Ethical and Practical Considerations for Integrating Cellular (“Stem Cell”) Therapy into Clinical Practice

Nicolas S. Piuze¹ · Ahmed Emara¹ · Jorge Chahla² · Bert R. Mandelbaum³

Published online: 28 May 2020

© Springer Science+Business Media, LLC, part of Springer Nature 2020

Abstract

Purpose of Review Cellular therapies, also known as “stem cell” interventions (SCI), have undergone a rapid popularization in the USA and worldwide. The current review aimed at outlining (1) the ethical challenges facing the implementation of SCI; (2) the applicability of the currently available SCI; and (3) recommendations to achieve ethical, well-regulated incorporation of SCI in the clinical setting.

Recent Findings Concerns regarding the inadequate characterization, poor adverse effects disclosure, and unorthodox, often inappropriate, market practices have engendered a genuine concern regarding the SCI compliance with ethical standards. Six instances of litigation on the basis of misrepresentation or inappropriate informed consent were recorded between 2012 and 2018. Such concerns have been furthered by the loopholes in the regulatory aspect governing the use of SCI coupled with the unclear literature-reported efficacy and diverse spectrum of profess indications. Similarly, the application of SCI in the clinical field is yet to prove its value. The uncertain efficacy, coupled with obscure true-costs of utilization, impedes a value-based assessment.

Summary A multidisciplinary approach involving legislative and medical professional societies should continue to advance regulations that govern SCI. A well-regulated system that allows for the ethical integration of SCI with appositely evidenced-based described benefits and risks should be sought.

Keywords Stem cells · Direct-to-consumer marketing · Ethics · Legislation · Litigation · Efficacy · Clinical applications

Introduction

The use of cellular therapies oftentimes referred to as “stem cell interventions” (SCI) has exponentially increased for the treatment of orthopedic and musculoskeletal conditions such as osteoarthritis [1, 2]. In the context of a 98.6% appreciation from 2012 to 2016, the global stem cell market is projected to reach a market valuation of \$14.8 billion US dollars by 2022

[3]. Given the significant burden of musculoskeletal diseases, with osteoarthritis alone costing an estimated \$87.1 billion annually and affecting 27 million Americans, there exists a significant need for regenerative disease-modifying biologics such as stem cell therapy [4, 5]. Although the majority of current SCI utilize autologous preparation such as the bone marrow aspirate concentrate (BMAC), or adipose-derived cells, there are reports of other “stem cells” currently being tested for a variety of indications [6, 7]. Therefore, SCI can be segregated into proven vs. unproven interventions. Proven interventions require further evidence in the form of well-conducted randomized controlled trials and post-marketing registries within centers offering such therapeutics. Conversely, minimally processed unproven SCI should be designated as “cellular therapies” and require appropriate characterization and scrutiny.

Despite the significant hype surrounding the potential benefits of SCI [8], current clinical evidence supporting its use is of low quality and limited to small cohorts with considerable methodological variability [9–12]. Therefore, care must be taken to balance the promise of “stem cell” regenerative

---

This article is part of the Topical Collection on *Stem Cells in Orthopaedic Surgery*

✉ Nicolas S. Piuze
piuzin@ccf.org

¹ Department of Orthopaedic Surgery, Cleveland Clinic, Cleveland, OH, USA

² Department of Orthopaedic Surgery, Division of Sports Medicine, Rush University Medical Center, Chicago, IL, USA

³ Department of Orthopaedic Surgery, Cedars Sinai Kerlan Jobe Institute, Santa Monica, CA, USA

potential against the lack of established clinical efficacy and high out-of-pocket patient costs associated with them [2, 13, 14•, 15•]. To date, most of the clinical claims being made are substantiated on basic science studies and not on clinical research. Furthermore, there is even a lack of basic science studies that enlighten the mechanism of action of several of the clinically offered SCI [13, 14•, 15•]. In short, the demand for regenerative intervention should be regulated by an intricate balance of ethical guardianship/regulation and the subsequent practicality/limitations of implementation.

Ethical Challenges of SCI

SCI have become a frequent target of scrutiny, owing to its questionable alignment with cornerstone ethical principles [16]. Indeed, Horner et al. [17] reported nine major class-action lawsuits between 2012 and 2018, targeting the application of unapproved autologous SCI for arthritis and various autoimmune derangements, cosmetics, and ophthalmologic disorders. Six of the nine class actions cite claims of misrepresentation, false advertisement, or the lack of proper informed consent. The aforementioned pattern highlights a discrepancy between patient perception and the available evidence. Such discrepancy could be attributed to the novel nature of the field in addition to the occasional unethical marketing practices [18•]. Therefore, the current ethical dilemmas facing the application of SCI can be identified as (1) the lack of clarity regarding the nature of SCI, their indications, and expected outcomes; and (2) the phenomenon of direct-to-consumer marketing which compounds, and often benefits, from the poor characterization.

The term “stem cell therapy” for musculoskeletal disorders has often been stretched beyond its capacity, to encompass an array of heterogeneous uncharacterized cell sources in variable concentrations, obtained from the bone marrow, adipose tissue, blood, umbilical, and placental tissues being the most commonly utilized cell sources [15•, 19–22]. In addition, extracted substrates undergo highly variable degrees of alteration ranging from density separation (centrifugation), mechanical disgregation, and even culture-expansion prior to re-injection, all the while being presented as “stem cell treatment” to prospective patients [14•, 15•, 16, 23, 24].

Scientific literature has not gone unscathed from the inadequate characterization of SCI, with only 30% of the available studies providing the number of nucleated cells delivered after processing [14•, 18]. Furthermore, the available clinical trials are, in the most part, early-stage Phase I/II clinical trials with significant limitations, including small patient size, diversity of cell preparation techniques, and lack of long-term follow-up [25–29]. In addition, while there is evidence indicating SCI are safe, these are never without risk and include the possibility of infection, swelling, and bleeding [25, 28, 30]. Similarly, the lack of established standard of care to serve as controls to

compare SCI is concerning, considering the importance of the placebo effect of intraarticular injections for knee osteoarthritis, which demonstrates significant efficacy in reducing pain, improving functional outcomes, and stiffness [31, 32]. Therefore, the currently available cell products can be grossly divided into proven vs. unproven SCI [14•]. The International Society for Cellular Therapies has proposed criteria in an attempt to regulate these therapies. Proven stem cell therapies are defined as well-characterized SCI that have undergone duly authorized clinical trials with sufficient documentation and reporting of outcomes for a specific indication. Conversely, unproven stem cell therapies generally exhibit an unclear scientific rationale to suggest efficacy, insufficient data from *in vitro* assays, animal model experiments, and clinical studies as well as a significant lack of standardization and consistency in cell extraction and alteration [33].

Over 716 clinics in the USA drive the direct to consumer marketing of often uncharacterized and unproven SCI, with claims of effectiveness exceeding 80% for an array of heterogeneous disorders [18•, 19, 34]. Frow et al. [19] investigated the direct to consumer “stem cell” marketing patterns in 169 operational “stem-cell” clinics in the Southwestern USA as of May 2019. The authors described a spectrum of marketed indications for “stem cell therapy”, including autism, cancer, cosmetic, gastrointestinal, hepatic, dystrophic, neurodegenerative, urological, inflammatory, and orthopedic disorders, with the latter having the biggest share of the marketed indications. Furthermore, they highlighted that 25% of businesses offered more than one source of utilized cellular therapy, while 40% of businesses offered more than one cell type for the marketed interventions, adding to the complexity of adequate substrate characterization. Knoepfle et al. [35] furthered this by illustrating the unfounded claims of, superior safety compared with the standard of care absence of potential adverse effects, and attainment of FDA approval being routinely made in advertisement or so-called “educational seminars.” Such claims are often received by vulnerable patients with serious medical conditions, which, coupled with the poorly characterized nature of the intervention, poses significant concerns. Similarly, Piuze et al. [2] studied the marketing patterns of 273 businesses offering SCI for knee OA. The authors outlined that an average of 82% efficacy was claimed by the studied businesses, a rate that is significantly dissonant from published literature.

The stem cell market is fraught with conflated messages that over-emphasize potential benefits and trivialize established risks of SCI. Additionally, advertisement utilized in direct-to-consumer marketing may describe a treatment that is inconsistent with that provided to the patient. Marketers of unproven SCI often misuse terminology, in addition to engaging in predatory practices. Such behavior includes the dissemination of publications in journals with little to no peer-review in addition to seeking scientific legitimacy by renting

laboratory spaces within credible scientific institutions, followed by claims of an unfounded affiliation.

While certain businesses may be implicated in initiating the SCI marketing hype, both mainstream and social media are clearly implicated in its widespread [14•, 15•, 16]. Media practices tapped into the public fascination with a perceived revolutionary regenerative potential that is yet to be established. Early research findings are often trumpeted by media outlets as breakthroughs that are expected to be clinically implemented in a so-called near future [36]. In addition, “stem cell” marketers are, with or without deliberation, portrayed as the good mavericks who side with patients in their search of an unorthodox but effective cure despite the efforts of the “misguided” medical institutions and the big pharma [14•, 36]. Such marketing strategies, whether intentional or unintentional, have the potential for misleading patients who are often cornered between severe pain and the dread of surgical interventions.

The Applicability of SCI

The applicability of SCI in clinical practice is contingent upon (1) the provision of equivalent or superior value (cost vs. effectiveness) compared with the current standard of care and (2) establishing appropriate regulations governing the implementation of novel therapeutics ensuring patient safety.

The value of SCI is yet to be asserted owing to a lack of studies exploring true-cost coupled with the lack of high-quality evidence supporting the efficacy of the various forms of SCI for a range of musculoskeletal indications including joint osteoarthritis, rotator cuff pathology, healing of fractures, and long bone defects, osteonecrosis of the hip and the knee, tendon regeneration, and the regeneration of osteochondral defects [37]. Piuze et al. [2] investigated the average cost of SCI for knee osteoarthritis, one of the most common SCI applications in orthopedics. The authors reported the mean price of a single unilateral stem-cell injection in the USA to be \$5156 ± 2446, which is significantly under the \$29,488 cost of a unilateral total knee arthroplasty (TKA) recently described by Palsis et al. [38]. However, the current body of literature is devoid of an overall comparison of cost between both interventions that take into account the added expenses of complications, the need for reinjection, conversion to TKA, or reoperation. Furthermore, the extent to which the absence of insurance coverage of SCI impacts the patient-perceived cost is yet to be determined [2]. Similarly, the vagueness of the SCI efficacy is closely tied to the absence of high-quality evidence comparing the outcomes of SCI to those of the standard of care [18•, 39].

Achieving a balance that avoids overtly lax or strictly prohibitive regulatory measures over SCI has been a notoriously precarious aspect of legislation [40]. The marketing of

uncharacterized and unproven SCI poses a controversy based on medical ethics [16, 34]. While the “right to try” act may provide a legislative escape clause for the use of unproven “stem cell” therapies in certain fields, musculoskeletal disorders rarely satisfy the conditions of posing a threat to life and the exhaustion of alternative therapies [14•, 41]. Therefore, despite the pervasiveness of its regulatory complexity, musculoskeletal disorders stand to benefit the most from regulations with clear definitions and robust inclusion/exclusion criteria regarding the type and indication of SCI [14•, 15•]. However, it is also important to present a fair recreation of the status of knowledge in the field, so that patients can also gain access to early-stage novel treatment that has the potential to provide ailment to their pain and limitations.

Recommendations for Safe and Ethical Incorporation in Practice

To date, there is a limited amount of high-quality clinical evidence supporting the use of “stem cell” therapies for musculoskeletal conditions [10, 29]. Adequately powered randomized controlled studies should be conducted with the standard of care as the control to assess the superiority, or lack thereof, of SCI. Furthermore, studies should utilize validated patient-reported outcome measures and tests for the attainment of a minimal clinically important difference (MCID), in order to maintain the clinical relevance of potential findings [10–12, 25, 28–30, 42]. An active, interdisciplinary, and well-coordinated approach involving physicians, legislators, and professional communities as well as media and market stakeholders is required. Medical licensing boards could effectively curb the spread of the unindicated use of SCI through disciplinary actions ranging from issued warnings to revoking of licensure [16, 34, 43]. Civil litigation, including the aforementioned class-actions, could act as a deterrent against bland violations in the form of misrepresentation that invalidates informed consent [40]. The Federal Trade Commission (FTC) has instituted a campaign to halt the deceptive health claims by certain SCI businesses advertisement. The FTC recommendations for appropriate marketing of SCI include the avoidance of “cure” claims without statistically and clinically significant results in addition to the proper use of medical terminology. Moreover, the FTC has enforced federal injunctions on deceptive SCI advertisement with a recently recorded \$3.31 million judgment for infractions committed by an amniotic stem cell business.

Professional societies as the International Society for Cellular Therapy and the American Academy of Orthopaedic Surgeons (AAOS) have issued recommendations regarding the use of SCI for musculoskeletal disorders. The AAOS issued a consensus in 2018 recommending that practitioners appreciate the “untested and uncharacterized nature

of these treatments”, and that this nature is “clearly communicated within the profession, to patients, and to the public.” [15•]. The American Association of Hip and Knee Surgeons (AAHKS) recommendations are consistent with those of AAOS, and state “It is our position that biologic therapies, including stem cell and PRP injections, cannot be currently recommended for the treatment of advanced hip or knee arthritis [44].” Of note, given the need for novel nonsurgical therapies to manage OA and the potential promise of biologics such as “stem cell” therapies, the AAOS recommends standardization of study design/reporting, the establishment of registries for postmarket monitoring, and the organization of a multicenter knee OA clinical trial consortium that includes randomized controlled trials assessing MCID [15•].

Conclusion

SCI are being popularized as a regenerative therapeutic intervention for multiple musculoskeletal disorders. Upholding the principles of ethical medical practice requires clear disclosure of the specific nature of the intervention and a proper informed consent of the potential risk and benefit. The poor characterization of SCI, as well as irresponsible marketing practices, compromise the transparency of SCI thereby jeopardizing patient safety along with the potential of developing meaningful cell-based therapeutics and their routine application in the musculoskeletal field. It is especially important for clinicians to properly educate patients on the risks and benefits of “stem cell” injections. Furthermore, a multifaceted intervention that encompasses all stakeholders is essential to prevent further abuse.

Compliance with Ethical Standards

Institutional Review Board approval was not required for the current study.

Conflict of Interest Nicolas S. Piuze has the following declarations: ISCT: board or committee member; Journal of Hip Surgery: editorial or governing board; Journal of Knee Surgery: editorial or governing board; Orthopaedic Research Society: board or committee member; RegenLab: research support; Zimmer: research support. Ahmed K. Emara has no conflict of interest. Jorge Chahla has the following declarations: Arthrex, Inc.: unpaid consultant; CONMED Linvatec: unpaid consultant; Smith & Nephew: unpaid consultant. Bert R. Mandelbaum has the following declarations: AJSM, cartilage: editorial or governing board; Arthrex, Inc.: IP royalties; paid consultant; Chairman CONCACAF Medical Committee: board or committee member; DePuy, A Johnson & Johnson Company: paid consultant; Exactech, Inc.: PAID consultant; Kerlan Jobe Institute: board or committee member.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:

- Of importance
- Of major importance

1. Bauer TW. Stem cell therapy for knee pain—what exactly are we injecting, and why? *J Bone Jt Surg.* 2016;98(18):1509–10. <https://doi.org/10.2106/JBJS.16.00872>.
2. Piuze NS, Ng M, Chugtai M, Khlopas A, Ng K, Mont M, et al. The stem-cell market for the treatment of knee osteoarthritis: a patient perspective. *J Knee Surg.* 2018;31(6):551–6. <https://doi.org/10.1055/s-0037-1604443>.
3. Ng M, Song S, Piuze NS, et al. Stem cell industry update: 2012 to 2016 reveals accelerated investment, but market capitalization and earnings lag. *Cytotherapy.* 2017;19(10):1131–9. <https://doi.org/10.1016/j.jcyt.2017.07.006> **Outlines the rising trends within the stem cell market.**
4. Nho SJ, Kymes SM, Callaghan JJ, Felson DT. The burden of hip osteoarthritis in the United States: epidemiologic and economic considerations. *J Am Acad Orthop Surg.* 2013;21(suppl):S1–6. <https://doi.org/10.5435/JAAOS-21-07-S1>.
5. Bitton R. The economic burden of osteoarthritis. *Am J Manag Care.* 2009;15(8 Suppl):S230–5.
6. Maumus M, Guérit D, Toupet K, Jorgensen C, Noël D. Mesenchymal stem cell-based therapies in regenerative medicine: applications in rheumatology. *Stem Cell Res Ther.* 2011;2(2):1–6. <https://doi.org/10.1186/scrt55>.
7. Syed BA, Evans JB. Stem cell therapy market. *Nat Rev Drug Discov.* 2013;12(3):185–6. <https://doi.org/10.1038/nrd3953>.
8. Ng MK, Mont MA, Piuze NS. Analysis of readability, quality, and content of online information available for “stem cell” injections for knee osteoarthritis. *J Arthroplasty.* 2020;35(3):647–651.e2. <https://doi.org/10.1016/j.arth.2019.10.013> **Highlights the poor characterization of the marketed stem cell interventions on digital platforms.**
9. Pas HI, Winters M, Haisma HJ, Koenis MJ, Tol JL, Moen MH. Stem cell injections in knee osteoarthritis: a systematic review of the literature. *Br J Sports Med.* 2017;51(15):1125–33. <https://doi.org/10.1136/bjsports-2016-096793>.
10. Jevotovsky DS, Alfonso AR, Einhorn TA, Chiu ES. Osteoarthritis and stem cell therapy in humans: a systematic review. *Osteoarthritis Cartil.* 2018;26(6):711–29. <https://doi.org/10.1016/j.joca.2018.02.906>.
11. Papakostidis C, Tosounidis TH, Jones E, Giannoudis PV. The role of “cell therapy” in osteonecrosis of the femoral head. *Acta Orthop.* 2016;87(1):72–8. <https://doi.org/10.3109/17453674.2015.1077418>.
12. Chahla J, Piuze NS, Mitchell JJ, Dean CS, Pascual-Garrido C, LaPrade RF, et al. Intra-articular cellular therapy for osteoarthritis and focal cartilage defects of the knee: a systematic review of the literature and study quality analysis. *J Bone Jt Surg - Am.* 2016;98(18):1511–21. <https://doi.org/10.2106/JBJS.15.01495>.
13. Murray IR, Chahla J, Frank RM, Piuze NS, Mandelbaum BR, Dragoo JL, et al. Rogue stem cell clinics. *Bone Joint J.* 2020;102-B(2):148–54. <https://doi.org/10.1302/0301-620X.102B2.BJJ-2019-1104.R1>.
14. Piuze NS, Dominici M, Long M, et al. Proceedings of the signature series symposium “cellular therapies for orthopaedics and musculoskeletal disease proven and unproven therapies—promise, facts and fantasy,” international society for cellular therapies, montreal, canada, may 2, 2018. *Cytotherapy.* 2018;20(11):1381–400. <https://doi.org/10.1016/j.jcyt.2018.09.001> **Provides guidelines and**

- recommendations that aid in the identification of proven vs. unproven stem cell therapies.**
- 15.●● Chu CR, Rodeo S, Bhutani N, et al. Optimizing clinical use of biologics in orthopaedic surgery: consensus recommendations from the 2018 AAOS/NIH U-13 conference. *J Am Acad Orthop Surg.* 2019;27(2):e50–63. <https://doi.org/10.5435/JAAOS-D-18-00305> **Provides guidelines elucidating the proper use designation of stem cell therapies in orthopaedics.**
  16. Ellison B. Stem cell research and social justice : aligning scientific progress with social need. *Curr Stem Cell Reports.* 2016;2:328–35. <https://doi.org/10.1007/s40778-016-0063-3>.
  17. Nherera LM, Trueman P, Horner A, Johnstone AJ, Watson TJ, Fatoye FA. Comparing the costs and outcomes of an integrated twin compression screw (ITCS) nail with standard of care using a single lag screw or a single helical blade cephalomedullary nail in patients with intertrochanteric hip fractures. *J Orthop Surg Res.* 2018;13(1): 1–8. <https://doi.org/10.1186/s13018-018-0923-x>.
  - 18.●● Murray IR, Chahla J, Frank RM, Piuze NS, Mandelbaum BR, Dragoo JL. Rogue stem cell clinics. *Bone Joint J.* 2020;102-B(2): 148–54. <https://doi.org/10.1302/0301-620X.102B2.BJJ-2019-1104.R1> **Outlines the magnitude of the direct-to-consumer marketing practices and provides recommendations for sufficient regulation.**
  19. Frow EK, Brafman DA, Muldoon A, Krum L, Williams P, Becker B, et al. Characterizing direct-to-consumer stem cell businesses in the Southwest United States. *Stem Cell Reports.* 2019;13(2):247–53. <https://doi.org/10.1016/j.stemcr.2019.07.001>.
  20. Piuze NS, Chahla J, Jiandong H, Chughtai M, LaPrade RF, Mont MA, et al. Analysis of cell therapies used in clinical trials for the treatment of osteonecrosis of the femoral head: a systematic review of the literature. *J Arthroplast.* 2017;32(8):2612–8. <https://doi.org/10.1016/j.arth.2017.02.075>.
  21. Marcucio RS, Nauth A, Giannoudis PV, Bahney C, Piuze NS, Muschler G, et al. Stem cell therapies in orthopaedic trauma. *J Orthop Trauma.* 2015;29(Suppl 12):S24–7. <https://doi.org/10.1097/BOT.0000000000000459>.
  22. Vakharia RM, Roche MW, Alcerro JC, Lavernia CJ. The current status of cell- based therapies for primary knee osteoarthritis. *Orthop Clin NA.* 2019;50(4):415–23. <https://doi.org/10.1016/j.ocl.2019.06.001>.
  23. Shakouri-Motlagh A, Khanabdari R, Heath DE, Kalonis B. The application of decellularized human term fetal membranes in tissue engineering and regenerative medicine (TERM). *Placenta.* 2017;59:124–30. <https://doi.org/10.1016/j.placenta.2017.07.002>.
  24. Pogozhykh O, Prokopyuk V, Figueiredo C, Pogozhykh D. Review article placenta and placental derivatives in regenerative therapies : experimental studies. *Hist Prospects.* 2018;2018.
  25. Jo CH, Lee YG, Shin WH, Kim H, Chai JW, Jeong EC, et al. Intra-articular injection of mesenchymal stem cells for the treatment of osteoarthritis of the knee: a proof-of-concept clinical trial. *Stem Cells.* 2014;32(5):1254–66. <https://doi.org/10.1002/stem.1634>.
  26. Wyles CC, Houdek MT, Behfar A, Sierra RJ. Mesenchymal stem cell therapy for osteoarthritis: current perspectives. *Stem Cells Cloning Adv Appl.* 2015;8:117–24. <https://doi.org/10.2147/SCCAA.S68073>.
  27. Koh YG, Choi YJ. Infrapatellar fat pad-derived mesenchymal stem cell therapy for knee osteoarthritis. *Knee.* 2012;19(6):902–7. <https://doi.org/10.1016/j.knee.2012.04.001>.
  28. Lamo-Espinosa JM, Mora G, Blanco JF, Granero-Moltó F, Nuñez-Córdoba JM, Sánchez-Echenique C, et al. Intra-articular injection of two different doses of autologous bone marrow mesenchymal stem cells versus hyaluronic acid in the treatment of knee osteoarthritis: multicenter randomized controlled clinical trial (phase I/II). *J Transl Med.* 2016;14(1):1–9. <https://doi.org/10.1186/s12967-016-0998-2>.
  29. Hurley ET, Yasui Y, Gianakos AL, Seow D, Shimozono Y, Kerkhoffs GMMJ, et al. Limited evidence for adipose-derived stem cell therapy on the treatment of osteoarthritis. *Knee Surgery, Sport Traumatol Arthrosc.* 2018;26(11):3499–507. <https://doi.org/10.1007/s00167-018-4955-x>.
  30. Peeters CMM, Leijns MJC, Reijman M, van Osch GJVM, Bos PK. Safety of intra-articular cell-therapy with culture-expanded stem cells in humans: a systematic literature review. *Osteoarthritis Cartil.* 2013;21(10):1465–73. <https://doi.org/10.1016/j.joca.2013.06.025>.
  31. Zhang W, Robertson J, Jones AC, Dieppe PA, Doherty M. The placebo effect and its determinants in osteoarthritis: meta-analysis of randomised controlled trials. *Ann Rheum Dis.* 2008;67(12): 1716–23. <https://doi.org/10.1136/ard.2008.092015>.
  32. Zhang W. The powerful placebo effect in osteoarthritis. *Clin Exp Rheumatol.* 2019;37(5):118–23.
  33. Bauer G, Elsallab M, Abou-El-Enin M. Concise review: a comprehensive analysis of reported adverse events in patients receiving unproven stem cell-based interventions. *Stem Cells Transl Med.* 2018;7(9):676–85. <https://doi.org/10.1002/sctm.17-0282>.
  34. Turner L. The US Direct-to-consumer marketplace for autologous stem cell interventions. *Perspect Biol Med.* 2018;61(1):7–24. <https://doi.org/10.1353/pbm.2018.0024>.
  35. Knoepfler PS. The stem cell hard sell: report from a clinic's patient recruitment seminar. *Stem Cells Transl Med.* 2017;6(1):14–6. <https://doi.org/10.5966/sctm.2016-0208>.
  36. Caulfield T, Sipp D, Murry CE, Daley GQ, Kimmelman J, SCIENTIFIC COMMUNITY. Confronting stem cell hype. *Science.* 2016;352(6287):776–7. <https://doi.org/10.1126/science.aaf4620>.
  37. Im G-I. Clinical use of stem cells in orthopaedics. *Eur Cell Mater.* 2017;33:183–96. <https://doi.org/10.22203/eCM.v033a14>.
  38. Palsis JA, Brehmer TS, Pellegrini VD, Drew JM, Sachs BL. The cost of joint replacement: comparing two approaches to evaluating costs of total hip and knee arthroplasty. *J Bone Joint Surg Am.* 2018;100(4):326–33. <https://doi.org/10.2106/JBJS.17.00161>.
  39. Piuze NS, Mantripragada VP, Sumski A, Selvam S, Boehm C, Muschler GF. Bone marrow-derived cellular therapies in orthopaedics: part I: recommendations for bone marrow aspiration technique and safety. *JBJS Rev.* 2018;6(11):e4. <https://doi.org/10.2106/JBJS.RVW.18.00007>.
  40. Horner C, Tenenbaum E, Sipp D, Master Z. Can civil lawsuits stem the tide of direct-to-consumer marketing of unproven stem cell interventions. *NPJ Regen Med.* 2018;3(1):1–4. <https://doi.org/10.1038/s41536-018-0043-6>.
  41. Turner L. Direct-to-consumer marketing of stem cell interventions by Canadian businesses. *Regen Med.* 2018;13(6):643–58. <https://doi.org/10.2217/rme-2018-0033>.
  42. Jones IA, Togashi R, Wilson ML, Heckmann N, Vangsness CT. Intra-articular treatment options for knee osteoarthritis. *Nat Rev Rheumatol.* 2019;15(2):77–90. <https://doi.org/10.1038/s41584-018-0123-4>.
  43. Sipp D. The malignant niche: safe spaces for toxic stem cell marketing. *NPJ Regen Med.* 2017;2(1). <https://doi.org/10.1038/s41536-017-0036-x>.
  44. Browne JA, Nho SJ, Goodman SB, Della Valle CJ. American association of hip and knee surgeons, hip society, and knee society position statement on biologics for advanced hip and knee arthritis. *J Arthroplast.* 2019;34(6):1051–2. <https://doi.org/10.1016/j.arth.2019.03.068>.