Not Missing the Future: A Call to Action for Investigating the Role of Regenerative Medicine Therapies in Pediatric/Adolescent Sports Injuries

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Abstract

In August 2016, a group including sport medicine clinicians, researchers, and a bioethicist met in Vail, Colorado to discuss regenerative medicine and its potential role in youth sports injuries. There was consensus that a call to action is urgently needed to understand the current evidence base, the risks and rewards, and future directions of research and clinical practice for regenerative medicine therapies in youth sports. We present here a summary of our meeting, which was supported by the National Youth Sports Health and Safety Institute (NYSHSI), a partnership between the American College of Sports Medicine (ACSM) and Sanford Health. The group's goal is to educate practitioners and the public, and to pioneer a means of accumulating meaningful clinical data on regenerative medicine therapies in pediatric and adolescent athletes.

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Introduction

John F. Kennedy, the 35th President of the United States, said "Those who look only to the past or the present are sure to miss the future." This Special Communication is intended to help us examine that future. Regenerative medicine encompasses the use of stem cell and other cell-based therapies, growth factors, and biologics in the management of each individual's innate capabilities for tissue repair and regeneration to optimize a therapeutic outcome. These therapies are increasingly being used to treat sports injuries, for the most part without a clearly defined evidence base. The use of these therapies in young athletes is particularly understudied.

In August 2016, a group including sport medicine clinicians, researchers, and a bioethicist met in Vail, Colorado to discuss regenerative medicine and its potential role in youth sports injuries. There was consensus that a call to action is urgently needed to understand the current evidence base, the risks and rewards, and future directions of research and clinical practice for regenerative medicine therapies in youth sports. We present here a summary of our meeting, which was supported by the National Youth Sports Health and Safety Institute (NYSHSI), a partnership between the American College of Sports Medicine (ACSM) and Sanford Health. The group's goal is to educate practitioners and the public, and to pioneer a means of accumulating meaningful clinical data on the safe and efficacious use of regenerative medicine therapies in pediatric and adolescent athletes.

The Current Situation

Treatment of Musculoskeletal Injuries in Youth

Musculoskeletal disorders cost an estimated US $213 billion in 2011 in direct and indirect costs, or 1.4% of the U.S. Gross Domestic Product (GDP) (81). A search of the National Health

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Interview Survey (NHIS) child sample revealed that musculoskeletal conditions accounted for 10.9% of parent-reported health conditions for children and adolescents age 0 to 17 years in the United States in 2012 (14).

Overuse musculoskeletal injuries

Recent studies have begun to estimate the incidence and prevalence of nonsurgical sports-related injuries in the adolescent population. Time loss can vary from a few days to end-of-season or beyond, hence the morbidity of these acute and overuse problems can be considerable (65,76). Treatment strategies, including rest, physical therapy, and pharmaceutical medications, often lack data from randomized controlled trials (RCT) to support their efficacy. Overuse injuries in pediatric and adolescent athletes are becoming much more prevalent. Mounting evidence from laboratory and veterinary research suggests that mesenchymal stem cells (MSC) may provide an adjuvant or alternative treatment option for conditions that affect muscle, tendons, ligaments, and cartilage. This evidence however is based largely on studies in adults and it remains unknown whether these results will be duplicated in our younger populations. In addition, several lower and upper extremity injuries discussed below are still in search of optimal treatments that return the athlete to sports and mitigate the risks for long-term problems, such as osteoarthritis (OA).

Lower extremity injuries

1. ACL injuries: Anterior cruciate ligament (ACL) injuries are forefront in the young athletic population, with rates of surgical intervention increasing at a rapid pace (19). While physicians, physical therapists, and athletic trainers have focused on injury prevention, once the tear occurs most opt for surgical intervention (19). While limited data support the role of platelet-rich plasma (PRP) in ACL graft maturation, clinical outcomes seem to be unaffected (22). There is currently no evidence to support the use of PRP for augmenting ACL graft incorporation (22). Some evidence shows that PRP may reduce graft donor site pain after patella tendon ACL reconstruction (35). The data on stem cells and ACL reconstruction is limited to preclinical research and small trials. A recent trial of noncultivated adult stem cells on graft-to-bone healing in ACL reconstruction showed no effect (35,68).
2. Meniscal repair: The majority of evidence regarding PRP and meniscal repair does not support its use; however, the majority of these studies are limited in regard to power (29). While there are some animal data regarding stem cell treatment and meniscal repair, we are lacking well-designed human studies. An RCT on a small sample of adult subjects showed that MSC injection after meniscectomy led to an improved clinical outcome (82). However, other human studies in meniscal repair are lacking (36).
3. Articular Cartilage repair: Chondral injuries are treated with varied techniques, all of which have substantial rehabilitation requirements as well as prolonged recovery timelines (33). While recent studies have reported enhanced outcomes with cartilage repair (30,44), much more evaluation is needed before stem cell therapy might become part of the standard of care.
4. Osteochondritis dissecans (OCD) of the knee: OCD treatment can prove challenging and strategies include both conservative and surgical interventions, with widely variable outcomes (84). Currently, there is no evidence to guide the use of PRP and or stem cell therapy in OCD of the knee. Cell-based treatment modalities may offer options to improve the clinical outcomes of this very challenging entity.

Upper extremity injuries

We have identified four conditions seen in youth sports that may be amenable to stem cell therapy and warrant further clinical investigation:

1. Partial ulnar collateral ligament ruptures: PRP injections for partial ulnar collateral ligament tears in throwers have already been shown to lead to clinical recovery and return-to-play at a higher rate than would be expected from standard rehabilitation protocols (58). MSC may be another treatment option in these patients. Further investigation will be necessary to determine whether there is a benefit to MSC injections alone or in combination with PRP in terms of long-term clinical recovery and actual ligament healing.
2. OCD of the capitellum: Regardless of treatment, long-term studies have shown that up to fifty percent of patients with OCD lesions develop degenerative changes of the radiocapitellar joint as adults (16,62). Because this condition is still far from solved, research into treatment with MSC theoretically could result in better restoration of the articular surface and better long-term results than with treatment options currently available.
3. Internal impingement: The results of SLAP repair, especially when combined with rotator cuff repair, has been extremely discouraging in overhead throwers (20). MSC injections may be an option to assist in operative and nonoperative rehabilitation for these athletes and improve the rate of return to previous levels of play.
4. Distal clavicle osteolysis: Distal clavicle osteolysis is the final condition we suggest that could be treated with MSC injections. Breakdown of the cartilage and subchondral bone often requires surgical treatment (66). Injection with MSC may reduce the number of patients who require surgery.

Regenerative Cell Therapies: The Current Evidence

Preclinical Assessment of Regenerative Cell Therapies

Regenerative cell therapies comprise a broad range of potential approaches, from autologous cells isolated at point-of-care to genetically engineered cells and combination products (51). Clinical considerations, such as optimal timing of treatment and mechanism of action (*e.g.*, anti-inflammatory, antiapoptotic, tissue regeneration), are important considerations in weighing the choice between autologous versus allogeneic, and point-of-care versus cultured cell sources. As biologics (*i.e.*, not chemically synthesized but manufactured in a living system), regenerative cell therapies are governed by the axiom "the process is the product." For

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example, clear and longstanding evidence indicates that cell culture using xenogeneic reagents elicits immunological responses in recipient animals (74), and regenerative capacity and immunomodulatory effects may be influenced by age and sex of the donor (67). Preclinical requirements for progressing new regenerative medicines such as cell-based products to clinical trials necessitate a standardized production process and characterization of key parameters that may influence safety, such as identification of potential toxicities, biodistribution, and cell fate (78). Regenerative cells may become part of living, renewable tissue, and thus may require long-term follow-up to assess safety. Immunological considerations regarding xenograft animal models, and the typical short duration of many such experiments, limit the utility of many research animal models for clinical translation. In this context, veterinary patients provide a compelling paradigm for translating regenerative cell therapies to clinical application in humans (34).

Evidence Base in Equine Populations

The MSC therapy is currently one of the most commonly used cell therapies and evidence is mounting for its potential uses for musculoskeletal diseases in horses (31,71). Stem cells most commonly used in equine populations are those in the adult MSC arena and are derived from equine bone marrow aspirates or fat harvest. The indications within tendon/ligament and joint therapies also are becoming more familiar. Based on delivery mechanisms, intralesional implantation of MSC (10–20 million per site) still seems to be the preferred and most efficacious method to deliver the cells (31,71). Regional perfusion via venous delivery as well as intra-arterial delivery (without a tourniquet) also have been used. However intralesional delivery continues to be most effective in terms of cell survival at the site of the lesion (3). In horses, lesions within and involving the periphery of tendons and ligaments are the most commonly treated. Results from multiple evidence-based studies have suggested that treated horses experience: 1) return-to-function and athleticism at higher percentage than nontreated animals, and 2) reinjury rates are decreased (compared with nontreated) (31,71). MSC therapy for joint disease has revealed successes in cases, such as meniscal disease, OA, and cartilage damage (8,9,21,52). Effects of MSC on various stages of joint disease are still under intense investigation, and clinical studies are forthcoming.

There remain many unknowns regarding stem cell therapies for musculoskeletal disease in the horse. These unknowns include dose, timing of injection, source, other biologics to use with the MSC treatment to maximize effect, and whether allogeneic cells (MSC from other donors) are as effective as autologous cells (MSC from the patient's own tissues). Biologics, such as PRP (75,83), Interleukin Receptor Antagonist Protein (26,75), and autologous protein solution (6) also are intensively used in equine practice.

Managing the Body's Innate Regenerative Potential: The Role of MSC

Every tissue in the body without exception has stem cells. To conduct tissue engineering, one must understand the lineage pathways that give rise to a specific target tissue, even which specific *type* of target tissue (*e.g.,* cartilage in the ear is not interchangeable with that in the knee.) Mesenchymal stem cells can be derived from multiple tissue sources, not just adult bone marrow. MSC can even derive from fat. While it is possible to get MSC to differentiate into various cell types in cell culture, it is far more challenging to achieve that result *in vivo*.

Pericytes are cells that reside on capillaries and microvessels—when they squeeze blood vessels, blood pressure increases. These perivascular cells are progenitors for MSC (12). It is hypothesized that when a vessel is injured, the pericyte detaches and gives rise to an MSC, which then becomes activated and ultimately regenerative (10). MSC dock at sites of broken blood vessels and become the sentinel for damage. They are the body's first line of defense against the aggressive autoimmune system. They also establish a microenvironment for regeneration that is anti-apoptotic, anti-scarring, angiogenic, and pro-mitotic.

While all MSC have this regenerative capacity, they have different molecular marker profiles depending on the source of the MSC (fat, muscle, etc.). These injury-specific 'drug stores' may therefore be more aptly named **M**edicinal **S**ignaling **C**ells (11). MSC are actually not stem cells at all, as they do not differentiate *in vivo*. MSC are multifactorial site-specific sensors with genetically wired molecular responses. MSC are enormously sensory—they sense the microenvironment, and their response is hard-wired for that particular environment. The same MSC in two different environments could yield opposite results, such as proinflammatory or anti-inflammatory (5). The microenvironment dictates the response. MSC work everywhere in the body. When considering their regenerative potential for clinical applications, it is best to think of MSC as medicinal signaling cells (73).

It also is important to note that the MSC mechanism of action in the repair process appears to be related to the secretion of molecules that trigger the repair process through the chemo-attraction of host cells. The host's response cells are tissue intrinsic stem cells. In the case of the heart, the cardiac stem cells are sensitized by MSC which come in to an area of injury (for example, a heart attack). These MSC stimulate the cardiac stem cells to divide and form cardiac myocytes which replace the dying cells or fabricate new heart tissue to replace the damaged tissue. Therefore, the use of this MSC technology relies on the ability and functionality of host cells. In young athletes, it is expected that these host cells would be more reactive than in older athletes. More experiments are therefore required to determine the efficacy of MSC therapy in younger animals and the results should be compared with the same technology applied in older animals.

Adipose-Derived Regenerative Cell Therapy in Clinical Practice of Adult Orthopedics

Traumatic and degenerative diseases are commonly treated surgically by orthopedic surgeons and sports medicine physicians trying to restore function. In most cases, ultimate interventions, such as arthroplasty, are the main treatment options. Novel approaches aimed at promoting structural and functional restoration of the damaged tissues have gained popularity and momentum, in an effort to improve biological autologous healing (25,37,39,43,54). Adult stem cells constitute a promising alternative given their established regenerative capacities including immunomodulatory and trophic

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activities exerted in injured tissues via secretion of paracrine factors (5,13,69). As stated above, they are present in every tissue of the body as perivascular cells (12,17,18,63) including bone marrow and adipose tissue where they are typically harvested. From these sources, it is possible to obtain heterogeneous cell formulations, such as the bone marrow aspiration concentrate (BMAC) and the adipose-derived collagenase-processed stromal vascular fraction (SVF), in which various other cell types are present along with MSC (*e.g.,* endothelial progenitor cells, hematopoietic precursors, monocytes, etc.) (87). Alternatively, more homogeneous cell populations of MSC can be obtained after their culture expansion, called BMSC and ADSC, when derived from bone marrow and adipose tissue, respectively (2). It is important to note that given the cellular density per unit of tissue volume, adipose tissue in particular offers a large source of undifferentiated MSC (85). A number of preclinical and clinical studies are being conducted using either heterogeneous or culture-expanded MSC for various orthopedic indications with initial positive effects (*e.g.,* OA) (45,72). These properties provide new treatment possibilities for joint preservation by preventing deterioration of preexisting structural damage in degenerative conditions and increasing the natural healing response in acute or trauma cases.

Biological Approaches to Improve Muscle Healing After Sports-Related Muscle Injuries

After skeletal muscle injuries, regeneration usually begins during the first week, peaks at 2 weeks, and then gradually slows down during the next 3 to 4 weeks. It has been shown in many reports that various growth factors (IGF-1, bFGF, NGF) play important roles during muscle healing (46,53). While these factors tend to be safe and easy to inject, efficacy is limited by the need for high concentrations (7,53), rapid clearance, and short half-lives.

Some research suggests that the stimulatory action of IGF-1 on myofibroblast proliferation and the deposition of ECM (*i.e.*, scar tissue) might interfere with the ability of this growth factor, even at high concentrations, to improve muscle healing after injury. Our research findings strongly indicate that scar tissue formation precludes complete regeneration of muscle tissue (28). Various studies have implicated TGF-β1 in the onset of fibrosis in various tissues. The few that have examined its role in skeletal muscle fibrosis find an association with fibrosis, including our study that showed strong expression of TGF-β1 in injured skeletal muscle (47,48). These results support the hypothesis that the expression of TGF-β1 in skeletal muscle plays an important role in the fibrotic cascade that occurs after the onset of muscle disease or trauma. It is very feasible that neutralization of TGF-β1 expression in injured muscle could inhibit formation of scar tissue. The use of antifibrotic agents that inactivate TGF-β1 (*e.g.,* decorin) appears to reduce muscle fibrosis and improve muscle healing, leading to nearly complete recovery of injured muscle (27,48,49). However, most antifibrotic agents are not Food and Drug Administration (FDA) approved.

Losartan, an antifibrotic agent that is FDA approved for cardiothoracic surgery, is a potential drug to improve muscle healing after injury. Animal model studies show that losartan improves muscle healing through reduction of fibrosis and enhancement of muscle regeneration and angiogenesis (4,42). Losartan has been tested in two patients with muscle injuries (28). The results, though limited, suggest that this agent can safely improve muscle healing. A clinical trial is underway to determine the efficacy of losartan in sports- and military-related muscle injuries (28).

Transplantation of muscle-derived stem cells (MDSC) could theoretically improve muscle regeneration after injury, however their beneficial effect appears to be limited by the differentiation of the cells toward a fibrotic lineage (47,48). In fact, MDSC under the influence of TGF-β1 from the muscle injury microenvironment not only undergo myofibroblast differentiation but also it has recently been reported that combinatorial treatment of contusion-injured muscle via losartan and MDSC treatment significantly improved skeletal muscle healing when compared to each of these treatments alone (41). Losartan enhanced MDSC differentiation toward a myogenic lineage and inhibited fibrosis via increased Smad7 expression (42). These results suggest a synergistic effect of losartan and MDSC transplantation on skeletal muscle healing after injury and highlight the potential of combinatorial treatment to improve muscle healing after injury (41).

Use of PRP in Adolescent Athletes

PRP is a promising treatment for many musculoskeletal injuries. Because it uses autologous tissue, side effects are uncommon, and it is considered safe (64). There is a paucity of literature describing its use in pediatric and adolescent athletes, as most IRBs require subjects to be 18 years or older. A recent critical review (24) has shown PRP to be effective for patellar tendinopathy, but not ACL reconstruction. Similarly, there is moderate to strong evidence for the use of a single ultrasound-guided PRP injection in the treatment of tendinopathy (23). It should be noted however that these studies only looked at adult patients. Nevertheless, a small randomized controlled study showed PRP use led to more rapid return to play for female soccer players aged 14 to 18 years with acute hamstring muscle injuries (32).

Difficulties in interpreting the current literature arise from a lack of standardization of protocols: different types of PRP are compared; study subjects may receive single versus multiple injections; rehabilitation may or may not be used; and injections may or may not be done under ultrasound guidance. Future studies for all cell-based therapies should include careful consideration of standardized rehabilitation programs in addition to standardized injection techniques.

Ethical, Legal, and Regulatory Issues

Ethical and Legal Dimensions of Regenerative Medicine in Youth Sport

There are three general and interrelated ethical considerations for orthopedic applications of regenerative medicine in children and adolescents: 1) informed consent and family dynamics, 2) mitigating harm, and 3) stem cell tourism.

Informed consent and family dynamics

Informed consent is a process of dialog with a young patient and their family about a planned course of action. Requests for stem cell interventions should include the adolescent in the discussion and respect his or her concerns, and support developmentally appropriate decision making.

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Treating physicians should be adept at explaining information to their patients in an age-appropriate and descriptive manner. This can be difficult when treatment modalities are complex and the state of the clinical science is in flux.

The growing prevalence of adolescent sports injuries and the desires of parents and families for new cellular therapies suggest that treating physicians use the standard principles of care when considering whether to support or discourage parents from seeking risky or noneffective interventions. Treating physicians must be aware of undue influence and possible coercion by the family or health care team in an effort to see an athletic child return to competitive play. Health care providers have legal and ethical duties to provide a standard of care that meets the patient's needs and not necessarily what the parents' desire or request. In this context, parental decision making is a responsibility to support the interests of their child and to preserve family relationships, rather than an exercise of a right to express their own autonomous choices. By moving family conversation from parental rights toward parental responsibility, physicians can minimize conflicts encountered in the course of decision-making about regenerative medical treatments in sports injuries (38).

As discussed below, there may be instances when parents seek regenerative treatments that are not supported by clinical evidence. If parents insist on an unproven stem cell transplant for their child, physicians must be guided by the duties they owe to their minor patients and should consider the best interests of that patient. The first and likely most important step in the discharge of these duties will be to give the parents and in appropriate cases, the adolescents and children as much information as possible about the potential risks, even when those risks are largely unknown (86).

Mitigating harm

Codes of professional ethics require physicians to consider the well-being of patients and to take reasonable steps to prevent them from harm. It is possible that taking a child to an unregulated clinic may trigger concern about the child's safety. If they are aware of a risk of harm, physicians' fiduciary duties may require them to protect their minor patients from unproven and potentially risky stem cell treatments. The challenge, however, is that some physicians may not have enough information about these treatments to ascertain harm and trigger a fiduciary duty (86). However, if no clear treatment guidelines exist, and there is genuine uncertainty about possible future harm, young patients should be protected from both known and unknown harms arising from emerging and unproven interventions (55).

Stem cell tourism

Stem cell tourism is a broad phenomenon referring to patients who travel to pursue unproven regenerative treatments not available locally. As defined above, these clinics sell unproven stem cell therapies, which lack such evidence for safety and efficacy (50). There is a startling rise in unregulated clinics offering unproven transplants to patients seeking treatments for a wide array of conditions, including orthopedic and sports injuries. These clinics—often with direct-to-consumer and Web-based business models—appear in both developing and developed countries and raise significant ethical and legal questions related to safety, vulnerable patient populations including children, and erosion of the public trust in medicine (61).

But travel need not be international. A recent survey estimates 570 unregulated cell therapy clinics in the United States alone, quadrupling in number over the last several years (Fig. 1). Nearly half of these clinics use autologous bone MDSC and 20% inject allogenic stem cells (77). Orthopedic and sports injuries represent significant markets for these clinics, comprising 400% or 70% of the total number (Fig. 2).

Unregulated clinics present a pressing concern for treating physicians involved with young athletes and their families seeking aggressive regenerative therapy. The mainstream media is rife with stories about professional athletes turning to regenerative medicine to treat their injuries. Analysis of media reports of sports stars frequenting unregulated stem cell clinics reveal that uncritical portrayals of the treatments begin with assumptions of efficacy and turn to criticism to why these treatments are being withheld or delayed (60).

Regulation of Cell Therapies in the United States

The US FDA regulates stem cell use through "Human Cells, Tissues, and Cellular and Tissue-Based Products" regulations (15). The FDA oversees cell therapies using a three-tiered, risk-based regulatory framework (79). There are significant legal and regulatory obstacles to using adult stem cells in sport medicine. These complex rules affect what can and cannot be done.

Regulation in cell-based therapy is designed to ensure that the potential therapeutic alternatives are safe and effective for the use they are intended (1). The *in vivo* biological activity and safety profile of the investigational CT (CTS: is this cell therapy CTS) is influenced by the product origin, the level of manipulation, and the stage of differentiation at the time of administration (80). Safety concerns include: administration site reactions, potential immune response and systemic/local toxicities, migration from the site of administration, potential to differentiate into an unintended cell type, unregulated/dysregulated proliferation within the host, and tumorigenicity (80).

Preclinical programs include proof-of-concept studies to establish feasibility and rationale for the use of a particular product, and further studies to assess the targeted cellular phenotype; minimum cell dose required to achieve a response; and the fate of the cells post-administration, which includes survival and engraftment, distribution, differentiation and integration, and tumorigenicity (80).

Regulation level results from the product's potential risk, and depending on how a product is categorized, may require simple registration or demanding premarket approval. Degree of manipulation is crucial in determining in which category a product fits.

A First Draft for the Future: A Collective Call to Action

The playwright George Bernard Shaw noted "We are made wise not by the recollection of our past, but by the responsibility for our future." Based on the Vail, Colorado 2016 meeting, the following action items were endorsed by the group.

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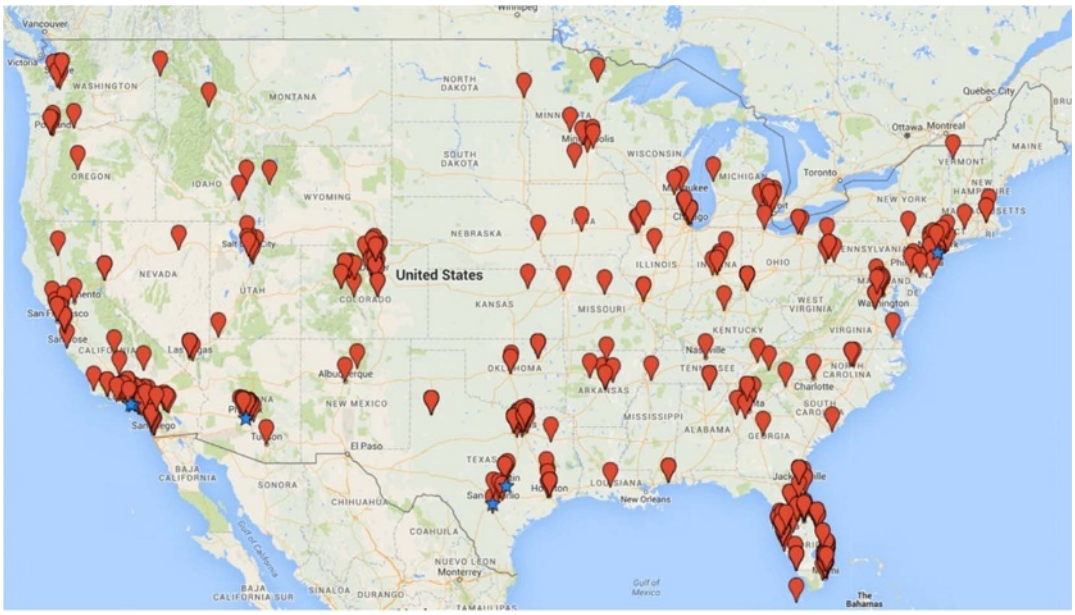

Figure 1: Map of locations of included businesses. We conducted data collection on the cities and states of stem cell businesses including multiple location for individual businesses. "Hotspot" cities are indicated with blue stars. See Supplemental information for additional details concerning the production of the map.

Action 1: exercise caution in treating youth as research continues. While PRP and many cell-based therapies appear to be relatively safe for treating adult musculoskeletal injuries, caution should prevail in considering such treatments in youth, pending scientific and clinical research. The data available now in adults suggest that PRP use for musculoskeletal injuries is safe. Adult-derived, autologous and allogeneic, cultured and noncultured cells all appear to be relatively safe for musculoskeletal applications. The side effects of these treatments compare favorably to those of drug treatments. However, while it is considered relatively safe in the populations in which it has been tested, it has been shown that cells injected into a tumor will make the tumor grow more quickly (40,59). In addition, there are limited long-term outcomes data, and limited data in adolescents. A recent position statement by the Australasian College of Sports Physicians (55) reviews the evidence base for MSC use in sports injuries, and all adverse events and applications reported in the literature. Among other conclusions, the article states the following: "To date, research into the safe use of MSC has not demonstrated tumor-forming potential or other significant side effects in phase I and II musculoskeletal research (56,57,70). However long-term safety cannot be assured." A healthy caution should be exercised when examining these treatments in youth, when considering long-term consequences, and when considering applications outside of musculoskeletal injuries.

Action 2: improve regulatory oversight. While relatively safe, these therapies are often provided without regulatory oversight. There are currently 570 clinics offering unregulated cell-based therapies in the United States, approximately 70% of which are related to sports and orthopedics (77). In addition, some unregulated clinics register on clinical trials on ClinicalTrials.gov to increase their credibility, but without following through to conduct a clinical trial. This burgeoning industry is subject to limited regulatory oversight and must be addressed with a high sense of urgency and resolve.

Action 3: expand governmental and other funding of research. Government funding would help create the evidence base to guide the already widespread use of cell-based therapies to treat injuries in young athletes. Research in the field of cell-based therapies has focused primarily on aging. It would be novel to examine the use of cell-based therapies in young athletes. Preclinical studies should be expanded to include physiologically immature animals to critically evaluate the potential for cell-based therapies and their safety/efficacy. From a clinical perspective, one strategy might be to identify the top 2 to 3 musculoskeletal injuries

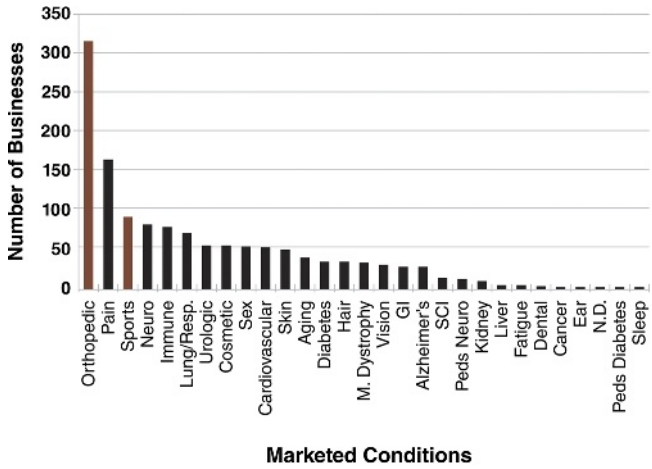

Figure 2: Stem cell conditions marketed. Data from the stem cell business web sites were collected for a range of marketed conditions. Of those identified, orthopedic and sports comprised approximately 400 (70%) of 570 total.

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or overuse conditions seen in adolescents (*e.g.,* OCD of the knee, partial UCL tear of the elbow) and develop studies with strictly defined criteria that examine the continuum of cell-based therapies from PRP or prolotherapy to stem cells.

Action 4: create a system of registries. An important early step is the creation of outcomes and patient registries. This group strongly encourages the formation of patient data registries for all regenerative therapies, whether PRP, MSC, or a point-of-care cell preparation such as bone marrow or adipose SVF cells. These registries would help establish use and outcomes data that would provide key information to fill knowledge gaps in the field. For example, we do not understand why PRP works in some clinical scenarios and not others and how composition of the PRP affects outcome. Based on patient registries, we could potentially look at the patient's blood chemistry profile and determine optimal processing that highly personalizes the patient's treatment. Outcome data from this registry will ideally point to procedures and practices that yield optimal clinical outcomes—information that would be publicly available. The data would tell us which formulations and procedures, enriched for which specific cell types and concentrations, using a specified number of injections, would work best for a specific muscle, tendon, or injury. Perhaps more importantly, the safety profiles of these cell-based therapies need to be evaluated in a systematic fashion, both in the adult and pediatric populations.

Action 5: develop a multiyear policy agenda and build support for it. Policy and outreach will be important going forward. Unlike a biologic such as a monoclonal antibody, it is relatively easy to isolate MSC, making it easy for companies or even individual clinics to engage in their use. Future guidelines must be relatively easy to follow and at the same time strictly enforced. They should encourage compliance with regulations and best practices versus creation and use of uncharacterized products without regulatory oversight, which is the current practice at many "stem cell" clinics.

The REGROW Act is a bill to amend the Federal Food, Drug, and Cosmetic Act with respect to cellular therapies. The goal is to speed development of regenerative therapies to help patients living with diseases such as Alzheimer's disease, Parkinson's disease, diabetes, and stroke. This bill was assigned to a Congressional committee on March 16, 2016, which will consider it before possibly sending it on to the House or Senate. Only three senators support the REGROW Act. While this particular act is forecast to have a very low chance of success, it is an important first step in bringing these issues into public awareness. We look forward to increasing policy efforts in this field.

Action 6: build a multidisciplinary consortium. Outreach by emissaries to professional societies will be key. We have approached this issue through the field of Sports Medicine and recognize that the topic of regenerative practices clearly expands just Sports Medicine. Nevertheless, practitioners in specific disciplines (*e.g.,* elbow, knee societies) could help involve their respective professional organizations to help advance the evidence base and promote regulation in a systematic way.

Action 7: develop and pursue a clear collective impact agenda. Few developments in Sports Medicine have been accompanied by as much hype as the field of regenerative medicine. While the potential benefits may seem endless, few cell preparations have made their way through formal regulatory procedures and into practice. Our group plans to convene future meetings at which we hope a representative from the FDA will attend to address this urgent need specifically in the pediatric population. In addition, the International Society for Stem Cell Research provides guidelines on their publicly accessible website for the ethical conduct of stem cell research and clinical translation (http://www.isscr.org/home/publications/2016-guidelines). As a community of clinicians, scientists, and ethicists we encourage the highest degree of rigor and transparency within the field of regenerative medicine and its application to the pediatric sports patient.

Conclusions

Regenerative medicine therapies potentially offer a very potent way of assisting in the treatment of a variety of sports-related injuries given their regenerative and immunoregulatory potential. Despite the media attention and perceived benefits of these therapies, there are still limited data as to efficacy and long-term safety. In particular, the careful study and documentation of outcomes, as well as potential side effects, in the adolescent athlete are largely unavailable at the present time in the published literature. The involvement of clinicians, scientists, and ethicists as well as others with knowledge in the field is essential in our quest for the truth. The study of other approaches such as PRP, with or without other regenerative therapies, also should be carefully evaluated. Indeed, we should look beyond the past and the present and not miss the future for our patients.

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