckner, 2006). Lemmens and Elliot maintain that for-profit IRBs have "a fundamental conflict of interest" (Emanuel et al., 2006). Because IRBs rely financially on the research organizations and companies who pay them, they are incentivized to be more efficient and possibly more lenient. They also note the lack of adequate federal oversight of these IRBs for approving the members of a new commercial IRB and the free-form design of the system allowing companies to shop around and select the commercial IRB most least likely to delay the study or impose difficult restrictions (Emanuel et al., 2006). This incentivization for for-profit IRBs to be minimally strict and very efficient at getting proposals through the IRB, in combination with lax federal oversight, leaves a system where it is easy to imagine poor or dangerous studies slipping through the cracks.

Knoepfler notes in his 2018 paper that there is concern that "stem cell clinics touting their IRB approval may often have received that approval via IRBs that are not wholly or functionally independent, sometimes including members who are stem cell clinic operators themselves or proponents of an FDA oversight of stem cells" (Knoepfler, 2018). These conflicts of interest could indicate that IRB approval of studies mean much less rigor and independence than generally assumed.

In addition, IRB members often have a huge workload to manage, perhaps leading to errors due to a lack of time. A 1998 review of IRBs found that the average amount of time spent on one proposal for a full board review was 21.3 minutes for a low volume IRB and just over 3 minutes for a high volume IRB (Bell et al., 1998). While this does not include the amount of time members spent individually reading proposals outside of IRB meetings, 3 minutes for discussion of any potential issues or critiques of the protocol appears untenable. I argue that some combination of potential conflict of interest from the for-profit IRB model paired with inadequate time to discuss potential issues with study design and risks could contribute to the common trend of adverse events seen coming from for-profit stem cell clinics who are clients of IRBs.

Journals

You may notice that there are two very similar items in the network: Journals and "Journals". Knoepfler is noting the difference between highly regarded, peer-reviewed journals and the "journals" with lax peer review which can allow improperly statistically powered, observational, or poorly conducted studies to achieve "peer-reviewed publication" status (Knoepfler, 2018). There is concern that this lends legitimacy to for-profit stem cell clinics who can point to their study published in one of these journals as scientific proof their treatment

works and is safe, when the data or experiment may not be robust enough to show that (Sipp et al., 2017). Few patients have the time or scientific and statistical knowledge to look critically at these studies to determine if they are scientifically convincing. And while in the network model Journals and "Journals" are clearly delineated, that is not as easily determined in real life, especially for patients.

Gaps in the Network Model

Although Knoepfler's new model was a great characterization of the ecosystem surrounding stem cell and regenerative interventions, it is still missing a few notable components: insurance companies and doctors. As such, I propose a modified network map including both of these groups.

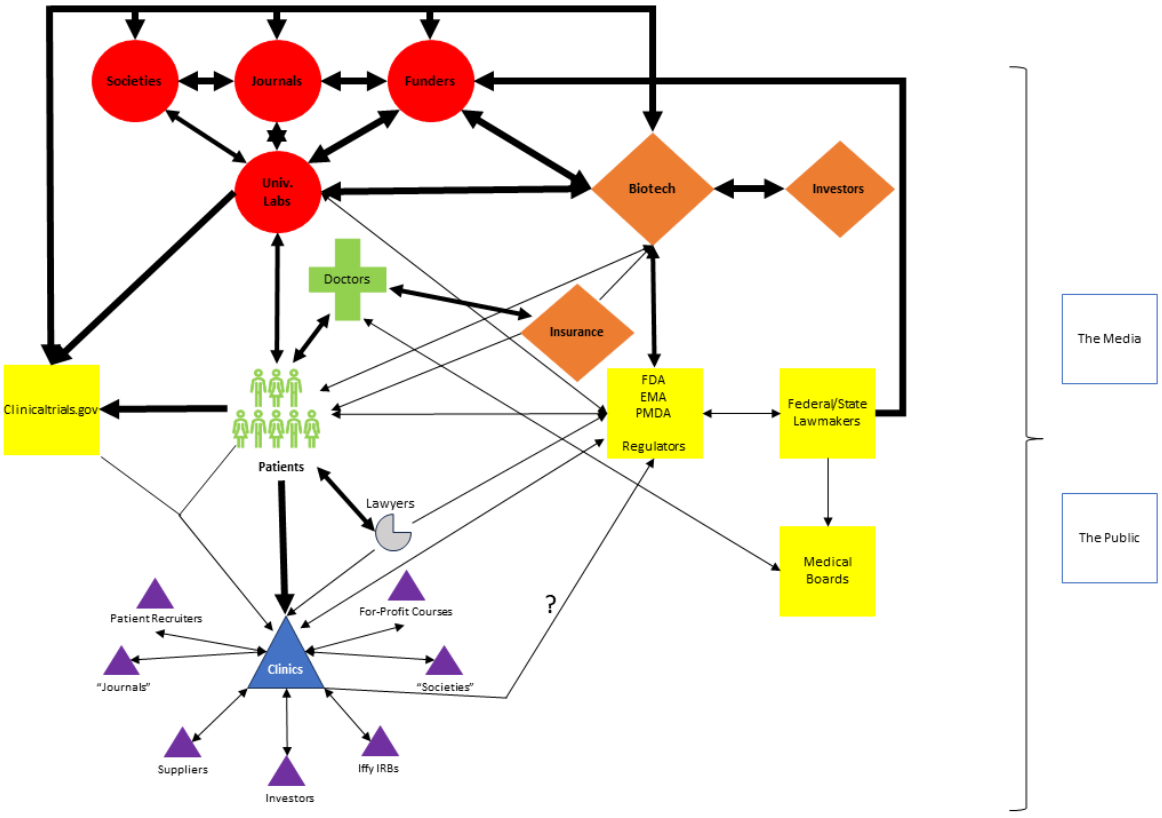

Figure 3: Modified version of Knoepfler's Stem Cell Ecosystem. Note the additions of Insurance and Doctors.

Insurance

Insurance, both private companies and government sponsored Medicare and Medicaid, make up a group that Knoepfler neglected in his paper. However, insurance companies are vital for the functioning of the stem cell ecosystem once a product has been approved by the FDA. Because insurance coverage of a treatment greatly influences who can access that treatment, the willingness of insurance companies to pay for stem cell therapies, and how much of the cost they will cover, will drive who has access. Wealthier individuals have greater access to these treatments because they have the disposable income to be able to pay for expensive therapies out of pocket, a luxury that poorer patients do not have. Knoepfler does note that often for-profit clinics will direct patients to raise money online for the treatment, a common method of paying for stem cell treatments (Knoepfler, 2018; Snyder et al., 2018).

Insurance coverage for stem cell treatments is typically limited to FDA approved treatments, as insurance companies are reluctant to pay for experimental treatments. Well-established treatments which are considered the gold standard in the field, such as bone marrow transplants, are commonly covered (BeTheMatch.org, 2019; *How Much Does a Bone Marrow Transplant Cost?*, n.d.). But experimental and non-FDA approved treatments such as the ones offered at for-profit stem cell clinics likely would not be covered, typically leaving insurance companies with no interactions with those clinics.

Doctors

The most glaring omission in Knoepfler's network is doctors, especially primary care physicians. In this case, I am defining this group to be doctors who are focused on patient care in a clinic or hospital setting. This does not include doctors involved in research, at a university, in a biotech company, or providing care at a for-profit stem cell clinic. These physicians are uniquely situated to provide medical advice to patients and help them make decisions as to whether to participate in a clinical trial or receive a particular treatment. Their knowledge of the patient's medical history and (hopefully) longstanding rapport with the patient gives them a

special ability to advise their patient on experimental stem cell treatments. A 2022 paper by Jennifer Arthurs and colleagues emphasizes the unique and powerful role that primary care providers have in correcting misinformation around the stem cell product market and lays our some guidelines to help providers most effectively and empathetically do so (Arthurs et al., 2022). However, according to a 2023 report by the National Association of Community Health Centers, over 100 million Americans do not have a primary care provider (National Association of Community Health Centers, 2023). This primary care crisis is a larger issue, but could substantially diminish the resources patients in medically disenfranchised areas have available to them to make the best decisions on stem cell treatments for their health.

Solutions

Regulatory

Using regulation and enforcement to limit misinformation and improper marketing without FDA approval of stem cell treatments is an obvious place to start. Some scholars have already proposed improving control of ClinicalTrials.gov to prevent the posting of trials for treatments which are not in the process of being approved by the FDA by requiring listing the Investigational New Drug (IND) number for the treatment, a number assigned after filing paperwork to begin the FDA approval process. This would guard against for-profit stem cell clinics using ClinicalTrials.gov to list treatments patients would need to pay thousands of dollars for while using the perceived legitimacy of being on a government database to win the trust of patients (Wagner et al., 2018).

Others have also suggested increased funding and staffing for FDA's CBER, the department which regulates biologics including stem cell products. CBER has not kept up with

the proliferation of for-profit stem cell clinics by issuing warning letters to clinics selling improperly vetted products (Knoepfler & Turner, 2018). By increasing funding, CBER would have the resources needed to better enforce regulation.

In addition to these, reducing the ability of for-profit stem cell clinics to point to published papers or IRB approval of study protocols as a sign of legitimacy could prevent some of the manipulative marketing the clinics are able to do. Fixing the problem of poorly peer-reviewed journals is a complex problem better addressed elsewhere. Additional oversight of IRBs would help prevent bad protocols slip through the cracks of overburdened or lax IRBs. The FDA does currently conduct inspections of IRBs, in addition to several other entities such as laboratories and sponsors of research trials, under the Bioresearch Monitoring Program. If deficiencies are found, the FDA will issue a Form FDA 483 listing all deviations from good practice (*FDA Institutional Review Board Inspections*, 2006; Garmendia et al., 2018). A review of released FDA records from fiscal years 2006-2015 by Craig Garmendia found that the FDA issued 665 Form 483s, with an average of 3.85 citations for specific issues per inspection receiving a Form 483. Garmendia does note that the number of inspections had increased by 30% from 2007 while the number of inspections resulting in a Form 483 has decreased by 36% since 2009 (Garmendia et al., 2018). However, it is unclear what proportion of IRB inspections resulted in Form 483s and whether the increased rate of inspections and decreased rate of citations is uniform across all 7 types of groups the FDA was inspecting. Greater research is needed to determine if these inspections are working and effective, especially in relation to lax IRBs used by for-profit stem cell clinics.

Patient-Facing

In addition to better regulation and enforcement of regulations for stem cell clinics and their satellite entities, we also need to address the problem from the other side of the equation: the patient. An educational campaign to inform patients about the potential risks and misinformation surrounding unapproved stem cell therapies is a good option, and one which has been proposed in much better detail than I can provide here (Kawam et al., 2023). In this paper, Owan Kawam mostly addresses why a persuasive approach is better than a didactic or manipulative approach to patient education in preserving patient autonomy when addressing common misconceptions, conspiracies, and misinformation in stem cell treatment marketing. While it is certainly vital to educate patients on how for-profit stem cell clinics often market misleadingly and try to provide corrections to conspiracy theories, patients may view this as telling them what to do. I propose that an educational campaign be focused partially on debunking misinformation but have a central part of the focus be to talk with their primary care provider about any treatment they are considering. By utilizing an already existing connection with an authority the patient trusts, the message is much broader, simpler, and less likely to be misunderstood. The more specific details of correcting misinformation and evaluating the treatments the patient is considering can be done far more effectively and personally by the primary care provider, as laid out in Jennifer Arthurs' paper (Arthurs et al., 2022).

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