Economic Realities of Orthobiologics

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KEYWORDS

• Orthobiologics • Economics • Platelet-rich plasma • Bone marrow aspirate • Cost-analysis • Mesenchymal stem cells

KEY POINTS

- With orthobiologics playing an increasing role in the nonsurgical management of orthopedic conditions, issues have arisen related to the regulation, marketing, and overall economics of these treatments.
- Many cell therapies are regulated under the strict guidelines by the Food and Drug Administration's Center for Biologics Evaluation and Research and some products, like platelet-rich plasma and concentrated bone marrow aspirate, are exempt from stringent regulatory pathways, which leads to insurance coverage issues and financial burdens for patients due to their off-label use and lack of standardized pricing.
- Aggressive and often misleading marketing practices, along with significant regional and setting-based cost variations, exacerbate the financial burden on patients, highlighting the need for improved insurance coverage and increased research funding to validate the efficacy and cost-effectiveness of orthobiologic therapies.

BACKGROUND

Musculoskeletal pathology imposes significant health care costs that range from direct medical costs, such as treatments, medications, and hospitalizations, to indirect costs, such as lost productivity, disability payments, and the need for long-term care. Osteoarthritis, in particular, is a large burden to the health care system with the prevalence projected to increase in developed regions with established market economies, such as North America and Europe, due to aging populations and rising obesity rates.[1] The considerable financial burden for patients with osteoarthritis has been noted to come out to a lifetime mean cost of around $140,000 per affected patient.[2]

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The field of orthobiologics continues to rapidly evolve and includes non-cell and cell-based therapies that are derived from substances that naturally exist in the body. In particular, platelet-rich plasma (PRP), concentrated bone marrow aspirate (cBMA), adipose-derived mesenchymal stem cells (ADMSCs), and amniotic cell therapies have become increasingly popular in the past decade.[3] While nomenclature of these mesenchymal "stem" cells (MSCs) and aggressive marketing may lead to thoughts of pluripotent stem cells, in reality, the cell-based therapies contain multipotent cells known as mesenchymal stromal cells that can differentiate into a mesenchymal lineage, such as osteoblasts, chondroblasts, or adipocytes, at a concentration lower than 1%. It is likely that these mechanisms of action are not actively occurring nor leading to tissue regeneration in most clinical settings where these agents are utilized today. Each of these therapies enhances the biologic ability to heal and potentially regenerate tissues by concentrating anti-inflammatory proteins and growth factors.[3] Interest in orthobiologics continues to rise, both among the public and scientific community. Google trends searches pertaining to orthobiologic treatments since 2009 have significantly increased overtime,[4] paralleling a rise in the volume of peer-reviewed publications and a steep rise in citations, which underscores the growing interest and research impact in this field.[5–7]

Specific to "cell-based" therapeutics used to treat musculoskeletal conditions, it is likely that the therapeutic impact is derived from the delivery of mesenchymal stromal cells in combination with anti-inflammatory and immunomodulatory mediators. It must be noted that the prospects for true regeneration from so-called "MSCs" are largely aspirational at this juncture. Their impact is predominately symptom modifying rather than disease modifying or structure modifying with true tissue regeneration. In most instances, their mechanisms include modulation of a pro-regenerative tissue microenvironment with paracrine-mediated modulation with or without direct release of growth factors and anti-inflammatory mediators from exosomes.

Despite the rapid increase in use, public interest, and research on orthobiologics, there is sparse literature regarding the economic landscape as well as limited cost transparency found across the country. Findings from a survey of physicians who provide regenerative medicine procedures show significant variability in patient costs and a failure to analyze an association between treatment costs and outcomes.[8] The purpose of this article is to provide a current, comprehensive review of the economic impact of orthobiologic treatments.

FOOD AND DRUG ADMINISTRATION

Orthobiologics fall under the Food and Drug Administration (FDA) section of Center for Biologics Evaluation and Research (CBER). CBER is responsible for regulating human cells, tissues, and cellular tissue-based products (HCT/Ps).[9] Furthermore, the FDA regulates interstate commerce for these products through the Public Health Service Act (PHSA), a law enacted in 1944 by the federal government. The PHSA establishes regulatory requirements for the marketing and safety of HCT/Ps. The PHSA is broken down into 2 sections, PHSA 351 and PHSA 361, which categorizes blood products into groups with different regulations and necessary requirements before they can be brought to market with specific indications in the United States (**Table 1**).[10,11]

The Code of Federal Regulations (CFR) is produced annually by the FDA to provide policies and instructions for manufacturers, health care providers, and sponsors in the development of products. Specifically, title 21, part 1271 of the CFR (21 CFR 1271), relates to orthobiologics and addresses "articles containing or consisting of human cells or tissues that are intended for implantation, transplantation, infusion, or transfer

Table 1
Food and drug administration Public Health Service Act 361 versus 351

Category	Characteristics	Regulation
361 Products	The HCT/P: 1. Is minimally manipulated 2. Is intended for homologous use only 3. Does not involve the combination of the cells or tissues with another article except for water, crystalloids, or a sterilizing, preserving, or storage agent 4. Either • Does not have a systemic effect and is not dependent upon the metabolic activity of living cells for its primary function OR • Has a systemic effect or is dependent upon the metabolic activity of living cells for its primary function, and: a. Is for autologous use b. Is for allogenic use in a first-degree or second-degree blood relative; or c. Is for reproductive use	1. HCT/P is regulated solely under section 361 of the PHSA, and regulations in 21 CFR Part 1271 2. No premarket approval required 3. Must Follow Current Good Tissue Practices (CGTPs)
351 Products	The HCT/P: 1. Fails to meet criteria for 361 products 2. Regulated as a drug, device, and/or biologic product depending on the primary mode of action	1. HCT/P is regulated under section 351 of the PHSA 2. Regulated under the Federal Food, Drug, and Cosmetic Act (FD&C) and applicable regulations 3. CGTPs and Current Good Manufacturing Practices (cGMP) 4. Premarket approval, safety, and effectiveness required 5. Investigational New Drug (IND)

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into a human recipient."[12] As noted in **Table 1**, the approval process for various HCT/Ps significantly varies depending on which PHSA section a product is grouped into. 21 CFR 1271 states that for an HCT/P to be regulated under PHSA 361, it must meet the 4 criteria laid out in Table 1. With these criteria met, 361 products are exempt from having to go through animal and clinical studies, as well as premarket FDA review. Those who do not meet these criteria are characterized as 351 products and are, therefore, subject to premarket requirements and approval, as well as preclinical laboratory and animal testing before progression to testing in humans.[10,11,13] These 351 products must be studied extensively under the provisions of Investigational New Drugs (INDs), and biologics licensing applications to the FDA are required prior to marketing.[13]

Under certain conditions, the FDA does not require regulation under 21 CFR 1271. One situation in which these regulations may not apply is procedures in which autologous HCT/Ps are implanted into the same individual during the same surgical procedure.[14] Furthermore, certain blood products, such as PRP, as well as cBMA, are exempt from regulation under 21 CFR 1271.[9,12] The preparation system used to create PRP and cBMA can be regulated under the 510(k) pathway. This pathway involves a premarket submission to the FDA demonstrating that these products are "substantially equivalent" to another marketed device, thereby exempting them from the traditional regulatory pathway.[12] Additionally, the use of PRP, for example, has been cleared for use in an operative setting to mix with bone graft materials to enhance bone graft handling properties.[9] Therefore, its utilization in an alternative clinical setting, such as an injection in an office setting, would be considered "off-label."

The lack of FDA approval for orthobiologic injections, coupled with their classification as an "off-label" usage of products, has contributed to the notion that insurance companies are often not required to cover the costs of these treatments. They will consistently deny coverage based upon the fact that they are considered "experimental and or investigational" in nature.[15] This has led to significant financial burdens on patients who must pay out-of-pocket. Additionally, there is a lack of standardization in the pricing of these injections, resulting in large variations in cost. This inconsistency further complicates the financial impact on patients seeking these treatments.

ORTHOBIOLOGICS MARKETING

US markets have drastically increased direct-to-consumer marketing and sales of orthobiologic treatments over recent years. In 2021, over 2750 clinics in the United States reported selling "stem cell" treatments for various indications, 4 times as many as were reported 5 years prior.[15] This substantial rise in marketing efforts of orthobiologic products has raised issues as these endeavors have in many cases outpaced clinical evidence and regulatory control. The content and tactics utilized by clinics and businesses in the marketplace have compounded these problems further. A social media analysis conducted by Ramkumar and colleagues[16] evaluating the marketing of cellular therapy in musculoskeletal medicine found that 94% of posts had an exclusively positive tone without necessarily providing a fair balance of the risks, benefits, and limitations of such treatments. Other literature on the matter reports an overwhelmingly positive portrayal and framing of "stem cell" clinics in print media overviews. This has persuaded patients to travel far and wide for treatments, contributing to the increasing business of "stem cell tourism" in recent decades.[17,18] Furthermore, a large percentage of businesses selling stem cell therapies use vague language to avoid making explicit claims about the regulatory status of their marketed product.[18,19]

In recent years, the FDA has made efforts to address some of the problems related to direct-to-consumer orthobiologic marketing approaches taken by many businesses by exercising discretion concerning its enforcement of federal laws and regulations applicable to these products. In 2017, new guidance documents were released by the administration, which clarified the regulatory framework for regenerative medicine. During the era of enforcement discretion, which spanned almost 4 years from 2017 to 2021, the FDA emphasized continued authority to take action against businesses selling and advertising products with potential safety concerns but provided a grace period with the hope that this period of enforcement discretion would encourage businesses to contact the FDA to clarify the regulatory status of their stem cell-based medical products. The idea was to help companies that were not complying with relevant federal regulations make the transition to compliant practices by providing feedback and guidance, and to give companies a chance to either seek FDA approval for their products or adjust their practices to meet regulatory requirement. Unfortunately, this did not come to pass as few businesses reached out to the FDA and instead continued advertising their products in a similar, improper manner after the discretionary period ended.[18]

Overall, these marketing issues in the stem-cell therapy and orthobiologics industry have made it difficult for patients to make informed decisions and, in some cases, have compromised their informed consent rights. Furthermore, many companies do not disclose the costs of their therapies on their Web sites, leading to high out-of-pocket expenses for potentially misleading products. Despite these concerns, businesses have continued to exploit patients' hope and desperation with forceful sales tactics and deceptive claims.[18,19] In addition, regulations regarding ethical and legal marketing vary by country, further complicating matters.[20] While the unethical marketing practices in the orthobiologics industry are concerning, they should not overshadow the clinicians who follow the literature, clearly explain potential benefits and limitations to patients, and offer these therapies with the sincere goal of enhancing patient outcomes. Despite the issues discussed, when utilized appropriately, orthobiologics hold tremendous promise in the sports medicine world from the typical otherwise active patient to professional athletes.[21,22] Orthopedic surgeons, particularly those in sports medicine and those who treat osteoarthritis, should familiarize themselves not only with their mechanisms of action, indications, and evidence-based efficacy, but also their regulations and costs.

PLATELET-RICH PLASMA

Platelet-rich plasma consists of platelet concentrates from autologous blood, which have gained popularity in fields such as wound healing and sports medicine for its powerful anti-inflammatory, pro-angiogenic, and tissue regenerative growth factors.[23,24] PRP preparation involves centrifugation of whole venous blood with many systems utilizing a 2 speed spin protocol that reduces the number of erythrocytes and concentrates platelets.[24] There are a variety of PRP preparation systems that differ in platelet collection efficiency, final leukocyte count, and platelet activation, and these should be understood and accounted for when selecting a PRP formulation and in research studies.[25] In addition, 2 main preparation differences involve the inclusion or removal of the leukocyte-rich (LR) buffy coat layer that provide increased numbers of platelets and growth factors, but also pro-inflammatory cytokines. In a national survey conducted by Noback and colleagues[26] of orthopedic surgeons who are members of the American Orthopedic Society for Sports Medicine, results showed

that the most commonly used orthobiologics is leukocyte-poor (LP) PRP, utilized by 76.1% of members. The most common indication for LP-PRP in this group was osteoarthritis, accounting for 71.6% of its use.[27] In contrast, LR PRP was demonstrated to be the most popular orthobiologic in muscle, ligament, and tendon injuries, while cBMA is most popular for articular cartilage injuries.[26]

The lack of formal indications and labeling for PRP therapy has resulted in limited reimbursement from insurance programs and Medicare and Medicaid Services. Currently, the Centers for Medicare and Medicaid Services (CMS) only considers reimbursement for the use of autologous PRP for patients with nonhealing diabetic, pressure, and/or venous wounds who meet certain criteria.[27] Despite increasing evidence of the benefits of PRP therapy for patients with orthopedic conditions, CMS has limited approved indications for musculoskeletal conditions. In 2010, a current procedural terminology (CPT) code (CPT-0232T) was introduced for PRP injections that made tracking the use of PRP more accessible, but also more billable. In a study conducted by Werner and colleagues[27], it was found that the annual charges to Medicare for PRP injections increased 400% in the 4 years after the introduction of the CPT code, from $500,000 in 2010 to more than $2 million in 2014. In a further analysis from 2010 to 2014 of patient data analyzed by demographics and geographic regions, it was found that the highest percentage of injections were provided in the south (42%), with the fewest amount of PRP injections administered in the northeast (15%).[27] In a study by Berlinberg and colleagues[28] which examined data from 2010 to 2020 using the PearlDiver database, they demonstrated that 20,483 PRP injections were provided in 15,961 patients in the United States during this 10 year period, which would place the country on a trajectory to provide 3952 injections in 3012 patients per year by 2030 as demonstrated in **Fig. 1**.

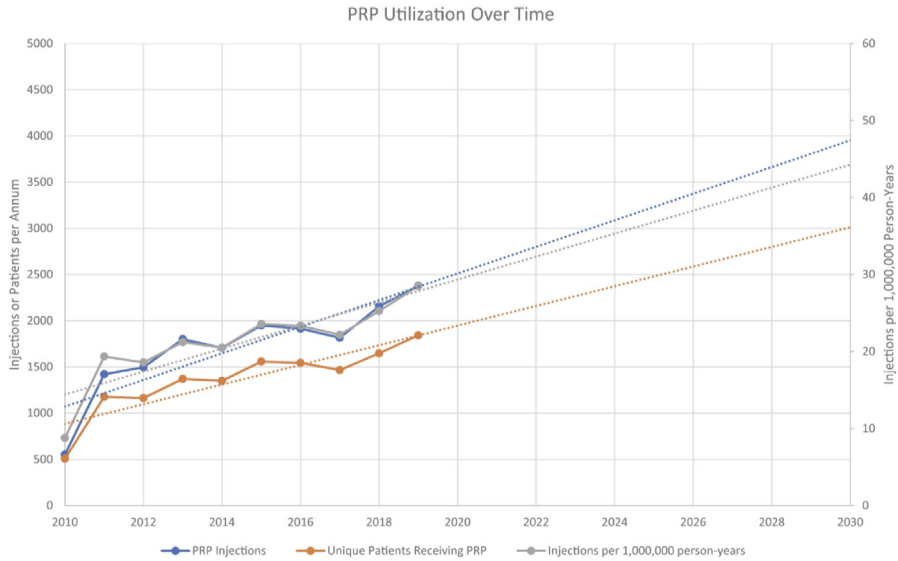

Fig. 1. Graph showing platelet-rich plasma (PRP) utilization in a large insurance claims database from 2010 to Q1.2020 with projections for PRP utilization during insurance-covered visits by 2030. (Berlinberg, Elyse J. BS et al., The Epidemiology of Platelet-Rich Plasma Injections From 2010 to 2020 in a Large US Commercial Insurance Claims Database: A Recent Update. Journal of the American Academy of Orthopaedic Surgeons 31(3):p e135-e147, February 1, 2023. DOI: 10.5435/JAAOS-D-22-00397.).

With the rapid expansion of both interest and utilization, along with the persistent lack of consistent insurance coverage, out-of-pocket costs for PRP injections have emerged as a major impediment for patients interested in these therapies. In published literature evaluating the economic impact of PRP injections, there has been increasing cost variability overtime. The estimated charge for a single injection ranged from $200 to $500 in 2012, according to a review performed by Dhillon and colleagues.[29] The estimated range was reported to be between $450 and $2500 in 2015, and in 2018, the mean price for a same-day PRP unilateral knee injection for the treatment of osteoarthritis was $714 with prices ranging from $380 to $1390.[30] In a more recent study conducted by Momaya and colleagues[15] in 2020, 818 US practices that were contacted were found to offer PRP injections for a mean price of $707 +/− $388 (range $175–$4973).

In addition to the general cost variability for these injections, there has also been variable pricing among different medical specialties, types of medical practices, and location of medical practices that have been reported in the literature. A 2023 study by Charnoff and colleagues[8] found that non-orthopedic surgery providers charge more for PRP injections than orthopedic surgeons, with physical medicine and rehabilitation providers in particular charging the highest average price per injection. This same study found that private practices typically charge more than providers working in academic settings for both PRP and cBMA injections. Regarding medical practice location, it has been noted that the highest median price for PRP injections is found in the northeast with the lowest prices being found in the south.[31] A 2024 study by Tiao and colleagues[31] examined the relationship between hospital orthopedic scores, assigned by US News & World Report as a measure of hospital performance, and PRP injection prices. The study found that PRP injection prices were inversely correlated with the orthopedic scores of the hospitals where they were administered.

After examining the intricacies of price point variability and the numerous factors involved in the business of PRP injections, the critical question arises: Are these treatments cost-effective overall? Additionally, is there a specific price point that would make these treatments universally worthwhile under the right conditions? The answers to these questions remain a subject of debate within the medical community. In a systematic review of 9 level 1 randomized controlled trials, Bendich and colleagues[32] found that for symptomatic knee osteoarthritis, PRP is cost-effective at a total price (inclusive of clinic visit, procedure cost, and the actual PRP) of less than $3703.03 over a 6 month period and less than $1192.08 over a 12 month period, relative to hyaluronic acid injections or saline placebo. In another study, Rajan and colleagues conducted a cost-effectiveness analysis to evaluate the value of PRP in delaying the need for total knee arthroplasty (TKA). They concluded that PRP injections for knee osteoarthritis are not cost-effective compared to TKA at outset. The conclusion of this study was not due to the cost of the injections but rather the lack of robust and consistent data regarding PRP's effectiveness in relieving pain, improving function, and delaying the need for TKA.[33] When looking into usage in rotator cuff tears, Vavken and colleagues[34] found that PRP may promote healing of small-sized and medium-sized tears to reduce retear rates but that at the current price, it would likely not be cost-effective to warrant usage. In a cost-effectiveness evaluation in utilization for lateral epicondylitis, Klifto and colleagues[35] found a net monetary benefit for PRP administration in their 5 year analysis using a Markov model design. As demonstrated in published literature, there is currently no clear consensus on the overall cost-effectiveness of PRP injections for various indications. To critically evaluate the economic viability of PRP injections, continued examination of their clinical efficacy,

associated costs, and long-term outcomes compared to conventional treatments are still necessary.

CELL-BASED THERAPY

Cell-based therapies represent another innovative approach related to the use of orthobiologics. When focusing on applications specifically for orthopedic conditions, cell therapies aim to repair or replace damaged tissues and joints by utilizing living cells. Misunderstanding and mischaracterization are rampant in this field with the power of "stem cells" used as a buzzword to attract patients and providers alike. However, the use of most cell-based therapies in musculoskeletal medicine, such as cBMA or ADMSCs, contains very minute concentrations of stem cells. And unlike pluripotent stem cells that can differentiate into any cell lineage, these are MSCs, which are multipotent and develop into multiple cell types within a single-cell lineage (osteoblasts, chondroblasts, etc.). The MSCs within therapies such as cBMA or ADMSCs provide powerful anti-inflammatory, angiogenic, and potentially regenerative effects through paracrine signaling of growth factors but are present in extremely low concentrations in these preparations. Thus, we prefer to refer to these MSCs as mesenchymal stromal, or signaling, cells. In musculoskeletal health care, cell therapies leverage these cells' ability to promote healing and regeneration, offering promising treatments for conditions such as osteoarthritis, tendon injuries, and cartilage defects.

The economics of these therapies is also notable, as the initial costs of cell therapies can be high due to the complex and specialized nature of the treatments. In a study conducted by Momaya and colleagues[15] in 2020 which looked into 288 orthopedic sports medicine practices that offered "stem cell therapy" at the time, it was found that the mean cost per injection was $2728 +/− $1584 (range $300–$12,000). In 2018, Piuzzi and colleagues found a mean cost of $5156 +/− $2446 (range $1150–$12,000) for 65 clinics that reported pricing on stem cell treatment. Of the clinics contacted in this study, 36 provided additional information on the clinical efficacy of their injections, with a mean reported efficacy of 82.2% (range 55%–100%). The study found no correlation between the treatment cost and the marketed clinical efficacy.[36] Alcerro and colleagues[37] found that of 91 South Florida orthopedic offices contacted, 14 offered stem cell therapy with a mean price per treatment of $3100 (range $1200–$6000).

Bone marrow can be utilized as a form of cell-based therapy particularly when prepared as cBMA. Depending upon the specific use, cBMA can fall under the CPT codes 38220, 38,232, and 38,241.[28] The process involves the extraction and concentration of MSCs and growth factors from a patient's own bone marrow followed by reinjection into areas of injury to promote healing and, potentially, regeneration. When higher concentrations of bone marrow-derived MSCs (BM-MSCs) are desired, the processing of the aspirated bone marrow requires an added step in which they are cultured in a laboratory for expansion, followed by specific selection for MSCs, a process which is not FDA approved for use in the United States. Indications and effectiveness of cBMA remain controversial. In a study examining in vitro effects of cBMA on inflammation and cartilage metabolism in a culture model mimicking the osteoarthritis intra-articular environment, Hannon and colleagues[38] found no significant differences in cytokine concentration at 96 hours between the cBMA and control groups. In ACL reconstructions, use of cBMA has demonstrated increased rates of graft maturation and ligamentization in a randomized control trial (RCT) of allograft reconstructions conducted by Forsythe and colleagues.[39] In another recent RCT conducted by Cole and colleagues[40], cBMA augmentation demonstrated improved rates of rotator cuff healing and lower retear rates, but similar to ACLs, no clinically significant outcome

differences. In a 2017 study, Oladeji and colleagues[41] found that the use of cBMA in osteochondral allograft transplantation leads to a significantly higher amount of graft integration at 6 weeks, 3 months, and 6 months postoperatively compared to patients who underwent osteochondral allograft transplantation without cBMA. Multiple reviews have shown superiority of BM-MSCs to MSCs extracted from other sources, such as adipose tissue or umbilical cord tissue, in the treatment of knee osteoarthritis. Ding and colleagues[42] conducted a network meta-analysis on the effectiveness and safety of various sources of MSCs and found that while most treatments did not show statistically significant differences, BM-MSCs may have clinical advantages over other sources at both 6 month and 12 month follow-ups. Chen and colleagues[43] performed a systematic review and meta-analysis of 15 studies involving 585 patients, similarly finding that BM-MSCs provided the most improvement in knee range of motion and pain relief compared to umbilical cord and ADMSCs.

As previously discussed, bone marrow products are exempt from the traditional FDA regulatory pathway and, similarly to PRP, are not covered by insurance in most cases, as they are typically classified as experimental or investigational treatments. Charnoff and colleagues reported that the out-of-pocket cost for a cBMA injection by orthopedic surgeons averaged $3,113, with a standard deviation of $1190. The study also found that, like PRP, cBMA injections are most expensive in the Northeast and that private practices typically charge more than academic settings ($4155 compared to $3000).[8]

Another cell therapy available on the market is ADMSCs. Adipose tissue has been noted as an effective option due to its easy accessibility, abundance, and safety.[44] Readily available from abdominal or gluteal fat, or intra-articular sources such as the infrapatellar fat pad, ADMSCs have been shown to be effective in the treatment of knee osteoarthritis in multiple studies. Kim and colleagues[45] found that a single ADMSC injection provided safe and clinical improvement without radiologic aggravation for 5 years. In an ensuing phase III, randomized, double-blind, placebo-controlled trial, Kim and colleagues[46] demonstrated significant pain relief and functional improvements in patients with Kellgren–Lawrence grade 3 osteoarthritis at 6 months post-ADMSC injection. While ADMSC therapy has been recognized as an effective treatment option for osteoarthritis by multiple studies in the literature, further cost-benefit analysis is needed to determine an optimal and cost-effective price point for these injections.

Umbilical cord MSCs have also been used in orthopedic cell therapy and have been shown in some studies to be effective in cartilage repair. Lee and colleagues[47] compared human umbilical cord blood (hUCB)-derived MSCs (hUCB-MSCs) to cBMA in patients who underwent high tibial osteotomy for medial unicompartmental osteoarthritis and found improved cartilage regeneration in patients who received the umbilical cord MSC product. Palka and colleagues performed a similar study comparing hUCB-MSCs to cBMA in patients who underwent cartilage repair procedures and found substantial overall improved clinical outcomes in both groups.[48] Lee and colleagues[49] performed a systematic review that demonstrated the safety, efficacy, and quality of repaired cartilage following hUCB-MSC therapy. The costs for such treatments can range from $5000 to $7000. In an analysis of the economics of hUCB-MSC therapy in comparison to other treatment options for knee osteoarthritis, Suh and colleagues[50] found that hUCB-MSC therapy for patients with knee OA was cost-effective when compared with microfracture from both the health care payer and societal perspectives.

SUMMARY

The economic dynamics of orthobiologics present a complex landscape influenced by multiple factors, including the evolving nature of insurance coverage and regulatory

pathways, marketing practices, type of health care setting and practice, and geographic location. Understanding these economic aspects is crucial for both health care providers and patients as they navigate these treatment options for various musculoskeletal conditions.

The issue of insurance coverage for orthobiologics remains challenging. While some insurance providers offer partial or full coverage for certain orthobiologic treatments, many consider these therapies as experimental or investigational, leading to significant out-of-pocket expenses for patients. This lack of coverage forces patients to bear the full cost of therapies in many cases, creating a financial barrier to access these treatments, which can be worsened by the frequency and number of treatments required, such as a series of 3 weekly PRP injections. This reality underscores the need for ongoing advocacy and research to support the inclusion of orthobiologics that have proven clinically beneficial in insurance plans, ensuring broader accessibility and reducing costs. Multiple studies highlight cost variability of orthobiologics, demonstrating that PRP and cBMA injections are most expensive in the Northeast region of the United States, a disparity that may be attributed to the higher cost of living and increased operational expenses in the Northeast. Practice setting influences cost, as well, with private practices tending to charge significantly more for orthobiologic treatments compared to academic institutions. This difference may be influenced by the profit-oriented nature of private practices, where pricing strategies are often designed to maximize revenue.

Marketing and pricing strategies employed by some providers for these therapies remain unregulated. Many businesses employ aggressive sales tactics and misleading claims to target vulnerable patients searching for the right treatment. Notably, some clinics market efficacy rates that are higher than what is realistically reported by patients, leading to a disparity between advertised and actual outcomes. These marketing claims must be critically evaluated, as the perceived value may not always align with the actual clinical outcomes experienced by patients.

Addressing the economic challenges associated with orthobiologics requires a multifaceted approach. Policymakers and health care stakeholders must work together to establish clear guidelines and criteria for the coverage of orthobiologic treatments. Increased funding for research to further validate the efficacy and cost-effectiveness of these therapies can support their inclusion in insurance plans. Additionally, efforts to standardize pricing and improve cost transparency are essential to mitigate the financial burden on patients. Moreover, the development of cost-effectiveness models that consider both direct and indirect costs associated with musculoskeletal conditions can provide valuable insights for health care providers and policymakers. These models can help determine the most economically viable treatment options that balance clinical efficacy with financial sustainability. Looking forward, the future of orthobiologics holds significant promise despite the current economic and regulatory challenges. However, for these treatments to become widely accessible, standardized pricing, transparent marketing practices, and increased insurance coverage are crucial. Policymakers, health care providers, and stakeholders must collaborate with each other to establish clear guidelines and support robust clinical trials to validate these therapies' cost-effectiveness.

CLINICS CARE POINTS

- Manage Patient Expections: Based on current evidence, the primary benefits of orthobiologic treatments are predominantly for symptom relief rather than true tissue regeneration. Clearly explaining this to patients is essential to set realistic expectations.

- Address Financial Implications Upfront: Orthobiologic treatments often lack insurance coverage, leading to significant out-of-pocket expenses. Discuss the potential costs during patient consultations to help patients make informaed decisions.
- Highlight the Risk of Misleading Marketing Claims: Be aware that aggressive marketing tactics can exaggerate the efficacy of orthobiologic therapies. Emphasize the need for patients to make informaed decisions based on evidence rather than commercial claims.

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REFERENCES

1. Leifer VP, Katz JN, Losina E. The burden of OA-health services and economics. Osteoarthritis Cartilage 2022;30(1):10–6.
2. Losina E, Paltiel AD, Weinstein AM, et al. Lifetime medical costs of knee osteoarthritis management in the United States: impact of extending indications for total knee arthroplasty. Arthritis Care Res 2015;67(2):203–15.
3. Obana KK, Schallmo MS, Hong IS, et al. Current trends in orthobiologics: an 11-year review of the orthopaedic literature. Am J Sports Med 2022;50(11):3121–9.
4. Cohen SA, Zhuang T, Xiao M, et al. Google trends analysis shows increasing public interest in platelet-rich plasma injections for hip and knee osteoarthritis. J Arthroplasty 2021;36(10):3616–22.
5. Oeding JF, Hernandez HC, Bi AS, et al. The 50 most cited publications on concentrated bone marrow aspirate with application in orthopaedic surgery. J Knee Surg 2023;36(14):1467–72.
6. Strotman PK, Novicoff WM, Nelson SJ, et al. Increasing public interest in stem cell injections for osteoarthritis of the hip and knee: a google trends analysis. J Arthroplasty 2019;34(6):1053–7.
7. Bi AS, Hernandez HC, Oeding JF, et al. The 50 most cited publications in adipose-derived "stem cell therapies" with application in orthopaedic surgery. J Knee Surg 2024;37(2):142–8.
8. Charnoff J, Rothman R, Andres Bergos J, et al. Variability in patient-incurred costs and protocols of regenerative medicine procedures for musculoskeletal conditions in the United States. HSS J 2023;19(1):77–84.
9. Beitzel K, Allen D, Apostolakos J, et al. US definitions, current use, and FDA stance on use of platelet-rich plasma in sports medicine. J Knee Surg 2015;28(1):29–34.

10. Fang WH, Vangsness CT Jr. Governmental regulations and increasing Food and Drug administration oversight of regenerative medicine products: what's new in 2020? Arthroscopy 2020;36(10):2765–70.
11. Regulation of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps) Small Entity Compliance Guide Guidance for Industry. Available at: https://www.fda.gov/media/70689/download (Accessed 1 August 2024).
12. 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(2):488–503.
13. Marks P, Gottlieb S. Balancing safety and innovation for cell-based regenerative medicine. N Engl J Med 2018;378(10):954–9.
14. Food and Drug Administration. Same surgical procedure exception under 21 CFR 1271.15(b): questions and answers regarding the scope of the exception, . Guidance for industry. Washington, DC: US Department of Health and Human Services; 2017.
15. Momaya AM, McGee AS, Dombrowsky AR, et al. The cost variability of orthobiologics. Sport Health 2020;12(1):94–8.
16. Ramkumar PN, Navarro SM, Haeberle HS, et al. Cellular therapy injections in today's orthopedic market: a social media analysis. Cytotherapy 2017;19(12):1392–9.
17. Zarzeczny A, Rachul C, Nisbet M, et al. Stem cell clinics in the news. Nat Biotechnol 2010;28:1243–6.
18. Turner L, Martinez JR, Najjar S, et al. Regulatory claims made by US businesses engaged in direct-to-consumer marketing of purported stem cell treatments and exosome therapies. Regen Med 2023;18(11):857–68.
19. Turner L. The American stem cell sell in 2021: U.S. businesses selling unlicensed and unproven stem cell interventions. Cell Stem Cell 2021;28(11):1891–5.
20. Murray IR, Chahla J, Wordie SJ, et al. Regulatory and ethical aspects of orthobiologic therapies. Orthop J Sports Med 2022;10(11). 23259671221101626.
21. Cole BJ, Gilat R, DiFiori J, et al. The 2020 NBA orthobiologics consensus statement. Orthop J Sports Med 2021;9(5). 23259671211002296.
22. Murray IR, McAdams TR, Hammond KE, et al. The use of biologics in NFL athletes: an expert consensus of NFL team physicians. Orthop J Sports Med 2023;11(2). 23259671221143778.
23. Frykberg RG, Driver VR, Carman D, et al. Chronic wounds treated with a physiologically relevant concentration of platelet-rich plasma gel: a prospective case series. Ostomy Wound Manage 2010;56(6):36–44.
24. Boswell SG, Cole BJ, Sundman EA, et al. Platelet-rich plasma: a milieu of bioactive factors. Arthroscopy 2012;28(3):429–39.
25. McLellan J, Plevin S. Does it matter which platelet-rich plasma we use? Equine Vet Educ 2011;23:101–4.
26. Noback PC, Donnelley CA, Yeatts NC, et al. Utilization of orthobiologics by sports medicine physicians: a survey-based study. J Am Acad Orthop Surg Glob Res Rev 2021;5(1):e20.00185.
27. Werner BC, Cancienne JM, Browning R, et al. An analysis of current treatment trends in platelet-rich plasma therapy in the Medicare database. Orthop J Sports Med 2020;8(2). 2325967119900811.
28. Berlinberg EJ, Swindell BS, Patel HH, et al. The Epidemiology of platelet-rich plasma injections from 2010 to 2020 in a large US commercial insurance claims database: a recent update. J Am Acad Orthop Surg 2023;31(3):e135–47.
29. Dhillon RS, Schwarz EM, Maloney MD. Platelet-rich plasma therapy - future or trend? Arthritis Res Ther 2012;14(4):219.

30. Piuzzi NS, Ng M, Kantor A, et al. What is the price and claimed efficacy of platelet-rich plasma injections for the treatment of knee osteoarthritis in the United States? J Knee Surg 2019;32(9):879–85.
31. Tiao J, Wang K, Herrera M, et al. There is wide variation in platelet-rich plasma injection pricing: a United States nationwide study of top orthopaedic hospitals. Clin Orthop Relat Res 2024;482(4):675–84.
32. Bendich I, Rubenstein WJ, Cole BJ, et al. What is the appropriate price for platelet-rich plasma injections for knee osteoarthritis? A cost-effectiveness analysis based on evidence from level I randomized controlled trials. Arthroscopy 2020;36(7):1983–91.e1.
33. Rajan PV, Ng MK, Klika A, et al. The cost-effectiveness of platelet-rich plasma injections for knee osteoarthritis: a Markov decision analysis. J Bone Joint Surg Am 2020;102(18):e104.
34. Vavken P, Sadoghi P, Palmer M, et al. Platelet-rich plasma reduces retear rates after arthroscopic repair of small- and medium-sized rotator cuff tears but is not cost-effective. Am J Sports Med 2015;43(12):3071–6.
35. Klifto KM, Colbert SH, Richard MJ, et al. Platelet-rich plasma vs. corticosteroid injections for the treatment of recalcitrant lateral epicondylitis: a cost-effectiveness Markov decision analysis. J Shoulder Elbow Surg 2022;31(5):991–1004.
36. Piuzzi NS, Ng M, Chughtai M, et al. The stem-cell market for the treatment of knee osteoarthritis: a patient perspective. J Knee Surg 2018;31(6):551–6.
37. Alcerro JC, Lavernia CJ. Stem cells and platelet-rich plasma for knee osteoarthritis: prevalence and cost in south Florida. J Am Acad Orthop Surg 2019;27(20):779–83.
38. Hannon C, Dandu N, Huddleston H, et al. Paper 19: the influence of amniotic suspension allografts and bone marrow aspirate concentrate on inflammation & cartilage matrix metabolism in osteoarthritic chondrocytes. Orthop J Sports Med 2022;10(7 suppl5). 2325967121S00583.
39. Forsythe B, Chahla J, Korrapati A, et al. Bone marrow aspirate concentrate augmentation may accelerate allograft ligamentization in anterior cruciate ligament reconstruction: a double-blinded randomized controlled trial. Arthroscopy 2022;38(7):2255–64 [published correction appears in Arthroscopy. 2023 Jun;39(6):1595.].
40. Cole BJ, Kaiser JT, Wagner KR, et al. Prospective randomized trial of biologic augmentation with bone marrow aspirate concentrate in patients undergoing arthroscopic rotator cuff repair. Am J Sports Med 2023;51(5):1234–42.
41. Oladeji LO, Stannard JP, Cook CR, et al. Effects of autogenous bone marrow aspirate concentrate on radiographic integration of femoral condylar osteochondral allografts. Am J Sports Med 2017;45(12):2797–803.
42. Ding QX, Wang X, Li TS, et al. Comparative analysis of short-term and long-term clinical efficacy of mesenchymal stem cells from different sources in knee osteoarthritis: a network meta-analysis. Stem Cells Int 2024;2024:2741681.
43. Chen X, Zheng J, Yin L, et al. Transplantation of three mesenchymal stem cells for knee osteoarthritis, which cell and type are more beneficial? a systematic review and network meta-analysis. J Orthop Surg Res 2024;19(1):366.
44. Wang J, Zhou L, Zhang Y, et al. Mesenchymal stem cells - a promising strategy for treating knee osteoarthritis. Bone Joint Res 2020;9(10):719–28.
45. Kim KI, Lee WS, Kim JH, et al. Safety and efficacy of the intra-articular injection of mesenchymal stem cells for the treatment of osteoarthritic knee: a 5-year follow-up study. Stem Cells Transl Med 2022;11(6):586–96.

46. Kim KI, Lee MC, Lee JH, et al. Clinical efficacy and safety of the intra-articular injection of autologous adipose-derived mesenchymal stem cells for knee osteoarthritis: a phase III, randomized, double-blind, placebo-controlled trial. Am J Sports Med 2023;51(9):2243–53.
47. Lee NH, Na SM, Ahn HW, et al. Allogenic human umbilical cord blood-derived mesenchymal stem cells are more effective than bone marrow aspiration concentrate for cartilage regeneration after high tibial osteotomy in medial unicompartmental osteoarthritis of knee. Arthroscopy 2021;37(8):2521–30.
48. Pałka K, Sadlik B, Kamiński P, et al. Comparison of the efficacy of human umbilical cord-derived and bone marrow aspirate concentrate mesenchymal stem cells for cartilage repair defects of the knee via arthroscopic implementation on scaffolds in a retrospective study. J Pers Med 2024;14(3):220.
49. Lee DH, Kim SA, Song JS, et al. Cartilage regeneration using human umbilical cord blood derived mesenchymal stem cells: a systematic review and meta-analysis. Medicina (Kaunas) 2022;58(12):1801.
50. Suh K, Cole BJ, Gomoll A, et al. Cost effectiveness of allogeneic umbilical cord blood-derived mesenchymal stem cells in patients with knee osteoarthritis. Appl Health Econ Health Policy 2023;21(1):141–52 [published correction appears in Appl Health Econ Health Policy. 2023 Jan;21(1):153.].