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 SCRs 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 SCRs 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 SCRs.4 (See Appendix B for a full list of AEs associated with unapproved SCRs 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. 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. 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.

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. 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.

These adverse events highlight many of the risks of unapproved SCRI s, and are particularly concerning given that unapproved SCRI s 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. Use of unapproved SCRI s 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 SCRI s, the findings from the literature also underscore the fundamental importance of evaluating SCRI s 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 SCRI s are beneficial and which are useless or harmful.

**FDA’s database of adverse events captures some reports linked to unapproved SCRI s**

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. 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. 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 SCRLs 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 SCRLs 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.\textsuperscript{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 SCRLs. 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 \textit{JAMA} and encouraged patients and their providers to more thoroughly report AEs.\textsuperscript{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.

\textbf{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 SCRLs, which means that these sites can be a potential resource for identifying self-reported cases of AEs.\textsuperscript{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.\textsuperscript{17} To
test this hypothesis, Pew analyzed all patient reviews of businesses offering unapproved SCRs 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 SCRs. (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 SCRs (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 SCRs 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 SCRIIs; many, in fact, were positive. This finding correlates with other perception studies that report on patients’ positive experiences with these interventions.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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 SCRIIs —omitting negative reports.\textsuperscript{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 SCRIIs.\textsuperscript{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.\textsuperscript{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,\textsuperscript{27} have not yet demonstrated definitive efficacy in treating particular conditions or diseases.\textsuperscript{28} However, clinics continue to market this therapy to patients for a range of indications.\textsuperscript{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 SCRIIs 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 SCRIIs, 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 SCRIIs. 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 SCRIIs—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. The agency should consider analyzing social media sites for AEs associated with unapproved SCRIIs. 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. 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 SCRIIs 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 SCRLs 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>
<thead>
<tr>
<th>Year</th>
<th>Reported cases</th>
<th>Reported deaths</th>
<th>Patient country of origin</th>
<th>Location of intervention</th>
<th>Condition being treated</th>
<th>Alleged intervention</th>
<th>Administration route</th>
<th>Reported adverse event</th>
<th>Notes</th>
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<tbody>
<tr>
<td>2004a</td>
<td>5</td>
<td>-</td>
<td>Not reported</td>
<td>China</td>
<td>Spinal cord injury</td>
<td>Olfactory ensheathing fetal cells</td>
<td>Spinal injection</td>
<td>Meningitis, cerebrospinal fluid pleocytosis&lt;sup&gt;b&lt;/sup&gt;, gastrointestinal bleeding, pneumonia, fever, headache&lt;sup&gt;c&lt;/sup&gt;</td>
<td>-</td>
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<tr>
<td>2005d</td>
<td>1</td>
<td>-</td>
<td>Israel</td>
<td>Russia</td>
<td>Ataxia telangiectasia&lt;sup&gt;e&lt;/sup&gt;</td>
<td>Fetal neural stem cells (SCs)</td>
<td>Direct injection into brain, spine</td>
<td>Tumors in brain, spine originating from donor fetal neural SCs</td>
<td>-</td>
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<tr>
<td>2006f</td>
<td>1</td>
<td>-</td>
<td>Not reported</td>
<td>Egypt</td>
<td>Acute inflammation of spinal cord segments</td>
<td>Mesenchymal SCs (MSCs), embryonic, and fetal neural SCs</td>
<td>Spinal injection</td>
<td>Acute inflammation of brain, spinal cord that damaged myelin sheath protecting nerve fibers</td>
<td>-</td>
</tr>
<tr>
<td>2006g</td>
<td>1</td>
<td>-</td>
<td>Thailand</td>
<td>Thailand</td>
<td>Kidney inflammation due to lupus</td>
<td>Hematopoietic SCs</td>
<td>Injection into renal regions (no ultrasound guidance)</td>
<td>Multiple lesions in kidney, liver, adrenal gland</td>
<td>-</td>
</tr>
<tr>
<td>2009h</td>
<td>1</td>
<td>-</td>
<td>U.S.</td>
<td>U.S. (California)</td>
<td>Face-lift</td>
<td>Adipose-derived stromal cells</td>
<td>Injections around eye</td>
<td>Bonelike growth in eyelid</td>
<td>-</td>
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<th>Notes</th>
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<tbody>
<tr>
<td>2010</td>
<td>3</td>
<td>2</td>
<td>Italy; Azerbaijan; U.S. (Ohio)</td>
<td>Germany</td>
<td>Unspecified neurological conditions</td>
<td>Bone marrow-derived SCs</td>
<td>Direct injection into brain</td>
<td>Brain hemorrhage; death</td>
<td>Although the treating clinic in Germany was shut down, provider subsequently opened a similar clinic in Lebanon</td>
</tr>
<tr>
<td>2010-12</td>
<td>2</td>
<td>2</td>
<td>U.S. (Indiana, Florida)</td>
<td>U.S. (Florida)</td>
<td>Leg numbness, difficulty walking after cancer treatment; pulmonary hypertension</td>
<td>Grossly filtered bone marrow aspirate; adipose-derived stromal cells</td>
<td>Different methods of administration</td>
<td>Stroke; cardiac arrest; death in both cases</td>
<td>Provider was subsequently barred from practicing medicine in Florida but continues to treat patients in the Dominican Republic</td>
</tr>
<tr>
<td>2011</td>
<td>1</td>
<td>1</td>
<td>U.S.</td>
<td>U.S. (Nevada)</td>
<td>Spontaneous widening of bronchi (for unknown reasons)</td>
<td>Nonspecified SC intervention</td>
<td>Unknown</td>
<td>Death</td>
<td>-</td>
</tr>
<tr>
<td>2012-14</td>
<td>At least 10</td>
<td>At least 7</td>
<td>Several countries, including U.S. (Illinois)</td>
<td>Italy; Spain; Russia; U.K.; Sweden; U.S.</td>
<td>Various conditions affecting trachea function</td>
<td>SC-coated plastic or cadaveric trachea</td>
<td>Surgical transplant</td>
<td>Pulmonary embolism, postoperative infection, transplant failure; death</td>
<td>Patients were treated by the same surgeon, who was found to have engaged in numerous instances of scientific misconduct</td>
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<tr>
<th>Year</th>
<th>Reported cases</th>
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<th>Notes</th>
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<tr>
<td>2012-15a</td>
<td>242</td>
<td>-</td>
<td>Not reported</td>
<td>U.S.</td>
<td>Osteoarthritis</td>
<td>Autologous stem cells (not specified); donor stem cells (not specified); or both</td>
<td>Direct injection into knee, hip, shoulder</td>
<td>Tumor (6); infection (42); chronic effusion (41); vasovagal, syncope, 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)</td>
<td>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</td>
</tr>
<tr>
<td>2012b</td>
<td>1</td>
<td>-</td>
<td>Not reported</td>
<td>Japan</td>
<td>Chronic kidney failure</td>
<td>Adipose-derived MSCs</td>
<td>Intravenous infusion</td>
<td>Unspecified neurological event</td>
<td>-</td>
</tr>
<tr>
<td>2013 (or earlier)c</td>
<td>1</td>
<td>-</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Stroke, macular degeneration, osteoarthritis, and depression</td>
<td>Stem cells (not specified)</td>
<td>Spinal injection</td>
<td>Spinal inflammation and damage</td>
<td>-</td>
</tr>
<tr>
<td>2013d</td>
<td>3</td>
<td>-</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Herniated intervertebral disc</td>
<td>Adipose-derived MSCs</td>
<td>Intravenous infusion</td>
<td>Pulmonary embolism</td>
<td>-</td>
</tr>
<tr>
<td>2013e</td>
<td>1</td>
<td>1</td>
<td>U.S.</td>
<td>Florida</td>
<td>Chronic obstructive pulmonary disease (COPD)</td>
<td>Adipose-derived MSCs</td>
<td>Intravenous infusion</td>
<td>Death</td>
<td>-</td>
</tr>
</tbody>
</table>

Continued on next page.
<table>
<thead>
<tr>
<th>Year</th>
<th>Reported cases</th>
<th>Reported deaths</th>
<th>Patient country of origin</th>
<th>Location of intervention</th>
<th>Condition being treated</th>
<th>Alleged intervention</th>
<th>Administration route</th>
<th>Reported adverse event</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>2013(^v)</td>
<td>1</td>
<td>1</td>
<td>Australia</td>
<td>Australia</td>
<td>Dementia</td>
<td>Autologous adipose stromal cells</td>
<td>Unknown</td>
<td>Uncontrolled blood loss during liposuction procedure, shock, death</td>
<td>Patient was on anticoagulant medication, which caused uncontrolled bleeding</td>
</tr>
<tr>
<td>2013(^v)</td>
<td>2</td>
<td>-</td>
<td>Unknown</td>
<td>U.S. (North Carolina)</td>
<td>Osteoarthritis</td>
<td>Autologous platelet-rich plasma and a human placental tissue-derived allograft product</td>
<td>Intra-articular injections</td>
<td>Staphylococcus aureus-dependent septic arthritis</td>
<td>-</td>
</tr>
<tr>
<td>2014(^w)</td>
<td>6</td>
<td>-</td>
<td>Canada; U.S. (New York)</td>
<td>Germany</td>
<td>Not reported</td>
<td>Live cell therapy/fresh cell therapy(^x)</td>
<td>Intramuscular injections</td>
<td>Q fever</td>
<td>-</td>
</tr>
<tr>
<td>2013-14(^v)</td>
<td>1</td>
<td>1</td>
<td>Australia</td>
<td>Russia</td>
<td>Stiff person syndrome</td>
<td>Bone marrow-derived SCs</td>
<td>Unknown</td>
<td>Heart attack</td>
<td>-</td>
</tr>
<tr>
<td>2016-17(^z)</td>
<td>1</td>
<td>-</td>
<td>U.S.</td>
<td>Dominican Republic</td>
<td>Retinitis pigmentosa</td>
<td>Autologous adipose tissue-derived stem cell injections (AASCIs)</td>
<td>Injected into eye</td>
<td>Retinal detachment and proliferative vitreoretinopathy</td>
<td>Male patient</td>
</tr>
<tr>
<td>Year</td>
<td>Reported cases</td>
<td>Reported deaths</td>
<td>Patient country of origin</td>
<td>Location of intervention</td>
<td>Condition being treated</td>
<td>Alleged intervention</td>
<td>Administration route</td>
<td>Reported adverse event</td>
<td>Notes</td>
</tr>
<tr>
<td>------</td>
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<td>-------------------------</td>
<td>---------------------</td>
<td>---------------------</td>
<td>------------------------</td>
<td>-------</td>
</tr>
<tr>
<td>2016-17&lt;sup&gt;a&lt;/sup&gt;</td>
<td>At least 5</td>
<td>-</td>
<td>Not reported</td>
<td>U.S. (California, other locations not specified)</td>
<td>Various conditions, including COPD</td>
<td>Adipose-derived stromal cells</td>
<td>Infusion; direct injection into brain, knee, and eyes; inhalation</td>
<td>Loss of consciousness, headaches, confusion, inability to walk, infection, retinal detachment, hospitalization</td>
<td>These adverse events occurred at several affiliated clinics</td>
</tr>
<tr>
<td>2018&lt;sup&gt;b&lt;/sup&gt;</td>
<td>At least 13</td>
<td>-</td>
<td>U.S. (Texas, Florida, Arizona, Kansas)</td>
<td>Various conditions, including joint and back pain</td>
<td>Umbilical cord blood-derived SCs</td>
<td>Injection or infusion</td>
<td>Acute bacterial infections of spine, bones, joints; abscesses; hospitalization</td>
<td>One news source identified 17 affected patients over 2018-19&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>2018&lt;sup&gt;ad&lt;/sup&gt;</td>
<td>1</td>
<td>-</td>
<td>Not reported</td>
<td>U.S. (Florida)</td>
<td>Arthritis</td>
<td>Not reported</td>
<td>Injection</td>
<td>Vomiting, hospitalization, coma</td>
<td>-</td>
</tr>
<tr>
<td>2018&lt;sup&gt;ae&lt;/sup&gt;</td>
<td>1</td>
<td>-</td>
<td>Not reported</td>
<td>Ukraine</td>
<td>Type I diabetes with end-stage kidney failure; cardiovascular disease</td>
<td>Nonautologous stem cells of unknown origin (supposedly embryonic)</td>
<td>Injection into peripheral vein</td>
<td>Jaundice and necrotizing skin ulcers, hepatitis, and deteriorating heart failure beginning six months after treatment</td>
<td>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</td>
</tr>
</tbody>
</table>

*Continued on next page.*
<table>
<thead>
<tr>
<th>Year</th>
<th>Reported cases</th>
<th>Reported deaths</th>
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<th>Administration route</th>
<th>Reported adverse event</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>2019&lt;sup&gt;a&lt;/sup&gt;</td>
<td>At least 1</td>
<td>-</td>
<td>U.S.</td>
<td>U.S. (Nebraska)</td>
<td>Unknown</td>
<td>Exosome products derived from placenta</td>
<td>Injection or inhalation</td>
<td>Bacterial infection, sepsis</td>
<td>News reports stated that fewer than five patients became seriously ill</td>
</tr>
<tr>
<td>Not reported&lt;sup&gt;™&lt;/sup&gt;</td>
<td>1</td>
<td>-</td>
<td>U.S.</td>
<td>Costa Rica</td>
<td>Multiple sclerosis</td>
<td>Allogeneic cord blood MSCs and autologous adipose-derived stromal cells</td>
<td>Spinal injection, intravenous infusion</td>
<td>Catastrophic demyelinating encephalomyelitis&lt;sup&gt;b&lt;/sup&gt;</td>
<td>-</td>
</tr>
<tr>
<td>Not reported&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1</td>
<td>-</td>
<td>U.S.</td>
<td>China; Argentina; Mexico</td>
<td>Ischemic stroke</td>
<td>MSCs, embryonic, fetal neural SCs</td>
<td>Spinal injections</td>
<td>Lesions in spinal cord and surrounding membranes causing lower-back pain, paraplegia, urinary incontinence</td>
<td>-</td>
</tr>
<tr>
<td>Not reported&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1</td>
<td>-</td>
<td>U.S.</td>
<td>U.S.</td>
<td>Face-lift</td>
<td>Fatty aspirate from abdominal wall in a procedure called “stem cell face-lift”</td>
<td>Facial injection</td>
<td>Necrotizing&lt;sup&gt;a&lt;/sup&gt; facial ulcerations</td>
<td>-</td>
</tr>
<tr>
<td>Not reported&lt;sup&gt;a&lt;/sup&gt;</td>
<td>2</td>
<td>-</td>
<td>U.S., Canada&lt;sup&gt;™&lt;/sup&gt;</td>
<td>Portugal&lt;sup&gt;™&lt;/sup&gt;</td>
<td>Spinal fracture, associated spinal cord injury</td>
<td>Olfactory mucosal cells</td>
<td>Intraspinal transplantation</td>
<td>Spinal mass consisting of large amounts of mucus</td>
<td>-</td>
</tr>
</tbody>
</table>

Continued on next page.
<table>
<thead>
<tr>
<th>Year</th>
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<th>Administration route</th>
<th>Reported adverse event</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not reported&lt;sup&gt;ao&lt;/sup&gt;</td>
<td>3</td>
<td>-</td>
<td>U.S.</td>
<td>U.S. (Florida)</td>
<td>Age-related macular degeneration</td>
<td>Adipose-derived stromal cells</td>
<td>Eye injections</td>
<td>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</td>
<td>-</td>
</tr>
<tr>
<td>Not reported&lt;sup&gt;ao&lt;/sup&gt;</td>
<td>1</td>
<td>1</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Heart disease</td>
<td>Autologous “precursor” cells</td>
<td>Direct injection into heart</td>
<td>Ventricular fibrillation; unable to undergo heart transplantation; death</td>
<td>-</td>
</tr>
<tr>
<td>Not reported&lt;sup&gt;ao&lt;/sup&gt;</td>
<td>1</td>
<td>-</td>
<td>U.K.</td>
<td>Netherlands</td>
<td>Unknown</td>
<td>Umbilical cord blood-derived SCs</td>
<td>Unknown</td>
<td>Serious acute allergic reaction, hospitalization</td>
<td>-</td>
</tr>
<tr>
<td>Not reported&lt;sup&gt;ar&lt;/sup&gt;</td>
<td>2</td>
<td>2</td>
<td>Not reported</td>
<td>Japan, China</td>
<td>Different conditions</td>
<td>Adipose-derived stromal cells</td>
<td>Unknown</td>
<td>Pulmonary embolism; death</td>
<td>-</td>
</tr>
<tr>
<td>Not reported&lt;sup&gt;am&lt;/sup&gt;</td>
<td>2</td>
<td>2</td>
<td>China</td>
<td>China</td>
<td>Disabilities from a minor stroke; late-stage liver cirrhosis</td>
<td>Allogenic SCs (not specified)</td>
<td>Spinal, intramuscular injections</td>
<td>Death</td>
<td>Patient with late-stage liver cirrhosis died as a result of being taken off hepatitis B medication in order to undergo stem cell treatment</td>
</tr>
</tbody>
</table>

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

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<table>
<thead>
<tr>
<th>Year</th>
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<th>Administration route</th>
<th>Reported adverse event</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not reporteda</td>
<td>1</td>
<td>-</td>
<td>Nicaragua</td>
<td>Dominican Republic</td>
<td>Retinitis pigmentosa associated with Usher syndrome</td>
<td>Autologous adipose tissue-derived stem cell injection (AASCI)</td>
<td>Injection in eye</td>
<td>Retinal detachment; glaucoma; pain</td>
<td>-</td>
</tr>
<tr>
<td>Not reportedb</td>
<td>1</td>
<td>-</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Retinitis pigmentosa</td>
<td>Bone marrow-derived SCs</td>
<td>Injection into eye</td>
<td>Severe vision loss</td>
<td>-</td>
</tr>
<tr>
<td>Not reportedc</td>
<td>1</td>
<td>-</td>
<td>U.S.</td>
<td>Thailand</td>
<td>Charcot-Marie-Tooth disease</td>
<td>Fetal SCs</td>
<td>Intravenous infusion</td>
<td>Multiple lesions over the body caused by bacterial infection; fever</td>
<td>-</td>
</tr>
<tr>
<td>Not reportedd</td>
<td>1</td>
<td>-</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Retinitis pigmentosa</td>
<td>Autologous-derived SCs</td>
<td>Injection into eye</td>
<td>Scar tissue on retina</td>
<td>-</td>
</tr>
<tr>
<td>Not reportede</td>
<td>1</td>
<td>-</td>
<td>Not reported</td>
<td>Russia</td>
<td>Parkinson’s disease</td>
<td>SCs of unknown source</td>
<td>Spinal injection</td>
<td>Spinal tumors, lesions</td>
<td>-</td>
</tr>
<tr>
<td>Not reportedf</td>
<td>1</td>
<td>-</td>
<td>Russia</td>
<td>Weakness and fatigue</td>
<td>SCs of unknown source</td>
<td>Spinal injection</td>
<td>Spinal injection</td>
<td>Growth/lesions on spine; progressive lower extremity weakness and urinary incontinence</td>
<td>-</td>
</tr>
<tr>
<td>Not reportedg</td>
<td>1</td>
<td>-</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Stargardt’s macular dystrophy</td>
<td>Autologous bone marrow-derived SCs</td>
<td>Injection into eye</td>
<td>Retinal detachment</td>
<td>-</td>
</tr>
</tbody>
</table>

*Continued on next page.*
<table>
<thead>
<tr>
<th>Year</th>
<th>Reported cases</th>
<th>Reported deaths</th>
<th>Patient country of origin</th>
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<th>Condition being treated</th>
<th>Alleged intervention</th>
<th>Administration route</th>
<th>Reported adverse event</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not reported&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1</td>
<td>-</td>
<td>Egypt</td>
<td>Egypt</td>
<td>Acute transverse myelitis</td>
<td>Cord-blood-derived SCs</td>
<td>Spinal injection</td>
<td>Severe inflammation of the brain and spinal cord</td>
<td>-</td>
</tr>
<tr>
<td>Not reported&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1</td>
<td>-</td>
<td>Not reported</td>
<td>Iran</td>
<td>Diabetes</td>
<td>Fetal SCs</td>
<td>Intravenous injection</td>
<td>Brain tumor</td>
<td>Biopsy found tumor cells related to transplanted stem cells</td>
</tr>
</tbody>
</table>

**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.

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b Pelocytosis means increased cell count.

c Reaction to antibodies in the recipient blood.


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


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.


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.


ac Wan and McGinley, “Miraculous” Stem Cell Therapy.”


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


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


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 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)*

**Filtering**

Unique case reports submitted by mandatory reporters *(n=495)*

Unique case reports submitted by voluntary reporters, such as health care providers, patients, and consumers *(n=178)*

Unique case reports with complete information of the patient condition being treated AND the primary suspect drug used *(n=60)*

Unique case reports with incomplete information *(n=118)*

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 SCRs *(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 SCRs *(n=5)*
Table C.1
Adverse Event Reports Related to Unapproved SCRIIs Identified in FAERS

<table>
<thead>
<tr>
<th>Date FDA received report</th>
<th>Condition being treated</th>
<th>Type of stem cell therapy</th>
<th>Adverse event</th>
<th>Outcome</th>
<th>Age of patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>10/1/2007</td>
<td>Drug therapy</td>
<td>Cord blood cryopreservation laboratory autologous bone marrow stem cell</td>
<td>Medication error, product complaint, wrong technique in product usage process</td>
<td>Not reported</td>
<td></td>
</tr>
<tr>
<td>9/4/2008</td>
<td>Acute myocardial infarction</td>
<td>Autologous bone marrow stem cell</td>
<td>Burning sensation, coronary artery stenosis, myocardial infarction</td>
<td>Hospitalization</td>
<td>Not reported</td>
</tr>
<tr>
<td>3/3/2010</td>
<td>Autologous bone marrow transplantation therapy</td>
<td>Autologous bone marrow stem cell, Presbyterian apheresis †</td>
<td>Cytokine storm, multiple organ dysfunction syndrome, systemic inflammatory response syndrome</td>
<td>Death</td>
<td>64</td>
</tr>
<tr>
<td>10/16/2012</td>
<td>Cardiac failure</td>
<td>Autologous stem cells</td>
<td>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</td>
<td>Life-threatening</td>
<td>4</td>
</tr>
<tr>
<td>9/27/2018</td>
<td>Arthritis</td>
<td>Regen</td>
<td>Arthritis, bacterial infection</td>
<td>Hospitalization, life-threatening</td>
<td>58</td>
</tr>
</tbody>
</table>

* 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.

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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 SCRIIs. 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 SCRIIs. 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.
- Bone-like 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 SCRs (n=21)
<table>
<thead>
<tr>
<th>Year patient posted review</th>
<th>Condition being treated</th>
<th>Alleged intervention</th>
<th>Administration route</th>
<th>Reported adverse event</th>
<th>Review source</th>
</tr>
</thead>
<tbody>
<tr>
<td>2014</td>
<td>Not specified</td>
<td>Stem cells</td>
<td>Direct injection into the knee</td>
<td>Severe stiffness, swelling, pain</td>
<td>Yelp</td>
</tr>
<tr>
<td>2016</td>
<td>Lower back pain</td>
<td>Stem cells</td>
<td>Not specified</td>
<td>Loss of mobility, severe nerve pain</td>
<td>Yelp</td>
</tr>
<tr>
<td>2017</td>
<td>Unspecified condition requiring hip replacement</td>
<td>Stem cells</td>
<td>Direct injection into hip joints</td>
<td>Severe autoimmune response, loss of mobility, pain</td>
<td>Yelp</td>
</tr>
<tr>
<td>2018</td>
<td>Not specified</td>
<td>PRP</td>
<td>Direct injection into the shoulder</td>
<td>Pain</td>
<td>Yelp</td>
</tr>
<tr>
<td>2019</td>
<td>Not specified</td>
<td>PRP</td>
<td>Direct injection</td>
<td>Pain</td>
<td>Yelp</td>
</tr>
<tr>
<td>2019</td>
<td>Shoulder pain</td>
<td>Stem cell and PRP</td>
<td>Direct injection into shoulders</td>
<td>Pain</td>
<td>Google</td>
</tr>
<tr>
<td>2019</td>
<td>Lower back pain</td>
<td>PRP</td>
<td>Direct injections into sacroiliac joints</td>
<td>Nerve and joint pain</td>
<td>Google</td>
</tr>
<tr>
<td>2019</td>
<td>Not specified</td>
<td>Stem cells</td>
<td>Not specified</td>
<td>Pain, numbness, loss of mobility,</td>
<td>Google</td>
</tr>
<tr>
<td>2019</td>
<td>Not specified</td>
<td>Stem cells</td>
<td>Not specified</td>
<td>Pain</td>
<td>Google</td>
</tr>
<tr>
<td>2019</td>
<td>Not specified</td>
<td>Stem cells</td>
<td>Direct injection into the knee</td>
<td>Joint inflammation, pain</td>
<td>Google</td>
</tr>
<tr>
<td>2019</td>
<td>Systemic lupus erythematosus*</td>
<td>Stem cells</td>
<td>Not specified</td>
<td>Severe allergic reaction/autoimmune response, pain, fatigue</td>
<td>Google</td>
</tr>
<tr>
<td>2019</td>
<td>Not specified</td>
<td>Stem cells</td>
<td>Not specified</td>
<td>Infection requiring surgical intervention, pain</td>
<td>Yelp</td>
</tr>
<tr>
<td>2019</td>
<td>Not specified</td>
<td>Stem cells</td>
<td>Direct injection into the elbow</td>
<td>Worse outcome than before</td>
<td>Facebook</td>
</tr>
<tr>
<td>2019</td>
<td>Not specified</td>
<td>Stem cells</td>
<td>Direct injection</td>
<td>Pain</td>
<td>Facebook</td>
</tr>
<tr>
<td>2019</td>
<td>Not specified</td>
<td>Stem cells</td>
<td>Direct injection into the knee</td>
<td>Serious infection resulting in hospitalization, emergency surgeries, and two courses of antibiotics</td>
<td>Google</td>
</tr>
</tbody>
</table>

*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.

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**Endnotes**


Pritchett, “The Debit Side.”


Pritchett, “The Debit Side.”


For further information, please visit:
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