American Medical Society for Sports Medicine Position Statement: Principles for the Responsible Use of Regenerative Medicine in Sports Medicine

Jonathan T. Finnoff, DO,* Tariq M. Awan, DO,† Joanne Borg-Stein, MD,‡ Kimberly G. Harmon, MD,§ Daniel C. Herman, MD, PhD,¶ Gerard A. Malanga, MD,‖ Zubin Master, PhD,** Kenneth R. Mautner, MD,††‡‡ and Shane A. Shapiro, MD§§

Abstract: Many sports medicine physicians are currently considering introducing regenerative medicine into their practice. Regenerative medicine and the subclassification of orthobiologics are a complicated topic and have produced widely varying opinions. Although there is concern by government regulators, clinicians, scientists, patient advocacy organizations, and the media regarding the use of regenerative medicine products, there is also excitement about the potential benefits with growing evidence that certain regenerative medicine products are safe and potentially efficacious in treating musculoskeletal conditions. Sports medicine physicians would benefit from decision-making guidance about whether to introduce orthobiologics into their practice and how to do it responsibly. The purpose of this position statement is to provide sports medicine physicians with information regarding regenerative medicine terminology, a brief review of basic science and clinical studies within the subclassification of orthobiologics, regulatory considerations, and best practices for introducing regenerative medicine into clinical practice. This information will help sports medicine physicians make informed and responsible decisions about the role of regenerative medicine and orthobiologics in their practice.

Key Words: orthobiologics, osteoarthritis, regenerative medicine, tendinopathy

(*Clin J Sport Med* 2021;31:530–541)

BACKGROUND AND PURPOSE

In the United States, the number of clinics offering "stem-cell therapy" is estimated to be well over 1000.[1,2] Many clinics advertise unproven and unapproved regenerative medicine interventions for musculoskeletal conditions.[1,2] A press release from the US Food and Drug Administration (FDA) in 2018 stated that, "The potential health benefits of regenerative medicine have spurred major progress in stem-cell biology over the past several decades. But we continue to see bad actors exploit the scientific promise of this field to mislead vulnerable patients into believing they are being given safe, effective treatments; when instead these stem-cell producers are leveraging the field's hype to push unapproved, unproven, illegal, and potentially unsafe products."[3]

Many sports medicine physicians are currently considering the role of regenerative medicine in their practice. The purpose of this position statement created by the American Medical Society for Sports Medicine (AMSSM) is to provide sports medicine physicians with information regarding regenerative medicine terminology, a brief review of the basic science and clinical studies related to the musculoskeletal field (now commonly referred to as orthobiologics), regulatory considerations, and best practices for introducing regenerative medicine into clinical practice.[4] This information will help sports medicine physicians make informed and responsible decisions about the role of regenerative medicine in their practice.

About the organization: AMSSM is a multidisciplinary organization of sports medicine physicians dedicated to education, research, advocacy, and the care of athletes of all ages. Most AMSSM members are primary care physicians with fellowship training and added qualification in sports medicine, who then combine their practice of sports medicine with their primary specialty. American Medical Society for Sports Medicine includes members who specialize solely in nonsurgical sports medicine and serve as team physicians at the youth level, National Collegiate Athletic Association, National Football League, Major League Baseball, National Basketball Association, Women's National Basketball Association, Major League Soccer, and National Hockey League, as well as with Olympic and Paralympic teams. By nature of their training and experience, sports medicine physicians are ideally suited to provide comprehensive medical care for athletes, sports teams, or active individuals who are simply looking to maintain a healthy lifestyle (www.amssm.org).

Submitted for publication July 7, 2021; accepted July 19, 2021.

*From the *Department of Physical Medicine and Rehabilitation, Mayo Clinic College of Medicine and Science, Rochester, Minnesota; †Department of Orthopedic Surgery, University of Michigan, Ann Arbor, Michigan; ‡Division of Sports and Musculoskeletal Rehabilitation, Department of Physical Medicine and Rehabilitation, Harvard Medical School, Boston, Massachusetts; §Departments of Family Medicine and Orthopedics and Sports Medicine, University of Washington School of Medicine, Seattle, Washington; ¶Department of Orthopedics and Rehabilitation, University of Florida, Gainesville, Florida; ‖Department of Physical Medicine and Rehabilitation, Rutgers School of Medicine-New Jersey Medical School, Newark, New Jersey; **Biomedical Ethics Research Program and the Center for Regenerative Medicine, Mayo Clinic College of Medicine and Science, Rochester, Minnesota; ††Department of Physical Medicine and Rehabilitation, Emory University, Atlanta, Georgia; ‡‡Department of Orthopedics, Emory University, Atlanta, Georgia; and §§Department of Orthopedic Surgery, Mayo Clinic College of Medicine and Science, Jacksonville, Florida.*

The authors report no conflicts of interest.

Corresponding Author: Kenneth R. Mautner, MD, 1968 Hawks Lane, Atlanta, GA 30329 (kmautne@emory.edu).

http://dx.doi.org/10.1097/JSM.0000000000000973

WRITING GROUP SELECTION AND PROCESS

The AMSSM Board of Directors established a Regenerative Medicine Task Force in 2019, with a subgroup charged to develop a regenerative medicine position statement. The Task Force submitted a recommended writing group that included sports medicine physicians and scientists who are recognized leaders in bioethics, research, and regenerative medicine clinical applications to the AMSSM Board of Directors. The position statement writing group, proposed timeline, and outline were approved by the AMSSM Board of Directors after their December 2019 meeting. The writing group communicated by conference calls and electronically to produce the final document that was reviewed and approved by the AMSSM Board of Directors on May 19, 2021.

Terminology

The field of regenerative medicine is rapidly growing with terms and definitions that have not been standardized or may be overlapping especially in the subspecialty of orthobiologics. For the purposes of establishing a common understanding, regenerative medicine terms are described in Table 1.[7–9]

BASIC AND CLINICAL SCIENCE

The understanding of the exact mechanisms by which regenerative medicine products have their therapeutic effect is evolving. The following is a brief discussion of the basic science, proposed therapeutic mechanisms of action, and clinical evidence related to regenerative medicine products. This is not meant to be an exhaustive or systematic review of the literature and should not be considered as an endorsement of any particular product or procedure. For the purposes of this position article, we have limited the references to those procedures that are commonly performed in the United States and do not require an Investigational New Drug Application or Investigational Device Exemption. Table 2 provides a summary of the literature search criteria used to create Tables 3-5 of this section.

Platelet-Rich Plasma

Platelet-rich plasma (PRP) is broadly defined as plasma with a platelet concentration higher than whole blood.[77,78] The term PRP was coined by hematologists in the 1970s and was initially used as a transfusion product to treat patients with thrombocytopenia. It was almost 30 years later before its use in musculoskeletal medicine. Platelet-rich plasma can be further categorized based on its cellular composition, most commonly as leukocyte-rich PRP or leukocyte-poor PRP. Platelets participate in blood clot formation and in the modulation of inflammation and healing which are achieved through the release of various growth factors, cytokines, and chemokines from the platelet's mitochondria and all 3 granules (dense, alpha, and lysosomal).[79] Generally, it is believed that 70% to 95% of the platelet's growth factors are released within 10 minutes of platelet activation, which occurs after exposure to connective tissue collagen or the addition of a platelet activator such as calcium chloride or thrombin, with the remainder being slowly released over a few days.[77,80,81] Although the evidence for the clinical efficacy of PRP in a variety of musculoskeletal conditions is evolving, PRP is primarily used to treat tendinopathies and osteoarthritis (OA).[78]

Platelet-Rich Plasma for Tendinopathy

A summary of recent meta-analyses and systematic reviews evaluating the efficacy and major adverse events of PRP injections for tendinopathy is presented in Table 3.[10–30,32,82,83] For tendinopathy, the most robust data supporting treatment with PRP injections are in lateral epicondylopathy. Multiple randomized controlled trials have demonstrated that lateral epicondylopathy responds positively to PRP injections.[84–86] There have also been positive results seen in randomized controlled trials for the treatment of gluteus medius tendinopathy[77] and plantar fasciopathy[87] with PRP. The recent meta-analysis by Hurley et al[88] suggests that PRP may augment rotator cuff repairs resulting in improved healing rates, reduced pain levels, and improved functional outcomes.[88] In Achilles tendinopathy, well-designed, randomized controlled trials have found no difference between PRP and saline injections[15,89,90] and results in patellar tendinopathy have been mixed.[82,91,92]

Platelet-Rich Plasma for Osteoarthritis

Table 4 summarizes recent meta-analyses and systematic reviews evaluating the efficacy and major adverse events of PRP injections for OA.[11,12,33–54] The research suggests that PRP injections are more effective in reducing pain and improving function than steroid or hyaluronic acid injections for knee OA, particularly in those who are younger and have mild to moderate disease.[71,93–97] Sufficient evidence has not been acquired to determine if PRP injections are an effective treatment for OA in other joints.

Platelet-Rich Plasma for Ligament and Muscle Injuries

The evidence for PRP in ligament injuries is limited. A few preliminary studies suggested PRP may facilitate improved outcomes in partial thickness ulnar collateral ligament injuries of the elbow,[98,99] but a more recent large, retrospective controlled study of major league baseball players questioned these findings.[100] Currently, the efficacy of PRP injections for muscle injuries is unknown as this area has not been well studied.[101]

Cellular Therapies

The most commonly referred to cellular therapy involves mesenchymal stem cells (MSCs). The multipotent nature of these cells allows them to differentiate into various tissues in the mesenchymal lineage including bone, cartilage, adipose, and other soft tissues in vitro.[102] However, the exact mechanism of action of MSCs in vivo is poorly understood. Many experts believe their primary mechanism of action is by paracrine activity because of their secretory function resulting in anti-inflammatory, immunomodulatory, proangiogenic, antiapoptotic, antifibrotic, and proliferative effects.[103,104] Mesenchymal stem cells have also been shown to elicit differentiation of resident and nonresident cells to functional tissue, resulting in improved function of the degenerative tissue.[105–107] Although there has been in vitro and animal data

TABLE 1. Regenerative Medicine Terminology*

Term	Definition
BMAC	A concentrate of BMA containing multiple cell types, including a small number of MSCs, typically created through a centrifugation process
Cell-based medicinal product	Medicinal product consisting of viable cells. These products may contain genetically modified human cells and can be combined with noncellular components
Cell therapy	Administration of living cells to a patient for the treatment of disease or condition
Cell therapy product	Biological product that contains or consists of substantially manipulated living cells/tissues that is administered to humans to treat, prevent, or diagnose a disease through the pharmacological, immunological, or metabolic action of its cells/tissues
Embryonic stem cell	Pluripotent cell derived from the undifferentiated inner cell mass of an embryo
IDE	US FDA designation that permits the use of an investigational device in a clinical trial for the purpose of collecting safety and effectiveness data, which can be used to support a premarket approval application
IND	Request to the US FDA for permission to administer an investigational drug to humans as part of a clinical investigation or to administer an approved drug for a new indication or in a new patient population
MSC	Nonhematopoietic multipotent adult stem cell identified in multiple tissues that can differentiate into specialized stromal cells
	Reported to be present in bone marrow, umbilical cord blood, adipose tissue, and muscle
	Has the capability to differentiate into specialized stromal cells of skeletal tissues such as tenocytes, osteoblasts, chondrocytes, and adipocytes
	Also referred to as mesenchymal stromal stem cells
Orthobiologics	Use of biological substances to enhance biological healing of orthopedic injuries or alter the natural course of an orthopedic disease
Perinatal products	Perinatal-derived allogeneic biomaterials donated and recovered from healthy individuals
PRP	Blood plasma enriched in platelets, which contains cytokines and growth factors in higher concentrations than in blood plasma
Pluripotent	Capable of developing into any of the 3 primary germ cell layers and therefore all cells of the adult body, but not extraembryonic tissue (ie, placenta)
Prolotherapy	Hyperosmolar dextrose injection which triggers the inflammatory cascade and healing. The treatment targets fibroosseous junctions or entheses and well as intra-articular applications.[5]
Regenerative medicine	Interdisciplinary therapeutic approach that aims to repair, replace, regenerate, and/or rejuvenate lost, damaged, or diseased cells, tissues, or organs to restore or establish normal form and function.
Somatic cell	Any cell that makes up a multicellular organism that is not a germinal, reproductive, or undifferentiated cell
Stem cell	Undifferentiated cell of multicellular organisms with the ability to carry out both self-renewal and asymmetric cell division and to provide cells that can differentiate into other cell types
Stromal cells	Nonhematopoietic connective tissue cell that indirectly influences and supports blood cell growth, typically derived from bone marrow.
Viscosupplement	Injectable HA-based products that reduce pain through shock absorption and decreased inflammation by arachidonic acid and IL1 inhibition[6]

** Adapted from Refs. 7, 8.*

BMA, bone marrow aspirate; BMAC, bone marrow aspirate concentrate; FDA, Food and Drug Administration; HA, hyaluronic acid; IDE, Investigational Device Exemption; IL1, interleukin 1; IND, Investigational New Drug Application; MSC, mesenchymal stem cell; PRP, platelet-rich plasma.

showing significant cartilage preservation and restoration, these results have not, so far, been demonstrated with any consistency in clinical studies using MSC treatments.[108–111]

Autologous Cellular Therapies for Osteoarthritis

At present, the literature supporting cellular therapies for musculoskeletal conditions consists of some basic science and animal studies along with case reports, case series, and cohort studies in humans. Human clinical studies have focused predominantly on the treatment of knee OA using bone marrow aspirate (BMA), bone marrow aspirate concentrate (BMAC), and adipose tissue. All the products have a small percentage of MSCs despite varying cellular composition.

Unfortunately, many studies used methods that are outside of the FDA regulatory considerations (eg, culture expansion and more than minimal manipulation), thus limiting their applicability to clinical practice in the United States. Since the most commonly used product is BMAC, a literature search was completed to provide a summary of recent meta-analyses

TABLE 2. Summary of the Literature Search Criteria Used to Create Tables 3-5 in the Basic and Clinical Science Section

Table Number	Literature Search Criteria
Table 3	The literature search was performed using PubMed with the search terms (((PRP) OR (Platelet Rich Plasma)) AND ((Tendon) OR (Tendinopathy))) filtering for meta-analyses and systematic reviews in human subjects written in the English language between 2019 and 2020. Individual studies were reviewed for relevance.
Table 4	The literature search was performed using PubMed with the search terms (((PRP) OR (Platelet Rich Plasma)) AND ((Osteoarthritis) OR (OA) OR (Arthritis))) filtering for meta-analyses and systematic reviews in human subjects written in the English language between 2019 and 2020. Individual studies were reviewed for relevance.
Table 5	The literature search was performed using PubMed with the search terms (((BMAC) OR (Bone Marrow Aspirate Concentrate) OR (MSC) OR (Mesenchymal Stem Cell)) AND ((Osteoarthritis) OR (OA) OR (Arthritis))) filtering for meta-analyses and systematic reviews in human subjects written in the English language between 2016 and 2020. Individual studies were reviewed for relevance.

BMAC, bone marrow aspirate concentrate; MSC, mesenchymal stem cell; OA, osteoarthritis; PRP, platelet-rich plasma.

and systematic reviews evaluating the efficacy and major adverse events of BMAC injections for OA. This information is presented in Table 5.[43,46,55–70,72–76,112–116] The most methodologically sound study to date is the randomized controlled trial by Shapiro et al[116] that compared BMAC with saline injections in patients with bilateral knee OA. Using a within-subjects design, they reported similar reductions in pain between the 2 interventions at both 6-month and 12-month follow-up.[117] A few studies have shown that adipose-derived stem cells may reduce articular cartilage damage and degeneration, thereby reducing the progression of knee OA.[118,119] Furthermore, well-designed studies are needed to determine the clinical efficacy of MSCs for OA.

Autologous Cellular Therapies for Tendinopathy

There have been few studies evaluating the efficacy of MSC injections for the treatment of tendinopathy, but there are some preliminary data to suggest that MSCs may lessen pain, improve function, and induce a healing response in tendon injuries.[59] The most studied area is the rotator cuff. Hernigou et al[120] demonstrated that patients who received a BMAC injection at the time of their rotator cuff repair had enhanced healing, improved repair quality, and less retears than a control group who did not receive a BMAC injection. In addition, those with a higher number of MSCs in their BMAC had a higher likelihood of treatment success than those with a lower number of MSCs.[121] Although promising, it is difficult to extrapolate these results to other tendons. At this time, adipose-derived MSC products for tendons remain in the preclinical phase of inquiry or are moving toward clinical trials. No well-designed studies, systematic reviews, or meta-analyses have been completed. Based on the available evidence, the efficacy of MSCs in tendon pathology is still unknown and further studies are warranted.

Perinatal Products

Multiple perinatal products (umbilical cord blood, amniotic tissues, Wharton Jelly, etc) are being used in clinical practice. Currently available perinatal products that have been tested have been shown to contain biologically active molecules, but no viable human cells, MSC, or otherwise.[122,123] Owing to regulatory restrictions and a lack of clinical data (see Regulatory Considerations section), they will not be discussed further in this section and are not recommended for clinical use at this time.

REGULATORY CONSIDERATIONS

The use of human cells, tissues, and tissue products, commonly abbreviated HCT/Ps, such as blood products, stem cells, and adipose tissue, is regulated by the FDA under the authority of the federal Food, Drug, and Cosmetic Act and the Public Health Services Act.[124,125] A thorough discussion of the regulatory landscape is beyond the scope of this position article; those considering introducing regenerative medicine into their clinical practice should review and have a thorough understanding of FDA guidance documents.[126] Rossi et al[127] have summarized current regenerative medicine products, their derivation, and regulatory considerations (Figure 1).

The FDA has released a developmental framework and guidance for developers and providers of regenerative therapies. Two key concepts for sports medicine physicians

TABLE 3. Summary of Meta-Analyses and Systematic Reviews Evaluating the Efficacy and Major Adverse Events of Platelet-Rich Plasma Injections for Tendinopathy From 2019 to 2020

Tendinopathy	Treatment Effective	Treatment Ineffective	Treatment Mixed Efficacy	Major Adverse Events
Unspecified location	3 studies[10–12]	0 studies	0 studies	0 studies
Achilles tendinopathy	1 study[13]	2 studies[14,15]	2 studies[16,17]	0 studies
Lateral epicondylopathy	5 studies[18–22]	1 study[23]	1 study[24]	1 study[23]
Patellar tendinopathy	4 studies[25–28]	0 studies	0 studies	0 studies
Rotator cuff tendinopathy	3 studies[29–31]	0 studies	1 studies[32]	0 studies

TABLE 4. Summary of Meta-Analyses and Systematic Reviews Evaluating the Efficacy and Major Adverse Events of Platelet-Rich Plasma Injections for OA From 2019 to 2020

OA	Treatment Effective	Treatment Ineffective	Treatment Mixed Efficacy	Major Adverse Events
Unspecified location	1 study[33]	1 study[34]	0 studies	0 studies
Ankle	1 study[35]	0 studies	0 studies	0 studies
Foot	1 study[36]	0 studies	0 studies	0 studies
Hand	1 study[36]	0 studies	0 studies	0 studies
Hip	3 studies[11,37,38]	1 study[39]	0 studies	1 study[39]
Knee	14 studies[11,12,19,40–50]	0 studies	0 studies	1 study[46]
Temporo-mandibular	4 studies[51–54]	0 studies	0 studies	0 studies

OA, osteoarthritis.

include *homologous use* and *minimal manipulation*.[124,128] *Homologous use* is defined by the FDA as the repair, reconstruction, replacement, or supplementation of a recipient's cells or tissues with an HCT/P that performs the same basic function(s). *Minimal manipulation* for structural tissue is processing that does not alter the original relevant characteristics of the tissue relating to the tissue's utility for reconstruction, repair, or replacement. Minimal manipulation of cells or nonstructural tissues is processing that does not alter the relevant biological characteristics of cells or tissues.

These 2 concepts determine whether a regenerative medicine product complies with the Code of Federal Regulations under Title 21, parts 1270 and 1271.[124] All biologic products are regulated according to the current good tissue practice regulations, which ensure that HCT/Ps do not contain communicable disease agents and are not and do not become contaminated. The current preparation systems used to create PRP and BMAC are regulated under the 510 (k) pathway because they are considered "substantially equivalent" to a currently marketed device and therefore exempt from the traditional regulatory pathway. The products that they create are still regulated as HCT/Ps by the FDA. HCT/Ps that physically support, act as a conduit, connect, cover, or cushion are generally considered structural tissues and are regulated differently.

Despite the regulatory framework the FDA has put in place, uncertainty and controversy remains in orthopedic and sports medicine regarding whether a product (or procedure) will be regulated as a drug/device or whether it should be considered the practice of medicine.[126] An additional guidance document on the Same Surgical Procedure Exception outlines the FDA's view on the use of HCT/Ps within a procedure as a part of the practice of medicine and not separate from it[129]; however, within this framework, the HCT/P should be minimally manipulated and not combined with another product or substance.

Given some degree of uncertainty regarding minimal manipulation and homologous use, some practitioners have sought to define this as it pertains to sports medicine procedures.[130] Others have sought to challenge the FDA's oversight of orthobiologics with the most notable case in orthopedic and sports medicine being the United States versus Regenerative Sciences, 2012.[131] The US Federal Court of Appeals confirmed the FDA's regulatory authority and stance on the use of cells in clinical practice.[131]

Currently, a physician is considered a "manufacturer" of HCT/Ps if they are involved in any step of HCT/P recovery, processing, screening, testing, storage, or distribution. Many of the procedures performed in regenerative sports medicine use these elements and can limit the procedures sports medicine practitioners can perform in practice for the time being or at least until commercially available therapies that have been given FDA-licensed approval become available on the market.[125]

A wide range of allogeneic cell and cell-derived products largely harvested from perinatal sources have also emerged in clinical practices that market regenerative therapies directly to patients. Owing to wide availability and ease of use (ie, no bone marrow or fat harvest required), these products present an additional layer of growing disagreement between regulators, industry, and providers. To date, no such product has been licensed for musculoskeletal pathology, and the FDA has been consistent that injectable perinatal tissues are considered non-homologous use and more than minimally manipulated and should not be used in clinical practice until approved and licensed.[126,128] There are some manufacturers who have engaged the FDA and have ongoing clinical trials using perinatal products for the purpose of bringing such therapies to market for orthopedic indications.[132,133]

American Medical Society for Sports Medicine advocates for the responsible use of regenerative therapies for the purpose of protecting patients, public health, and the individual practitioners. American Medical Society for Sports Medicine also advocates that sports medicine physicians keep up to date on regenerative medicine regulations. In addition, clinicians should use clear patient communication regarding science, research, and the benefits and harms of individual regenerative medicine options. Providers need to be cautious and truthful in marketing interventions that have limited clinical evidence and are yet unproven.

TABLE 5. Summary of Meta-Analyses and Systematic Reviews Evaluating the Efficacy and Major Adverse Events of Bone Marrow Aspirate Concentrate Injections for OA From 2016 to 2020

OA	Treatment Effective	Treatment Ineffective	Treatment Mixed Efficacy	Major Adverse Events
Unspecified location	6 studies[55–60]	0 studies	0 studies	1 study[58]
Knee	11 studies[46,61–70]	2 studies[71,72]	5 studies[45,73–76]	1 study[64]

OA, osteoarthritis.

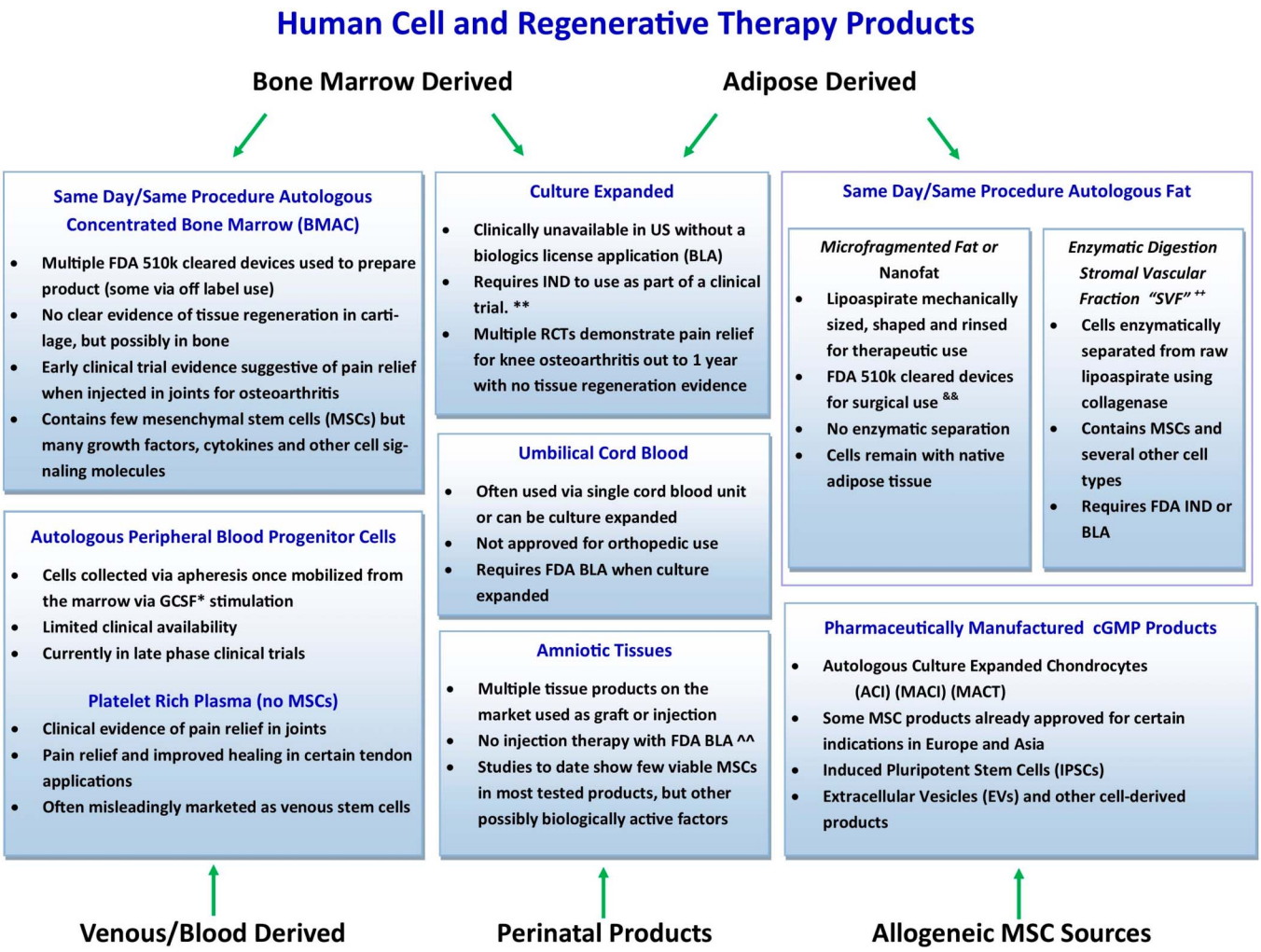

Figure 1. The derivation and regulatory considerations of commonly used regenerative medicine products. *GCSF granulocyte colony-stimulating factor. **Limited access worldwide, although some options are available in countries with less regulatory oversight. ^^multiple companies investigating injectable therapies sourced from perinatal tissues through clinical trials under FDA IND. &&Practice in the United States requires adherence to minimal manipulation: not more than rinsing, sizing, and shaping, as outlined in the US FDA Same Surgical Procedure Exception (SSPE). ++Multiple devices are available that use enzymatic digestion of SVF cells from adipose tissue. Considered by the FDA to be more than minimal manipulation and thus outside the scope of SSPE. Would require FDA IND or BLA to comply with current US regulatory framework. BLA, biologics license application; BMAC, bone marrow aspirate concentrate; cGMP, current good manufacturing process; EV, extracellular vesicles; FDA, US Food and Drug Administration; IND, Investigational New Drug; IPSC, induced pluripotent stem cells; MSC, mesenchymal stem cell; SVF, stromal vascular fraction. ACI, autologous chondrocyte implantation; MACI- matrix- induced autologous chondrocyte implantation; MACT- matrix-assisted autologous chondrocyte transplantation; RCT- randomized controlled trial. Adapted from Rossi et al 127 used with permission of Mayo Foundation for Medical Education and Research, all rights reserved.

Sports medicine physicians play a crucial role in ensuring patient safety while protecting the legitimacy of regenerative sports medicine as it evolves into a subspecialty. The FDA believes that each practitioner is responsible for interpreting their guidance documents and determining how the information in those documents apply to their individual practice. Whenever in doubt, the FDA offers a "toolkit" to help practitioners and those developing regenerative medicine therapies such as the INTERACT (Initial Targeted Engagement for Regulatory Advice on CBER products)[134] program that can help practitioners unsure of the regulatory status of a procedure that got guidance from regulators.[125,135,136]

Additional considerations include Federal Trade Commission oversight that regulates how physicians and their practices market regenerative therapies to protect patients (consumers) from deceptive, misleading, false, and fraudulent medical claims or practices.[137] This applies not only to physician patient interactions but also physician claims, advertising, and websites about unproven regenerative therapies.[126]

Finally, although the discussion of regenerative therapy regulations often focuses on FDA authority, it is the state medical boards that regulate the practice of medicine. The Federation of State Medical Boards has published recommendations pertaining to regenerative and stem-cell therapy treatments that outlines best practices for physicians using treatments that remain unproven or unapproved.[134,138]

INTRODUCING REGENERATIVE MEDICINE INTO CLINICAL PRACTICE

Providers need to take a rigorous and structured approach when making the decision to introduce regenerative medicine

procedures into clinical practice. Such an approach needs to consider the science and clinical evidence behind the product or procedure, feasibility of implementation, and regulatory considerations.

It is imperative that the procedure has a measure of scientific validity. Translation of novel therapeutics into clinical practice conventionally proceeds along a 4-phase clinical trial pathway to prove safety and efficacy. As discussed in the regulatory section, certain elements of regenerative medicine are not required to pass through such a development process. Despite this, it is incumbent on the provider to identify and review the relevant literature, including basic science, preclinical, and clinical studies to ensure such treatments meet the minimum criteria for evidence-based clinical standards. This review should be as free of influence of unsubstantiated claims and publicity regarding the treatment. The review should also demonstrate that there is at least clinical equipoise—a clinician's best judgment given a genuine uncertainty among the scientific community about whether the novel intervention is safer or more effective than the current treatment.

After making the decision to perform a regenerative medicine procedure, the sports medicine physician must then consider how this procedure fits into their algorithm of treatment for specific conditions. In general, treatments that are the least invasive, safest, most cost-effective treatment with the highest level of evidence are implemented first. Only after these treatment options are exhausted should more invasive and novel treatments, such as orthobiologics, be considered. For example, as was discussed in the basic and clinical science section of this article, treatment options, such as PRP, are relatively inexpensive, less invasive, and have more evidence in the treatment of specific musculoskeletal conditions (ie, OA and lateral epicondylopathy) than other orthobiologic options. This information should be considered when formulating a treatment algorithm.

Although there is strong interest among patients for regenerative medicine to treat orthopedic and sports-related conditions, the provider must explain the evidence-based rationale for such treatments and avoid patient motivations that are not supported by evidence.[139] Similarly, the provider must guard against the potential to be unduly influenced by internal and external commercial motivations when completing their evaluation of the scientific support for a given procedure.

As with the potential introduction of any clinical procedure, the provider will need to consider several aspects to ensure that the procedure can be implemented in their practice environment. The provider will need to account for the availability, feasibility of purchase, upkeep and maintenance, and physical space needed for the equipment related to the procedure. Many clinicians who would like to provide these options to their patients will require additional training to become proficient in the relevant procedures.[140] A plan should be developed to ensure appropriate training or certification of the provider and clinical staff to ensure the regenerative medicine therapy can be delivered in a safe manner in accordance with current research and manufacturer recommendations; these may include, but are not limited to, training related to cell or tissue harvest, material and equipment processing, biologic material assays, image guidance, and product delivery. Regenerative medicine treatments often require a multidisciplinary team and, in some practice environments, may require coordination with groups within or external to their organization. Setting standard operating procedures for communication between these groups is a key step toward successful and practical implementation.

Finally, the provider will need to have a firm understanding of how the regenerative medicine procedure fits into the existing regulatory landscape discussed above. Similar to the review of the scientific evidence in support of the procedure, so too should several sources be used during this assessment including internal and external regulatory and compliance personnel. The experiences and protocols of outside experts, institutions, and professional societies, such as AMSSM, may also be very helpful with this analysis. It is important to note that this review of the regulatory landscape is not a single static assessment. The regulatory environment is dynamic, and a plan should be in place to regularly reassess how new rules may impact the regenerative medicine therapies the practice offers. The provider may also communicate directly with the FDA as necessary.[140] Clinicians also must remember that regulatory considerations are not limited to biological materials alone as the processing equipment may be novel or specific to the procedure and requires regulatory approval.

Procedures lacking clinical evidence on safety and efficacy should only be introduced under the internal review board oversight. Food and Drug Administration oversight may also be required. Even in cases where the regulatory environment is permissive, the provider should regularly assess patient outcomes, perform internal quality control, and improve their processes accordingly. If able, publishing their results to assist in the acquisition and dissemination of knowledge is recommended.

Knowledge and Training

Most regenerative medicine procedures are dependent on precise delivery of the product(s) to the affected location. As such, those performing regenerative medicine procedures must be proficient in image-guided procedures. These may include musculoskeletal ultrasound and fluoroscopy, alone or in combination with other image guidance techniques. The physician should have a full understanding of how to select the appropriate guidance technique for the regenerative medicine product being used as well as the anatomic target for the procedure given patient's characteristics (eg, body habitus) and its associated risks and costs.

The knowledge required in each of these areas is large and rapidly expanding. Sports medicine physicians may achieve and maintain competency in the field through a number of different pathways. Options include self-study, attending regenerative medicine courses and lectures, or attending courses related to ancillary skills development (such as musculoskeletal ultrasound courses). Industry-sponsored courses are common and may be a valuable adjunct for learning; however, to avoid potential bias, sports medicine physicians should not rely solely on these courses and avail themselves of a wide variety of learning opportunities. Orthobiologic principles and techniques are also taught in many sports medicine fellowships; however, this is not currently an Accreditation Council for Graduate Medical Education requirement, and the level of knowledge and competency provided during fellowship training varies significantly. Finally, rapidly evolving FDA rules and regulations will require those performing regenerative medicine procedures to engage in ongoing CME both in the form of self-study, formal courses, and symposia.

Informed Consent

Informed consent is the process where patients (or their surrogates) are provided sufficient information so they can make an informed choice about their health care options. The ethical premise of informed consent is a respect for patient autonomy.[141,142] Although many of the features of informed consent are common in both research and clinical care contexts, given the novelty of regenerative interventions, many of the elements of informed consent for research apply. Valid informed consent has 3 components: patients must be informed, consent must be obtained voluntarily, and consent must be given by a competent person (or surrogate).[143]

Clinicians are obligated to provide appropriate, understandable information to patients and address their questions so patients can make informed decisions about their care. The informed consent process should include the provision of information agreed on by professional standards or reasonable people[143] and should be conveyed in verbal and written manner, with forms being written at a low-grade school reading level. The information should be discussed in an honest and balanced manner focusing on clinically indicated and scientifically justified options.[144,145] In the context of orthobiologics where evidence of safety and efficacy is evolving, physicians should rigorously scrutinize the sources of scientific information to ensure a sound scientific rationale before presenting options to patients. Information should be offered without threat or coercion. Particularly egregious tactics include overemphasizing benefits or steering patients to a procedure after having been offered financial incentives such as a discount.[143,146]

A description of each care option should include the procedures involved, the risks, and potential benefits. The risk of infection, immune rejection, product/cell contamination, and other identifiable and unanticipated risks should be addressed.[147] Benefits should be described accurately and not overemphasized, particularly in light of misinformation surrounding "stem-cell therapies" that may heighten patient expectations such that patients may not give adequate consideration to other treatment options.[137,148–154]

The patient should be informed that regenerative medicine interventions are not currently considered standard of care. The FDA approval status of the intervention being proposed should be provided, and if the intervention is being offered as part of a research protocol, the internal review board status of the research study should be discussed.[126]

The out-of-pocket costs for orthobiologic treatments should be clearly communicated to the patient. Relevant conflicts of interest by the physician, clinic, or employer should be clearly disclosed. The patient should be informed that they have the right to withdraw their consent from the procedure for any reason and at any time.

Quality Control

Quality control is defined as a system to maintain standards of manufacturing or procedures and to ensure they adhere to a defined set of criteria. Regarding regenerative medicine, quality control can take many forms. Acknowledging that the known and theoretical mechanisms of action for regenerative medicine products depend on the delivery and release of biologically active molecules that are "manufactured" by the clinician or practitioner, lack of precise control and biological characterization of the product can become an impediment to procedural validation and clinical outcomes. In addition, there are many opportunities for contamination during the formulation of many regenerative medicine products that may create safety issues. Therefore, although pharmaceutical grade good manufacture practice is not required for many office-based orthobiologic procedures because of the same surgical procedure exception, it is still important to implement and monitor quality control measures to ensure delivery of a safe and standardized product.

Documentation should include time and date of the procedure, patient demographics, condition being treated, medications, medical comorbidities, prior surgical history, social history (eg, tobacco use, alcohol consumption, and illicit drug use), regenerative medicine processing technique, equipment used, cellular composition of the final product in absolute terms and in relation to baseline parameters, how the product was delivered, where it was delivered to, amount delivered in the target location, activation of the product, and any associated procedures performed (eg, needle fenestration). With respect to PRP and other cellular products, baseline cellular count and differential, postprocessing cellular count and differential, changes in cellular concentrations, injectate volume, and total cells delivered (broken down by the cell type) should be recorded at least periodically if possible. Finally, to provide effective quality control, practitioners must familiarize themselves with test variability between laboratories, Clinical Laboratory Improvement Amendment regulations, individual state laws, and other regulatory bodies.

Outcome Measures

Patient-Reported Outcome Measures (PROMs) are an important part of medical practice. Practices performing regenerative medicine procedures should collect PROMs on their patients for multiple reasons including the following:

1. The experimental nature of some regenerative medicine procedures
2. Quality control and patient safety purposes
3. Improving the informed consent process by discussing efficacy and safety outcomes among your patients
4. Conducting clinical research
5. Providing information that may assist with reimbursement of these procedures in the future
6. Assisting regulatory bodies, such as the FDA, and third-party payers in examining the cost-effectiveness of these procedures

There are many relevant and validated musculoskeletal-specific PROMs that sports medicine physicians can use to assess physical function and pain of patients treated with regenerative medicine procedures.[155] These PROMs are questionnaires that allow patients to report on their own health directly without interpretation from a medical professional.[156] Currently, the FDA has stated that they will also consider real-world evidence (RWE) and outcomes (RWO) when reviewing information on regenerative medicine treatments.[157] Real-world evidence and RWO are gathered outside of conventional clinical trials and includes data obtained from patient charts, laboratory reports, patient registries, pragmatic clinical trials, surveys, and mobile health devices.[158] Real-world evidence and RWO complement evidence obtained from randomized controlled trials and provides information about the long-term safety and effectiveness in

large populations in a more natural setting. Furthermore, RWE and RWO allow stakeholders and health insurance companies to assess the risk-benefit and economic value of medical interventions.[158,159]

CONCLUSION

The field of regenerative medicine, and the subclassification of orthobiologics, involves a variety of therapies and techniques focused on the repair or replacement of damaged or diseased tissue to restore function. Despite these novel therapies being very attractive to sports medicine physicians and patients alike, this is a complex and controversial topic as we have outlined above. This position statement provides sports medicine physicians with information on regenerative medicine terminology, a brief review of the basic science and clinical studies, regulatory considerations, and best practices for introducing the orthobiologic classification of regenerative therapies into their clinical practice. Armed with this knowledge, sports medicine physicians can make an informed and educated decision about whether to introduce certain regenerative medicine products and procedures into their clinical practice and as well as how to do so in a responsible manner.

References

1. Turner L, Knoepfler P. Selling stem cells in the USA: assessing the direct-to-consumer industry. *Cell Stem Cell*. 2016;19:154–157.
2. Knoepfler PS. Rapid change of a cohort of 570 unproven stem cell clinics in the USA over 3 years. *Regen Med*. 2019;14:735–740.
3. United States Food and Drug Administration. *FDA Warns StemGenex Biologic Laboratories LLC of Illegally Marketing an Unapproved Cellular Product Manufactured in a Facility With Significant Manufacturing Violations, Putting Patients at Risk*. Silver Spring, MD: United States Food and Drug Administration; 2018. Available at: https://www.fda.gov/news-events/press-announcements/fda-warns-stemgenex-biologic-laboratories-llc-illegally-marketing-unapproved-cellular-product. Accessed January 29, 2020.
4. Harmon KG, Clugston JR, Dec K, et al. American Medical Society for Sports Medicine position statement on concussion in sport. *Br J Sports Med*. 2019;53:213–225.
5. Hauser RA. Journal of prolotherapy international editorial board consensus statement on the use of prolotherapy for musculskeletal pain. *J Prolotherapy*. 2011;3:744–764.
6. Tehranzadeh J, Booya F, Root J. Cartilage metabolism in osteoarthritis and the influence of viscosupplementation and steroid: a review. *Acta Radiol*. 2005;46:288–296.
7. Bell R, Fuller B, Griffith M, et al. The glossary for cell and gene therapy and regenerative medicine. *Regen Med*. 2018;13:2–115.
8. Moore MC, Van De Walle A, Chang J, et al. Human perinatal-derived biomaterials. *Adv Healthc Mater*. 2017;6. doi: 10.1002/adhm.201700345.
9. Regenerative Medicine Advisory Panel. The glossary for cell & gene therapy and regenerative medicine 2020. *Regen Med*. 2020;15:1–174.
10. Cruciani M, Franchini M, Mengoli C, et al. Platelet-rich plasma for sports-related muscle, tendon and ligament injuries: an umbrella review. *Blood Transfus*. 2019;17:465–478.
11. Pachito DV, Latorraca COC, Riera R. Efficacy of platelet-rich plasma for non-transfusion use: overview of systematic reviews. *Int J Clin Pract*. 2019;73:e13402.
12. Trams E, Kulinski K, Kozar-Kaminska K, et al. The clinical use of platelet-rich plasma in knee disorders and surgery—a systematic review and meta-analysis. *Life (Basel)*. 2020;10:94.
13. Rhim HC, Kim MS, Choi S, et al. Comparative efficacy and tolerability of nonsurgical therapies for the treatment of midportion Achilles tendinopathy: a systematic review with network meta-analysis. *Orthop J Sports Med*. 2020;8:2325967120930567.
14. Nauwelaers AK, Van Oost L, Peers K. Evidence for the use of PRP in chronic midsubstance Achilles tendinopathy: a systematic review with meta-analysis. *Foot Ankle Surg*. 2021;27:486–495.
15. Wang Y, Han C, Hao J, et al. Efficacy of platelet-rich plasma injections for treating Achilles tendonitis: systematic review of high-quality randomized controlled trials. *Orthopade*. 2019;48:784–791.
16. Liu CJ, Yu KL, Bai JB, et al. Platelet-rich plasma injection for the treatment of chronic Achilles tendinopathy: a meta-analysis. *Medicine (Baltimore)*. 2019;98:e15278.
17. Madhi MI, Yausep OE, Khamdan K, et al. The use of PRP in treatment of Achilles Tendinopathy: a systematic review of literature. Study design: systematic review of literature. *Ann Med Surg (Lond)*. 2020;55:320–326.
18. Barnett J, Bernacki MN, Kainer JL, et al. The effects of regenerative injection therapy compared to corticosteroids for the treatment of lateral Epicondylitis: a systematic review and meta-analysis. *Arch Physiother*. 2019;9:12.
19. Johal H, Khan M, Yung SP, et al. Impact of platelet-rich plasma use on pain in orthopaedic surgery: a systematic review and meta-analysis. *Sports Health*. 2019;11:355–366.
20. Li A, Wang H, Yu Z, et al. Platelet-rich plasma vs corticosteroids for elbow epicondylitis: a systematic review and meta-analysis. *Medicine (Baltimore)*. 2019;98:e18358.
21. Tang S, Wang X, Wu P, et al. Platelet-rich plasma vs autologous blood vs corticosteroid injections in the treatment of lateral epicondylitis: a systematic review, pairwise and network meta-analysis of randomized controlled trials. *PM R*. 2020;12:397–409.
22. Xu Q, Chen J, Cheng L. Comparison of platelet rich plasma and corticosteroids in the management of lateral epicondylitis: a meta-analysis of randomized controlled trials. *Int J Surg*. 2019;67:37–46.
23. Lian J, Mohamadi A, Chan JJ, et al. Comparative efficacy and safety of nonsurgical treatment options for enthesopathy of the extensor carpi radialis brevis: a systematic review and meta-analysis of randomized placebo-controlled trials. *Am J Sports Med*. 2019;47:3019–3029.
24. Gao B, Dwivedi S, DeFroda S, et al. The therapeutic benefits of saline solution injection for lateral epicondylitis: a meta-analysis of randomized controlled trials comparing saline injections with nonsurgical injection therapies. *Arthroscopy*. 2019;35:1847–1859.e12.
25. Andriolo L, Altamura SA, Reale D, et al. Nonsurgical treatments of patellar tendinopathy: multiple injections of platelet-rich plasma are a suitable option: a systematic review and meta-analysis. *Am J Sports Med*. 2019;47:1001–1018.
26. Chen PC, Wu KT, Chou WY, et al. Comparative effectiveness of different nonsurgical treatments for patellar tendinopathy: a systematic review and network meta-analysis. *Arthroscopy*. 2019;35:3117–3131.e2.
27. Lopez-Royo MP, Ortiz-Lucas M, Gomez-Trullen EM, et al. The effectiveness of minimally invasive techniques in the treatment of patellar tendinopathy: a systematic review and meta-analysis of randomized controlled trials. *Evid Based Complement Alternat Med*. 2020;2020:8706283.
28. Vander Doelen T, Jelley W. Non-surgical treatment of patellar tendinopathy: a systematic review of randomized controlled trials. *J Sci Med Sport*. 2020;23:118–124.
29. Lin MT, Chiang CF, Wu CH, et al. Comparative effectiveness of injection therapies in rotator cuff tendinopathy: a systematic review, pairwise and network meta-analysis of randomized controlled trials. *Arch Phys Med Rehabil*. 2019;100:336–349.e15.
30. Lin MT, Wei KC, Wu CH. Effectiveness of platelet-rich plasma injection in rotator cuff tendinopathy: a systematic review and meta-analysis of randomized controlled trials. *Diagnostics (Basel)*. 2020;10:189.
31. Chen XT, Jones IA, Park C, et al. Use of platelet-rich plasma for the improvement of pain and function in rotator cuff tears: response. *Am J Sports Med*. 2020;48:NP39–NP41.
32. Hurley ET, Hannon CP, Pauzenberger L, et al. Nonoperative treatment of rotator cuff disease with platelet-rich plasma: a systematic review of randomized controlled trials. *Arthroscopy*. 2019;35:1584–1591.
33. Fice MP, Miller JC, Christian R, et al. The role of platelet-rich plasma in cartilage pathology: an updated systematic review of the basic science evidence. *Arthroscopy*. 2019;35:961–976.e3.
34. Chen L, Ye L, Liu H, et al. Extracorporeal shock wave therapy for the treatment of osteoarthritis: a systematic review and meta-analysis. *Biomed Res Int*. 2020;2020:1907821.
35. Boffa A, Previtali D, Di Laura Frattura G, et al. Evidence on ankle injections for osteochondral lesions and osteoarthritis: a systematic review and meta-analysis. *Int Orthop*. 2021;45:509–523.
36. Evans A, Ibrahim M, Pope R, et al. Treating hand and foot osteoarthritis using a patient's own blood: a systematic review and meta-analysis of platelet-rich plasma. *J Orthop*. 2020;18:226–236.

37. Medina-Porqueres I, Ortega-Castillo M, Muriel-Garcia A. Effectiveness of platelet-rich plasma in the management of hip osteoarthritis: a systematic review and meta-analysis. *Clin Rheumatol*. 2021;40:53–64.
38. Zhao Z, Ma JX, Ma XL. Different intra-articular injections as therapy for hip osteoarthritis: a systematic review and network meta-analysis. *Arthroscopy*. 2020;36:1452–1464.e2.
39. Gazendam A, Ekhtiari S, Bozzo A, et al. Intra-articular saline injection as effective as corticosteroids, platelet-rich plasma and hyaluronic acid for hip osteoarthritis pain: a systematic review and network meta-analysis of randomised controlled trials. *Br J Sports Med*. 2021;55:256–261.
40. Arias-Vazquez PI, Tovilla-Zarate CA, Hernandez-Diaz Y, et al. Short-term therapeutic effects of ozone in the management of pain in knee osteoarthritis: a meta-analysis. *PM R*. 2019;11:879–887.
41. Arias-Vazquez PI, Tovilla-Zarate CA, Legorreta-Ramirez BG, et al. Prolotherapy for knee osteoarthritis using hypertonic dextrose vs other interventional treatments: systematic review of clinical trials. *Adv Rheumatol*. 2019;59:39.
42. Belk JW, Kraeutler MJ, Houck DA, et al. Platelet-rich plasma versus hyaluronic acid for knee osteoarthritis: a systematic review and meta-analysis of randomized controlled trials. *Am J Sports Med*. 2021;49:249–260.
43. Charlesworth J, Fitzpatrick J, Perera NKP, et al. Osteoarthritis—a systematic review of long-term safety implications for osteoarthritis of the knee. *BMC Musculoskelet Disord*. 2019;20:151.
44. Chen Z, Wang C, You D, et al. Platelet-rich plasma versus hyaluronic acid in the treatment of knee osteoarthritis: a meta-analysis. *Medicine (Baltimore)*. 2020;99:e19388.
45. Delanois RE, Etcheson JI, Sodhi N, et al. Biologic therapies for the treatment of knee osteoarthritis. *J Arthroplasty*. 2019;34:801–813.
46. Di Matteo B, Polignano A, Onorato F, et al. Knee intraosseous injections: a systematic review of clinical evidence of different treatment alternatives. *Cartilage*. 2020 [epub ahead of print]. doi: 10.1177/1947603520959403.
47. Han Y, Huang H, Pan J, et al. Meta-analysis comparing platelet-rich plasma vs hyaluronic acid injection in patients with knee osteoarthritis. *Pain Med*. 2019;20:1418–1429.
48. Hohmann E, Tetsworth K, Glatt V. Is platelet-rich plasma effective for the treatment of knee osteoarthritis? A systematic review and meta-analysis of level 1 and 2 randomized controlled trials. *Eur J Orthop Surg Traumatol*. 2020;30:955–967.
49. Luo P, Xiong Z, Sun W, et al. How to choose platelet-rich plasma or hyaluronic acid for the treatment of knee osteoarthritis in overweight or obese patients: a meta-analysis. *Pain Res Manag*. 2020;2020:7587936.
50. Vilchez-Cavazos F, Millan-Alanis JM, Blazquez-Saldana J, et al. Comparison of the clinical effectiveness of single versus multiple injections of platelet-rich plasma in the treatment of knee osteoarthritis: a systematic review and meta-analysis. *Orthop J Sports Med*. 2019;7:2325967119887116.
51. Al-Hamed FS, Hijazi A, Gao Q, et al. Platelet concentrate treatments for temporomandibular disorders: a systematic review and meta-analysis. *JDR Clin Trans Res*. 2021;6:174–183.
52. Al-Moraissi EA, Wolford LM, Ellis E III, et al. The hierarchy of different treatments for arthrogenous temporomandibular disorders: a network meta-analysis of randomized clinical trials. *J Craniomaxillofac Surg*. 2020;48:9–23.
53. Chung PY, Lin MT, Chang HP. Effectiveness of platelet-rich plasma injection in patients with temporomandibular joint osteoarthritis: a systematic review and meta-analysis of randomized controlled trials. *Oral Surg Oral Med Oral Pathol Oral Radiol*. 2019;127:106–116.
54. Li F, Wu C, Sun H, et al. Effect of platelet-rich plasma injections on pain reduction in patients with temporomandibular joint osteoarthrosis: a meta-analysis of randomized controlled trials. *J Oral Facial Pain Headache*. 2020;34:149–156.
55. Filardo G, Perdisa F, Roffi A, et al. Stem cells in articular cartilage regeneration. *J Orthop Surg Res*. 2016;11:42.
56. Gianakos AL, Sun L, Patel JN, et al. Clinical application of concentrated bone marrow aspirate in orthopaedics: a systematic review. *World J Orthop*. 2017;8:491–506.
57. Gong J, Fairley J, Cicuttini FM, et al. Effect of stem cell injections on osteoarthritis-related structural outcomes—a systematic review. *J Rheumatol*. 2021;48:585–597.
58. Jevotovsky DS, Alfonso AR, Einhorn TA, et al. Osteoarthritis and stem cell therapy in humans: a systematic review. *Osteoarthritis Cartilage*. 2018;26:711–729.
59. Law L, Hunt CL, van Wijnen AJ, et al. Office-based mesenchymal stem cell therapy for the treatment of musculoskeletal disease: a systematic review of recent human studies. *Pain Med*. 2019;20:1570–1583.
60. McIntyre JA, Jones IA, Han B, et al. Intra-articular mesenchymal stem cell therapy for the human joint: a systematic review. *Am J Sports Med*. 2018;46:3550–3563.
61. Chahla J, Dean CS, Moatshe G, et al. Concentrated bone marrow aspirate for the treatment of chondral injuries and osteoarthritis of the knee: a systematic review of outcomes. *Orthop J Sports Med*. 2016;4:2325967115625481.
62. Di Matteo B, Vandenbulcke F, Vitale ND, et al. Minimally manipulated mesenchymal stem cells for the treatment of knee osteoarthritis: a systematic review of clinical evidence. *Stem Cells Int*. 2019;2019:1735242.
63. Ha CW, Park YB, Kim SH, et al. Intra-articular mesenchymal stem cells in osteoarthritis of the knee: a systematic review of clinical outcomes and evidence of cartilage repair. *Arthroscopy*. 2019;35:277–288.e2.
64. Ma W, Liu C, Wang S, et al. Efficacy and safety of intra-articular injection of mesenchymal stem cells in the treatment of knee osteoarthritis: a systematic review and meta-analysis. *Medicine (Baltimore)*. 2020;99:e23343.
65. Migliorini F, Rath B, Colarossi G, et al. Improved outcomes after mesenchymal stem cells injections for knee osteoarthritis: results at 12-months follow-up: a systematic review of the literature. *Arch Orthop Trauma Surg*. 2020;140:853–868.
66. Pas HI, Winters M, Haisma HJ, et al. Stem cell injections in knee osteoarthritis: a systematic review of the literature. *Br J Sports Med*. 2017;51:1125–1133.
67. Prodromos C, Finkle S, Rumschlag T, et al. Autologous mesenchymal stem cell treatment is consistently effective for the treatment of knee osteoarthritis: the results of a systematic review of treatment and comparison to a placebo group. *Medicines (Basel)*. 2020;7:42.
68. Shi WJ, Tjoumakaris FP, Lendner M, et al. Biologic injections for osteoarthritis and articular cartilage damage: can we modify disease? *Phys Sportsmed*. 2017;45:203–223.
69. Song Y, Zhang J, Xu H, et al. Mesenchymal stem cells in knee osteoarthritis treatment: a systematic review and meta-analysis. *J Orthop Translat*. 2020;24:121–130.
70. Yubo M, Yanyan L, Li L, et al. Clinical efficacy and safety of mesenchymal stem cell transplantation for osteoarthritis treatment: a meta-analysis. *PLoS One*. 2017;12:e0175449.
71. Dai WL, Zhou AG, Zhang H, et al. Efficacy of platelet-rich plasma in the treatment of knee osteoarthritis: a meta-analysis of randomized controlled trials. *Arthroscopy*. 2017;33:659–670.e1.
72. Zhou W, Lin J, Zhao K, et al. Single-cell profiles and clinically useful properties of human mesenchymal stem cells of adipose and bone marrow origin. *Am J Sports Med*. 2019;47:1722–1733.
73. Ding W, Xu YQ, Zhang Y, et al. Efficacy and safety of intra-articular cell-based therapy for osteoarthritis: systematic review and network meta-analysis. *Cartilage*. 2020 [epub ahead of print]. doi: 10.1177/1947603520942947.
74. Kim SH, Djaja YP, Park YB, et al. Intra-articular injection of culture-expanded mesenchymal stem cells without adjuvant surgery in knee osteoarthritis: a systematic review and meta-analysis. *Am J Sports Med*. 2020;48:2839–2849.
75. Kim SH, Ha CW, Park YB, et al. Intra-articular injection of mesenchymal stem cells for clinical outcomes and cartilage repair in osteoarthritis of the knee: a meta-analysis of randomized controlled trials. *Arch Orthop Trauma Surg*. 2019;139:971–980.
76. Maheshwer B, Polce EM, Paul K, et al. Regenerative potential of mesenchymal stem cells for the treatment of knee osteoarthritis and chondral defects: a systematic review and meta-analysis. *Arthroscopy*. 2020;37:362–378.
77. Fitzpatrick J, Bulsara MK, O'Donnell J, et al. The effectiveness of platelet-rich plasma injections in gluteal tendinopathy: a randomized, double-blind controlled trial comparing a single platelet-rich plasma injection with a single corticosteroid injection. *Am J Sports Med*. 2018;46:933–939.
78. Malanga GA, Goldin M. PRP: review of the current evidence for musculoskeletal conditions. *Curr Phys Med Rehabil Rep*. 2014;2:1–15.
79. Li M, Zhang C, Ai Z, et al. Therapeutic effectiveness of intra-knee-articular injection of platelet-rich plasma on knee articular cartilage degeneration [in Chinese]. *Zhongguo Xiu Fu Chong Jian Wai Ke Za Zhi*. 2011;25:1192–1196.
80. Mautner K, Colberg RE, Malanga G, et al. Outcomes after ultrasound-guided platelet-rich plasma injections for chronic tendinopathy: a multicenter, retrospective review. *PM R*. 2013;5:169–175.
81. Sampson S, Reed M, Silvers H, et al. Injection of platelet-rich plasma in patients with primary and secondary knee osteoarthritis: a pilot study. *Am J Phys Med Rehabil*. 2010;89:961–969.

82. Chen X, Jones IA, Park C, et al. The efficacy of platelet-rich plasma on tendon and ligament healing: a systematic review and meta-analysis with bias assessment. *Am J Sports Med*. 2018;46:2020–2032.
83. Habbu R, Putnam MD, Adams JE. Percutaneous release of the A1 pulley: a cadaver study. *J Hand Surg*. 2012;37A:2273–2277.
84. Houck DA, Kraeutler MJ, Thornton LB, et al. Treatment of lateral epicondylitis with autologous blood, platelet-rich plasma, or corticosteroid injections: a systematic review of overlapping meta-analyses. *Orthop J Sports Med*. 2019;7:2325967119831052.
85. Lhee SH, Park JY. Prospective randomized clinical study for the treatment of lateral epicondylitis: comparison among PRP (platelet-rich plasma), prolotherapy, physiotherapy and ESWT. *J Shoulder Elbow Surg*. 2013;22:E30–E31.
86. Mishra AK, Skrepnik NV, Edwards SG, et al. Efficacy of platelet-rich plasma for chronic tennis elbow: a double-blind, prospective, multicenter, randomized controlled trial of 230 patients. *Am J Sports Med*. 2014;42:463–471.
87. Hohmann E, Tetsworth K, Glatt V. Platelet-rich plasma versus corticosteroids for the treatment of plantar fasciitis: a systematic review and meta-analysis. *Am J Sports Med*. 2021;49:1381–1393.
88. Hurley ET, Lim Fat D, Moran CJ, et al. The efficacy of platelet-rich plasma and platelet-rich fibrin in arthroscopic rotator cuff repair: a meta-analysis of randomized controlled trials. *Am J Sports Med*. 2019;47:753–761.
89. de Vos RJ, Weir A, van Schie HT, et al. Platelet-rich plasma injection for chronic Achilles tendinopathy: a randomized controlled trial. *JAMA*. 2010;303:144–149.
90. Zhang YJ, Xu SZ, Gu PC, et al. Is platelet-rich plasma injection effective for chronic Achilles tendinopathy? A meta-analysis. *Clin Orthop Relat Res*. 2018;476:1633–1641.
91. Fitzpatrick J, Bulsara M, Zheng MH. The effectiveness of platelet-rich plasma in the treatment of tendinopathy: a meta-analysis of randomized controlled clinical trials. *Am J Sports Med*. 2017;45:226–233.
92. Gholami M, Ravaghi H, Salehi M, et al. A systematic review and meta-analysis of the application of platelet rich plasma in sports medicine. *Electron Physician*. 2016;8:2325–2332.
93. Campbell KA, Saltzman BM, Mascarenhas R, et al. Does intra-articular platelet-rich plasma injection provide clinically superior outcomes compared with other therapies in the treatment of knee osteoarthritis? A systematic review of overlapping meta-analyses. *Arthroscopy*. 2015;31:2213–2221.
94. Huang Y, Liu X, Xu X, et al. Intra-articular injections of platelet-rich plasma, hyaluronic acid or corticosteroids for knee osteoarthritis: a prospective randomized controlled study. *Orthopade*. 2019;48:239–247.
95. Laudy AB, Bakker EW, Rekers M, et al. Efficacy of platelet-rich plasma injections in osteoarthritis of the knee: a systematic review and meta-analysis. *Br J Sports Med*. 2015;49:657–672.
96. Lin KY, Yang CC, Hsu CJ, et al. Intra-articular injection of platelet-rich plasma is superior to hyaluronic acid or saline solution in the treatment of mild to moderate knee osteoarthritis: a randomized, double-blind, triple-parallel, placebo-controlled clinical trial. *Arthroscopy*. 2019;35:106–117.
97. Meheux CJ, McCulloch PC, Lintner DM, et al. Efficacy of intra-articular platelet-rich plasma injections in knee osteoarthritis: a systematic review. *Arthroscopy*. 2016;32:495–505.
98. Deal JB, Smith E, Heard W, et al. Platelet-rich plasma for primary treatment of partial ulnar collateral ligament tears: MRI correlation with results. *Orthop J Sports Med*. 2017;5:2325967117738238.
99. Dines JS, Williams PN, ElAttrache N, et al. Platelet-rich plasma can Be used to successfully treat elbow ulnar collateral ligament insufficiency in high-level throwers. *Am J Orthop (Belle Mead NJ)*. 2016;45:296–300.
100. Chauhan A, McQueen P, Chalmers PN, et al. Nonoperative treatment of elbow ulnar collateral ligament injuries with and without platelet-rich plasma in professional baseball players: a comparative and matched cohort analysis. *Am J Sports Med*. 2019;47:3107–3119.
101. Finnoff JT. Regenerative rehabilitative medicine for joints and muscles. *Curr Phys Med Rehabil Rep*. 2020;8:8–16.
102. Nejadnik H, Hui JH, Feng Choong EP, et al. Autologous bone marrow-derived mesenchymal stem cells versus autologous chondrocyte implantation: an observational cohort study. *Am J Sports Med*. 2010;38:1110–1116.
103. Baraniak PR, McDevitt TC. Stem cell paracrine actions and tissue regeneration. *Regen Med*. 2010;5:121–143.
104. Han Y, Li X, Zhang Y, et al. Mesenchymal stem cells for regenerative medicine. *Cells*. 2019;8:886.
105. Ferreira JR, Teixeira GQ, Santos SG, et al. Mesenchymal stromal cell secretome: influencing therapeutic potential by cellular pre-conditioning. *Front Immunol*. 2018;9:2837.
106. Fitzsimmons REB, Mazurek MS, Soos A, et al. Mesenchymal stromal/stem cells in regenerative medicine and tissue engineering. *Stem Cells Int*. 2018;2018:8031718.
107. Samsonraj RM, Raghunath M, Nurcombe V, et al. Concise review: multifaceted characterization of human mesenchymal stem cells for use in regenerative medicine. *Stem Cells Transl Med*. 2017;6:2173–2185.
108. Desando G, Cavallo C, Sartoni F, et al. Intra-articular delivery of adipose derived stromal cells attenuates osteoarthritis progression in an experimental rabbit model. *Arthritis Res Ther*. 2013;15:R22.
109. Lee KB, Hui JH, Song IC, et al. Injectable mesenchymal stem cell therapy for large cartilage defects—a porcine model. *Stem Cells*. 2007;25:2964–2971.
110. Murphy JM, Fink DJ, Hunziker EB, et al. Stem cell therapy in a caprine model of osteoarthritis. *Arthritis Rheum*. 2003;48:3464–3474.
111. Toghraie FS, Chenari N, Gholipour MA, et al. Treatment of osteoarthritis with infrapatellar fat pad derived mesenchymal stem cells in Rabbit. *Knee*. 2011;18:71–75.
112. Centeno C, Pitts J, Al-Sayegh H, et al. Efficacy of autologous bone marrow concentrate for knee osteoarthritis with and without adipose graft. *Biomed Res Int*. 2014;2014:370621.
113. Dai W, Leng X, Wang J, et al. Intra-articular mesenchymal stromal cell injections are no different from placebo in the treatment of knee osteoarthritis: a systematic review and meta-analysis of randomized controlled trials. *Arthroscopy*. 2021;37:340–358.
114. Kim JD, Lee GW, Jung GH, et al. Clinical outcome of autologous bone marrow aspirates concentrate (BMAC) injection in degenerative arthritis of the knee. *Eur J Orthop Surg Traumatol*. 2014;24:1505–1511.
115. McIntyre JA, Jones IA, Danilkovich A, et al. The placenta: applications in orthopaedic sports medicine. *Am J Sports Med*. 2018;46:234–247.
116. Shapiro SA, Kazmerchak SE, Heckman MG, et al. A prospective, single-blind, placebo-controlled trial of bone marrow aspirate concentrate for knee osteoarthritis. *Am J Sports Med*. 2017;45:82–90.
117. Shapiro SA, Arthurs JR, Heckman MG, et al. Quantitative T2 MRI mapping and 12-month follow-up in a randomized, blinded, placebo controlled trial of bone marrow aspiration and concentration for osteoarthritis of the knees. *Cartilage*. 2019;10:432–443.
118. Jo CH, Lee YG, Shin WH, 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;32:1254–1266.
119. Koh YG, Choi YJ, Kwon SK, et al. Clinical results and second-look arthroscopic findings after treatment with adipose-derived stem cells for knee osteoarthritis. *Knee Surg Sports Traumatol Arthrosc*. 2015;23:1308–1316.
120. Hernigou P, Flouzat Lachaniette CH, Delambre J, et al. Biologic augmentation of rotator cuff repair with mesenchymal stem cells during arthroscopy improves healing and prevents further tears: a case-controlled study. *Int Orthop*. 2014;38:1811–1818.
121. Hernigou P, Merouse G, Duffiet P, et al. Reduced levels of mesenchymal stem cells at the tendon-bone interface tuberosity in patients with symptomatic rotator cuff tear. *Int Orthop*. 2015;39:1219–1225.
122. Becktell L, Matuska AM, Hon S, et al. Proteomic analysis and cell viability of nine amnion, chorion, umbilical cord, and amniotic fluid-derived products. *Cartilage*. 2020 [epub ahead of print]. doi: 10.1177/1947603520976767.
123. Panero AJ, Hirahara AM, Andersen WJ, et al. Are amniotic fluid products stem cell therapies? A study of amniotic fluid preparations for mesenchymal stem cells with bone marrow comparison. *Am J Sports Med*. 2019;47:1230–1235.
124. United States Food and Drug Administration. *Tissue and Tissue Products*. Silver Spring, MD: United States Food and Drug Administration; 2019. Available at: https://www.fda.gov/vaccines-blood-biologics/tissue-tissue-products. Accessed July 11, 2019.
125. Lamplot JD, Rodeo SA, Brophy RH. A practical guide for the current use of biologic therapies in sports medicine. *Am J Sports Med*. 2020;48:488–503.
126. The PEW Trusts. FDA's framework for regulating regenerative medicine will improve oversight. In: The Pew Charitable Trusts, ed. Philadelphia, PA: The Pew Charitable Trusts; 2019:52.
127. Rossi LA, Piuzzi NS, Shapiro SA. Glenohumeral osteoarthritis: the role for orthobiologic therapies: platelet-rich plasma and cell therapies. *JBJS Rev*. 2020;8:e0075.
128. United States Food and Drug Administration. *Regulatory Considerations for Human Cells, Tissues, and Cellular and Tissue-Based Products: Minimal Manipulation and Homologous Use*.

Guidance for Industry and Food and Drug Administration Staff. Washington, DC: United States Food & Drug Administration; 2020:28.
129. United States Food and Drug Administration. *Same Surgical Procedure Exception under 21 CFR 1271.15(b): Questions and Answers Regarding the Scope of the Exception*. Silver Spring, MD: United States Food and Drug Administration; 2017. Available at: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/same-surgical-procedure-exception-under-21-cfr-127115b-questions-and-answers-regarding-scope. Accessed May 16, 2019.
130. Manchikanti L, Centeno CJ, Atluri S, et al. Bone marrow concentrate (BMC) therapy in musculoskeletal disorders: evidence-based policy position statement of American Society of Interventional Pain Physicians (ASIPP). *Pain Physician*. 2020;23:E85–E131.
131. Civil action no. 10-1327 (RMC). United States District Court, District of Columbia. United States v Regenerative Sciences LLC. 878F. Supp 2d 248 (D.D.C. 20102), 2012. Decided July 23, 2012.
132. Willett NJ, Thote T, Lin AS, et al. Intra-articular injection of micronized dehydrated human amnion/chorion membrane attenuates osteoarthritis development. *Arthritis Res Ther*. 2014;16:R47.
133. Zelen CM, Poka A, Andrews J. Prospective, randomized, blinded, comparative study of injectable micronized dehydrated amniotic/chorionic membrane allograft for plantar fasciitis—a feasibility study. *Foot Ankle Int*. 2013;34:1332–1339.
134. United States Food and Drug Administration. *FDA INTERACT Meetings (Initial Targeted Engagement for Regulatory Advice on CBER Products)*. Washington, DC: US Food & Drug Administration; 2020. Available at: https://www.fda.gov/vaccines-blood-biologics/industry-biologics/interact-meetings#:~:text=INitial%20Targeted%20Engagement%20for%20Regulatory%20Advice%20on%20CBER%20producTs%20(INTERACT,Research%20(CBER)%20at%20FDA. Accessed July 9, 2020.
135. FDA In Brief. *FDA Announces Program to Enhance Early Communications with Biological Product Developers*. Washington, DC: US Food & Drug Administration; 2018. Available at: https://www.fda.gov/news-events/fda-brief/fda-brief-fda-announces-program-enhance-early-communications-biological-product-developers. Accessed June 22, 2018.
136. FDA in Brief. *FDA Announces Temporary Streamlined Program to Help Manufacturers of Human Cell, Tissue, and Cellular and Tissue-Based Products—Including Stem Cell Treatments—Understand the Appropriate Regulatory Pathways for Their Products*. Washington, DC: U Food & Drug Administration; 2019. Available at: https://www.fda.gov/news-events/fda-brief/fda-brief-fda-announces-temporary-streamlined-program-help-manufacturers-human-cell-tissue-and. Accessed June 12, 2019.
137. Federal Trade Commission. *FTC Takes Aim at Deceptive Stem Cell Therapy Claims*. Washington, DC: United States Federal Trade Commission; 2018. Available at: https://www.ftc.gov/news-events/press-releases/2018/10/ftc-stops-deceptive-health-claims-stem-cell-therapy-clinic. Accessed October 18, 2018.
138. Steingard SA, Boe DJ, Coletta SL, et al. *Regenerative and Stem Cell Therapy Practices. Report and Recommendations of the Workgroup to Study Regenerative and Stem Cell Therapy Practices*. Washington, DC: Federation of State Medical Boards; 2018.
139. Smith C, Martin-Lillie C, Higano JD, et al. Challenging misinformation and engaging patients: characterizing a regenerative medicine consult service. *Regen Med*. 2020;15:1427–1440.
140. Fu W, Smith C, Turner L, et al. Characteristics and scope of training of clinicians participating in the US direct-to-consumer marketplace for unproven stem cell interventions. *JAMA*. 2019;321:2463–2464.
141. Emanuel EJ, Wendler D, Grady C. What makes clinical research ethical? *JAMA*. 2000;283:2701–2711.
142. Brennan T, Cohen JJ, Kimball H, et al. Medical professionalism in the new millennium: a physician charter. *Ann Intern Med*. 2002;136:243–246.
143. Brock DW. Philisophical justifications of informed consent in research. In: Emanuel EJ, Grady C, Crouch RA, et al, eds. *Textbook of Clinical Research Ethics*. Oxford: Oxford University Press; 2008:606–612.
144. Kon AA. The shared decision-making continuum. *JAMA*. 2010;304:903–904.
145. Hoffmann TC, Montori VM, Del Mar C. The connection between evidence-based medicine and shared decision making. *JAMA*. 2014;312:1295–1296.
146. Knoepfler PS. The stem cell hard sell: report from a clinic's patient recruitment seminar. *Stem Cells Transl Med*. 2017;6:14–16.
147. International Society for Stem Cell Research. *Informed Consent Standard for Stem Cell-Based Interventions Offered Outside of Formal Clinical Trials*. Skokie, IL: International Society for Stem Cell Research; 2019.
148. Kamenova K, Caulfield T. Stem cell hype: media portrayal of therapy translation. *Sci Transl Med*. 2015;7:278ps4.
149. Lau D, Ogbogu U, Taylor B, et al. Stem cell clinics online: the direct-to-consumer portrayal of stem cell medicine. *Cell Stem Cell*. 2008;3:591–594.
150. Marcon AR, Murdoch B, Caulfield T. Fake news portrayals of stem cells and stem cell research. *Regen Med*. 2017;12:765–775.
151. Master Z, Smith C, Tilburt JC. Informed consent for stem cell-based interventions. *JAMA*. 2020;323:893.
152. Murdoch B, Zarzeczny A, Caulfield T. Exploiting science? A systematic analysis of complementary and alternative medicine clinic websites' marketing of stem cell therapies. *BMJ Open*. 2018;8:e019414.
153. Regenberg AC, Hutchinson LA, Schanker B, et al. Medicine on the fringe: stem cell-based interventions in advance of evidence. *Stem Cells*. 2009;27:2312–2319.
154. Ryan KA, Sanders AN, Wang DD, et al. Tracking the rise of stem cell tourism. *Regen Med*. 2010;5:27–33.
155. Fidai MS, Saltzman BM, Meta F, et al. Patient-reported outcomes measurement information system and legacy patient-reported outcome measures in the field of orthopaedics: a systematic review. *Arthroscopy*. 2018;34:605–614.
156. Wilson I, Bohm E, Lubbeke A, et al. Orthopaedic registries with patient-reported outcome measures. *EFORT Open Rev*. 2019;4:357–367.
157. Gottlieb S. *Harnessing Real World Evidence for Safety and Innovation* Washington, DC: US Food & Drug Administration; 2018. Available at: https://www.fda.gov/news-events/speeches-fda-officials/harnessing-real-world-evidence-safety-and-innovation-11192018. Accessed November 19, 2018.
158. Blonde L, Khunti K, Harris SB, et al. Interpretation and impact of real-world clinical data for the practicing clinician. *Adv Ther*. 2018;35:1763–1774.
159. Barnish MS, Turner S. The value of pragmatic and observational studies in health care and public health. *Pragmat Obs Res*. 2017;8:49–55.