

Position Statement



Bone Marrow Concentrate (BMC) Therapy in Musculoskeletal Disorders: Evidence-Based Policy Position Statement of American Society of Interventional Pain Physicians (ASIPP)

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Background: The use of bone marrow concentrate (BMC) for treatment of musculoskeletal disorders has become increasingly popular over the last several years, as technology has improved along with the need for better solutions for these pathologies. The use of cellular tissue raises a number of issues regarding the US Food and Drug Administration's (FDA) regulation in classifying these treatments as a drug versus just autologous tissue transplantation. In the case of BMC in musculoskeletal and spine care, this determination will likely hinge on whether BMC is homologous to the musculoskeletal system and spine.

Objectives: The aim of this review is to describe the current regulatory guidelines set in place by the FDA, specifically the terminology around "minimal manipulation" and "homologous use" within Regulation 21 CFR Part 1271, and specifically how this applies to the use of BMC in interventional musculoskeletal medicine.

Methods: The methodology utilized here is similar to the methodology utilized in preparation of multiple guidelines employing the experience of a panel of experts from various medical specialties and subspecialties from differing regions of the world. The collaborators who developed these position statements have submitted their appropriate disclosures of conflicts of interest. Trustworthy standards were employed in the creation of these position statements. The literature pertaining to BMC, its effectiveness, adverse consequences, FDA regulations, criteria for meeting the standards of minimal manipulation, and homologous use were comprehensively reviewed using a best evidence synthesis of the available and relevant literature.

Results/Summary of Evidence: In conjunction with evidence-based medicine principles, the following position statements were developed:

Statement 1: Based on a review of the literature in discussing the preparation of BMC using accepted methodologies, there is strong evidence of minimal manipulation in its preparation, and moderate evidence for homologous utility for various musculoskeletal and spinal conditions qualifies for the same surgical exemption.

Statement 2: Assessment of clinical effectiveness based on extensive literature shows emerging evidence for multiple musculoskeletal and spinal conditions.

- The evidence is highest for knee osteoarthritis with level II evidence based on relevant systematic reviews, randomized controlled trials and nonrandomized studies. There is level III evidence for knee cartilage conditions.
- Based on the relevant systematic reviews, randomized trials, and nonrandomized studies, the evidence for disc injections is level III.
- Based on the available literature without appropriate systematic reviews or randomized controlled trials, the evidence for all other conditions is level IV or limited for BMC injections.

Statement 3: Based on an extensive review of the literature, there is strong evidence for the safety of BMC when performed by trained physicians with the appropriate precautions under image guidance utilizing a sterile technique.

Statement 4: Musculoskeletal disorders and spinal disorders with related disability for economic and human toll, despite advancements with a wide array of treatment modalities.

Statement 5: The 21st Century Cures Act was enacted in December 2016 with provisions to accelerate the development and translation of promising new therapies into clinical evaluation and use.

Statement 6: Development of cell-based therapies is rapidly proliferating in a number of disease areas, including musculoskeletal disorders and spine. With mixed results, these therapies are greatly outpacing the evidence. The reckless publicity with unsubstantiated claims of beneficial outcomes having putative potential, and has led the FDA Federal Trade Commission (FTC) to issue multiple warnings. Thus the US FDA is considering the appropriateness of using various therapies, including BMC, for homologous use.

Statement 7: Since the 1980's and the description of mesenchymal stem cells by Caplan et al, (now called medicinal signaling cells), the use of BMC in musculoskeletal and spinal disorders has been increasing in the management of pain and promoting tissue healing.

Statement 8: The Public Health Service Act (PHSA) of the FDA requires minimal manipulation under same surgical procedure exemption. Homologous use of BMC in musculoskeletal and spinal disorders is provided by preclinical and clinical evidence.

Statement 9: If the FDA does not accept BMC as homologous, then it will require an Investigational New Drug (IND) classification with FDA (351) cellular drug approval for use.

Statement 10: This literature review and these position statements establish compliance with the FDA's intent and corroborates its present description of BMC as homologous with same surgical exemption, and exempt from IND, for use of BMC for treatment of musculoskeletal tissues, such as cartilage, bones, ligaments, muscles, tendons, and spinal discs.

Conclusions: Based on the review of all available and pertinent literature, multiple position statements have been developed showing that BMC in musculoskeletal disorders meets the criteria of minimal manipulation and homologous use.

Key words: Cell-based therapies, bone marrow concentrate, mesenchymal stem cells, medicinal signaling cells, Food and Drug Administration, human cells, tissues, and cellular tissue-based products, Public Health Service Act (PHSA), minimal manipulation, homologous use, same surgical procedure exemption

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Musculoskeletal disorders represent a major cause of morbidity and result in enormous costs for health and social care systems (1-11). Chronic and inflammatory diseases of joints and the spine, including osteoarthritis, and low back pain caused by intervertebral disc degeneration with involvement of the 3-joint complex, are major causes of disability in

young and elderly alike (12). The disability and cost of health care continue to increase despite the number of available treatment modalities and significant increases in health care expenditures (3-49). Consequently, a shift in health care strategies has been advocated involving novel pharmacologic and biological therapies that can effectively treat these disorders.

Development of cell-based therapies is being rapidly incorporated into treatment plans for a number of disease processes, including musculoskeletal disorders and spine. The results are mixed. The use of cell-based therapy is greatly outpacing the evidence (12,49-71). The public awareness that biologics have regenerative potential has been acknowledged by their highly publicized use in professional athletes, and because of the national debate on embryonic stem cells (49,72). Consequently, the result of this irresponsible publicity with unsubstantiated claims of miraculous outcomes (57) has led the Federal Trade Commission (FTC) to take action against stem cell therapy clinics found to be in violation of the truth in advertising law (58). In addition, misrepresentation of uncharacterized, minimally manipulated, allogenic cell preparation as "stem cells," or the use of more than minimally manipulated cell preparations, have led to a widespread clinical use of unproven biologic therapies (49,73,74). The US Food and Drug Administration (FDA) has had no recourse but to investigate multiple stem cell clinics and publish new guidance (59-74). Physicians using bone marrow-derived medicinal signaling cells or mesenchymal stem cells (BM-MSC) therapy must elucidate, justify, and recommend that the FDA consider bone marrow concentrate (BMC) as "homologous use." The sheer volume of unsubstantiated claims and lack of high-level research has led to a health Canada policy position paper on the use of autologous cell therapy products (75). In addition, concerns over misinformation and inappropriate application of stem cell therapy have led to recent calls to action from professional organizations including the National Academy of Sciences (NAS), the International Society for Cellular Therapy (ISCT), the American Association for the Advancement of Science (AAAS), the American Academy Orthopedic Surgeons (AAOS), and American Society of Interventional Pain Physicians (ASIPP) (3,49,50,76-78). Each of these groups recognize the potential value of cell therapies and the risk that the current environment may erode the public trust. Responsible investments are needed to bring legitimate cellular and biological therapies to patients (49).

Regenerative medicine continues to develop based on the scientific principles of evidence-based medicine with its effectiveness shown in multiple musculoskeletal disorders and in managing spinal pain (3,49,50,78-112). In contrast to traditional medical therapies, stem cell-based therapies integrate tissue-engineering technologies and biomaterial science fundamental to the science of regenerative medicine. Thus, tissue engineering

approaches for cartilage and intervertebral disc repair will benefit from advances in MSCs based repair strategies (106).

The 21st Century Cures Act was enacted in December 2016, with provisions to accelerate the development and translation of promising new therapies into clinical evaluation and use (52,113). This bipartisan and bicameral legislation increased funding for medical research, and for combatting the opioid epidemic, including measures to streamline approval of new therapies for clinical trials (49,52). The 21st Century Cures Act also provided a new expedited biologics product development program called Regenerative Medicine Advanced Therapy (RMAT) (63). The key elements of RMAT include accelerated FDA approval for regenerative medicine therapy that is intended to treat a condition and shows a potential to address unmet clinical needs for some diseases or conditions, such as chronic musculoskeletal and spine conditions.

In regenerative medicine the present focus of cell therapy has been on 2 types of stem cells, namely bone marrow-derived stem cells and adipose-derived stem cells. However, with the FDA regulations on stem cell therapy, adipose-derived cell therapies have been considered as a drug. Thus BMC is currently the only viable strategy left in the United States covered under the 21 CFR 1271.15 (b) same surgical exemption despite many emerging autologous cell therapy products. Unfortunately, some countries, including Canada, have regulated all types of stem cells, essentially restricting cell therapy in their countries (75).

Bone marrow is the organ responsible for the generation of blood and immune cells, with mesenchymal cells supporting hematopoiesis (107,108,114). Bone marrow transplants begin in the 1960s and beginning in the 1980s, BMC began to be used in musculoskeletal pathologies. Based on the therapeutic properties of the cells and growth factors contained in the bone marrow, its use has been tested in several types of disease entities and injuries with positive outcomes, including musculoskeletal disorders and spinal disorders (108,114-118). Historically, Till and McCulloch (117) in 1963 demonstrated that bone marrow transplantation (BMT) was able to reconstitute the hematopoietic system of mice that had their system completely depleted by irradiation. In 1966, Friedenstein et al (115) showed that bone marrow contained a distinct type of cell capable of forming bone tissue when cultured in diffusion chambers and then implanted in mice. These cells were later described

as mesenchymal cells (116). Since then, in the 1980s, Arnold Caplan and colleagues published their work on the isolation of MSCs from BMC and the ability of these cells to differentiate into bone and cartilage in specific *in vitro* conditions (107,119-122). Caplan (120) also renamed mesenchymal stem cells as medicinal signaling cells with the acronym remaining the same—MSCs. Since Caplan, there has been rapid expansion of the basic and clinical literature investigating the potential therapeutic application of stem cell therapy and regenerative medicines (3,49,50,79-108). *In vitro* studies showed that (BM-MSCs can be purified, culture expanded, and induced to differentiate into mesodermal tissue types (57,123-125). Investigations into potential clinical applications for musculoskeletal injury and disease (including spinal disorders), range from a variety of soft issue biologic treatment modalities, including direct soft tissue and osseous injections, as well as intravascular therapy to intraarticular therapy, and intradiscal therapy, all of which have increased exponentially (50). Despite the development of a clinical and therapeutic basis for use of BM-MSCs and other forms of stem cell therapy, clinical applications have far outpaced the basic and transitional science required to confirm their potential effectiveness and safety (3,46,50-71,107,126-134).

The Public Health Service Act (PHSA) defines the laws surrounding the control of the spread of communicable diseases in organ or tissue transplants. The FDA has since created regulations found in 21 CFR 1271 based on the PHSA, which control the use of human cells, tissues, and cellular and tissue-based products (HCT/Ps), including both autologous and allogenic bone marrow-derived tissue preparations (52,61,62,135). Two broad categories of tissue preparations intended to be injected or infused into human recipients are described in 21 CFR 1271 applying to HCT/Ps that are minimally manipulated and intended for homologous use (135) or those that are more than minimally manipulated or intended not to be used in a homologous way. The FDA described that the processing procedure for minimally manipulated cells or tissues must not “alter the original relevant characteristics relevant to the tissues’ utility for reconstructive, repair, and replacement,” and must not “alter relevant biological characteristics of cells or tissue.” Further, the FDA defines homologous use as, “the repair, reconstruction, replacement, or supplementation of the recipient’s cells or tissues with an HCT/P that performs the same basic function or functions in the recipient as

in the donor” (135). In addition to these 2 important aspects of the regulation, 21 CFR 1271 also requires that the cells are not combined with any other tissue or product except for “water, crystalloids, or a sterilizing, preserving, or storage agent.” Thus cell and tissue preparations that meet the criteria described in 1271 can be administered to patients without obtaining premarket clearance or an investigational new drug (IND) classification from the FDA.

In addition, if the HCT/Ps have passed a minimal manipulation test as described earlier, then they are eligible to be exempt under 21 CFR 1271.15(b). This same surgical procedure exemption contemplates that the cells are extracted and reintroduced into the same patient (autologous) during the same surgical procedure (135).

Based on the FDA regulation and present concepts, autologous BMC meets the definitions of minimal manipulation without controversy. In addition, it meets the definition of the 21 CFR 1271.15(b) same surgical procedure exemption as well. However, the second aspect of the definition, which is homologous use when used to treat musculoskeletal applications, has still yet to be decided. This issue has evolved into not only a subject of discussion, but also of concern based on the Canadian position on autologous cell therapy products (75). A Health Canada Policy position paper with the regulatory frameworks under the Food and Drug Act provided oversight of safety, efficacy, and quality, while enabling patient access to potentially promising new therapies in 2019, declared that autologous cell therapy products meeting the definition of “drug” in persons who prepare or manufacture and administer or distribute must comply with Sections 8 and 11 of the Food and Drug Act (75,136,137). This Health Canada policy change now includes BMC in the “drug” category. However, Health Canada continues to work to identify and overcome challenges specific to meeting regulatory requirements for the manufacturing and sale of autologous cell therapy products.

Other international regulatory authorities, such as the European Medicine Agency, have laws similar to Canada’s that allow them to regulate the distribution of cell therapy products in their respective jurisdictions. However, the European Union has enacted regulations specifically for cell therapy products, whereas US FDA and Health Canada applied existing drug regulatory frameworks. In addition, some regulatory authorities have special exemptions for cell therapy products, including those that are prepared at the bedside during

the “same surgical procedure” or “hospital exemptions” where all of the tissue processing with administration occurs within the same establishment.

In reviewing US FDA guidance documents, the way in which the FDA ultimately addresses this issue will depend on classification of bone marrow as “homologous” or “nonhomologous.” Fulfillment of this criteria for autologous BMC that is used as part of same surgical procedure exemption is required for this procedure to be regulated by the state medical boards and not the FDA. If BMC does not meet all of these criteria it will fall outside of the same surgical procedure exemption and require an IND classification with FDA approval for use. Therefore to be FDA compliant and exempt from an IND, the use of BMC for treatment of musculoskeletal tissues, such as cartilage, bone, ligaments, muscle, tendons, and spinal discs, must be considered homologous.

This position paper provides a comprehensive, focused review of bone marrow MSC therapy. This policy position paper describes the current regulatory guidelines set in place by the FDA, specifically the terminology around “homologous use” with specific application to BMC.

ASIPP has been at the forefront of guideline development for the use of interventional techniques, opioids, and biologics in the management of low back pain, antithrombotics in interventional techniques, and the use of sedation (3,4,138-140). The present position statement has been developed to describe the role of BM-MSCs therapy in musculoskeletal disorders, with a comprehensive review of the literature of BM-MSC therapy. This position statement includes an overview of the current literature applicable to BMC and MSC applications in the musculoskeletal system, including the spine. This position statement specifically incorporates the various aspects of FDA guidance and provides a basis for asserting that BMC meets the criteria for minimal manipulation, same surgical procedure exemption, and homologous use.

METHODS

Rationale

The National Uniform Claims Committee (NUCC) defines interventional pain management as the discipline of medicine devoted to the diagnosis and treatment of pain-related disorders, principally with the application of interventional techniques in managing subacute, chronic, persistent, and intractable pain,

independently or in conjunction with other modalities of treatment (141). In addition, the Medicare Payment Advisory Commission (MedPAC) defines interventional pain management techniques as “minimally invasive procedures including percutaneous precision needle placement of drugs in targeted areas or ablation of targeted nerves; surgical techniques such as laser and endoscopic discectomy; and the placement of intrathecal infusion pumps and spinal cord stimulators for the diagnosis and management of chronic, persistent, or intractable pain” (142).

Chronic musculoskeletal and spinal pain are complex and multifactorial disease processes. The high prevalence of chronic musculoskeletal and spinal pain, the numerous treatment modalities applied in the management of the problem, and the growing social and economic costs continue to influence medical decision-making. Interventional pain physicians are familiar with various image-guided interventional techniques for the management of spinal pain and musculoskeletal pain. The technical skills and training required for the various delivery methods of BMC fall well within interventional pain management’s purview.

Objectives

This position paper provides a comprehensive, focused review of bone marrow MSC therapy. This policy position paper describes the current regulatory guidelines set in place by the FDA, specifically the terminology around “homologous use” with specific application to BMC.

Adherence to Trustworthy Standards

In preparation of this position statement for BMC, the standards from the Institute of Medicine (IOM) and the National Guideline Clearinghouse Extent Adherence to Trustworthy Standards (NEATS) were followed (143-145). The NEATS instrument was developed and tested as a tool to be used with strict adherence by the trained staff at the Agency for Healthcare Research and Quality (AHRQ) in providing an assessment focused on NEATS.

Disclosure of Funding Source for Position Statement

The evidence-based policy position statement on BMC therapy in musculoskeletal and spinal disorders were commissioned, prepared, edited, and endorsed by ASIPP without seeking or obtaining any external funding.

Disclosure and Management of Financial Conflicts of Interest

Potential conflicts of interest for all panel members within the last 5 years were evaluated prior to the finalizing of these guidelines. Conflicts of interests extended beyond financial relationships, including personal experiences, practice patterns, academic interests, and promotions. Participants with previously established conflicts are considered those with opinions not being in line with the previously developed ASIPP guidelines or the overall philosophical approach of ASIPP. The panel members with potential conflicts were recused from discussion or preparation of the guidelines in which they had conflicts of interest, and these members agreed not to discuss any aspect of a given guideline with the related industry before data publication.

Composition of Position Development Group

A panel of experts in BMC from various medical fields, convened by ASIPP, reviewed the evidence and formulated recommendations for BMC therapy as it applies to musculoskeletal and spinal disorders. The panel constituted a broad representation of academic and non-academic clinical practitioners with an interest and expertise in the application of BMC in musculoskeletal and spinal disorders.

Evidence Review

This position statement was developed with consensus among the panel members after review of the published literature concerning the use and safety of BMC therapy in musculoskeletal and spinal disorders with chronic noncancer pain.

The recommendations for this position statement have been developed using the principles of best

evidence synthesis developed by Cochrane Review, and have incorporated multiple guidelines modified by ASIPP, as shown in Table 1 (146).

Grading or Rating the Quality or Strength of Evidence

An evidence-based position statement has both similarities and differences when compared with practice guidelines. For the development of this position statement, the evidence is based on literature review and consensus. The traditional instruments for the grading of evidence based on randomized controlled trials, observational studies, and other clinical reports, with a major focus on systematic reviews and meta-analysis may not be utilized, to the same extent as in the preparation of guidelines (3,4,138,140). However, the grading of evidence based on ASIPP guidelines, founded on the quality of evidence and the strength of recommendations as proposed by AHRQ (144,145), as shown in Table 2, were utilized.

Assessment and Recommendations of Benefits and Harms

This position statement clearly describes the potential beneficial evidence summary recommendations.

Evidence Summary of Recommendations

This position statement summarizes the relevant supporting evidence.

Specificity of the Statement

This position statement is specific and unambiguous, providing guidance on BMC therapy in musculoskeletal and spinal disorders.

Table 1. Qualitative modified approach to grading of evidence.

Level I	Strong	Evidence obtained from multiple relevant high-quality randomized controlled trials for effectiveness.
Level II	Moderate	Evidence obtained from at least one relevant high-quality randomized controlled trial or multiple relevant moderate- or low-quality randomized controlled trials.
Level III	Fair	Evidence obtained from at least one relevant high-quality nonrandomized trial or observational study with multiple moderate- or low-quality observational studies.
Level IV	Limited	Evidence obtained from multiple moderate- or low-quality relevant observational studies.
Level V	Consensus based	Opinion or consensus of large group of clinicians and/or scientists for effectiveness as well as to assess preventive measures, adverse consequences, effectiveness of other measures.

Adapted from Manchikanti L, Falco FJE, Benyamin RM, Kaye AD, Boswell MV, Hirsch JA. A modified approach to grading of evidence. *Pain Physician* 2014; 17:E319-E325 (146).

Table 2. *Guide for strength of recommendations.*

Rating for Strength of Recommendation	
Strong	There is high confidence that the recommendation reflects best practice. This is based on: a) strong evidence for a true net effect (e.g., benefits exceed harms); b) consistent results, with no or minor exceptions; c) minor or no concerns about study quality; and/or d) the extent the panelists' agreement. Other compelling considerations (discussed in the guideline's literature review and analyses) may also warrant a strong recommendation.
Moderate	There is moderate confidence that the recommendation reflects best practice. This is based on: a) good evidence for a true net effect (e.g., benefits exceed harms); b) consistent results, with minor and/or few exceptions; c) minor and/or few concerns about study quality; and/or d) the extent of panelists' agreement. Other compelling considerations (discussed in the guideline's literature review and analyses) may also warrant a moderate recommendation.
Weak	There is some confidence that the recommendation offers the best current guidance for practice. This is based on: a) limited evidence for a true net effect (e.g., benefits exceed harms); b) consistent results, but with important exceptions; c) concerns about study quality; and/or d) the extent of panelists' agreement. Other considerations (discussed in the guideline's literature review and analyses) may also warrant a weak recommendation.

Source: National Guideline Clearinghouse Extent Adherence to Trustworthy Standards (NEATS) instrument (144).

External Review

This position statement has been subjected to external peer review as per the policies of the publishing journal, *Pain Physician*.

Updating the Position Statement

BMC therapy in musculoskeletal disorders will be updated within 5 years or less, based on significant changes in the scientific evidence, public policy, or adverse events occurring on or before March 2025.

IMPACT OF MUSCULOSKELETAL DISORDERS

Health Care and Disability

Health care expenditures have been escalating over the years. Recent estimates of the US health care spending reached \$3.66 trillion in 2018 (147). In addition, expenditures will continue to grow each year with estimates showing that national health expenditures will grow at an average annual growth rate of 5.5% from 2018 to 2027 (148). Simply put, the 2018 cost of \$3.65 trillion in spending represents \$11,212 per person, but keeping all variables stable, that cost per person in 2027 will rise to \$12,197.04. US spending on personal and public health care from 1996 to 2013 (1), showed an estimated spending of \$87.6 billion in managing low back and neck pain, and \$95.5 billion in managing musculoskeletal disorders, with a total spending on musculoskeletal disorders and spinal pain of approximately \$183 billion.

The impact of chronic pain is enormous (1,2,4-9,12,138,147-155). The annual US expenditures alone (including direct medical costs and lost wages) may be higher than those for cancer, heart disease, and diabetes combined (1,2,5). Despite high expenditures

and numerous treatment options, disability continues to escalate. Figure 1 shows expenditures related to musculoskeletal conditions, including back and neck pain, as determined in 2016 based on US spending on health care (1).

Musculoskeletal conditions are the leading contributors to disability in the United States and worldwide. In addition to musculoskeletal pain contributing to disability, it has also been associated with a number of conditions in older people, such as low physical activity, poor mobility, frailty, depression, cognitive impairment, and poor sleep quality (155).

A study of the state of the US health between 1990 and 2010, describing the burden of diseases, injuries, and risk factors (6), showed that with increasing life expectancy, morbidity, and chronic disability accounted for nearly half of the US health burden, despite substantial progress and improvement in health. Among the 30 leading diseases and injuries contributing to years lived with disability in the United States between 1990 and 2010, low back pain, other musculoskeletal disorders, and neck pain ranked numbers 1, 3, and 4, respectively (6). More recent analysis of the state of US health from 1990 to 2016 (7) showed similar results with low back pain, other musculoskeletal disorders, and neck pain ranking numbers 1, 4, and 6, respectively. Similar to low back pain, other musculoskeletal disorders (specifically osteoarthritis) caused substantial pain and disability impacting the quality of life. Hip and knee osteoarthritis has been ranked at the 11th highest contributor to global disability, and 38th highest in years lived with disability (156).

Chronic persistent spinal pain lasting longer than 1 year is reported in 25% to 60% of patients (3,8,138,157). Similarly, the prevalence of knee and hip

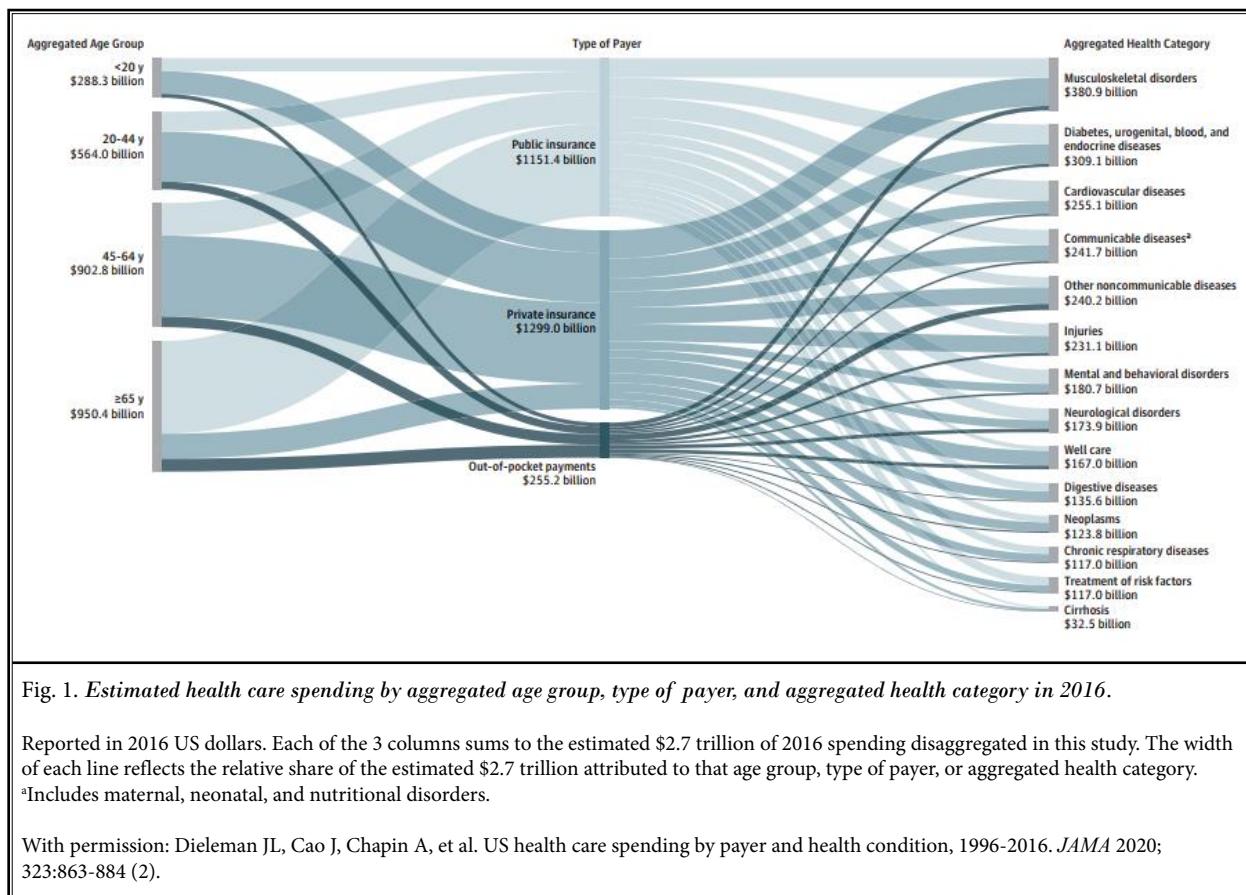


Fig. 1. Estimated health care spending by aggregated age group, type of payer, and aggregated health category in 2016.

Reported in 2016 US dollars. Each of the 3 columns sums to the estimated \$2.7 trillion of 2016 spending disaggregated in this study. The width of each line reflects the relative share of the estimated \$2.7 trillion attributed to that age group, type of payer, or aggregated health category.

*Includes maternal, neonatal, and nutritional disorders.

With permission: Dieleman JL, Cao J, Chapin A, et al. US health care spending by payer and health condition, 1996-2016. *JAMA* 2020; 323:863-884 (2).

osteoarthritis is over 25% in individuals over the age of 45 (158). Although the literature shows that over 27 million adults in the United States age 25 years and older have a clinical diagnosis of osteoarthritis of any joint, 5.6 million cases of these present with lower extremity osteoarthritis (159-163). It is also estimated that 13 million adults age 60 years and older in the United States have radiographic osteoarthritis, with approximately 4 million of those individuals classified as having symptomatic knee osteoarthritis (162). Further, individuals sustaining a knee injury are 4.2 times more likely to develop osteoarthritis than those without a history of knee injury (164). In addition to osteoarthritis of hip and knee, shoulder osteoarthritis is ranked as the third most common cause of osteoarthritis. A multitude of other osteoarthritis conditions occur commonly after trauma (162).

Of the estimated spending of \$264.3 billion as annual expenditures for musculoskeletal disorders, including spinal disorders, as shown by Dieleman et al (1,2), \$134.6 billion was spent in managing low back

and neck pain, an increase from \$87.6 billion in 2013, a 44.4% increase from \$183.5 billion from 2013 to 2016 for musculoskeletal disorders and spinal disorders. A multitude of other assessments have also shown significant health care spending and its impact for musculoskeletal disorders. An IOM study (5) showed the cost of chronic pain to range from \$560 to \$635 billion per year, which includes spinal pain, chronic pain, and other painful conditions (Table 3) (5,150,165). The literature has been explicit in showing unsustainable increases in all types of therapies starting with over-the-counter drug therapy, alternative modalities to prescription drugs, conservative management, minimally invasive procedures, and surgical interventions (3,4,10-49).

Thus, the impact of musculoskeletal disorders on health care is enormous with substantial human toll leading to a multitude of issues, the most important being disability with reduced quality of life.

Opioid Epidemic

Opioid use has become a major issue in the United

States, with its escalating use, treatment costs, and preventative measures used in effort to control the explosion of the opioid epidemic (4,13,16,23,25,166-181). The US drug overdosage data of drug-related deaths from 2017 shows escalating statistics with over 70,000 drug overdoses, of which 47,600 were related to opioid overdoses, as shown in Fig. 2 (177). It has been shown that the majority of the increases are related to synthetic opioids, as well as heroin. The recent data shows a 14.5% drop in prescription drug opioid deaths to less than 12,000. However, heroin deaths continue to increase, and in 2017 there were over 15,000 deaths due to heroin, as shown in Fig. 3. Fentanyl deaths are the category largely responsible for the escalating opioid epidemic (178).

Sixty-three percent of deaths involve various other drugs in addition to prescription opioids with 34% cocaine, 33% benzodiazepines, and 12% methamphetamines (179). Even though deaths due to prescription opioids are declining, the overall opioid deaths continue to increase. Further, the age-old comparison of increasing prescriptions correlating with increasing deaths has been nullified now that prescriptions are declining (Fig. 4). In fact, opioid prescription data in the United States shows a significant decline from 251.8 million prescriptions in 2013 to 168.8 million prescriptions in 2018, as shown in Fig. 5 (181).

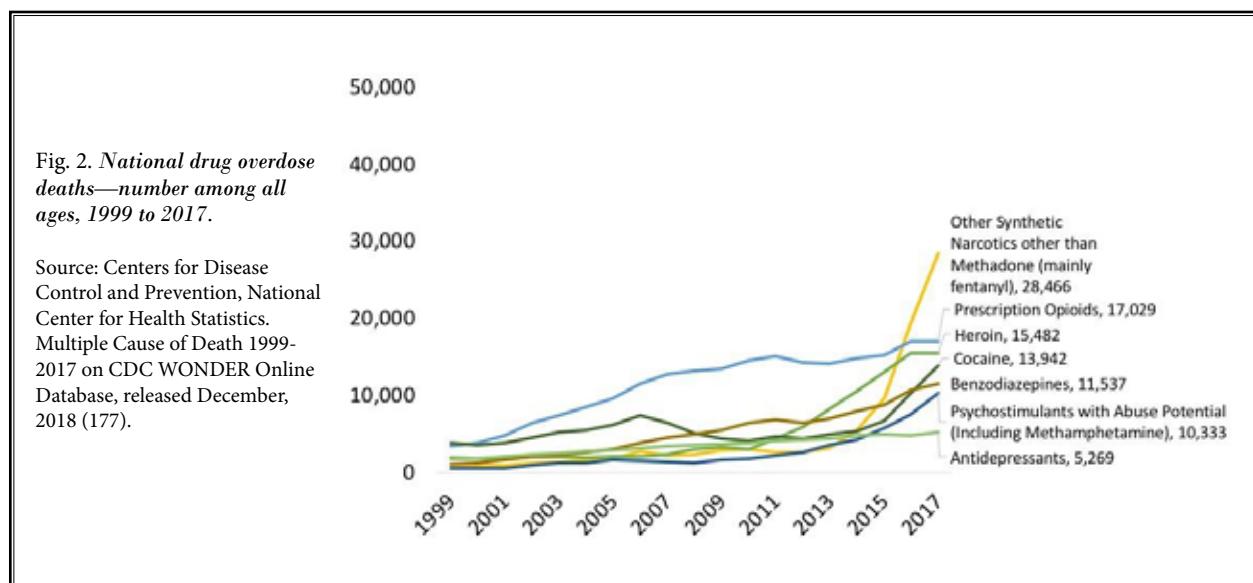
Even though there is overwhelming evidence that the epidemic of opioid use involves not only the use of prescription opioids, but fentanyl and heroin,

Table 3. *The prevalence and cost of chronic pain.*

◆ The annual cost of chronic pain is \$560 to \$635 billion a year
• Direct cost due to pain is \$261 – \$300 billion
◆ Prevalence estimates
• 10% moderate pain
• 11% severe pain
• 33% joint pain
• 25% arthritis
• 12% functional disability
} Total 21%
◆ Moderate pain \$4,516
◆ Severe pain \$3,210
◆ Joint pain \$4,048
◆ Arthritis \$5,838
◆ Functional disability \$9,680

Source: Gaskin DJ, Richard P. The economic costs of pain in the United States. *J Pain* 2012; 13:715-724 (149).

policy experts appear to have focused on prescription opioids as the main target in the United States (16). Manchikanti et al (16) described various issues related to the opioid epidemic and pointed out the tragic failure of current systems to control opioid misuse. It was this misuse that propagated the epidemic, starting with the pain movement together with a confluence of interest and failure of oversight from the opioid industry, which was largely responsible for the epidemic. Multiple issues related to the confluence of interest included promotion of opioids based on inadequate evidence with advocacy from Portenoy and Foley (182). Subsequently, the Fifth Vital Sign was established in 1995, which became a universal phenomenon (16). Further, fuel was added by guidelines implemented



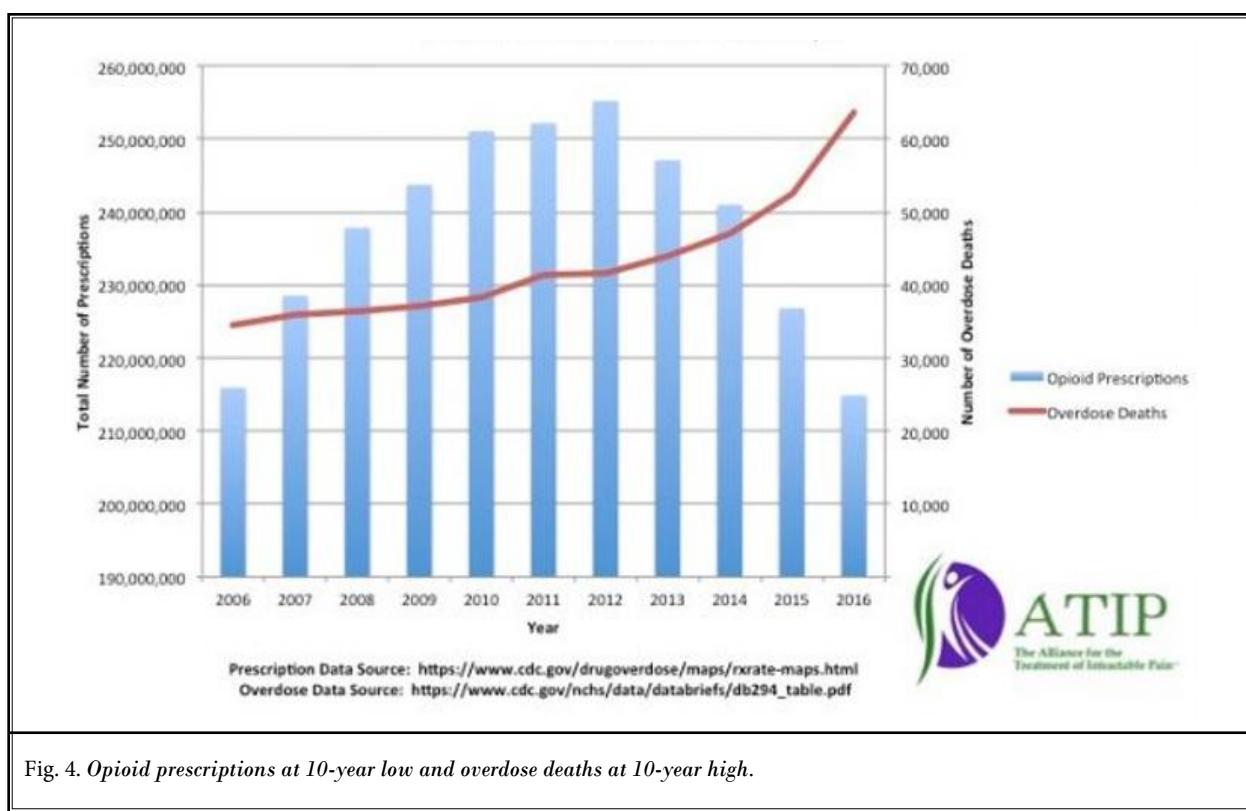
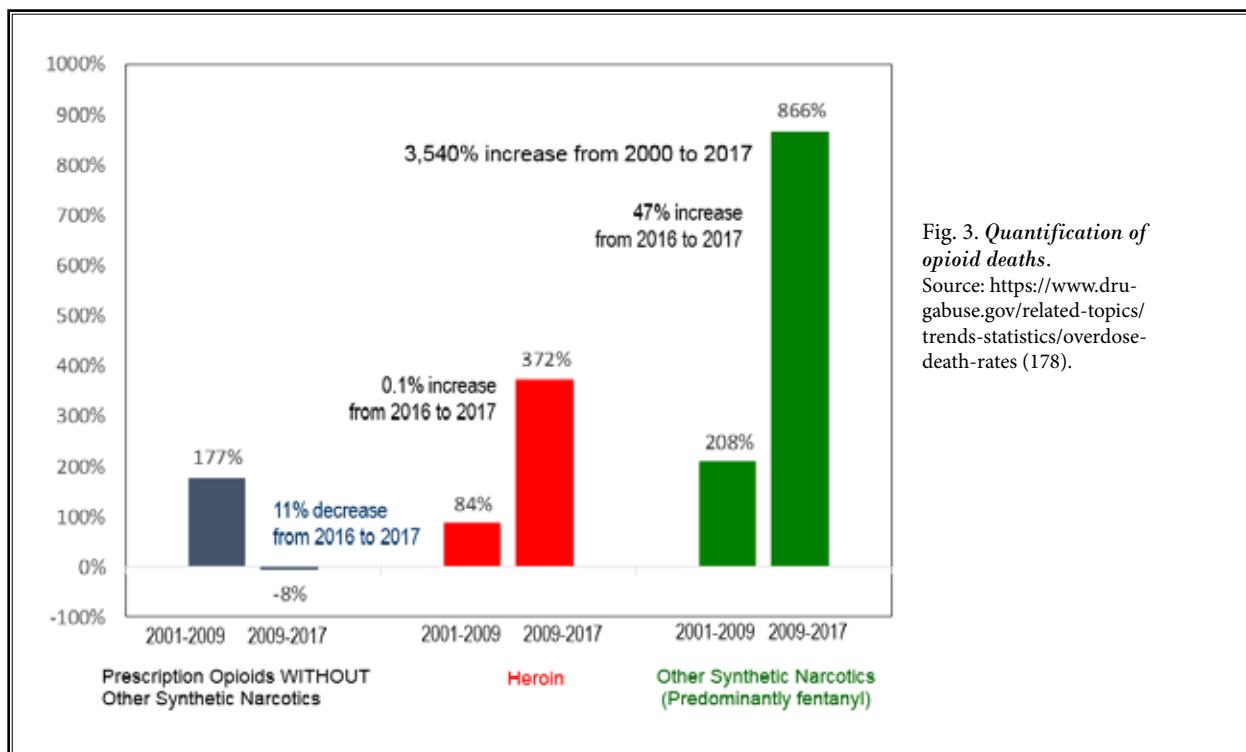


Fig. 5. Total opioid prescriptions in the United States in millions.
 Source: <https://www.end-opioid-epidemic.org/wp-content/uploads/2019/06/AMA-Opioid-Task-Force-2019-Progress-Report-web.pdf>.



by the medical boards. These guidelines were written theoretically for appropriate opioid usage, but were essentially being developed by the opioid industry. There were also failures in oversight of not only opioid manufacturing, distribution, diversion, and import, but also in medical necessity and appropriate monitoring of opioid prescriptions (16).

The significant movement to control the opioid epidemic in the United States was initiated with prescription drug monitoring programs, state regulations, curbing opioid productions, and increasing the focus on education. Overall federal spending increasing by 128% from 2017 to 2018 with the major increases in federal spending due to treatment and recovery programs with costs ranging from approximately \$599 million to \$2.1 billion (183-195). Total opioid spending increased from \$3.3 billion in 2017 to \$7.4 billion in 2018 in the United States (183). The numerous regulations and enhanced prescription drug monitoring programs have also contributed to the decreases in opioid prescriptions from a high of 255 million in 2012 to 191 million in 2017, a decrease of 25%.

Overall the decline in the number of prescriptions with reduced dosages, faces a multitude of criticisms against the Centers for Disease Control and Prevention (CDC) guidelines and other measures (193-198). Consequently, US Department of Health & Human Services, as well as the CDC, have clarified and are encouraging providing opioids for patients with appropriate medi-

cal necessity, even though they continue to focus on reduced utilization (197,198).

BMC

Bone marrow is a semi-solid tissue found within spongy or cancellous portions of bones. The cellular components of bone marrow include osteoblasts, osteoclasts, macrophages, endothelial progenitor cells (EPCs), hematopoietic stem cells (HSCs), and MSCs (108,199). BMC, also known as bone marrow aspirate concentrate (BMAC), is created by centrifuging bone marrow aspirate. This process results in 3 layers with the plasma in the supernatant, the buffy coat in the middle, and the red blood cell layer in the infranatant (108). To create BMC, the buffy coat is isolated. Contained in this layer is a number of cells, including MSCs, HSCs, myelopoietic and erythropoietic cells, mature leukocytes, platelets, and megakaryocytes (108). Among the cellular components, MSCs are largely credited with the therapeutic potential of BMC to treat musculoskeletal pathology due to their ability to self-replicate and differentiate into other cell types such as osteoblasts and chondrocytes (200).

The use of bone marrow in medicine can be traced back to the 1940s and 1950s when the first discoveries of irradiating and protecting mice with a BMT were performed (201). Studies followed showing leukemic mice could be treated by infusion of normal mouse bone marrow (201-203). Early human studies infusing

allogeneic marrow were ineffective at establishing a graft other than in identical twins (201-203). The first successful graft treatment in a human patient with leukemia was published in 1965 (204,205). By the late 1960s, increasing knowledge of human histocompatibility antigen systems made successful BMT possible (201). By the 1970s, BMT became more commonly used in refractory cases of leukemia (205). In the late 1980s, Caplan and colleagues published their work on the isolation of the MSCs from the bone marrow and the ability of MSCs to differentiate into bone and cartilage *in vitro* (107,119-122).

There has been significant discussion in reference to the effectiveness of BMC and in the nomenclature, as well as the inconsistencies (206). The ISCT in 2016 defined specific criteria that must be met for cells to be considered MSCs. The criteria included that the cells must be plastic-adherent in standard culture conditions, must display specific surface antigens, and must show *in vitro* differentiation into osteoblasts, adipocytes, and chondroblasts (207). As the understanding continues to evolve, MSCs have been defined as mesenchymal stem cell, mesodermal stem cell, and mesenchymal stromal cell, often simultaneously by different groups that continue to disagree on the most accurate name for the cell type (120). In addition, based on the ability to undergo *in vitro* osteogenesis and costochondral genesis (206-208), MSCs were initially thought to maintain their multipotency after injection into an injured joint. Thus the term "mesenchymal stem cell" was used to describe the hypothesized ability to differentiate and regenerate injured cartilage or soft tissue (107). However, subsequent evidence has demonstrated that MSCs are rather derived from pericytes or perivascular cells surrounding capillary endothelium (120-122,209). Further, studies also have suggested that injected MSCs do not undergo differentiation *in vivo* and the primary functionality is not that of a stem cell (210,211). Despite the hypothesis that MSCs are no longer thought to exhibit stem-like properties *in vivo*, they have been shown to induce endogenous stem cell activity and secrete bioactive factors that promote tissue healing (122,212-217). Consequently, the perivascular source and immunomodulatory effects of the BMC make both "stem cell" and "stromal cell" inaccurate descriptions of MSCs. This has led to a modification of the meaning of MSC being changed from "mesenchymal stem cell" to "medicinal signaling cell" to emphasize their role as trophic mediators by Caplan (120).

Charbord (206) in a review provided the historical emergence of the concept of bone marrow MSCs, sum-

marizing the data on hematopoietic inductive microenvironment (218), hematopoiesis supportive stromal cells (219), osteogenic cells (220), trilineal osteoblastic, chondrocytic, and adipocytic precursors (124,220), to finally introduce the specific bone marrow MSCs with differentiation potential, and stromal and immunomodulatory capacities. Charbord (206) described 2 points in detail. The first point envisioned the stem cell attributes as having multipotentiality, self-renewal, tissue regeneration, population heterogeneity, plasticity, and lineage priming, compared with the attributes of paradigmatic HSCs. In the second point, believing the possible existence of bone marrow cells with even larger differentiation potential, eventually pluripotential cells were discussed. This review led to the conclusion that bone marrow MSCs can constitute a specific adult tissue stem cell population. The multiple characteristics of this stem cell type accounts for the versatility of the mechanisms of injured tissue repair.

In a consensus statement, Chu et al (49) describe the characteristics of stem cells and minimally manipulated autologous cell preparations with BMC, as shown in Table 4 (221).

Since the discovery of MSCs, BMC has been used extensively to treat musculoskeletal diseases since the 1980s (222). The first case series on the use of BMC to treat nonunion fracture and avascular necrosis was published by Hernigou et al (223) in the mid-2000s. In the last decade, many physicians have started utilizing BMC to address common musculoskeletal conditions, such as osteoarthritis and tendon injuries. The body of literature to support this use is growing and at present includes multiple randomized controlled trials (49,80,81,87-112,224-248).

US FDA REGULATORY CONTEXT

The FDA uses the term "human cells, tissues or tissue-based products" (or "HCT/Ps") when describing human cells or tissues that are "intended for implantation, transplantation, infusion or transfer into a human recipient." The FDA's regulation of HCT/Ps involves a tiered risk structure and a multipart test (135).

The "tiered, risk-based approach" to the regulation of HCT/Ps was first announced by the FDA in 1997, and was finalized in regulations found at 21 CFR Part 1271 in 2005. The 21 CFR Part 1271.10 includes an important criteria through which all HCT/Ps must be vetted to determine whether any specific HCT/P will be subject to the FDA's IND and Biologics License Application requirements, or will merely qualify for the

Table 4. Characteristics of MSCs and minimally manipulated cell preparations of BMC.

Cell Type	Definition
MSCs	Three minimum characteristics: 1. Capable of division and self-renewal for long periods of time 2. Unspecialized 3. Can give rise to specialized cell types
BMC, minimally manipulated autologous cell preparations	Cleared for homologous use Processing must not alter the relevant biological characteristics of cells or tissues Mixed cell populations, with variable composition Stem or progenitor cells may be present at lower prevalence Biological attributes and function highly variable

Adapted from: Chu CR, Rodeo S, Bhutani N, et al. Optimizing clinical use of biologics in orthopaedic surgery: Consensus recommendations from the 2018 AAOS/NIH U-13 Conference. *J Am Acad Orthop Surg* 2019; 27:e50-e63 (49).

Part 1271 regulations themselves (135). In the present context (physician use in offices or operating rooms), these regulations create a binary regulatory pathway in which one category is regulated only by the Part 1271 regulations themselves, whereas the other is regulated as a drug requiring the full gamut of the FDA drug approval process.

Autologous HCT/Ps that are either "more than minimally manipulated" or used for a "nonhomologous" purpose are deemed by the FDA to present more risk and cannot be used in the United States without the FDA's permission in the form of an approved IND or biologic license application. Alternatively, autologous HCT/Ps that are "minimally manipulated" and used for homologous purposes may either be regulated as a tissue product, subject to FDA's registration, listing, in Part 1271 requirements, or as surgical procedures, which would fall into FDA's "same surgical procedure" exemption found at 21 CFR 1271.15 and regulated primarily at the state level. Finally, bone marrow is exempt from regulation as an HCT/P if it is minimally manipulated and used for a homologous purpose; 21 CFR 1271.3(d) (135). Hence throughout this analysis, the HCT/Ps that are minimally manipulated and also used for a homologous purpose fall within critical distinctions that govern how the HCT/P is regulated.

Given the minimal processing involved in the creation of BMC, it fits under the FDA's minimal manipulation definition. Indeed, using a parallel example involving a blood product, the FDA wrote in its guidance that when a "manufacturer performs cell selection...to obtain a higher concentration of hematopoietic stem/progenitor cells (HPCs) for transplantation...[t]he HCT/P would generally be considered minimally manipulated

because the concentrated peripheral blood stem/progenitor cells are not altered with regard to their relevant biological characteristic" (249).

However, the second part of the regulatory classification, homologous use, is now open to interpretation. This paper will address this last remaining question, that is what constitutes the "homologous use" of autologous bone marrow? Homologous use is defined as "the repair, reconstruction, replacement, or supplementation of a recipient's cells or tissues with an HCT/P that performs the same basic function or functions in the recipient as in the donor" 21 CFR Part 1271.3(c). However, with respect to bone marrow, to date the FDA has only provided the following guidance:

First, in a subsequently withdrawn Guidance Document published in 2016, the FDA wrote as follows: "The basic functions of hematopoietic stem/progenitor cells (HPCs) include to form and to replenish the hematopoietic system. Sources of HPCs include cord blood, peripheral blood, and bone marrow." Thus as of 2016, if a procedure involved the use of HPCs to address a disorder affecting the hematopoietic system, the procedure would have been considered to be a homologous use of the HPCs (250).

Second, in its finalized Guidance dated November 2017, the FDA wrote as follows: "Sources of hematopoietic stem/progenitor cells (HPCs) include cord blood, peripheral blood, and bone marrow. The basic functions of HPCs include forming and replenishing the lymphohematopoietic system" (249). Thus as of today, if a procedure involves the use of HPCs to address a disorder affecting the lymphohematopoietic system, the procedure will be considered the homologous use of the HPCs.

Hence what the existing medical literature states about how the body uses bone marrow to maintain or heal musculoskeletal and spinal disorders will have a profound effect on the regulation of BMC in musculoskeletal medicine. In other words, if BMC is homologous to common musculoskeletal tissues and disc, then it is left unregulated by the FDA, but if nonhomologous, then it can be classified as a drug, and is subject to the FDA's drug approval requirement (135).

IMPACT OF BONE MARROW CELLS ON HEALING

As shown in the literature, the historical emergence of the concept of bone marrow mesenchymal cells is complex with a number of clinical applications ranging from musculoskeletal to neurologic indications, but more specifically musculoskeletal disorders as described herewith.

Bone

Bone has the ability to self-repair largely because the cells responsible for initiation and completion of the repair reside within the bone marrow. Many of these bone marrow cells are capable of osteogenesis and vasculogenesis (251). This osteogenic potential has prompted many physicians through the decades to use bone grafts or bone marrow to help heal delayed-union and nonunion fractures (252). The components in bone marrow that help bone naturally heal are those present in BMC.

Bone marrow is a multifunctional mixture of anucleate red blood cells and platelets, as well as nucleated cells that include multipotent stem cells and progenitor cells (253). The nucleated cells within this mixture have hematopoietic, angiogenic, and osteogenic potential (254). The 3 primary multipotent cell types that populate bone marrow are HSCs, MSCs, and EPCs. Bone marrow's essential functions include hematopoiesis, osteogenesis, and vasculogenesis (255).

When a fracture occurs, the liquid portion of the bone marrow flows into the space created. The cellular content of this liquid is believed to drive the fracture repair (251). The osteogenic potential of bone marrow was first discovered in BM-MSCs in the 1960s (256,257), with later work illuminating MSCs' ability to differentiate into osteoblasts and osteocytes depending on local environmental cues (125,258). It has been shown *in vitro* and *in vivo* that a single HSC can also have hematopoietic or osteogenic potential depending on environmental factors and the surrounding conditions (259).

Vasculogenesis is another essential function of bone marrow cells (260). Bone healing has been shown to occur via mobilization of EPCs from bone marrow, which encourage vasculogenesis in the setting of structural damage and ischemia (254,260-262). Bone marrow cells require transportation via this newly established vasculature to initiate the healing cascade, induce callus formation, and instigate bone remodeling and healing (253). Evidence suggests special populations of EPCs in specific bone marrow niches are available for rapid release in response to ischemic conditions, as well as matrix metalloproteinases (MMPs). This environment induces tubulization and new vessel formation to restore adequate oxygen delivery and allow for bony remodeling (262-264).

Surgeons have long used the ability of bone to heal fractures by utilizing the natural elements found in structural bone and bone marrow. For example, autologous and allogeneic bone grafts have been commonly used for more than a century to heal nonunion fracture (252). In the 1990s, Hernigou et al (222,264) again published on the use of autologous BMC to heal nonunion fracture in addition to its application in the treatment of avascular necrosis.

BMC contains multipotent cells capable of osteogenesis, as well as growth factors, cytokines, and chemokines active in osteopoiesis (265-267). It has been shown that an intraosseous injection of BMC can help heal nonunion fracture by replenishing the native and healthy cellular composition of the normal bone (126). Hence injecting BMC into the bone is performed, in part, to reestablish osteogenic potential with newly engrafted cells that can serve to replace and/or enhance native cell functionality (199).

Cartilage

Cartilage is an avascular tissue made up of chondrocytes and extracellular matrix (ECM) that consists of water, collagen, and proteoglycans (251). It derives its nutrition and ability for self-repair largely by its communication with the underlying bone marrow through the subchondral plate. This natural relationship between bone and cartilage has been utilized by surgeons to help heal cartilage lesions using bone marrow stimulation techniques since the late 1980s to early 1990s (268,269).

Articular cartilage is produced during bone development when chondrocytes are replaced by osteoblasts in the long bone during the endochondral ossification process (270). It is important in the overall health of

diarthrodial joints and serves to protect the joint by reducing friction between surfaces and absorbing impact (251). It is primarily composed of an ECM and chondrocytes (251). Varying ratios of collagen fibers, ECM, and chondrocytes contribute to the superficial, middle, deep, and calcified zones of cartilage (271). Cartilage has several known healing mechanisms. The cellular response involves progenitor cells at the cartilage surface, as well as MSCs recruited from the synovial fluid and membrane (272). In addition, there is another cellular response that can occur from beneath the cartilage, which is mediated through the bone marrow (273). More recently, the connection between the cartilage health, local microenvironment, and the interaction with cell-based therapies have been explored (270).

Injury to cartilage can naturally expose the subchondral bone marrow, which contains various cellular components, such as MSCs and a variety of growth factors that assist in healing and repair (273-275). One of the most important functions of MSCs is directing chondrogenesis through paracrine activity, which reduces cell apoptosis and inflammation, while activating cell proliferation and mobilization (276). For an isolated cartilage lesion to heal in which there has been no subchondral plate exposure, there must be natural communication between the cartilage and bone marrow through channels in the subchondral plate (268). The formation of sclerosis and calcification of cartilage in osteoarthritis can interfere with this communication, as can an increase in fatty marrow (277). However, in acute trauma to the cartilage with a normal subchondral plate, blood flow via healthy subchondral fenestrae is drastically increased in the cancellous bone to assist in the healing process. Madry et al (199) demonstrated that MSCs from the nearby subchondral bone are subsequently mobilized, migrate to form a clot, and differentiate into chondrocytes/osteoblasts, which over time form repair tissue to fill the defect.

In addition to cellular components, cartilage repair also involves growth factors such as fibroblast growth factor (FGF), vascular endothelial growth factor (VEGF), insulin growth factor-1 (IGF-1), and transforming growth factor beta, which all play different roles and are able to stimulate chondrocyte differentiation of MSCs, increase chondrocyte proliferation, as well as decrease the catabolic effects of cytokines, such as interleukin-1 (IL-1) and MMPs (278).

Undifferentiated bone marrow MSCs can be seen at the chondral lesion by day 7 post injury and a cartilaginous matrix at day 10 (199). At 6 weeks, the chon-

dral lesion is fully populated with fibrocartilaginous cells and chondrocytes (199). Any traumatic injuries to the subchondral plate are reestablished by 24 weeks when the majority of cartilage healing has taken place, replacing cancellous bone with the lamellar bone (199).

Surgeons have developed surgical techniques utilizing bone marrow as a natural reservoir of cartilage healing cells for decades. The microfracture and microdrilling techniques used to treat cartilage lesions create holes in the subchondral plate to release adjacent bone marrow, which initiates a healing response in osteochondral injury (268,269). These procedures have been shown to cause fibrocartilaginous healing that can provide a return to normal function in select patients (279). However, the cartilage produced is type I cartilage and not the original type II hyaline cartilage. As such it is more friable. BMC therapy has been shown to produce type II cartilage.

Ligament

Both intrinsic and extrinsic cellular mechanisms play a role in ligament healing. Evidence regarding the relationship of ligament healing to bone marrow can be found in dental models involving the periodontal ligament (PDL) (280). BM-MSCs have been shown to mobilize the injured knee's anterior cruciate ligament (ACL) (281). In addition, the health of the underlying bone and the knee ACL ligament appear to be interrelated (281). Similarly, surgeons have made use of this relationship by performing microfracture at the ACL origin or insertion to liberate BM-MSCs to enhance ligament healing (282).

Ligaments are fibrous bands that attach bone to bone. The area where the ligament makes that connection is known as the enthesis. The cellular components of ligaments include fibroblasts, collagen, elastin, proteoglycans, glycolipids, and fibronectin, with fibroblasts being the predominant cell type and collagen fibrils a key structural feature (283). These fibrils are predominantly comprised of type I collagen and to a lesser extent type III collagen. Although considered relatively hypovascular, there are blood vessels found in close proximity to the fibrils, with penetrating vascular channels that provide nutrition (284). Ligamentous injury involves structural disruption of these penetrating vessels, in addition to the ECM. Cellular insult occurs, and similar to other tissues, a healing response comprised of inflammation, proliferation, and remodeling follows (249).

Disrupted blood vessels result in localized bleeding and hematoma formation. The immediate response is

one of vasoconstriction of the injured vessels and the initiation of the coagulation cascade to achieve hemostasis. Hematoma and clot formation ensue, which are vital for a subsequently successful healing response (283-288). Platelets contained within the clot release a multitude of cytokines and growth factors, which promote vascular dilation and permeability, resulting in local edema and the recruitment of inflammatory mediators. Neutrophils and monocytes infiltrate the region, where they digest and remove necrotic tissue and debris, while also signaling for the infiltration of fibroblasts (251,283,285). Fibroblasts, along with numerous growth factors, direct the transition from inflammation to proliferation (251). Key features of proliferation include collagen deposition, new ECM production, and angiogenesis in an attempt to bridge the ends of a torn ligament. Type III collagen is the predominant collagen early in the healing process (251,285). Proliferation ultimately gives way to remodeling. During this stage, the ECM is strengthened and further organized, with a shift from type III to type I collagen (251,285).

In the vast majority of knee cruciate ligaments, vascular channels at the ligament entheses form direct contact between the ligament and the underlying bone marrow (289). In addition, many entheses have a blood vessel that enters the bone situated underneath the part of attachment site that moves the least during joint motion. Ligament health and the status of the bone it inserts on are interrelated. For example, in one study showing bone cysts at ACL insertion sites, 82% demonstrated ligament pathology (290). Hence structurally this connection demonstrates that the ligament has a relationship with the bone onto which it inserts.

MSCs possess the ability to migrate to sites of injury, and do so under the direction of a multitude of growth factors, cytokines, and chemokines known to be prevalent in the natural healing process of ligaments (212,285,291,292). Additionally, there is evidence that supports BM-MSCs as having a direct role in the natural healing response following ligamentous injury. Much of this evidence comes from dental literature investigating the response to injury of the PDL, a structure that provides an attachment between the alveolar bone and root surface cementum, and which is commonly injured during root canal treatments (280,293). Multiple studies have analyzed the postinjury activity at the PDL via mouse models, with green fluorescent protein-labeled bone marrow (GFP+ BM) transplanted into experimental mice via injection through the tail vein (293-296). In each of these studies, GFP+ BM was

observed to migrate to the PDL following injury (293-296). In addition to demonstrating migration to the site of injury, 3 of the studies also indicated differentiation of the transplanted bone marrow into fibroblasts at the PDL injury site, thus suggesting that BM-MSCs are actively recruited to sites of ligamentous injury and differentiate into fibroblasts, thus being directly involved in the natural healing process (293,294,296).

In a study by Kaku et al (280), GFP+ BM was transplanted directly into the femoral bone marrow of recipient mice. Four weeks following transplantation, teeth containing PDL were either extracted and immediately analyzed or immediately replanted, simulating injury to the PDL in the replantation group (280). In the extraction-only group, GFP+ BM-MSCs were detected within the PDL, predominantly with perivascular localization near the bone surface of the PDL. In the replantation group, following replantation, GFP+ BM-MSCs were detected in larger quantities and dispersed throughout the PDL. These findings suggest that bone marrow plays a direct role in the natural PDL postinjury response (280). Further, given that the GFP+ BM had been transplanted into femoral bone marrow, and thus located at a distance from the PDL, the study's findings suggest that these BM-MSCs are released into systemic circulation to reach the target site (280).

Other studies focused on the ACL have also provided evidence of a direct role for bone marrow in ligamentous injury response. Morito et al (297) aspirated synovial fluid from humans who had suffered ACL ruptures and found a significantly increased concentration of MSCs in the synovial fluid as compared with noninjured controls. Although this study did not elucidate the origin of the MSCs, it clearly indicated an increase in response to the injury (297). A later study in ACL-injured rat models indicated, via flow cytometry, a significant increase in the MSC concentration in whole blood at 3 days postinjury in injured rats versus control group (281). Though short of being confirmatory, the panel of cell-surface receptors used were chosen based on their ability to be used to identify BM-MSCs, and therefore suggested that BM-MSCs are actively mobilized in a systemic fashion following injury to the ACL in rats (281). In a second arm of this study, additional rats were intravenously injected with fluorescently labeled BM-MSCs following ACL rupture (293). These labeled BM-MSCs were observed to actively migrate to the injured joint, providing further evidence that BM-MSCs migrate to the location of acute ligamentous injury (281). The fact that these BM-MSCs seemed to localize to the synovium

and myotendinous junction, as opposed to the actual ACL, may be explained by the ACL's well-recognized poor self-healing potential (283,286,287).

Clinical studies in which local bone marrow cells are used to facilitate ligament healing are also important as they demonstrate the simple surgical methods, such as bone marrow stimulation, can release adjacent bone marrow capable of healing the tear (282). For example, Gobbi and Whyte (282) published a case series of athletes with partial ACL tears who were treated with a local marrow stimulation procedure and who had excellent outcomes. Rodkey et al (298) also confirmed this local healing marrow-based ligament response with experimentally created PCL injuries in dogs. These studies clearly indicate that if a natural fracture were to occur simultaneously with the knee ligament injury, causing bone marrow to leak onto the damaged ligament, that the natural ligament healing response would be augmented (282,298). Centeno et al (286,288) also demonstrated improvements in pain and functional outcomes out to 3 years following percutaneous, fluoroscopically guided BMC injection into the ACL for treatment of grade 1, 2, and 3 tears with minimal retraction in a 2 case series.

In conclusion, the natural healing response following ligamentous injury is like that of other tissues, with phases of inflammation, proliferation, and remodeling. Multiple cells and signaling molecules are involved in the process. Currently, available evidence suggests BM-MSCs play an active role in this process, likely through increased migration via systemic circulation to the site of ligamentous injury.

Tendon

There is a clear relationship between the tendon and the bone on which it inserts. Tendon healing involves both intrinsic and extrinsic cellular factors (299). In addition, the health of the tendon has been tied to the underlying number of MSCs in the bone marrow of the insertion (300). Surgeons have taken advantage of this association by using natural local bone marrow cells, as well as BMC injections to improve the quality of surgical tendon repairs (301).

Tendons have poor blood supply in certain regions and can be notoriously difficult to heal (302). Normal tendon healing involves both intrinsic and extrinsic cellular mechanisms. These include local tendon-derived MSCs and progenitor cells, as well as cells recruited to the site of injury from the surrounding periphery (287). In a labelled bone marrow MSC mouse model, Kaji-

kawa et al (303) demonstrated that bone marrow MSCs entered the peripheral circulation and were recruited to the injured tendon at various times in the healing process. These worked synergistically with local tendon-derived MSCs to repair the tendon injury (303). Tendon healing follows 3 main phases that occur with overlap and variations in duration (299). During the inflammatory stage, monocytes, neutrophils, and macrophages travel to the injury site. Several days later, the proliferation stage involves the synthesis of type III collagen in the ECM and activation of local progenitor cells, followed last by the remodeling stage during which type I collagen predominates to restore the tendon strength, orchestrated through a cascade of local growth factors (299).

The relationship between the tendon and its underlying bone do appear linked, similarly to the interrelation between cartilage and bone. Hernigou et al (304) found reduced levels of MSCs at the tendon-bone interface in patients with symptomatic rotator cuff tear. Considering this association, surgeons have used this natural relationship between tendon and bone by using marrow stimulation (304). In this technique, the surgeon drills holes in the bone at the tendon insertion to release natural bone marrow cells into the repair site to augment the healing process (305-307). Effectively, this allows direct access of these cells to the damaged tendon rather than the cells mobilizing to the peripheral circulation and then to the area being repaired, which would only occur if a blood supply existed in this poorly vascularized injury region.

In addition to creating channels from the bone marrow to the tendon to enhance the healing process, BMC taken from other areas can also enhance tendon healing (133,304). It has been demonstrated that injecting BMC into surgical rotator cuff tendon repairs halves the retear rate of those tendons (133). This is also supported by animal models, which demonstrate that higher failure to load and enhanced tendon-to-bone healing is observed in tendons treated with BMC and surgical repair (308). Finally, partially torn rotator cuff tendons injected with BMC showed improved pain and function versus those treated by physical therapy alone (309).

Muscle

Muscle has several self-repair mechanisms, both intrinsic and extrinsic. This includes local satellite cells and cells recruited from other areas, including the bone marrow (251). One rationale for supplementing muscle

repair is that it is often imperfect, with many animal models demonstrating bone marrow MSCs can assist in the repair process (310).

Like other musculoskeletal tissues, skeletal muscle follows 3 phases of muscle tissue repair: the initial inflammatory phase, followed by a repair phase, and finally a remodeling phase (311,312). The inflammatory phase starts with the initial muscle rupture, hematoma formation, and muscle necrosis, which triggers the complement cascade and recruitment of neutrophils and macrophages to the site of injury. These cells phagocytose and digest the damaged tissue and cellular debris while releasing cytokines (tumor necrosis factor (TNF)-alpha, IL-1, IL-6 and IL-8, as well as IGF-1) that recruit additional inflammatory mediators and also signal resident satellite cells to proliferate (313). In the repair phase, M2 macrophages promote satellite cell differentiation into new myoblasts (312). These myoblasts will subsequently bind to one another or to existing myofibrils to fill the muscle defect. At the same time, MSCs will communicate via paracrine signaling with the surrounding environment, recruiting fibroblasts, which will attempt to bridge the defect with dense scar, and prompting new blood vessel and nerve growth, via the secretion of numerous growth factors (IGF-1, hepatocyte growth factor, FGF, VEGF-A, brain derived neurotrophic factor, etc.) and immunomodulatory cytokines, which ultimately provides the building blocks for muscle regeneration (314-316). The last phase in muscle injury is the remodeling phase characterized by reorganization of both scar and myofibers to ultimately optimize efficient force production. It has been shown that MMPs can digest fibrotic scar tissue and signal an influx of new progenitor cells, capable of further differentiation into new myofibers (313,317).

Muscle fibers do not multiply, rather they are repaired and maintained by many neighboring cell types throughout adult life (318). It has been demonstrated that satellite cells, which lie adjacent to muscle fibers along the basement membrane are mitotically active, capable of self-renewal, and possess the ability to differentiate into myonuclei, which replace the damaged muscle fibers (319). Satellite cells were traditionally thought to be the primary myogenic stem cell equivalent, responsible for muscle regeneration and maintained entirely by self-renewal, however, this has been called into question as others have found that several other neighboring progenitor cells, such as endothelial-associated cells, interstitial cells, and BM-MSCs, also function to maintain and replete the satellite cell pool

(319). In response to skeletal muscle injury, BM-MSCs react by mobilizing through the peripheral circulation, ultimately differentiating into both functioning satellite cells and new myofibers (320,321). Thus the relationship of bone marrow progenitor cells and their importance in supporting the muscle satellite cell pool is thought to be crucial to normal muscle tissue repair.

The muscle repair process is often imperfect in the injury model. New muscle fibers have been found to have various structural abnormalities, can deposit themselves outside of the basal lamina, and can form aberrant attachments to the surrounding scar tissue, all of which can result in functional impairment of the new muscle tissue (322). Thus emerging concepts in the treatment of muscle injury focus on augmentation of the natural inflammatory and repair mechanism discussed earlier, with BM-MSCs to the site of injury. It is well documented in the cardiac literature that autologous transplanted bone marrow cells can be used to regenerate portions of infarcted myocardium (323-326). In a rat crush injury model, local injection of BM-MSCs to injured muscle was shown to increase postinjury muscle contractile force when compared with injection with saline (327). Winkler et al (328) demonstrated a dose-response relationship to the administration of BM-MSCs, which resulted in greater maximum twitch strength and tetanic contraction force. It was shown by Natsu et al (329) that implantation of BM-MSC into rat tibialis anterior muscles following laceration injury promoted myofiber maturation and return to baseline contractile force.

It is clear that the muscle repair mechanism is similar to that of tendon, cartilage, and bone with phases of inflammation, repair, and remodeling, which function to restore myofiber structure and function to best produce efficient force production. There is ample evidence suggesting that BM-MSCs function is not only to replace depleted muscle satellite cells, but is also to differentiate into new myofibers *in vivo*. They also possess the capability to both migrate to nearby sites of injury, as well as distant injuries via the circulation. As such, there is increasing interest in regenerative musculoskeletal treatment strategies that augment this natural muscle repair mechanism through additional supplementation of BM-MSCs into an area of muscle injury.

The Spinal Joint Complex and Disc

Spinal pain is the most common condition of all chronic pain conditions. Based on the available evi-

dence, lumbar intervertebral discs, facet joints, sacroiliac joints, ligaments, fascia, muscles, the nerve root and its dorsal root ganglion, and the dural sleeve have all been shown to be capable of transmitting pain in the spine with resulting symptoms of spinal pain, chest wall pain, and extremity pain (1-9,12,138,151-154). Spinal pain is a complex and multifactorial entity, encompassing mechanical, physiological, and psychosocial dimensions. Genetic predisposition and environmental factors including smoking, obesity, and abnormal mechanical loading have been implicated in the pathogenesis of low back pain (1-5,12). Based on the theory of the structural basis of spinal pain, coupled with advances in imaging and increased understanding of the mechanisms of pain, there is increasing evidence that a significant proportion of low back pain is associated with degenerative disease of the spine involving spinal joints and the disc. Studies have shown that osteoarthritis of the spine with involvement of facet joints and degenerative disc disease provide direct mechanistic association with spinal pain due to nociceptive nerve in growth occurring in the painful degenerative intervertebral discs, as well as into osteoarthritis of the arthritic facet joints and sacroiliac joints (138).

Apart from the sacroiliac joint, which is a true synovial joint, the spine consists of a 3-joint complex (the articular triad), which is the basic anatomic and functional unit of the spine, consisting of the intervertebral disc and 2 symmetrical facet joints, which connect the adjacent vertebrae (3,4,138,330-348). Many biomechanical studies have demonstrated that the intervertebral disc and the 2 adjacent facet joints carry loads together in the normal lumbar spine (335). Multiple studies have demonstrated that the intervertebral disc is the initial site of spinal degeneration and that the adjacent facet joint degenerates as a result of disc degeneration (337-339,347). However, other studies have indicated that disc degeneration does not necessarily precede facet degeneration (340-343). Consequently, it is quite likely that the intervertebral disc and facet joints contribute as a unit to the degenerative process (341,344,345). Lv et al (346) concluded that there was a significant correlation between endplate defects, Modic magnetic resonance imaging (MRI) signal changes, disc degeneration, facet tropism, facet orientation, and low back pain.

Although facet joints are true synovial joints, intervertebral discs are composed of an annulus fibrosus, nucleus pulposus, and cartilaginous endplates (349). During the process of degeneration, discs undergo morphologic changes with tears and dehydration. They also

undergo changes in the molecular composition of their structure such as apoptosis, accumulation of debris with decreased diffusion of waste products, and decreased proteoglycan synthesis (349). The molecular changes are components of disc degeneration, which can lead to spinal stenosis, radiculopathy, myelopathy, and mechanical low back pain. Facet joint arthritis is a clinical and pathological process that involves the functional degeneration of the synovial facet joints. Even though it is viewed as a disease of articular cartilage loss and bony hypertrophy, the process of degeneration actually involves the whole joint, including the subchondral bone, cartilage, ligaments, capsule, synovium, and periartricular paraspinal muscles and soft tissues (347). As described earlier, in the 3-joint complex, the intervertebral disc and the facet joints degenerate together.

Degenerative vertebral endplate and subchondral bone marrow changes were first noted on MRI by de Roos et al (350) in 1987. These MRI changes were formally classified in 1988 by Modic et al (351). Type 1 Modic change is defined as a hypointense signal of the vertebral endplate and body on the T1 images and hyperintense on T2 images, especially on the STIR sequence. This signal change represents bone marrow edema and inflammation and is associated with disruption and fissuring of endplates and the formation of fibrovascular granulation tissue. These changes reflect the inflammatory stage of disc degeneration. Type 2 Modic change is defined as a hyperintense signal of the vertebral endplate and body on the T1 images and hyperintense on nonfat suppressed T2 images. This is a result of the conversion of normal red hemopoietic bone marrow into yellow fatty marrow as a result of marrow ischemia. Modic type 3 changes are hypointense on both T1 and T2 secondary to subchondral bone sclerosis. Modic 1 and 2 changes are much more prevalent than Modic 3, and these changes are most commonly seen at the L4, L5, and S1 levels next to degenerated discs. Modic changes are uncommon in asymptomatic individuals without degenerative disc disease (352). Kokkonen et al (353) have shown that, based on MRI and computed tomography discography, there is a strong correlation between vertebral endplate changes and disc degeneration (346). The edema producing Modic 1 signal changes are secondary to microfractures of the endplates and contiguous cancellous bone. There is an increase in vascular density, in the number of nerve endings due to nociceptive ingrowth, and in the levels of proinflammatory chemical mediators, with these vascular and inflammatory changes following the initial

mechanical phenomena (352). Ohtori et al (354) found that inflammatory cytokines and nerve ingrowth into vertebral endplates may be a cause of discogenic low back pain and that Modic type 1 changes, representing more active inflammation, seem to be mediated by pro-inflammatory cytokines, whereas type 2 and 3 changes are more quiescent stages of the process. Kjaer et al (355) has demonstrated that degenerative disc disease by itself is a fairly benign condition, whereas degenerative disc disease with Modic changes is much more frequently associated with clinical symptoms. Among Modic changes, type 1 changes are the ones most strongly associated with low back pain (352). Mitra et al (356) has found that type 1 Modic changes are dynamic lesions that, in most cases, either increase in size or convert into type 2 changes. They have also demonstrated that the evolution of type 1 Modic changes into type 2 changes result in the improvement of symptoms. In addition, they observed that patients in whom type 1 changes increased were clinically worse. Finally, various types of Modic changes can coexist with each other in the same vertebrae (330).

BMC in the Spine

The intervertebral disc and the bone marrow located in the vertebral body are in constant communication in the same way that cartilage and subchondral marrow in all joints (including the facet joints) make up one biologic unit. The spine also contains ligaments and muscles, and the earlier described principles of homology would apply to those structures as well, meaning that bone marrow is homologous to the functional spinal unit.

The vertebral bone marrow and the intervertebral disc are in constant communication to maintain the health of that structure. For example, Dudli et al (332) found that in intervertebral discs with Modic changes, fibrogenic and pro-inflammatory cross talk between the vertebral bone marrow and adjacent disc is a critical part of the disease process. In addition, other authors have found that the degenerative processes in the disc, endplate, and bone marrow are highly associated (334). In a recent MRI diffusion study, the lack of bone marrow perfusion across the endplate was associated with degeneration of the intervertebral disc (336). Hence the status of the bone marrow in the vertebral body impacts the health of the disc, meaning that the vertebral bone marrow and the intervertebral disc are one homologous biologic unit.

Increases in the level of high-sensitivity C-reactive protein in patients with low back pain and Modic type

1 changes indicate local inflammation in vertebral endplates. The same is not shown for Modic type 2 and type 3 changes. However, it is now clear that subchondral bone sclerosis and endplate fissuring is present in all types of Modic changes. The different Modic types are believed to represent different stages of the same pathological process. Modic changes can convert from one type to another, most commonly from type 1 to type 2. Type 1 can also be reversed to normal only if the underlying mechanical and molecular abnormalities are resolved, which is very rare. Modic type 2 is more stable. Rarely, type 2 will convert to type 3. There is evidence to suggest that patients with an increased tendency to inflammation and changes in bone marrow at the vertebral endplates also have an increased tendency to develop long-term back pain (357).

The endplate is the primary pathway for transport between vertebral capillaries and the many cells within the annulus and the sparse cells within the disc nucleus. Blood vessels and marrow spaces abut the cartilaginous and cortical bone layer of the endplate, providing channels for glucose and oxygen to enter the disc and for waste products to exit the disc.

BMC therapies in intervertebral disc degeneration repopulate the intervertebral disc and restore functional tissue through matrix synthesis by implanted cells and potentially beneficial influences on native cells (3,79,80,82-87,98,105-107,349). Stem cells serve as a source to replace the nonviable cells of the annulus fibrosus and nucleus pulposus (349). Autologous nucleus pulposus cell reimplantation has been shown to retard degenerative changes in a dog model (358,359); however, as the nucleus pulposus is relatively hypocellular, harvesting sufficient cells for reimplantation may result in injury to the disc. Further, nucleus pulposus cells from degenerated discs display, premature senescence and a catabolic metabolism (334,337,359-361), which make them unsuitable for transplantation in which normal cell function is required. Thus MSCs have been proposed as an ideal cell source of regeneration. An increasing number of studies have demonstrated the ability of BM-MSCs to differentiate into nucleus pulposus-like phenotype (discogenic differentiation). The literature has shown that BM-MSCs can differentiate into osteoblasts, adipocytes, chondroblasts, and cells having the phenotypic features of the intervertebral disc under proper in vitro conditions (362-364). Further, the capability of BM-MSCs to differentiate into nucleus pulposus-like cells and their ability to stimulate production of a new cell matrix has been described

(365). This hypothesis was tested by Mochida et al (366) for intervertebral disc repair with activated nucleus pulposus cell transplantation over a 3-year prospective clinical study of its safety. Multiple other investigators also have studied the results of implantation of MSCs (87,366-371).

In vivo studies have also demonstrated the ability of implanted MSCs to enhance matrix production, particularly glycosaminoglycan synthesis, resulting in increased disc height and hydration (372-377). Early studies on discogenic differentiation of MSCs relied on the fact that nucleus pulposus cells are chondrocyte-like and express chondrogenic markers, such as SOX-9, type II collagen, and aggrecan (378). In preclinical studies of the use of stem cells in the spine (379-381), adult stem cells derived from bone marrow showed promise for both osteogenesis and chondrogenesis. Further, various growth factors and scaffolds have also been shown to enhance the properties and eventual clinical potential of these cells.

The descriptions of immunomodulation of MSCs in discogenic pain by Miguélez-Rivera et al (382) showed that conditioned media from MSCs downregulated the expression of various proinflammatory cytokines produced in the pathogenesis of discogenic pain, such as IL-1, IL-6, IL-17, and TNF. Discogenic cells generated from different adult human donors were also evaluated for surface marker expression profile, matrix deposition, and tumorigenic potential (383). Subcutaneous injection of discogenic cells into nude mice to assess cell survival and possible ECM production in vivo, and assessment of therapeutic potential of discogenic cells after disc injury in a rabbit model of disc degeneration showed that discogenic cells have a consistent surface marker profile, are multipotent for mesenchymal lineages, and produce ECM consisting of aggrecan, collagen 1, and collagen 2 (383). This study concluded that intradiscal injection of discogenic cells may be a viable treatment for human degenerative disc disease with production of ECM that may rebuild the depleting tissue within the degenerated discs without any significant safety concerns.

The role of MSCs in healing and regeneration by studying autologous BMC MSC migration into the injured intervertebral disc has been investigated (384-389). MSC homing has been reported to play a role in the endogenous regeneration of different skeletal tissues, including bone and cartilage. In vivo, this process is tightly controlled by a gradient of signalling molecules. In the intervertebral disc, recruitment of bone

marrow cells toward the regenerating intervertebral disc has been demonstrated in a mouse tail model in vivo. However, the findings from the intervertebral disc degeneration model suggests that the pool of available cells or their recruitment efficiency may need to be enhanced by exogenous means to achieve a significant regenerative effect (384). Thus, migration of exogenously delivered BM-MSCs through the endplate into the intervertebral disc has been described as an alternative approach for intradiscal cell treatment in several whole intradiscal organ culture models (388-391). Wangler et al (384) in an experimental study with human MSC and intervertebral disc tissue samples showed that MSC homing was involved directly in the maintenance of the human intervertebral disc (392).

Wang et al (83), in a systematic review and meta-analysis of controlled trials using animals to investigate the efficacy of intervertebral disc regeneration with stem cells, demonstrated that stem cells transplanted into the intervertebral discs of quadrupedal animals decelerate or arrest the intervertebral disc degenerative process. In another systematic review of comparative controlled studies regarding the potential benefits of using MSCs in disc degeneration, Yim et al (393) showed that bone marrow MSCs produced a significant inhibition of disc degeneration with a better quality of repair compared with non-MSC treatments.

Bone marrow MSCs that can be altered genetically to express specific genes and differentiate into terminal cells used in bone fusion are also currently being investigated for spine fusion. Comparisons are made to local or harvest autografts (349,394). In vivo experiments involve the injection of genetically engineered MSCs that express recombinant human bone morphogenic protein into sites for spinal fusion (395). BMC MSCs with the ability to differentiate into adipocytes, osteoblasts, and chondroblasts continue to proliferate, providing an important source of bone formation to enhance the spinal fusion (124,396). However, the therapeutic potential of BMC MSCs is curtailed by the small number of osteoprogenitor cells (397). Consequently, selective cell retention technology has been described as a novel method to enrich the graft material with BMC MSCs obtained with bone marrow aspiration through a simple and effective method for intraoperative concentration of MSCs without the need for ex vivo expansion that improves the characteristics of the graft material (398,399). Further, a study of long-term radiologic and clinical outcome after using bone marrow MSC concentrate obtained with selective retention cell technology

in posterolateral spinal fusion showed a fusion rate of 100% (396). This is in contrast to nonunion rate of 25% to 30% and pseudoarthrosis of 23% to 44% (400,401), with the incidence of reoperation following lumbar fusion surgery of 20.1% (402). Multiple other studies have been published showing increased levels of fusion (394).

CLINICAL OUTCOMES

BMC-MSCs are utilized in managing all types of musculoskeletal conditions, including for spine regeneration and fusion.

A literature search was carried out utilizing multiple databases. The literature search involved bone marrow stem cell research with key words of BMC and BMC implant into various musculoskeletal and spine structures. A total of 3,488 manuscripts were identified through December 2019.

Spine

BMC is utilized for multiple types of interventions in the spine, including intraarticular injections of facets and sacroiliac joints, disc injections, and epidural injections.

Disc Injections

An overwhelming majority of the research with BMC stem cells is focused on the lumbosacral spine. Navani et al (3) published guidelines based on appropriate search criteria, study selection, methodologic quality assessment, and analysis of evidence that included qualitative, as well as quantitative, analysis with conventional dual arm and single arm meta-analysis. Navani et al (3) identified 5 systematic reviews (79,83-86). The overall majority of the studies used BM-MSCs, concluding that BM-MSCs were the gold standard.

Khan et al (84) studied not only intervertebral disc repair and spinal fusion, but also spinal cord injury. This review identified almost 2,600 manuscripts; however, only 53 met eligibility criteria. Of these, there were 28 studies on intervertebral disc repair and 9 studies on spinal fusion. This systematic review concluded that MSCs were a very good source for treatment of spinal conditions.

Wu et al (86) reported the results of 6 studies with a 44.2 point decrease in the pooled mean difference in pain scores, and a 32.2 point pooled mean difference in the Oswestry Disability Index with no adverse effects. In this systematic review, 3 studies used stem cells (369,403,404) and 3 studies used chondrocytes

(87,366,368). The mean follow-up time among the 6 trials was 22 months. In this analysis, they reported that one study found improvements in the disc contour or height posttreatment (368). Another study showed increase in the fluid content of the discs at 12 months (369).

Basso et al (85) in a systematic review identified 4 manuscripts (366,369,403,405) that involved the use of stem cells. All of the studies reported that the intradiscal injection of stem cells was safe with variable effectiveness.

Sanapati et al (79) in a systematic review of 26 manuscripts, included 7 studies utilizing stem cells (87,367-404,406,407) with one study having 3 publications. The results showed level III evidence for disc injections of MSCs, and level IV evidence for epidural injections, lumbar facet joint injections, and sacroiliac joint injections, with qualitative and quantitative synthesis of evidence using conventional and single-arm meta-analysis. Appendix Table 1 shows the characteristics of the included studies of stem cell therapy in disc degeneration as stated in ASIPP guidelines that were derived from the systematic review of Sanapati et al (79).

Sanapati et al (79) in a single-arm meta-analysis, as shown in Fig. 6, showed changes in the pain scores (87,354,368,369,371,406). The pooled mean difference in the decreased pain scores from baseline to the 12-month follow-up was 36.943 points (95% confidence interval [CI]: -49.855 to -24.030, $P < 0.001$). Heterogeneity across the studies was high ($I^2 = 86\%$). They also showed changes in the functional scores, as shown in Fig. 7. Six studies reported on outcome assessment over a period of 12 months (87,368,369,406,407). The pooled mean difference in the decreased disability scores from baseline to the 12-month follow-up was 26.342 points (95% CI: -32.359 to -20.325, $P < 0.001$). Heterogeneity across the studies was moderate ($I^2 = 55\%$).

Based on multiple systematic reviews (79,83-86), as well as randomized and nonrandomized studies included in systematic reviews and guideline development (3,87,354,366-407), there is level III evidence for intradiscal injections of BMC.

Spinal Fusion

For a variety of spinal disorders, including trauma, deformity, tumors, infection, instability, and degenerative spine disease, the rate of spinal fusion has been increasing at an escalating pace (396). However, following fusion, repeat surgery was shown to be present in approximately 20% of the patients (402), pseudoar-

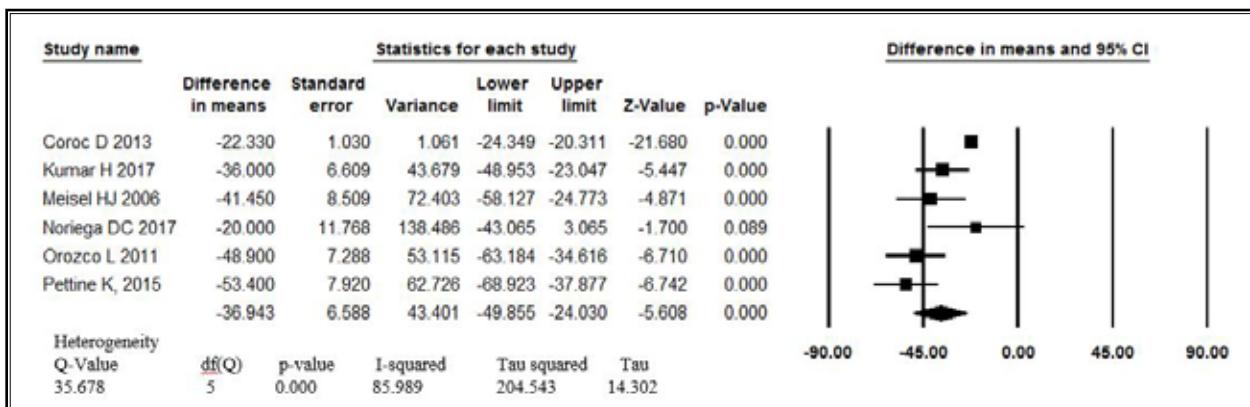


Fig. 6. Changes in pain score (Numerical Rating Scale or Visual Analog Scale, 0-100) after treatment (12 months follow-up data) of cell therapy of lumbar disc.

Adapted from: Sanapati J, et al. Do regenerative medicine therapies provide long-term relief in chronic low back pain: A systematic review and metaanalysis. *Pain Physician* 2018; 21:515-540 (79).

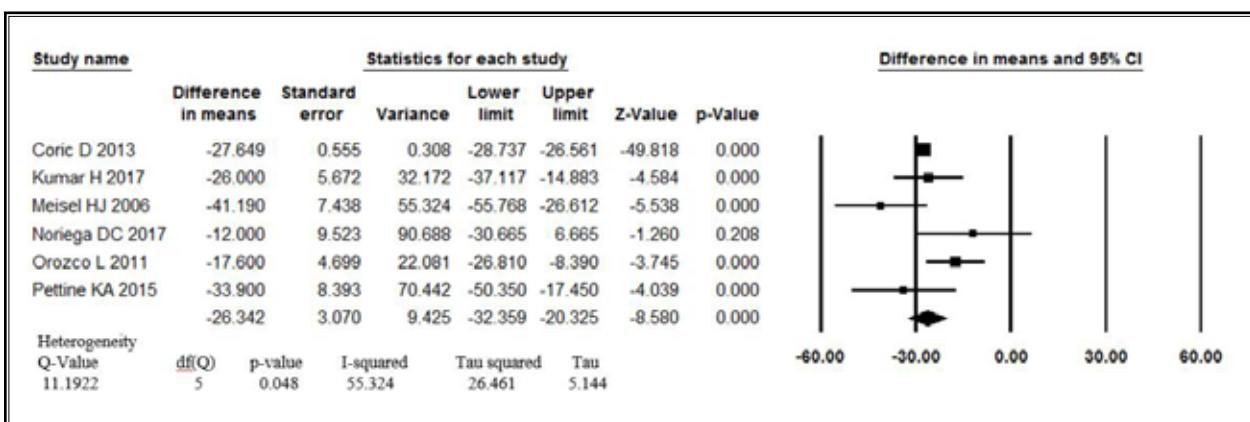


Fig. 7. Changes in Oswestry Disability Index after treatment (12 months follow-up data) of cell therapy of lumbar disc.

Adapted from: Sanapati J, et al. Do regenerative medicine therapies provide long-term relief in chronic low back pain: A systematic review and metaanalysis. *Pain Physician* 2018; 21:515-540 (79).

throsis after posterolateral lumbar fusion varying from 23% to 44% (400,401), and nonunion in 25% to 30% depending on the procedure (394). Shah and Hsu (394) reviewed all of the studies available using autologous MSCs ($n = 11$) from bone marrow aspirate. Overall, the studies have shown increased fusion rates as high as 100% (396,408-412).

Facet Joint Intraarticular Injections

Facet joints are true synovial joints and have been proven to cause neck, upper extremity, mid back, upper

back and chest wall, and low back and lower extremity pain (138). The majority of the literature of biologics is based on intraarticular injections in the lumbar spine of platelet-rich plasma (PRP), which have been shown to have positive results (79). Controlled diagnostic studies have shown the prevalence of facet joint pain in 36% to 67% in the cervical spine, 34% to 48% in the thoracic spine, and 27% to 41% in the lumbar spine based on controlled comparative local anesthetic blocks in patients without disc herniation or radiculitis (138,412-416). Based on the results of PRP injections (79), the

Table 5. Overall results of the comparisons of MSC injections for knee osteoarthritis with 72% of included studies injected BMC.

Outcome	Baseline	12 months	Estimated effect, IV, Random (95% confidence interval)	
	Mean (SD)	Mean (SD)	0-12 Months	P
VAS score	55.28 (18.37)	20.08 (91.54)	36.91 (30.36 to 43.43)	< 0.0001
WOMAC	25.66 (15.10)	24.98 (14.39)	15.60 (10.10 to 21.10)	< 0.0001
Walking Distance	71.90 (28.41)	57.33 (270.31)	316.72 (-696.54 to 63.10)	0.10
Lequesne Scale	33.76 (19.72)	20.70 (19.07)	12.90 (-1.35 to 27.15)	0.08
KOOS				
Overall	41.07 (12.17)	65.13 (13.56)	18.94 (27.00 to 10.88)	< 0.0001
Symptoms	51.27 (15.21)	69.57 (14.99)	14.14 (21.35 to 6.93)	0.001
Pain	49.55 (14.51)	69.57 (14.99)	22.03 (29.39 to 14.67)	< 0.0001
Function	50.36 (18.90)	76.87 (16.02)	21.54 (28.84 to 14.24)	< 0.0001
Recreation	27.84 (17.46)	57.97 (21.17)	23.07 (32.10 to 14.04)	< 0.0001
Quality of Life	32.69 (23.40)	54.87 (17.07)	14.07 (38.98 to -10.84)	0.27

VAS = Visual Analog Scale; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index; KOOS = Knee injury and Osteoarthritis Outcome Score.

Adapted from: 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* 2019 [Epub ahead of print] (109).

results with BMC are expected to be equivalent or superior to PRP injections.

Sacroiliac Joint

The sacroiliac joint is a true synovial joint and has been proven to cause low back and lower extremity pain (138,417). Diagnostic studies have shown the prevalence of sacroiliac joint causing low back pain in approximately 10% to 25% of patients (138,417). Even though there is extensive literature discussing the use and effectiveness of biologicals in the management of peripheral joint pain, similar to facet joints, there is no literature on sacroiliac joint injections with BMC. However, based on the results of PRP injections (79), the results with BMC are expected to be equivalent or superior to PRP injections, which have been shown to have positive results.

Epidural Injections

Epidural injections are performed to treat various types of spinal and extremity pain secondary to disc herniation, nerve root irritation, discogenic pain with radiation into the extremity, spinal stenosis, and the postsurgery syndrome (138,418-422). There is vast literature regarding the effectiveness of various modalities in managing discogenic and nerve root pain (138,418-422). The effects of epidural injections of PRP have been studied; however, there are no studies showing the effects of epidural BMC.

Knee

Multiple publications of systematic reviews, randomized controlled trials, and continuing research, show that injections of BMC or isolated bone marrow and MSCs show promise as a safe and effective treatment for multiple knee conditions (88,109-111,134,239,421-433). A recent systematic review by Migliorini et al (109), assessing the stem cell injections for knee osteoarthritis identified 18 studies, comprising 1,069 treated knees. BMC-MSCs were administered in 72% of the included studies with a mean Visual Analog Scale score improvement from 18.37 to 30.98 and 36.91 at 6- and 12-month follow-up, respectively. The evaluation also showed improvement in functional scores with improvement in the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) score from 25.66 to 25.23 and 15.6 at 6- and 12-month follow-up, respectively. The mean walking distance improved from 71.9 to 152.22 and 316.72 at 6- and 12-month follow-up, respectively. Multiple other scores also improved significantly. The authors have concluded that according to the current evidence BMC infiltration for knee osteoarthritis can represent a feasible option, leading to an overall remarkable improvement of all clinical and functional outcomes. Further, they have also shown that patients treated at earlier degeneration stages reported statistically significant better outcomes (134,229,232,233,239,423-433). Table 5 shows

Table 6. Clinical outcomes of studies of osteoarthritis using MSCs, with 8 of 17 studies using BMC.

Author	No. of Patients (Study/Control)	Age	Gender (F/M)	BMI	FU* (mo)	Clinical Outcome	Description
Wakitani et al (229), 2002	24 (12/12)	63	15/9	NS	16	HSS	81.3 vs. 79.2 No significant difference
Davatchi et al (231), 2011	4	58	2/2	30.3	12	Pain VAS, walking time, number of stairs	Pain, walking time, and number of stairs to climb improved
Emadeddin et al (232), 2012	6	55	6/0	31.6	12	Pain VAS, WOMAC, walking distance	All outcomes improved
Wong et al (237), 2013	56 (28/28)	51	29/27	23.9 (median)	24	IKDC, Lysholm, Tegner	All outcomes improved Better scores in the MSC group*
Orozco et al (234), 2013	12	49	6/6	NS	12	VAS, WOMAC, SF-36	All outcomes improved
Vega et al (239), 2015	30 (15/15)	57	19/11	NS	12	VAS, WOMAC, Lequesne, SF-12	All outcomes improved Better scores in the MSC group*
Gupta et al (435), 2016	60 (40/20)	56	45/15	27.8	12	VAS, ICOAP, WOMAC	No significant differences in all groups
Lamo-Espinosa et al (433), 2016	30 (20/10)	61	11/19	28.4	12	VAS, WOMAC	All outcomes improved Better improvement in the MSC group* Much improvement in the high-dose group

BMI = body mass index; HSS = hospital for specific surgery; ICOAP = intermittent and constant osteoarthritis pain; IKDC = International Knee Documentation Committee; VAS = Visual Analog Scale score; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index; SF-36 = Short Form-36; SF-12 = Short Form-12; MSC = mesenchymal stem cell; NS = not specified; F/U = follow-up.

Adapted from: Ha CW, Park YB, Kim SH, Lee HJ. 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 (111).

the comparisons of outcomes after MSC injections for knee osteoarthritis, published in the systematic review by Migliorini et al (109).

There have been multiple other systematic reviews (88,110,111,134,434). Ha et al (111) performed a systematic review assessing intraarticular MSCs for the osteoarthritis of the knee along with evidence of cartilage repair including a total of 17 studies, with 8 studies (229,232,233,237,239,424,425,433,435,436) using bone marrow derived MSCs. They concluded that intraarticular MSCs provided improvement in pain and function in knee osteoarthritis with follow-up of less than 28 months in many cases. They also showed efficacy of MSCs for cartilage repair in osteoarthritis. However, they concluded that evidence of efficacy of intraarticular MSCs on both clinical outcomes and cartilage repair was limited to level III evidence. Table 6 shows the characteristics and clinical outcomes of the studies of osteoarthritis using BMC.

Chahla et al (88) also performed a systematic review of outcomes of the concentrated bone marrow

aspirate for the treatment of chondral injuries and osteoarthritis of the knee. They identified 8 studies evaluating the efficacy of BMAC on focal cartilage injuries (430-433,435-445), and 3 studies evaluating the clinical efficacy of BMAC in the treatment of osteoarthritis (430,437,446). All 11 studies with patients having osteoarthritis and chondral effects reported good to excellent overall outcomes with the use of BMAC.

Cavinatto et al (434) in a systematic review and critical analysis in animal and clinical studies of assessing the role of BMAC for the treatment of focal chondral lesions of the knee reported the results of 13 clinical studies. Overall, all clinical studies, independent of the study group or level of evidence, reported improved clinical outcomes and higher macroscopic, MRI, and histology scores. However, clinical studies were scant and showed low scientific rigor, poor methodologic quality, and low levels of evidence on average.

In a systematic review of human studies of office-based MSC therapy for the treatment of a variety of musculoskeletal disease, Law et al (110) identified 8 studies

with a total of 941 patients (228,236,406,430,447-450). Overall, they concluded that support in the literature is strongest for the use of BMC injections for the treatment of knee injuries.

Two recent randomized controlled trials have also been published that use BMC injections to treat knee osteoarthritis. Centeno et al (451) published a randomized cross-over trial of high-dose BMC injected versus physical therapy showing excellent results compared with control. Gobbi et al (470-471) published a smaller group of patients who used low-dose BMC diluted with high volumes of platelet poor plasma and observed good results in both the osteoarthritis and saline control groups.

BMC injection using fluoroscopic guidance has also been used to repair ACL injuries. Centeno et al (451) have published 2 case series with imaging outcomes showing evidence of healing both on MRI and with functional questionnaires (453,454). In these cases, similar to surgical results were obtained only through precise injection.

In summary, BMC demonstrated beneficial effects not only in knee osteoarthritis, but in the repair of ACL and other injuries involving cartilage and cortical bone.

Based on the evidence derived from multiple systematic reviews (88,109-111), relevant randomized controlled trials (229,231,232,234,237,239,430,433,435,437,446), and multiple observational studies, there is moderate or level II evidence for treatment of knee osteoarthritis, there is level III evidence based on systematic reviews, randomized controlled trials, and observational studies of focal cartilage injuries (88,440,445).

Hip

BMC has been shown to produce reasonable outcomes for hip injections (108). Despite the emerging literature with overall hip injections, the literature related to implantation of autologous bone marrow stem cells compared with other modalities of treatments in osteonecrosis of the femoral head is significant (109,455). In fact, Wang et al (455) in a meta-analysis of core decompression combined with autologous bone marrow stem cells versus core decompression alone for patients with osteonecrosis of the femoral head included 14 studies with 540 patients (456-469). They included studies from 2004 to 2018. Further, studies were mainly published in Belgium and China. Results of meta-analysis showed the core decompression combined with bone marrow stem cells was superior in pain reduction at 6 months, 12 months, and 24 months, and a decrease in number

of hips undergoing total hip arthroplasty, the WOMAC score, and the volume of the postoperative necrotic zone. Among the multiple reports available, Centeno et al (470) evaluated 196 patients with hip osteoarthritis treated with BMC percutaneous-guided injection. Patients reported relief of pain and better function; there were no severe or serious adverse events (470). In 2006, the same authors (471) had already demonstrated a partial regeneration of a severely degenerated hip 8 weeks after bone marrow aspirate injection; the results were confirmed by MRI. Chahla et al (472) described in a review article the successful use of BMC for hip osteoarthritis in their institution, with good clinical results and no adverse effects reported.

Regarding soft tissues injuries of the hip, there is a lack of publications showing BMC use in humans. However, there are several reports of bone marrow use on animals, some in other body parts, and a vast literature about PRP (108). Due to biological similarities between BMC and PRP, as well as the verified safety of the former, its use for this purpose must increase in the next years. Torricelli et al (473) demonstrated impressive results using a combination of BMC and PRP to treat overuse injuries in competition horses, achieving an almost 85% rate of return to competition. Campbell et al (474) treated a professional soccer player with capsular injury and tear of the gluteus minimus tendon using both BMC and PRP. They described improvement of pain and strength, as well as the morphologic changes on MRI.

Recent studies of hip osteonecrosis have demonstrated that there is a decrease in the number and function of mesenchymal cells in the trochanteric region and in the femoral head of patients resulting in a limited healing capacity of the necrotic areas (470,471). Mononuclear cell transplantation appears to be a minimally invasive technique capable of reducing pain and preventing the progression of these lesions (470-473).

Data show that after femoral head collapse, the rate of treatment failure increases greatly. Other factors that may impair biological treatment would be the use of corticosteroids and alcoholism (472-474).

The most common technique for grafting the mononuclear cell concentrate into the hip is through the decompression tunnels into the necrotic areas of the femoral head. The concentrate can be applied alone or in combination with a scaffold that guarantees mechanical support and the presence of the cells in the areas of necrosis (475-477). A few studies have used transplantation of mononuclear cells by selective catheterization of the medial circumflex artery (450,478), or

the intravenous injection of mesenchymal cells betting on the ability of the cells to home in on injured tissues (479).

The variation in the techniques of collection, concentration, and grafting shows the lack of uniformity of the methods, which leads to the difficulty of comparing the data in the literature.

Ankle

The use of BMC for the treatment of osteochondral defects and osteoarthritis of the talus was reviewed by Chahla et al (480). In this systematic review, 4 studies that used BMC to augment a variety of surgical techniques for the treatment of osteochondral lesions of the talus were analyzed.

Clinical improvement in Orthopaedic Foot and Ankle Society (AOFAS) score and MRI scan were observed in 48 patients with posttraumatic type II lesion of the talar dome. These patients underwent a one-step arthroscopic technique for cartilage repair and treated with BMC and collagen powder or hyaluronic acid membrane as scaffolds for cells and platelet gel (481). The studies also showed that at 24 months follow-up new tissue was formed. The clinical outcomes were maintained in these patients for 4 years after treatment, although there was a decline in the AOFAS scores between 24 and 48 months of follow-up (482).

Outcome measures were reported in Foot and Ankle Outcome Score and in Short Form-12 general health questionnaire in patients with lesions of the talus after autologous osteochondral transplantation with BMC (483).

Retrospective outcomes after osteochondral lesions of the talus treated with arthroscopy followed by talar bone marrow stimulation with and without BMC as a biological adjunct were analyzed in 22 patients (484). The results show that the use of BMC resulted in similar functional outcomes, but improved border repair tissue integration, with less evidence of fissuring and fibrillation on MRI.

The use of BMC for acute sports-related Achilles tendon rupture was demonstrated in studies with 27 patients (485). In this group of patients, there were no adverse outcomes or reruptures.

Shoulder

Poor microcirculation of the human rotator cuff results in chronic lesions that do not heal and tend to increase in size over time, increasing the number of symptomatic patients (108,486,487).

Several experimental studies on the use of mesenchymal cells for the treatment of tendinopathies have shown encouraging results. The healing of the surgical repair occurs with the formation of fibro-cicatricial tissue of low quality. The use of BMC in the treatment of the rotator cuff aims to improve the quality of tendons and their healing (108). The BMC can be applied at the lesion site by direct injection or associated with scaffolds.

In a clinical study (488) of rotator cuff repair using the mini-open technique with transosseous suture and application of bone marrow mononuclear cells, a full tendon reconstruction was observed in patients at 12 months follow-up. In this study, the improvement of University of California at Los Angeles score (31 ± 3.2) in 13 of 14 patients remained unchanged up to the second year follow-up.

The BMC outcomes were demonstrated in a group of 90 patients undergoing arthroscopic repair of the supraspinatus tendon (133). Half of the patients received BMC injection at the tenodesis site and half were included in the control group (without BMC treatment). After 6 months of follow-up, the BMC group had 100% repair healing versus 67% in the control group. After 10 years of follow-up, 87% of the cases in the BMC group still had intact tendon against 44% in the control group. Those patients in the treated group without intact tendons had received the lowest number of applied MSCs. Centeno et al (489) published a midterm analysis of a randomized crossover trial comparing percutaneous BMC with platelet-product injection versus exercise alone treatment of partial or full nonretracted supraspinatus tears. Outcomes of the 25 patients who had reached 1 year follow-up showed significant improvements in pain at 3 and 6 months, and functional improvements at 3 months with the majority of post-treatment MRI scan demonstrated decrease in tear size. No adverse outcomes were reported (489).

A prospective study (490) was performed in patients with glenohumeral osteoarthritis and in patients with lesions of less than 1.5 cm of the rotator cuff. Both groups were treated with an injection of BMC plus PRP guided by ultrasound or radioscopy. BMC/PRP treatment led to significant improvement in the Disability of the Arm, Shoulder, and Hand score, and in the numeric scale of pain with subjective improvement in 48.8% of the patients. There was no influence of age, gender, body mass index, or BMC cell count on the result.

POSITION STATEMENTS

The position statements here are based on the

survey of all the literature available, evidence synthesis based on randomized controlled trials, observational studies obtained from systematic reviews, guidelines, and finally an academic Delphi investigation performed on use of BMC to treat pain and musculoskeletal disorders (3,49,50,78-112,491).

STATEMENT 1

Based on a review of the literature in discussing the preparation of BMC using accepted methodologies, there is strong evidence of minimal manipulation in its preparation, and moderate evidence for homologous utility for various musculoskeletal and spinal conditions qualifies for the same surgical exemption.

STATEMENT 2

Assessment of clinical effectiveness based on extensive literature shows emerging evidence for multiple musculoskeletal and spinal conditions.

- The evidence is highest for knee osteoarthritis with level II evidence based on relevant systematic reviews, randomized controlled trials, and nonrandomized studies. There is level III evidence for knee cartilage conditions.
- Based on the relevant systematic reviews, randomized trials, and nonrandomized studies, the evidence for disc injections is level III.
- Based on the available literature without appropriate systematic reviews or randomized controlled trials, the evidence for all other conditions is level IV or limited for BMC injections.

STATEMENT 3

Based on an extensive review of the literature, there is strong evidence for the safety of BMC when performed by trained physicians with the appropriate precautions under image guidance utilizing a sterile technique.

STATEMENT 4

Musculoskeletal disorders and spinal disorders with related disability are common with extensive health care expenditures, taking a human toll with expenditures in 2013 in the United States of \$183 billion per year for musculoskeletal disorders, including back and neck pain. Even then, disability continues to escalate despite advancements with a wide array of treatment modalities.

STATEMENT 5

The 21st Century Cures Act was enacted in Decem-

ber 2016 with provisions to accelerate the development and translation of promising new therapies into clinical evaluation and use. This bipartisan and bicameral legislation increased funding for medical research for combating the opioid epidemic and included measures to streamline approval of new therapies for clinical trials. It also provided a new expedited biologics product development program called RMAT. Multiple activities have been enforced by regulatory agencies at the federal and state levels to combat overuse, misuse, fraud, and abuse; however, with no specific standards established in delivery of BMC therapy.

STATEMENT 6

Development of cell-based therapies is rapidly proliferating in a number of disease areas, including musculoskeletal disorders and spine. With mixed results, these therapies are greatly outpacing the evidence (79,88,110,111,351-373). The reckless publicity with unsubstantiated claims of beneficial outcomes having putative potential has led the FDA FTC to issue multiple warnings. Thus the US FDA is considering the appropriateness of using various therapies, including BMC, for homologous use.

STATEMENT 7

Since the 1980's and the description of mesenchymal stem cells by Caplan et al (120), (now called medicinal signaling cells [MSCs]), the use of BMC in musculoskeletal and spinal disorders has been increasing in the management of pain and promoting tissue healing.

STATEMENT 8

As part of the regulation of HCT/Ps, including both autologous and allogenic bone marrow-derived tissue preparations, are regulation by the FDA using the PHSA. If the biologic is minimally manipulated and falls under the same surgical procedure exemption found at 21 CFR 1271.15(b), the biologic is exempt from FDA regulation. BMC falls into this same surgical procedure exemption jurisdiction from a minimal manipulation standpoint, but only as long as it is also in treatments that constitute homologous use.

STATEMENT 9

If the FDA does not accept BMC as homologous, then it will require an IND classification with FDA (351) cellular drug approval for use.

STATEMENT 10

This literature review and these position state-

ments establish compliance with the FDA's intent and corroborates its present description of BMC as homologous with same surgical exemption, and exempt from IND, for use of BMC for treatment of musculoskeletal tissues, such as cartilage, bones, ligaments, muscles, tendons, and spinal discs.

CONCLUSIONS

Based on the review of all available and relevant literature, position statements have been developed showing the impact of musculoskeletal and spine disorders on health care costs, the opioid epidemic, and disability; evidence of minimal manipulation and homologous use based on MSCs and growth factors of BMC for multiple musculoskeletal structures including the disc; effectiveness and safety; and finally the evidence to show that BMC in musculoskeletal disorders meets the criteria of minimal manipulation and homologous use.

Consequently, using the FDA's tiered, risk-based approach to the regulation of HCT/Ps, BMC is minimally manipulated within the same surgical procedure exemption, and meets criteria of homologous use. We hope that this review is helpful to regulators as they seek to regulate regenerative musculoskeletal medicine.

Disclaimer

These position statements are based on the best available evidence and do not constitute inflexible treatment recommendations. Because of the changing body of evidence, this document is not intended to be a "standard of care." These position statements are meant to provide a basis for the understanding behind the role of BMC in the healing of musculoskeletal disorders, including the spine, to provide a source of appropriate indications for the use of BMC, to facilitate and to help standardize BMC. These statements are also to facilitate the FDA to continue to approve without IND classification for BMC in musculoskeletal and spinal disorders. Finally, these statements are expected to encourage the performance of high-quality studies in an effort to document outcomes, and adverse consequences, to advance BMC applications, and to encourage high-quality training and competency assessment, and the performance of high-quality studies in an effort to document outcomes, adverse consequences to advance BMC applications.

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Author Contributions

The issue of BMC therapy was identified by CJC. LM conceived the idea of the position statement. CJC and LM prepared initial manuscripts with literature search and evidence presentation, developing position statements.

SA, SLA, SS, GAM, AK, and JH reviewed the manuscripts and made significant contributions.

All authors reviewed the manuscripts and contributed to the content. All authors agreed with the contents of the manuscript.

Disclosures

Dr. Abd-Elsayed is a consultant for Medtronic, StimWave, Sollis, and Avanos.

Dr. Buford is a consultant for Conmed Linvatec, Celling Biosciences, Trice Medical, is on the Speakers' Bureau for Orthotalk, Inc., and a board member of Interventional Orthopedic Foundation.

Dr. Calodney is a consultant for Medtronic, SI-Bone, Stryker, Nevro, and APEX Biologix.

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APPENDIX TABLE 1.

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