Fulton County Superior Court
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Date: 9/14/2020 8:08 AM
Cathelene Robinson, Clerk

IN THE SUPERIOR COURT OF FULTON COUNTY
STATE OF GEORGIA

STATE OF GEORGIA *ex rel.* CHRISTOPHER M. CARR, Attorney General State of Georgia, Plaintiff, vs. ELITE INTEGRATED MEDICAL, LLC f/k/a Superior Healthcare of Woodstock, LLC d/b/a Superior Healthcare Group, Superior Healthcare Sandy Springs, and Superior Healthcare Morrow, and JUSTIN C. PAULK, Individually Defendants.	)))))))))))))))))	CIVIL ACTION FILE NO. 2020CV340369

COMPLAINT FOR INJUNCTIVE RELIEF, CIVIL PENALTIES, RESTITUTION AND OTHER RELIEF

COMES NOW Plaintiff State of Georgia through Christopher M. Carr, Attorney General for the State of Georgia ("Attorney General"), and files this Complaint as follows:

NATURE OF THE ACTION

1.

This Attorney General brings this action pursuant to the Georgia Fair Business Practices Act, O.C.G.A. §§ 10-1-390 *et seq.* ("FBPA"). The purpose of the FBPA is to protect consumers and legitimate business enterprises from "unfair or deceptive practices in the conduct of any trade or commerce in part or wholly in the state." O.C.G.A. § 10-1-391(a). It prohibits, among other things, acts and practices that cause confusion as to the source, sponsorship, approval, or certification of goods or services; acts or practices that cause confusion as to certification by another; the making of representations that goods or services have sponsorship, approval,

characteristics, ingredients, uses, benefits, or quantities that they do not have; and the use of a computer or computer network to engage in these practices.

2.

The Attorney General brings this action against Elite Integrated Medical, LLC f/k/a Superior Healthcare of Woodstock, LLC d/b/a Superior Healthcare Group, Superior Healthcare Sandy Springs, and Superior Healthcare Morrow ("Elite"), and Justin C. Paulk (an individual) (collectively "Defendants") pursuant to the FBPA, seeking remedies available under O.C.G.A. § 10-1-397(b) and O.C.G.A. § 10-1-851, including but not limited to injunctive relief, civil penalties, restitution to consumers, and reimbursement of costs.

PARTIES, JURISDICTION, AND VENUE

3.

Plaintiff is the State of Georgia, ex rel. Georgia Attorney General Christopher M. Carr. The Attorney General has authority to enforce the FBPA, and is authorized to act in the public interest to protect consumers from unfair and deceptive practices. In his official capacity pursuant to O.C.G.A. § 10-1-397, the Attorney General commences this lawsuit against the above-named defendants.

4.

Defendant Elite Integrated Medical, LLC ("Elite") is a Georgia limited liability company, having its principal place of business at 7100 Peachtree Dunwoody Road, Suite 100, Sandy Springs, Fulton County, Georgia 30328. Elite's registered agent for service of process is Michael B. Weinstein, 3050 Amwiler Rd., Suite 200-C, Atlanta, Fulton County, Georgia 30360. Prior to March, 2019, Elite's entity name was Superior Healthcare of Woodstock, LLC and it operated using the tradenames Superior Healthcare Group, Superior Healthcare Sandy Springs, and Superior Healthcare Morrow. At all times material to this Complaint, Elite operated a

medical practice that advertises and offers regenerative medicine products to Georgia consumers to treat, cure, and mitigate various diseases and health conditions.

5.

Defendant Justin C. Paulk ("Paulk") is an individual residing at 395 Jep Wheeler Rd., Woodstock, Cherokee County, Georgia 30188. Paulk owns and manages the day to day operations of Elite. At all times material to this Complaint, Paulk had the authority to control, and participated in the acts and practices of Elite including the acts and practices that are set forth in this Complaint. Among other things, Paulk has the sole authority to approve all marketing content relating to the regenerative medicine products offered by Elite and regularly communicates with the company that published and disseminated marketing content on behalf of Elite and with other individuals and entities that provided advice about the content of Elite's marketing content. Likewise, Paulk approved the use of all regenerative medicine products offered by Elite despite the fact that he knew or should have known about the FDA's published guidelines concerning regulation of the types of regenerative medicine products offered by Elite and that those products had not been approved by the FDA for clinical use.

6.

Pursuant to the provisions of O.C.G.A. § 10-1-403, the Attorney General conducted an investigation into the acts and practices of Elite and Paulk that appeared to be unlawful under the FBPA. Pursuant to O.C.G.A. § 10-1-402, at the conclusion of the investigation Elite and Paulk were given the opportunity to appear before the Attorney General and to propose a resolution acceptable to the Attorney General. Neither defendant proposed a resolution acceptable to the Attorney General.

7.

This Court has jurisdiction over this action and the parties pursuant to GA. CONST. Art. 6, § 4, ¶ 1, O.C.G.A. § 10-1-397(b)(2), O.C.G.A. § 15-6-8, and O.C.G.A. § 9-10-91.

8.

Venue for this action against Elite is proper in this Court, pursuant to GA. CONST. Art. 6, § 2, ¶ 6, O.C.G.A. § 10-1-397(b)(2), O.C.G.A. § 9-10-93, and O.C.G.A. § 14-2-510 because Elite's principal place of business is in Fulton County, and a substantial part of Elite's business was transacted in Fulton County. Venue as to Paulk is proper in Fulton County pursuant to O.C.G.A. § 9-10-31 because these defendants are joint obligors and/or joint participants in the acts and practices described below.

BACKGROUND ON STEM CELLS AND REGENERATIVE MEDICINE

9.

Regenerative Medicine involves replacing, engineering, or regenerating human cells, tissues, or organs to establish, restore, or enhance normal function.[1] Regenerative medicine products include cell therapies, therapeutic tissue-engineering products, human cell and tissue products, and certain combination products involving cells and devices.[2]

10.

The US Food and Drug Administration ("FDA") has the authority to regulate regenerative medicine products under the 1938 Food, Drug and Cosmetic Act ("FD&C Act) and the Public Health Service Act ("PHS"). Generally, all stem cell products and exosome products require FDA approval. Currently the only stem cell products that are FDA-approved consist of

[1] The New England Journal of Medicine, Balancing Safety and Innovation for Cell-Based Regenerative Medicine, https://www.nejm.org/doi/full/10.1056/NEJMsr1715626, a copy is attached hereto as Exhibit "A".
[2] *Id.*

blood-forming stem cells that are approved for use in patients with disorders that affect the production of blood but they are not approved for other uses.[3]

11.

Regenerative medicine products that have not been approved for use by the FDA are considered investigational products that must go through a thorough FDA review process as investigators prepare to determine safety and effectiveness of products in well-controlled human studies, called clinical trials.[4] During the last several years, the FDA has issued several warning letters to regenerative medicine product manufacturers and clinics that offer regenerative medicine products directly to consumers regarding their unapproved marketing of products derived from amniotic tissue, umbilical cord blood, and umbilical tissue.[5]

12.

Dr. Stephen Hahn, the current Commissioner of the FDA, and Dr. Peter Marks, the Director of the FDA's Center for Biologics Evaluation and Research, recently published a viewpoint article stating "[i]t is time for unproven and unapproved regenerative medicine products to be identified and recognized for what they frequently are: uncontrolled experimental procedures at a cost to patients, both financially and physically.[6] Additionally, the FDA issued a consumer alert about regenerative medicine products on July 22, 2020, advising "[a]nyone considering the use of anything purported to be a regenerative medicine product, including stem cell products, exosome products, or other widely promoted products such as products derived from.....human umbilical cord blood, Wharton's Jelly or amniotic fluid should know" among

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[3] https://www.fda.gov/consumers/consumer-updates/fda-warns-about-stem-cell-therapies, attached hereto as Exhibit "B"; https://www.fda.gov/vaccines-blood-biologics/consumers-biologics/consumer-alert-regenerative-medicine-products-including-stem-cells-and-exosomes, attached hereto as Exhibit "C".

[4] https://www.fda.gov/consumers/consumer-updates/fda-warns-about-stem-cell-therapies, attached hereto as Exhibit "B".

[5] https://www.fda.gov/news-events/press-announcements/fda-announces-comprehensive-regenerative-medicine-policy-framework, https://www.fda.gov/news-events/press-announcements/fda-sends-warning-company-selling-unapproved-umbilical-cord-blood-and-umbilical-cord-products-may, https://www.fda.gov/news-events/press-announcements/fda-puts-company-notice-marketing-unapproved-stem-cell-products-treating-serious-conditions, https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/invitrx-therapeutics-inc-581182-03162020, copies are attached hereto as Exhibit "D".

[6] A copy of the article is attached hereto as Exhibit "E".

other material facts, that none of these products have been approved to treat any orthopedic condition, neurological disorder, or cardiovascular or pulmonary diseases.[7]

13.

Practicing physicians, scientists, and regulatory experts in the field of regenerative medicine condemned practices involving advertising and offering unproven stem cell products, in a joint consensus statement issued on February 18, 2019, stating "[t]he aggressive marketing approach currently used by practitioners and clinics regarding various birth tissue products as safe and effective "stem cell therapy" is not supported by the existing scientific literature."[8] "While there are early clinical data on stem cells that are isolated from fresh birth tissues and culture expanded, these studies used treatments which are not analogous to the commercially available, cryopreserved, FDA registered birth tissue products."[9]

14.

In conjunction with announcing the entry of a consent order against a clinic that misrepresented its amniotic stem cell products as able to treat, cure, or mitigate a variety of diseases and health conditions, the Federal Trade Commission warned that marketers should not create confusion by playing fast and loose with the facts as the phrase "stem cell treatment" covers a broad range of therapies – from promising research to flat-out fraud. It may not be easy for consumers to make nuanced distinctions.[10]

15.

Google has likewise taken action to curb marketing practices involving unproven regenerative medicine products. It announced in September 2019, that it would no longer accept

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[7] https://www.fda.gov/vaccines-blood-biologics/consumers-biologics/consumer-alert-regenerative-medicine-products-including-stem-cells-and-exosomes, attached hereto as Exhibit "C".

[8] https://interventionalorthobiologics.org/wp-content/uploads/2019/02/Consensus-Statement-on-Aggressive-Marketing-of-Birth-Tissues-as-Stem-Cell-Therpeies-Final-Published-Feb-18-2019-v2-1.pdf, a copy of the consensus statement is attached hereto as Exhibit "F".

[9] *Id.*

[10] https://www.ftc.gov/news-events/blogs/business-blog/2018/10/stemming-unproven-stem-cell-therapy-claims, a copy is attached hereto as Exhibit "G".

new ads for "unproven or experimental medical techniques," including most stem cell therapy, cellular therapy and gene therapy.[11] Google said it was taking the step after seeing "a rise in bad actors" trying to take advantage of patients by offering "untested, deceptive treatments."[12]

DEFENDANTS' BUSINESS ACTS AND PRACTICES

16.

Defendants operate a medical clinic that advertises, offers for sale, sells, and distributes regenerative medicine products derived from birth tissues including placental tissue, umbilical cord blood and Wharton's jelly ("regenerative medicine products") to Georgia consumers.

17.

At all times relevant to this Complaint, Defendants purchased regenerative medicine products from third-party manufacturers including Surgenex, LLC in Arizona, Predictive Biotech, Inc. in Utah, and BioIntegrate, LLC in New York.

18.

The regenerative medicine product Defendants purchased from Surgenex, LLC, Surforce, is a product processed from placental tissue and described by Surgenex as an "amniotic membrane injectable" and/or an "amniotic membrane allograft".[13]

19.

The regenerative medicine product Defendants purchased from Predictive Biotech, Inc., CoreCyte, is a product derived from Wharton's jelly of the umbilical cord.[14]

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[11] https://www.washingtonpost.com/health/2019/09/06/new-google-policy-bars-ads-unproven-stem-cell-therapies/, https://support.google.com/google-ads/answer/9475042?hl=en, a copy is attached hereto as Exhibit "H".
[12] *Id.*
[13] A copy of a previous webpage from: https://surgenexcatalog.com/surforce.html, is attached hereto as Exhibit "I".
[14] https://www.predictivebiotech.com/products/#products, a copy is attached hereto as Exhibit "J".

20.

Predictive Biotech, Inc. describes CoreCyte as a "minimally manipulated human tissue allograft" that is "processed to preserve the structural integrity of Wharton's jelly.....and cryogenically preserved".[15]

21.

The regenerative medicine product Defendants purchased from BioIntegrate, Inc., GeneXStem, is a product derived from Wharton's jelly of the umbilical cord and described by BioIntegrate, Inc. as "minimally manipulated human tissue allografts."[16]

22.

BioIntegrate, Inc. funded a study of its GeneXStem product and the results were recently published in the Journal of Orthopaedic Surgery and Research.[17] The conclusion of the study was that the product demonstrated the presence of growth factors, cytokines, hyaluronic acid, and extracellular vesicles including exosomes and that "[t]hese factors represent *potential* expanded applications for regenerative medicine". (emphasis added).

23.

According to all three of the manufacturers, the regenerative medicine products advertised and offered by Defendants are human cellular and tissue products ("HCT/P") that are regulated by the FDA.

24.

The regenerative medicine products offered by Defendants do not fall under any exceptions from the FDA's regulation of HCT/P's.[18]

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[15] *Id.*

[16] A copy of a previous website page from: http://biointegrate.com/genextend-products/ is attached hereto as Exhibit "K".

[17] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7017504/ . A copy is attached hereto as Exhibit "L".

[18] 21 C.R.F. 1271.15.

25.

The regenerative medicine products offered by Defendants are regulated by the FDA as a "drug" and "biologic product" as the products do not meet each of the criteria necessary to be regulated solely as a HCT/P.[19]

26.

Each of the regenerative medicine products offered by Defendants require pre-market approval from the FDA and an investigational new drug application ("IND") for clinical use in humans.

27.

None of the regenerative medicine products offered by Defendants have been approved by the FDA for marketing and distribution, nor are they the subject of an IND that has been submitted to the FDA.

28.

The FDA issued a warning letter to Predictive Biotech on August 17, 2020, stating that CoreCyte is an unapproved drug and a biological product that may not be distributed for clinical use.[20]

29.

On information and belief, Defendants have not conducted any of their own clinical or scientific studies to evaluate the reliability, safety, or efficacy of the regenerative medicine products they offer.

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[19] 21 CFR 1271.10.
[20] A copy of the letter is attached hereto as Exhibit "M".

30.

Instead, Defendants represent, expressly and by implication, that studies and reports of third-parties that involve live stem cells derived from a patient's own bone marrow or fat that are injected or transplanted back into the patient, substantiate the claims they make about the regenerative medicine products they offer.

31.

Defendants also represent, expressly and by implication, that studies and reports of third-parties involving live stem cells that are isolated from birth tissues and then cultured expanded for use in another person, substantiate the claims they make about the regenerative medicine products they offer.

32.

The regenerative medicine products offered by Defendants are not essentially equivalent to either of the live stem cell therapies that are the subject of third-parties' studies and reports because the regenerative medicine products offered by Defendants are derived from a different source, do not contain the same ingredients, and are not processed or manufactured using the same processes or procedures.

33.

In reality, there is no competent and reliable scientific evidence establishing that Defendants' regenerative medicine products cure, treat, or mitigate any diseases or health conditions and/or that their regenerative medicine products are superior or comparable to conventional medical treatments used to cure, treat, or mitigate diseases and health conditions.

Website Advertising

34.

Defendants advertised their regenerative medicine products through the websites: superiorhealthcarega.com, superiorhealthcaregroup.com, and eliteintegratedmedical.com. Examples of statements appearing on Defendants' website are referenced below at Figures 1., 2. and 3., and are attached hereto as Exhibits "N", "O", and "P" respectively.

Figure 1. (superiorhealthcarega.com)

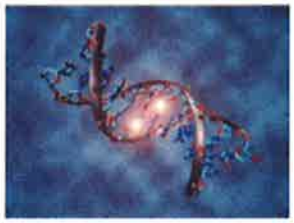
OUR REGENERATIVE CELLULAR MEDICINE TREATMENTS CAN PROVIDE REMARKABLE IMPROVEMENT WHEN OTHER TRADITIONAL MEDICAL PROCESSES HAVE FAILED OR HAD LIMITED EFFICACY.

REGENERATIVE CELLULAR MEDICINE TREATS MANY MEDICAL CONDITIONS

- Alzheimer's Disease
- Parkinson's Disease
- Ataxia
- Diabetes Type I & II
- Rheumatoid Arthritis
- Osteoarthritis
- Multiple Sclerosis (MS)
- Autoimmune Diseases
- COPD
- Pulmonary Fibrosis
- Chronic Bronchitis
- Stroke
- Scleroderma
- Psoriasis
- Kidney Disease
- Joint Repair

DISCOVER WHAT STEM CELL AND REGENERATIVE THERAPY CAN DO FOR YOU!

Stem Cell and Regenerative Therapy can provide incredible improvement and benefit to a person whether for medical and/or pain relief purposes without surgery.



To find out more about what Superior Healthcare's **Stem Cell and Regenerative Therapy** can do for you, **call us today or fill out the contact form above** and one of our patient advocates will get back to you right away.

Figure 2. (superiorhealthcaregroup.com)

What Can Regenerative Cell Therapy Treat?

- Neck Pain
- Shoulder Pain
- Tennis Elbow
- Tendonitis
- Back Pain
- Knee Pain
- ACL/MCL/PCL Injury
- Joint Pain
- Joint Injury
- Carpal Tunnel Syndrome
- Neuropathy
- Plantar Fasciitis
- Ligament Strains
- Bursitis
- Degenerative Arthritis
- Osteoarthritis of the Knee
- Degenerative Cartilage and Ligaments
- Low Back Pain
- Degenerative Joint Disease
- Shoulder Injury
- Rotator cuff tears
- Shoulder Degeneration
- Shoulder Bursitis
- Facet Syndrome
- Degenerative Disc Disease
- Lumbar Arthritis / Osteoarthritis
- Wrist/Hand Pain Treated
- Planter Fasciitis
- Golfer's Elbow
- Distal Biceps Tendon Tear
- Hip Pain
- Labrum tear
- Hip Osteoarthritis
- Hip Degeneration
- Hip Bursitis
- Meniscus Tear
- Chrondomalacia
- Foot and Ankle Pain

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How Does Our Stem Cell Therapy Work?

Stem Cell and Regenerative Therapy is an extremely effective non-surgical option for patients considering an elective surgery or joint replacement by utilizing specialized regenerative cells to assist in healing the damaged tissues.

Regenerative Cellular Medicine works with the body's natural ability to heal itself. Unlike treatments that simply address the symptoms, Regenerative Therapy actually promotes the natural process of repair in the body, assisting in repairing and restoring degenerated tissue.

These remarkable treatments can repair tissue in the body that has been damaged from age, disease or degeneration. They do this by pinpointing the damaged areas, removing the swelling with powerful anti-inflammatory properties and healing them by regenerating new cells and tissue.

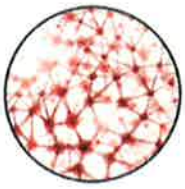
Stem Cell and Regenerative Therapy is an extremely effective non-surgical option for patients considering an elective surgery or joint replacement by utilizing specialized regenerative cells to assist in healing the damaged tissues.

Figure 3. (eliteintegratedmedical.com)

REGENERATIVE CELL THERAPY TREATS MANY MEDICAL CONDITIONS

- **Neck Pain Treated**
  Cervical Pain, Cervical Joint Degeneration, Cervical Arthritis, and more
- **Shoulder Pain Treated**
  Shoulder Injury, Rotator cuff tears, Shoulder Degeneration, Shoulder Bursitis, and more
- **Back Pain Treated**
  Back Pain, Facet Syndrome, Degenerative Disc Disease, Lumbar Arthritis / Osteoarthritis, and more
- **Wrist/Hand Pain Treated**
  Carpal Tunnel Syndrome, Wrist Arthritis, and more
- **Elbow Pain Treated**
  Variety of Elbow Conditions, Lateral Epicondylitis, Golfer's Elbow, Distal Biceps Tendon Tear, and more
- **Hip Pain Treated**
  Variety of Hip Pain Conditions, Labrum tear, Hip Osteoarthritis, Hip Degeneration, Hip Bursitis, and more
- **Knee Pain Treated**
  Meniscus Tear, Knee Degeneration, ACL or PCL Injury, Chrondomalacia, and more
- **Foot/Ankle Pain Treated**
  Foot and Ankle Pain, Planter Fasciitis, and more

DISCOVER WHAT REGENERATIVE CELL THERAPY CAN DO FOR YOU!



Regenerative Cell Therapy can provide improvement and benefits to a person whether for medical and/or pain relief purposes without surgery.

To find out more about what **Elite Integrated Medical Regenerative Therapy** can do for you, **call us today or fill out the contact form below** and one of our patient advocates will get back to you right away.

35.

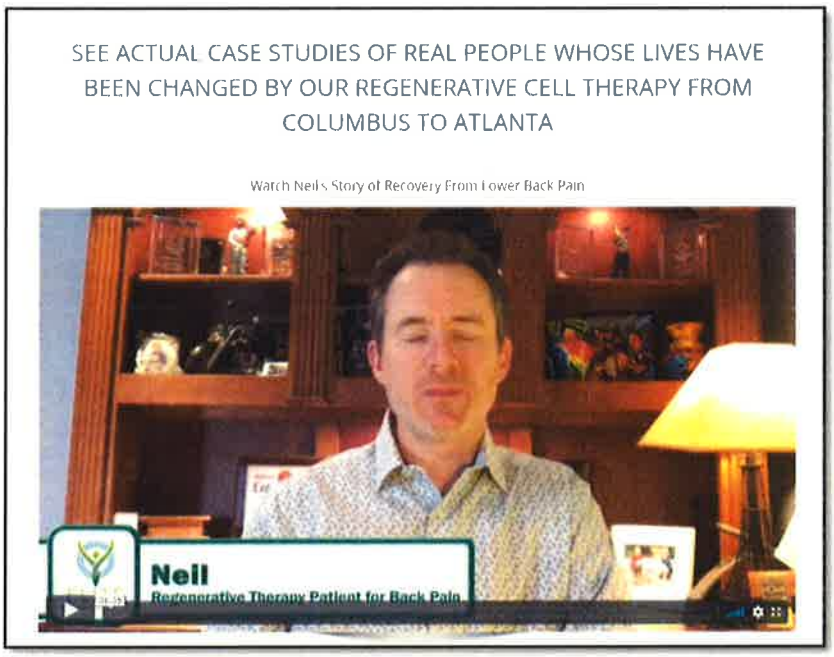
Defendants attempt to substantiate the claims they make about their regenerative medicine products through the use of consumer testimonials. The websites: superiorhealthcaregroup.com and eliteintegratedmedical.com contained in excess of 90

testimonials purportedly made by consumers who purchased the products. Copies of the webpages containing the testimonials are attached hereto as Exhibits "Q" and "R".

36.

Defendants' websites also include a video-taped testimonial of Neil Gass, an owner of the marketing company that maintained and published Defendants' websites. See Figure 4. below; a copy is attached as Exhibit "S".

Figure 4.



Neil Gass presents himself as a consumer that received a regenerative medicine product from Defendants. Neil Gass received the product from Defendants at no charge. Defendants do not disclose in the websites the material connections between Neil Gass and Defendants.

37.

Defendants represent that Elite has a staff of medical doctors who are involved in providing their regenerative medicine products. Examples of statements appearing on

Defendants' websites are referenced below at Figures 5., 6., 7., and 8., and are attached hereto as Exhibits "T", "U", "V", and "W" respectively.

Figure 5.

Figure 6.

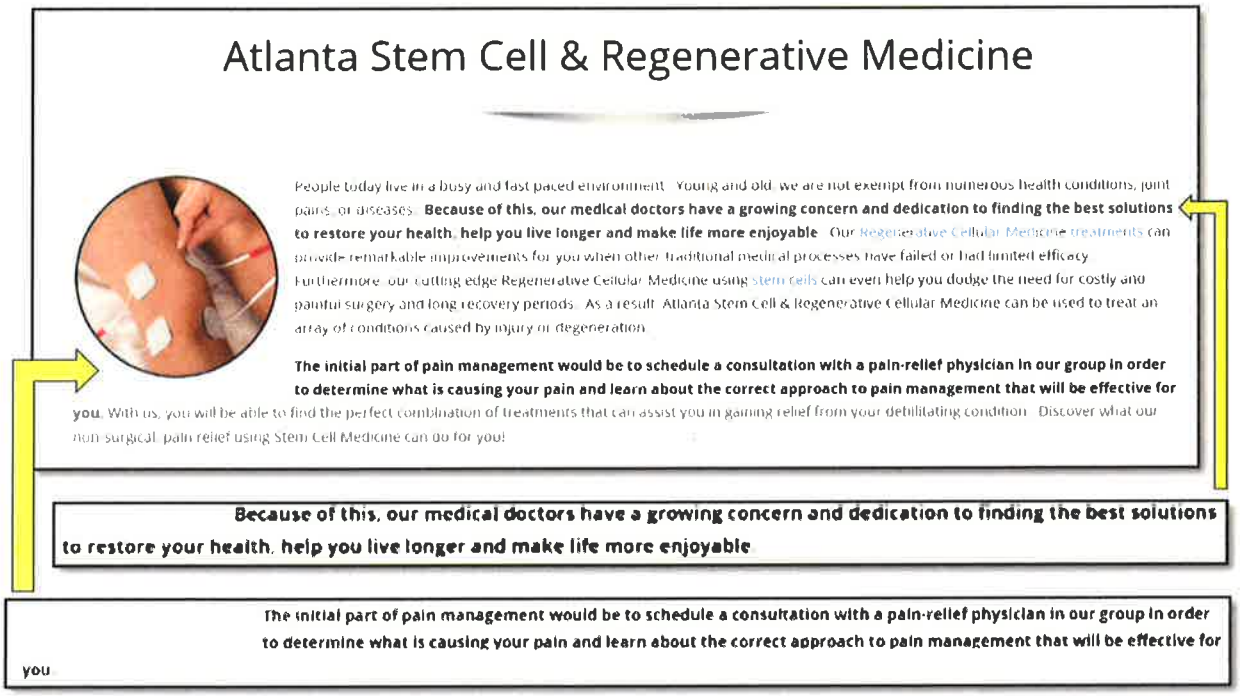


Figure 7.

(678) 883-7835 info@superiorhealthcaregroup.com

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LATERAL EPICONDYLITIS (TENNIS ELBOW), MEDIAL EPICONDYLITIS (GOLFER'S ELBOW) AND DISTAL BICEPS TENDON TEAR

Many patients with tennis elbow run away from surgery and steroid injections. At Superior Healthcare Group, we offer an effective, non-invasive alternative to steroid injections and surgery. Our procedures treat all the underlying damages that cause the elbow pain.

REGENERATIVE MEDICINE FOR FOOT / ANKLE PAIN

Superior Healthcare Group's doctors have extensive experience when it comes to foot and ankle pain treatment. We have pioneered the industry's latest proven alternatives to surgery and steroids. Our same day procedures will alleviate your foot and ankle pain regardless of the cause.

Superior Healthcare Group's doctors have extensive experience when it comes to foot and ankle pain treatment. We have pioneered the industry's latest proven alternatives to surgery and steroids. Our

Figure 8.

THE WONDERS OF REGENERATIVE CELL THERAPY

People today live in a busy and fast paced environment. young and old, we are not exempt from numerous health conditions and diseases. Because of this, our doctors are dedicated to finding the best solutions to restore your health, help you live longer, and make life more enjoyable.

Our **Regenerative Cell Therapy Program** can provide remarkable improvements for you where other traditional medical processes have failed or had limited results. Furthermore, these treatments can even help you avoid the need for costly, painful surgery and long recovery periods. As a result, **Regenerative Cell Therapy** can be used to treat an array of conditions caused by injury or degeneration.*

Because of this, our doctors are dedicated to finding the best solutions to restore your health, help you live longer, and make life more enjoyable.

The person in this video is a paid actor, not a medical doctor employed by Elite.

38.

In reality, Elite employs medical doctors as independent contractors for the limited purpose of administering injections of regenerative medicine products into consumers' spines and hips through the use of fluoroscopy, a live x-ray procedure. Defendants' regenerative medicine products were administered to a relatively small percentage of consumers utilizing this method.

39.

The majority of consumers interact solely with chiropractors who perform medical assessments and nurse practitioners who administer injections of regenerative medicine products.

Newspaper and Social Media Advertising

40.

Defendants advertised their regenerative medicine products and promoted live seminars using social media and through newspaper advertisements. Examples of Defendants' newspaper and social media advertisements are referenced below as Figures 9. and 10., and are attached hereto as Exhibits "X" and "Y" respectively.

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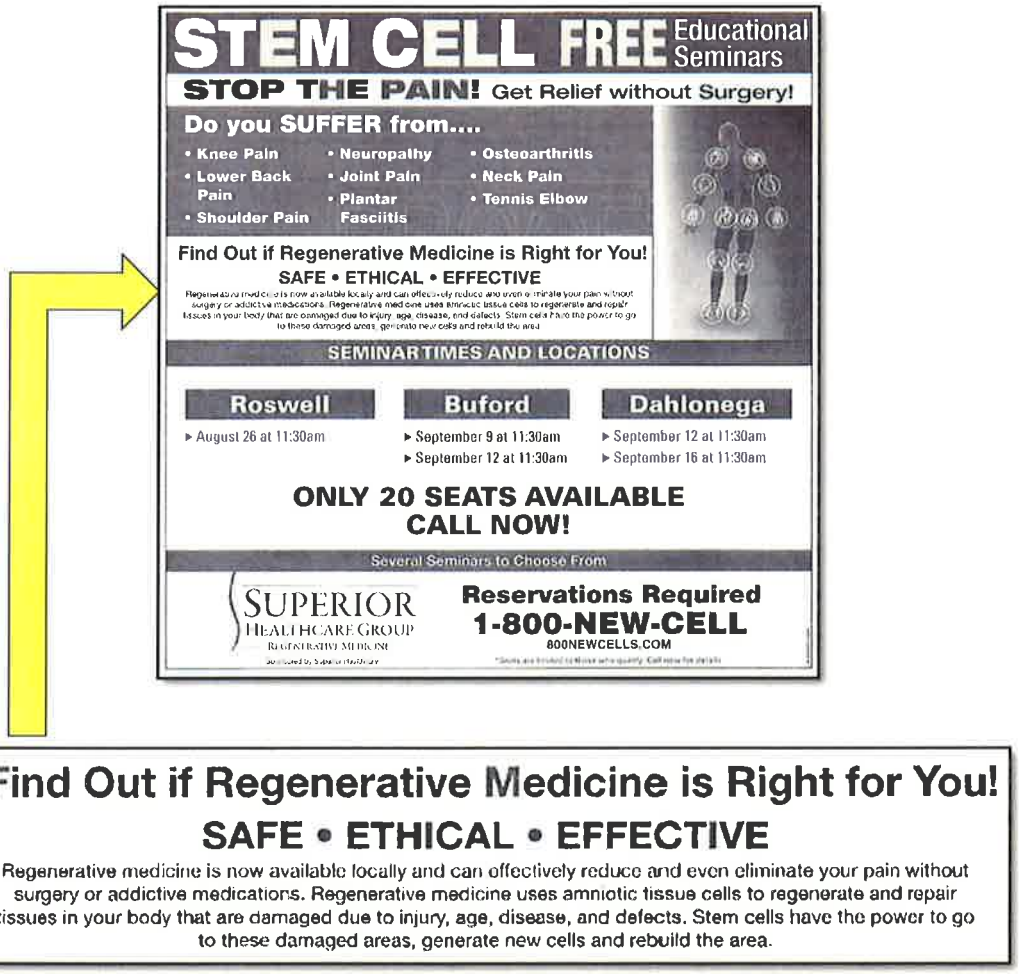
Figure 9.



Find Out if Regenerative Medicine is Right for You!

SAFE • ETHICAL • EFFECTIVE

Regenerative medicine is now available locally and can effectively reduce and even eliminate your pain without surgery or addictive medications. Regenerative medicine uses amniotic tissue cells to regenerate and repair tissues in your body that are damaged due to injury, age, disease, and defects. Stem cells have the power to go to these damaged areas, generate new cells and rebuild the area.

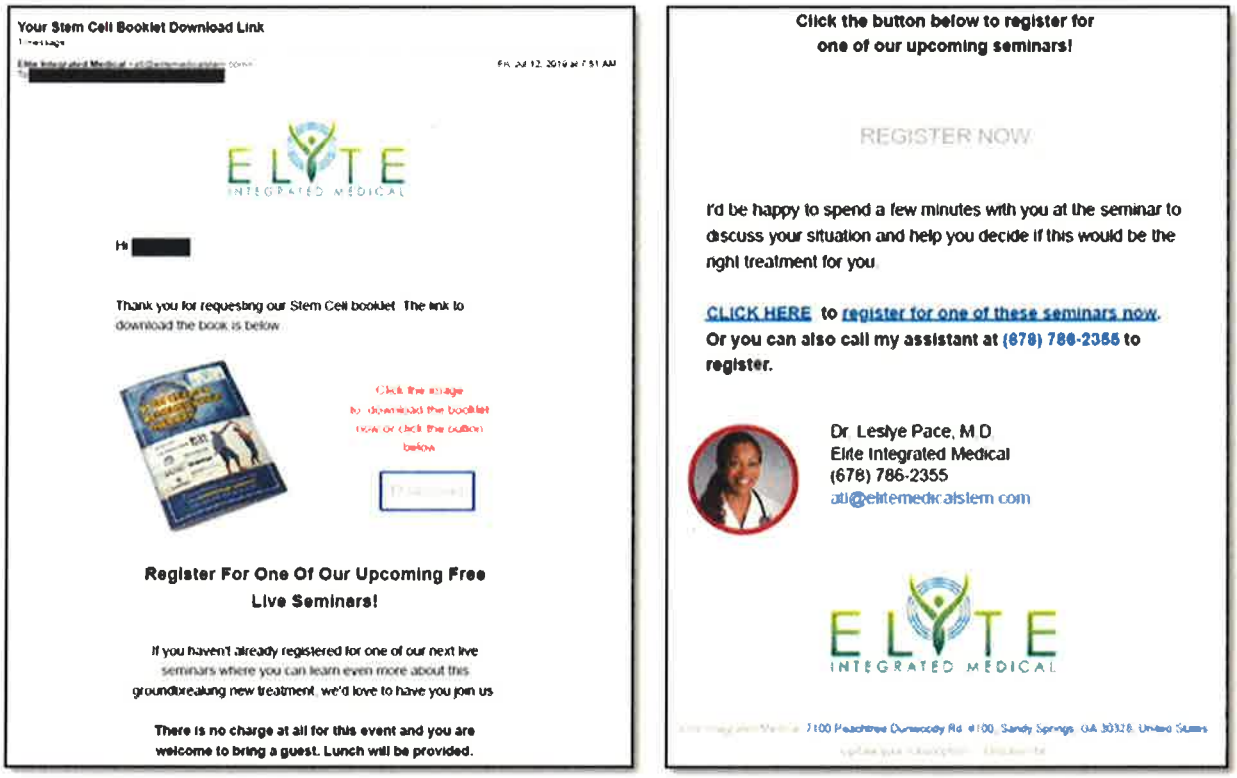
Figure 10.

Stem Cell Booklet and Emails

41.

Defendants promote a "Stem Cell Booklet" that can be accessed through a link provided in social media advertisements. In order to obtain a copy of the Stem Cell Booklet, a consumer must provide an email address where the booklet can be sent. An example of Defendant's marketing email is referenced below as Figure 11., and is attached hereto as Exhibit "Z".

Figure 11.



42.

The Stem Cell Booklet is a 37-page document that contains representations about the wonders of Defendants' regenerative medicine products, Defendants' specialization in various health conditions, and Defendants' pioneering of "the industry's latest proven alternatives to surgery and steroids". Examples are referenced below as Figures 12. and 13. A copy of the Stem Cell Booklet is attached hereto as Exhibit "AA".

Figure 12.

Welcome To A New And Better Solution

Chronic pain robs sufferers of their quality of life and often leads to unnecessary pain medications and even depression. It *is* possible to turn the clock of time backwards and *get your life back*.

During our unique 1 hour presentation, you will learn *everything* there is to know about Regenerative Medicine and other advanced regenerative cellular therapies, including how they work, the different types, where they work best, research studies and effectiveness.

Regenerative Medicine is changing the lives of thousands across this great country for the better and our doctors are fully trained to present this amazing educational work shop to help you decide if this is the right treatment for you.

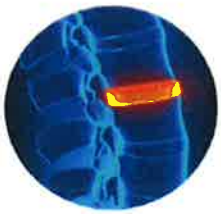
By the end of this workshop you'll be fully educated on these new forms of regenerative cellular treatments and will know if this could be the correct treatment for your particular condition.

Figure 13.

Back Pain

If you suffer with the Following Back Conditions; learn more about how Regenerative Cellular Therapy can help restore your health and help you live Pain-Free!

- Back Pain
- Facet Syndrome
- Degenerative Disc Disease
- Lumbar Arthritis
- Osteoarthritis



Regenerative Medicine for Back Pain

At Elite Integrated Medical we specialize in back pain treatment. We have pioneered the industry's latest proven alternatives to surgery and steroids. Our in-office, same-day procedures will alleviate your back pain regardless of the cause. We treat a range of conditions including spondylolisthesis, spinal arthritis, intervertebral disc degeneration, spinal stenosis and herniated discs.

Elite Integrated Medical's revolutionary Regenerative Cellular Therapy procedures treat all the damage *and underlying conditions* that cause you pain. Our doctors will inject the regenerative cellular matrix into the injured joint, and they then act as an immunologically privileged material to *rebuild and strengthen the damaged tissue* which causes back pain.

Defendants did not create and do not manufacture their regenerative medicine products.

43.

Defendants use the email addresses they obtain when a consumer requests the Stem Cell Booklet to send a series of additional marketing emails.

44.

Each email appears to have been sent from Elite's medical director, Dr. Pace. The first email contains a link to register for a seminar where Dr. Pace will be present to discuss a consumer's situation. See figure 14. below; a copy is attached as Exhibit "BB".

Figure 14.

Following Up

ELITE INTEGRATED MEDICAL

Hi [redacted]

I wasn't sure if you had a chance to download the **Stem Cell Booklet** that you requested yesterday, so I wanted to check back with you to make sure you received it. The link to download the book is below

Click the image below to download the booklet now

Download

Register For One Of Our Upcoming Free Live Seminars!

If you haven't already registered for one of our next live seminars where you can learn even more about this groundbreaking new treatment, we'd love to have you join us.

There is no charge at all for this event and you are welcome to bring a guest. Lunch will be provided.

Click the button below to register for one of our upcoming seminars!

REGISTER NOW

I'd be happy to spend a few minutes with you at the seminar to discuss your situation and help you decide if this would be the right treatment for you.

CLICK HERE to register for one of these seminars now. Or you can also call my assistant at (678) 786-2355 to register.

Dr. Leslye Pace, M.D.
Elite Integrated Medical
(678) 786-2355
atl@elitemedicalstem.com

ELITE INTEGRATED MEDICAL

7100 Peachtree Dunwoody Rd. #100, Sandy Springs, GA 30328, United States

45.

A subsequent second email contains a link to the https://clinicaltrials.gov website, where consumers can learn more about Defendants' regenerative medicine products. See figure 15. below; a copy is attached as Exhibit "CC".

Figure 15.

6,422 ongoing stem cell research studies
1 message

Elite Integrated Medical <atl@elitemedicalstem.com> Sun, Jul 14, 2019 at 8:00 AM
To: [redacted]

Hey there [redacted]

As you're most likely doing your research on stem cell treatments, I thought you might appreciate having a few more resources at your fingertips. Here is a wealth of information, straight from the source.

On this site, you can learn about **over 6,400 ongoing stem cell research studies** being done on the use of stem cells for various healthcare applications.

It's a government run website, mainly for doctors, so it's not always "easy reading" material. But my hope is that *you will see just how serious the field of stem cell medicine has become*, and how many different medical applications they are finding for it.

https://clinicaltrials.gov/ct2/results?term=stem+cell&Search=Search

Check it out and let me know what you think.

I'll talk to you soon,

Dr. Leslye Pace, M.D.
Elite Integrated Medical
(678) 786-2355
atl@elitemedicalstem.com

The 6,400 stem cell research studies do not involve Defendants' regenerative medicine products.

46.

Two additional emails contain links to articles and quotes from professional athletes and physicians regarding the use of stem cell therapy. These references are used to imply that Defendants' regenerative medicine products can provide the same results. See figures 16. and 17. below; copies of the emails and articles are attached hereto as Exhibits "DD" and "EE".

Figure 16.

Hundreds of NFL players treated with stem cells
1 message

Elite Integrated Medical <atl@eliteemedicalstem.com>
To [redacted]

Mon, Jul 15, 2019 at 8:04 AM

ELITE
INTEGRATED MEDICAL

Hi [redacted]

I just wanted to share this Sports Illustrated article that talks about all of the **NFL players that are now getting stem cell therapy**. It's a great article that just goes to show how mainstream this type of treatment has become

" *Dr. Andrews quietly has been using these stem cells to treat pro athletes for about three years. The count of NFL players he's treated with stem cells is a couple hundred.* "

You can read the full article at: https://www.si.com/2014/07/30/stem-cell-treatment-nfl-sports-medicine

I'd love to meet with you to share many of the great stories of patients (many whom are well into their 70's & 80's) who have received this treatment and been able to return to the *"playing field"* of travel, quality family time, and even just simple daily routines like cooking & cleaning

If you haven't already, please give me a call at the number below to book your free no-obligation consultation for us to take a look at your situation to see if this could be a viable solution for you

I look forward to meeting you

Dr. Leslye Pace, M.D.

Elite Integrated Medical
(678) 786-2355
atl@eliteemedicalstem.com

Figure 17.

NBA team doctor uses stem cells for player injuries...

1 message

Elite Integrated Medical <atl@elitemedicalstem.com> Sat, Jul 20, 2019 at 8:20 AM

To [redacted]

ELITE INTEGRATED MEDICAL

Hi [redacted]

Today I wanted to send you an article written by Medical Director & Head Team Physician for the Brooklyn Nets (NBA) & New York Red Bulls (MLS soccer), Dr. Riley Williams III.

In the article, he writes:

"There is very little downside to trying a stem cell treatment on a patient who fits the right profile. I've been treating athletes' knees with stem cell therapy for the past 10 years or so. I've used these methods alone and in concert with surgical procedures. In general, I have observed faster healing rates using these cells as surgical adjuncts. Moreover, some athletes have been able to avoid surgery using stem cell injections. The short- to mid-range results that I've observed are very encouraging."

You can read the full article here:

https://www.hss.edu/playbook/stem-cell-therapy-right-move-athlete/

As you can imagine, *there's no "one-size-fits-all" solution that fits everyone* - stem cells included. We often have to tell people that they are just not a good candidate for this treatment.

But we've also helped hundreds of people of all ages and walks of life avoid joint replacement surgery and return to a pain free life, without harmful drugs.

I am here to help you find the best course of action for you! By the end of our no-cost consultation together, you'll be fully educated on the various forms of stem cell treatments and will be informed enough to know if this could be the correct treatment for your particular condition.

Many of the patients I meet have been searching for a solution for a long time and I am thrilled to be able to help. Simply call me at the number below to schedule a one-on-one consultation that could possibly change everything.

I'm really looking forward to meeting you.

Dr. Leslye Pace, M.D.
Elite Integrated Medical
(678) 786-2355
atl@elitemedicalstem.com

ELITE INTEGRATED MEDICAL

Sent to [redacted]

Elite Integrated Medical, 7100 Peachtree Dunwoody Rd. #100, Sandy Springs, GA 30328, United States

Don't want future emails? Unsubscribe

The stem cell therapy used by these athletes are stem cells obtained from the athletes' own bone marrow or fat and is not the same type of regenerative medicine products Defendants offer.

Seminars

47.

Consumers who register for seminars receive emails from Defendants prior to the seminar containing testimonials and endorsements of consumers that purportedly have received Defendants' regenerative medicine products. An example of the email is referenced below in Figure 18. and is attached hereto as Exhibit "FF".

Figure 18.

From: "Superior Healthcare Group Sandy Springs" <stem2@superiorhealthcaregroup.com>
Date: January 14, 2019 at 6:01:32 AM EST
To: [redacted]
Subject: A recent patient's experience

Hi [redacted]

As the stem cell seminar draws near, I just wanted to share a great story from a recent patient, Ms. Johnson.

Ms. Johnson was an active person in her everyday life until time took its toll on her back and knees. She could barely get herself up or down the stairs in her home anymore without agonizing pain. She could not stand for longer than 30 seconds at a time, and eventually, something as simple as carrying grocery bags was out of the question. Within the first week of getting her stem cell injection, Ms. Johnson could already feel a noticeable difference. By 2 weeks, the pain in her leg was gone. And by 6 weeks, she was 85% better in her back as well!

Click on the video below to see her tell her story.

Stories like these are the reason I do what I do. I'm passionate about helping people to get back to living their best lives.

If you'd like to hear more stories like this, please visit our review page at https://pd.superiorhealthga.com/reviews

48.

The post-registration emails appear to be sent from Dr. Pace, representing that she will see the consumer at the seminar and will be available to answer questions. See figure 19. below, attached as Exhibit "GG".

Figure 19.

If you have any burning questions, please write them down and bring them with you to the seminar so we can be sure to get you the answers you need. I look forward to meeting you in person very soon!

Take Care!

Dr. Leslye Pace, M.D.
Superior Healthcare Group Sandy Springs
(678) 883-7422
stem2@superiorhealthcaregroup.com

Dr. Pace does not attend seminars. Instead, a pre-recorded video of Dr. Pace welcoming consumers to the seminar is played at the beginning of the seminar.

49.

Seminars are often conducted by chiropractors wearing white lab coats who introduce themselves as "doctor".

50.

During seminars, chiropractors show slides of graphic pictures of surgery and emphasize statistics about the failures of surgery and other conventional medical treatments. See figures 20. and 21.; copies are attached hereto as Exhibits "HH" and "II".

Figure 20.

Cost of Surgery

- Pain.
- 3-6 months of healing and rehabilitation time.
- No guarantee of result.
- High percentage of failure and complications.
- 50% or more will need additional surgery.
- Total Average Cost for Uncomplicated Case = $55,000.00. Much comes out of deductible.
- What's the cost of your lost time, function, pain and suffering?

21

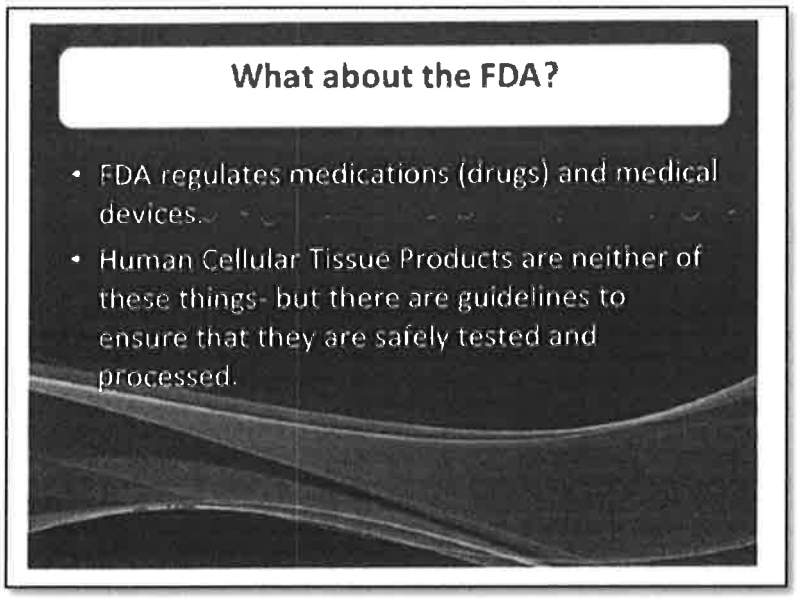
https://www.healthleadersmedia.com/finance/planned-orthopedic-surgery-costs-increase-44-8-years (DR5f)
Lavernia, et al (2006). Postdischarge costs in Arthroplasty Surgery. The Journal of Arthroplasty, 21(6): 144-150. (DR5g)

Figure 21.

51.

During seminars, the presenter misrepresents through the use of a power point slide that Defendants' regenerative medicine products are not regulated by the FDA as a "drug". See figure 22. below; a copy is attached as Exhibit "JJ".

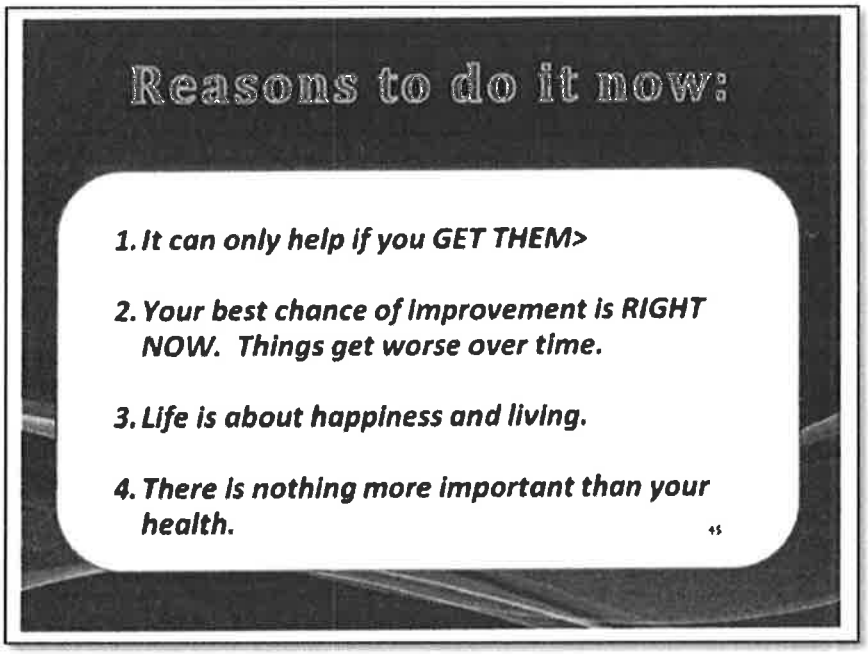
Figure 22.



52.

At the conclusion of the seminar, chiropractors make a hard sales pitch, and offer same day appointments. See figure 23. below; a copy is attached as Exhibit "KK".

Figure 23.



53.

In order to close the sale, chiropractors offer discounts for multiple injections of the product and injections for additional family members, and no charges for x-rays and exams, but stress that consumers need to take advantage of the offer (described as a "gift") within the week. See figures 24. and 25.; copies are attached as Exhibits "LL" and "MM".

Figure 24.

IT'S A FREE CONSULTATION WITH X-RAYS!

- **Fill out our forms describing your condition, and bring them with you to your appointment.**
- **If you have MRI/Xrays- bring them to your appointment.**
- **Please pull out your calendar for appointment scheduling.**

Normal fees will apply, $200 Consultation & X-Ray Fee if appointment is not within the next week.

My first gift is to waive the fee for the initial exam and x-ray and this is a $200 fee. The reason I'm doing this is many of you as I look at your surveys have been to multiple doctors without any success and I do not want to charge you unless I know I can help you. Please bring in you're x-rays and MRIs if you have them we will not need to retake the films

Figure 25.

ONE INJECTION - As a gift for coming, when you sign up today, **you will receive 10% off** your first injection.

TWO INJECTIONS - If you need two injections **we're happy to give you 20% off.**

These are HUGE SAVINGS and we are happy to give them to you!

Many patients need our low monthly payment options. **If approved for treatment our team has you covered with payment plans.**

My second gift is to save you money and I know many of you need more than one area to be fixed so one area we will give you a 10% discount If you need more than one then you'll get a 20% discount
I will even allow you to combine body parts with your spouse or loved one. This means if your wife has a knee problem and you have a shoulder problem both of you will see 20% on the procedures. I do not want money to be the reason for you not to receive help. This is why I've instructed my staff to help you with financing programs that are as little as $300 per month if you need that type of help

Now I need to reiterate one thing the free exam and x-rays and the gifts that save you money are stamped with a time limit. I need everyone that is interested in getting help to show up this week if you want to receive those gifts

Hand this survey to your appointment scheduler and tell everyone to accept an appointment if their name is circled. Leave the building

54.

The average cost of one injection is $5,000.00. The cost of Defendants' regenerative medicine products is not covered by insurance or medicare. Financing options through other companies, such as CareCredit and Greensky, are offered as options.

55.

From January 2017 until April 2019, Defendants conducted no less than 187 live seminars promoting their products.

TARGETING OF ELDERLY AND DISABLED CONSUMERS

56.

Defendants frequently include testimonials and pictures of elderly persons in their marketing materials. See figures 26. and 27. below; copies are attached as Exhibits "NN" and "OO".

Figure 26.

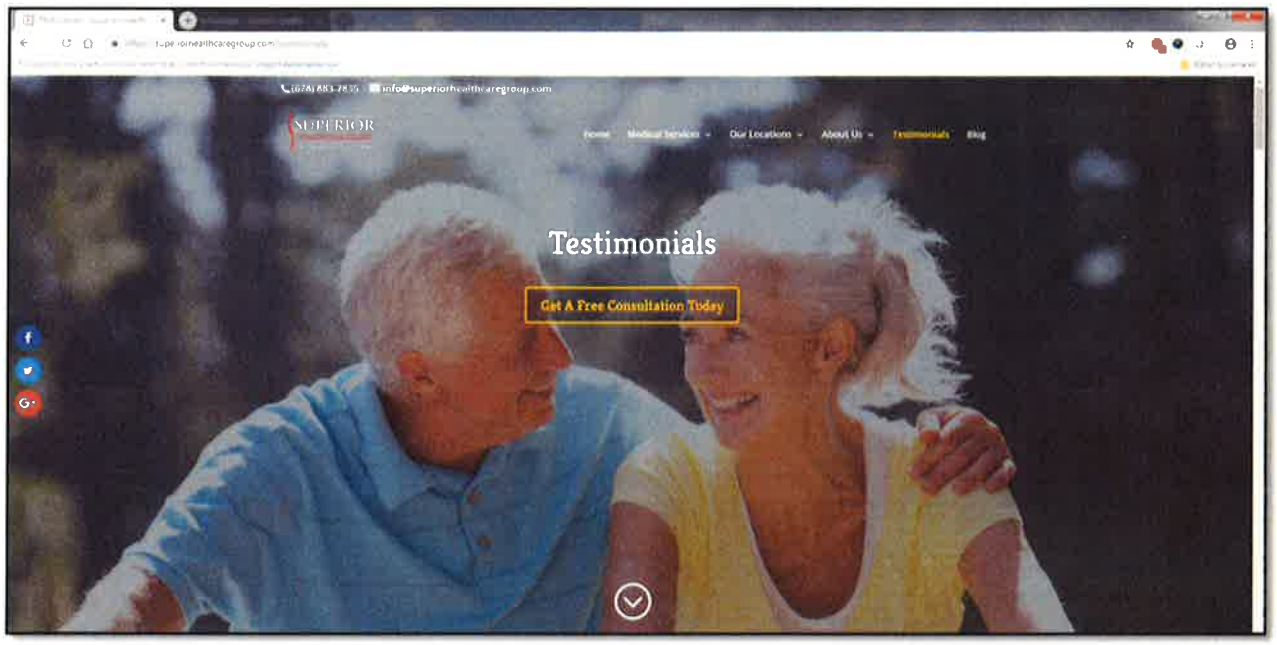
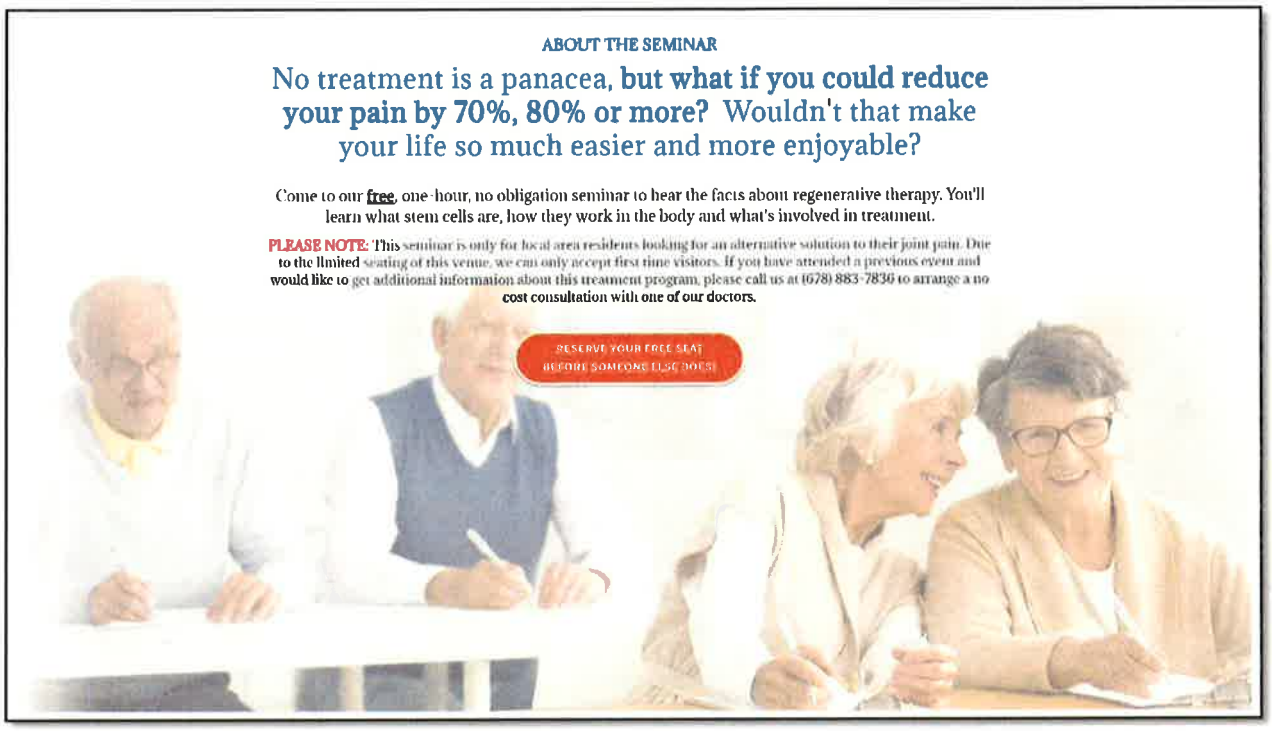


Figure 27.



57.

Defendants' facebook advertising campaigns were designed specifically to target consumers with diseases and health conditions that substantially limit consumers' major life activities, including but not limited to orthopedic conditions.

58.

Defendants sold the products to no less than 842 consumers from January 7, 2017 until April 3, 2019 and generated no less than $6,429,309.14 in gross sales. Consumers over the age of 59 made at least 58% of the purchases during this period of time. Defendants were advertising and offering the products as early as December 2016 and continue to advertise and offer the products as of the filing of this Complaint.

COUNT I – FALSE AND MISLEADING REPRESENTATIONS THAT REGENERATIVE MEDICINE PRODUCTS TREAT, CURE, OR MITIGATE DISEASES AND HEALTH CONDITIONS

59.

Plaintiff incorporates the preceding paragraphs as if specifically stated herein.

60.

Defendants made representations to consumers, on websites, facebook.com, in emails and other written marketing materials, and during live seminars, that the regenerative medicine products they offer, including Surforce, CoreCyte, and GeneXStem, treat, cure, or mitigate a variety of diseases and health conditions. These representations are not substantiated by reliable and competent scientific evidence and are therefore false and/or misleading.

61.

Defendants' acts and practices violate O.C.G.A. § 10-1-393(a), the FBPA's general prohibition against unfair and deceptive acts and practices; O.C.G.A. § 10-1-393(b)(2) that prohibits causing actual confusion or misunderstanding as to the source, sponsorship, approval, or certification or goods and services; O.C.G.A. § 10-1-393(b)(5) which prohibits representing that goods or services have sponsorship, approval, characteristics, ingredients, uses, benefits, or quantities that they do not have.

COUNT II – FALSE AND MISLEADING REPRESENTATIONS THAT REGENERATIVE MEDICINE PRODUCTS ARE COMPARABLE AND/OR SUPERIOR TO CONVENTIONAL MEDICAL TREATMENTS

62.

Plaintiff incorporates the preceding paragraphs as if specifically stated herein.

63.

Defendants made representations to consumers, on websites, facebook.com, in emails and other written marketing materials, and during live seminars, that the regenerative medicine products they offer, including Surforce, CoreCyte, and GeneXStem, are comparable to or superior to conventional medical treatments that are used to treat, cure, or mitigate a variety of diseases and health conditions. The claims are not substantiated by reliable and competent scientific evidence and are therefore false and/or misleading.

64.

Defendants' acts and practices violate O.C.G.A. § 10-1-393(a), the FBPA's general prohibition against unfair and deceptive acts and practices, and O.C.G.A. § 10-1-393(b)(5), which prohibits representing that goods or services have sponsorship, approval, characteristics, ingredients, uses, benefits, or quantities that they do not have.

COUNT III – FALSE AND MISLEADING REPRESENTATIONS REGARDING REGULATION OF REGENERATIVE MEDICINE PRODUCTS

65.

Plaintiff incorporates the preceding paragraphs as if specifically stated herein.

66.

Defendants misrepresented to consumers that the regenerative medicine products they offer, including Surforce, CoreCyte, and GeneXStem, are not regulated for use by the FDA and/or that the products are not required to be approved by the FDA.

67.

Defendants' acts and practices violate O.C.G.A. § 10-1-393(a), the FBPA's general prohibition against unfair and deceptive acts and practices; O.C.G.A. § 10-1-393(b)(2) that prohibits causing actual confusion or misunderstanding as to the source, sponsorship, approval, or certification or goods and services; O.C.G.A. § 10-1-393(b)(3) that prohibits causing actual

confusion or actual misunderstanding as to affiliation, connection, or association with or certification by another; and O.C.G.A. § 10-1-393(b)(5), which prohibits representing that goods or services have sponsorship, approval, characteristics, ingredients, uses, benefits, or quantities that they do not have.

COUNT IV – USE OF A COMPUTER OR COMPUTER NETWORK TO DISSEMINATE FALSE AND MISLEADING REPRESENTATIONS ABOUT REGENERATIVE MEDICINE PRODUCTS

68.

Plaintiff incorporates the preceding paragraphs as if specifically stated herein.

69.

Defendants used a computer or computer network to disseminate false and misleading representations to consumers regarding the regenerative medicine products they offer. While engaging in these acts and practices, Defendants intentionally targeted elderly and disabled consumers.

70.

Defendants' acts and practices violate O.C.G.A. § 10-1-393.5(b), which prohibits using a computer or computer network to engage in an act or practice that would operate as a deceit upon any person.

WHEREFORE, Plaintiff prays that this Court enter an Order:

(a) Finding that Defendants have violated §§10-1-393(a), 10-1-393(b)(2), 10-1-393(b)(3), 10-1-393(b)(5), 10-1-393(b)(9), and 10-1-393.5(b) of the FBPA;

(b) Assessing a civil penalty against Defendants in the amount of $10,000.00 for each violation of the FBPA committed against elderly and/or disabled consumers pursuant to O.C.G.A. § 10-1-851; and

(c) Granting relief pursuant to O.C.G.A. § 10-1-397(b)(2) including:

i. Permanently enjoining Defendants from engaging in the unfair or deceptive acts or practices as alleged in Counts I through IV above;

ii. Permanently enjoining Defendants from violating the FBPA;

iii. Requiring Defendants to pay restitution in an amount equal to the gross sales to consumers of their regenerative medicine products;

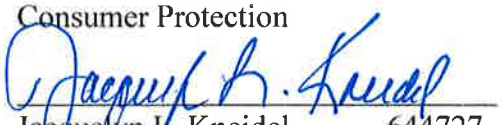
iv. Assessing a civil penalty against Defendants in the amount of $5,000.00 per violation of the FBPA; and

v. Granting other relief as the Court deems just and equitable.

This 14th day of September, 2020.

CHRISTOPHER M. CARR
Attorney General 112505

Anne S. Infinger 382918
Deputy Attorney General
Consumer Protection



Jacquelyn L. Kneidel 644727
Assistant Attorney General

PLEASE DIRECT ALL
COMMUNICATIONS TO:
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Consumer Protection Division
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Atlanta, Georgia 30334
(404) 656-3959
jkneidel@law.ga.gov

The NEW ENGLAND JOURNAL of MEDICINE

SPECIAL REPORT

Balancing Safety and Innovation for Cell-Based Regenerative Medicine

Peter Marks, M.D., Ph.D., and Scott Gottlieb, M.D.

March 8, 2018
N Engl J Med 2018; 378:954-959
DOI: 10.1056/NEJMsr1715626

Article Figures/Media

Metrics

7 References
45 Citing Articles

Introduction

REGENERATIVE MEDICINE IS A FIELD THAT INVOLVES REPLACING, ENGINEERING, OR regenerating human cells, tissues, or organs to establish, restore, or enhance normal fi[illegible] [1] It is an area with great promise that goes directly to the role of the Food and Drug Adm[illegible] (FDA) in helping to facilitate the availability of safe and effective treatments. The broad scope of regenerative medicine products includes cell therapies, therapeutic tissue-engineering products, human cell and tissue products, and certain combination products involving cells and devices, such as scaffolds upon which cells can grow. Recently, there has been much interest specifically in the potential of adult stem cells to address a wide variety of conditions.

The Expanding Use of Stem-Cell–Based Products

Advances in the field of hematopoietic stem-cell biology have led to the development of treatments such as hematopoietic stem-cell transplantation (HSCT), which has been associated with improved survival for patients with benign and malignant hematologic disorders.[2] However, despite the increasingly widespread

use of stem cells in techniques being labeled as regenerative medicine, clinical benefit has not been clearly shown in most instances. What can be done to help advance the development of safe and effective cell-based products in the field of regenerative medicine?

Scientific advances have shown us that stem cells are indeed remarkably complex biologic entities. To complicate matters, the term "stem cells" has been used to describe a variety of cells that have the capacity to divide and differentiate, including hematopoietic stem cells and adipose-derived stem cells (mesenchymal stem cells). The potential benefits to human health have spurred major progress in stem-cell biology over the past several decades. The field has moved from characterization of the properties of these cells toward therapeutic applications. This history is instructive in informing our current policy.

Today, there are thousands of citations in the literature related to clinical HSCT that have clearly documented the side-effect profile and efficacy of such procedures. Yet such scientific and clinical progress in HSCT contrasts with the current situation for a number of other stem-cell products, such as mesenchymal stem cells. Despite a proliferation of early-phase trials of mesenchymal stem cells, definitive studies regarding the safety and efficacy of such procedures as compared with the standard of care have been lacking.[3,4] For example, mesenchymal stem cells have been used in patients with a wide range of conditions, from cancer to disorders affecting the central nervous system, including Alzheimer's disease, despite the paucity of information from well-designed clinical trials. Two explanations that are often cited as to why mesenchymal stem cells should be safe and effective for so many different conditions are that the cells are immunomodulatory and that they can differentiate appropriately on the basis of the environment into which they are introduced. We now know with reasonable certainty from the scientific literature that this is not always the case.

At the same time, the administration of such stem cells may be associated with serious adverse events.[5,6] Even in the absence of serious adverse events, the use of therapies that are of unproven efficacy is a disservice to patients and to public health. An increasing number of safe and effective therapies are becoming available on the basis of the findings of well-designed clinical trials. It is critical to focus on efforts to facilitate the development of such therapies, rather than propagating products with dub clinical efficacy and possible risks. Facilitating the availability of safe and effective therapies is the the FDA's recently released comprehensive policy framework for the development and oversight of regenerative medicine products, including new stem-cell therapies.

PDF
Help

Regulatory Context for Regenerative Medicine

HUMAN CELLS, TISSUES, AND CELLULAR AND TISSUE-BASED PRODUCTS

To put this comprehensive policy framework in perspective, the FDA's statutory authority in this area is based in part on the Public Health Service Act. Section 351 of this act provides the FDA with authorities surrounding the licensure of biologic products, and Section 361 mandates that the agency will issue and

enforce regulations necessary to prevent the introduction, transmission, or spread of infectious disease. That regulatory framework is risk-based and divides human cells, tissues, and cellular and tissue-based products (HCT/Ps) into those requiring and those not requiring premarket approval. The products that are regulated under both Sections 351 and 361 of the act are biologic products and must be studied under the provisions for investigational new drugs. In addition, the manufacturers of such products are required to submit a biologics license application to the FDA for approval before marketing. In contrast, the products that are regulated solely under Section 361 and under the implementing regulations do not need premarket approval. Instead, they require registration and listing with the FDA before marketing, provided they are produced in compliance with the appropriate provisions to prevent the transmission of infectious diseases.

Table 1.

Table 1. Categories of Human Cells, Tissues, or Cellular and Tissue-Based Products (HCT/Ps)
HCT/P
Cardiovascular tissue
Cell-derived therapeutic products (e.g., pancreatic islets, mesenchymal stem or stromal cells, fibroblasts)
Dura mater
Hematopoietic progenitor cells derived from peripheral and cord blood (including hematopoietic stem cells)
Musculoskeletal tissue (include adipose derived stem cells)
Ocular tissue
Placenta (amnion)
Reproductive cells and tissues
Skin
Not HCT/P
Blood vessels that are part of an organ intended for transplantation
Human collagen
Human milk
[illegible]
Minimally manipulated bone marrow for homologous use and not combined with another drug (with a few exceptions described in the tissue regulations)
Nonfunctional cells, tissues, or organs
Vascular composite allografts
Vascularized human organs for transplantation
Whole blood or blood components, including platelet-rich plasma

Categories of Human Cells, Tissues, or Cellular and Tissue-Based Products (HCT/Ps).

The decision regarding which regulatory pathway a given product must follow rests in part on whether the product meets or does not meet the criteria of the regulations promulgated under the Code of Federal Regulations part 1271 of Title 21, which have been in place since 2005. In brief, products that are regulated solely under Section 361 generally are those that do not undergo substantial processing (minimal manipulation), are used in a manner in the recipient that is similar to that in the donor (homologous use), are not combined with another drug or biologic product, and do not have a systemic effect, unless they are designed for autologous transplantation, first- or second-degree–related allogeneic transplantation, or reproductive use (**Table 1**). Examples include corneas and heart valves. Such cells and tissues are subject to FDA regulations only to prevent the transmission of communicable diseases. All other HCT/P products are regulated as drugs, biologics, or devices and require appropriate regulatory submissions for the conduct of clinical trials and marketing.

EXPEDITING THE DEVELOPMENT OF NEW THERAPIES

The FDA recognizes the time and effort that go into the creation of regulatory submissions and the effect that working through the regulatory process can have on the time lines for the development of innovative

products. Although the FDA has traditionally focused on ensuring the quality, safety, and efficacy of medical products, its mandate has expanded to encompass a role in expediting the development of new therapies, particularly those aimed at serious or life-threatening conditions. The expedited programs — including fast-track designation, priority review, accelerated approval, and designation as a breakthrough therapy — have been successful in accomplishing this goal.[7] The role of the FDA in facilitating innovation while upholding the agency's approval standards, especially when it comes to areas of unmet medical need and new technologies, is also clearly expressed in the legislative initiatives contained in the 21st Century Cures Act, which was enacted on December 13, 2016.

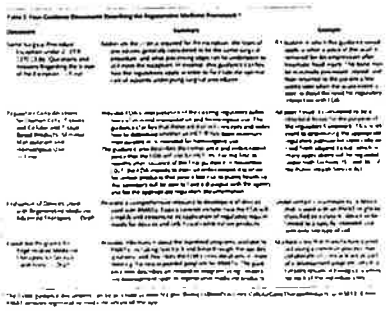
To facilitate therapeutic advances from stem-cell therapies, along with other HCT/Ps, the 21st Century Cures Act introduced an additional expedited program in which a product is designated as a regenerative medicine advanced therapy (RMAT). This designation provides sponsors of a qualified regenerative medicine product that is intended for the treatment of serious or life-threatening conditions with advantages similar to those of the breakthrough-therapy designation, provided that preliminary clinical evidence indicates that the therapy addresses unmet medical needs. The simple requirement for preliminary clinical evidence of efficacy distinguishes RMAT from the breakthrough designation, which requires preliminary clinical evidence of a substantial improvement over existing therapies. In addition, RMAT-designated products that receive accelerated approval may be eligible to use an expanded range of options to fulfill their postapproval commitments. Such options include the use of traditional studies as well as the submission of patient registries or other sources of real-world evidence. As of December 29, 2017, the FDA had received 43 requests for RMAT designation, had acted on 35 of these requests, and had granted 13 of them.

Comprehensive Framework for Regenerative Medicine

Table 2.

PDF

Help



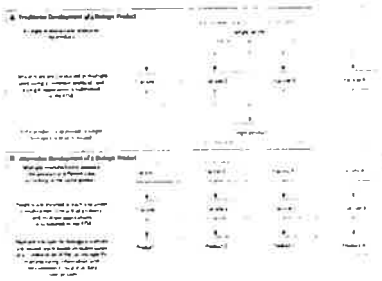
Four Guidance Documents Describing the Regenerative Medicine Framework.

In November 2017, building on these policy and scientific opportunities, the FDA released a comprehensive framework for the oversight of regenerative medicine to help the field continue to advance. This regulatory framework is articulated in two final and two draft guidance documents (**Table 2**). Since the FDA is highly

cognizant of the importance to sponsors of the distinction between therapies that require premarket authorization and those that do not, the FDA's new policy framework more clearly describes for the developers of regenerative medicine therapies how these distinctions are made under the regulations, particularly with regard to the criteria for minimal manipulation and homologous use. The FDA strove to take a modern approach to existing regulations and statutes, balancing the objective of fostering expedient development of innovative products for patients who have medical needs with the need to ensure that such therapies are both safe and effective. As part of the regulatory framework, the FDA also articulated a risk-based compliance and enforcement policy. This policy will allow developers of lower risk products up to 36 months from November 16, 2017, to determine whether they need to submit an application for an investigational new drug or a marketing application in light of the recently published guidance documents and, if such an application is needed, to prepare the new-drug or marketing application. The FDA intends to take additional enforcement actions in cases in which it believes unproven products may put patients at risk.

Working within the existing regulatory framework, the FDA will make use of all available regulatory pathways and will adopt the use of some new principles that we believe will make the appropriate premarket evaluation of stem-cell–based therapies more efficient. On a large scale, the FDA will be incorporating some new concepts for how small investigators and firms can seek and meet the approval standard for products through efficient, expedited pathways.

Figure 1.



PDF

Traditional versus Alternative Development of a Biologic Product.

Help

For example, the FDA will provide tools to encourage individual or small groups of physicians to collaborate in support of the development of a stem-cell or other regenerative medicine product, which will ultimately lead to the receipt of a biologics license by each of the physicians or groups (**Figure 1**). How might this work? The investigators who manufacture the product will need to agree on and follow a common manufacturing protocol and develop a common clinical trial protocol. Each site will then produce the product to treat the patients who are enrolled in the clinical trial at its own site. Subsequently, the pooled safety and efficacy data from the various sites that are participating in the trial will be submitted as part of a biologics license application for each.

If the clinical data that are submitted in conjunction with the manufacturing information show a favorable benefit–risk profile, the FDA could rely on that pooled data in determining whether the product is safe and effective. The agency would then issue a stand-alone biologics license to each of the physicians or groups so that each could proceed to produce the product independently. This approach, with appropriate planning and statistical analysis, would provide an alternative to how development generally has been conducted in the past to support approval. Such a pathway toward licensure may be well suited to groups of investigators or small firms that are able to consistently follow a common manufacturing and clinical protocol but that may not have access to the patient populations or infrastructure needed to conduct separate development programs. The approach may be particularly well suited to the development of products that involve manufacturing that is not highly complex yet is more than minimal manipulation and to clinical applications amenable to trials of relatively simple design.

Such an approach is just one example of how the FDA is taking an original policy approach to the regulation of a highly innovative field, one in which our traditional approach to regulation may not be as efficient or effective as in more mature fields. As part of its efforts in the area of regenerative medicine, the FDA is also encouraging investigators who are involved in innovative product development to engage in dialogue with the agency early on in the process, including through informational meetings, before more formal discussions are held about submitting an application for an investigational new drug. (Additional details about this process can be obtained by emailing **industry.biologics@fda.hhs.gov**.) Our aim is to refashion our traditional tools for regulation to meet the challenges and opportunities presented by such highly innovative products as cell-based regenerative medicine.

Funding and Disclosures

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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Supplementary Material

Disclosure Forms	PDF	96KB

FDA Warns About Stem Cell Therapies

Some patients may be vulnerable to stem cell treatments that are illegal and potentially harmful.

Watch Out for Unapproved Stem Cell Therapies!

Español (/consumers/articulos-en-espanol/la-fda-advierte-sobre-las-terapias-con-celulas-madre)

Researchers hope stem cells will one day be effective in the treatment of many medical conditions and diseases. But unproven stem cell treatments can be unsafe—so get all of the facts if you're considering any treatment.

Stem cells have been called everything from cure-alls to miracle treatments. But don't believe the hype. Some unscrupulous providers offer stem cell products that are both unapproved and unproven. So beware of potentially dangerous procedures—and confirm what's really being offered before you consider *any* treatment.

The facts: Stem cell therapies may offer the potential to treat diseases or conditions for which few treatments exist. Sometimes called the body's "master cells," stem cells are the cells that develop into blood, brain, bones, and all of the body's organs. They have the potential to repair,

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restore, replace, and regenerate cells, and could *possibly* be used to treat many medical conditions and diseases.

But the U.S. Food and Drug Administration is concerned that some patients seeking cures and remedies are vulnerable to stem cell treatments that are illegal and potentially harmful. And the FDA is increasing its oversight and enforcement to protect people from dishonest and unscrupulous stem cell clinics, while continuing to encourage innovation so that the medical industry can properly harness the potential of stem cell products.

To do your part to stay safe, make sure that any stem cell treatment you are considering is either:

- FDA-approved, or;
- Being studied under an Investigational New Drug Application (IND), which is a clinical investigation plan submitted and allowed to proceed by the FDA.

And see the boxed section below for more advice.

Stem Cell Uses and FDA Regulation

The FDA has the authority to regulate stem cell products in the United States.

Today, doctors routinely use stem cells that come from bone marrow or blood in transplant procedures to treat patients with cancer and disorders of the blood and immune system.

With limited exceptions, investigational products must also go through a thorough FDA review process as investigators prepare to determine the safety and effectiveness of products in well-controlled human studies, called clinical trials. The FDA has reviewed many stem cell products for use in these studies.

As part of the FDA's review, investigators must show how each product will be manufactured so the FDA can make sure appropriate steps are being taken to help assure the product's safety, purity, and strength (potency). The FDA also requires sufficient data from animal studies to help evaluate any potential risks associated with product use. (You can learn more about clinical trials on the FDA's website (https://www.fda.gov/forpatients/clinicaltrials/default.htm).)

That said, some clinics may inappropriately advertise stem cell clinical trials without submitting an IND. Some clinics also may falsely advertise that FDA review and approval of the stem cell therapy is unnecessary. But when clinical trials are not conducted under an IND, it means that the FDA has not reviewed the experimental therapy to help make sure it is reasonably safe. So be cautious about these treatments.

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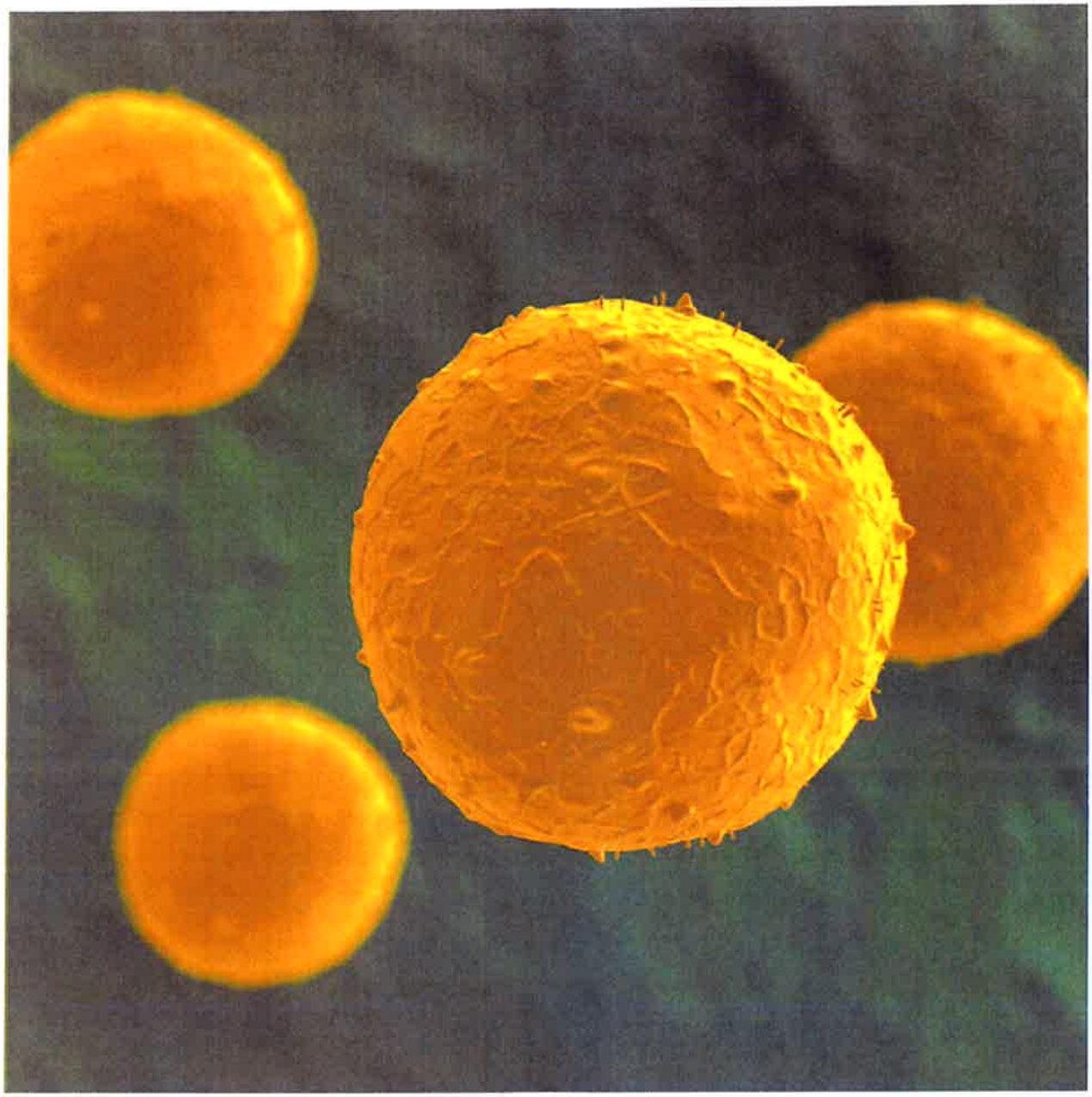

Electron micrograph of stem cells, color-enhanced for visual clarity.

About FDA-approved Products Derived from Stem Cells

The only stem cell-based products that are FDA-approved for use in the United States consist of blood-forming stem cells (hematopoietic progenitor cells) derived from cord blood.

These products are approved for limited use in patients with disorders that affect the body system that is involved in the production of blood (called the "hematopoietic" system). These FDA-approved stem cell products are listed on the FDA website (/vaccines-blood-

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biologics/cellular-gene-therapy-products/approved-cellular-and-gene-therapy-products). Bone marrow also is used for these treatments but is generally not regulated by the FDA for this use.

Safety Concerns for Unproven Stem Cell Treatments

All medical treatments have benefits and risks. But unproven stem cell therapies can be particularly unsafe.

For instance, attendees at a 2016 FDA public workshop (/vaccines-blood-biologics/workshops-meetings-conferences-biologics/public-workshop-scientific-evidence-development-human-cells-tissues-and-cellular-and-tissue-based) discussed several cases of severe adverse events. One patient became blind due to an injection of stem cells into the eye. Another patient received a spinal cord injection that caused the growth of a spinal tumor.

Other potential safety concerns for unproven treatments include:

- Administration site reactions,
- The ability of cells to move from placement sites and change into inappropriate cell types or multiply,
- Failure of cells to work as expected, and
- The growth of tumors.

Note: Even if stem cells are your own cells, there are still safety risks such as those noted above. In addition, if cells are manipulated after removal, there is a risk of contamination of the cells.

FDA Actions on Unapproved Stem Cell Products

When stem cell products are used in unapproved ways—or when they are processed in ways that are more than minimally manipulated, which relates to the nature and degree of processing—the FDA may take (and has already taken) a variety of administrative and judicial actions, including criminal enforcement, depending on the violations involved.

In August 2017, the FDA announced increased enforcement of regulations and oversight of stem cell clinics. To learn more, see the statement from FDA Commissioner Scott Gottlieb, M.D., on the FDA website (/news-events/press-announcements/statement-fda-commissioner-scott-gottlieb-md-fdas-new-policy-steps-and-enforcement-efforts-ensure).

And in March 2017, to further clarify the benefits and risks of stem cell therapy, the FDA published a perspective article in the *New England Journal of Medicine* (http://www.nejm.org/doi/full/10.1056/NEJMp1613723?query=featured_home&) (http://www.fda.gov/about-fda/website-policies/website-disclaimer).

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The FDA will continue to help with the development and licensing of new stem cell therapies where the scientific evidence supports the product's safety and effectiveness.

Advice for People Considering Stem Cell Therapies

Know that the FDA plays a role in stem cell treatment oversight. You may be told that because these are your cells, the FDA does not need to review or approve the treatment. That is not true.

Stem cell products have the potential to treat many medical conditions and diseases. But for almost all of these products, it is not yet known whether the product has any benefit—or if the product is safe to use.

If you're considering treatment in the United States:

- **Ask if the FDA has reviewed the treatment.** Ask your health care provider to confirm this information. You also can ask the clinical investigator to give you the FDA-issued Investigational New Drug Application number and the chance to review the FDA communication acknowledging the IND. Ask for this information *before* getting treatment—even if the stem cells are your own.
- **Request the facts and ask questions if you don't understand.** To participate in a clinical trial that requires an IND application, you must sign a consent form that explains the experimental procedure. The consent form also identifies the Institutional Review Board (IRB) that assures the protection of the rights and welfare of human subjects. Make sure you understand the entire process and known risks before you sign. You also can ask the study sponsor for the clinical investigator's brochure, which includes a short description of the product and information about its safety and effectiveness.

If you're considering treatment in another country:

- **Learn about regulations that cover products in that country.**
- **Know that the FDA does not have oversight of treatments done in other countries.** The FDA typically has little information about foreign establishments or their stem cell products.
- **Be cautious.** If you're considering a stem cell-based product in a country that may not require regulatory review of clinical studies, it may be hard to know if the experimental treatment is reasonably safe.

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Consumer Alert on Regenerative Medicine Products Including Stem Cells and Exosomes

Date: July 22, 2020

If you were hurt or had a bad side effect following treatment with anything that was supposed to be a regenerative medicine product, including, for example, stem cell products and exosome products, we encourage you to report it to the FDA's MedWatch Adverse Event Reporting program (/safety/medwatch-fda-safety-information-and-adverse-event-reporting-program). Additional information for patients on reporting adverse events for these products can be found here (/vaccines-blood-biologics/consumers-biologics/reporting-adverse-events-related-stem-cells-exosomes-or-other-products-marketed-regenerative).

The US Food and Drug Administration (FDA) has authority to regulate regenerative medicine products, including stem cell products and exosome products. There is a lot of misleading information on the internet about these products, including statements about the conditions they can be used to treat. FDA is concerned that many patients seeking cures and remedies may be misled by information about products that are illegally marketed, have not been shown to be safe or effective, and, in some cases, may have significant safety issues that put patients at risk. FDA wants to help consumers be informed about how these products are regulated, and what to look for when considering treatment with one of these products.

Stem cell products are regulated by FDA, and, generally, all stem cell products require FDA approval. Currently, the only stem cell products that are FDA-approved for use in the United States consist of blood-forming stem cells (also known as hematopoietic progenitor cells) that

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are derived from umbilical cord blood. These products are approved for use in patients with disorders that affect the production of blood (i.e., the "hematopoietic" system) but they are not approved for other uses.

Exosome products are also regulated by FDA. As a general matter, exosome products intended to treat diseases or conditions in humans require FDA approval. There are currently no FDA-approved exosome products.

Anyone considering the use of anything purported to be a regenerative medicine product, including stem cell products, exosome products, or other widely promoted products such as products derived from adipose tissue (this product is also known as stromal vascular fraction), human umbilical cord blood, Wharton's Jelly, or amniotic fluid should know:

- None of these products have been approved for the treatment or prevention of COVID-19, acute respiratory distress syndrome (ARDS), or any other complication related to COVID-19.
- None of these products have been approved for the treatment of any orthopedic condition, such as osteoarthritis, tendonitis, disc disease, tennis elbow, back pain, hip pain, knee pain, neck pain, or shoulder pain.
- None of these products have been approved to treat any neurological disorder, such as multiple sclerosis, amyotrophic lateral sclerosis (ALS; Lou Gehrig's disease), Alzheimer's disease, Parkinson's disease, epilepsy, or stroke.
- None of these products have been approved for the treatment of any cardiovascular or pulmonary (lung) diseases, such as heart disease, emphysema, or chronic obstructive pulmonary disease (COPD).
- None of these products have been approved to treat autism, macular degeneration, blindness, chronic pain, or fatigue.

FDA has posted information for consumers and patients (/consumers/consumer-updates/fda-warns-about-stem-cell-therapies) that discusses the potential risks, and provides advice for people considering the use of these products. Consumers should be cautious of any clinics, including regenerative medicine clinics, or health care providers, including physicians, chiropractors, or nurses, that advertise or offer any of these products. FDA also issued a public safety notification (/vaccines-blood-biologics/safety-availability-biologics/public-safety-notification-exosome-products) on exosome products on December 6, 2019.

Resources for Consumers

- FDA Video – Watch Out for Unapproved Stem Cell Therapies! (https://youtu.be/onnlZeQlaio) (http://www.fda.gov/about-fda/website-policies/website-disclaimer)

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- For information on the different types of actions FDA can take when products are found to be in violation of the law, visit this page (/vaccines-blood-biologics/guidance-compliance-regulatory-information-biologics/regulatory-actions-issued-cber)
- FDA Consumer Update - FDA Warns About Stem Cell Therapies (/consumers/consumer-updates/fda-warns-about-stem-cell-therapies)

Contacting FDA

If you are considering a regenerative medicine product and have questions about how it is regulated (including whether FDA approval is required), whether it is FDA-approved, or what to consider before participating in a clinical trial, we urge you to call (800-835-4709) or email (ocod@fda.hhs.gov) (mailto:ocod@fda.hhs.gov) for information.

Healthcare professionals and consumers should report any adverse events related to the use of stem cells, exosomes, or other products purported to be regenerative medicine products to the FDA's MedWatch Adverse Event Reporting program (/safety/medwatch-fda-safety-information-and-adverse-event-reporting-program). To report an adverse event online, click here: Report a Problem (https://www.accessdata.fda.gov/scripts/medwatch/index.cfm). Additional information for patients on reporting adverse events associated with stem cells, exosomes, or other products purporting to be regenerative medicine products can be found here (/vaccines-blood-biologics/consumers-biologics/reporting-adverse-events-related-stem-cells-exosomes-or-other-products-marketed-regenerative). The FDA monitors these reports and takes appropriate action to help ensure the safety of medical products in the U.S. marketplace.

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FDA NEWS RELEASE

FDA announces comprehensive regenerative medicine policy framework

Framework aims to spur innovation, efficient access to potentially transformative products, while ensuring safety and efficacy

For Immediate Release:

November 15, 2017

Today the U.S. Food and Drug Administration announced a comprehensive policy framework for the development and oversight of regenerative medicine products, including novel cellular therapies.

The framework – outlined in a suite of four guidance documents – builds upon the FDA's existing risk-based regulatory approach to more clearly describe what products are regulated as drugs, devices, and/or biological products. Further, two of the guidance documents propose an efficient, science-based process for helping to ensure the safety and effectiveness of these therapies, while supporting development in this area. The suite of guidance documents also defines a risk-based framework for how the FDA intends to focus its enforcement actions against those products that raise potential significant safety concerns. This modern framework is intended to balance the agency's commitment to safety with mechanisms to drive further advances in regenerative medicine so innovators can bring new, effective therapies to patients as quickly and safely as possible. The policy also delivers on important provisions of the 21st Century Cures Act (/21st-century-cures-act).

"We're at the beginning of a paradigm change in medicine with the promise of being able to facilitate regeneration of parts of the human body, where cells and tissues can be engineered to grow healthy, functional organs to replace diseased ones; new genes can be introduced into the body to combat disease; and adult stem cells can generate replacements for cells that are lost to injury or disease. This is no longer the stuff of science fiction. This is the practical promise of modern applications of regenerative medicine," said FDA Commissioner Scott Gottlieb, M.D. "But this field is dynamic and complex. As such, it has presented unique challenges to researchers, health care providers, and the FDA as we seek to provide a clear pathway for those developing new therapies in this promising field, while making sure that the FDA meets its obligation to ensure the safety and efficacy of the medical products that patients rely upon. Alongside all the promise, we've also seen products marketed that are dangerous and have harmed people. With the policy framework the FDA is announcing today, we're adopting a risk-

based and science-based approach that builds upon existing regulations to support innovative product development while clarifying the FDA's authorities and enforcement priorities. This will protect patients from products that pose potential significant risks, while accelerating access to safe and effective new therapies."

The framework includes two final guidance documents and two draft guidance documents.

New Final Guidance Documents

The two final guidance documents clarify the FDA's interpretation of the risk-based criteria manufacturers use to determine whether a product is subject to the FDA's premarket review.

The first guidance (/regulatory-information/search-fda-guidance-documents/evaluation-devices-used-regenerative-medicine-advanced-therapies) provides greater clarity around when cell and tissue-based products would be excepted from the established regulations if they are removed from and implanted into the same individual within the same surgical procedure and remain in their original form. The second final guidance (/regulatory-information/search-fda-guidance-documents/regulatory-considerations-human-cells-tissues-and-cellular-and-tissue-based-products-minimal) helps stakeholders better understand how existing regulatory criteria apply to their products by clarifying how the agency interprets the existing regulatory definitions "minimal manipulation" and "homologous use." As this field advances, the FDA has noted that there are a growing number of regenerative medicine products subject to FDA premarket authorization. These guidance documents will help explain how the FDA will provide a risk-based framework for its oversight. The policy framework defines how we intend to take action against unsafe products while facilitating continued innovation of promising technologies.

To accomplish this goal, the guidance document has clarified the FDA's view of "minimal manipulation" and "homologous use." These are two concepts that are defined in current regulation to establish the legal threshold for when a product is subject to the FDA's premarket approval requirements. By further clarifying these terms in the final guidance, the FDA is applying a modern framework for its oversight. Under the new policy, in order to allow manufacturers of products time to comply with the requirements, for the first 36 months following issuance of the final guidance document the FDA intends to exercise enforcement discretion for certain products that are subject to the FDA's premarket review under the existing regulations, but are not currently meeting these requirements. The FDA does not intend to exercise such enforcement discretion for those products that pose a potential significant safety concern. Going forward, the FDA will apply a risk-based approach to enforcement, taking into account how products are being administered as well as the diseases and conditions for which they are being used. This risk-based approach allows product manufacturers time to engage with the FDA, as to determine if they need to submit a marketing authorization application and, if so, submit their application to the FDA for approval.

New Draft Guidance Documents

The two draft guidances provide important information to help spur development and access to innovative regenerative therapies. The first draft guidance (/regulatory-information/search-fda-guidance-documents/evaluation-devices-used-regenerative-medicine-advanced-therapies), which builds off the regenerative medicine provisions in the 21st Century Cures Act (/21st-century-cures-act), addresses how the FDA intends to simplify and streamline its application of the regulatory requirements for devices used in the recovery, isolation, and delivery of regenerative medicine advanced therapies (RMATs) (/vaccines-blood-biologics/cellular-gene-therapy-products/regenerative-medicine-advanced-therapy-designation), including combination products. The guidance specifies that devices intended for use with a specific RMAT may, together with the RMAT, be considered to comprise a combination product.

The second draft guidance (/media/109203/download) describes the expedited programs that may be available to sponsors of regenerative medicine therapies, including the new Regenerative Medicine Advanced Therapy (RMAT) designation (/vaccines-blood-biologics/cellular-gene-therapy-products/regenerative-medicine-advanced-therapy-designation) created by the 21st Century Cures Act, Priority Review (/patients/fast-track-breakthrough-therapy-accelerated-approval-and-priority-review/priority-review), and Accelerated Approval (/patients/fast-track-breakthrough-therapy-accelerated-approval-and-priority-review/accelerated-approval). In addition, the guidance describes the regenerative medicine therapies that may be eligible for RMAT designation – including cell therapies, therapeutic tissue engineering products, human cell and tissue products, and combination products using any such therapies or products, as well as gene therapies that lead to a durable modification of cells or tissues (including genetically modified cells).

"As a molecular and cell biologist and physician, it has been exciting to witness the approval of the first two gene therapies in the U.S. this year. Given the great opportunities that the field of regenerative medicine presents, we have undertaken a rigorous process to clarify our regulations that included solicitation of public input, and I believe today marks a significant step forward for all stakeholders," said Peter Marks, M.D., Ph.D., director of the FDA's Center for Biologics Evaluation and Research. "In addition to clarifying some of the more complex areas of the regulations, we have taken meaningful new steps to encourage and expedite the development of innovative therapies. We welcome public comment on our draft guidance documents as we work toward finalizing this framework."

Both draft guidance documents will have 90-day comment periods.

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Inquiries

FDA NEWS RELEASE

FDA sends warning to company for selling unapproved umbilical cord blood and umbilical cord products that may put patients at risk; continues to warn patients of the risk of unapproved stem cell therapy

Stemell sold stem cell products without required FDA approval

For Immediate Release:

September 03, 2019

The U.S. Food and Drug Administration has warned (/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/stemell-inc-579013-08282019) Stemell, Inc. (Stemell), of San Juan Capistrano, California, and its president and Chief Executive Officer, Peyman Taeidi, Ph.D., for manufacturing and distributing unapproved products derived from umbilical cord blood and umbilical cord and for significant deviations from current good tissue practice (CGTP) and current good manufacturing practice (CGMP) requirements, including deficient donor eligibility practices and environmental monitoring, creating potential significant safety concerns that put patients at risk. Stemell's unapproved products derived from umbilical cord blood and umbilical cord are StemL UCB-Plus and StemL UCT-Plus.

"We know that there are manufacturers and clinics across the country that manufacture or market violative stem cell products to patients, claiming that they don't fall under the regulatory provisions for drugs and biological products. The FDA has consistently stated that this is not true," said Acting FDA Commissioner Ned Sharpless, M.D. "This company failed to take appropriate measures to protect patient safety. The FDA will be increasing our oversight related to cell-based regenerative medicine as part of our comprehensive plan to promote beneficial innovation while protecting patients. Those who are manufacturing or marketing unapproved, potentially unsafe products must understand that there's a clear line between appropriate development of these products and those practices that sidestep important statutory and regulatory controls that are in place to protect patients."

The FDA's recent inspection of the Stemell facility in March revealed that the company was manufacturing products derived from human umbilical cord blood and umbilical cord for use in recipients unrelated to the donors of the products. Because these Stemell products are not intended for homologous use only (i.e., to perform the same basic function or functions in the recipient as in the donor) and fail to meet other criteria set forth in applicable FDA regulations, they are regulated as both drugs and biological products. To lawfully market these products, an

approved biologics license application is needed. While in the development stage, the products may be used in humans only if an investigational new drug application (IND) is in effect. However, no such licenses or INDs exist for these Stemell products.

During the inspection, the FDA documented evidence of significant deviations from CGTP and CGMP requirements in the manufacture of Stemell's products, including deficient donor eligibility practices, unvalidated manufacturing processes, deficient environmental monitoring and inadequate aseptic processes. These deviations pose a risk that the products may be contaminated with viruses or microorganisms or have other serious product quality defects.

"The FDA remains highly committed to facilitating the development and availability of safe and effective cellular therapy products. However, we will not hesitate to take appropriate action to protect people from being harmed by products with potential significant safety concerns," said Peter Marks, M.D., Ph.D., director of the FDA's Center for Biologics Evaluation and Research. "In addition to the warning letter issued today, we sent another 20 letters to manufacturers and health care providers across the country who may be offering unapproved stem cell products, reiterating the FDA's compliance and enforcement policy. We remain very concerned that countless clinics across the country continue to market violative stem cell products to patients that have not been appropriately evaluated for safety or efficacy."

As highlighted in 2017 with the release of the FDA's comprehensive regenerative medicine policy framework (/news-events/press-announcements/fda-announces-comprehensive-regenerative-medicine-policy-framework), including the FDA's final guidance (Regulatory Considerations for Human Cell, Tissues, and Cellular and Tissue-Based Products: Minimal Manipulation and Homologous Use (/regulatory-information/search-fda-guidance-documents/regulatory-considerations-human-cells-tissues-and-cellular-and-tissue-based-products-minimal)), the FDA intends to apply a risk-based approach to compliance and enforcement of cell-based regenerative medicine products, taking into account how products are being administered as well as the diseases and conditions for which they are intended to be used. The agency noted that it intends to exercise enforcement discretion for certain products until November 2020 with respect to FDA's investigational new drug application and premarket approval requirements when the use of the product does not raise reported safety concerns or potential significant safety concerns. However, the FDA does not intend to exercise such enforcement discretion for those products that pose a potential significant safety concern to patients. As reflected by this warning letter, the other letters issued today, and other correspondence issued recently, the FDA will take appropriate steps to protect the public health.

The FDA offers opportunities for engagement between potential manufacturers and the agency, such as through the INTERACT (/vaccines-blood-biologics/industry-biologics/interact-meetings) program, to facilitate product development. It also encourages the use of its expedited programs whenever applicable, in addition to the collaborative development of products as the former FDA Commissioner and Center for Biologics Evaluation and Research director discussed

in a New England Journal of Medicine (https://www.nejm.org/doi/full/10.1056/NEJMsr1715626) (http://www.fda.gov/about-fda/website-policies/website-disclaimer) perspective. In addition, the FDA recently announced (/news-events/fda-brief/fda-brief-fda-announces-temporary-streamlined-program-help-manufacturers-human-cell-tissue-and) a temporary program called the Tissue Reference Group (TRG) Rapid Inquiry Program (TRIP), which is intended to assist manufacturers of human cells, tissues, and cellular and tissue-based products (including stem cells) to obtain a rapid, preliminary, informal, non-binding assessment from the agency regarding how their specific products are regulated.

The FDA requested a response from Stemell, within 15 working days of the letter's issuance, that details how the deviations noted in the warning letter will be corrected. Deviations not corrected by companies and owners could lead to enforcement action such as seizure, injunction or prosecution.

Health care professionals and consumers should report any adverse events related to treatments with the Stemell products or other stem cell treatments to the FDA's MedWatch (/safety/medwatch-fda-safety-information-and-adverse-event-reporting-program) Adverse Event Reporting program. To file a report, use the MedWatch Online Voluntary Reporting Form (https://www.accessdata.fda.gov/scripts/medwatch/index.cfm?action=reporting.home). The completed form (/safety/medical-product-safety-information/medwatch-forms-fda-safety-reporting) can be submitted online or via fax to 1-800-FDA-0178. The FDA monitors these reports and takes appropriate action necessary to ensure the safety of medical products in the marketplace.

The FDA, an agency within the U.S. Department of Health and Human Services, protects the public health by assuring the safety, effectiveness, and security of human and veterinary drugs, vaccines and other biological products for human use, and medical devices. The agency also is responsible for the safety and security of our nation's food supply, cosmetics, dietary supplements, products that give off electronic radiation, and for regulating tobacco products.

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FDA NEWS RELEASE

FDA puts company on notice for marketing unapproved stem cell products for treating serious conditions

Arizona company claims their products can treat Lyme disease, diabetes, Parkinson's disease and more, but have not been approved for any use

For Immediate Release:

May 30, 2019

Español (/news-events/press-announcements/la-fda-envio-una-advertencia-una-compania-que-esta-comercializando-productos-derivados-de-celulas)

The U.S. Food and Drug Administration has sent an untitled letter to R3 Stem Cell, LLC (/media/126709/download) of Scottsdale, Arizona, and its chief executive officer, David Greene, M.D. The company, through its affiliated centers or clinics throughout the U.S., offers unapproved stem cell products to treat a variety of diseases and conditions, such as Lyme disease, diabetes, Parkinson's disease, stroke, kidney failure and amyotrophic lateral sclerosis (ALS). The products offered by R3 Stem Cell, LLC are not approved by the FDA.

The FDA has notified each of R3 Stem Cell, LLC's more than 50 affiliate centers or clinics of this action.

"We continue to see companies and individuals use questionable marketing campaigns to take advantage of vulnerable patients and their families with unproven claims about their unapproved stem cell products. The reality is that at this time, there isn't enough evidence to support the use of stem cells for purposes other than reconstitution of blood formation and the immune system," said FDA Acting Commissioner Ned Sharpless, M.D. "We've made it clear to the industry and the public that while we are taking a risk-based approach to regulatory actions, the FDA will continue to protect patients from the most egregious actors in this field. We will prioritize appropriate regulatory actions against those who place people's health at risk by promoting unapproved products."

In the FDA's review of the R3 Stem Cell, LLC website, the agency found that the company promotes stem cell therapies for numerous diseases or conditions, such as dementia and Parkinson's disease, and directs patients with ALS, diabetes, kidney failure, Lyme disease, Parkinson's disease and stroke to certain "R3 Stem Cell Centers of Excellence" for stem cell treatment. The untitled letter notes that the company advertises that a variety of other conditions can be treated at R3 Stem Cell Clinics, including rheumatoid arthritis, spinal stenosis, and trigeminal neuralgia (nerve pain).

It appears that the products offered by the company would be regulated as drugs and biological products under the Federal Food Drug and Cosmetic Act and the Public Health Service Act. Prior to marketing, such products require a demonstration that the products are safe and effective for their intended uses. Manufacturers who fail to comply with FDA requirements may be subject to enforcement action, such as seizure, injunction, or prosecution.

"We encourage firms to engage with the FDA about regulatory oversight of this field and work with the agency for appropriate development, including designing clinical trials, to explore the safety and potential benefits of these products. We intend to step up our oversight of those sponsors who have not engaged the regulatory process in the proper development of their stem cell products that are regulated as drugs, devices, and/or biological products under the statutes and existing regulations, and whose products create more significant potential risks because of the way that they're manipulated or delivered," said Peter Marks, M.D., Ph.D., director of the FDA's Center for Biologics Evaluation and Research. "Over the past year, the FDA has sent 46 manufacturers and health care

professionals regulatory correspondence, including today's untitled letter. We have also sent warning letters, and we have two court cases pending. We're committed to taking appropriate steps to address those that jeopardize public health."

As highlighted in 2017 with the release of the FDA's comprehensive regenerative medicine policy framework (/news-events/press-announcements/fda-announces-comprehensive-regenerative-medicine-policy-framework), the FDA is applying a risk-based regulatory approach to the oversight of regenerative medicine products, taking into account how products are being administered as well as the diseases and conditions for which they are intended. The agency noted that it intends to exercise enforcement discretion for certain products until November 2020 with respect to the FDA's investigational new drug application and premarket approval requirements when the use of the product does not raise reported safety concerns or potential significant safety concerns.

The FDA offers opportunities for engagement between potential manufacturers and the agency, such as through the INTERACT (/vaccines-blood-biologics/industry-biologics/interact-meetings) program, to facilitate product development. It also encourages the use of its expedited programs whenever applicable, in addition to the collaborative development of products as discussed in a New England Journal of Medicine (https://www.nejm.org/doi/full/10.1056/NEJMsr1715626) (http://www.fda.gov/about-fda/website-policies/website-disclaimer) perspective authored by the FDA.

Health care professionals and consumers should report any adverse events related to treatments with R3 Stem Cell, LLC products and/or other stem cell treatments to the FDA's MedWatch (/safety/medwatch-fda-safety-information-and-adverse-event-reporting-program) Adverse Event Reporting program. To file a report, use the MedWatch Online Voluntary Reporting Form (https://www.accessdata.fda.gov/scripts/medwatch/index.cfm?action=reporting.home). The completed form (/safety/medical-product-safety-information/medwatch-forms-fda-safety-reporting) can be submitted online or via fax to 1-800-FDA-0178. The FDA monitors these reports and takes appropriate action necessary to ensure the safety of medical products in the marketplace.

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The FDA, an agency within the U.S. Department of Health and Human Services, protects the public health by assuring the safety, effectiveness, and security of human and veterinary drugs, vaccines and other biological products for human use, and medical devices. The agency also is responsible for the safety and security of our nation's food supply, cosmetics, dietary supplements, products that give off electronic radiation, and for regulating tobacco products.

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Inquiries

Media:

Stephanie Caccomo (mailto:stephanie.caccomo@fda.hhs.gov)

301-348-1956

Consumer:

888-INFO-FDA

Related Information

WARNING LETTER

Invitrx Therapeutics Inc.

MARCS-CMS 581182 – MARCH 16, 2020

Delivery Method:

VIA UNITED PARCEL SERVICE

Product:

Biologics

Recipient:

Habib (nmi) Torfi
Chief Executive Officer
Invitrx Therapeutics Inc.
20503 Crescent Bay Drive
Lake Forest, CA 92630
United States

Issuing Office:

Center for Biologics Evaluation and Research (CBER)
10903 New Hampshire Avenue
Silver Spring, MD 20993
United States

WARNING LETTER

March 16, 2020

Warning Letter #OBPO 20-581182

Dear Mr. Torfi,

During an inspection of your firm Invitrx Therapeutics, Inc., located at 20503 Crescent Bay Drive, Lake Forest, CA 92630, conducted between March 25, 2019 and April 3, 2019, the Food and Drug Administration (FDA) documented that your firm processes products for allogeneic use, including the following products (referred to collectively in this letter as "your products"): human umbilical cord blood, or umbilical cord derived products,

Invitra CBSC™ and Invitra WJ™ (Cellular and Acellular); amniotic fluid derived product Invitra AF™; and amniotic membrane derived product Invitra AT™. You distribute your products to **(b)(4)**, located in **(b)(4)**. These products are intended for injection and are purported to be sterile.

Information and records gathered during the course of the inspection and information available on your website, www.invitrx.com, and the **(b)(4)**, reflect that your products are intended to treat a variety of diseases or conditions. Therefore, your products are drugs as defined in section 201(g) of the Federal Food, Drug, and Cosmetic Act (the FD&C Act) [21 U.S.C. 321(g)] and biological products as defined in section 351(i) of the Public Health Service Act (PHS Act) [42 U.S.C. 262(i)].[1]

Certain of your products are also human cells, tissues, or cellular or tissue-based products (HCT/Ps) as defined in 21 CFR 1271.3(d)[2] and are subject to regulation under 21 CFR Part 1271, issued under authority of section 361 of the PHS Act [42 U.S.C. 264]. Invitrx does not qualify for any exception in 21 CFR 1271.15, and your HCT/Ps fail to meet all the criteria in 21 CFR 1271.10(a). Therefore, your HCT/Ps are not regulated solely under section 361 of the PHS Act [42 U.S.C. 264] and the regulations in 21 CFR Part 1271.

Specifically, an HCT/P meets the criterion established by 21 CFR 1271.10(a)(2) if it is "intended for homologous use only, as reflected by the labeling, advertising, or other indications of the manufacturer's objective intent."[3] As noted above, your products are intended to treat a variety of diseases or conditions. The umbilical cord blood and umbilical cord products are intended to treat orthopedic conditions, for example, and are not intended to perform the same basic function or functions of umbilical cord blood or umbilical cord in the recipient as in the donor, such as forming and replenishing the lymphohematopoietic system (for cord blood) and serving as a conduit (for umbilical cord). It appears that your product derived from amniotic membrane is also intended to treat orthopedic conditions, for example, and is not intended to perform the same basic function or functions of amniotic membrane in the recipient as in the donor, such as covering, protecting, serving as a selective barrier for the movement of nutrients between the external and in utero environment, and retaining fluid in utero. Using these products to treat orthopedic conditions is not homologous use as defined in 21 CFR 1271.3(c).

Your HCT/Ps fail to meet other criteria set forth in 21 CFR 1271.10(a). Your products derived from umbilical cord blood fail to meet 21 CFR 1271.10(a)(4). These products, manufactured from donated umbilical cord blood, are dependent on the metabolic activity of living cells for their primary function and are not for autologous use, allogeneic use in a first-degree or second-degree blood relative, or reproductive use. In addition, your products derived from umbilical cord and amniotic membrane fail to meet the minimal manipulation criterion set forth in 21 CFR 1271.10(a)(1) and defined for structural tissue in 21 CFR 1271.3(f)(1), because your processing alters the original relevant characteristics of the umbilical cord and amniotic membrane related to their utility for reconstruction, repair, or replacement.

As stated above, because your HCT/Ps do not meet all the criteria in 21 CFR 1271.10(a), and Invitrx does not qualify for any exception in 21 CFR 1271.15, your HCT/Ps are regulated as drugs as defined in section 201(g) of the FD&C Act [21 U.S.C. 321(g)] and biological products as defined in section 351(i) of the PHS Act [42 U.S.C. 262(i)].

Please be advised that to lawfully market a drug that is a biological product, a valid biologics license must be in effect [42 U.S.C. 262(a)]. Such licenses are issued only after showing that the product is safe, pure, and potent. While in the development stage, such products may be distributed for clinical use in humans only if the sponsor has an investigational new drug application (IND) in effect as specified by FDA regulations [21 U.S.C.

355(i); 42 U.S.C. 262(a)(3); 21 CFR Part 312]. None of your products are the subject of an approved biologics license application (BLA), nor is there an IND in effect for any of them. Based on this information, we have determined that your actions have violated the FD&C Act and the PHS Act.

Additionally, during the inspection, FDA investigators documented evidence of significant deviations from current good manufacturing practice (CGMP) and current good tissue practice (CGTP), including deviations from section 501(a)(2)(B) of the FD&C Act and 21 CFR Parts 210, 211, and 1271. The deviations in manufacturing processes observed as well as those noted in documents collected during the inspection indicate that the use of your products raises potential significant safety concerns. For example, Invitrx's deficient donor eligibility practices, unvalidated manufacturing processes, deficient environmental monitoring, and inadequate aseptic practices, as described below, pose a significant risk that your products may be contaminated with viruses or microorganisms or have other serious product quality defects.

At the close of the inspection, the FDA investigators issued a Form FDA 483 to you listing inspectional observations, which described a number of significant deviations from CGMP applicable to your products as well as significant CGTP deviations applicable to your HCT/Ps. FDA has found additional significant deviations upon further review of the information collected during the inspection, as discussed below. The deficiencies include, but are not limited to, the following:

1. Failure of a responsible person to determine and document the eligibility of a cell or tissue donor based upon the results of donor screening and donor testing [21 CFR 1271.50(a)]. For example:

a. Invitrx is the establishment responsible for making the donor eligibility determination, but since operations began in March 2018, Invitrx has failed to document whether over **(b)(4)** HCT/P donors are eligible.

b. When Invitrx receives relevant medical records, including the donor medical history interview and physical exams from its suppliers, those records are not reviewed to determine donor eligibility.

2. Failure to determine a donor to be ineligible whose specimen tests reactive on a screening test for a communicable disease agent in accordance with 21 CFR 1271.85 [21 CFR 1271.80(d)(1)]. Specifically, cord blood donor **(b)(6)** tested positive for Hepatitis B (HBc) on August 24, 2018, and donor eligibility was not determined. The cord blood was used to manufacture thirty-three vials of Invitra CBSC™ product (label number **(b)(4)**) on August 18, 2018. **(b)(4)** of these vials were distributed. We acknowledge below that your firm initiated a voluntary recall of the distributed product.

3. Failure to screen a donor of human cells or tissue by reviewing the donor's relevant medical records for risk factors for, and clinical evidence of, relevant communicable disease agents and diseases [21 CFR 1271.75(a)]. For example, FDA has identified Zika virus (ZIKV) as a relevant communicable disease agent or disease (RCDAD) under 21 CFR 1271.3(r)(2). Therefore, review of relevant medical records, as defined in 21 CFR 1271.3(s), must indicate that a potential donor is free from risk factors for, or clinical evidence of, ZIKV infection for the purpose of determining donor eligibility. The DT-001 Form 4 "Donor Risk Assessment Interview" you receive from your primary cord blood supplier, **(b)(4)**, does not adequately assess a donor's risk for ZIKV. We note that **(b)(4)** is located in **(b)(4)**, which has been identified by the Centers for Disease Control and Prevention as an area with current or past transmission of ZIKV. We recommend that you review FDA Guidance for Industry, Donor Screening Recommendations to Reduce the

Risk of Transmission of Zika Virus by Human Cells, Tissues, and Cellular and Tissue-Based Products (updated May 2018). This and all tissue guidances available to industry can be found at: https://www.fda.gov/vaccines-blood-biologics/biologics-guidances/tissue-guidances.

4. Failure to establish and maintain procedures for all steps performed in testing, screening, and determining donor eligibility, and complying with all other requirements of Subpart C "Donor Eligibility" in 21 CFR 1271.45-1271.90. "Establish and maintain" means define, document (in writing or electronically), and implement; then follow, review, and as needed, revise on an ongoing basis [21 CFR 1271.47(a)]. Specifically, you failed to establish and maintain procedures for determining donor eligibility to adequately and appropriately reduce the risk of transmission of relevant communicable diseases.

5. Failure to retain the accompanying records with the HCT/Ps at all times following a donor eligibility determination including a statement whether, based on the results of screening and testing, the donor has been determined to be eligible or ineligible; and a summary of records used to make the donor-eligibility determination [21 CFR 1271.55(a)]. For example, your HCT/Ps distributed to **(b)(4)**, were distributed without a statement of donor eligibility.

6. Failure to establish and follow appropriate written procedures designed to prevent microbiological contamination of drug products purporting to be sterile, including procedures for validation of all aseptic and sterilization processes [21 CFR 211.113(b)]. For example:

a. Your firm failed to validate the aseptic process used to manufacture Invitra AF™, Invitra AT™, Invitra CBSC™, and Invitra WJ™ since product manufacturing began in 2018. By the nature of their routes of administration, your products purport to be sterile and are expected to be sterile.

b. During the inspection, FDA investigators observed personnel practices that do not adequately protect against microbiological contamination of your products, including:

i. Operators donned sterile outer gloves over non-sterile inner gloves in the Biological Safety Cabinets (BSCs).
ii. An operator was observed processing cord blood in a BSC with only the inner non-sterile gloves.

c. Open sharps containers were observed with visible accumulation of debris and dried residues inside the BSCs where human umbilical cord blood is aseptically processed.

7. Failure to reject drug products that do not meet established standards or specifications and any other quality control criteria [21 CFR 211.165(f)]. For example:

a. You failed to reject batch **(b)(4), (b)(6)** of umbilical cord blood product due to microbial growth on the initial cord blood (donor **(b)(6)**) plate. **(b)(4)** vials of final product (label number **(b)(4)**) were distributed.

b. You failed to reject batch **(b)(4), (b)(4)** of umbilical cord blood product due to the inprocess plasma **(b)(4)** sterility positive test result for gram positive cocci. **(b)(4)** vials of final product (label number **(b)(4)**) were distributed.

8. Failure to establish and follow written procedures for cleaning and maintenance of equipment used in the manufacture, processing, packing, or holding of a drug product [21 CFR 211.67(b)]. For example:

a. Your firm failed to validate the cleaning process for your BSCs.

b. There is no data or rationale for the cleaning agents used or their rotation.

9. Failure to thoroughly investigate any unexplained discrepancy, or the failure of a batch or any of its components to meet any of its specifications [21 CFR 211.192]. Specifically, you failed to adequately investigate all sterility failures from March 2018 to present. Numerous batches of your umbilical cord blood and umbilical cord products failed sterility and were discarded after speciation without further investigation, including identification of the contamination source, and without implementing corrective actions.

10. Failure to establish written procedures for production and process control designed to assure that the drug products have the identity, strength, quality, and purity they purport or are represented to possess [21 CFR 211.100(a)]. Specifically, the manufacturing process has not been validated for your products.

11. Failure to have separate or defined areas or such other control systems for operations as are necessary to prevent contamination or mix-ups during the course of manufacturing and processing operations [21 CFR 211.42(c)(5)]. For example:

a. FDA investigators observed operators conducting processing of two separate umbilical cord product lots (**(b)(4)** and **(b)(4)**), in separate BSCs, and removing unlabeled vials from the BSCs for centrifugation using one shared **(b)(4)**. Products manufactured from different donors lacked unique identifiers.

b. Freezers for quarantine of finished product and released finished product are not labeled.

12. Failure to have an adequate system for monitoring environmental conditions in an aseptic processing area [21 CFR 211.42(c)(10)(iv)]. Specifically, your firm has not established an adequate system for environmental and personnel monitoring in the aseptic processing areas where the products are manufactured.

13. Failure to test your Invitra AT™ and Invitra WJ™ products, non-penicillin drug products, for the presence of penicillin although a reasonable possibility exists that the non-penicillin drug products have been exposed to cross contamination with penicillin [21 CFR 211.176]. Specifically, penicillin was used in an antibiotic wash during manufacture of approximately **(b)(4)** vials of Invitra AT™ and approximately **(b)(4)** vials of Invitra WJ™ from March 2018 to April 2019, and there is no documentation that testing for penicillin has been performed.

14. Failure to establish and follow written procedures describing the handling of all written and oral complaints regarding a drug product [21 CFR 211.198(a)]. You have not established and followed written procedures that describe a process for documenting and investigating complaints. The inspection revealed that Invitrx received at least 19 complaints, in the form of an e-mail, but there was no documentation that your firm performed adequate follow-up and/or investigations of those complaints.

15. Failure to establish and follow a written testing program designed to assess the stability characteristics of drug products and to use results of such stability testing to determine appropriate storage conditions and expiration dates [21 CFR 211.166(a)]. Specifically, you assign a two-year expiration date without supporting data.

16. Failure to establish and follow written procedures describing in sufficient detail the control procedures employed for the issuance of labeling [21 CFR 211.125(f)]. For example:

a. Your firm has not established a written procedure for the control of printed labels.

b. Four additional primary labels are printed and included in every shipment for "physician use" without documentation, accounting, or reconciliation.

17. Failure to withhold from use each lot of components, drug product containers, and closures until the lot has been sampled, tested, or examined, as appropriate, and released for use by the quality control unit [21 CFR 211.84(a)]. For example, the following components and containers are not tested or examined before release:

a. **(b)(4)** used to homogenize amniotic and umbilical cord tissue in the manufacture process of Invitra AT™ and Invitra WJ™.

b. **(b)(4)** used to "wash" amniotic and umbilical cord tissue in the manufacture process of Invitra AT™ and Invitra WJ™.

c. **(b)(4)** GMP grade cryopreservation solution used in the final formulation of Invitra AF™, Invitra CBSC™, and Invitra WJ™.

We received your written responses, dated May 1 and October 1, 2019, to the inspectional observations on the Form FDA 483, and we have reviewed their contents. FDA acknowledges your decision to voluntary recall distributed Invitra CBSCTM (label number **(b)(4)**) manufactured from cord blood of a donor who tested positive for Hepatitis B, and your decision to temporarily cease the receipt of HCT/Ps from **(b)(4)**, located in **(b)(4)**. We also acknowledge the other corrective actions you represent that you have taken in response to the observations and your hiring of **(b)(4)**, a third-party consultant, to assist with investigations and the implementation of corrective actions. However, the responses do not provide sufficient detail to fully assess the adequacy of your corrective actions to date, lack a timeline for completion of all necessary corrective actions, and lack documentation to demonstrate that you have corrected your violations.

In addition, as noted above, in order to lawfully market a drug that is a biological product, a valid biologics license must be in effect [42 U.S.C. 262(a)]. Such licenses are issued only after showing that the product is safe, pure, and potent. While in the development stage, such products may be distributed for clinical use in humans only if the sponsor has an IND in effect as specified by FDA regulations [21 U.S.C. 355(i); 42 U.S.C. 262(a)(3); 21 CFR Part 312]. Your products are not the subject of an approved BLA nor is there an IND in effect for your products.

Neither this letter nor the observations noted on the Form FDA 483, which were discussed with you at the conclusion of the inspection, are intended to be an all-inclusive list of deficiencies that may exist at your facility. It is your responsibility to ensure full compliance with the FD&C Act, PHS Act, and all applicable regulations.

You should take prompt action to correct these violations. Failure to promptly do so may result in regulatory action without further notice. Such actions include seizure and/or injunction.

For further information about IND requirements for biological products, contact the Center for Biologics Evaluation and Research (CBER), Division of Regulatory Project Management, Office of Tissues and Advanced Therapies, at (240) 402-8190, or OTATRPMS@fda.hhs.gov. Please include a copy of this letter with your

initial submission to CBER.

We request that you respond in writing within fifteen (15) working days from your receipt of this letter, outlining the specific steps you have taken or plan to take to correct the noted violations and prevent their recurrence. Include any documentation necessary to show that correction has been achieved. If you do not believe your products are in violation of the FD&C Act, PHS Act, or applicable regulations, include your reasoning and any supporting information for our consideration. If you cannot complete all corrections within fifteen (15) working days, please explain the reason for your delay and the time frame within which the remaining corrections will be completed.

Your response should be sent to the following address: Daniel W. Cline, Compliance Officer, U.S. Food and Drug Administration, 19701 Fairchild, Irvine, CA 92612 or emailed to Daniel.Cline@fda.hhs.gov. If you have any questions, please contact Mr. Cline at (949) 608-4433 or via e-mail.

Sincerely,
/S/
Karlton Watson
Program Division Director
Office of Biological Products Operations - Division 2

cc: **(b)(4), (b)(6)**

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1 FDA investigators gathered evidence pertaining to your exosome product, Invitra EXTM (or, **(b)(4)**), but FDA's inspection did not focus on that product. Nor does this letter. Nevertheless, please be advised that as a general matter, exosome products intended to treat diseases or conditions in humans are regulated as drugs and biological products under section 351 of the PHS Act and the FD&C Act and are subject to premarket review and approval requirements. We also direct your attention to FDA's recent Public Safety Notification on Exosome Products, available at https://www.fda.gov/vaccinesblood-biologics/safety-availability-biologics/public-safety-notification-exosome-products.

2 HCT/Ps are defined as "articles containing or consisting of human cells or tissues that are intended for implantation, transplantation, infusion, or transfer into a human recipient." 21 CFR 1271.3(d). The definition of HCT/P excludes secreted or extracted human products; accordingly, secreted body fluids, such as amniotic fluid, are generally not considered HCT/Ps subject to regulation under 21 CFR Part 1271. Although not an HCT/P, your product derived from amniotic fluid is also regulated as a drug and biological product under section 351 of the PHS Act and the FD&C Act.

3 Under 21 CFR 1271.3(e), manufacture "means, but is not limited to, any or all steps in the recovery, processing, storage, labeling, packaging, or distribution of any human cell or tissue, and the screening or testing of the cell or tissue donor." Because both Invitrx and **(b)(4)** manufacture the products, within the meaning of 21 CFR 1271.3(e), FDA considered both firms' objective intent in evaluating whether the products are "intended for homologous use only" under 21 CFR 1271.10(a)(2).

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June 17, 2020

Identifying the Risks of Unproven Regenerative Medicine Therapies

Peter W. Marks, MD, PhD[1]; Stephen Hahn, MD[1]

Author Affiliations | Article Information

[1]US Food and Drug Administration, Silver Spring, Maryland

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Related Articles

In the middle of the coronavirus disease 2019 (COVID-19) public health response, many priorities are currently competing for the attention of the US Food and Drug Administration (FDA). Some of these are directly related to the pandemic, but others have been challenging issues for years. Over the past several years, hundreds of clinics across the US have been offering unproven regenerative medicine therapies to patients for the treatment of conditions ranging from aging to arthritis to autism.[1,2] Some of these same clinics are now offering similar unproven products for the treatment of complications of COVID-19 and are making claims that are simply not supported by compelling clinical data. Overall, the safety and efficacy of regenerative medicine products outside a narrow range of indications have yet to be demonstrated.[3]

The products administered by clinics under the broad rubric of regenerative medicine include those derived from individuals' own bone marrow or fat, those derived from birthing tissues such as placenta or cord blood obtained from a donor unrelated to the recipient, as well as products that are secreted or derived from unrelated donor cells. Despite assertions by some individuals to the contrary, these products, whether autologous or allogeneic, are not inherently safe and may be associated with serious adverse

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numerous serious bacterial infections requiring hospitalization. Such lapses may also be responsible for noninfectious complications due to substances introduced during the manufacturing process, as potentially was the case for 3 individuals who developed blindness following treatment with unproven and unapproved stem cell products.[4] The increasing number of adverse events being reported following the widespread use of unapproved regenerative medicine therapies at hundreds of clinics across the country make it necessary for the FDA to act to prevent harm to individuals receiving them.[1]

Unapproved regenerative medicine therapies are concerning precisely because they have not been treated as what they are: investigational therapeutics for which evidence for safety and efficacy is not available. Many of these products do not meet the criteria of the FDA's regulations to obviate the need for premarket authorization because they require significant manufacturing or are used in a different way in the recipient than in the donor, so they require study under an Investigational New Drug application and premarket approval. Companies involved in selling products that violate the regulations do so under the erroneous assertion that they are exempt from these FDA provisions. Because these unproven regenerative medicine therapies are being administered without regard to the FDA's regulatory oversight, it is impossible to know with certainty the number of individuals who have experienced serious adverse events following their administration.

To protect the public from unproven regenerative medicine therapies that have caused harm or have the potential to cause significant harm, the FDA has taken a variety of compliance and enforcement actions over the past several years, ranging from letters to manufacturers telling them that they are in violation of federal statutes and FDA regulations to seizing products that were considered dangerous to public health. However, the agency needs the engagement of both clinicians and patients to help to ensure that instead of remaining unintentionally or intentionally hidden, potentially harmful unapproved regenerative medicine therapies are identified and removed from the market. Medical professionals, such as primary care physicians and advanced practice nurses, are often in the best position to help patients identify whether a regenerative medicine therapy is appropriate for them to pursue, including whether a proposed therapy is being administered under the appropriate regulatory oversight.[5]

To summarize, in addition to consulting with their primary health care clinician, prior to considering cellular therapies, patients should ask if the therapy is approved by the FDA. If it is not, they should ensure that an active Investigational New Drug application is on file with the FDA, and they should expect to review and sign an informed consent (**Box**). Patients and their families also should not expect to be charged for investigational products they receive. An exception is cost recovery, whereby the sponsor provides evidence from a clinical trial to the FDA that a product may provide clinical benefit and the sponsor is then permitted to charge for manufacturing of the product but may not make a profit. Patients participating in clinical research should also expect to receive information regarding the results of the trial in which they have taken part. If questions remain, clinicians should consider contacting the FDA directly

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Box. Appropriate Practices for the Investigation of Unproven Regenerative Medicine Therapies

- Active Investigational New Drug (IND) application for the specific product in development is on file with the Food and Drug Administration
- Requirement for the provision of written informed consent in an institutional review board-approved clinical trial under an IND
- No charge is requested from the patient for the unapproved product or for participation in the clinical trial[a]
- Reporting of potential adverse events is encouraged and clear mechanisms are provided on how to do so
- A summary of results is reported back to those enrolled in the clinical trial

[a] Under circumstances in which there is some evidence of clinical benefit, the Food and Drug Administration permits sponsors to obtain cost recovery for direct costs associated with providing an investigational product under an IND. However, the amount charged cannot exceed the actual cost to make the product, as documented by a certified public accountant.

Perhaps most important, individuals who have chosen to pursue cellular therapies should be encouraged to report adverse events for products or treatments that they may have received, even if they have paid for them. They should also be encouraged to allow family, friends, or clinicians to report such events. Patients and their clinicians should use the MedWatch form FDA 3500 (Voluntary Reporting for Use by Health Professionals, Consumers, and Patients) or the more patient-friendly form FDA 3500B to report adverse events that they perceive may be related to the administration of a cellular product.[7] If a patient, family member, or their clinician is unsure of the nature of the cellular product that the patient has received, simply noting "stem cell therapy" as the administered product is sufficient. The FDA will investigate the nature of the product as part of its evaluation of the event. Only through the reporting of such events will it be possible for the FDA to gain a better understanding of the potential spectrum of adverse events associated with these therapies. Having these data could help future patients make more informed decisions and identify products for which FDA intervention is rapidly required because they are causing patient harm.

It is time for unproven and unapproved regenerative medicine products to be identified and recognized for what they frequently are: uncontrolled experimental procedures at a cost to patients, both financially and

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them into compliance and thereby help protect more patients from harm. This goes to the core of the mission to which the FDA is committed: promoting and protecting the public health.

Article Information

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Conflict of Interest Disclosures: Dr Hahn is Commissioner of Food and Drugs, US Food and Drug Administration (FDA). Prior to his appointment to the FDA, he was Chief Medical Executive at MD Anderson Cancer Center. Dr Marks does not have any conflicts of interest to disclose.

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Comment

2 Comments for this article **EXPAND ALL**

June 17, 2020

Need Quotation Marks

Robert Roth, MD | Retired GP

Any reason not to refer to the subject of your paper as "regenerative therapies," in quotes? Use of the quotation marks implies that you doubt the claim -- which I gather you do, and rightly so. Not using them implies that such things do exist. I don't think there is a middle ground there.

CONFLICT OF INTEREST: None Reported

June 18, 2020

Real World data Essential For Determining Safety and Efficacy of "Regenerative Treatments"

Gerard Malanga, M.D., Clin Prof Rutgers NJ | DataBiologics

It was with great interest that I read the article by Drs. Marks and Hahn: "Identifying the Risks of Unproven Regenerative Medicine Therapies". As a clinician and clinical researcher in "regenerative treatments" for orthopedic conditions, I fully agree that this area needs to be more done by clinicians to determine the safety and potential efficacy of these treatments. There is a great deal of lab and animal studies to support the potential benefit of these treatments for common diagnoses such as knee osteoarthritis and tendinopathies. In additional, there is an increasing number of clinical studies that demonstrated both safety and ...

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Consensus Statement by Physicians, Academics, and Regulatory Experts on the Aggressive Marketing of Non-viable Birth Tissues as Live "Stem Cell" Products to Cure Chronic Disease

Feb 18, 2019

Background:

As practicing physicians, scientists, and regulatory experts we have increasingly observed aggressive advertising and sales tactics being used by alternative health clinics (chiropractors, naturopaths, and acupuncturists) as well as physicians and mid-level providers to market "stem cell" treatments derived from birth tissues. One example is full-page print ads in major newspapers used to recruit elderly patients and others desperate for effective treatments to seminars where prospective patients are informed that they can be injected with millions of live and functional stem cells to relieve their symptoms. The products used are derived from birth tissues such as umbilical cord blood and/or Wharton's Jelly or amniotic fluid/membrane. Many patients spend thousands of dollars on these therapies to treat orthopedic problems and/or a myriad of other incurable diseases. The seminars typically state that there are robust clinical data supporting the safety and efficacy of these products, regardless of the condition or pathology being treated, when no such clinical evidence exists. In addition, some manufacturers of birth tissues claim that their products contain live and functional stem cells, while other manufacturers do not make these same claims. Claims of live cells are not compliant with FDA regulations, which require this type of donor tissue to be non-viable.

To date, two research investigations have been conducted which document the content of commercially available amniotic and cord blood products sold by FDA-registered manufacturers (those regulated solely under section 361 of the Public Health Service (PHS) Act). We are aware of additional investigations that are in progress. Both Berger, et al. and Becktell from the Fortier laboratory at Cornell University, found that these amniotic and cord blood products did not contain live or functional stem cells. In addition, both research groups found that many of the growth factor levels in these products were significantly lower than those found in common autologous orthobiologic products like platelet-rich plasma. Fortier et al. did report that these products do contain proteins like lumican and cytokines, which may positively impact orthopedic injuries, but concluded that more research is needed before any claims can be made. While there are early clinical data on stem cells that are isolated from fresh birth tissues and culture expanded, these studies used treatments which are not analogous to the commercially available, cryopreserved, FDA registered birth tissue products. In addition, it should be noted that while the clinical evidence in this area is evolving and one day may support the clinical efficacy of cryopreserved birth tissues for some orthopedic applications, no such evidence exists at this time. In particular, we are aware of FDA approved clinical trials that use these tissues for diseases such as knee osteoarthritis, which are ongoing.

Consensus Statement:

The aggressive marketing approach currently used by practitioners and clinics regarding various birth tissue products as safe and effective "stem cell therapy" is not supported by the existing scientific literature.

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FEDERAL TRADE COMMISSION
PROTECTING AMERICA'S CONSUMERS

Stemming unproven stem cell therapy claims

Share This Page

Lesley Fair
Oct 18, 2018

TAGS: Bureau of Consumer Protection | Consumer Protection | Advertising and Marketing | Health Claims

Old West nostrum sellers used to market treatments for a broad range of diseases with the slogan "Good for what ails ya." California-based Regenerative Medical Group used a current buzzword in science – stem cell therapy – to peddle what they claimed were treatments for conditions as varied as cerebral palsy and autism to Parkinson's disease, stroke, and macular degeneration. But according to the FTC, they didn't have proof to back up their expansive promises. "What ails ya?" For consumers struggling with serious diseases, the lawsuit demonstrates the FTC's concern with "what fails ya" – in other words, unproven "cures" that lack scientific support.

Advertising online and through social media, the defendants, including owner Bryn Jarald Henderson, D.O., promoted stem cell treatments derived from the amniotic fluid of women who have given birth via C-section. Their marketing claims were – to say the least – dramatic. According to a promotional letter from Dr. Henderson, "Lives are being saved, the blind see, the crippled walk and the patients with heart, lung, kidney and nerve diseases can alter the course of their suffering with a simple therapy [that] lasts for years and impacts their lives NOW!"

The defendants' ads also made express claims about specific intractable medical conditions:

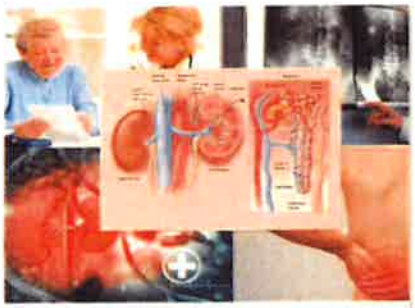
> "Stem Cell Treatments have been shown to improve sight in patients with Macular degeneration."
>
> "We can make blinded People see again!"
>
> "We can reverse Autism symptoms."
>
> "Can stem cell therapy help patients with chronic kidney disease? Yes it can. It can make new cells that replace damaged cells and reverse chronic kidney disease symptoms."
>
> "Cure for Parkinson's? The only Medical Group worldwide that treats Parkinson's with amniotic Stem Cells!"
>
> For stroke victims with damaged brain tissue, "Stem Cell treatment acts as a form of medical time machine, reversing the damage that has already been made."

One of the company's YouTube videos featured an 11-year-old girl with cerebral palsy who purportedly spoke "her first words" after receiving treatment from the defendants.

Regenerative Medical Group and Dr. Henderson charged consumers between $9,500 to $15,000 for an initial treatment with recommended "boosters" going for between $5,000 to $8,000. What's more, they claimed that what they offered was comparable to or even better than conventional medical care.

That's what the defendants said, but what's the real story on stem cells? In fact, there are many different kinds of stem cells – amniotic stem cells are only one variety – and they vary widely in potency. According to the National Institutes of Health (NIH) website, "Much work remains to be done in the laboratory and the clinic to understand how to use these cells for cell-based therapies to treat disease."

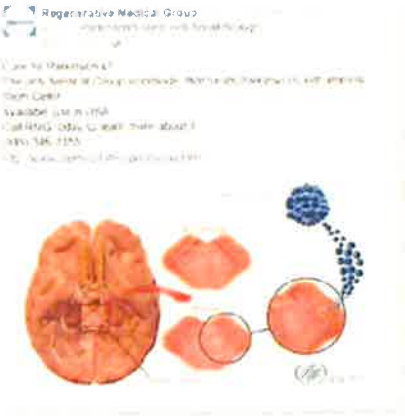
Furthermore, the vast majority of amniotic stem cell research has been conducted on animal models. According to the FTC, there are no human clinical studies showing that amniotic stem cell therapy treats *any* diseases in humans and certainly not the long list of conditions the defendants claimed to cure.



The proposed settlement requires the defendants to have human clinical testing to support future claims related to the treatment of any disease or health condition. Based on the defendants' financial status, the $3.3 million judgment – which represents what patients paid for the treatments – will be partially suspended when the defendants turn over $525,000. That money will be returned to consumers. The company also has to send a letter about the lawsuit to their customers and others who have expressed an interest in their stem cell therapy treatments.

What does the FTC prescribe for misleading health representations? Here are some suggestions.

"Cure" claims command clinical confirmation. Products that promise to treat or cure diseases need the support of human clinical testing. Don't draft your ad copy until you have methodologically sound testing in hand that demonstrates statistically and clinically significant results. The FTC's action against Regenerative Medical Group is the latest in a long line of cases challenging unproven treatments for autism, arthritis, macular degeneration, and other serious conditions. Claims like that are at the center of the enforcement radar screen and they're likely to stay there.



Exercise caution when using in-the-headlines medical terms. The phrase "stem cell treatment" covers a broad range of therapies – from promising research to flat-out fraud – and it may not be easy for consumers to make nuanced distinctions. Marketers shouldn't add to the confusion by playing fast and loose with the facts. Don't overstate the results consumers are likely to receive or falsely state or imply that your product is superior to other treatments.

Patients should study treatment options carefully. People diagnosed with serious diseases can find a wealth of information online, but not every site is trustworthy. Before diving into the deep end of the internet, start your research with agencies like the NIH or FDA. Take stem cells therapies as an example. While encouraging scientists to continue their research, the FDA also has warned consumers about the dangers of questionable stem cell "treatments."

The Washington Post
Democracy Dies in Darkness

New Google policy bars ads for unproven stem cell therapies

"Untested, deceptive treatments" can endanger consumers, Internet giant says.

By **William Wan** and **Laurie McGinley**

September 6, 2019 at 2:20 a.m. EDT

Responding to ubiquitous online marketing by stem cell clinics selling unapproved treatments for everything from achy joints to Alzheimer's, Google announced Friday it will no longer accept ads for "unproven or experimental medical techniques," including most stem cell therapy, cellular therapy and gene therapy.

The Internet giant said it was taking the step after seeing "a rise in bad actors" trying to take advantage of patients by offering "untested, deceptive treatments." Often, Google said in a post explaining the new policy, "these treatments can lead to dangerous health outcomes and we feel they have no place on our platforms." Its new policy will prohibit ads for treatments that have "no established biomedical or scientific basis."

The new position comes as stem cell clinics have grown into a sprawling direct-to-consumer industry. Some clinics have told patients their treatments can help them with ailments such as macular degeneration, ALS, multiple sclerosis and degenerative lung diseases. Scientists and medical associations have likened the procedures to modern snake oil and accused the purveyors of preying on the hopes of seriously ill patients. The untested treatments, many researchers say, is imperiling patients and the reputation of a promising field.

After years of little enforcement, the federal regulators have begun to crack down on the clinics. And the new Google policy will add to the growing scrutiny and pressure, industry experts said.

When asked by The Washington Post last December about its policies about advertising by stem cell clinics, Google declined to answer questions about actions against specific companies. In a statement, the company said: "If we find ads that violate our policies, we take immediate action, which can include taking down violating ads or suspending an account altogether."

At the time, the company said its existing policies already prohibited marketing potentially dangerous and fraudulent health products — a stance some stem cell experts criticized as insufficient.

"Google's new policy banning advertising for speculative medicines is a much-needed and welcome step to curb the marketing of unscrupulous medical products," said Deepak Srivastava, president of the International Society for Stem Cell Research, a leading group of scientists that gave Google advice on the policy. "The premature marketing and commercialization of unproven stem cell products threatens public health, the confidence in biomedical research, and undermines the development of legitimate new therapies," he said.

Some treatments have resulted in severe injuries, including at least five women who were blinded after stem cell clinics injected its product into their eyes.

Stem cell clinics say they are offering treatment to patients who have few other options and that their treatment may have ways of helping patients that science can't yet explain.

Some industry representatives criticized Google's new ad policy on Friday. The ban on ads will unfairly devastate

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In the past two years, Google had already begun refusing ads from several stem cell companies on a case-by-case basis, said Ittleman, who has been hired by a few such companies to try, unsuccessfully, to appeal such decisions with Google.

"It puts Google in the position of being a quasi regulator, taking on quite a significant amount of jurisdiction," Ittleman said. "They're painting the industry with a broad brush and companies with legitimate arguments are going to be collateral damage."

Google's new ad policy, however, is unlikely to put the industry out of business. Many clinics have shown an ability to adapt nimbly to new regulatory rules and changes such as Google's ad policy.

"This kind of ad ban hits hard because most companies rely on Google for a large share of their quality sales leads," said a former marketing head for a Florida stem cell company. "But there are plenty of other channels you can switch to — Facebook, Bing, Yahoo."

The marketing executive, who spoke on the condition of anonymity to avoid professional retaliation, said "These kinds of businesses are pretty savvy and have had to adapt a lot already. Many have previously been kicked off Google already. You learn to pivot and be resourceful."

Another recent example of the industry's ability to adapt, experts note, came when the Food and Drug Administration won a landmark lawsuit in June against a stem cell company selling stem cell procedures that extract clients' fat tissue, spin it to isolate certain cells, and inject them back into the body.

Health officials hailed the case as a turning point in the government's struggle to regulate the booming industry. But ahead of the legal victory, the industry had already begun to shift. Because the FDA was focusing on fat-based treatments, many clinics switched to treatments derived instead from s blood, bone marrow and birth-related tissues, such as amniotic fluid and umbilical cord blood.

Google officials said Friday they would continue to accept ads for clinical trials cleared by the government. It said that while important medical discoveries often start as unproven ideas, "we believe that monitored, regulated clinical trials are the most reliable way to test and prove important medical advances."

The ban will take effect across Google's ad services, including YouTube and ads Google helps place on third-party websites. And the ban includes treatments that are rooted in scientific findings and preliminary clinical experience "but currently have insufficient formal clinical testing" to justify widespread use. The new policy, which will take effect in October, was detailed in a blog post by Adrienne Biddings, the company's policy adviser.

The post said that the "digital ads ecosystem can only flourish if it's a place that is safe and trustworthy for users." The company said it will use a combination of machine learning and human review to enforce it.

To formulate the new approach, a spokeswoman said, the company's policy team has reviewed the literature on the field and worked with various stem-cell experts.

Paul Knoepfler, a stem cell biologist at the University of California at Davis and longtime critic of the for-profit stem cell industry, called the new Google policy a big deal. Many patients who have been seriously harmed, he noted, were initially recruited as customers via Google ads.

"A number of us have pushed for this kind of policy over the years so this news is a welcome surprise," Knoepfler said.

Read more:

Miracle cures or modern quackery? Stem cell clinics multiply, with heartbreaking results for some patients.

What you should know about stem cells, from promising research to dubious uses

'Miraculous' stem cell therapy has sickened people in five states

A new policy on advertising for speculative and experimental medical treatments

September 6, 2019

Digital advertising helps fuel an open internet for people all over the world – allowing billions of people to ask questions, find answers, and discover new ideas. We know the digital ads ecosystem can only flourish if it's a place that is safe and trustworthy for users. That's why we have robust Google Ads Policies outlining what kind of advertising is, and is not, allowed on our platform.

We regularly review and revise our advertising policies. Today, we're announcing a new Healthcare and medicines policy to prohibit advertising for unproven or experimental medical techniques such as most stem cell therapy, cellular (non-stem) therapy, and gene therapy. This new policy will prohibit ads selling treatments that have no established biomedical or scientific basis. The new policy also includes treatments that are rooted in basic scientific findings and preliminary clinical experience, but currently have insufficient formal clinical testing to justify widespread clinical use.

We know that important medical discoveries often start as unproven ideas – and we believe that monitored, regulated clinical trials are the most reliable way to test and prove important medical advances. At the same time, we have seen a rise in bad actors attempting to take advantage of individuals by offering untested, deceptive treatments. Often times, these treatments can lead to dangerous health outcomes and we feel they have no place on our platforms.

Experts in this field support such restrictions. The International Society for Stem Cell Research President Deepak Srivastava says, "Google's new policy banning advertising for speculative medicines is a much-needed and welcome step to curb the marketing of unscrupulous medical products such as unproven stem cell therapies. While stem cells have great potential to help us understand and treat a wide range of diseases, most stem cell interventions remain experimental and should only be offered to patients through well-regulated clinical trials. The premature marketing and commercialization of unproven stem cell products threatens public health, their confidence in biomedical research, and undermines the development of legitimate new therapies."

We know that there are good actors in this space as well, doing important research that may lead to major advances in medicine. We'll continue to allow advertising for research happening in this space for clinical trials and the ability for clinicians to promote their research findings to the public.

As new findings come to light and regulatory bodies oversee developments in this field, we will continue to evaluate our policies and make updates as needed.

Posted by Adrienne Biddings, Policy Adviser

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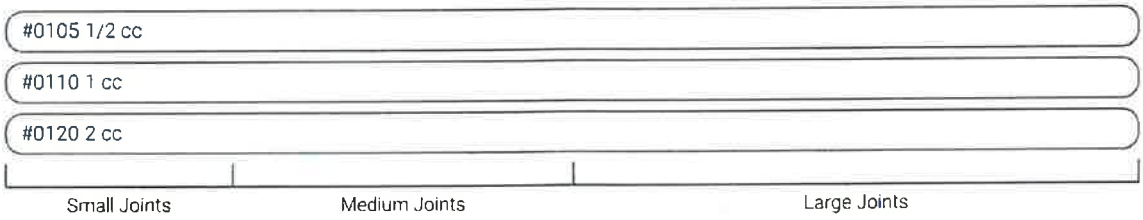

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PRODUCTS

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AMNIOCYTE DETAILS

AmnioCyte Plus™

Amniotic Matrix Allograft

AmnioCyte Plus™ is a minimally manipulated human tissue allograft derived from the extracellular matrix of the amniotic membrane. AmnioCyte Plus™ is processed to preserve cytokines, growth factors and scaffolding proteins in the amniotic membrane for homologous use.

AMNIOCYTE PLUS DETAILS

PolyCyte™

Wharton's Jelly Allograft

PolyCyte™ is a minimally manipulated human tissue allograft derived from the Wharton's jelly of the umbilical cord. PolyCyte™ is processed to preserve cytokines, growth factors, and proteins of Wharton's jelly for homologous use.

POLYCYTE DETAILS

CoreCyte™

Wharton's Jelly Allograft

CoreCyte™ is a minimally manipulated human tissue allograft derived from the Wharton's jelly of the umbilical cord. CoreCyte™ is processed to preserve the integrity of Wharton's jelly for homologous use and cryogenically preserved.

COREYCYTE DETAILS

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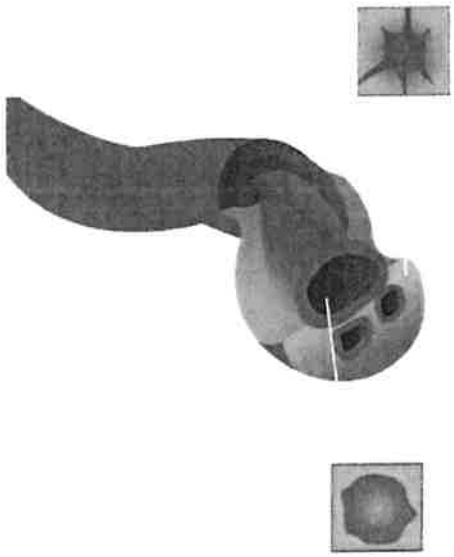
BioIntegrate™ Products

GeneXSTEM Wharton's Jelly - Umbilical Cord Tissue Product



GeneXSTEM™ is derived from Wharton's Jelly of the non-

embryonic umbilical cord and is intended for homologous use. Wharton's Jelly contains thousands of growth factors, cytokines, long-chain hyaluronic acid, and extracellular vesicles (EV) including exosomes and provides cushioning, protection and structural support within the umbilical cord. It is known for its anti-inflammatory and healing properties. Some patients and providers are choosing human umbilical cord tissue over NSAIDs, corticosteroid injections and platelet rich plasma (PRP) therapy. GeneXSTEM™[1] is processed using proprietary methods to preserve the structural integrity of Wharton's Jelly.

GeneXSTEM™ Injectables are minimally manipulated human tissue allografts derived from the Wharton's Jelly of umbilical cord tissue for homologous use and are not dependent upon the metabolic activity of living cells for its primary function. They comply with the HCT/P 21 CFR 1271 Regulations and Section 361 of the Public Health Service Act.

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PMID: 32054483

Umbilical cord-derived Wharton's jelly for regenerative medicine applications

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Abstract

Background

The last decade has seen an explosion in the interest in using biologics for regenerative medicine applications, including umbilical cord-derived Wharton's Jelly. There is insufficient literature assessing the amount of growth factors, cytokines, hyaluronic acid, and extracellular vesicles including exosomes

in these products. The present study reports the development of a novel Wharton's jelly formulation and evaluates the presence of growth factors, cytokines, hyaluronic acid, and extracellular vesicles including exosomes.

Methods

Human umbilical cords were obtained from consenting caesarian section donors. The Wharton's jelly was then isolated from the procured umbilical cord and formulated into an injectable form. Randomly selected samples from different batches were analyzed for sterility testing and to quantify the presence of growth factors, cytokines, hyaluronic acid, and extracellular vesicles.

Results

All samples passed the sterility test. Growth factors including IGFBP 1, 2, 3, 4, and 6, TGF-α, and PDGF-AA were detected. Several immunomodulatory cytokines, such as RANTES, IL-6R, and IL-16, were also detected. Pro-inflammatory cytokines MCSFR, MIP-1a; anti-inflammatory cytokines TNF-RI, TNF-RII, and IL-1RA; and homeostatic cytokines TIMP-1 and TIMP-2 were observed. Cytokines associated with wound healing, ICAM-1, G-CSF, GDF-15, and regenerative properties, GH, were also expressed. High concentrations of hyaluronic acid were observed. Particles in the extracellular vesicle size range were also detected and were enclosed by the membrane, indicative of true extracellular vesicles.

Conclusion

There are numerous growth factors, cytokines, hyaluronic acid, and extracellular vesicles present in the Wharton's jelly formulation analyzed. The amount of these factors in Wharton's jelly is higher compared with other biologics and may play a role in reducing inflammation and pain and augment healing of musculoskeletal injuries.

Keywords: Regenerative medicine, Musculoskeletal injuries, Osteoarthritis, Biologics, Umbilical cord, Wharton's jelly, Growth factors, cytokines, Hyaluronic acid, Exosomes

Background

Ligament, muscle, and tendon injuries produce pain, loss of function, instability, and secondary osteoarthritis [1, 2]. Traditionally, these injuries have been managed using activity modification; physical therapy; pharmacological agents, such as non-steroidal anti-inflammatory drugs, corticosteroids, viscosupplementation, and narcotics; and surgical procedures when conservative management fails [3]. These modalities have limitations and potential side effects [4].

Over the last decade, there has been an increased interest in the use of biologics for regenerative medicine applications [5]. Biologics currently used in clinical practice include platelet-rich plasma, bone marrow aspirate, adipose tissue aspirate, amniotic fluid, amniotic membrane, umbilical cord-derived Wharton's jelly and cord blood [6, 7]. The healing capabilities of these products are attributed to the presence of stem cells, growth factors, cytokines, hyaluronic acid, and/or extracellular vesicles including exosomes [8].

Stem cells, including mesenchymal stem cells isolated from bone marrow, periosteum, adipose tissue, trabecular bone, and deciduous teeth, have produced marked interest for their applications to regenerative medicine [7]. Stem cells are able to differentiate along specific lineage in response to signal transduction mediated by growth factors and cytokines [8]. Growth factors and cytokines often have overlapping activities. They are able to target mesenchymal, endothelial, and epithelial cells, and can act in an autocrine or paracrine manner [8]. In addition, one cytokine can stimulate the synthesis

and release of other cytokines leading to a network of interacting molecules. This complex network of cytokines and growth factors can guide cell division, differentiation, and regeneration of different tissues and organs [8].

Hyaluronic acid, a polysaccharide found in most tissues, is a major component of extracellular matrix of the skin, joints, and eyes [9]. Hyaluronic acid has been used to manage knee osteoarthritis via its chondroprotection, proteoglycan and glycosaminoglycan synthesis, and anti-inflammatory, mechanical, subchondral, and analgesic actions [10].

Exosomes are small extracellular vesicles with diameter ranging from ~ 30 to 150 nm, developed from a sequential process of multivesicular body membrane remodeling [11]. Exosomes are found in multiple body fluids including blood plasma, amniotic fluid, and Wharton's jelly [12, 13]. Exosomes are secreted from several cell types including stem cells and represent an important mode of intercellular communications [13]. Recently, exosomes have also emerged as an attractive cell-free therapeutic alternative that holds great regenerative potential [14].

The increasing applications of biologic therapies for regenerative medicine have led to considerable marketing, patient demand, and clinical utilization [5]. To be compliant in the United States (U.S.), biologics that adhere to the U.S. Food and Drug Administration (FDA) regulation of human cells, tissues, and cellular and tissue-based products (HCT/Ps) regulated under title 21, part 1271 of the Code of Federal Regulations (CFR), must meet all the criteria under section 361 of Public Health Safety (PHS) Act to be regulated solely under this section [5]. According to this regulation, HCT/Ps must meet the criteria of being minimally manipulated, for homologous use only, not to be combination products, to have no systemic effect, and to be non-dependent on the metabolic activity of the living cells [5]. Despite increased use, there is insufficient literature assessing the amount of growth factors, cytokines, hyaluronic acid and extracellular vesicles including exosomes present in these products, and, more specifically, umbilical cord-derived Wharton's jelly.

Wharton's jelly is a primordial mucous connective tissue of the umbilical cord present between the amniotic epithelium and the umbilical vessels [15]. The key role of Wharton's jelly is to provide cushion, protection, and structural support to umbilical vessels by preventing their compression, torsion, and bending [15]. The umbilical vessels also provide bi-directional flow of oxygen, glucose, and amino acids to developing fetus and aids in depleting the fetus of carbon dioxide and other waste products [15]. This gelatinous substance contains primitive mesenchymal stem cells (MSC) [15] and yields the highest concentration of MSC per milliliter of other allogenic tissues [16]. Wharton's jelly MSC may be more effective than MSC from adult tissues in the treatment of several conditions, and though safe and efficacious, more studies are required to justify their routine use in the clinics [17]. Wharton's jelly also contains high amounts of extracellular matrix components, including collagen, hyaluronic acid, and sulfated proteoglycans [18].

The present study reports the results of experiments aimed to characterize a novel umbilical cord-derived Wharton's jelly formulation and to evaluate the presence of growth factors, cytokines, hyaluronic acid, and extracellular vesicles including exosomes. We hypothesized that numerous growth factors, cytokines, hyaluronic acid, and extracellular vesicles including exosomes are present in Wharton's jelly; all may play a role in reducing inflammation and pain and augment healing of musculoskeletal injuries.

Methods

Human umbilical cords were obtained from consenting caesarian section donors following standards established by the FDA and the American Association of Tissue Banks. Donors underwent comprehensive medical, social and blood testing prior to donation. Infectious disease testing was performed at an independent certified laboratory in accordance with the Clinical Laboratory

Improvement Amendments of 1988 (CLIA) and 42 CFR part 493 and the FDA. Each donor was tested for HIV I/II Plus O Ab (antibodies to human immunodeficiency virus type 1 & 2), HBsAg (HEPATITIS B surface antigen), HBcAb (hepatitis B core Antibody), HBcTotal, HCV NAT (hepatitis C virus nucleic acid test), HTLV (Human T-lymphotropic virus) I/II Ab, RPR (Rapid plasma reagin) syphilis screening - nontreponemal, CMV (*Cytomegalovirus*), HIV-1/HCV (hepatitis C antibody)/HBV NAT Ultrio, WNV (West Nile Virus) NAT.

The procured umbilical cord was rinsed with saline followed by the removal of blood vessels. The Wharton's jelly was then isolated from the remaining umbilical cord and formulated into an injectable form using proprietary steps for which patent is pending. All the processing was performed under aseptic conditions. This methodology intends to preserve the structural integrity of Wharton's jelly and does not include use of digestive enzymes, use of cryoprotectants such as dimethyl sulfoxide (DMSO), or isolation and in vitro expansion of cells. This formulation is prepared according to the criteria of minimal manipulation by FDA, does not include any combination products, and is not intended to depend on the metabolic activity of living cells.

A total of 60 samples from three different batches (20 samples per batch) were tested for sterility at an independent CLIA accredited laboratory, Eurofins VRL Laboratories (Centennial, CO, USA), under United States Pharmacopeia Chapter 71 - Sterility Testing guidelines. Six randomly selected samples from two different batches were sent to an independent laboratory, RayBiotech (Norcross, Georgia, USA), and were analyzed for the presence of growth factors and cytokines using Quantibody® Human Growth Factor Array 1 and Quantibody® Human Inflammation Array 3 respectively. The signals were visualized using Innopsys InnoScan (Carbonne, France) at Cy3 wavelength (~ 550-nm excitation, ~ 570-nm emission). Data were analyzed using Q-Analyzer tool and the concentration of cytokines was determined using serial standard curve provided by the manufacturer (RayBiotech, Norcross, Georgia, USA). In addition, six randomly selected samples from two different batches were analyzed for the presence of hyaluronic acid using Hyaluronan Quantikine ELISA (enzyme-linked immunosorbent assay) kit (R&D systems, Minneapolis, MN, USA) according to the manufacturer's protocol.

Twelve randomly selected samples from the three different batches were sent to an independent laboratory, Extracellular Vesicle Core at Children's Hospital Los Angeles (California, USA), and were analyzed by nanoparticle tracking analysis for the presence of particles in the extracellular vesicle size range using Malvern Panalytical Nanosight NS300. These samples were also analyzed after staining with a general fluorescent membrane marker, CellMask Orange™ (Thermo Fisher Scientific, Waltham, MA, USA), as previously described [19].

Results

All samples passed the sterility test. Growth factors, including, Insulin-like growth factor binding proteins (IGFBP) 1, 2, 3, 4, and 6, transforming growth factor alpha (TGF-α), and platelet-derived growth factor-AA (PDGF-AA) were detected in the formulated Wharton's jelly (Table 1).

Table 1

Growth factors (GFs) expressed in the formulated Wharton's jelly

Growth factors		Average amount (pg/mL)
IGFBP-3	Insulin-like growth factor binding proteins 3	24,985.5
IGFBP-4	Insulin-like growth factor binding proteins 4	12,302
IGFBP-6	Insulin-like growth factor binding proteins 6	7711.1
IGFBP-2	Insulin-like growth factor binding proteins 2	6900.6
IGFBP-1	Insulin-like growth factor binding proteins 1	5211.4
TGF-α	Transforming growth factor alpha	311.4
HGF	Hepatocyte growth factor	266.6
FGF-7	Fibroblast growth factor	102.2
EG-VEGF	Endocrine gland-derived vascular endothelia growth	32.2
PDGF-AA	Platelet-derived growth factor AA	31.9
VEGF R3	Vascular endothelia growth factor receptor 3	16.8
VEGF	Vascular endothelia growth factor	14.4
β-NGF	Beta nerve growth factor	12.8

The expression of several immunomodulatory cytokines, such as RANTES (regulated on activation, normal T cell expressed and secreted), interleukin 6 receptor (IL-6R), interleukin 16 (IL-16), and interferon gamma (IFN-γ) was also detected (Table 2).

Table 2

Immunomodulatory cytokines expressed in the formulated Wharton's jelly

Immunomodulatory cytokines		Average amount (pg/mL)
RANTES	Regulated upon activation, normally T-expressed, and secreted; aka C-C motif chemokine ligand 5 (CCL5)	551.0
IL-6R	Interleukin 6 receptor	53.3
MIP-1D	Macrophage inflammatory protein 5; aka C-C motif chemokine ligand15 (CCL15)	44.9
SCF R	Stem cell factor, aka KIT Proto-oncogene receptor tyrosine Kinase	40.3
MCSF	Macrophage colony-stimulating factor 1	12.2
IL-16	Interleukin 16	8.7
I-309	C-C motif chemokines ligand1 (CCL1)	3.1
IFN-γ	Interferon gamma	1.8
IL-1β	Interleukin 1 beta	1.3
EOTAXIN	C-C motif chemokine ligand 11, 24, 26 (CC11, 24, 26)	1.3

Additionally, the expression of pro-inflammatory cytokines such as macrophage colony stimulating factor (MCSF), macrophage stimulating protein 1-alpha (MIP-1α); anti-inflammatory cytokines, such as tumor necrosis factor receptor superfamily member 1A and 1B (TNF-RI and TNF-RII), interleukin 1 receptor antagonist (IL-1RA); and homeostatic cytokines, such as tissue inhibitor of metalloproteinase 1 and 2 (TIMP-1 and TIMP-2) was also observed (Table 3).

Table 3

Pro-inflammatory, anti-inflammatory and homeostatic cytokines expressed in the formulated Wharton's jelly

		Average amount (pg/mL)
Pro-inflammatory cytokines		
MCSF	Macrophage colony-stimulating factor	930.8
MIP-1α	Macrophage-stimulating protein 1-alpha; aka C-C motif chemokine ligand 3 (CCL3)	1.2
Anti-inflammatory cytokines		
TNF-RI	Tumor necrosis factor receptor superfamily member 1A	191.6
TNF-RII	Tumor necrosis factor, member 1B	89.8
IL-1RA	Interleukin 1 receptor antagonist	58.8
Homeostatic cytokines		
TIMP-2	Tissue inhibitor of metalloproteinases 2	8663.6
TIMP-1	Tissue inhibitor of metalloproteinases 1	7386.7

Cytokines associated with wound healing including intercellular adhesion molecule 1 (ICAM-1), granulocyte-stimulating factor (G-CSF), growth differentiation factor 15 (GDF-15), and regenerative properties such as growth hormone (GH) were also expressed (Table 4).

Table 4

Wound-healing and regenerative cytokines expressed in the formulated Wharton's jelly

		Average amount (pg/mL)
Wound-healing cytokines		
ICAM-1	Intercellular adhesion molecule-1	1554.9
MCP-1	Monocyte chemotactic protein-1, aka CC motif chemokine ligand 2 (CCL2 Gene)	119.0
G-CSF	Granulocyte-stimulating factor, aka Colony-stimulating factor 3 (CSF3)	91.6
GDF-15	Growth differentiation factor 15	89.2
NT-4	Neurotropin-4	33
Regenerative cytokines		
GH	Growth hormone or somatotropin, aka human growth hormone (hGH or HGH)	31.1
GDNF	Glia cell-derived neurotrophic factor	19.5

Hyaluronic acid (average amount of 8.7 μg/mL) was detected in the formulated Wharton's jelly. The nanoparticle tracking analysis demonstrated the presence of billions of particles (average amount of 17.4 billion/mL) in the extracellular vesicles size range in the light scattering mode. CellMask Orange™ staining showed the presence of 4.18 billion particles/mL in the fluorescent mode, indicative of true membrane-enclosed particles, i.e. extracellular vesicles. Representative images for nanoparticle tracking analysis in the light scattering and fluorescent mode are shown as Fig. 1a and b, respectively.

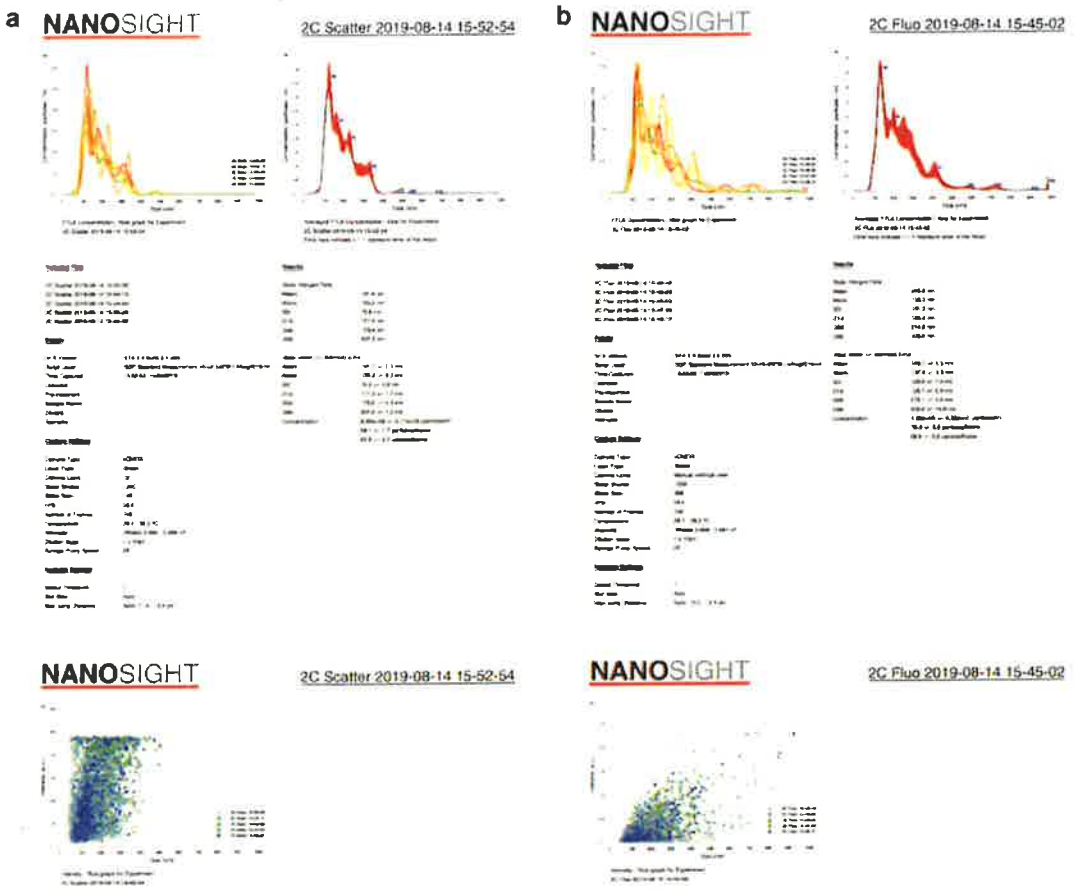

Fig. 1

a A representative nanoparticle tracking analysis showed the presence of 9.90 ± 0.32 billion particles/mL in the light scattering mode with a mode size of 136.3 ± 8.2 nm. **b** A representative nanoparticle tracking analysis showed the presence of 4.90 ± 0.08 billion particles/mL in the fluorescent mode with a mode size of 137.9 ± 4.0 nm. Values are shown as mean ± standard error

Discussion

Biologics hold great potential in treating a variety of musculoskeletal ailments [6]. At present, the published literature related to umbilical cord-derived Wharton's jelly focuses on the isolated cells, and despite the commercial use, there is still insufficient characterization of these formulations [18, 20, 21]. In the present study, we formulated a novel umbilical cord-derived Wharton's jelly product and evaluated it for the presence of growth factors, cytokines, hyaluronic acid and extracellular vesicles including exosomes. The essential components of regenerative medicine, namely growth factors, cytokines, hyaluronic acid and extracellular vesicles, are all present in the formulated Wharton's jelly. The results from this study are an essential preliminary first step to better characterize Wharton's jelly. This is necessary to perform clinical trials to determine safety and efficacy of this novel formulation for regenerative medicine applications.

Numerous growth factors were detected in our Wharton's jelly formulation. We detected IGFBP 1, 2, 3, 4 and 6, which acts as a carrier protein for insulin-like growth factor – 1 (IGF-1). IGF-1 improves osteogenic differentiation, induces chondrogenic differentiation of mesenchymal stem cells, and

stimulates extracellular matrix production [22]. We also detected TGF-α, a transforming growth factor which is a ligand for the epidermal growth factor receptor (EGFR). EGFR promotes proliferation and survival of osteoprogenitors and plays an anabolic role in bone metabolism [23]. In addition, platelet-derived growth factor-AA (PDGF-AA), a potent mitogen for cells of mesenchymal origin, was detected. PDGF-AA exhibits chemotactic effects toward human osteoblasts, and its downregulation is associated with cartilage degeneration [24]. We also detected expression of vascular endothelial growth factor (VEGF), a signal protein produced by cells to stimulate blood vessel formation. VEGF is involved in bone tissue remodeling and new bone formation and is downregulated in patients with osteoarthritis [25].

Several immunomodulatory cytokines essential for regenerative medicine were identified. We detected high levels of chemokine (C-C motif) ligand 5 (CCL5), also known as RANTES (regulated on activation, normal T cell expressed and secreted), which has been reported to be involved in modulation of macrophage phenotype from M1 (pro-inflammatory) to M2 (tissue healing) leading to enhanced osteogenesis [26]. RANTES also plays a vital role in chemotaxis, survival of osteoblasts and bone remodeling [27]. We also observed expression of interleukin 6 receptor (IL-6R). IL-6 plays an important role in immune regulation and tissue regeneration, and, when binding with IL-6R, it activates the downstream STAT3 signaling pathway that promotes osteogenic differentiation in mesenchymal stem cells via autocrine/paracrine feedback loop [28].

We detected pro-inflammatory and anti-inflammatory cytokines in the formulated Wharton's jelly. Pro-inflammatory cytokines usually exert deleterious effects, including mediation of foreign body response and initiating inflammatory response against implants leading to their premature failure. Recent studies have explored their potential as initiators of regeneration. These studies have proposed a pro-regenerative function of the inflammatory signals initiated by these cytokines, and that a proper sequence of inflammatory signals followed by anti-inflammatory signals is essential for proper healing [29]. We detected macrophage colony-stimulating factor (MCSF), as well as macrophage stimulating protein 1-alpha (MIP1-α), which are essential for osteoclast formation [30, 31]. Osteoclasts play a vital role during early bone healing: they maintain and improve the structural strength of bone tissue in conjunction with osteoblasts in a fine adjusted system [32].

We also identified interleukin 1 receptor antagonist (IL-1RA), a specific interleukin-1 (IL-1) receptor antagonist that competitively binds to the same receptor as IL-1 (including inflammatory IL-α and IL-1β), thereby blocking IL-1 mediated cellular changes [33]. IL-1RA attenuates or prevents cytokine-mediated inflammatory hyperalgesia [34]. Intraarticular injection of IL-1RA in patients with knee osteoarthritis slow its progression while improving pain and WOMAC (The Western Ontario and McMaster Universities Osteoarthritis Index) global score [35]. We detected homeostatic cytokines, tissue inhibitor of metalloproteinases (TIMP) 1 and 2, which regulate the activity of matrix metalloproteinases (MMP) [36]. MMPs can degrade all components of connective tissue at physiological pH and may be involved in bone matrix degradation [37]. TIMPs are downregulated in aged tendons, and mechanical stresses, including injuries, further reduce their levels [38]. In addition, TIMPs regulate several biological processes such as cell growth, differentiation and apoptosis that are independent of its MMP activity [39].

We identified several cytokines involved in wound healing. For example, we detected intercellular adhesion molecule-1 (ICAM-1), which promotes leukocyte accumulation into the wound site required for wound healing [40]. ICAM-1 also has immunosuppressive effects on dendritic cells and T cells, which may aid in the treatment of graft versus host diseases [41]. We detected expression of monocyte chemotactic protein-1 (aka CCL2), a pro-inflammatory cytokine, which promotes wound healing, including in hard to heal diabetic wounds [42]. We detected growth differentiation factor 15 (GDF-15), one of the members of transforming growth factor beta superfamily, which modulates bone microenvironment, including suppression of formation or activation of osteoclasts leading to

accumulation of bone matrix [43]. We also detected regenerative cytokines, including growth hormone, which stimulates cell growth, reproduction and regeneration, and plays an important role in cartilage regeneration [44].

We detected expression of hyaluronic acid. The umbilical cord tissue contains high molecular weight hyaluronic acid (HMW), which is associated with high fluid retention in joints and has strong anti-inflammatory properties [45]. In addition, it is useful in the management of knee osteoarthritis via its chondroprotection, proteoglycan and glycosaminoglycan synthesis, and anti-inflammatory, mechanical, subchondral, and analgesic actions [10]. Hyaluronic acid accelerates tendon-to-bone healing after rotator cuff repair and has shown potential in the treatment of enthesopathies such as lateral epicondylitis, patellar tendinopathy, insertional Achilles tendinopathy and plantar fasciitis [46].

We also detected the presence of membrane-enclosed particles in the extracellular vesicle size range. Extracellular vesicles including exosomes have demonstrated potential anti-inflammatory and pro-regenerative effects essential for inducing healing in different tissue types [47]. They positively affect cell proliferation and viability, angiogenesis, and immunomodulation in different physiological systems [47]. Exosome uptake by cells significantly reduces pro-inflammatory gene expression and level of M1 phenotypic marker, increase cell migration, and increase expression of osteogenic markers, which play a unique osteo-immunomodulatory role in regulation of bone dynamics [48]. Exosomes stimulate secretion of favorable cellular factors required to accelerate the healing response for tendon injuries including rotator cuff tears [49, 50]. Exosomes also promote cartilage repair and chondrocyte proliferation in osteoarthritis [51].

These results confirmed our hypothesis that growth factors, cytokines, hyaluronic acid, and extracellular vesicles are present in the formulated Wharton's jelly. Several published basic science and preliminary clinical studies indicate that the combination of these factors may have added advantages for regenerative medicine applications [46]. For example, a co-injection of growth hormone and hyaluronic acid was more effective in treating osteoarthritis compared with injections of hyaluronic acid alone [52], demonstrating the advantage of different factors in one formulation.

We also compared the amount of growth factors, cytokines, hyaluronic acid, and exosomes in Wharton's jelly with other biologics based on the published literature. The amount of growth factors in Wharton's jelly is higher compared with the umbilical cord artery [18]. Jin et al. demonstrated biological advantages of umbilical cord-derived tissue compared with bone marrow- and adipose-derived tissue [53]. Wharton's jelly-derived tissue offers many advantages over bone marrow-derived tissue [54]. This is attributed to upregulation of genes involved in wound healing and immune response in Wharton's jelly compared with bone marrow-derived tissue [54]. Amable et al. demonstrated higher expression of factors including RANTES, MCP-1, IL-1RA, and PDGF-AA in supernatant derived from Wharton's jelly stromal cells compared with bone marrow- and adipose-derived stromal cell supernatant [55]. The amount of VEGF, MCSF, RANTES and MCP-1 is higher in our formulation compared with the amount reported by Amable et al. in the activated platelet-rich plasma (PRP) in another study [56]. Cryopreserved amniotic membrane secreted intermediate levels of TIMP1 and TIMP2, low levels of MCP-1, and no detectable levels of RANTES [57]. In contrast, our formulation expressed high levels of these growth factors and cytokines. The amount of hyaluronic acid detected in our formulation is much higher compared with the amount found in amniotic fluid [58]. Other biologics, such as PRP and bone marrow aspirate concentrate, lack hyaluronic acid. Combining these biologics with hyaluronic acid can further improve the functional outcomes in the management of knee osteoarthritis [59]. The total exosome yield adjusted to 1 million mesenchymal stem cells was 1.3 times higher in amniotic fluid compared with bone marrow [60]. The amount of exosome particles/mL released by 1 million amniotic fluid stem cells is estimated to be 0.3 billion [61]. In contrast, the amount of exosome particles/mL adjusted to 1 million Wharton's jelly mesenchymal stem cells is

around 4 billion [62], higher than both amniotic fluid- and bone marrow-derived stem cells. The amount of growth factors, cytokines, hyaluronic acid, and exosomes in Wharton's jelly are therefore higher compared with other biologics.

Our study has several limitations. Basic science studies have demonstrated the presence of a large number of growth factors in Wharton's jelly [18]. However, the assay kits used in our analysis can detect only 40 growth factors and 40 cytokines. Future studies are required to determine other growth factors and cytokines expressed in this formulation. Another limitation is the possible presence of microvesicles in addition to the exosomes in the detected extracellular vesicles. Further analysis is needed to confirm the presence of exosomes using exosome-specific markers via immunoblotting assay. In addition to hyaluronic acid, the extracellular matrix of Wharton's jelly contains a significant amount of collagen and sulphated glycosaminoglycans required for regenerative medicine applications [20, 21]. Future studies are required to determine the amount of these extracellular matrix components in our formulation and examine their benefits.

Conclusion

Our Wharton's jelly formulation demonstrated the presence of growth factors, cytokines, hyaluronic acid, and extracellular vesicles in clinically relevant quantities, in amounts greater compared with other biologics. The presence of multiple factors within one formulation may help reduce inflammation, decrease pain and augment healing of musculoskeletal injuries. These factors represent potential expanded applications for regenerative medicine.

Acknowledgements

Not applicable.

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Availability of data and materials

Not applicable.

Abbreviations

WARNING LETTER

Predictive Biotech

MARCS-CMS 608322 – AUGUST 17, 2020

Product:

Drugs

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WARNING LETTER

CBER-20-04

Date: August 17, 2020

TO: 615 Arapeen Drive, Suite 300
Salt Lake City, UT 84108

RE: Unapproved and Misbranded Product Related to Coronavirus Disease 2019 (COVID-19)

This is to advise you that the United States Food and Drug Administration (FDA) reviewed your websites at www.predictivebiotech.com and https://predtechgroup.com and social media website at www.facebook.com/PredictiveBiotech/, most recently in August 2020. You use these websites to promote your umbilical cord derived product CoreCyte™. The FDA has learned that you market CoreCyte™for sale in the United States to mitigate, prevent, treat, diagnose, and/or cure COVID-19[1] in people.

CoreCyte™ is a human cell, tissue, or cellular or tissue-based product (HCT/P) as defined in 21 C.F.R. § 1271.3(d)[2] and is subject to regulation under 21 C.F.R. Part 1271, issued under the authority of section 361 of the Public Health Service Act (PHS Act), 42 U.S.C. § 264.

HCT/Ps that do not meet all the criteria in 21 C.F.R. § 1271.10(a), and when no exception in 21 C.F.R. § 1271.15 applies, are not regulated solely under section 361 of the PHS Act, 42 U.S.C. § 264, and the regulations in 21 C.F.R. Part 1271. Such products are regulated as drugs, devices, and/or biological products under the Federal Food, Drug, and Cosmetic Act (FD&C Act) and/or the PHS Act, and are subject to additional regulation, including appropriate premarket review.

Predictive Biotech, Inc. (Predictive Biotech) does not qualify for any exception in 21 C.F.R. § 1271.15, and CoreCyte™ fails to meet all the criteria in 21 C.F.R. § 1271.10(a). Specifically, CoreCyte™ fails to meet the criterion in 21 C.F.R. § 1271.10(a)(2) that the HCT/P be "intended for homologous use only, as reflected by the labeling, advertising, or other indications of the manufacturer's objective intent." Using CoreCyte™ to prevent or treat COVID-19, is not homologous use as defined in 21 C.F.R. § 1271.3(c). In addition, available information regarding CoreCyte™ suggests that it fails to meet the minimal manipulation criterion set forth in 21 C.F.R. § 1271.10(a)(1) and defined for structural tissue in 21 C.F.R. § 1271.3(f)(1). Although your promotional materials describe the product as minimally manipulated, in fact the product does not appear to meet this criterion, because available information regarding your processing suggests that it alters the original relevant characteristics of the umbilical cord related to its utility for reconstruction, repair, or replacement. Therefore, CoreCyte™ is not regulated solely under section 361 of the PHS Act, 42 U.S.C. § 264, and the regulations in 21 C.F.R. Part 1271.

CoreCyte™ is an unapproved new drug under section 505 of the FD&C Act, 21 U.S.C. § 355. Furthermore, this product is a misbranded drug under section 502 of the FD&C Act, 21 U.S.C. § 352. The introduction or delivery for introduction of this product into interstate commerce is prohibited under sections 301(a) and (d) of the FD&C Act, 21 U.S.C. § 331(a) and (d), and misbranding your product while it is held for sale after shipment of the drug or one or more of its components in interstate commerce is prohibited under section 301(k) of the FD&C Act, 21 U.S.C. § 331(k).

Your product is also a biological product under section 351 of the PHS Act, 42 U.S.C § 262. In order to lawfully market a drug that is also a biological product, a valid biologics license application (BLA) must be in effect under the PHS Act, 42 U.S.C. § 262(a). Such licenses are issued only after a demonstration that the product is safe, pure, and potent. While in the development stage, such products may be distributed for clinical use in humans only if the sponsor has an investigational new drug (IND) application in effect as specified by FDA regulations, 21 U.S.C. § 355(i); 42 U.S.C. § 262(a)(3); 21 C.F.R. Part 312. Your product is not the subject of an approved BLA; nor is there an IND in effect for your product.

There is currently a global outbreak of respiratory disease caused by a novel coronavirus that has been named "severe acute respiratory syndrome coronavirus 2" (SARS-CoV-2). The disease caused by the virus has been named "Coronavirus Disease 2019" (COVID-19). On January 31, 2020, the Department of Health and Human Services (HHS) issued a declaration of a public health emergency related to COVID-19 and mobilized the Operating Divisions of HHS.[3] In addition, on March 13, 2020, the President declared a national emergency in response to COVID-19.[4] Therefore, FDA is taking urgent measures to protect consumers from certain products that, without licensure, approval, or authorization by FDA, claim to mitigate, prevent, treat, diagnose, or cure COVID-19 in people. As described below, you have offered a product for sale

that is intended to mitigate, prevent, treat, diagnose, and/or cure COVID-19 in people. We request that you take immediate action to cease the marketing, sale, and distribution of any such unlicensed, unapproved, and unauthorized products for the mitigation, prevention, treatment, diagnosis, or cure of COVID-19.

You are marketing and distributing CoreCyte™ to health care providers to administer to patients to treat and/or prevent COVID-19. Zenaib Choucair, MD, Regional Vice President for Predictive Biotech, offers to sell and distribute CoreCyte™ to prospective healthcare provider customers to treat and/or prevent COVID-19 via intravenous administration. Dr. Choucair's promotion of the product includes references to an Emergency Use Authorization that Predictive Biotech filed with FDA for CoreCyte™.

As you are aware, FDA has not issued an Emergency Use Authorization to permit the emergency use of CoreCyte™ under any circumstances.

You should take immediate action to correct any violations of the FD&C Act, the PHS Act, and FDA's implementing regulations. This letter is not meant to be an all-inclusive list of violations that exist in connection with your products or operations.[5] It is your responsibility to ensure that you and your products fully comply with the law.

Due to the serious public health concerns related to the marketing and sale of unapproved drugs for the mitigation, prevention, treatment, diagnosis, or cure of COVID-19, it is essential that you do not resume marketing or distributing your product for the treatment or prevention of COVID-19.

We advise you to review your websites, product labels, and other labeling and promotional materials to ensure that you are not misleadingly representing your product as safe and effective for a COVID-19-related use for which it has not been licensed by FDA and that you do not make claims that misbrand the product in violation of the FD&C Act. We request that you alert any customers to whom you marketed CoreCyte™ for use in the treatment or prevention of COVID-19 that the product is not authorized by FDA for such use.

Within 48 hours, please send an email to COVID-19-Task-Force-CBER@fda.hhs.gov (mailto:COVID-19-Task-Force-CBER@fda.hhs.gov) describing the specific steps you have taken to correct these violations. Include an explanation of each step being taken to prevent the recurrence of violations, as well as copies of related documentation. Failure to immediately correct the violations cited in this letter may result in legal action, including, without limitation, seizure and injunction.

FDA is advising consumers not to purchase or use certain products that have not been licensed, approved, cleared, or authorized by FDA and that are being misleadingly represented as safe and/or effective for the treatment or prevention of COVID-19. Your firm will be added to a published list on FDA's website of firms and websites that have received warning letters from FDA concerning the sale or distribution of COVID-19 related products in violation of the FD&C Act.[6] This list can be found at http://www.fda.gov/consumers/health-fraud-scams/fraudulent-coronavirus-disease-covid-19-products (http://www.fda.gov/consumers/health-fraud-scams/fraudulent-coronavirus-disease-covid-19-products). Once you have taken corrective actions to cease the sale of your unlicensed, unapproved, and unauthorized products for the mitigation, prevention, treatment, diagnosis, or cure of COVID-19, and such actions have been confirmed by the FDA, the published list will be updated to indicate that your firm has taken appropriate corrective action.

If you cannot complete corrective action within 48 hours, state the reason for the delay and the time within which you will complete the corrections. If you believe that your product is not in violation of the FD&C Act, include your reasoning and any supporting information for our consideration.

If you are not located in the United States, please note that products that appear to be misbranded or unapproved new drugs are subject to detention and refusal of admission if they are offered for importation into the United States. We may advise the appropriate regulatory officials in the country from which you operate that FDA considers your product(s) referenced above to be unapproved and misbranded products that cannot be legally sold to consumers in the United States.

Please direct any inquiries to FDA at **COVID-19-Task-Force-CBER@fda.hhs.gov** (mailto:COVID-19-Task-Force-CBER@fda.hhs.gov).

Sincerely,

/S/

Mary A. Malarkey
Director
Office of Compliance and Biologics Quality
Center for Biologics Evaluation and Research

[1] As explained in a later paragraph, there is currently an outbreak of a respiratory disease named "Coronavirus Disease 2019" (COVID-19).

[2] HCT/Ps are defined as "articles containing or consisting of human cells or tissues that are intended for implantation, transplantation, infusion, or transfer into a human recipient." 21 CFR 1271.3(d).

3 Secretary of Health and Human Services Alex M Azar, Determination that a Public Health Emergency Exists. Jan. 31, 2020. (Accessible at https://www.phe.gov/emergency/news/healthactions/phe/Pages/2019-nCoV.aspx (https://www.phe.gov/emergency/news/healthactions/phe/Pages/2019-nCoV.aspx)). The declaration was renewed for another 90 days twice. The most recent renewal went into effect on July 25, 2020. Secretary of Health and Human Services Alex M. Azar II, Renewal of Determination that a Public Health Emergency Exists. July 23, 2020. (Accessible at https://www.phe.gov/emergency/news/healthactions/phe/Pages/covid19-23June2020.aspx (https://www.phe.gov/emergency/news/healthactions/phe/Pages/covid19-23June2020.aspx)).

4 President Donald J. Trump, Proclamation on Declaring a National Emergency Concerning the Novel Coronavirus Disease (COVID-19). Mar. 13, 2020. (Accessible at https://www.whitehouse.gov/presidential-actions/proclamation-declaring-national-emergency-concerning-novel-coronavirus-disease-covid-19-outbreak/ (https://www.whitehouse.gov/presidential-actions/proclamation-declaring-national-emergency-concerning-novel-coronavirus-disease-covid-19-outbreak/)).

[5] For example, you also market CoreCyte™ for intravenous administration to treat autoimmune conditions and dementia, and for intramuscular or intraarticular administration for "cushioning and protection." Although these claims are not the focus of this letter, please be advised that you must have an approved premaketing application on file with FDA to lawfully market CoreCyte™ for such indications.

[6] We note this Warning Letter also concerns the offer for sale of a COVID-19 related product in violation of the PHS Act.

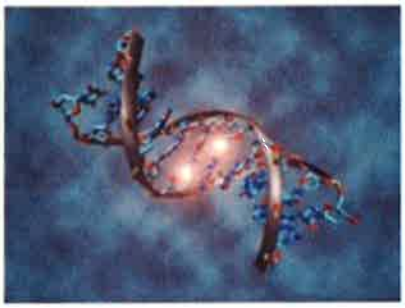
More Warning Letters (/inspections-compliance-enforcement-and-criminal-investigations/compliance-actions-and-activities/warning-letters)

OUR REGENERATIVE CELLULAR MEDICINE TREATMENTS CAN PROVIDE REMARKABLE IMPROVEMENT WHEN OTHER TRADITIONAL MEDICAL PROCESSES HAVE FAILED OR HAD LIMITED EFFICACY.

REGENERATIVE CELLULAR MEDICINE TREATS MANY MEDICAL CONDITIONS

- Alzheimer's Disease
- Parkinson's Disease
- Ataxia
- Diabetes Type I & II
- Rheumatoid Arthritis
- Osteoarthritis
- Multiple Sclerosis (MS)
- Autoimmune Diseases
- COPD
- Pulmonary Fibrosis
- Chronic Bronchitis
- Stroke
- Scleroderma
- Psoriasis
- Kidney Disease
- Joint Repair

DISCOVER WHAT STEM CELL AND REGENERATIVE THERAPY CAN DO FOR YOU!



Stem Cell and Regenerative Therapy can provide incredible improvement and benefit to a person whether for medical and/or pain relief purposes without surgery.

To find out more about what Superior Healthcare's **Stem Cell and Regenerative Therapy** can do for you, **call us today or fill out the contact form above** and one of our patient advocates will get back to you right away.

What Can Regenerative Cell Therapy Treat?

- Neck Pain
- Shoulder Pain
- Tennis Elbow
- Tendonitis
- Back Pain
- Knee Pain
- ACL/MCL/PCL Injury
- Joint Pain
- Joint Injury
- Carpal Tunnel Syndrome
- Neuropathy
- Plantar Fasciitis
- Ligament Strains
- Bursitis
- Degenerative Arthritis
- Osteoarthritis of the Knee
- Degenerative Cartilage and Ligaments
- Low Back Pain
- Degenerative Joint Disease
- Shoulder Injury
- Rotator cuff tears
- Shoulder Degeneration
- Shoulder Bursitis
- Facet Syndrome
- Degenerative Disc Disease
- Lumbar Arthritis / Osteoarthritis
- Wrist/Hand Pain Treated
- Planter Fasciitis
- Golfer's Elbow
- Distal Biceps Tendon Tear
- Hip Pain
- Labrum tear
- Hip Osteoarthritis
- Hip Degeneration
- Hip Bursitis
- Meniscus Tear
- Chrondomalacia
- Foot and Ankle Pain

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How Does Our Stem Cell Therapy Work?

Stem Cell and Regenerative Therapy is an extremely effective non-surgical option for patients considering an elective surgery or joint replacement by utilizing specialized regenerative cells to assist in healing the damaged tissues.

Regenerative Cellular Medicine works with the body's natural ability to heal itself. Unlike treatments that simply address the symptoms, Regenerative Therapy actually promotes the natural process of repair in the body, assisting in repairing and restoring degenerated tissue.

These remarkable treatments can repair tissue in the body that has been damaged from age, disease or degeneration. They do this by pinpointing the damaged areas, removing the swelling with powerful anti-inflammatory properties and healing them by regenerating new cells and tissue.

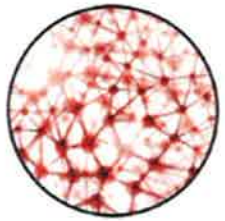
Stem Cell and Regenerative Therapy is an extremely effective non-surgical option for patients considering an elective surgery or joint replacement by utilizing specialized regenerative cells to assist in healing the damaged tissues.

REGENERATIVE CELL THERAPY TREATS MANY MEDICAL CONDITIONS

- **Neck Pain Treated**
  Cervical Pain , Cervical Joint Degeneration, Cervical Arthritis, and more
- **Shoulder Pain Treated**
  Shoulder Injury, Rotator cuff tears, Shoulder Degeneration, Shoulder Bursitis, and more
- **Back Pain Treated**
  Back Pain, Facet Syndrome, Degenerative Disc Disease, Lumbar Arthritis / Osteoarthritis, and more
- **Wrist/Hand Pain Treated**
  Carpal Tunnel Syndrome, Wrist Arthritis, and more
- **Elbow Pain Treated**
  Variety of Elbow Conditions, Lateral Epicondylitis, Golfer's Elbow, Distal Biceps Tendon Tear, and more
- **Hip Pain Treated**
  Variety of Hip Pain Conditions, Labrum tear, Hip Osteoarthritis, Hip Degeneration, Hip Bursitis, and more
- **Knee Pain Treated**
  Meniscus Tear, Knee Degeneration, ACL or PCL Injury, Chrondomalacia, and more
- **Foot/Ankle Pain Treated**
  Foot and Ankle Pain, Planter Fasciitis, and more

*As with any medical procedure, results are not guaranteed. Individual results are not typical or likely.

DISCOVER WHAT REGENERATIVE CELL THERAPY CAN DO FOR YOU!



Regenerative Cell Therapy can provide improvement and benefits to a person whether for medical and/or pain relief purposes without surgery.

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Watch Ms. Johnson's Story of Stem Cell Therapy for Back & Knee Pain

Watch Ms. McGinness' Story of Recovery From Shoulder Pain

Watch Ms. Mullinax's Story of Recovery From Hip Pain Relief

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Watch Ms. Settles' Story of Stem Cell Therapy for Foot Pain

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Watch Ms. Sheila's Story of Stem Cell Therapy for Knee Pain

THE WONDERS OF STEM CELL THERAPY IN OHIO & GEORGIA

People today live in a busy and fast paced environment. Young and old, we are not exempt from numerous health conditions and diseases. Because of this, our doctors have a growing concern and dedication to finding the best solutions to restore your health, help you live longer and make life more enjoyable.

Our **Cleveland, OH Regenerative Stem Cell Therapy** can provide remarkable improvements for you when other traditional medical processes have failed or had limited results. Furthermore, these treatments can even help you avoid the need for costly and painful surgery and long recovery periods.

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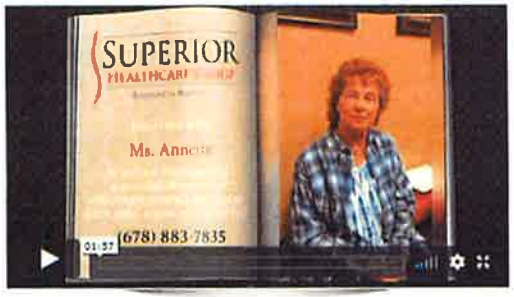

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Learn how you could be a candidate for a more active and healthy life

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Barbara's Story of Recovery From Knee Pain

Terri's Story of Recovery From Back Pain

Mr. Fermil's Story of Recovery From Hip Pain

Mr. Jackson's Story of Recovery From Knee Pain

Mr. James' Story of Recovery From Shoulder Pain

Mr. Johnston's Story of Recovery From Knee Pain

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Watch Mr. & Mrs. Tucker's Story of

Pain

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Relief

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Pain

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Recovery from Knee Pain

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Watch Ms. Johnson's Story Recovery from Back & Knee Pain

Watch Ms. McGinness' Story of Recovery From Shoulder Pain

Watch Ms. Mullinax's Story of Recovery From Hip Pain Relief

Watch Ms. O'Gara's Story of Cell Therapy for Hip Pain

Watch Ms. Settles' Story of Cell Therapy for Foot Pain

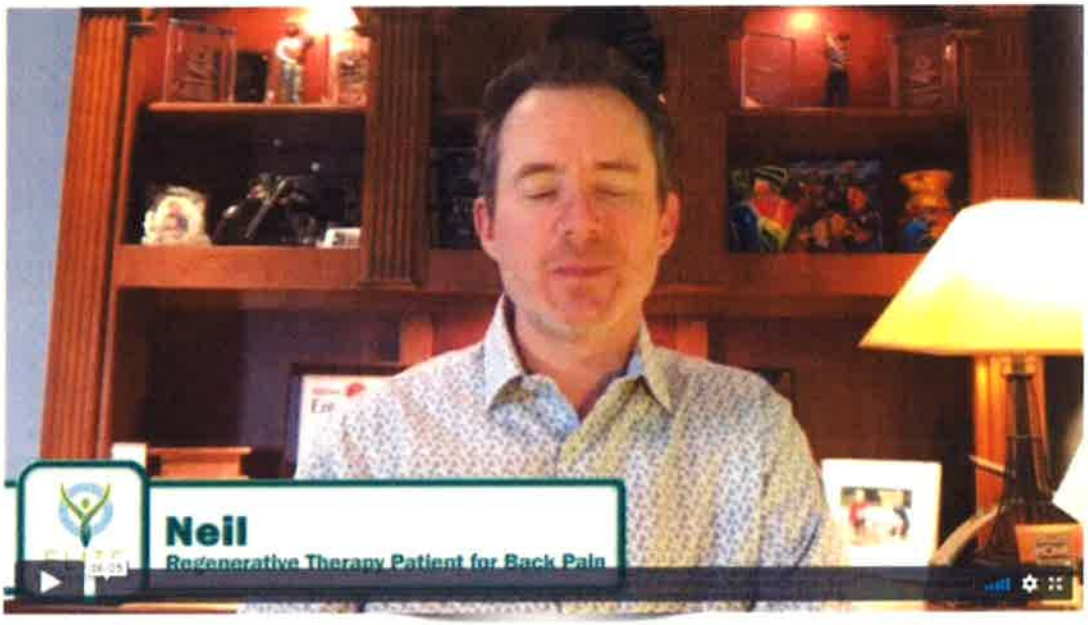
Watch Mr. Jones' Story of Stem Cell Therapy for Knee Pain

Watch Ms. Wood's Story of Recovery From Knee Pain Relief

Watch Ms. Sheila's Story of Cell Therapy for Knee Pain

SEE ACTUAL CASE STUDIES OF REAL PEOPLE WHOSE LIVES HAVE BEEN CHANGED BY OUR REGENERATIVE CELL THERAPY FROM COLUMBUS TO ATLANTA

Watch Neil's Story of Recovery From Lower Back Pain



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Meet Our Medical Doctors Providing The #1 Treatments For Hashimoto's, Autoimmune Diseases, & Regenerative Cell Therapy For Joint Pain

Atlanta Stem Cell & Regenerative Medicine

People today live in a busy and fast paced environment. Young and old, we are not exempt from numerous health conditions, joint pains, or diseases. **Because of this, our medical doctors have a growing concern and dedication to finding the best solutions to restore your health, help you live longer and make life more enjoyable**. Our Regenerative Cellular Medicine treatments can provide remarkable improvements for you when other traditional medical processes have failed or had limited efficacy. Furthermore, our cutting edge Regenerative Cellular Medicine using stem cells can even help you dodge the need for costly and painful surgery and long recovery periods. As a result, Atlanta Stem Cell & Regenerative Cellular Medicine can be used to treat an array of conditions caused by injury or degeneration.

The initial part of pain management would be to schedule a consultation with a pain-relief physician in our group in order to determine what is causing your pain and learn about the correct approach to pain management that will be effective for you. With us, you will be able to find the perfect combination of treatments that can assist you in gaining relief from your debilitating condition. Discover what our non-surgical pain relief using Stem Cell Medicine can do for you!

Because of this, our medical doctors have a growing concern and dedication to finding the best solutions to restore your health, help you live longer and make life more enjoyable

The initial part of pain management would be to schedule a consultation with a pain-relief physician in our group in order to determine what is causing your pain and learn about the correct approach to pain management that will be effective for you.

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tissue.

LATERAL EPICONDYLITIS (TENNIS ELBOW), MEDIAL EPICONDYLITIS (GOLFER'S ELBOW) AND DISTAL BICEPS TENDON TEAR

Many patients with tennis elbow run away from surgery and steroid injections. At Superior Healthcare Group, we offer an effective, non-invasive alternative to steroid injections and surgery. Our procedures treat all the underlying damages that cause the elbow pain.

REGENERATIVE MEDICINE FOR FOOT / ANKLE PAIN

Superior Healthcare Group's doctors have extensive experience when it comes to foot and ankle pain treatment. We have pioneered the industry's latest proven alternatives to surgery and steroids. Our same-day procedures will alleviate your foot and ankle pain regardless of the cause.

Superior Healthcare Group's doctors have extensive experience when it comes to foot and ankle pain treatment. We have pioneered the industry's latest proven alternatives to surgery and steroids. Our

THE WONDERS OF REGENERATIVE CELL THERAPY

People today live in a busy and fast paced environment. young and old, we are not exempt from numerous health conditions and diseases. Because of this, our doctors are dedicated to finding the best solutions to restore your health, help you live longer, and make life more enjoyable.

Our **Regenerative Cell Therapy Program** can provide remarkable improvements for you where other traditional medical processes have failed or had limited results. Furthermore, these treatments can even help you avoid the need for costly, painful surgery and long recovery periods. As a result, **Regenerative Cell Therapy** can be used to treat an array of conditions caused by injury or degeneration.*

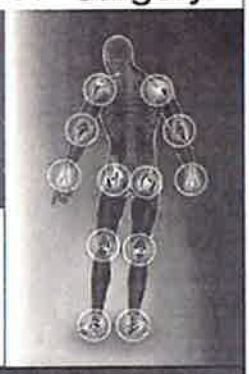
Because of this, our doctors are dedicated to finding the best solutions to restore your health, help you live longer, and make life more enjoyable.

STEM CELL FREE Educational Seminars

STOP THE PAIN! Get Relief without Surgery!

Do you SUFFER from....

- Knee Pain
- Lower Back Pain
- Shoulder Pain
- Neuropathy
- Joint Pain
- Plantar Fasciitis
- Osteoarthritis
- Neck Pain
- Tennis Elbow



Find Out if Regenerative Medicine is Right for You!

SAFE • ETHICAL • EFFECTIVE

Regenerative medicine is now available locally and can effectively reduce and even eliminate your pain without surgery or addictive medications. Regenerative medicine uses amniotic tissue cells to regenerate and repair tissues in your body that are damaged due to injury, age, disease, and defects. Stem cells have the power to go to these damaged areas, generate new cells and rebuild the area.

SEMINAR TIMES AND LOCATIONS

Roswell
- August 26 at 11:30am

Buford
- September 9 at 11:30am
- September 12 at 11:30am

Dahlonega
- September 12 at 11:30am
- September 16 at 11:30am

ONLY 20 SEATS AVAILABLE
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Several Seminars to Choose From

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Upcoming Events

Mar 9 **Free Seminar: Stem Cell & Regenerative Ther...**
Mar 5 - Mar 9 · Dominick's · Buford, Georgia
Health
★ Interested

Mar 12 **Free Seminar: Stem Cell & Regenerative Ther...**
Mar 12 - Mar 16 · Ray's at Killer Creek · Alpharetta, Georgia
Health
★ Interested

See All

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1 message

Elite Integrated Medical <info@elitemedicalstem.com> Fri, Jul 12, 2019 at 7:51 AM
To [redacted]

Hi [redacted]

Thank you for requesting our Stem Cell booklet. The link to download the book is below.

Click the image to download the booklet now or click the button below

Download

Register For One Of Our Upcoming Free Live Seminars!

If you haven't already registered for one of our next live seminars where you can learn even more about this groundbreaking new treatment, we'd love to have you join us.

There is no charge at all for this event and you are welcome to bring a guest. Lunch will be provided.

Click the button below to register for one of our upcoming seminars!

REGISTER NOW

I'd be happy to spend a few minutes with you at the seminar to discuss your situation and help you decide if this would be the right treatment for you.

CLICK HERE to register for one of these seminars now. Or you can also call my assistant at (678) 786-2355 to register.

Dr. Leslye Pace, M.D.
Elite Integrated Medical
(678) 786-2355
atl@elitemedicalstem.com

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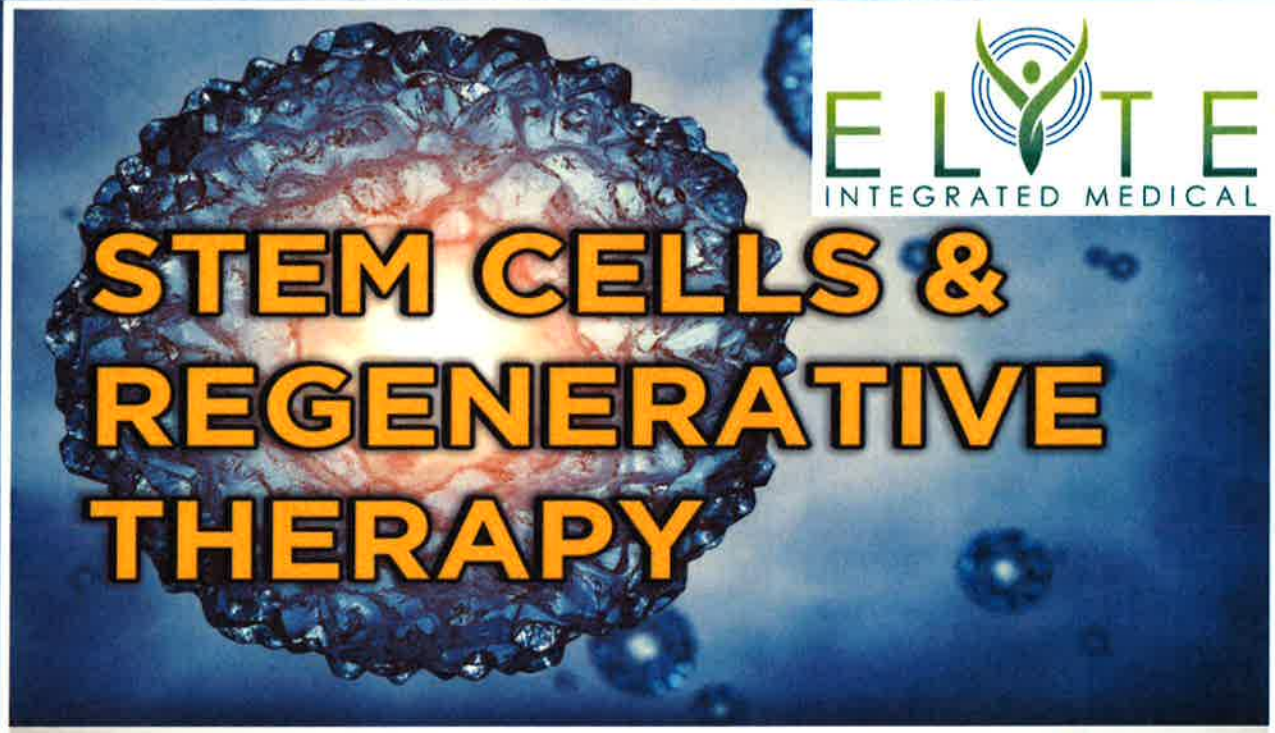

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As Seen On:

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CBS NEWS

NBC NEWS

Miami Herald

The Network Journal

Bio-Medicine

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If you suffer with chronic pain, this new **breakthrough treatment** may very well change your life!

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Welcome To A New And Better Solution

Chronic pain robs sufferers of their quality of life and often leads to unnecessary pain medications and even depression. It *is* possible to turn the clock of time backwards and *get your life back.*

During our unique 1 hour presentation, you will learn *everything* there is to know about Regenerative Medicine and other advanced regenerative cellular therapies, including how they work, the different types, where they work best, research studies and effectiveness.

Regenerative Medicine is changing the lives of thousands across this great country for the better and our doctors are fully trained to present this amazing educational work shop to help you decide if this is the right treatment for you.

By the end of this workshop you'll be fully educated on these new forms of regenerative cellular treatments and will know if this could be the correct treatment for your particular condition.

"I've been pain free for months now and no longer have to walk with a cane. It has definitely given me my life back. I've had such an improvement that my wife had her shoulder treated with regenerative cellular therapy and she feels younger because she's no longer in pain. This therapy can change your life." - Rob M-

Where is Your Pain?

Neck Pain - p. 8

Shoulder Pain - p. 12

Back Pain - p. 16

Wrist/Hand Pain - p. 21

Elbow Pain - p. 24

Hip Pain - p. 27

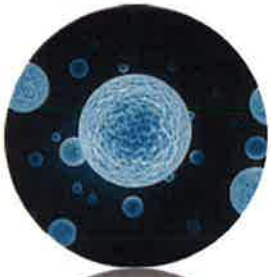
Knee Pain - p. 32

Foot/Ankle Pain - p. 37

"It's been almost 5 months since I had my first treatment and I can honestly say that I'm pain free for the first time in years. Losing my favorite activities and then having the chance to now do these again has felt like getting a second chance. Not only feeling better but seeing the changes on my x-rays has been incredible. I would definitely do it again if I had to. I recommend regenerative cellular therapy to anyone with chronic knee pain." - Jane C.

What Is Regenerative Cellular Therapy?

What Are Stem Cells?



Stem cells are the building blocks of the human body. A stem cell can not only replicate itself, but it can also turn into other specialized cells, such as blood cells, skin cells, bone cells, cartilage cells, and just about any cell in the human body.

Everyone already has hundreds of millions of stem cells in their body. They're the reason that your skin is completely replaced every 35 days. Stem cells cause your hair and nails to grow. They're replacing the worn out and damaged cells in your organs and tissues throughout your body. And they're creating 2 million new red blood cells for you *every second*!

It's been said that you wouldn't live for more than just a few hours if you had no stem cells.

Your Body's Built-In Repair System

Your body has its own incredible repair systems. When you fall down and skin your knee, your body sends stem cells to the injured area to begin repairing and replacing the damaged skin and tissue. When you break a bone, your body sends immune and healing cellular activity including stem cells to help the broken bones grow back together.

For almost any kind of damage or injury, your body has the tools and systems in place to make the needed repairs to keep you going. ***It is sending your own stem cells in a matrix (along with other specialized healing and regenerative cells) to repair the damage***.

But as we age, our body produces fewer stem cells on its own. And the stem cells that it does produce, are **just not quite as "healthy and strong" as when you were young**. This is the reason why a baby's skin is always so soft and smooth compared to a more "mature" adult.

As a result, when our "more mature" joints are injured or damaged from arthritis or degeneration, we just don't have as many stem cells to repair the damage as when we were young, nor are the stem cells as strong and healthy to make the repairs. This is why most of the recent advancements in Regenerative Medicine have focused on using regenerative cellular therapies or matrix stem cells and growth factors from healthy young umbilical cord tissue.

And that's where regenerative cellular therapy comes in.

Why Umbilical Cord Tissue?

Researchers have recently discovered that umbilical cord tissue is a rich and plentiful source of safe and healthy young mesenchymal stem cells (MSCs), as well as other important regenerative cells such as cytokines, growth factors and hyaluronic acid (for joint lubrication). The umbilical cords are donated from mothers who have had a healthy cesarean section delivery, so **there is no harm or pain to the mother or her new baby**. In fact, until very recently, the umbilical cords were typically discarded and thrown away after the baby's delivery.

And because umbilical cord stem cells have "immunosuppressors" and "immunomodulatory properties" they do not pose any threat of rejection or concerns for any type of infection or disease (sometimes referred to as "graft vs host disease"). (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3999777/)

Our regenerative cellular therapy program uses a matrix of these special cells to enhance the body's own built-in repair mechanisms and boost the concentration of regenerative cellular activity by dramatically increasing the number of MSCs and growth factors in the injured area. We're really just helping your own body be

more efficient and effective at repairing the damage caused by injury, disease or degeneration.

How Do Stem Cells Function?

Stem cells have the ability to travel to injured tissues, a phenomenon called *homing*. This occurs by injury/disease signals that are released from the distressed cells/tissue. Once stem cells arrive at the site of injury they go to these "distress signals" and dock on the cells to begin performing their job.

1. **Serve as a cell replacement** where they change into the needed cell type such as a muscle cell. This is ideal for traumatic injuries and orthopedic indications.

2. They do not express specific HLAs which help them **avoid the immune system**. In fact, mesenchymal stem cells (MSCs) do this so well that they are in clinical studies for graft vs host disease and have been approved for pediatric graft vs host disease in Canada. These studies and data support the notion that the cells are safe to use as an "off the shelf" product.

3. They dock on an adjacent cell and **release proteins called growth factors, cytokines and chemokines**. These proteins and growth factors help control many aspects of the repair process:

- **Control the immune system and regulate inflammation** which is a key mediator of diseases of aging and autoimmune diseases such as rheumatoid arthritis and multiple sclerosis

- Help to **increase new blood vessel formation** which aids in adding vasculature so that tissues can receive proper blood flow and the correct nutrients needed to heal such is the case in stroke, peripheral artery disease and heart disease.

- **Provide trophic support for surrounding tissues** and help host endogenous repair. This works great when used for orthopedics as it

causes signals to be released which may now activate your own stem cells to repair a knee for instance. In case of diabetes, it may help any remaining beta cells to reproduce or function optimally.

As research continues, the field of Regenerative Medicine and regenerative cellular therapy continues to evolve into the greatest hope for those suffering from injuries and degenerative disease and looking for methods to improve their quality of life.

Neck Pain

If you suffer with the following neck conditions; learn more about how Regenerative Cellular Therapy can help restore your health and help you live Pain-Free!

- Cervical Pain
- Cervical DJD
- Cervical Arthritis

Regenerative Medicine For Cervical Pain, DJD & Arthritis

The bones of the neck are made up of several cervical vertebrae. Between each vertebrae sits a cartilage disc that acts as a cushion, allowing the neck bones to move smoothly without friction. When cartilage starts to deteriorate or becomes damaged, cervical neck pain and stiffness can occur. Cervical neck pain from an injury, inflammation, or disc degeneration can become chronic and increasingly difficult to treat.

Regenerative Medicine has revolutionized treatment options for those suffering from chronic neck pain. Regenerative Cellular Therapy targets the painful areas, helps recharge the immune system, and greatly reduces inflammation. This allows the body to heal itself naturally and quickly. **Many patients have been able to avoid the risks of surgery and medication with our non-invasive, in-office procedures.**

Regenerative Cellular Therapy is a revolutionary solution to *heal cervical joint degeneration,* and a safe alternative to medications, steroid injections, and surgery. We use a high concentration of umbilical cord-derived stem cells to reduce inflammation, alleviate pain, and trigger an immune response to heal damaged tissues. While aging and inflammation can slow down the body's natural healing process, our regenerative medicine techniques aim to jumpstart

this system and target specific areas of the body. These non-invasive procedures can be done in a same-day, in-office visit.

Regenerative Medicine for Cervical Arthritis

Cervical arthritis is chronic inflammation of the tendons, ligaments, and soft tissues surrounding the vertebrae of the neck. Between each vertebrae sit discs of cartilage that provide support for the moving joints in the neck, and keep the bones from rubbing against each other. When this cartilage dehydrates or becomes damaged, signs of inflammation and arthritis can develop.

Stem Cell & Regenerative Cellular Therapy can reduce the inflammation that causes arthritic pain. By using the stem cells with a high concentration of immune cells and healing factors, this procedure helps the body naturally repair the damaged tissue and cartilage between each vertebrae in the neck. With our same-day, in-office procedures, we can help you start feeling better fast.

Regenerative Cellular Therapy

Regenerative Cellular Therapy is one of the newest and most cutting-edge therapies for chronic joint pain. Umbilical cord-derived regenerative cellular therapy offers patients 3 essential properties for healing and restoring joint health:

- A high concentration of regenerative cells
- Hyaluronic Acid for joint lubrication and movement
- Anti-inflammatory cytokines and cellular growth factors essential for building new joint tissue

The Regenerative Cellular matrix (i.e. the umbilical mesenchymal stem cells along with cytokines, growth factors, hyaluronic acid, etc.) are injected directly into the painful area where they signal the body's repair process to begin working, and provide the building blocks needed to regenerate and repair the damaged tissue.

Since these regenerative cells are collected from healthy baby c-section deliveries, they are ***not*** *derived from embryonic stem cells or fetal tissue*, so there are no ethical issues with the treatment.

Regenerative cellular therapy has the potential to *actually alter the course of the condition* and not simply mask the pain. This therapy has significant potential for those in pain, and could actually *repair structural problems* while treating pain and inflammation simultaneously.

When the umbilical cord regenerative cellular matrix is obtained, *it comes from consenting donors who have undergone elective c-sections*. The fluid or tissue is processed at an FDA regulated lab, and is checked for a full slate of diseases per FDA guidelines.

This Regenerative Cellular Matrix has been *used over 100,000 times in the US*. It also acts as an "immunologically privileged" material, meaning it has NOT been shown to cause any rejection reaction in the body. This means there is no "graft versus host" problem.

If you're suffering with chronic neck pain, find out if you are a good candidate for our Regenerative Cellular Therapies. Schedule your free consultation with our specialists today!

"Originally, my shoulder and neck pain issues started after I had a severe car accident. A torn bicep and torn rotator cuff injury created constant pain in my right shoulder and arm. Initially, I thought I had escaped major problems but after a few months, I started to experience significant weakness and pain in my right arm. My doctor at the time prescribed me powerful pain medication that nearly made me addicted to them and really left me feeling groggy. After seeing multiple doctors and physical therapists, I was left feeling like I had to accept that pain was to be apart of my life. I had stumbled upon information about Regenerative Cell therapy and found a local provider with Elite Integrated Medical. He sat down with me and for the first time I felt like someone understood what was causing my arm pain and had a real solution. So I started with an injection on my shoulder blade, which I almost felt an immediate relief. After a month and a half, I started to get the strength back in my arm. My pain decreased by about 80% and I only had an occasional soreness and stiffness. Now, 7 months later, I feel like a new person. My shoulder and neck pain are completely gone. I have full strength in my arm and hands and I even started to work out and again with a trainer."
- Susan L

Shoulder Pain

If you suffer with the Following Shoulder Conditions; learn more about how Regenerative Cellular Therapies can help restore your health and help you live Pain-Free!

- Shoulder Injuries
- Rotator Cuff Tears
- Shoulder Degeneration and Arthritis
- Bursitis

Regenerative Medicine For Shoulder Injuries

Sports activities that require repeating overhead movements like lifting weights, swimming, throwing or pitching, and swinging of the arms put a lot of strain on the shoulder. Even regular, everyday activities can damage the shoulder such as gardening, hanging curtains, or even scrubbing the floors or walls. Often, injury to the shoulder is difficult to heal, and can easily become a recurring problem, even if the immediate pain has subsided. Once ligaments and tissues have been damaged, scar tissue and inflammation can continue to form and build. It is also common for the same injury to reappear, and flare up at later times.

Sports or other injury to the shoulder can now be treated with non-invasive, Regenerative Medicine procedures like Regenerative Cellular Therapy. This is a revolutionary treatment option that has helped many patients avoid prescription medications, steroid injections, and even surgery.

Regenerative Medicine For Rotator Cuff Tears

Your shoulder is a ball-and-socket joint in which the ball of your upper arm bone fits into the socket of your shoulder blade. The rotator cuff is a network of four

muscles that come together as tendons forming a covering around the head of the upper arm bone keeping the arm bone firmly attached to the socket of the shoulder blade (scapula).

The rotator tears usually develop gradually due to stress, overuse and natural wear and tear. People who repeatedly lift their arm overhead are more vulnerable to overuse tears. These include athletes such as tennis players, swimmers, weight lifters and baseball pitchers. A tear in the rotator cuff produces a lot of pain and also contributes to instability in the shoulder joint. If it is severe, there may be weakness or an inability to lift the arm.

Our Regenerative Cellular Therapy treatment matrix has been fortified and enhanced with **cytokines** and additional natural **growth factors** to aid in the recovery of rotator cuff injuries. After an injection directly into the rotator cuff, these cells combine with the body's own natural immune cells and aid the body in *repairing* the tear.

Regenerative Medicine For Shoulder Degeneration

Degeneration of the shoulder joints is usually a progressive condition that evolves and worsens over time. Shoulder degeneration occurs when the cartilage that protects and surrounds the bones begins to wear down. Without this cushioning between the bones, movement causes friction within the joint. This friction causes pain, inflammation, swelling, and can lead to the development of bone spurs.

Regenerative Cellular Therapy takes a high concentration of immune cells, and uses them to target specific areas with damaged tissues. Inflammation and aging slows down the natural production of these cells, and the development of scar tissue limits the range of motion needed for proper rehabilitation. Using concentrated levels of umbilical cord-derived regenerative cellular matrix stem cells, these cells can quickly reduce pain, inflammation, and scar tissue. This supports the immune system in healing damage within the shoulder joint.

Regenerative Medicine for Shoulder Bursitis

The larger joints of the body contain small, fluid-filled sacs called bursae that provide cushioning between muscles, bones and tissues, allowing them to move smoothly without friction. Bursitis is the inflammation of one or more of these bursae, and often occurs within the shoulder joint, causing stiffness and making movement painful.

The best treatments for bursitis aim to reduce the inflammation that is causing the pain and stiffness. Regenerative Cellular Therapy is a revolutionary treatment protocol that takes concentrated amounts of healing and regenerative cells, and distributes them directly in the area of inflammation and damage. This is a non-surgical procedure that can be done in-office, and quickly and naturally alleviates shoulder pain.

Regenerative Cellular Therapy

Regenerative Cellular Therapy is one of the newest and most cutting-edge therapies for chronic joint pain. Umbilical cord-derived regenerative cellular therapy offers patients 3 essential properties for healing and restoring joint health:

- A high concentration of regenerative cells
- Hyaluronic Acid for joint lubrication and movement
- Anti-inflammatory cytokines and cellular growth factors essential for building new joint tissue

The regenerative cellular matrix (i.e. the umbilical mesenchymal stem cells along with cytokines, growth factors, hyaluronic acid, etc.) are injected directly into the painful area where they signal the body's repair process to begin working, and provide the building blocks needed to regenerate and repair the damaged tissue.

Since these umbilical cord regenerative cells are collected from healthy baby c-section deliveries, they are ***not*** *derived from embryonic stem cells or fetal tissue*, so there are no ethical issues with the treatment.

The therapy has the potential to *actually alter the course of the condition* and not simply mask the pain. This therapy has significant potential for those in pain, and could actually *repair structural problems* while treating pain and inflammation simultaneously.

When the umbilical cord regenerative cellular matrix is obtained, *it comes from consenting donors who have undergone elective c-sections*. The fluid is processed at an FDA regulated lab, and is checked for a full slate of diseases per FDA guidelines.

The regenerative cellular matrix has been *used over 100,000 times in the US*. It also acts as an "immunologically privileged" material, meaning it has NOT been shown to cause any rejection reaction in the body. This means there is no "graft versus host" problem.

If you're suffering with chronic shoulder pain, find out if you are a good candidate for our Regenerative Cellular Therapy. Schedule your free consultation with our specialists today!

"I attended a seminar that Dr. Steve & Dr. Dave gave at church on Regenerative Medicine, and I figured it would favorable for me. I had severe pain in my shoulder & had surgery about 9 years ago. They injected my shoulder and my thumb where I was having joint problems. My shoulder is now back to 99%... and my thumb is not nearly as painful as it was. I'm very happy with the therapy I get here. Everyone has been really excited about me being here. I would definitely recommend this service for both shoulder and thumb problems. "
- Harold F, Age 75

Back Pain

If you suffer with the Following Back Conditions; learn more about how Regenerative Cellular Therapy can help restore your health and help you live Pain-Free!

- Back Pain
- Facet Syndrome
- Degenerative Disc Disease
- Lumbar Arthritis
- Osteoarthritis

Regenerative Medicine for Back Pain

At Elite Integrated Medical we specialize in back pain treatment. We have pioneered the industry's latest proven alternatives to surgery and steroids. Our in-office, same-day procedures will alleviate your back pain regardless of the cause. We treat a range of conditions including spondylolisthesis, spinal arthritis, intervertebral disc degeneration, spinal stenosis and herniated discs.

Elite Integrated Medical's revolutionary Regenerative Cellular Therapy procedures treat all the damage *and underlying conditions* that cause you pain. Our doctors will inject the regenerative cellular matrix into the injured joint, and they then act as an immunologically privileged material to *rebuild and strengthen the damaged tissue* which causes back pain.

Regenerative Medicine for Facet Syndrome

Facet syndrome is a condition that affects the small joints between the vertebrae that make up the spine, and is one of the most common conditions causing lower back and neck pain. These joints are constantly moving, providing the stability

and flexibility needed to walk, sit, turn, and bend. Each of these small joints of the neck and spine contain soft tissues and cartilage that absorb shock during these movements and are important to protect the bones from rubbing against each other and causing friction. This can cause inflammation and swelling of the joints, headaches, and make even slight movements painful.

Facet syndrome has historically been difficult to treat, but new developments in regenerative medicine offer new, advanced treatment options. Regenerative Cellular Therapy is a natural alternative to the risks of medications, steroid injections, and surgery. By using the regenerative cellular matrix, our specialists can target specific areas of pain and inflammation to alleviate pain and trigger an immune response that helps heal damaged tissues. Our non-invasive procedures can be done in a same-day, in-office visit.

Regenerative Medicine for Degenerative Disc Disease

The spine is made up of several vertebrae, separated by soft tissue and cartilage that provides cushioning between the bones. The cartilage between each bone is called a disc, and each disc keeps the bones from rubbing against one another. Disc degeneration occurs when this cartilage wears down or becomes damaged.

If left untreated, disc degeneration can limit mobility, and lead to bone spurs and chronic pain. People suffering from back problems no longer have to settle for pain medications, steroid injections, or risky surgical procedures. Regenerative Cellular Therapy is an advanced, non-surgical procedure that rebuilds degenerating discs and tissues. Our team of specialists is experienced in finding

"I was so worried because all the injections I've had before were extremely painful, and I was scared to go through that again. But these injections were painless. I didn't even feel them. I am out of low back pain for the first time in many years. I actually can't believe it. I am so happy! Thank you from the bottom of my heart!" - T.R.

the right treatment options that can reduce inflammation and the development of scar tissue, and get you feeling better fast.

Regenerative Medicine for Lumbar Arthritis

Lumbar arthritis is chronic inflammation of the soft tissues within the joints of the lower back. Cartilage discs that sit between each vertebrae provide support and stability for the constant movement in the back. When the supportive tissues are damaged from injury or begin to deteriorate, painful swelling and inflammation can occur from friction between the bones.

Arthritis can become an ongoing, chronic issue that not only causes pain, stiffness, and swelling, but can limit mobility and the ability to perform daily activities. The use of regenerative medicine techniques can eliminate the inflammation that causes symptoms of lumbar arthritis. Regenerative Cellular Therapy is a procedure that uses healing cells to target pain areas, reduce inflammation, and even generate new growth of supportive soft tissues.

Regenerative Medicine for Osteoarthritis

Osteoarthritis is the degeneration of the protective cartilage that covers the ends of the bones in the joints. It is also known as "degenerative arthritis" or "wear and

"I decided to have the regenerative cellular therapy because I am only 50 years old and I did not want to end up with sciatic pain on a daily basis. I kept hearing the recommendation to have this procedure done earlier rather than later and I thought to myself that I don't want it to get out of control, but over the years it has just gotten worse – more episodes, and the episodes lasted longer as time went on. I had my lower back and SI joints injected 8 weeks ago. I can tell you that since I had my procedure with the regenerative cells, I have been on 2 airplane trips and 2 long car drive trips and I actually can't believe it.....no pain – no episodes! This is amazing! Thank you Elite Integrated Medical – I think you saved my life – I am living without pain!" - Debra L.

tear" arthritis. The protein that makes up the cartilage degenerates by forming tiny cracks or by flaking. This can eventually result into a total loss of cartilage. Once the cartilage is lost, the friction between the bones can stimulate spurs or bony growths to form around the joints.

Rather than going for the traditional surgical treatments, you can visit Elite Integrated Medical for a non-invasive alternative. Our same-day Regenerative Cellular Therapy procedure eliminates the pain, recovery time and risk associated with traditional treatments. Our procedure also *treats the underlying damage that causes the pain.*

Regenerative Cellular Therapy

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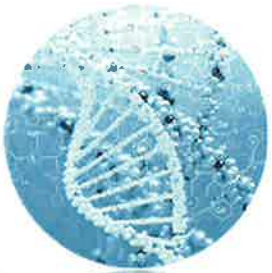
- A high concentration of regenerative cells
- Hyaluronic Acid for joint lubrication and movement
- Anti-inflammatory cytokines and cellular growth factors essential for building new joint tissue

The regenerative cellular matrix (i.e. regenerative cells or MSCs along with cytokines, growth factors, hyaluronic acid, etc.) are injected directly into the painful area where they signal the body's repair process to begin working, and provide the building blocks needed to regenerate and repair the damaged tissue.

Since these MSCs or regenerative cells are collected from healthy baby c-section deliveries, they are ***not*** *derived from embryonic stem cells or fetal tissue*, so there are no ethical issues with the treatment.

The therapy has the potential to *actually alter the course of the condition* and not simply mask the pain. This therapy has significant potential for those in pain, and could actually *repair structural problems* while treating pain and inflammation simultaneously.



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If you're suffering with chronic back pain, find out if you are a good candidate for our Regenerative Cellular Therapy. Schedule your free consultation with our specialists today!

"I had been suffering with low back pain for the last 25 years. I had my injection a week and half ago and my pain levels went from 10/10 to a 1/10 pain level. I was so surprised at how quickly the pain was reduced. I had my injection to the low back on the Thursday before Easter and was able to prepare and cook my Easter dinner for two days without any pain. I have been cooking holiday dinners for over 25 years and have had to sit down while preparing dinner because of the pain. I had no pain during the two days of holiday prepping and cooking. The injection did not hurt – it was only an ache the first two days and it was completely gone the third day – just in time to prepare Easter dinner. I decided to do this procedure because I was tired of living in pain and surgery was not an option that I would consider. I would absolutely recommend this procedure to others and hope that my testimonial allows others to make the decision to have the injections. I am still shocked at how good it feels." - Linda H

Wrist/Hand Pain

If you suffer with the Following Hand / Wrist Conditions; learn more about how Regenerative Cellular Therapy can help restore your health and help you live Pain-Free!

- Carpal Tunnel Syndrome
- Wrist Arthritis

Regenerative Medicine for Carpal Tunnel Syndrome

Applying too much pressure to the carpal tunnel causes the median nerve to become pinched resulting in many problems that are experienced in the wrist and hand including pain, tingling and difficulty functioning. The carpal tunnel is a pathway that runs from the elbow down to the hand. It is located on the inner aspect of your arm and houses a median nerve and many other tendons.

If you have carpal tunnel syndrome and you do not want to risk the side effects associated with steroid injections or you don't want to go for surgery, you can schedule a free consultation with one of our doctors. We offer a non-invasive alternative to steroid injections and surgery for carpal tunnel syndrome. We will treat all of the underlying issues that are causing you pain by utilizing Regenerative Cellular Therapy to help heal the *cause* of your wrist pain.

Regenerative Medicine for Wrist Arthritis

Arthritis of the hands and wrists is inflammation of the various tissues within the joints. Each joint is made up of tendons, ligaments, cartilage, and other soft tissues that provide cushioning where the bones meet, keeping them from rubbing against each other. When there is damage or deterioration within the joints, arthritis is likely to develop. Usually, the condition progressively develops

and worsens over time. Sudden, traumatic injury to the delicate soft tissues of the hand and wrist joints can also lead to the inflammation, stiffness, and pain of arthritis. Arthritis pain can easily become a chronic condition, and becomes increasingly more difficult to treat.

Despite the risks involved, many have tried prescription pain medications, steroid injections, and even surgery to relieve their pain. Now there are advanced, non-surgical techniques to reduce inflammation and arthritic pain. Regenerative Cellular Therapy takes healing cells from umbilical cord tissue that contains a high concentration of mesenchymal or regenerative cells and growth factors that help not only heal your inflamed joint but *also helps to regenerate tissue*. This is a same-day, in-office procedure that helps your body heal the arthritis in your hands and wrists naturally, without the need for surgery.

Regenerative Cellular Therapy

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The Regenerative Cellular Matrix (i.e. the MSC or regenerative cells along with cytokines, growth factors, hyaluronic acid, etc.) are injected directly into the painful area where they signal the body's repair process to begin working, and provide the building blocks needed to regenerate and repair the damaged tissue.

Since these regenerative cells are collected from healthy baby c-section deliveries, they are ***not*** *derived from embryonic stem cells or fetal tissue*, so there are no ethical issues with the treatment.

The therapy has the potential to *actually alter the course of the condition* and not simply mask the pain. This therapy has significant potential for those in pain, and could actually *repair structural problems* while treating pain and inflammation simultaneously.

When the mesenchymal or regenerative cell matrix is obtained, *it comes from consenting donors who have undergone elective c-sections*. The fluid or tissue is processed at an FDA regulated lab, and is checked for a full slate of diseases per FDA guidelines.

The regenerative cellular matrix has been *used over 100,000 times in the US*. It also acts as an "immunologically privileged" material, meaning it has NOT been shown to cause any rejection reaction in the body. This means there is no "graft versus host" problem.

If you're suffering with hand or wrist joint pain pain, find out if you are a good candidate for our Regenerative Cellular Therapy. Schedule your free consultation with our specialists today!

Elbow Pain

Commonly treated elbow conditions

The doctors and physical therapists at Elite Integrated Medical have extensive experience when it comes to treating conditions of the elbow. We have pioneered the industry's latest proven alternatives to surgery and steroids. Our in-office, same-day procedures will alleviate your elbow pain regardless of the cause. We treat a range of elbow conditions resulting from distal biceps tendon partial tear, osteoarthritis of the elbow, ulnar collateral ligament injury, etc. Our revolutionary regenerative medical procedures treat all the damages *and underlying conditions* that cause you pain. Our doctors use Regenerative Cellular Therapy to help rebuild and strengthen the damaged tissue.

This list does not contain all the conditions we treat, so please contact us to find out if we can treat your condition.

- Medial epicondylitis (Golfer's elbow)
- Post-traumatic elbow arthritis
- Distal biceps tendon partial tear
- Ulnar collateral ligament injury
- Lateral epicondylitis (Tennis elbow)
- Osteoarthritis of the elbow

Lateral Epicondylitis (Tennis elbow)

Many patients with tennis elbow run away from surgery and steroid injections. At Elite Integrated Medical, we offer an effective, non-invasive alternative to steroid

injections and surgery. **Our procedures treat all the underlying damages that cause the elbow pain.**

Medial epicondylitis (Golfer's Elbow)

At Elite Integrated Medical we offer these alternative procedures to ensure that your treatment is painless. We utilize the umbilical cord regenerative cellular matrix which stimulate the body's own repair systems to do their work and repair damaged tissues in the body. This innovative treatment method has already been proven effective in clinical studies.

Distal Biceps Tendon Tear

Distal biceps tendon tear typically occurs as a result of sudden injury and is not a result of other medical conditions. The tear can occur during heavy lifting without bending the elbows. In a situation where the elbow joints are forcefully straightened the distal tendon gets separated from the bicep.

Regenerative Cellular Therapy

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Since these umbilical cord MSC or regenerative cells are collected from healthy baby c-section deliveries, they are *not derived from embryonic stem cells or fetal tissue*, so there are no ethical issues with the treatment.

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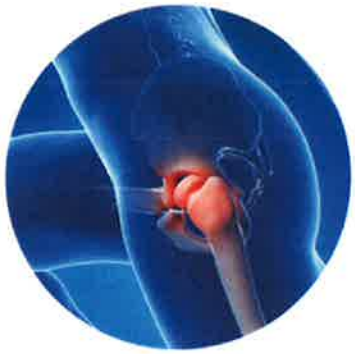
If you're suffering with chronic elbow pain, find out if you are a good candidate for our Regenerative Cellular Therapy. Schedule your free consultation with our specialists today!

Hip Pain

If you suffer with the Following Hip Conditions; learn more about how Regenerative Cellular Therapy can help restore your health and help you live Pain-Free!

- Hip Pain
- Labrum Tear
- Hip Osteoarthritis
- Hip Degeneration
- Hip Bursitis



Regenerative Medicine for Hip Pain

Hip pain is a common problem that affects many people making it difficult to walk, stand and sit. Hip pain has many causes making essential to be evaluated properly to find the true cause. There are many conditions that can cause hip pain, including osteoarthritis, bursitis, tendonitis, and osteonecrosis.

Elite Integrated Medical's doctors have extensive experience when it comes to hip pain treatment. We have pioneered the industry's latest proven alternatives to surgery and steroids. Our in-office, same-day procedures will alleviate your hip pain regardless of the cause. We use regenerative cellular therapy to **rebuild and strengthen the damaged tissue of your hip**, eliminating your pain and improving your quality of life.

Regenerative Medicine for Labrum Tears

Labrum tear is caused in many different ways. Sports injuries are the main cause of labrum tears. The reason is, the outermost part of the labrum attaches directly to the tendon. So the athletes who use a lot of force and motion such as weightlifters, golfers and baseball pitchers are at high risk of this type of injury.

Traumatic injury is the most common cause of a tear. Traumatic injury may result from a situation such as falling in a manner that puts strain on the hip or a direct blow or sudden pull. Furthermore, labrum tear can result from degradation of the cartilage from overuse, repetitive motion and a dislocated hip.

If you are suffering from labrum tear, you can visit us for a painless alternative to cortisone injections and/or surgery. After undergoing our procedure it will typically take a very short time to recover. Elite Integrated Medical's procedure for labrum tears includes Regenerative Cellular Therapy. This procedure reduces the risk associated with traditional surgery and treats the underlying damage causing the pain. These cells accelerate the healing process by making the conditions in the affected area more conducive to repair and stimulating the movement of regenerative cells towards the site of inflammation.

Regenerative Medicine for Hip Osteoarthritis

Osteoarthritis of the hip results from years of wear and tear. Cartilage provides a buffer in the joint between the bones to allow smooth, easy movement. Over time, this cartilage begins to break down and become brittle. Without enough cartilage to protect the bones from rubbing together and causing damage, this friction leads to swelling and painful inflammation. Ultimately, stiffness and soreness can limit mobility, and make moving the joint very painful.

Traditionally, hip pain has been difficult to treat, with pain medications, steroid injections, or even total joint replacement surgery being the best possible treatment options. Fortunately, recent developments in technology and medicine

make it possible to treat osteoarthritis pain naturally. MSC or regenerative cells are powerful healing agents that, when used in concentrated doses, can quickly reduce inflammation and scar tissue, and enhance the natural healing processes of the body. Regenerative Cellular Therapy is a non-invasive, in-office procedure that safely and effectively alleviates osteoarthritis pain.

Regenerative Medicine for Hip Degeneration

The hips are often the most used joint in the body, and over time take a lot of wear and tear. Hip degeneration is a condition that usually develops and worsens over a long period of time, and with the aging process. Some may not notice any symptoms in the first stages, and then may appear suddenly. When the cartilage protecting and surrounding the hip bones begins to wear down, those bones can begin to rub together. This friction between the bones eventually causes severe pain, inflammation, and swelling. It may cause stiffness, limit the joint's range of motion, or even lead to the development of bone spurs.

Advanced developments in Regenerative Medicine now make it possible to effectively treat pain from hip degeneration without prescription medications or steroid injections. In many cases, it may even help some sufferers avoid high-risk surgeries. Elite Integrated Medical's revolutionary Regenerative Cellular Therapy procedures treat all the damage *and underlying conditions* that cause you pain. When inflammation and aging slows down the natural production of these cells, providing the body with them in concentrated levels, quickly reduces pain, inflammation, and scar tissue. This process provides support for the body's own repair systems to heal damage and degeneration within the hip joint.

Regenerative Medicine for Hip Bursitis

Inside the larger joints of the body are small, fluid-filled sacs called bursae that provide cushioning between muscles, bones and tissues, allowing them to move

smoothly without friction. Bursitis is a condition involving the inflammation of one or more of these bursae. It can occur within the hip joints, causing mild to severe pain and stiffness, while making movement uncomfortable.

Treatment for bursitis should first reduce the inflammation that is causing the pain and stiffness in the hip joint. Regenerative Cellular Therapy is one of our advanced treatment options that takes concentrated amounts of healing regenerative cells, and uses them to treat the specific area of inflammation and damage. This is a revolutionary solution to heal degeneration of soft joint tissues, and a safe alternative to medications, steroid injections, and surgery. This is a non-surgical procedure that can be done in-office, to quickly and naturally alleviate your hip pain.

Regenerative Cellular Therapy

Regenerative Cellular Therapy is one of the newest and most cutting-edge therapies for chronic joint pain. Umbilical cord-derived regenerative cellular therapy offers patients 3 essential properties for healing and restoring joint health:

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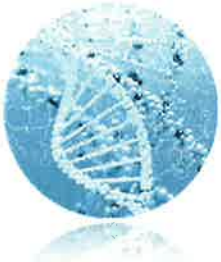

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Since these umbilical cord regenerative cells or MSCs are collected from healthy baby c-section deliveries, they are *not derived from embryonic stem cells or fetal tissue*, so there are no ethical issues with the treatment.

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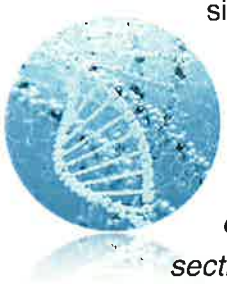

When the umbilical cord regenerative cell matrix is obtained, *it comes from consenting donors who have undergone elective c-sections.* The fluid is processed at an FDA regulated lab, and is checked for a full slate of diseases per FDA guidelines.

The regenerative cellular matrix has been *used over 100,000 times in the US.* It also acts as an "immunologically privileged" material, meaning it has NOT been shown to cause any rejection reaction in the body. This means there is no "graft versus host" problem.

If you're suffering with chronic hip pain, find out if you are a good candidate for our Regenerative Cellular Therapy. Schedule your free consultation with our specialists today!

"I had been suffering with low back and hip pain for the past 20 years and bilateral thumb pain for the past 15 years. I had gotten information regarding the breakthrough medical treatment regarding Regenerative Cellular treatment and called to schedule a complimentary consultation to find out more about this treatment.

I was desperate! I was tired of living with the pain. I couldn't walk distances, I couldn't stand for periods of time. I coach the high school softball team and just wanted my normal life back.

I had my low back and hip injected 3 weeks ago and I saw pretty quick improvement in my pain levels. I cut back on my pain medication, which is great. I was tired of taking so many pain pills just to get through a day, a softball practice, or game. The injection did not hurt.

I have family members that I would like to recommend this procedure for and would like to help others experience similar results." - Warren C.

Knee Pain

If you suffer with the Following Knee Conditions; learn more about how Regenerative Cellular Therapy can help restore your health and help you live Pain-Free!

- Meniscus Tear
- Knee Degeneration
- ACL or PCL Injury
- Chondromalacia

Regenerative Medicine for Meniscus Tear

When the meniscus cartilage ruptures due to traumatic injuries or due to age-related wear and tear it is referred to as meniscus tear. Meniscus tear is usually very painful and limiting. *The knee will not operate correctly with this type of injury.* The meniscus is located at the knee joint. It is a rubbery piece of cartilage that acts as the body's shock absorber and also acts as a pad to stabilize and protect the knee.

Meniscus tear are of three degrees: severe, moderate and minor. Severe meniscus is when bits of ruptured meniscus enter the knee joint and affects the function of the knee causing a lot of pain. But for minor and moderate meniscus tears, the pain usually disappears after conventional treatment or a few weeks of rest. Those suffering from meniscus tear are increasingly becoming aware of the implications of removing the meniscus though surgical operation, they also prefer not to risk the side effects that come with steroid injections.

Elite Integrated Medical offers a non-invasive alternative to surgery and steroid injections for this problem. We also treat the *underlying issues* that cause the pain with our advanced form of Regenerative Cellular Therapy. By using this regenerative approach, the joint can repair itself and regain its function of holding

the knee bones in place, thus relieving pressure on other components such as the particular cartilage and meniscus.

Regenerative Medicine for Knee Degeneration

Degeneration of the joints can occur in any of the joints in the body, especially those that experience lots of wear and tear. The knees are used in so many daily motions, feeling pain with each movement is debilitating. Joint degeneration generally develops over time, but can suddenly worsen and become more severe and disabling. Cartilage or other soft tissues within the knee joint can begin to dehydrate, deteriorate, or become damaged from some type of injury. These tissues provide a protective cushion between the bones for smooth movement. Once these start to wear down, or degenerate, friction within the joint can lead to inflammation, swelling, bone spurs, and other painful symptoms. Recent developments in Regenerative Medicine make it possible to treat degenerative joint conditions naturally, without the need for medications, steroids, or surgery. Regenerative Cellular Therapy uses stem cells to target the damaged and deteriorating tissues. Concentrated amounts of these cells are injected into the affected area, and immediately reduce inflammation and reverse damage and deterioration of tissue.

"I've suffered with chronic knee pain for the last 10 years. It started out with just soreness and eventually led me to walking with a cane every day. I had tried injections before, nerve blocks and even orthovisc injections and each time, they would work for a few months and the pain would come back. I had heard about regenerative cellular therapy from a good friend who had tried it and had success with it. I was a little concerned because other treatments had not really given me long term success. Not wanting to do surgery, I decided to try my right knee and do the treatment on one side to see how well it worked. Well, 6 months later, I did the other knee. I've been pain free for months now and no longer have to walk with a cane. It has definitely given me my life back. I've had such an improvement that my wife had her shoulder treated with regenerative cellular therapy and she feels younger because she's not longer in pain. This therapy can change your life." - Rob M

Regenerative Medicine for ACL or PCL Injury

The posterior cruciate ligament (PCL) and anterior cruciate ligament (ACL) are both major ligaments providing strength and stability within the knee joint. Ligaments are thick bands of tissue that connect bones. Injuries to these connective tissues are painful, debilitating, and have historically been a challenge to treat and heal. In the past, these kinds of injuries could cause what was considered permanent damage to the knee joints. Traditionally, the most common treatment for torn ligaments in the knee is arthroscopic surgery and reconstruction. Developments in Regenerative Medicine make effective, natural treatment of PCL and ACL injuries within reach. Procedures like Regenerative Cellular Therapy offer non-surgical treatment options for those suffering from knee injuries and damage to soft tissues in the joints. Using these cells in concentrated amounts to target the injured area, the body is able to reduce inflammation and heal itself naturally.

Regenerative Medicine for Chondromalacia

Also known as "runner's knee," chondromalacia is inflammation of the underside of the kneecap, and deterioration of the cartilage that supports it. When this cartilage is damaged or wears down, it becomes difficult to bend and straighten out the leg. This condition is common among young athletes, but may also be present in older individuals with arthritis of the knee. Regenerative Cellular Therapy and other Regenerative Medicine techniques offer natural treatment alternatives to pain medications, steroid injections, and surgery. Using these cells, our specialists are able to target specific areas of inflammation or injury and restore damaged tissues. These are cutting-edge techniques that

"Last Thursday I had my regenerative cellular therapy done by Dr. Chowdhury and have been 100% out of pain ever since. I can't believe it. The procedure was painless and I walked out 5 minutes later. The Litmus Test was walking down the stairs with ZERO PAIN and putting weight on it first thing in the a.m. with ZERO PAIN! I'm so happy. Thank you!" - Don, age 75

have provided relief and healing to so many of our patients with knee pain.

Regenerative Cellular Therapy

Regenerative cellular therapy is one of the newest and most cutting-edge therapies for chronic joint pain. Umbilical cord-derived regenerative cellular therapy offers patients 3 essential properties for healing and restoring joint health:

- A high concentration of regenerative cells
- Hyaluronic Acid for joint lubrication and movement
- Anti-inflammatory cytokines and cellular growth factors essential for building new joint tissue

The regenerative cellular "matrix" (i.e. the mesenchymal stem cells along with cytokines, growth factors, hyaluronic acid, etc.) are injected directly into the painful area where they signal the body's repair process to begin working, and provide the building blocks needed to regenerate and repair the damaged tissue.

Since these umbilical cord regenerative cells are collected from healthy baby c-section deliveries, they are *not derived from embryonic stem cells or fetal tissue*, so there are no ethical issues with the treatment.

The therapy has the potential to *actually alter the course of the condition* and not simply mask the pain. This therapy has significant potential for those in pain, and could actually *repair structural problems* while treating pain and inflammation simultaneously.

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If you're suffering with chronic knee pain, find out if you are a good candidate for our Regenerative Cellular Therapy. Schedule your free consultation with our specialists today!

Foot/Ankle Pain

If you suffer with the Following Foot / Ankle Conditions; learn more about how Regenerative Cellular Therapy can help restore your health and help you live Pain-Free!

- Foot Pain
- Plantar Fasciitis

Regenerative Medicine for Foot / Ankle Pain

Elite Integrated Medical's doctors have extensive experience when it comes to foot and ankle pain treatment. We have pioneered the industry's latest proven alternatives to surgery and steroids. **Our same-day procedures will alleviate your foot and ankle pain regardless of the cause**.

Our revolutionary Regenerative Cellular Therapy *treats all the damage and underlying conditions* that cause you pain. With just one visit to our specialists you can be on the road to living a pain free life. Our doctors utilize Regenerative Cellular Therapy to rebuild and strengthen damaged tissue. We can start your healing process on the initial visit. Alleviate your foot and ankle pain today!

Regenerative Medicine for Plantar Fasciitis

The Plantar Fascia, or arch tendon, is located at the bottom of the foot. It is a broad connective tissue that runs across the bottom of the foot and spreads from the heel bone to the toes at the front of the foot. Its overuse is what causes plantar fasciitis. A common symptom of plantar fasciitis is pain when walking. The pain typically decreases during exercise, but intensifies after walking or standing for long periods of time. A major complaint is stabbing pain in the bottom of the foot near the heel. This condition is commonly identified as a heel spur, although

both are not entirely the same. This is because a heel spur arises at the point where the plantar fascia connects to the heel bone (calcaneus) and develops as a bony growth.

At Elite Integrated Medical we have introduced a new regenerative technique for the treatment of plantar fasciitis. We treat the stressed connective tissue with an injection of regenerative cells. ***Our procedure regenerates damaged tissue while reducing pain.*** So if you are not satisfied with the results that traditional orthopedic treatments have delivered for your plantar fasciitis, contact us to learn more about how regenerative cellular therapy can help.

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If you're suffering with chronic foot or ankle pain, find out if you are a good candidate for our Regenerative Cellular Therapy. Schedule your free consultation with our specialists today!

Next Steps...

If you're already registered for an upcoming seminar, then there's nothing more to do at this time. Please be sure to attend your session as these are very limited opportunities to learn first-hand about these breakthrough regenerative therapies that can change your life.

If you've not yet registered for an upcoming event, please be sure to contact our office to learn about the next available seminar in your area.

You can call our office and speak with one of our team members to find out when the next seminar will be held.

Learn More...

On our website below, we share the stories of the people who have received this breakthrough treatment and tell about their experience and the difference it has made in their lives.

7100 Peachtree Dunwoody Rd.
Suite 100
Atlanta, GA 30328
(678) 786-2355
http://atl.elitemedicalstem.com/reviews

Notes & Questions...

Following Up
1 message

Elite Integrated Medical <at@elitemedicalstem.com> Sat, Jul 13, 2019 at 7:55 AM
To [redacted]

Hi [redacted]

I wasn't sure if you had a chance to download the **Stem Cell Booklet** that you requested yesterday, so I wanted to check back with you to make sure you received it. The link to download the book is below

Click the image below to download the booklet now

Click the image to download the booklet now or click the button below.

Download

Register For One Of Our Upcoming Free Live Seminars!

If you haven't already registered for one of our next live seminars where you can learn even more about this groundbreaking new treatment, we'd love to have you join us.

There is no charge at all for this event and you are welcome to bring a guest. Lunch will be provided.

Click the button below to register for one of our upcoming seminars!

REGISTER NOW

I'd be happy to spend a few minutes with you at the seminar to discuss your situation and help you decide if this would be the right treatment for you.

CLICK HERE to register for one of these seminars now. Or you can also call my assistant at (678) 786-2355 to register.

Dr. Leslye Pace, M.D.
Elite Integrated Medical
(678) 786-2355
atl@elitemedicalstem.com

ELITE
INTEGRATED MEDICAL

Elite Integrated Medical 7100 Peachtree Dunwoody Rd. #100, Sandy Springs, GA 30328, United States

Update your subscription — Unsubscribe

6,422 ongoing stem cell research studies
1 message

Elite Integrated Medical <atl@elitemedicalstem.com> Sun, Jul 14, 2019 at 8:00 AM
To: [redacted]

Hey there [redacted]

As you're most likely doing your research on stem cell treatments, I thought you might appreciate having a few more resources at your fingertips. Here is a wealth of information, straight from the source.

On this site, you can learn about **over 6,400 ongoing stem cell research studies** being done on the use of stem cells for various healthcare applications.

It's a government run website, mainly for doctors, so it's not always "easy reading" material. But my hope is that *you will see just how serious the field of stem cell medicine has become*, and how many different medical applications they are finding for it.

https://clinicaltrials.gov/ct2/results?term=stem+cell&Search=Search

Check it out and let me know what you think.

I'll talk to you soon,

Dr. Leslye Pace, M.D.
Elite Integrated Medical
(678) 786-2355
atl@elitemedicalstem.com

Hundreds of NFL players treated with stem cells
1 message

Elite Integrated Medical <atl@elitemedicalstem.com> Mon, Jul 15, 2019 at 8:04 AM
To: [redacted]

Hi [redacted]

I just wanted to share this Sports Illustrated article that talks about all of the NFL players that are now getting stem cell therapy. It's a great article that just goes to show how mainstream this type of treatment has become.

"...Dr. Andrews quietly has been using these stem cells to treat pro athletes for about three years. The count of NFL players he's treated with stem cells is a couple hundred..."

You can read the full article at: https://www.si.com/2014/07/30/stem-cell-treatment-nfl-sports-medicine

I'd love to meet with you to share many of the great stories of patients (many whom are well into their 70's & 80's) who have received this treatment and been able to return to the *"playing field"* of travel, quality family time, and even just simple daily routines like cooking & cleaning.

If you haven't already, please give me a call at the number below to book your free no-obligation consultation for us to take a look at your situation to see if this could be a viable solution for you.

I look forward to meeting you.

Dr. Leslye Pace, M.D.

Elite Integrated Medical
(678) 786-2355
atl@elitemedicalstem.com

NBA team doctor uses stem cells for player injuries...
1 message

Elite Integrated Medical <atl@elitemedicalstem.com> Sat, Jul 20, 2019 at 8:20 AM
To: [redacted]

Hi [redacted]

Today I wanted to send you an article written by Medical Director & Head Team Physician for the Brooklyn Nets (NBA) & New York Red Bulls (MLS soccer), Dr. Riley Williams III.

In the article, he writes...

"There is very little downside to trying a stem cell treatment on a patient who fits the right profile. I've been treating athletes' knees with stem cell therapy for the past 10 years or so. I've used these methods alone and in concert with surgical procedures. In general, I have observed faster healing rates using these cells as surgical adjuncts. Moreover, some athletes have been able to avoid surgery using stem cell injections. The short- to mid-range results that I've observed are very encouraging."

You can read the full article here...

https://www.hss.edu/playbook/stem-cell-therapy-right-move-athlete/

As you can imagine, *there's no "one-size-fits-all" solution that fits everyone* - stem cells included. We often have to tell people that they are just not a good candidate for this treatment.

But we've also helped hundreds of people of all ages and walks of life avoid joint replacement surgery and return to a pain free life, without

harmful drugs.

I am here to help you find the best course of action for you! By the end of our no-cost consultation together, you'll be fully educated on the various forms of stem cell treatments and will be informed enough to know if this could be the correct treatment for your particular condition.

Many of the patients I meet have been searching for a solution for a long time and I am thrilled to be able to help. Simply call me at the number below to schedule a one-on-one consultation that could possibly change everything.

I'm really looking forward to meeting you.

Dr. Leslye Pace, M.D.
Elite Integrated Medical
(678) 786-2355
atl@elitemedicalstem.com

ELITE
INTEGRATED MEDICAL

Sent to [redacted]
Elite Integrated Medical, 7100 Peachtree Dunwoody Rd. #100, Sandy Springs, GA 30328, United States
Don't want future emails? Unsubscribe

From: "Superior Healthcare Group Sandy Springs" <stem2@superiorhealthcaregroup.com>
Date: January 14, 2019 at 6:01:32 AM EST
To: [redacted]
Subject: A recent patient's experience

Hi [redacted]

As the stem cell seminar draws near, I just wanted to share a great story from a recent patient, Ms. Johnson...

Ms. Johnson was an active person in her everyday life until time took its toll on her back and knees. She could barely get herself up or down the stairs in her home anymore without agonizing pain. She could not stand for longer than 30 seconds at a time, and eventually, something as simple as carrying grocery bags was out of the question. Within the first week of getting her stem cell injection, Ms. Johnson could already feel a noticeable difference. By 2 weeks, the pain in her leg was gone. And by 6 weeks, she was 85% better in her back as well!

Click on the video below to see her tell her story:

Stories like these are the reason I do what I do. I'm passionate about helping people to get back to living their best lives.

If you'd like to hear more stories like this, please visit our review page at https://pd.superiorhealthga.com/reviews

If you have any burning questions, please write them down and bring them with you to the seminar so we can be sure to get you the answers you need. I look forward to meeting you in person very soon!

Take Care!

Dr. Leslye Pace, M.D.
Superior Healthcare Group Sandy Springs
(678) 883-7422
stem2@superiorhealthcaregroup.com

Cost of Surgery

- Pain.
- 3-6 months of healing and rehabilitation time.
- No guarantee of result.
- High percentage of failure and complications.
- 50% or more will need additional surgery.
- Total Average Cost for Uncomplicated Case = $55,000.00. Much comes out of deductible.
- What's the cost of your lost time, function, pain and suffering?

21

https://www.healthleadersmedia.com/finance/planned-orthopedic-surgery-costs-increase-44-8-years (DR5f)

Lavernia, et al (2006). Postdischarge costs in Arthroplasty Surgery. The Journal of Arthroplasty, 21(6): 144-150. (DR5g)

Saying NO to Regenerative Therapy?

=

Saying Yes to:

- More drugs
- More steroid injections
- Surgery
- Maybe multiple surgeries
- (and more recovery drugs)

Read the slide

What about the FDA?

- FDA regulates medications (drugs) and medical devices.
- Human Cellular Tissue Products are neither of these things- but there are guidelines to ensure that they are safely tested and processed.

Reasons to do it now:

1. *It can only help if you GET THEM>*
2. *Your best chance of improvement is RIGHT NOW. Things get worse over time.*
3. *Life is about happiness and living.*
4. *There is nothing more important than your health.*

IT'S A FREE CONSULTATION WITH X-RAYS!

- **Fill out our forms describing your condition, and bring them with you to your appointment.**
- **If you have MRI/Xrays- bring them to your appointment.**

- **Please pull out your calendar for appointment scheduling.**

Normal fees will apply, $200 Consultation & X-Ray Fee if appointment is not within the next week.

My first gift is to waive the fee for the initial exam and x-ray and this is a $200 fee. The reason I'm doing this is many of you as I look at your surveys have been to multiple doctors without any success and I do not want to charge you unless I know I can help you. Please bring in you're x-rays and MRIs if you have them we will not need to retake the films

ONE INJECTION - As a gift for coming, when you sign up today, **you will receive 10% off** your first injection.

TWO INJECTIONS - If you need two injections **we're happy to give you 20% off**.

These are HUGE SAVINGS and we are happy to give them to you!

Many patients need our low monthly payment options. **If approved for treatment our team has you covered with payment plans.**

My second gift is to save you money and I know many of you need more than one area to be fixed so one area we will give you a 10% discount if you need more than one then you'll get a 20% discount
I will even allow you to combine body parts with your spouse or loved one. This means if your wife has a knee problem and you have a shoulder problem both of you will see 20% on the procedures. I do not want money to be the reason for you not to receive help. This is why I've instructed my staff to help you with financing programs that are as little as $300 per month if you need that type of help

.

Now I need to reiterate one thing the free exam and x-rays and the gifts that save you money are stamped with a time limit. I need everyone that is interested in getting help to show up this week if you want to receive those gifts

Hand this survey to your appointment scheduler and tell everyone to accept an appointment if their name is circled. Leave the building

Testimonials
Get A Free Consultation Today

ABOUT THE SEMINAR

No treatment is a panacea, **but what if you could reduce your pain by 70%, 80% or more?** Wouldn't that make your life so much easier and more enjoyable?

Come to our free, one hour, no obligation seminar to hear the facts about regenerative therapy. You'll learn what stem cells are, how they work in the body and what's involved in treatment.

PLEASE NOTE: This seminar is only for local area residents looking for an alternative solution to their joint pain. Due to the limited seating of this venue, we can only accept first time visitors. If you have attended a previous event and would like to get additional information about this treatment program, please call us at (678) 883-7836 to arrange a no cost consultation with one of our doctors.

RESERVE YOUR FREE SEAT BEFORE SOMEONE ELSE DOES!