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Assessing "Cell Therapy" Clinics Offering Treatments of Ocular Conditions using Direct-to-Consumer Marketing Websites in the United States

Rajinder S. Nirwan, MD,[1] *Thomas A. Albini, MD,*[2] *Jayanth Sridhar, MD,*[2] *Harry W. Flynn, Jr., MD,*[2] *Ajay E. Kuriyan, MD, MS*[1]

Purpose: "Cell therapy" is becoming increasingly available to the public via online direct-to-consumer advertisement within the United States (U.S.). The current study investigates the scope of "cell therapy" clinics across the U.S. that advertise and offer "cell therapy" for ocular conditions based on information provided on their websites.

Design: Cross-sectional study.

Participants: The study included companies that are U.S.-based, participate in direct-to-consumer online marketing, have websites that can be data-mined with content analysis, and advertise therapy for ocular conditions.

Methods: Using a systematic, extensive keyword-based Internet search, content analysis of company websites was utilized to identify, document, and analyze U.S. businesses marketing "cell therapy" for ocular conditions as of September 16, 2017.

Main Outcome Measures: Clinic locations, source of stem cells used, route of administration, marketed ocular conditions, and cost of treatment.

Results: Forty companies with 76 clinics use "cell therapy" to treat ocular conditions. California (23), Florida (12), and Illinois (10) contain the most clinics. All 40 companies specified sources of cells, which included autologous adipose-derived stem cells (35; 67%), autologous bone marrow–derived stem cells (8; 15%), amniotic stem cells (2; 4%), peripheral blood–derived stem cells (2; 4%), umbilical cord blood stem cells (2; 4%), allogenic bone marrow–derived stem cells (1; 2%), placental stem cells (1; 2%), and xenocells (1; 2%). The most commonly marketed ocular conditions included macular degeneration (35), optic neuritis (18), retinitis pigmentosa (17), and diabetic retinopathy (16). The most common routes of administration were intravenous (22) and "unspecified" (12); however, other companies listed more ocular-specific routes such as intravitreal injections (2), retrobulbar injections (2), eye injections (2), retrofundal injection (1), sub-Tenon injection (1), intraocular injection with vitrectomy (1), and eye drops (1). The cost of advertised "cell therapy" ranged from $4000 to $10 500.

Conclusions: "Cell therapy" for ocular conditions is readily available via direct-to-consumer marketing strategies across the United States. The "cells" are harvested from numerous sources and administered through different methods for multiple ocular conditions at these "cell therapy" clinics. Limited data for these treatments necessitates advocating caution to physicians and patients about treatments offered at commercial "cell therapy" clinics. *Ophthalmology 2019;■:1–6 © 2019 by the American Academy of Ophthalmology*

Cell therapies offer great potential for treatment of complex refractory medical conditions and have already been successfully implemented in the management of hematologic diseases.[1–3] There are multiple ongoing or recently completed clinical trials studying the use of cell therapies for ophthalmic diseases, including macular degeneration, Stargardt disease, hereditary retinal degenerations, diabetic retinopathy, retinal vein occlusion, glaucoma, and optic neuropathies.[4] Additionally, published studies demonstrated safety of specific cell therapy interventions for certain retinal conditions.[5–9] Dissociated cell therapy delivery approaches include transvitreal subretinal transplantation of human embryonic stem cell–derived retinal pigment epithelium cells for nonneovascular age-related macular degeneration (NNV-AMD) and Stargardt disease, and transcleral subretinal transplantation of human umbilical tissue–derived cells for NNV-AMD.[5,6] Successful and safe transplantation of induced pluripotent stem cell–derived and human embryonic stem cell–derived retinal pigment epithelium sheet for NNV-AMD and neovascular AMD have also been reported.[7–9]

Although these scientific clinical trials continue to progress toward the goal of providing new Food and Drug Administration (FDA)-approved treatments for patients with

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ophthalmic diseases, so-called "cell therapy" clinics currently provide "cell therapy" treatments for various medical diseases, including ocular conditions.[10,11] These "cell therapy" clinics use direct-to-consumer online marketing to advertise their treatments. There have been several reports of complications after "cell therapy" treatments at these clinics for ocular diseases. Patients have been reported to experience retinal and vitreous hemorrhages, retinal detachments with proliferative vitreoretinopathy, central retinal artery occlusion, and zonular weakness.[12–16] In 1 of these reports, patients' vision in the better-seeing eye ranged from 20/30 to 20/50 before injection, and ranged from 20/200 to no light perception in the better-seeing eye at the 1-year postinjection mark.[12] These alarming complications have sparked the need to increase awareness regarding the number and scope of these "cell therapy" clinics offering ophthalmic treatments. The purpose of this study is to assess the number and locations of "cell therapy" clinics offering treatments for ophthalmic diseases in the United States (U.S.). This study also describes the types of "cell therapies" at these clinics and the specific ocular disorders they advertise to treat.

Methods

An intensive, systematic, keyword-based Internet search was conducted to perform content analysis, along with text mining of company websites, to identify U.S.-based businesses marketing "cell therapy" for ocular conditions directly to patients. The approach to the website search was previously described by other investigators.[10,17] The Google and Bing search engines were used to identify, document, and analyze individual companies and their associated clinics. In addition, a search was conducted for companies on Facebook, YouTube, Twitter, and LinkedIn. Furthermore, 2 different web browsers, Safari and Google Chrome, were used to maximize our findings because their distinct search tools can produce varying results. Common marketing phrases were searched, including "cell treatment" and "cell therapy," as well as more specific phrases such as "cell treatment for age-related macular degeneration," to identify businesses offering "cell therapy" interventions directly to consumers. For each Internet-based search, 20 pages of results (with 10 sites/page) were reviewed. Shorter searches were utilized, or searches were concluded when search terms failed to identify new businesses. The formal search process took place from September 1, 2017 to September 16, 2017.

The following inclusion and exclusion criteria (Table 1) were utilized to aid in evaluation of websites. The search was restricted to U.S.-based companies with websites that promoted direct access to "cell therapies" for ocular conditions via online, direct-to-consumer marketing. Although companies that had headquarters or offices in the U.S. but administered interventions outside of the country were documented, they were excluded from final analysis. This study excluded U.S. and international companies that participated in mail order delivery of stem cell products or cell-processing medical devices. For companies that met those criteria, documentation included company name, website URL, geographic location, number of clinics, type or types of cells they claimed to use, specific location of administration of "cell therapy," cost of treatment, type of physician associated with company (if any), whether or not they reported participating in a clinical trial, and the marketed ophthalmologic conditions for treatment. During data analysis, some businesses were noted to use more than 1 name and have multiple websites. For these cases, only the primary company names and websites were listed. The dataset was reviewed numerous times to ensure accuracy; however, we discovered that certain websites were changing frequently in terms of content. In these instances, the findings on the initial search were recorded. When questions arose during the content analysis process, businesses were flagged for further review and discussion by authors R.S.N. and A.E.K. until a consensus was reached. A geographic map was created using the My Maps tool of Google Maps. The location data were imported as an Excel spreadsheet into My Maps. Each city was assigned a red pin. Pins were only used for the continental U.S. for purposes of maintaining appropriate map resolution.

Results

Number of Businesses

Forty businesses were identified that offered "cell therapy" for ophthalmic conditions via direct-to-consumer marketing. Most companies that offered "cell therapy" for ophthalmic conditions were found through clinics that advertised for many medical conditions, not just ophthalmic conditions. Certain businesses were discovered through franchise operations such as Cell Surgical Network and Regenexx.

Geographic Locations and Distribution of U.S. Businesses Marketing "Cell Therapy" for Ophthalmic Conditions

The 40 businesses identified marketed and delivered "cell therapy" interventions for ophthalmologic diseases at 76 clinics within the U.S. (Fig 1). Some companies operated multiple clinics. Multiple companies have clinic sites in varying locations within the U.S.; an additional 7 companies were discovered that stated to have their contacts, offices, or headquarters within the U.S. but carry out the procedures abroad in various countries. These countries included Peru, Mexico, Ukraine, Guatemala, India, and the Dominican Republic. "Cell therapy" clinics treating ocular conditions are more prevalent in certain states: California contained the most clinics (23), followed by Florida (12) and Illinois (10). Two of these 40 U.S.-based companies were noted to have additional international clinics outside of the U.S.

Marketed Ophthalmic Conditions Treated

All of the identified businesses provided information regarding the types of ocular conditions that they treat with "cell therapy"; however, the level of detail, as well as the range of conditions, was variable. We contacted several clinics by telephone to obtain more information about their treatments; however, none was willing to provide information outside of an in-person clinical consultation visit. All of the conditions marketed for treatment are summarized in Table 2. There were a total of 27 companies that claimed to treat more than 1 ocular condition and 13 companies that claimed to treat 5 or more conditions. The most common advertised ocular condition that businesses marketed "cell therapy" for was macular degeneration (35), followed by optic neuritis (18), retinitis pigmentosa (17), and diabetic retinopathy (16).

Table 1. Inclusion and Exclusion Criteria for Companies Offering Direct-to-Consumer "Cell Therapy" for Ocular Conditions

Inclusion Criteria	Exclusion Criteria
U.S.-based companies	International companies
Marketing "cell therapy" directly to consumer via the Internet	Administer cell therapy outside of U.S.
Websites that can be data-mined	Mail-order delivery of cell therapy
Advertise treatment for ocular conditions	Cell-processing medical devices

U.S. = United States.

Types of Advertised Cell Interventions

All 40 businesses provided information regarding the sources for their "cell therapy" interventions (Figure 2). The majority of interventions were autologous-based treatments, with only 2 businesses advertising only allogenic-based treatments. Three businesses offered both autologous- and allogenic-based treatments. Of the 40 businesses, 8 (20%) offered the use of multiple cell types. The remaining 32 (80%) made use of a single cell source. The most frequently used cell type was autologous adipose-derived stem cells (35; 67%). Other cell types included autologous bone marrow–derived stem cells (8; 15%), amniotic stem cells (2; 4%), peripheral blood–derived stem cells (2; 4%), umbilical cord blood stem cells (2; 4%), placental stem cells (1; 2%), allogenic bone marrow–derived stem cells (1; 2%), and xenocells (1; 2%).

Location of Administration

The businesses often advertised more than 1 route of administration. The most common route of administration was intravenous (22). Numerous companies did not mention their route of administration on their website and as such were categorized as "unspecified" (12). Other common administration techniques listed were joint injections (10), intrathecal (9), intraarterial (9), organ injections (7), subcutaneous injections (7), and targeted injections (6). Of note, many companies claim to participate in the treatment of other medical conditions aside from ocular disease and as a result some of their administration processes were not eye-specific. Of the companies that specifically listed ocular administration (6), advertised routes of administration included "eye injections" (2), intravitreal injections (2), retrobulbar injections (2), eye drops (1), retrofundal injection (1), sub-Tenon injection (1), and intraocular injection with vitrectomy (1). Two companies offered more than 1 ocular method of administration.

Cost of Treatment

The majority of businesses did not advertise the cost of treatment. Only 4 companies listed their prices, which varied from $4000 to $10 500 for a single treatment. Other companies noted that a consultation fee would apply and the price would be determined after the initial visit depending on type of cell required, method of administration, and the disease being treated.

Association with Medical Doctors and Clinical Trials

The use of a medical professional with MD credentials was affiliated with 33 of 40 companies (83%). Six of the 40 companies (15%) claimed to be associated with, or to participate in, clinical trials or clinical studies. Two companies were registered on the Clinicaltrials.gov website.

Figure 1. Geographic representation of "cell therapy" clinics marketing treatment for ophthalmologic conditions in the continental United States. Hawaii (not depicted) has 1 such clinic.

Table 2. Ophthalmologic Conditions Marketed by "Cell Therapy" Clinics

Marketed Condition	Number of Businesses
Macular degeneration	35
Optic neuritis	18
Retinitis pigmentosa	17
Diabetic retinopathy	16
Glaucoma	14
Optic neuropathy*	13
Retinal detachment	8
Dry eye	7
Stargardt macular dystrophy	4
Retinal degeneration	3
Macular hole	2
Blindness	2
Central retinal vein occlusion/retinal vascular occlusion	3
Plaquenil toxicity	2
Corneal diseases	2
Limbal stem cell deficiency	2
Corneal ulcers	2
Retinal microhemorrhage	1
Myopic macular degeneration	1
Ischemic retinopathy	1
Retinitis	1
Ophthalmology	1
Stevens-Johnson syndrome	1
Trauma	1

*Optic neuropathy includes optic nerve atrophy, Leber hereditary optic neuropathy, and optic nerve injury.

Discussion

The number of "cell therapy" clinics throughout the U.S. has been increasing at an alarming rate. In 2016, 1 study found the U.S. to have 187 unique "cell therapy" clinic websites offering "cell therapy" at 215 different clinics for all diseases.[18] A similar study in 2016 discovered 351 companies that participated in direct-to-consumer marketing of "cell therapy" treatment in as many as 570 clinics.[10] "Cell therapy" clinics claim to bypass FDA regulation by reasoning that the cells are minimally manipulated and applied for homologous use and therefore do not fall under FDA regulatory oversight.[11,19–21] In December of 2014 and October of 2015, the FDA issued draft guidance statements to define the term "minimally manipulated" stem cells and to delineate homologous use.[22,23] This was done to clarify that autologous stem cells and their use fall within the regulatory auspices of the FDA.[22,23]

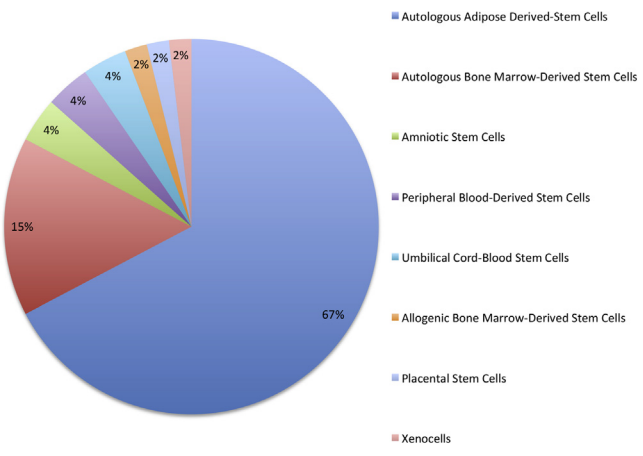

Figure 2. Marketed stem cell sources for ophthalmologic conditions.

Treatments at these "cell therapy" clinics have resulted in severe ocular complications. A recently published case series involved 3 patients who suffered blinding complications after receiving adipose-derived stem cells for AMD at a single clinic.[12] Although the "cell therapy" clinic had an active "study" listed on Clinicaltrials.gov, the 3 patients were not enrolled in the study, as they did not meet the eligibility criteria. Their preinjection visual acuity in their better-seeing eye ranged from 20/30 to 20/50. After their treatments, they developed severe complications including retinal and vitreous hemorrhages, retinal detachments with proliferative vitreoretinopathy, and zonular weakness. Their postinjection visual acuity in their better-seeing eye ranged from 20/200 to no light perception, 1 year after injection. Another case report described a patient with retinitis pigmentosa who was seen in a "cell therapy" clinic in Florida before being referred for treatment in the Dominican Republic.[13] The treatment was associated with a $4000 fee and he was not informed of any risks. Two months after injection of "cell therapy" the patient began to experience floaters, metamorphopsia, and enlarging scotoma. The patient ultimately lost vision owing to retinal detachment with proliferative vitreoretinopathy. Other cases of retinal detachment with proliferative vitreoretinopathy have been described following intravitreal and subretinal "cell therapy" administration at "cell therapy clinics."[14,15] Yet another patient with retinitis pigmentosa suffered from a central retinal artery occlusion after a peribulbar injection of autologous bone marrow cells.[16]

In light of the recent awareness of ocular complications, the American Academy of Ophthalmology issued a clinical statement in 2016 highlighting that there are no FDA-approved stem cell therapies for ocular conditions.[24] They went on further to mention that the risks associated with treatments are unknown.

In an effort to curb these "cell therapy" clinics, the FDA issued a warning to a "cell therapy" clinic where patients experienced blinding complications after bilateral intravitreal injections, owing to concern for the lack of evidence and safety for "cell therapy," as well as methods of tissue handling.[25] Upon revisiting company websites found in this study's initial search after the FDA warning letter, we found that 13 "cell therapy" clinics have either removed all ocular conditions from their list of treatable diseases or have discontinued their URLs.

Based on the experiences of patients who encountered complications from treatments at such "cell therapy" clinics, there are several potential signs that may indicate that a "cell therapy" clinic could put a patient's health at risk (summarized in Table 3). This list is not exhaustive, and some unregulated commercial clinics may not meet all the criteria listed in Table 3. Education of patients about the risks of these "cell therapy" clinics by physicians is

Table 3. Summary Guidelines to Help Identify Commercial "Cell Therapy" Clinics

Summary Guidelines
Consultation fees
Payments required/associated with treatment
No registration of clinical trial or not meeting eligibility for clinical trial
Bilateral treatment administration
Signing of waiver preventing discussion of personal results
Company headquarters outside of the U.S.
Treatment administered outside of the U.S.
Only treatments offered at clinic is "cell therapy"

U.S. = United States.

extremely important to decrease the chance that patients pursue treatments at these clinics.

The harm that these clinics cause is manifold. The majority of these clinics selectively advertise only positive outcomes through testimonials on their websites, which engenders a false sense of security for patients who are utilizing these treatments. For some patients, this expectation of no complications resulted in a delay of seeking care for complications associated with the treatments. The cost of these treatments is completely out of pocket, leading to some patients taking out loans to obtain treatments.

Though methodical scientific research continues to be the driving force for advancing novel therapies such as cell therapy, blinding complications that have occurred at "cell therapy" clinics have the potential to raise skepticism about even legitimate cell therapy research. The difficulty in distinguishing between these "cell therapy" clinics and legitimate cell therapy research is magnified by the listing of patient-funded research by some of these "cell therapy" clinics on Clinicaltrials.gov.[12,26] In an effort to combat this issue, Clinicaltrials.gov has added a prominent disclaimer stating that "listing a study does not mean it has been evaluated by the U.S. Federal Government" and recommending "before participating in a study, talk to your health care provider and learn about the risks and potential benefits." In addition to studies listed on Clinicaltrials.gov, there are a handful of case reports and a case series of positive outcomes from these "cell therapy" clinics that are published in the scientific literature.[27–30] Similar to the selected website testimonials, these cases are selected to show potential positive outcomes and do not include any patients with complications. By choosing which outcomes are reported in the scientific literature and not publishing a full dataset of the outcomes of treated patients, these "cell therapy" clinics are co-opting means of scientific dissemination to advance their goal of advertising positive results.

Early-phase, scientifically rigorous clinical trials examining cell therapy applications for ocular disorders provide hope for patients with end-stage ocular diseases.[5–9] In contrast, "cell therapy" clinics are commercially performing procedures for an assortment of ocular conditions without the appropriate safety or efficacy data and without FDA approval. Our study found that direct-to-consumer marketing of "cell therapy" for ocular conditions is a large problem, with over 27 sites remaining even after the FDA's recent warning letter. Owing to the potential complications after treatment at such "cell therapy" clinics, the medical and scientific communities need to continue educating the public about the potential risks associated with treatments at such clinics. Clinics offering these "cell therapy" treatments should disclose their complete outcome data, including complications. Further regulatory oversight of such clinics is key to protecting patients from these harmful complications. Nevertheless, positive strides are being made in scientifically rigorous and safe clinical trials studying the potential of cell therapies to treat ocular diseases.

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[1] Flaum Eye Institute, University of Rochester, Rochester, New York.

[2] Bascom Palmer Eye Institute, University of Miami, Miami, Florida.

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Author Contributions:

Conception and design: Nirwan, Albini, Sridhar, Flynn, Kuriyan

Analysis and interpretation: Nirwan, Kuriyan

Data collection: Nirwan, Kuriyan

Obtained funding: Kuriyan

Overall responsibility: Nirwan, Albini, Sridhar, Flynn, Kuriyan

Abbreviations and Acronyms:
FDA = Food and Drug Administration; **NNV-AMD** = nonneovascular age-related macular degeneration; **U.S.** = United States.

Correspondence:
Ajay E. Kuriyan, MD, MS, Flaum Eye Institute, University of Rochester Medical Center, 601 Elmwood Avenue, Box 659, Rochester, NY 14642. E-mail: Ajay.kuriyan@gmail.com.