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Online Seminars as an Information Source for Direct-to-Consumer Stem Cell Therapy

THESIS

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by

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ABSTRACT OF THE THESIS

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by

Mirna Hassoun

Master of Science in Biomedical and Translational Science

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Professor Sidney H. Golub, Chair

This study is a semi-quantitative analysis of stem cell therapy claims made by private, direct-to-consumer stem cell businesses during their presentation talks to potential consumers. Methods for data collection consisted of one live attendance of one seminar, independent audio and visual attendance of two recorded video webinars and four recorded seminars, and one video recording that was not titled as a "seminar" or "webinar" but was identified as a camera recorded talk by a clinic member to an audience and posted on the internet for further reach to potential patients. We found that the portrayal of stem cell therapies in this "early market" by direct-to-consumer stem cell clinics is too optimistic as they offer advertised therapies that are not supported by clinical evidence or substantiated by peer reviewed literature.

1. INTRODUCTION

The field of stem cells has shown promising signs for the treatment of various diseases and injuries due to the potential regenerative ability of stem cells to replace or repair organs and tissues. However, it is still unclear which stem cell types are safe and efficacious and for which indications. Nevertheless, the potential for stem cells has created demand from the general patient population for access to such innovative therapies. Although innovative stem cell therapies are exciting and at the forefront of research, it is important for stem cell treatments to be first carefully assessed through rigorous scientific investigation and to be approved by regulatory agencies to ensure safety and efficacy before translation into clinical practice.

For a medical treatment to be marketed and sold, it must first undergo clinical trials and provide sufficient evidence that suggests effectiveness and safety. Until clinical research has been completed, reviewed, and approved by the Food and Drug Administration (FDA), a new medical treatment cannot be approved. The FDA evaluates the safety and efficacy of new treatments before they can be marketed and sold by reviewing their pre-clinical and clinical trial results. For example, a stem cell provider wishing to administer experimental stem cell treatments must apply for an investigational new drug (IND) application with the FDA, have it approved for initiation of a clinical trial with the approval of the study plan (known as study protocol) and the informed consent form by a legitimate institutional review board (IRB).

IRBs are concerned with the welfare and protection of human subjects. Before a clinical trial can be started, the IRB assesses the risk involved to human subjects, reviews inclusion and exclusion criteria to ensure that an appropriate subset of the patient population is recruited for the treatment and approves the study protocol and the informed consent form that will be given to human subjects. Clinical trials are an integral step for new medical treatments and are required

by the FDA before a new therapy can be approved, marketed, and sold to patients. This process of ethical, regulatory, and legal guidelines may be lacking in the direct to consumer stem cell marketplace, as suggested by studies conducted in this area.

As a response to patient demands for innovative stem cell therapies, commercialization of unproven and unapproved stem cell therapies by private, for-profit clinics, have quickly proliferated. The rising number of clinics advertising and delivering unproven stem cell treatments that may lack scientific evidence of safety and efficacy (and therefore have not been approved or obtained pre-marketing authorization by FDA) is alarming. Such providers may be exposing patients to serious physical harm and financial distress, falling short of their medical responsibility to the public, and therefore raising legitimate ethical concerns. One such example is a Florida clinic that managed to register their unauthorized clinical trial on ClinicalTrials.gov and administered stem cell treatments to three women for macular degeneration. All three patients became permanently blind. This horrific episode is described in an article published in the Washington Post (McGinley, 2017) as representing "one of the most egregious examples of patient injury involving a stem cell clinic."

2. BACKGROUND

In 2009, the International Society for Stem Cell Research (ISSCR), a medical and scientific society focused on the pipeline from basic science to clinical therapies, and concerned with careful pathways for translation of scientific innovation to clinical practice, established guidelines to inform patients about the minimum standards for assessing safety and efficacy of stem cell treatments offered by providers (Weissman, 2009). These "Guidelines for the Clinical Translation of Stem Cells" recommend that stem cell therapies undergo structured and rigorous

clinical trials that are approved by the IRB for subject safety and overseen by the FDA for evaluation of efficacy for marketing approval.

The recommendations to patients by the ISSCR on assessing safety and efficacy of stem cell therapies state that providers should present consumers with realistic depictions of potential benefits while also communicating known risks and adverse events, and pointing to specific scientific support for the treatment they are offering by providing evidence of regulatory oversight and independent peer review and approval by a legitimate IRB (ISSCR 2008a). The FDA issued a consumer update, "FDA Warns About Stem Cell Therapies", advising consumers to ask stem cell providers about FDA approval, or an IND application number to ensure that the treatment they are considering is overseen by the FDA.

One common path that clinics use to avoid FDA oversight is by claiming that their offered treatment is "minimally manipulated" and of "homologous use", and therefore it does not require FDA oversight. The criteria in 21 CFR 1271.10(a)(1) and 21 CFR 1271.10(a)(2) for minimal manipulation and homologous use by the FDA is misinterpreted by many stem cell clinics and is used as justification to avoid regulatory oversight. Under very limited exceptions, where stem cell treatments are minimally manipulated and for homologous use, the treatments in question are exempt from FDA oversight. However, due to the abuse and misinterpretation of what constitutes "minimal manipulation" and "homologous use" of cells, the FDA has recently released guidance to clarify these criteria. For example, treating a burn wound by removing skin and transplanting it to cover the wound area is considered homologous use by the FDA. Homologous use as defined by the FDA (2020), means "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 (21 CFR 1271.3(c)), including when such cells or tissues are for autologous use".

Even with guidance from the FDA on what constitutes minimal manipulation and homologous use, there still exists an unfortunate number of stem cell clinics claiming to be exempt from FDA oversight because the stem cells are the patient's own cells being re-injected and are minimally processed. It is crucial to note that simply because the stem cells being injected are the patient's own cells does not automatically mean that those cells were minimally manipulated or constitutes homologous use under the FDA's criteria.

Shifting to preliminary data on direct-to-consumer stem cell clinics, an online content analysis of stem cell clinic websites was conducted in 2016 and found that 570 clinics across the United States engaged in direct-to-consumer marketing of stem cell treatments (Turner & Knoepfler, 2016). This analysis consisted of an evaluation of all identified business's locations, web addresses, types of stem cells advertised, diseases/illnesses/injuries that the providers claimed was treated by stem cell therapy. The study also analyzed the geographic distribution of the clinics and the marketing claims made by such providers. Most of the clinics (113) tended to be clustered in California (particularly in the Southern CA region), Florida (104), Arizona (36), Texas (71), and Colorado (37). Indications for treatments among the identified clinics included a wide range of diseases, such as various neurological disorders, cosmetic applications, orthopedic injuries, degenerative, immunological, and pulmonary conditions, cardiovascular disorders, and more! The most common type of stem cells provided by these clinics were autologous based interventions (uses the patient's own stem cells), although clinics providing allogeneic stem cells (uses stem cells from a donor source) were also reported.

Turner and Knoepfler (2016) state that the claims made by the identified clinics "raise significant ethical issues given the lack of peer-reviewed evidence that advertised stem cell interventions are safe and efficacious for the treatment of particular diseases", and that many of the interventions were not found to fit the criteria set by the FDA regarding "homologous use and minimal manipulation of cells and tissues".

Many US stem cell providers advertising stem cell interventions that are unapproved by the FDA are recruiting their patients by listing their studies on ClinicalTrials.gov as "pay-to-participate" studies. First, pay-to-participate may exploit study subjects, as well as hinder fair selection of subjects for a robust clinical trial design that emphasizes inclusion/exclusion criteria for enrollment (Emanuel, et al., 2015). Second, recruitment through ClinicalTrials.gov creates a false sense of treatment legitimacy to potential consumers as the requirements to list a study on the ClinicalTrial.gov database does not require submission of approval by the Food and Drug Administration (Turner, 2017). It is important to note that clinical trials registered on ClinicalTrials.gov are neither FDA approved, nor endorsed by the National Institute of Health. A document titled "ClinicalTrials.gov Protocol Registration Quality Control Review Criteria" found on ClinicalTrials.gov, explicitly states that "the posting of registration information following the QC process does not necessarily mean that the information complies with Section 801 of the Food and Drug Administration Amendments Act (FDAAA 801) and the Final Rule for Clinical Trials Registration and Results Information Submission (42 CFR Part 11)".

One La Jolla clinic that had operated under the name of "StemGenex" had disclosed its revenue from 2017 to be an estimated $8.2 million, as the clinic was recommending more than one treatment for their patients and charging per treatment (Hiltzik, 2019). StemGenex is such an example of a clinic that was registered on ClinicalTrials.gov while offering unregulated and

unproven stem cell therapies. The clinic filed for bankruptcy following a class-action lawsuit brought by former patients for the clinic's misleading advertisement and marketing claims.

A common recruitment strategy used by direct-to-consumer stem cell clinics is hosting seminars for potential patients. Knoepfler (2017) reported first-hand his experience attending a stem cell seminar in which he described as having felt more like "attending a persuasive entertainment show or something on a television shopping network than an educational seminar". Specifically, the medical claims made by the speakers at the seminar included: 1) stem cells are like a relative or an uncle in a family who is known as a "Mr. Fixit", as to mean he/she can fix anything, and implying stem cells have the power to do so, 2) embryonic stem cells cannot be studied or used as it is illegal to do so, 3) no observed side effects to their offered intervention, as well as report of 50% improvement or better in 90% of their patients, 4) speaker describing their offered intervention as being similar to a "new car", indicating no risk of immunorejection, and 5) speaker claiming for offered intervention to be FDA approved, although one might think otherwise based on the presented and available information. Similarly, a stem cell clinic by the name of "Stem Cell Institute of Orange County", has held a seminar where a hired actor spoke about the benefits of stem cell therapy, and falsely claimed to be FDA approved and affiliated with University of California, Irvine (Goldstein, 2018).

Most analyses to date have focused on conducting extensive online searches of stem cell clinic websites to analyze types of therapies offered, the indications for which such therapies are offered, the benefits and risks of therapies, and purported evidence to support the advertised therapies. Although there has been several single stem cell seminar reports, there has not been a comprehensive study of information presented at various stem cell seminars in order to investigate whether the single seminar reports are representative of most stem cell seminars

conducted by private stem cell clinics. To this day, studies reviewing and analyzing information presented at stem cell seminars hosted by private stem cell clinics are not common. In an effort to better understand the consistency of claims made among direct-to-consumer stem cell clinics, we set out to assess a series of seminars.

As demonstrated by the various studies discussed above, the results of such analyses raise scientific, ethical, and regulatory concerns about stem cell therapy providers. These concerns would include: deception, a lack of transparency on known negative outcomes or adverse events, unsupported discussion of the benefits of advertised therapies to consumers, and not providing peer reviewed data supporting the claims being made. Hence, there is a need for more rigorous examination of the direct-to-consumer stem cell market to improve patient awareness, as well as raise ethical concerns to appropriate regulatory agencies.

This study was undertaken to test the hypothesis that online seminars hosted by stem cell businesses would provide an insight into the patient experience with direct-to-consumer clinics. This study was also intended to test whether a comprehensive review of information presented at various stem cell seminars confirm consistent findings with the single seminar reports which are currently believed by some in the field to be representative of most stem cell seminars conducted by private stem cell clinics.

3. METHODS

This study is a semi-quantitative analysis of stem cell therapy claims made by private, direct-to-consumer stem cell businesses during their presentations to potential consumers. Methods for data collection consisted of one live attendance of a seminar, independent audio and visual attendance of two recorded video webinars and four recorded seminars, and one video recording that was not titled as a “seminar” or “webinar” but was identified as a camera recorded

talk by a clinic member to an audience and posted on the internet for further reach to potential consumers. All of the talks were sponsored and posted on the internet by the businesses themselves.

Additionally, the stem cell business websites were reviewed to note any further claims or information provided to consumers. For example, some clinic websites contained a list of references to serve as evidence of safety and efficacy of the advertised stem cell therapies. The list of references were reviewed to assess credibility of source, phase of reported studies, and whether there is a match between the cell source and therapeutic area with the business's advertised cell source and therapeutic area/s treated.

The aim of this study is to attempt to determine the level of regulatory oversight of the advertised stem cell therapies and evaluate the quality and accuracy of information provided to consumers via presentations hosted directly by the private stem cell businesses.

All businesses are located within the United States. A total of eight stem cell businesses were selected for this analysis; seven of which are stem cell clinics and one business that was not classified as a clinic but was included in our analysis as it directly sold to consumers products for which the business made stem cell claims for. All recordings were posted online between the years of 2016 and 2020. Letters were assigned for all eight businesses in this analysis in order to anonymize their identities.

A seminar checklist was developed as a data collection tool. The seminar checklist contains questions to support the gathering of essential information needed for this analysis, such as medical conditions treated, cost of advertised interventions, source and type of cells offered, number of treatments said to be typical, number of cells injected per intervention, route of administration, assurance of cell quality, mention of FDA or any regulatory oversight, mention

of supporting clinical evidence, reported adverse or side effects, reported clinical benefits, and safety claims.

4. RESULTS

4.1 Checklists

A total of eight checklists were completed. Seven checklists were completed for seven clinics, and one checklist was completed for one business that was not classified as a clinic but sold directly to consumers products for which the business made stem cell claims.

Table 1 presents assigned letters to each of the eight businesses, with a column presenting location/s of the businesses by state.

Table 1. Business letter assignment and location/s

Letter Assignment	Location/s
Business A	California
Business B	Illinois
Business C	Nevada
Business D	Florida
Business E	California
Business F	New York
Business G	Ohio
Business H	Michigan, South Carolina

4.2 Categories of checklist responses

We classified the responses within the stem cell checklist in which was used to collect data into the following categories:

4.2.1 Medical conditions treated

Business A, the business not classified as a clinic, advertised patches which the presenter claimed cures infections in dogs, bears, horses, and people. More importantly, the presenter's relative was walked over to the front of the room as an example of someone who has tremendously benefited from the advertised patches. Although the relative did not speak to the

audience himself, he stood while the presenter explained to us that he's been diagnosed with Alzheimer's disease and prescribed many medications, but the patches have led to: a) improved memory, b) being taken off all his medications, and c) having the ability to walk again. The presenter excitedly explained to us that their advertised patches are said to improve, if not completely cure, Alzheimer's disease, insomnia, anxiety, depression, stress, as well as lead to hair growth.

As for the seven clinics (businesses B through H), the presenters and their respective clinic websites mostly targeted their advertised treatments at orthopedic conditions. Although, some also made claims that their treatments can also be offered for anti-aging, preventative measures, general rejuvenation and wellness, autoimmune diseases, chronic fatigue, male hormone replacement, hair loss, and other various conditions. See **Table 2** for medical conditions treated by each business.

Table 2. Medical conditions treated by business

BUSINESS B

- Arthritis, regenerative therapy, degenerative joints
- Chronic pain and injury
- Anti-aging

BUSINESS C

- Regenerative orthopedic conditions and spine medicine
- Preventative measures

BUSINESS D

- Osteoarthritis of joints, tendinopathies, acute sports injuries, sacroiliac joint pain, degenerative disc disease, facet joint pain, carpal tunnel syndrome, piriformis syndrome

BUSINESS E

- Joint regenerative therapy
- Autoimmune diseases
- Chronic fatigue
- Anti-aging therapy
- Note: As quoted on the clinic website:
  "Beneficial uses of mesenchymal stem cell exosomes include but are not limited to:
  - ❖ Chronic inflammatory and autoimmune diseases
  - ❖ Chronic fatigue syndrome
  - ❖ Neurodegenerative diseases including: Parkinson disease, multiple sclerosis, stroke, chronic demyelinating inflammatory neuropathies etc (exosomes penetrate through the blood brain barrier)
  - ❖ Arthritis
  - ❖ Acute and chronic tendinitis and tendinosis
  - ❖ Muscle Fatigue and muscle weakness
  - ❖ Coronary artery disease and congestive heart failure
  - ❖ Chronic hepatitis and other liver diseases
  - ❖ Chronic kidney diseases"

BUSINESS F

- Orthopedic conditions, spine, hip, knee, foot and ankle, shoulder, elbow, hand and wrist
- Non-union fractures
- Osteonecrosis/avascular necrosis
- Temporomandibular joint dysfunction (TMJ syndrome)

BUSINESS G

- Degenerative joints
- Male hormone replacement (erectile dysfunction)
- Hair loss

BUSINESS H

- Osteoarthritis, arthritis, spinal cord injuries
- Chronic obstructive pulmonary disease (COPD)
- Auto-immune diseases, diabetes, multiple sclerosis, stroke

4.2.2 Intervention cost

Three of the seven clinics made their intervention costs available. For the four of the seven clinics that did not disclose a price in their presentation, their clinic websites were reviewed for any mention of costs, but treatment costs were not identified.

The three clinics had pricing ranging from $4,000.00 to $12,000.00 for their advertised interventions. One business charged by the "body part" and offered a "multiple body part discount", in addition to a seminar discount to those who've attended the seminar. Another business charged by the joint and by source of cells and offered a $200.00 off per joint if an attendee of the seminar stayed for a consultation and paid a $500 deposit following the seminar. A third business did not mention cost during the presentation and cost on their website was not identified, but the speaker stated that their interventions cost anywhere from $4,000.00 to $12,000.00 in response to a question from an audience member about cost.

Finally, the business that was not classified as a clinic but sells patches in which the business claim "activates and mobilizes the body's stem cells", had a bundle price for $149.00 for 30 patches or $89 for individual patches, and various other similar numbers for different patch types.

4.2.3 Source and type of cells

This category applies to the seven clinics (business B through H), but not to business A. As a reminder, business A sells patches.

Businesses B, C, D, F, G, and H advertise direct stem cell treatments. Business E, on the other hand, advertises exosome treatments in which are derived from stem cells. As quoted by business E clinic website: "our therapy uses exosomes excreted from mesenchymal stem cells derived from the umbilical cord, not the actual stem cells, as research has shown greater

beneficial outcomes from exosome over stem cells with minimal risk. Exosomes used in our clinic are obtained from human umbilical cord stem cells."

As exosomes may be believed by some to have a lower risk profile than direct stem cell therapy, given their lack of ability to replicate, exosomes remain unproven as treatments and remain to be researched at this time for their efficacy. To our knowledge, to date the FDA has not approved any exosome products for any use according to a public safety notification on exosome products by the FDA published in December 2019.

All seven clinics use either allogeneic, autologous, or a mixture of both as sources for their stem cells. Some clinics, such as Business C, process the cells in house and even combine their injection with platelet rich plasma. The presenter states: **"**We concentrate them and we activate them using platelet rich plasma therapy and then we re-inject them. It's safe, it's controlled, we have full control of the environment and to date I have never had a complication in doing this for 10 years because we regulate it and it's all done in house." The speaker or the clinic website does not mention how the harvesting of cells in house is regulated.

Business B claims that the cells they inject into their patients (derived from the umbilical cord), are provided by an FDA regulated lab, however, the business does not indicate whether the actual treatment being administered is proven and applied for uses that FDA has approved. The presenter states: "The FDA does not approve nor disapprove natural treatments. They approve food, drugs, and medical procedures. The FDA does regulate how these cells are housed and processed." But isn't the advertised stem cell intervention considered a "medical procedure"?

More claims by clinics about regulation of cells and mentions of FDA are discussed in Section 4.2.5. **Table 3** presents each clinic's source and type of cells used for the advertised interventions.

Table 3. Source and type of cells by business

Business	Cell Source	Cell Type
Business B	Allogeneic	Human umbilical cord
Business C	Autologous and Allogeneic	Umbilical cord, Bone marrow, and Adipose
Business D	Autologous	Bone marrow
Business E	Allogeneic	Umbilical cord
Business F	Autologous	Bone marrow
Business G	Allogeneic	Umbilical cord
Business H	Autologous and Allogeneic	Umbilical cord, Adipose

4.2.4 Number of treatments typical, number of cells injected, and route of administration

Table 4 presents the number of treatments typical, number of cells injected, and route of administration as specified by businesses B through H or otherwise unspecified. In regard to Business A, their advertised patches are non-transdermal, worn in 12 hour cycles (12 hours on/12 hours off), and are said, as the presenter states, to work "through high vibration frequencies." The website claims: "the patch duplicates young stem cells and deploys existing stem cells through epigenetics which works with our internal organs".

Table 4. Treatments typical, number of cells injected, and route of administration by business

Business	Number of treatments typical	Number of cells injected	Route of administration
Business B	1	1.1 million	Injection
Business C	Unspecified	Up to 500 million	Injection, Intravenous (method varies with disease treated)
Business D	2 to 3	Unspecified	Injection
Business E	Unspecified	Unspecified	Injection, Intravenous
Business F	Unspecified	Unspecified	Injection
Business G	Unspecified	10 to 30 million	Injection, intravenous
Business H	1 to 2	10 million	Injection, Intravenous, Inhalation

4.2.5 Assurance of cell quality and U.S. Food and Drug Administration Regulation

This category applies to the seven clinics (business B through H), but not to business A. As a reminder, business A sells non-transdermal patches.

Table 5 presents statements made by the presenters or identified on the clinic websites in relation to assurance of cell quality claims and mention of the U.S Food and Drug Administration on advertised interventions. The question that's commonly left unanswered, is whether the actual treatment/procedure/intervention being administered is proven and applied for indications that FDA has approved? To our knowledge, today stem cell therapies that are FDA approved for use outside of clinical trials are only for patients with "disorders that affect the body system that is involved in the production of blood", according to a warning by the FDA (2019).

None of the clinics reviewed in this paper were offering stem cell therapies that are FDA approved or are being investigated under an investigational new drug application. Nevertheless,

safety and efficacy of the advertised stem cell interventions were strongly implied. Some clinics claim that stem cell therapy is 100% legal in the United States. Section 4.2.6 presents safety and efficacy claims made by the clinics, and section 4.2.9 presents more in depth information on the reference to stem cell research by clinic presenters and their websites.

Table 5. Assurance of cell quality and U.S. Food and Drug Administration regulation

BUSINESS B

- "The cells are provided by [lab name], a lab that is FDA registered and FDA regulated." (FDA registered lab name was mentioned and verified).
- "The FDA does not approve nor disapprove natural treatments. They approve food, drugs, and medical procedures. The FDA does regulate how these cells are housed and processed."

BUSINESS C

- "We have to process the adipose tissue in minimal manipulation style under FDA compliance guidelines."
- "FDA allows for minimal manipulation [12] to happen during the transplantation phase.."

BUSINESS D

- Assurance of cells not discussed and no information about cell assurance was identified on the clinic website.
- FDA was not mentioned by the presenter or identified on the clinic website, however, presenter stated that the United States is usually last to get on board with regards to allowing use.

BUSINESS E

- "FDA has kind of highly guarded all this stuff, we're the only one in CA who are doing it right now. There are only 3 clinics in the country, you have to go through a special certification process."
- "Exosomes used in our clinic are obtained from human umbilical cord stem cells. Prior to use, the donated cords are extensively tested for a number of viruses. Exosomes are produced in an FDA registered tissue facility that follows cGMP production procedures and holds both ISO 9001 and ISO 13485 quality control certification. The production of exosomes is regulated as a 351 tissue product by the Food and Drug Administration." (FDA registered tissue facility name was not mentioned by the presenter or identified on the clinic website).

BUSINESS F

- No mention of cell quality assurance or FDA

BUSINESS G

- "After collected and tested to ensure safety, stem cells are stored frozen until they are to be used for a patient. Keeping them frozen ensures less cell death, and more viability for stem cell treatment…..stem cells are then harvested from the blood/amniotic fluid, and then it is frozen after being inspected for diseases/imperfections."
- "While stem cell therapy is overseen and regulated by the FDA it is NOT completely FDA approved. It's speculated that SCT will be FDA approved in time, but as of now it's only regulated by the FDA. Stem cell therapy is 100% legal to practice in the United

States as long as the stem cells are gathered from a legal source, and the clinic administering the therapy follows proper medical procedures."

BUSINESS H

- "[Business name] uses umbilical stem cells provided by an FDA tested lab as well as the fat from your own fat tissue." (FDA tested lab was not mentioned by the presenter or identified on the clinic website).

4.2.6 Safety and marketing claims, side effects, and reported clinical benefits

The safety and marketing claims for the advertised treatments were typically discussed by the presenter after emphasizing the side effects of standard therapy, such as surgery and other standard therapies, sometimes sharing a related "personal story", and sometimes even depicting the pharmaceutical industry as the "monster" that is in control of hindering the approval of "natural" therapy. One business used the example of the movie "The Good, The Bad, and The Ugly", labeling medications as "the ugly", surgery as "the bad", and mesenchymal stem cell facts as "the good". The question is, are they "facts"?

It was common for presenters to state that a lot of research on stem cell therapy has been done for years proving its effectiveness and safety. It was rare for the presenters to specifically mention the study team or the study publication source. Some clinics had a list of studies on their websites, which were reviewed for purposes of this paper and are discussed in Section 4.2.7. Referenced studies identified on some clinic websites tended to be pre-clinical and early phase trials needing further evidence, and some listed studies for therapeutic areas that did not match the therapeutic area for which the clinic is advertising the stem cell therapy.

All clinics made definitive medical claims, and did not discuss side or adverse effects other than some discomfort following the procedure. All clinics presented patient testimonies or have patient testimonials available on their website or YouTube channel..

Finally, none of the advertised interventions are covered by insurance. The following is an example quote about insurance by one of the presenters:

"If you want quality healthcare, your insurance is not going to cover it. There is no insurance coverage for natural therapy."

Table 6 presents some of the safety and marketing claims, side effects, and clinical benefits of the advertised stem cell therapies reported by the clinic presenters or clinic websites.

Table 6. Safety and marketing claims, side effects, and reported clinical benefits for advertised stem therapies by business

BUSINESS A

- Side effects
  - ❖ No side effects discussed
- Clinical benefits
  - ❖ Cure, pain management, general wellness/energy vitality
  - ❖ "Improves sleep quality by 66%."
  - ❖ "The patch duplicates young stem cells and deploys existing stem cells through epigenetics which works with our internal organs."
- Marketing and/or safety claims
  - ❖ "The [patch name] activates and mobilizes the body's stem cells which can support the natural wound healing process and immune function, elevate antioxidants, manage inflammation, stimulate the production of collagen and more."

BUSINESS B

- Side effects
  - ❖ "Small percentage of patients experience flu-like symptoms that last no longer than 24-48 hours. I personally never had that happen in my clinic, but that the lab does say that."
- Clinical benefits
  - ❖ "15% see results within 24 hours. 60% see results by 8 weeks. Most of the tissue growth occurs from 3 to 8 months. Improvements can take up to one year."
- Marketing and/or safety claims
  - ❖ "Stem cell therapy does not alter the DNA of other cells. Only carcinogens and viruses are able to negatively alter the DNA."
  - ❖ "We are not made of drugs, we are made of cells."
  - ❖ "Big pharma can only make money on things they can patent. You cannot patent anything natural. Stem cells area natural treatment. Thus, there is no money to be made in stem cells for big pharma."

BUSINESS C

- Side effects
  - ❖ Pain for 4 to 7 days post procedure
- Clinical benefits
  - ❖ Patients should notice changes in their levels of pain by 1 week, and notice most changes by 6 to 8 weeks
- Marketing and/or safety claims

- ❖ "Most studies have shown anywhere from 50% to 70% improvement in pain and can last anywhere from 1 to 3 years."
- ❖ "It wasn't until recently that practitioners have proved how universally effective stem cell can be in regenerating tissue after injuries or restoring the effects of natural wear-and-tear."

BUSINESS D

- Side effects
  - ❖ Inflammation post procedure, soreness for 2 weeks, maximum results achieved after 8 to 12 weeks
- Marketing and/or safety claims
  - ❖ "Stem cells hold the promise of treatment and cures far more than 70 major diseases that affect millions of people."

BUSINESS E

- Side effects
  - ❖ "Exosome transplantation is usually done on an outpatient basis; most patients should expect to walk out of the clinic without any major pain or problems."
  - ❖ Initial pain at injection site; less than 10% may experience a minor fever, headache, nausea or vomiting
  - ❖ "..these side effects have never lasted more than three days and usually resolve within 24 hours. No long term negative side effects have been reported."
- Clinical benefits
  - ❖ "Every individual is different, but two key determinants for success are the severity of your condition and your body's response to exosome therapy. Typically, early benefits of therapy are observed in 3 to 4 months. However, it is not uncommon to see the benefits after 9 to 12 months."

BUSINESS F

- Side effects
  - ❖ "There may be mild soreness in the joint for up to a week after the procedure. Heavy exertion should be avoided during this period."
  - ❖ The procedure is simple, nearly painless (a local anesthetic is used), and takes about 30 minutes to complete."
- Clinical benefits
  - ❖ Pain management

BUSINESS G

- Side effects
  - ❖ Flu-like symptoms for 24-48 hours
  - ❖ "Healing crisis, increased, intense signs and symptoms, 70%-80% of people do experience healing crisis. It is a good thing, it means the cells are working."
- Clinical benefits
  - ❖ Pain management
  - ❖ "25% experience results within the first 4 weeks. 50% notice improvement in 4-8 weeks. 25% experience results in 8-12 weeks. Patients can experience healing for up to 18 months."
- Marketing and/or safety claims

- ❖ "…all of our treatments such as Stem Cell Therapy,…are all safe, and effective when used correctly."

BUSINESS H

- Side effects
  - ❖ "Patients experience minimal discomfort during the procedure, it's a small injection that they can actually get up and walk out of the appointment that same days. There's no sedation and no down time and the symptoms can begin to improve within 1 to 2 months of the treatment."
- Clinical benefits
  - ❖ "Patients typically have 30% to 50% improvement from baseline."
- Marketing and/or safety claims
  - ❖ "There's no safety concerns or adverse effects that we've seen."
  - ❖ "I've never seen a rejection. I've never seen allergic reaction from them so they're safe."
  - ❖ "You've probably heard a lot about stem cells by now. There's a lot of buzz about stem cells in the news, on TV, and all the successes that have occurred with stem cells."

4.2.7 Mention of supporting clinical evidence/ pre-clinical data for efficacy

Five of the eight businesses listed some studies on their websites for potential customers to refer to in order to gain knowledge on clinical evidence of stem cell therapies.

The referenced studies seemed to be early phase trials, small sample size studies (such as a five year follow up of three patients), and case reports. One business referenced a few early phase studies but mostly a long list of what appeared to be general information about stem cells such as the definition of "blood stem cell" by National Cancer Institute and a Wikipedia page on "regeneration in humans".

Another business offering umbilical cord stem cell therapies for orthopedic diseases referenced a long list of early phase studies for embryonic, bone marrow, adipose, and other source of stem cells for a wide array of medical conditions, from obesity to various heart diseases, HIV-1 infections, spinal cord injuries and more. There wasn't a therapeutic or cell source match between most of the referenced studies and their advertised stem cell therapy.

The following quotes were pulled from some of the referenced studies mentioned on a couple of business's websites. These quotes are being included as examples to demonstrate the early phase studies that some stem cell businesses cite as proof of research for patients to reference when considering the clinic's advertised treatment that the clinic claims to be effective. These quotes from some of the referenced studies clearly acknowledge the need for further research yet the stem cell clinics do not advertise the incompleteness of the research they reference.

> "Undoubtedly, a great deal of progress is required at both basic and clinical research fronts before these cells can be used routinely in the clinic for treating patients with OA."

> "Although a growing interest for biological alternatives of treating knee pathology has been observed in the past few years, there still remains a paucity of high-quality studies."

5. DISCUSSION

This paper serves to bring awareness to researchers, ethicists, regulatory bodies, and potential consumers. The motivation behind this study was made in part by the increasing number of unregulated stem cell clinics in which we believe exposes patients to physical and financial risks, as well as jeopardizes the development of regulated and peer reviewed stem cell research. This study serves to present what the public is told by unregulated stem cell clinics, to strengthen pubic knowledge of the risks of direct-to-consumer stem cell therapies, as well as raise awareness to regulatory agencies about the increased misleading public representation by stem cell providers and the consequences to vulnerable patient populations in search of treatments for their disease.

This primary data collection paper takes a semi-quantitative approach and combines analyses of websites and presentations by stem cell clinics to build on the few published stem cell seminar reports as well as various published analyses of stem cell clinic websites to date.

Consistent with these works, we found that the portrayal of stem cell therapies in this "early market" by direct-to-consumer stem cell clinics is too optimistic where advertised therapies are not supported by clinical evidence or substantiated by peer reviewed literature. We undertook this study to test whether a comprehensive review of information presented at such various stem cell seminars confirm consistent findings with the single seminar reports. "I believe that such stem cell clinic marketing poses a significant threat to public perception and understanding of the legitimate stem cell translational medicine field", says cell biologist Paul Knoepfler in a report sharing his first-hand experience attending an "educational" stem cell seminar in which he described as "the stem cell hard sell" (Knoepfler, 2016). Consistent observations and conclusions were also found in another seminar report titled "I Went to a Stem Cell Sales Pitch Seminar and I feel Like Buying a Time Share" (Jarry, 2019).

We have noted key observations among the stem cell "educational" or "infomercial" presentations in this study. First, common recruiting strategies are used in which regular presentations are hosted by the stem cell clinics where the promise of stem cell therapies are hyped up with the strong implication that they've been well researched and proven. Oftentimes, outright safety claims are made stating that the advertised therapy is "safe" with "no side effects" other than common post procedure symptoms. Second, the risks of standard therapies are emphasized and contrasted with the "safety" and convenience of stem cell therapy. Third, assurance of cell quality and safety of allogeneic cell sources is often discussed using the argument that the cell injections are obtained from FDA regulated labs, or, if regulated labs are not mentioned, obtained from hospitals that "screen and test" the donated cells for safety. However, the regulation of the actual stem cell treatment being offered is often not discussed, said to be allowed under FDA's minimal manipulation guidelines, or implied that it is not

needed. The assurance and safety of autologous cell sources is usually discussed by using the argument that they are the patient's own cells and pose no risk for infection or rejection. Finally, the fourth observation relates to the common responses as to why insurance companies do not yet cover stem cell treatments. Often, the reason given is quality care is not covered, or insurance companies take a long time to "get on board". But one business took it a step further and implied that "big pharma" hinders the approval of "natural therapies" under insurance plans.

Some of the clinics treat conditions not listed in this paper using other interventions which they offer. However, for the purposes of this paper, only conditions treated by the clinics' interventions involving stem cells or derivatives of stem cells were reported.

Our observations confirm Knoepfler's sense that he expressed in the following statement: "While I do not know what other stem cell clinic infomercial seminars are like first-hand, my sense from watching clinic marketing videos, including those on YouTube, is that the one I attended was fairly representative of what goes on at such customer recruitment events" (Knoepfler, 2016).

In 2019, the FDA issued a warning about stem cell therapies: "FDA Warns About Stem Cell Therapies". In its warning, the FDA advises anyone considering stem cell therapy to ask if the advertised treatment has been reviewed by the FDA, request facts, and ask questions in regard to signing a patient consent form, IND applications, and IRB involvement. Someone considering stem cell therapy should note that simply because the stem cells are their own cells does not mean the treatment is safe. There remains safety risks with autologous treatments, as warned by the FDA. Additionally, cells removed and manipulated bear the risk of cell contamination, as also warned by the FDA.

This study reports on a collection of seminars in combination with clinic website content review and adds to the existing literature, which currently contains stem cell clinic website content reviews and two single seminar reports. Perhaps a next step to complement the current literature in this area is to survey patients which have experienced stem cell treatments by stem cell clinics similar to the ones reported on in this paper, i.e. treatments not conducted under an FDA IND application. Key points to note would be the patients' experiences, whether they have noticed benefits that were promised by the clinic administering the treatment, whether they have been harmed as a result of the intervention, how much it cost the subjects, and finally any informed consent documents or other paperwork which they may have signed as part of the process.

As this paper was written amidst the COVID-19 pandemic during the year of 2020, it was noted that some direct-to-consumer stem cell businesses were reported to authorities as using the COVID-19 pandemic as a business opportunity, claiming that stem cell interventions may strengthen the immune system, prevent, or even treat the COVID-19 virus.

Business H from this review was indicted by the FDA for using the COVID-19 pandemic to bill insurance companies for high dose infusions of Vitamin C to prevent the virus. Turner (2020) reported on some stem cell businesses that have claimed to treat or prevent the COVID-19 virus. One business issued a press stating, "Now Offering Mesenchymal Stem Cell Treatments to Support Lung Health During COVID-19". Another business advertised its stem cell interventions as a "precautionary measure" to prevent the COVID-19 virus, and a third business advertised their stem cell intervention via Facebook stating in their post, "Did you know that STEM CELLS can be administered intravenously and by inhalation through a nebulizer to treat lung damage caused by COVID-19 and other non-related lung conditions". In brief, it

appears that clinic claims similar to the ones shown in the Results of this paper are now being tailored to “fit” the current situation of the COVID-19 pandemic.

Our review is not to diminish or undermine the promise and potential benefits of stem cell therapies being studied and reported on in substantiated peer reviewed literature. Our review is rather meant to attract attention to the mushrooming of stem cell pseudoscience for unproven, unregulated, and potentially dangerous direct-to-consumer stem cell therapies. We acknowledge the former and ongoing clinical trials which are offering stem cell therapies that are approved for investigational study by the FDA and IRB.

The rising number of for-profit stem cell clinics in the United States advertising unproven and potentially harmful stem cell therapies necessitates the need for further regulatory measures and precautions in order to reduce or eliminate the risk that direct-to-consumer stem cell clinics pose on potential consumers’ health and on the field of stem cell research.

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