Harms Linked to Unapproved Stem Cell Interventions Highlight Need for Greater FDA Enforcement

Unproven regenerative medical products have led to infections, disabilities, and deaths

Overview

Stem cell products and other regenerative therapies have significant potential to treat traumatic injuries and serious diseases. Although some have earned approval from the Food and Drug Administration, most have not, and many of these unapproved interventions have led to life-threatening infections, chronic pain, and even death.[1]

More than 700 clinics in the U.S. offer unapproved stem cell and regenerative medicine interventions (SCRIs) for conditions such as Alzheimer's disease, muscular dystrophy, autism, spinal cord injuries, and, most recently, COVID-19.[2] The products made and sold by these businesses typically use cells from the patient's own body or from donated amniotic fluid, placental tissue, or umbilical cord blood, among other birth-derived cells and tissues. FDA has given manufacturers and marketers of SCRIs until May 31, 2021, to come into compliance with the agency's regulations governing human cell and tissue products, including submitting those products for FDA review when necessary.[3]

FDA uses reports of adverse events—undesirable patient experiences associated with the use of medical treatments—to help identify potentially dangerous products meriting further investigation. However, adverse events associated with any medical product are generally underreported, and providers of unapproved treatments are particularly unlikely to report patient harm to regulators or disclose such cases through public reporting—making it more difficult for the agency to prioritize its enforcement actions, and also leading policymakers and the public to underestimate the risks of these interventions.

To create a clearer picture of the risks that these interventions pose and underscore the need for increased FDA oversight, The Pew Charitable Trusts gathered reports of adverse events (AEs) linked to unapproved SCRIs administered outside of clinical trials. In total, we identified reports of 360 people who had AEs that occurred between 2004 and September 2020, including:

- 334 cases documented in peer-reviewed journals, government and news media reports, and other literature.
- 5 cases reported in FDA's adverse event reporting system (known as FAERS), a public database of reports submitted to the agency.
- 21 cases described in consumer reviews of stem cell businesses posted to Google, Yelp, and Facebook.

Pew's findings reinforce the need for increased FDA enforcement action against businesses that manufacture and market these unapproved—and, in many cases, unproven—products. (See Appendix A for definitions of key terms.) They also underscore how more frequent and thorough reporting of AEs by consumers and clinicians, and the FDA's use of social media data, could allow the agency to more quickly identify businesses that are putting patients' health at risk and target its limited oversight resources more effectively. More broadly, the findings highlight the importance of FDA oversight in ensuring that regenerative products on the market are safe and effective. The agency should move quickly to enforce its regulations governing human cell and tissue products for businesses that fail to comply by FDA's May 31 deadline, and regulators should not hesitate to seek legal injunctions and mandate product recalls when necessary.

Adverse events related to unapproved SCRIs continue to be reported in the literature

Most of the adverse events identified in this research (334, or 93%) came from the literature, which included peer-reviewed articles, media reports, and government publications. This literature review built upon previous Pew research published in 2019, which identified 69 reports of harm, including lifelong disabilities and death, dating as early as 2004. For this latest round of research, which covered literature published between November 2019 and January 2021, the team identified an additional 265 cases of harm related to these products, bringing the total number of AEs to 334 and the total number of subsequent deaths to 20. The majority of the new cases added to the updated list (242) were published in January 2021 as part of a prospective study of patient medical records drawn from a single insurance company database—complete with information on the type of treatment and complications—to identify AEs associated with unapproved SCRIs.[4] (See Appendix B for a full list of AEs associated with unapproved SCRIs and a description of the methodology for the literature review.)

Many of the AEs identified involved serious bacterial infection, including at least two cases of septicemia, a life-threatening blood infection. Others included serious and even lifelong disabilities such as partial or complete blindness (9); paraplegia (1); pulmonary embolism (6); cardiac arrest (5); tumors, lesions, or other growths (16); and organ damage or failure in several cases that resulted in death. Many of these AEs required hospitalization (104) and caused acute or worsening pain (55). The most common type of interventions linked to these AEs were autologous (that is, the stem cells were obtained from the patient's body) or donor stem cells administered

by injection into the eye, spine, hip, shoulder, or knee.

The prevalence of infection among the adverse events is likely due to several factors. In some cases, the infections can originate from the products themselves, which may not have been processed in compliance with good manufacturing practice. In one case, for example, FDA issued a warning to a California-based stem cell company for selling unapproved stem cell products that were manufactured without proper safety measures, including a failure to properly screen for communicable diseases such as HIV and hepatitis B and C, and failure to have a system in place to prevent contamination.[5] At least 13 people were hospitalized due to serious bacterial infection after receiving contaminated stem cell products manufactured by the company and then distributed to various clinics in Texas, Arizona, Kansas, and Florida.[6] Most recently, FDA sent a letter to a company, based in Las Vegas, warning of unsafe manufacturing practices after the company's stem cell product caused multiple serious AEs in patients in Nebraska.[7]

In other cases, the infections may have been due to unsafe injection practices on the part of the product distributor. The literature review identified several types of administration practices—direct injections, surgical transplantations, and IV infusions; it's unclear whether any of these methods of administration are safe or, alternately, if they may have contributed to an adverse event. The risks of infection or other serious complications are likely higher in cases in which the person administering the product has limited training in treating that patient's disease or condition, a fact that was acknowledged by FDA and highlighted by the Federation of State Medical Boards in a 2016 policy statement on stem cell interventions.[8] Likewise, a 2019 study of 166 stem cell companies found that nine did not have a physician on staff, and that only half of the remaining 157 businesses employed a physician with formal training that matched the conditions they claimed to treat. The problem was more acute when it came to clinics that used stem cells to treat nonorthopedic conditions: Only 13 companies (19%) employed physicians operating within the scope of their training.[9]

These adverse events highlight many of the risks of unapproved SCRIs, and are particularly concerning given that unapproved SCRIs not only haven't been shown to offer definitive benefits, but are also likely entirely paid for by the patient, at a cost often totaling thousands of dollars.[10] Use of unapproved SCRIs may also lead patients to delay seeking approved and evidence-based medical treatments under the false hope that stem cell therapies will cure them or improve their condition; a delay in proper medical care poses the additional risk of their condition worsening.

Finally, given that more than 70% of new identified AE reports came from a single prospective study of SCRIs,[11] the findings from the literature also underscore the fundamental importance of evaluating SCRIs in clinical trials that are designed to systematically assess their risks and benefits compared with the standard of care. Although case studies are very helpful to the medical and public health community in identifying potential harms associated with a treatment, it is only through rigorous studies that regulators and clinicians can fully understand which SCRIs are beneficial and which are useless or harmful.

FDA's database of adverse events captures some reports linked to unapproved SCRIs

FDA collects reports of AEs associated with drug and therapeutic biologic products in its adverse event reporting system (FAERS) through reports submitted to a public database known as MedWatch.[12] This database includes mandatory reports from manufacturers and other organizations that are involved in drug supply and distribution, as well as voluntary reports from health care providers, patients, and consumers.[13] The system serves as an important oversight tool for the agency; FDA staff routinely monitor the system to detect signs that a medical product may be causing harm. When such a safety signal is detected, FDA may follow up to determine if further action is required to protect public health. This follow-up can take the form of public health alerts, consumer

advisories, or other regulatory actions where necessary.

However, businesses that make or sell unapproved SCRIs are unlikely to report adverse events associated with their products to FDA, either because they do not know that they should or because they are evading oversight. Therefore, any adverse events related to unapproved SCRIs in the FAERS database are likely to have been reported voluntarily by physicians who may be treating complications that arise from these treatments, or from consumers themselves.[14] And these voluntary reports are more likely to be incomplete compared with submissions from mandatory reporters, which may limit the agency's ability to identify the source of the harm and take action. For instance, if a report does not include information on the type of stem cell intervention used or the condition that was being treated, it is more challenging to determine if that report is associated with an unapproved product.

Pew conducted a search of the database from November 1997 to March 2020 to better understand if AEs linked to unapproved products are being reported in FAERS. (See Appendix C for a full description of the methodology.) An initial keyword search of the FAERS database yielded 673 unique results. Of those, the 495 submitted by mandatory reporters—e.g., manufacturers with approved products—were excluded. The remaining 178 reports, which were submitted by voluntary reporters, included 118 that were deemed incomplete because they didn't meet the criteria for inclusion—that is, they didn't include information on the type of stem cell intervention used or the condition that was being treated—leaving 60 reports that could be considered "complete." Of those 60, a further 55 were excluded because they appeared related to an approved use—resulting in a final count of five reports that appear to be associated with unapproved SCRIs. Among the five reports, death was listed as an outcome in one case, and hospitalization or life-threatening reaction to treatment in three. Types of AEs listed in the five reports included bacterial infection, severe immune reaction and inflammatory response, and heart attack. (See Appendix Table C.1 for further details on these reports.) Importantly, though: Even for the five cases that met the inclusion criteria, there is no mechanism to verify the information provided. A report can indicate a correlation between the product and the AE but cannot establish causation.

But because this final number of five reports reflects only complete, nonduplicative, voluntary reports, it is likely an undercount. Some of the reports that were excluded from the final count—because they didn't include the condition being treated by a stem cell therapy (there are approved uses for such interventions) or list the type of stem cell therapy—may have been related to unapproved products.

FDA acknowledged the problem of underreporting in a recent article in *JAMA* and encouraged patients and their providers to more thoroughly report AEs.[15] Improved reporting would allow the agency to target enforcement activities more effectively and reinforce the case for tighter regulation of this market. As awareness of the harm grows, fewer patients may be willing to undergo these treatments in the first place.

Reviews on social media sites underscore that adverse events are underreported

Many consumers and patients use social media platforms to share their experiences with medical treatments, including SCRIs, which means that these sites can be a potential resource for identifying self-reported cases of AEs.[16] Social media posts may be more expansive than the information included in the FAERS database, and include important contextual information related to the event, such as the location where the intervention occurred and additional details describing the patient's experience. However, as with FAERS, consumer-generated reviews and testimonials can only identify a correlation, not causation. Additionally, these posts may still lack important information, such as the specific type of stem cell intervention received.

FDA has acknowledged that social media monitoring for AEs may have the potential for faster safety signal detection and may include important information that otherwise may not be available through FAERS.[17] To

test this hypothesis, Pew analyzed all patient reviews of businesses offering unapproved SCRIs posted before September 2020 across three websites: Google, Yelp, and Facebook. (See Appendix D for a full description of the methodology and a list of keywords.) This analysis identified 21 reviews describing AEs that appeared to be directly linked to unapproved SCRIs. (See Appendix Table D.1 for a full list of AEs that were identified.) Most of these reviews (17) identify the adverse event as pain—including new or worsening pain that in some cases is described as "extreme" and "excruciating." Other AEs mentioned in the reviews include infection, inflammation, allergic reactions (8), and loss of mobility and function in limbs (9). Three of the reviews were linked with a business that has been the target of FDA regulatory action in the past.[18]

The analysis also identified 67 reviews describing concerns about the quality of care received. These reviews did not have adequate information to conclude that an AE was directly associated with an unapproved product, but they described other negative experiences, including patients not receiving adequate care during or after the procedure (30) or delaying evidence-based medical treatments because they pursued unproven SCRIs (31).

Consumers' Online Reviews Illustrate Serious Risks and Complications

Select comments from adverse experiences with unapproved regenerative products

"Day 5 after my stem cell in my lumbar spine, I woke up in the most severe pain on my life. I couldn't walk and was bed ridden for 8 weeks." – *Reviewer on Google, 2020*

"I have a worse time walking and sleeping, which isn't good because of the pain, something that wasn't happening before the (stem cell) shot." – *Reviewer on Facebook, 2020*

"I contracted an infection which required 6 days of hospitalization, 2 emergency surgeries, 6 weeks of IV antibiotics and 6 months of oral antibiotics." – *Reviewer on Google, 2019*

"The procedure was very painful but initially there was some improvement then deterioration back to my original condition. One year later my knees are the same as before and my shoulder which had been getting better before the injections is now worse than when I went in. I am seriously wondering about the ethics and efficacy of this experience and practice." – *Reviewer on Google, 2019*

"I chose to try stem cell and blood platelet therapy for my hip with worn cartilage. … I did have significant relief for a few months after the joint injection. But the pain soon returned. The MRIs taken before and after the injection looked identical. There was no cartilage regrowth. The temporary relief was simply a result of the fluid injection. I then opted for an anterior entry hip replacement." – *Reviewer on Yelp, 2016*

Although Pew's research primarily focused on the physical harms associated with these SCRI interventions, the research also identified cases of patients reporting emotional and financial harms, which raises significant concerns and highlights that the harms associated with unproven SCRIs are not restricted to physical injuries. At least 87 reviews included complaints about the financial cost of these treatments, including reviews that describe spending money on treatments that did not work (45) or were painful to undergo or recover from (29). Because these procedures are typically not covered by insurance, patients are likely paying out of pocket or turning to crowdfunding sites to pay for care that is unlikely to benefit them.[19]

In line with other studies that analyzed social media data for AE reports, Pew's social media analysis did not reveal many new serious or life-threatening AEs.[20] This finding is reassuring as well as unsurprising: If an AE is life-threatening or otherwise serious, the treating physician may report the case to FDA or another regulator or

seek to publish case studies about it. However, the data collected from these reviews provides a window into how stem cell businesses operate and may be useful to FDA and other regulators or oversight bodies with jurisdiction over medical or business practices.

And it's worth noting that not all the reviews left on the social media sites were reports of negative experiences from undergoing SCRIs; many, in fact, were positive. This finding correlates with other perception studies that report on patients' positive experiences with these interventions.[21] Pew's analysis excluded 94 positive reviews that were not already eliminated in our initial search.

However, a little more than a third of the positive reviews (35) were posted within a few months—and in some cases, within a few days—after a patient received the treatment, and reports of positive outcomes shortly after receiving an SCRI do not necessarily indicate treatment efficacy.[22] Not only do such reports leave open the possibility that AEs (or concerns that the treatments did not work as promised) may have emerged later, but they also may be a result of other procedures done before or after receiving the treatment or continued evidence-based treatments, such as physical rehabilitation therapy. For example, one reviewer described experiencing "significant relief" for a few months after receiving an SCRI but associated it with the cushioning effects of the fluid injection they received rather than the effects of stem cells. Another reviewer described "noticeable improvement" six weeks post-treatment with continued rehabilitation therapy but described new symptoms and admitted that the procedure "did not work" one year after receiving the SCRI.

Stem cell businesses routinely use these testimonials to promote their unproven therapies.[23] But as with the negative reviews evaluated as part of the research, it's difficult to assess the validity of these positive reviews. Some researchers suggest that specific blogs, social media sites, and other venues and platforms run or produced by clinics likely control the patient narrative and thus provide only posts with a positive outlook or portrayal of SCRIs —omitting negative reports.[24] (Pew identified at least two negative reviews describing AEs that users reposted after they were deleted the first time.) Through this and other techniques—such as publishing results of quality-of-life surveys filled out by patients who receive treatments— businesses create a misleading picture of the safety and efficacy of SCRIs.[25]

For these reasons, the research likely did not capture all AEs associated with these businesses. Additionally, the analysis was limited to only English-language posts on three social media websites. The analysis also did not capture any businesses that may not exist under the same name or in the same location as they did when patients complained about them. These factors highlight the challenges facing FDA and other regulators that attempt to use social media to track businesses that offer unapproved treatments to patients.

And although Pew's search focused primarily on stem cell products, the social media analysis also identified AE reports associated with platelet-rich plasma (PRP), which has been marketed as a regenerative intervention for various ailments, including orthopedic conditions and hair loss.[26] PRP does not contain stem cells, and FDA does not consider it a cell- or tissue-based product. The therapy involves injecting patients with a concentrated dose of their own platelets—a type of blood cell that contains growth factors and plays an important role in the body's natural wound-healing process—to stimulate tissue regeneration in the targeted area. Blood drawn from the patient is run through a centrifuge to create a concentrated sample that contains high levels of platelets, then injected back into the patient. The more than 1,000 clinical studies investigating the effects of PRP that are listed in clinicaltrials.gov, a large registry of clinical trials maintained by the U.S. National Library of Medicine,[27] have not yet demonstrated definitive efficacy in treating particular conditions or diseases.[28] However, clinics continue to market this therapy to patients for a range of indications.[29]

Of the 21 AEs that Pew identified, seven were associated with PRP therapy. (See Appendix Table D.1 for a list of AEs associated with PRP). An additional 23 reviews associated with PRP therapy either described pain during the

procedure or complained about its ineffectiveness (16), resulting in a delay in receiving proper medical treatment, such as surgery or physical therapy (10).

Next steps for FDA and other stakeholders

This research aimed to systematically collect and analyze AE data about unapproved SCRIs from multiple sources and better characterize the risks of these interventions. Although it's impossible to know the true rate of AEs associated with unapproved SCRIs, it's clear from the cases that are reported that these procedures can cause serious and sometimes life-threatening harm, and that more should be done to protect patients.

These findings also highlight the need for strong FDA oversight, and help to underscore why the agency needs to fully implement its regulatory framework and significantly expand the scope of its enforcement activities against all businesses offering unapproved and unproven SCRIs. Hundreds of businesses continue to operate under the agency's current policy of enforcement discretion, which was due to end in November 2020 but was extended to May 2021 due to the coronavirus pandemic. FDA announced in April 2021 that it would not extend this period any further, which is an encouraging development. It should now move quickly to enforce its regulations and bring the industry into compliance. The agency also needs adequate resources to do so.

Because it is difficult to know the extent of the problems occurring from these procedures, FDA should work to improve reporting systems and consider alternative approaches to identifying adverse events. It should encourage more reporting of adverse events through MedWatch, the database it uses to collect such reports; such improved AE reporting will help the agency better target its limited resources toward those businesses engaging in risky practices that may be harming patients. The agency should consider updating the instructions for patients in the MedWatch online reporting system to facilitate easier and more complete reporting of AEs related to unapproved SCRIs—such as information on where patients receive these interventions. Targeted public awareness campaigns could also help boost knowledge of FAERS and encourage broader use of it.

As previously mentioned, FDA has acknowledged that, despite variability in the quality of reports submitted, social media monitoring for AEs has the potential for faster safety signal detection.[30] The agency should consider analyzing social media sites for AEs associated with unapproved SCRIs. Given the widespread underreporting of these AEs, data collected from online sources could potentially supplement data from traditional sources, such as FAERS, to create a more thorough understanding of the scope and type of harm associated with these products. A 2018 FDA white paper describes the agency's plans to adopt new and innovative data mining methods or tools to monitor social media data for signals of AEs associated with FDA-regulated medical products.[31] Tracking potential safety signals in this manner could provide new opportunities for the agency to gather more real-world evidence of harm.

Other Stakeholders Can Help Safeguard Public Health

Alongside enforcement by FDA, federal and state policymakers, medical licensing authorities, and other stakeholders can take steps to help protect patients from unapproved products. Opportunities include legal action by federal and state agencies, such as the Federal Trade Commission and state attorneys general offices; state legislation to tighten regulation of clinics; better oversight by state medical boards; and individual private action against clinics. Scientific and professional organizations can also take steps to improve both patient and provider education about unapproved SCRIs and increase awareness about their risks. Finally, companies that manage online platforms could do more to limit the spread of misinformation, and prevent clinics from advertising their products on their platforms.

Conclusion

As FDA's enforcement discretion period draws to a close, the agency should maintain pressure on businesses offering unapproved products and ensure that patients are protected from SCRIs that have caused harm or have the potential to cause harm. Encouraging patients and clinicians to report AEs and devising effective strategies to collect more real-world evidence of harm can help the agency in its efforts to curb the growth of this unregulated market and ensure that the regenerative medicine field develops into one that clinicians and patients can trust and safely access.

Appendix A

Definitions of key terms

Adverse event: Any undesirable experience associated with the use of a medical product in a patient.

Serious adverse event: An adverse event is considered serious when the patient outcome is death or involves a life-threatening incident or hospitalization, causes disability or permanent damage or required intervention to prevent permanent impairment or damage, causes congenital anomaly/birth defect, or other serious important medical events that may require medical or surgical intervention to prevent one of the other outcomes (e.g., serious allergic reactions, seizures, or convulsions).

Regenerative medicine: This term covers a range of treatments intended to repair or replace damaged cells, tissues, or organs. These treatments include cell therapies, bioengineered tissue products, and gene therapies.[32]

Unproven therapies/interventions: Therapies or interventions that lack definitive, high-quality clinical evidence of safety and efficacy. The phrases "unproven therapies" and "unapproved therapies" are often used interchangeably. However, the focus of Pew's research is to highlight adverse events associated with "unapproved therapies" that may also be unproven.

Unapproved therapies/interventions: Therapies or interventions that have not been reviewed by FDA for safety, effectiveness, or quality or potency.

Appendix B

Literature Review Methodology

Pew analyzed peer-reviewed publications in academic journals and gray literature, including government publications, media reports, case histories, and legal documents, to identify AEs associated with unapproved SCRIs from November 2019 through January 2021 to update a previously published list of AEs.

Pew staff conducted nonsystematic searches using the keywords "stem cell," "regenerative treatment/therapy," "exosome," and "platelet rich plasma (PRP) treatments," typically in combination with "adverse event," "complication," "infection," "inflammation," "swelling," "pain," "cancer," "lesion," or "tumor." Using these keywords, Pew searched available publications on the web, including databases such as Google Scholar, PubMed, and Ebsco, for articles published in major medical journals; the Centers for Disease Control and Prevention's *Morbidity and Mortality Weekly Report*; FDA website; and major newspaper websites, including *The New York Times* and *The Washington Post*, as well as local newspapers in regions with large numbers of stem cell clinics, such as Florida, Texas, and California.

Articles that directly referred to an AE in the title were reviewed for any discussion of AE outside of clinical trials or approved therapies. Articles with general discussions of the use of these treatments were examined for discussion of AEs, as were their references. AEs appearing to be associated with an unapproved SCRI were included in Table B.1.

Limitations: The number of AEs documented in Table B.1 likely does not reflect the true number of reported AEs associated with unapproved SCRIs. This result is because our study was not designed to be a systematic review and therefore may not have captured all available publications on the web. Additionally, many cases of AEs reported in scientific publications and the media do not include complete or necessary information to draw a correlation between the type of intervention and the AE. Therefore, cases that did not meet the minimum conditions for the event to be considered a confirmed case of AE caused by an unapproved SCRI were excluded from the final count.

Table B.1

Adverse Events Associated With Unapproved Stem Cell and Regenerative Interventions

Year	Reported cases	Reported deaths	Patient country of origin	Location of intervention	Condition being treated	Alleged intervention	Administration route	Reported adverse event	Notes
2004[a]	5	-	Not reported	China	Spinal cord injury	Olfactory ensheathing fetal cells	Spinal injection	Meningitis, cerebrospinal fluid pleocytosis[b], gastrointestinal bleeding, pneumonia, fever, headache[c]	-
2005[d]	1	-	Israel	Russia	Ataxia telangiectasia[e]	Fetal neural stem cells (SCs)	Direct injection into brain, spine	Tumors in brain, spine originating from donor fetal neural SCs	-
2006[f]	1	-	Not reported	Egypt	Acute inflammation of spinal cord segments	Mesenchymal SCs (MSCs), embryonic, and fetal neural SCs	Spinal injection	Acute inflammation of brain, spinal cord that damaged myelin sheath protecting nerve fibers	-
2006[g]	1	-	Thailand	Thailand	Kidney inflammation due to lupus	Hematopoietic SCs	Injection into renal regions (no ultrasound guidance)	Multiple lesions in kidney, liver, adrenal gland	-
2009[h]	1	-	U.S.	U.S. (California)	Face-lift	Adipose-derived stromal cells	Injections around eye	Bonelike growth in eyelid	-

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Year	Reported cases	Reported deaths	Patient country of origin	Location of intervention	Condition being treated	Alleged intervention	Administration route	Reported adverse event	Notes
2010[i]	3	2	Italy; Azerbaijan; U.S. (Ohio)	Germany	Unspecified neurological conditions	Bone marrow-derived SCs	Direct injection into brain	Brain hemorrhage; death	Although the treating clinic in Germany was shut down, provider subsequently opened a similar clinic in Lebanon
2010-12[j]	2	2	U.S. (Indiana, Florida)	U.S. (Florida)	Leg numbness, difficulty walking after cancer treatment; pulmonary hypertension	Grossly filtered bone marrow aspirate; adipose-derived stromal cells	Different methods of administration	Stroke; cardiac arrest; death in both cases	Provider was subsequently barred from practicing medicine in Florida but continues to treat patients in the Dominican Republic[k]
2011[l]	1	1	U.S.	U.S. (Nevada)	Spontaneous widening of bronchi (for unknown reasons)	Nonspecified SC intervention	Unknown	Death	-
2012-14[m]	At least 10	At least 7	Several countries, including U.S. (Illinois)	Italy; Spain; Russia; U.K.; Sweden; U.S.	Various conditions affecting trachea function	SC-coated plastic or cadaveric trachea	Surgical transplant	Pulmonary embolism, postoperative infection, transplant failure; death	Patients were treated by the same surgeon, who was found to have engaged in numerous instances of scientific misconduct

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Year	Reported cases	Reported deaths	Patient country of origin	Location of intervention	Condition being treated	Alleged intervention	Administration route	Reported adverse event	Notes
2012-15[n]	242	-	Not reported	U.S.	Osteoarthritis	Autologous stem cells (not specified); donor stem cells (not specified); or both	Direct injection into knee, hip, shoulder	Tumor (6); infection (14); chronic effusion (42); vasovagal[o], syncope[p], arrhythmia, septicemia (41); worsening pain and function (39); rash, injection site reaction (18); clear or bloody effusion (17); herpes zoster, viral syndrome (34); development of new allergies (31)	82 patients were hospitalized; two patients died shortly after receiving injections, but their death certificates did not list stem cell injections as the cause and no autopsy was done in either case
2012[q]	1	-	Not reported	Japan	Chronic kidney failure	Adipose-derived MSCs	Intravenous infusion	Unspecified neurological event	-
2013 (or earlier)[r]	1	-	Not reported	Not reported	Stroke, macular degeneration, osteoarthritis, and depression	Stem cells (not specified)	Spinal injection	Spinal inflammation and damage	-
2013[s]	3	-	Not reported	Not reported	Herniated intervertebral disc	Adipose-derived MSCs	Intravenous infusion	Pulmonary embolism	-
2013[t]	1	1	U.S.	Florida	Chronic obstructive pulmonary disease (COPD)	Adipose-derived MSCs	Intravenous infusion	Death	-

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Year	Reported cases	Reported deaths	Patient country of origin	Location of intervention	Condition being treated	Alleged intervention	Administration route	Reported adverse event	Notes
2013[u]	1	1	Australia	Australia	Dementia	Autologous adipose stromal cells	Unknown	Uncontrolled blood loss during liposuction procedure, shock, death	Patient was on anticoagulant medication, which caused uncontrolled bleeding
2013[v]	2	-	Unknown	U.S. (North Carolina)	Osteoarthritis	Autologous platelet-rich plasma and a human placental tissue-derived allograft product	Intra-articular injections	*Staphylococcus aureus*-dependent septic arthritis	-
2014[w]	6	-	Canada; U.S. (New York)	Germany	Not reported	Live cell therapy/fresh cell therapy[x]	Intramuscular injections	Q fever	-
2013-14[y]	1	1	Australia	Russia	Stiff person syndrome	Bone marrow-derived SCs	Unknown	Heart attack	-
2016-17[z]	1	-	U.S.	Dominican Republic	Retinitis pigmentosa	Autologous adipose tissue-derived stem cell injections (AASCIs)	Injected into eye	Retinal detachment and proliferative vitreoretinopathy	Male patient

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Year	Reported cases	Reported deaths	Patient country of origin	Location of intervention	Condition being treated	Alleged intervention	Administration route	Reported adverse event	Notes
2016-17[aa]	At least 5	-	Not reported	U.S. (California, other locations not specified)	Various conditions, including COPD	Adipose-derived stromal cells	Infusion; direct injection into brain, knee, and eyes; inhalation	Loss of consciousness, headaches, confusion, inability to walk, infection, retinal detachment, hospitalization	These adverse events occurred at several affiliated clinics
2018[ab]	At least 13	-	U.S.	U.S. (Texas, Florida, Arizona, Kansas)	Various conditions, including joint and back pain	Umbilical cord blood-derived SCs	Injection or infusion	Acute bacterial infections of spine, bones, joints; abscesses; hospitalization	One news source identified 17 affected patients over 2018-19[ac]
2018[ad]	1	-	Not reported	U.S. (Florida)	Arthritis	Not reported	Injection	Vomiting, hospitalization, coma	-
2018[ae]	1	-	Not reported	Ukraine	Type I diabetes with end-stage kidney failure; cardiovascular disease	Nonautologous stem cells of unknown origin (supposedly embryonic)	Injection into peripheral vein	Jaundice and necrotizing skin ulcers, hepatitis, and deteriorating heart failure beginning six months after treatment	Authors state: "Although the patient had a number of pre-existing diseases, we were not able to explain and meaningfully connect his new-onset health problems and medical findings with other pre-existent conditions...;" patient later died, although not clear if from stem cell treatment

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Year	Reported cases	Reported deaths	Patient country of origin	Location of intervention	Condition being treated	Alleged intervention	Administration route	Reported adverse event	Notes
2019[af]	At least 1	-	U.S.	U.S. (Nebraska)	Unknown	Exosome products derived from placenta	Injection or inhalation	Bacterial infection, sepsis	News reports stated that fewer than five patients became seriously ill
Not reported[ag]	1	-	U.S.	Costa Rica	Multiple sclerosis	Allogeneic cord blood MSCs and autologous adipose-derived stromal cells	Spinal injection, intravenous infusion	Catastrophic demyelinating encephalomyelitis[ah]	-
Not reported[ai]	1	-	U.S.	China; Argentina; Mexico	Ischemic stroke	MSCs, embryonic, fetal neural SCs	Spinal injections	Lesions in spinal cord and surrounding membranes causing lower-back pain, paraplegia, urinary incontinence	-
Not reported[aj]	1	-	U.S.	U.S.	Face-lift	Fatty aspirate from abdominal wall in a procedure called "stem cell face-lift"	Facial injection	Necrotizing[ak] facial ulcerations	-
Not reported[al]	2	-	U.S., Canada[am]	Portugal[an]	Spinal fracture, associated spinal cord injury	Olfactory mucosal cells	Intraspinal transplantation	Spinal mass consisting of large amounts of mucus	-

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Year	Reported cases	Reported deaths	Patient country of origin	Location of intervention	Condition being treated	Alleged intervention	Administration route	Reported adverse event	Notes
Not reported[ao]	3	-	U.S.	U.S. (Florida)	Age-related macular degeneration	Adipose-derived stromal cells	Eye injections	Hemorrhage and possible retinal detachment in both eyes; one year after injection, patients were either completely blind in both eyes or had minimal vision remaining in one eye	-
Not reported[ap]	1	1	Not reported	Not reported	Heart disease	Autologous "precursor" cells	Direct injection into heart	Ventricular fibrillation; unable to undergo heart transplantation; death	-
Not reported[aq]	1	-	U.K.	Netherlands	Unknown	Umbilical cord blood-derived SCs	Unknown	Serious acute allergic reaction, hospitalization	-
Not reported[ar]	2	2	Not reported	Japan, China	Different conditions	Adipose-derived stromal cells	Unknown	Pulmonary embolism; death	-
Not reported[as]	2	2	China	China	Disabilities from a minor stroke; late-stage liver cirrhosis	Allogenic SCs (not specified)	Spinal, intramuscular injections	Death	Patient with late-stage liver cirrhosis died as a result of being taken off hepatitis B medication in order to undergo stem cell treatment

Continued on next page.

Year	Reported cases	Reported deaths	Patient country of origin	Location of intervention	Condition being treated	Alleged intervention	Administration route	Reported adverse event	Notes
Not reported[at]	1	-	Russia	Russia	Aging	Human embryonic SCs	Skin injection	Pea-size facial tumors	-
Not reported[au]	1	-	Not reported	Not reported	Enlarged prostate	Blood-derived SCs	Intravenous infusion	Infection; vomiting; high-grade fever	Hospital treating AE symptoms located in Mexico; location of facility administering stem cells not disclosed
Not reported[av]	1	-	Not reported	U.K.	Not reported	Adipose-derived MSCs	Injection into the jaw	Blindness in one eye	-
Not reported[aw]	2	-	Italy	China	Amyotrophic lateral sclerosis (ALS)	Fetal SCs	Direct injection into brain	Scar tissue and inflammation in the brain	Adverse events discovered in autopsy; death was from progression of the disease, not attributable to SC treatment
Not reported[ax]	1	-	Not reported	U.S. (Georgia)	Exudative age-related macular degeneration	Adipose-derived "stem cells"	Injection into both eyes	Retinal detachment in both eyes	Reporting physician could not confirm injections contained actual stem cells
Not reported[ay]	1	-	Not reported	U.S.	Arthritis	Adipose-derived and placental SCs	Injection in knee	Arthritic pain from infection and/or intense inflammatory response leading to hospitalization and surgery	-

Continued on next page.

Year	Reported cases	Reported deaths	Patient country of origin	Location of intervention	Condition being treated	Alleged intervention	Administration route	Reported adverse event	Notes
Not reported[az]	1	-	Nicaragua	Dominican Republic	Retinitis pigmentosa associated with Usher syndrome	Autologous adipose tissue-derived stem cell injection (AASCI)	Injection in eye	Retinal detachment; glaucoma; pain	-
Not reported[ba]	1	-	Not reported	Not reported	Retinitis pigmentosa	Bone marrow-derived SCs	Injection into eye	Severe vision loss	-
Not reported[bb]	1	-	U.S.	Thailand	Charcot-Marie-Tooth disease	Fetal SCs	Intravenous infusion	Multiple lesions over the body caused by bacterial infection; fever	-
Not reported[bc]	1	-	Not reported	Not reported	Retinitis pigmentosa	Autologous-derived SCs	Injection into eye	Scar tissue on retina	-
Not reported[bd]	1	-	Not reported	Russia	Parkinson's disease	SCs of unknown source	Spinal injection	Spinal tumors, lesions	-
Not reported[be]	1	-	Not reported	Russia	Weakness and fatigue	SCs of unknown source	Spinal injection	Growths/lesions on spine; progressive lower extremity weakness and urinary incontinence	-
Not reported[bf]	1	-	Not reported	Not reported	Stargardt's macular dystrophy	Autologous bone marrow-derived SCs	Injection into eye	Retinal detachment	-

Continued on next page.

Year	Reported cases	Reported deaths	Patient country of origin	Location of intervention	Condition being treated	Alleged intervention	Administration route	Reported adverse event	Notes
Not reported[bg]	1	-	Egypt	Egypt	Acute transverse myelitis	Cord-blood-derived SCs	Spinal injection	Severe inflammation of the brain and spinal cord	-
Not reported[bh]	1	-	Not reported	Iran	Diabetes	Fetal SCs	Intravenous injection	Brain tumor	Biopsy found tumor cells related to transplanted stem cells
Total	**At least 334**	**At least 20**							

Note: All AEs included in this table are associated with unapproved regenerative medicine products, although the regulatory status for specific products cannot be individually verified—some SCRIs included in this study may not require FDA approval to be administered to patients.

a B.H. Dobkin, A. Curt, and J. Guest, "Cellular Transplants in China: Observational Study From the Largest Human Experiment in Chronic Spinal Cord Injury," *Neurorehabilitation Neural Repair* 20, no. 1 (2006): 5-13, http://dx.doi.org/10.1177/1545968305284675.

b Pelocytosis means increased cell count.

c Reaction to antibodies in the recipient blood.

d N. Amariglio et al., "Donor-Derived Brain Tumor Following Neural Stem Cell Transplantation in an Ataxia Telangiectasia Patient," *PLOS Medicine* 6, no. 2 (2009): e1000029, https://www.ncbi.nlm.nih.gov/pubmed/19226183.

e Ibid. Ataxia telangiectasia is a rare disorder characterized by degeneration of the brain region that controls movement and speech.

f N.A. Kishk, N.T. Abokrysha, and H. Gabr, "Possible Induction of Acute Disseminated Encephalomyelitis (ADEM)-Like Demyelinating Illness by Intrathecal Mesenchymal Stem Cell Injection," *Journal of Clinical Neuroscience* 20 (2013): 312-13, https://www.sciencedirect.com/science/article/pii/S096758681200330X.

g D. Thirabanjasak et al., "Angiomyeloproliferative Lesions Following Autologous Stem Cell Therapy," *Journal of the American Society of Nephrology* 21, no. 7 (2010): 1218-22, https://doi.org/10.1681/ASN.2009111156.

h F. Jabr, "In the Flesh: The Embedded Dangers of Untested Stem Cell Cosmetics," *Scientific American,* Dec. 17, 2012, https://www.scientificamerican.com/article/stem-cell-cosmetics.

i C. MacGregor, A. Petersen, and M. Munsie, "Stem Cell Tourism: Selling Hope Through Unproven Stem Cell Treatments—Lessons From the X-Cell Center Controversy," *EuroStemCell*, accessed Feb. 22, 2019, https://www.eurostemcell.org/stem-cell-tourism-selling-hope-through-unproven-stem-cell-treatments-lessons-x-cell-center; R. Mendick, "Stem Cell Clinic That 'Preyed on the Vulnerable,'" *The Telegraph*, April 8, 2012, https://www.telegraph.co.uk/news/health/news/9192157/Stem-cell-clinic-that-preyed-on-the-vulnerable.html.

j "Bonita Springs Stem Cell Doctor Grekos Loses Two More Rounds in Court," *Naples Daily News,* Sept. 1, 2014, http://archive.naplesnews.com/news/local/bonita-springs-stem-cell-doctor-grekos-loses-two-more-rounds-in-court-ep-589350147-337085341.html.

k Ibid.; C. Gentry and the Associated Press, "FDA: Florida Stem Cell Clinic Violates Law," *Health News Florida*, Feb. 8, 2016, http://health.wusf.usf.edu/post/fda-florida-stem-cell-clinic-violates-law.

l L. Turner, "Medical Malpractice Lawsuit Following Death for Stem Cell Recipient," *Health in the Global Village*, Nov. 27, 2012,, http://www.healthintheglobalvillage.com/medical-malpractice-lawsuit-following-death-of-stem-cell-recipient.

m W. Kremer, "Paolo Macchiarini: A Surgeon's Downfall," BBC, Sept. 10, 2016, https://www.bbc.com/news/magazine-37311038; J. Rasko and C. Power, "Dr Con Man: The Rise and Fall of a Celebrity Scientist Who Fooled Almost Everyone," *The Guardian*, Sept. 1, 2017, https://www.theguardian.com/science/2017/sep/01/paolo-macchiarini-scientist-surgeon-rise-and-fall.

n J. W. Pritchett, "The Debit Side of Stem Cell Joint Injections: A Prospective Cohort Study," *Current Orthopaedic Practice* 32, no. 2 (2021): 1-6, https://journals.lww.com/c-orthopaedicpractice/Abstract/2021/03000/The_debit_side_of_stem_cell_joint_injections__a.3.aspx. Most reports in this table are drawn from single case reports. However, this data is drawn from a cohort study that identified long-term complications from unapproved stem cell injections using data collected from medical records held by a single insurer.

o A temporary fall in blood pressure caused by overactivity of the vagus nerve.

p Temporary loss of consciousness caused by a fall in blood pressure.

q T. Ikka et al., "Recent Court Ruling in Japan Exemplifies Another Layer of Regulation for Regenerative Therapy," *Cell Stem Cell* 17, no. 5 (2015): 507-08, https://doi.org/10.1016/j.stem.2015.10.008.

r R. Hurst et al., "Inflammatory Hypertrophic Cauda Equina Following Intrathecal Neural Stem Cell Injection," *Muscle and Nerve*, 48, no. 5 (2013): 831-835, https://doi.org/10.1002/mus.23920.

s J.W. Jung, "Familial Occurrence of Pulmonary Embolism After Intravenous, Adipose Tissue-Derived Stem Cell Therapy," *Yonsei Medical Journal* 54, no. 5 (2013): 1293-96, http://dx.doi.org/10.3349/ymj.2013.54.5.1293.

t S. Hobbs, "Florida Takes Away License of Doctor With Troubled Past," *The Sun Sentinel*, Nov. 17, 2017, https://www.sun-sentinel.com/health/fl-doctor-discipline-kantzler-20171117-story.html; Florida Department of Health, Amended Administrative Complaint, Department of Health v. Mark G. Kantzler, Case No. 2013-10663 (filed July 13, 2015).

u Coroners Court New South Wales, "Inquest Into the Death of Sheila Drysdale" (2016), http://www.coroners.justice.nsw.gov.au/Documents/Findings%20Drysdale.pdf.

v S. K. Rhea et al., "Cluster of *Staphylococcus Aureus* Septic Arthritis Cases After Intra-Articular Injection of Autologous Platelet-Rich Plasma—North Carolina 2013," Proceedings of Epidemic Intelligence Services Annual Conference, 2014, https://www.cdc.gov/eis/downloads/2014-EIS-Conference.pdf.

w M.P. Robyn et al., "Q Fever Outbreak Among Travelers to Germany Who Received Live Cell Therapy—United States and Canada, 2014," *Morbidity and Mortality Weekly Report,* Oct. 2, 2015, https://www.cdc.gov/mmwr/preview/mmwrhtml/mm6438a3.htm.

x Live cell therapy, or fresh cell therapy, is the practice of injecting processed cells from organs or fetuses of nonhuman

animals into human recipients.

y A. Rollins, "Beware Stem Cell Doctors Trading on Hope," *Australian Medicine* 26, no. 15 (2014): 24, https://search.informit.org/doi/abs/10.3316/ielapa.561644836270530; M. Davey, "Stem Cell Therapies: Medical Experts Call for Strict International Rules," *The Guardian*, July 6, 2017, https://www.theguardian.com/science/2017/jul/06/stem-cell-therapies-medical-experts-call-for-strict-international-rules; N. Bodchenski and A. Brown, "Brisbane Woman Dies Undergoing Russian Stem Cell Treatment," *The Queensland Times*, July 28, 2014, https://www.qt.com.au/news/brisbane-woman-dies-undergoing-russian-stem-cell-t/2331189/.

z A. J. Rong et al., "Vision Loss Secondary to Autologous Adipose Stem Cell Injections: A Rising Problem," *JAMA Ophthalmology* 136, no. 1 (2018), https://jamanetwork.com/journals/jamaophthalmology/article-abstract/2664084.

aa United States v. California Stem Cell Treatment Center Inc., Cell Surgical Network Corp., Elliot B. Lander, M.D., and Mark Berman, M.D., No. 5:18-CV-1005 (U.S. District Court for the Central District of California, May 9, 2018), https://www.courtlistener.com/docket/6550705/1/united-states-v-california-stem-cell-treatment-center-inc.

ab K.M. Perkins et al., "Notes From the Field: Infections After Receipt of Bacterially Contaminated Umbilical Cord Blood-Derived Stem Cell Products for Other Than Hematopoietic or Immunologic Reconstitution—United States, 2018," *Morbidity and Mortality Weekly Report,* Dec. 21, 2018, https://www.cdc.gov/mmwr/volumes/67/wr/mm6750a5.htm?s_cid=mm6750a5_w#T1_down; W. Wan and L. McGinley, "'Miraculous' Stem Cell Therapy Has Sickened People in Five States," *The Washington Post*, Feb. 27, 2019, https://www.washingtonpost.com/national/health-science/miraculous-stem-cell-therapy-has-sickened-people-in-five-states/2019/02/26/c04b23a4-3539-11e9-854a-7a14d7fec96a_story.html; Andy Marso, "KC Woman Got *E. coli* Infection From Stem Cell Treatment at JoCo Clinic, Lawsuit Says," *The Kansas City Star*, Aug. 23, 2019, https://www.kansascity.com/news/business/health-care/article234306097.html.

ac Wan and McGinley, "'Miraculous' Stem Cell Therapy."

ad L. McGinley and W. Wan, "This Clinic's Experimental Stem Cell Treatment Blinded Patients. Four Years Later, the Government Is Still Trying to Shut It Down," *The Washington Post,* April 3, 2019, https://www.washingtonpost.com/national/health-science/this-clinics-experimental-stem-cell-treatment-blinded-patients-four-years-later-the-government-is-still-trying-to-shut-it-down/2019/04/03/432d6d04-ff2f-11e8-83c0-b06139e540e5_story.html.

ae Ž. Večerić-Haler et al., "Multiorgan Failure With Fatal Outcome After Stem Cell Tourism," *European Journal of Medical Research* 26, no. 5 (2021), https://doi.org/10.1186/s40001-020-00477-4.

af Nebraska Department of Health and Human Services, Health Alert Network Advisory, "Risk Associated With Unapproved Products Derived From Stem Cells, Placenta and Umbilical Cord Blood," Dec. 6, 2019, http://dhhs.ne.gov/han%20Documents/ADVISORY12062019.pdf; K. Fiore, "Serious Illnesses in Nebraska Tied to Exosome Therapy," MedPage Today, Dec. 16, 2019, https://www.medpagetoday.com/infectiousdisease/publichealth/83928.

ag Y.J. Alderazi, S.W. Coons, and K. Chapman, "Catastrophic Demyelinating Encephalomyelitis After Intrathecal and Intravenous Stem Cell Transplantation in a Patient With Multiple Sclerosis," *Journal of Child Neurology* 27, no. 5 (2012): 632-35, https://www.ncbi.nlm.nih.gov/pubmed/22156784.

ah Demyelinating encephalomyelitis is a widespread attack of inflammation in the spinal cord and brain that damages the protective covering of nerve fibers. See National Institutes of Neurological Disorders and Stroke, "Acute Disseminated Encephalomyelitis Information Page," accessed Dec. 11, 2018, https://www.ninds.nih.gov/Disorders/All-Disorders/Acute-Disseminated-Encephalomyelitis-Information-Page.

ai A.L. Berkowitz et al., "Glioproliferative Lesion of the Spinal Cord as a Complication of 'Stem-Cell Tourism,'" *New England Journal of Medicine* 375 (2016): 196-8, http://dx.doi.org/10.1056/NEJMc1600188.

aj M. Dobke et al., "Necrotizing Metachronous Facial Ulcerations After 'Stem Cell Face Lift,'" *Annals of Plastic Surgery* 70, no. 4 (2013): 392-96, http://dx.doi.org/10.1097/SAP.0b013e31827a7d7d.

ak Necrosis is the death of most or all of the cells in a tissue or organ.

al B.J. Dlouhy et al., "Autograft-Derived Spinal Cord Mass Following Olfactory Mucosal Cell Transplantation in a Spinal Cord Injury Patient," *Journal of Neurosurgery Spine* 21, no. 4 (2014): 618-22, https://doi.org/10.3171/2014.5.SPINE13992.

am C. F. Woodworth et al., "Intramedullary Cervical Spinal Mass After Stem Cell Transplantation Using an Olfactory Mucosal Cell Autograft," *CMAJ* 191, no. 27 (July 8, 2019): E761 https://www.cmaj.ca/content/191/27/E761.

an C. Wilson, "Stem Cell Treatment Causes Nasal Growth in Woman's Back," *New Scientist,* July 8, 2014, https://www.newscientist.com/article/dn25859-stem-cell-treatment-causes-nasal-growth-in-womans-back/#.U8nhAoBdWdw.

ao A.E. Kuriyan et al., "Vision Loss After Intravitreal Injection of Autologous 'Stem Cells' for AMD," *New England Journal of Medicine* 376 (2017): 1047-53, http://dx.doi.org/10.1056/NEJMoa1609583.

ap P. Pytel et al., "Ventricular Fibrillation Following Autologous Intramyocardial Cell Therapy for Inherited Cardiomyopathy," *Cardiovascular Pathology* 19, no. 2 (2010): e33-36, https://doi.org/10.1016/j.carpath.2008.09.004.

aq T. Sheldon, "Dutch Clinic Is Ordered to Stop Giving Stem Cell Therapy," *The BMJ* 333, no. 7572 (2006): 770,

https://doi.org/10.1136/bmj.333.7572.770-a.

ar J. Lee, "South Korean Company Cleared in Deaths Following Stem Cell Therapy," CNN, Dec. 14, 2010, http://edition.cnn.com/2010/WORLD/asiapcf/12/14/south.korea.stem.cell/index.html.

as T.E. Lyn, "China 'Stem Cell Therapies' Offer Heartbreak for Many," Reuters, Sept. 21, 2011, https://www.reuters.com/article/us-stemcell-scams/china-stem-cell-therapies-offer-heartbreak-for-many-idUSTRE78K18120110921.

at "Stem Cell Rip-Off," *Newsweek*, Nov. 7, 2004, http://www.newsweek.com/stem-cell-rip-124481.

au A. Olmedo-Reneaum et al., "Rogue 'Stem Cell Clinic' Leads to *Mycobacterium abscessus* Infection," *The Lancet* 393 (March 2, 2019): 918 https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(19)30299-5/fulltext.

av L. Curwen, "The Risks Behind the Hype of Stem-Cell Treatments," BBC Radio 4, Jan. 7, 2020, https://www.bbc.com/news/health-51006333; *Care Quality Commission, Inspection Report: The Regenerative Clinic* (2019) https://www.cqc.org.uk/location/1-5447933570/reports.

aw M. T. Giordana et al., "Neuropathology of Olfactory Ensheathing Cell Transplantation into the Brain of Two Amyotrophic Lateral Sclerosis (ALS) Patients," *Brain Pathology* 20 (2010): 730-737, https://pubmed.ncbi.nlm.nih.gov/19919605/.

ax S. S. Saraf et al., "Bilateral Retinal Detachments After Intravitreal Injection of Adipose-Derived 'Stem Cells' in a Patient With Exudative Macular Degeneration," *Ophthalmic Surgery, Lasers and Imaging Retina* 48, no. 9 (2017): 772-775, https://doi.org/10.3928/23258160-20170829-16.

ay J. Taliaferro et al., "Cash-Based Stem-Cell Clinics, The Modern Day Snake Oil Salesman? A Report of Two Cases of Patients Harmed by Intra-Articular Stem Cell Injections," *JBJS Case Connector* 9, no. 4 (October-December 2019): e0363, http://dx.doi.org/10.2106/JBJS.CC.19.00363.

az K. T. Khine et al., "Chronic Retinal Detachment and Neovascular Glaucoma After Intravitreal Stem Cell Injection for Usher Syndrome," *American Journal of Ophthalmology Case Reports* 18 (2020): 100647, https://doi.org/10.1016/j.ajoc.2020.100647.

ba K. Boudreault et al., "Complication of Autologous Stem Cell Transplantation in Retinitis Pigmentosa," *JAMA Ophthalmology* 134, no. 6 (June 2016), https://doi.org/10.1001/jamaophthalmol.2016.0803.

bb B. A. Kendall et al., "Disseminated Mycobacterial Infection After International Medical Tourism," *Open Forum Infectious Diseases, OFID Brief Report* 2, no. 2 (2015), https://doi.org/10.1093/ofid/ofv054.

bc J. Y. Kim et al., "Epiretinal Membrane Formation After Intravitreal Autologous Stem Cell Implantation in a Retinitis Pigmentosa Patient," *Retinal Cases & Brief Reports* 11, no. 3: 227–231, (July 2017), https://doi.org/10.1097/icb.0000000000000327.

bd R. Rahangdale et al., "Glioneuronal Growth of Spinal Cord Following Intrathecal Stem Cell Transplant," *Neurology* 90, no. 15 Supplement (April 10, 2018), http://n.neurology.org/content/90/15_Supplement/P4.164.

be A. A. Madhavan et al., "Polyclonal Lymphocytic Infiltrate With Arachnoiditis Resulting From Intrathecal Stem Cell Transplantation," *The Neuroradiology Journal* 3, no. 2(Feb. 3, 2020): 174-178, https://doi.org/10.1177/1971400920902451.

bf E. H. Leung et al., "Retinal Detachment After Subretinal Stem Cell Transplantation," *Ophthalmic Surgery, Lasers and Imaging Retina* 47, no. 6 (2016): 600-601 https://doi.org/10.3928/23258160-20160601-16.

bg G. Bauer et al., "Concise Review: A Comprehensive Analysis of Reported Adverse Events in Patients Receiving Unproven Stem Cell-Based Interventions," *Stem Cells Translational Medicine* 7, no. 9 (2018): 1–10, www.StemCellsTM.com; H. Butzkueven, "Commentary on 'Possible Induction of Acute Disseminated Encephalomyelitis (ADEM)-Like demyelinating Illness by Intrathecal Mesenchymal Stem Cell Injection,'" *Journal of Clinical Neuroscience* 20 (2013): 312–31, https://doi.org/10.1016/j.jocn.2012.06.003.

bh E. Nasli-Esfahani et al., "Transitional Meningioma After Fetal Liver-Derived Cell Suspension Allotransplant," *Experimental and Clinical Transplantation* 15, no. 2 (2017):231-234, https://pubmed.ncbi.nlm.nih.gov/26788941/.

Appendix C

FAERS Review Methodology

Pew contracted with an external provider with expertise in pharmacovigilance platforms such as the FDA Adverse Event Reporting System (FAERS) to review the type and frequency of AEs reported into the database. The contractor reviewed FAERS data for the period November 1997-March 2020. Original datasets containing raw data were downloaded from FDA's website. A proprietary cleaning protocol was applied to enhance user understanding of the data, and the following keywords and combination of keywords were used to conduct a search of the database: "stem cell (or equivalent)," "umbilical," "hematopoietic," "progenitor," "marrow," "cord," "blood," "hESC-RPE (human embryonic stem cell-derived retinal pigment epithelial cells)," "HSC835" and "regen."

Through a series of identification and filtration methods, 19 complete, nonduplicative, voluntary reports that appeared to be related to unapproved SCRIs were identified. These unique case reports were further reviewed by a pediatric oncologist to confirm that they were likely to be associated with an unapproved SCRI. A further 14 case reports were removed after determining that that they were most likely to be associated with an approved product, resulting in a final count of five unique case reports that were reasonably expected to be associated with unapproved SCRIs. The flow chart below illustrates how this information was obtained.

Figure C.1

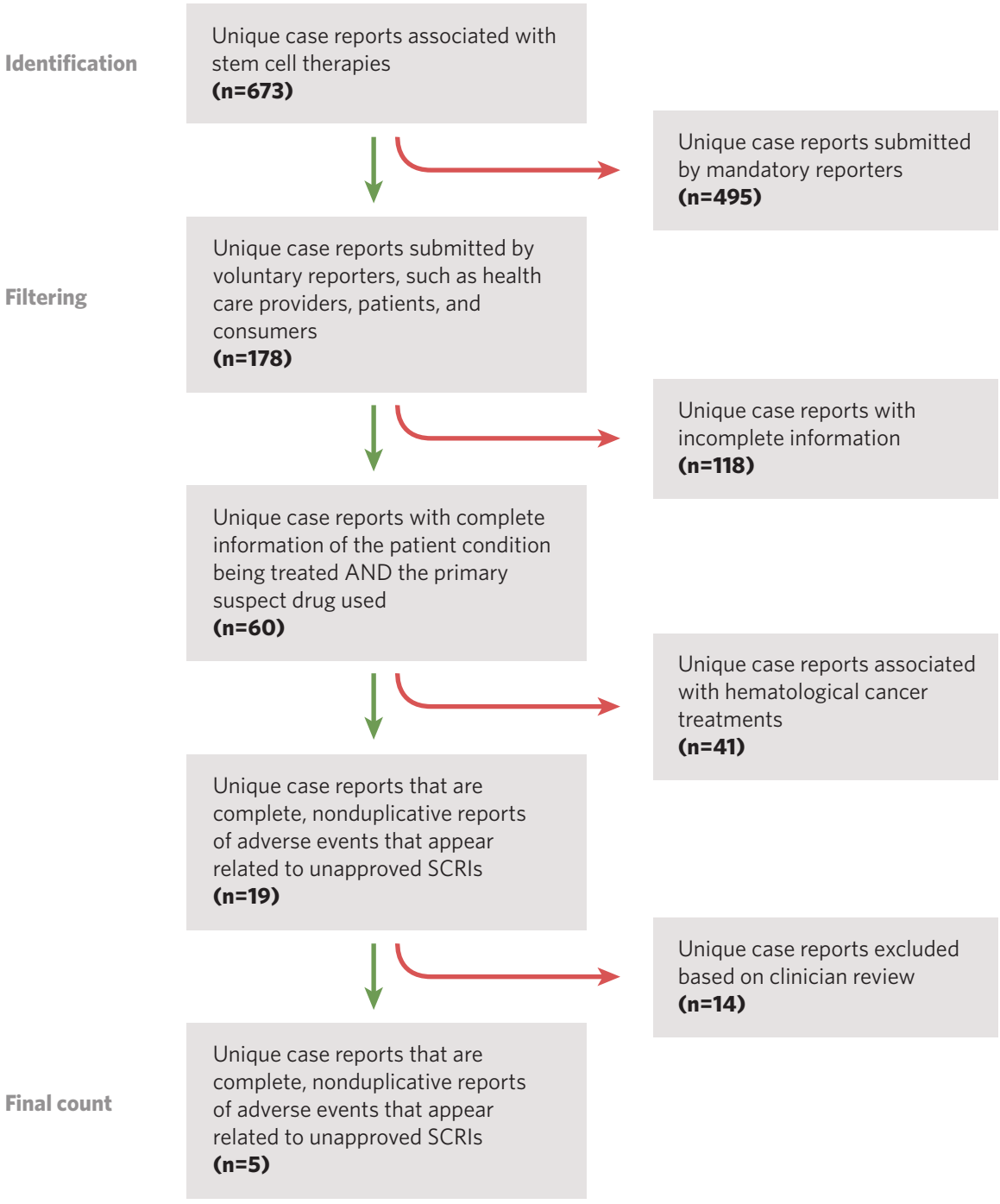
Identification
Unique case reports associated with stem cell therapies
(n=673)
Unique case reports submitted by mandatory reporters
(n=495)
Filtering
Unique case reports submitted by voluntary reporters, such as health care providers, patients, and consumers
(n=178)
Unique case reports with incomplete information
(n=118)
Unique case reports with complete information of the patient condition being treated AND the primary suspect drug used
(n=60)
Unique case reports associated with hematological cancer treatments
(n=41)
Unique case reports that are complete, nonduplicative reports of adverse events that appear related to unapproved SCRIs
(n=19)
Unique case reports excluded based on clinician review
(n=14)
Final count
Unique case reports that are complete, nonduplicative reports of adverse events that appear related to unapproved SCRIs
(n=5)

Table C.1

Adverse Event Reports Related to Unapproved SCRIs Identified in FAERS

Date FDA received report	Condition being treated	Type of stem cell therapy	Adverse event	Outcome	Age of patient
10/1/2007	Drug therapy	Cord blood cyropreservation laboratory autologous bone marrow stem cell		Medication error, product complaint, wrong technique in product usage process	Not reported
9/4/2008	Acute myocardial infarction	Autologous bone marrow stem cell	Burning sensation, coronary artery stenosis, myocardial infarction	Hospitalization	Not reported
3/3/2010	Autologous bone marrow transplantation therapy	Autologous bone marrow stem cell,* Presbyterian apheresis services†	Cytokine storm, multiple organ dysfunction syndrome, systemic inflammatory response syndrome	Death	64
10/16/2012	Cardiac failure	Autologous stem cells	Bradycardia, electrocardiogram change, electrocardiogram ST segment abnormal, hypoglycemia, hypotension, myocardial necrosis marker increased, nodal rhythm, post-procedural complication, post-procedural fever, procedural complication, procedural hypotension, tachycardia, ventricular fibrillation	Life-threatening	4
9/27/2018	Arthritis	Regen	Arthritis, bacterial infection	Hospitalization, life-threatening	58

* The original raw data in FAERS listed the treatment as: HPC-A W2333090900158-4 3.29E6 CD34+KG.

† Apheresis is a process that separates blood into its components and then selectively removes or redirects certain blood components back into the patient. Apheresis can be used to collect stem cells from blood.

Note: The original FAERS data reflected in this table may be incomplete and some of it may lack clarification; only the data for which enough information was available has been adapted to improve readability and comprehension.

Appendix D

Social Media Scrape Methodology

Pew contracted with an external data science research firm, Codex, to conduct an online scrape of patient reviews and testimonials posted on Facebook public pages, Yelp, and Google to gather AE data associated with unapproved SCRIs. Codex used the Selenium framework to automate a Chrome browser and turn web content into structured data.

Using a list of keywords provided by Pew, Codex used the Python programming language to develop a custom code to scrape reviews of businesses that market unapproved SCRIs. The names and locations of businesses were provided by Leigh Turner, a bioethics professor who tracks stem cell businesses and published an earlier version of the database in 2018. The list of therapy and AE keywords was adapted from Turner's paper on the U.S. direct-to-consumer stem cell market.[33]

Treatment/therapy keywords:

- Stem cell or regenerative therapy/treatment for: aging, arthritis, autism, COPD, diabetes, knees, pain, paralysis/paraplegia, erectile dysfunction, Alzheimer's, dementia, COVID-19/coronavirus.
- Adipose/fat/fat-derived stem cell therapy/treatment/adipose-derived stem cells (ADSC).
- Amyotrophic lateral sclerosis (ALS) stem cell therapy/treatment.
- Multiple sclerosis (MS) stem cell therapy/treatment.
- Amniotic stem cell therapy/treatment/umbilical/perinatal cord blood/placenta-derived stem cells/human embryonic stem cells.
- Sports stem cell therapy/treatment.
- Stem cell injections/infusions in: knee, spinal cord, eye, brain.
- Stromal vascular fraction stem cell therapy/treatment.
- Exosome therapy/treatment.
- Platelet-rich plasma (PRP) therapy/treatment.
- Mesenchymal stem cells (MSCs).
- Bone marrow-derived stem cells.
- Fetal neural stem cells (fNSC).
- Hematopoietic stem cells.
- Live cell/fresh cell therapy.
- Tennis elbow.
- Thinning/balding hair/hair loss.
- Plantar fasciitis.

Adverse events keywords:

- Sick.
- Sore.
- Pneumonia (cough, difficulty breathing).
- Meningitis (stiff neck, headache).
- Vomiting (throw up, puke).
- Gastrointestinal bleeding (blood in stool or abdominal pain).
- Fever.
- Pain.
- Headache.
- Bonelike growth.
- Brain tumors/tumors in the brain.
- Brain hemorrhage (brain bleed, uncontrollable bleeding, ruptured blood vessel).
- Spinal tumors/tumors in the spine.
- Inflammation/acute inflammation/redness/swelling/pain/tenderness of: brain, spinal cord, kidney, liver, adrenal gland, knee.
- Lesions/spotting or damage in: kidney, liver, adrenal gland, spinal cord.
- Stroke.
- Cardiac arrest/heart attack (loss of heart function/lack of oxygen to heart).
- Hospitalization/admitted to hospital/taken to the hospital/ER.
- Coma.
- Death.
- Infection.
- Abscess/blister/pus/redness/swelling.
- Pulmonary embolism/blood clot in the lungs.
- Bleeding/blood loss.
- Paralysis/paraplegia/spinal injury or disease.
- Urinary incontinence/involuntary urine leak/loss of bladder control.
- Blindness/loss of vision/flashes of light/light sensitivity/retinal detachment.

The contractor conducted a preliminary search using these keywords and provided a 10% sample of the data to Pew to ensure that the script was pulling the correct data for analysis before proceeding with the entire scrape. Additional therapy keywords such as PRP were added because reviews describing this therapy were organically identified during this preliminary search.

The custom script was used by an experienced scraper to gather review text, date of writing, star ratings, and hyperlinks to the original review location from all the reviews yielded by each of these searches. Where possible, the reviewer broke search terms into component parts to capture their varied use in natural language. For example, the reviewer searched for the word fragment "inflam" to identify reviews that use the words "inflamed,"

"inflammation," and "inflammatory." To counteract words that generated too many false positives, the reviewer provided the Python script with variations on the same term, such as "went blind," "go blind," and "blindness." The data was then saved to a Python data frame and exported as an Excel file.

Natural language processing was then applied to the dataset to extract reviews that mentioned both stem cell treatments and adverse events and to identify reviews with positive and negative sentiment. However, the traditional sentiment analysis using Python's VADER library (which is typically considered best-in-class for social media data) performed poorly. This is because many reviewers post lengthy discussion of pain and suffering *before* seeking treatment, and then state that stem cell therapy cured them, leading the VADER library to code the sentiment in these reviews as negative.

To counteract this issue, Codex referred to the user-supplied star ratings as a fallback and coded all reviews with fewer than four of five stars as potentially negative. A hybrid dataset was created using star reviews when possible and sentiment only when the user did not supply a numerical score. This method subsetting the data performed relatively well, although it still pulled some false positive reports that were manually highlighted by the contractor. Reports that were confirmed to be false positives were those that describe pretreatment pain or use keywords in an unexpected context. These were excluded from the final count that was submitted to Pew.

A total of 328 reviews were submitted to Pew for manual coding. Of those, 106 reviews were identified on Facebook, 101 on Google, and 121 on Yelp. These reviews were further categorized into three main buckets:

YES = reviews that mention adverse events appearing to be associated with an unapproved SCRI. These reviews can include words such as "infection," "inflammation/swelling," "more pain" (described as pain after treatment, NOT pain that is associated with a procedure or a result of treatment not working), or any words that indicate an allergic reaction, such as "numbness" or "immune system overdrive."

MAYBE = reviews that describe concerns about the quality of care received. These reviews mention: 1. AE (such as pain) appearing to be associated directly with the procedure 2. complaints about quality of care received at the clinic, 3. AE (such as pain or immobility) because treatment did not work and/or delayed evidence-based medical treatment, such as surgery.

NO = reviews that do not mention an AE related to the procedure or treatment, positive reviews (including false positives), reviews not associated with an SCRI. These reviews may be describing the reviewer's experience with treatments such as Liposonix, dextrose prolotherapy, viscosupplementation treatments (lubricant shots), discography, etc.

DUPLICATE = Reviews suspected to be about the same event after reading review text, checking the name of the person who posted the review, name of clinic, and date of posting.

The flowchart below illustrates the methodology Pew used to obtain the final count of AEs appearing to be directly associated with an unapproved SCRI.

Figure D.1

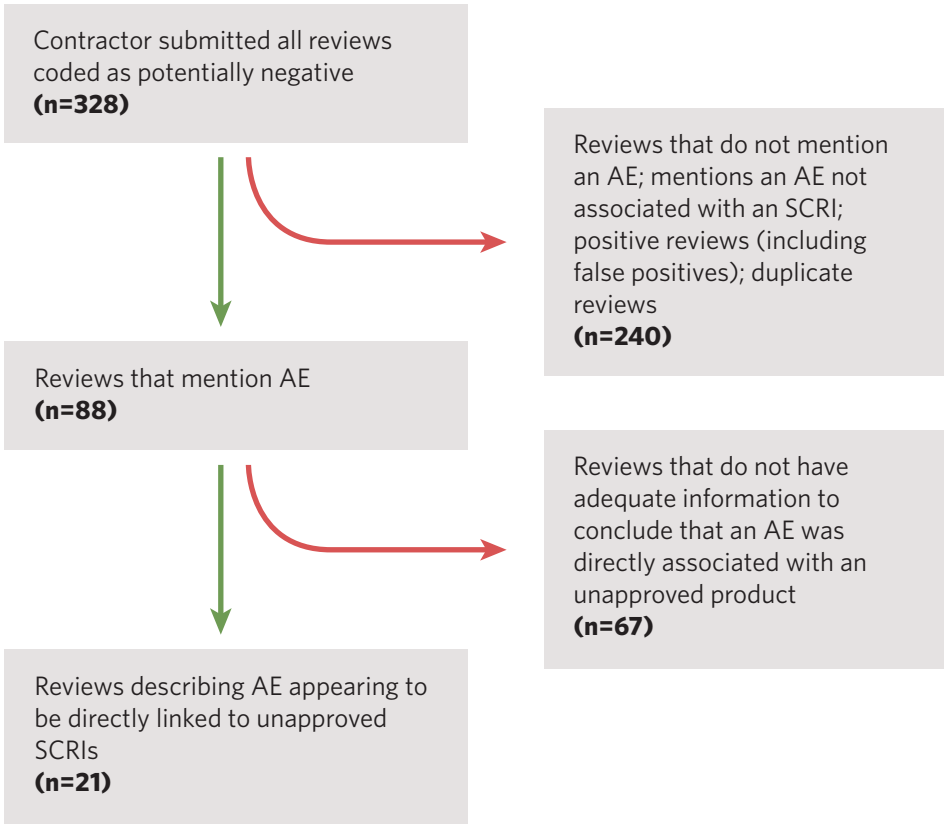
Contractor submitted all reviews coded as potentially negative
(n=328)
Reviews that do not mention an AE; mentions an AE not associated with an SCRI; positive reviews (including false positives); duplicate reviews
(n=240)
Reviews that mention AE
(n=88)
Reviews that do not have adequate information to conclude that an AE was directly associated with an unapproved product
(n=67)
Reviews describing AE appearing to be directly linked to unapproved SCRIs
(n=21)

Table D.1

Adverse Event Reports Identified in Public Consumer Reviews

Year patient posted review	Condition being treated	Alleged intervention	Administration route	Reported adverse event	Review source
2014	Not specified	Stem cells	Direct injection into the knee	Severe stiffness, swelling, pain	Yelp
2016	Lower back pain	Stem cells	Not specified	Loss of mobility, severe nerve pain	Yelp
2017	Unspecified condition requiring hip replacement	Stem cells	Direct injection into hip joints	Severe autoimmune response, loss of mobility, pain	Yelp
2018	Not specified	PRP	Direct injection into the shoulder	Pain	Yelp
2019	Not specified	PRP	Direct injection	Pain	Yelp
2019	Shoulder pain	Stem cell and PRP	Direct injection into shoulders	Pain	Google
2019	Lower back pain	PRP	Direct injections into sacroiliac joints	Nerve and joint pain	Google
2019	Not specified	Stem cells	Not specified	Pain, numbness, loss of mobility,	Google
2019	Not specified	Stem cells	Not specified	Pain	Google
2019	Not specified	Stem cells	Direct injection into the knee	Joint inflammation, pain	Google
2019	Systemic lupus erythematosus*	Stem cells	Not specified	Severe allergic reaction/autoimmune response, pain, fatigue	Google
2019	Not specified	Stem cells	Not specified	Infection requiring surgical intervention, pain	Yelp
2019	Not specified	Stem cells	Direct injection into the elbow	Worse outcome than before	Facebook
2019	Not specified	Stem cells	Direct injection	Pain	Facebook
2019	Not specified	Stem cells	Direct injection into the knee	Serious infection resulting in hospitalization, emergency surgeries, and two courses of antibiotics	Google

Continued on next page.

2020	Not specified	Stem cells	Direct injection into the lumbar spine	Severe pain, loss of mobility, infection, and inflammation	Google
2020	Not specified	Stem cells	Direct injection	Severe pain	Google
2020	Not specified	Stem cells	Direct injection into the knee	Pain	Facebook
2020	Cervical instability	PRP	Not specified	Neurological pain, immobility/loss of functionality	Google
2020	Tendinosis	PRP	Direct injection into the elbows	Muscle and possible nerve damage, pain	Google
2020	Spinal disc degeneration	PRP	Not specified	Pain, immobility	Yelp

* An inflammatory disease caused when the immune system attacks its own tissues.

Endnotes

1 G. Bauer, M. Elsallab, and M. Abou-El-Enein, "Concise Review: A Comprehensive Analysis of Reported Adverse Events in Patients Receiving Unproven Stem Cell-Based Interventions," *Stem Cells Translational Medicine* (July 31, 2018), https://doi.org/10.1002/sctm.17-0282.

2 L. Turner, "The U.S. Direct-to-Consumer Marketplace for Autologous Stem Cell Interventions," *Perspectives in Biology and Medicine* 61, no. 1 (2018): 7-24, https://muse.jhu.edu/article/694817; B. Schrotenboer, "Stem Cell Companies Sell Hope with Unproven Medicine for COVID-19," *USA Today*, last modified June 23, 2020, June 22, 2020, https://www.usatoday.com/story/money/business/2020/06/22/stem-cell-companies-selling-hope-unproven-treatments-covid-19/5348246002/.

3 The Pew Charitable Trusts, "FDA's Framework for Regulating Regenerative Medicine Will Improve Oversight," Oct. 17, 2019, https://www.pewtrusts.org/en/research-and-analysis/reports/2019/10/17/fdas-framework-for-regulating-regenerative-medicine-will-improve-oversight.

4 J.W. Pritchett, "The Debit Side of Stem Cell Joint Injections: A Prospective Cohort Study," *Current Orthopaedic Practice* 32, no. 2 (2021): 1-6, https://journals.lww.com/c-orthopaedicpractice/Abstract/2021/03000/The_debit_side_of_stem_cell_joint_injections__a.3.aspx.

5 K. Watson, program division director, Office of Biological Products Operations, U.S. Food and Drug Administration, letter to Edwin N. Pinos, president, Genetech, Inc., "Warning Letter OBPO 19-03," Nov. 29, 2018, https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/genetech-inc-561808-11292018; K. Watson, Program Division Director, Office of Biological Products Operations - Division 2, U.S. Food & Drug Administration, letter to Roya Panah, president/chief executive officer, Liveyon Labs Inc., "Warning Letter OBPO 20-588399," Dec. 5, 2019, https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/liveyon-labs-inc-588399-12052019; K.T. Watson, program division director, Office of Biological Products Operations – Division 2, U.S Food and Drug Administration, letter to Travis H. Bird, chief executive officer, EUCYT Laboratories LLC, "Warning Letter #OBPO 20-603498," June 4, 2020, https://www.fda.gov/inspections-compliance-enforcement-and-criminal-investigations/warning-letters/eucyt-laboratories-llc-607182-06042020.

6 D. Grady, "12 People Hospitalized With Infections From Stem Cell Shots," *The New York Times*, Dec. 20, 2018, https://www.nytimes.com/2018/12/20/health/stem-cell-shots-bacteria-fda.html; A. Marso, "KC Woman Got *E. Coli* Infection From Stem Cell Treatment at JoCo Clinic, Lawsuit Says," *The Kansas City Star*, Aug. 23, 2019, https://www.kansascity.com/news/business/health-care/article234306097.html.

7 U.S. Food and Drug Administration, "Public Safety Notification on Exosome Products," Dec. 6, 2019, https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/public-safety-notification-exosome-products; Watson, letter.

8 Federation of State Medical Boards, "Position Statement on Practice Drift," news release, April 2016, https://www.fsmb.org/siteassets/advocacy/policies/position-statement-on-practice-drift.pdf; U.S. Food and Drug Administration, "Regulatory Considerations for Human Cells, Tissues, and Cellular and Tissue-Based Products: Minimal Manipulation and Homologous Use: Guidance for Industry and Food and Drug Administration Staff" (2020), https://www.fda.gov/downloads/biologicsbloodvaccines/guidancecomplianceregulatoryinformation/

guidances/cellularandgenetherapy/ucm585403.pdf.

9 W. Fu et al., "Characteristics and Scope of Training of Clinicians Participating in the U.S. Direct-to-Consumer Marketplace for Unproven Stem Cell Interventions," *Journal of the American Medical Association* 321, no. 24 (2019): 2463-64, https://jamanetwork.com/journals/jama/fullarticle/2736545.

10 P. Knoepfler, "Update on Stem Cell Treatment Cost for 2018 from Ongoing Poll," *The Niche* (blog), Knoepfler Lab Stem Cell Blog, April 15, 2018, https://ipscell.com/2018/04/update-on-stem-cell-treatment-cost-for-2018-from-ongoing-poll.

11 Pritchett, "The Debit Side."

12 U.S. Food and Drug Administration, "FDA Adverse Event Reporting System (FAERS) Public Dashboard," last modified Oct. 29, 2020, https://www.fda.gov/drugs/questions-and-answers-fdas-adverse-event-reporting-system-faers/fda-adverse-event-reporting-system-faers-public-dashboard.

13 U.S. Food and Drug Administration, "Reporting Serious Problems to FDA," last modified May 22, 2018, https://www.fda.gov/safety/medwatch-fda-safety-information-and-adverse-event-reporting-program/reporting-serious-problems-fda#:~:text=Industry%20(Mandatory),process%2C%20review%2C%20and%20archive.

14 Pritchett, "The Debit Side."

15 P. Marks and S. Hahn, "Identifying the Risks of Unproven Regenerative Medicine Therapies," *Journal of the American Medical Association* 324, no. 3 (2020): 241-42, https://jamanetwork.com/journals/jama/article-abstract/2767586.

16 S. Golder, G. Norman, and Y.K. Loke, "Systematic Review on the Prevalence, Frequency and Comparative Value of Adverse Events Data in Social Media," *British Journal of Clinical Pharmacology* 80, no. 4 (2015): 878–88, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4594731/; J. Snyder and L. Turner, "Crowdfunding for Stem Cell-Based Interventions to Treat Neurologic Diseases and Injuries," *Contemporary Issues* 93, no. 6 (2019), https://n.neurology.org/content/93/6/252.

17 H.J. Duggirala, senior epidemiologist, Center for Veterinary Medicine, "FDA Perspectives on Social Media for Postmarket Safety Monitoring," Nov. 15, 2018, https://www.fda.gov/media/122897/download.

18 D. Grady and R. Abelson, "Stem Cell Treatments Flourish With Little Evidence That They Work," *The New York Times,* May 13, 2019, https://www.nytimes.com/2019/05/13/health/stem-cells-fda.html.

19 J. Snyder, L. Turner, and V.A. Crooks, "Crowdfunding for Unproven Stem Cell-Based Interventions," *Journal of the American Medical Association* 319, no. 18 (2018): 1935-36, http://doi.org/10.1001/jama.2018.3057; Snyder and Turner, "Crowdfunding for Stem Cell-Based Interventions to Treat Neurologic Diseases and Injuries."

20 Golder, Norman, and Loke, "Systematic Review."

21 B. Hawke et al., "How to Peddle Hope: An Analysis of YouTube Patient Testimonials of Unproven Stem Cell Treatments," *Stem Cell Reports* 12, no. 6 (2019): 1186-89, https://www.ncbi.nlm.nih.gov/pubmed/31189092; A. Petersen, K. Seear, and M. Munsie, "Therapeutic Journeys: The Hopeful Travails of Stem Cell Tourists," *Sociology of Health and Illness* 36, no. 5 (2014): 670-85, https://doi.org/10.1111/1467-9566.12092.

22 Pritchett, "The Debit Side."

23 J. Interlandi, "The Trouble With Stem Cell Therapy," *Consumer Reports*, Jan. 11, 2018, https://www.consumerreports.org/medical-treatments-procedures/trouble-with-stem-cell-therapy/.

24 C. Rachul, "'What Have I Got to Lose?': An Analysis of Stem Cell Therapy Patients' Blogs," *Health Law Review* 20, no. 1 (2011); Hawke et al., "How to Peddle Hope."

25 W. Wan and L. McGinley, "Clinic Pitches Unproven Treatments to Desperate Patients, With Tips on Raising the Cash," *The Washington Post*, Dec. 1, 2019, https://www.washingtonpost.com/national/health-science/clinic-pitches-unproven-treatments-to-desperate-patients-with-tips-on-raising-the-cash/2019/12/01/fe94cfcc-d3c6-11e8-8c22-fa2ef74bd6d6_story.html; J. Interlandi, "The Trouble with Stem Cell Therapy."

26 S. Giordano, M. Romeo, and P. Lankinen, "Platelet-Rich Plasma for Androgenetic Alopecia: Does It Work? Evidence From Meta Analysis," *Journal of Cosmetic Dermatology* 16, no. 3 (2017): 374-81, https://pubmed.ncbi.nlm.nih.gov/28296142/; N. Hussain, H. Johal, and M. Bhandari, "An Evidence-Based Evaluation on the Use of Platelet Rich Plasma in Orthopedics—A Review of the Literature," *SICOT-J* 3 (2017): 57, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5632954/.

27 ClinicalTrials.gov, "Platelet-Rich Plasma or PRP," U.S. National Library of Medicine, accessed Jan. 25, 2021, https://clinicaltrials.gov/ct2/results?cond=&term=platelet-rich+plasma+OR+PRP&cntry=&state=&city=&dist=.

28 I.A. Jones, R.C. Togashi, and C. Thomas Vangsness, Jr., "The Economics and Regulation of PRP in the Evolving Field of Orthopedic Biologics," *Current Reviews in Musculoskeletal Medicine* 11, no. 4 (2018): 558–65, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6220002/; P. Knoepfler, "What Is PRP Injection & Is It Worth It?," The Niche, accessed Jan. 25, 2021, https://ipscell.com/2020/05/

patient-qa-3-what-is-prp-is-it-worth-trying/.

29 Knoepfler, "What Is PRP Injection & Is It Worth It?"

30 Duggirala, "FDA Perspectives on Social Media for Postmarket Safety Monitoring."

31 U.S. Food & Drug Administration, "Data Mining at FDA—White Paper," last modified Aug. 20, 2018, https://www.fda.gov/science-research/data-mining/data-mining-fda-white-paper.

32 National Institutes of Health, "Regenerative Medicine Innovation Project," accessed March 17, 2021, https://www.nih.gov/rmi.

33 L. Turner, "The U.S. Direct-to-Consumer Marketplace for Autologous Stem Cell Interventions."

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