

Guidelines

Responsible, Safe, and Effective Use of Biologics in the Management of Low Back Pain: American Society of Interventional Pain Physicians (ASIPP) Guidelines

Annu Navani, MD¹, Laxmaiah Manchikanti, MD², Sheri L. Albers, DO³, Richard E. Latchaw, MD⁴, Jaya Sanapati, MD⁵, Alan D. Kaye, MD, PhD⁶, Sairam Atluri, MD⁷, Sheldon Jordan, MD⁸, Ashim Gupta, PhD, MBA⁹, David Cedeno, PhD¹⁰, Alejandro Vallejo, BS¹¹, Bert Fellows, MA¹², Nebojsa Nick Knezevic, MD, PhD¹³, Miguel Pappolla, MD¹⁴, Sudhir Diwan, MD¹⁵, Andrea M. Trescot, MD¹⁶, Amol Soin, MD¹⁷, Adam M. Kaye, PharmD, FASCP, FCPHA¹⁸, Steve M. Aydin, DO¹⁹, Aaron K. Calodney, MD²⁰, Kenneth D. Candido, MD²¹, Sanjay Bakshi, MD²², Ramsin M. Benyamin, MD²³, Ricardo Vallejo, MD, PhD²⁴, Art Watanabe, MD²⁵, Douglas Beall, MD²⁶, Todd P. Stitik, MD²⁷, Patrick M. Foye, MD²⁸, Erik M. Helander, MBBS²⁹, and Joshua A. Hirsch, MD³⁰

From: American Society of Interventional Pain Physicians

Author Affiliations and Disclosures on pp. S61-S62

Address Correspondence:
Laxmaiah Manchikanti, MD
2831 Lone Oak Road
Paducah, Kentucky 42003
E-mail: drlm@thepainmd.com

Manuscript received: 09-15-2018

Revised manuscript received:
10-15-2018

Accepted for publication:
11-19-2018

Free full manuscript:
www.painphysicianjournal.com

Background: Regenerative medicine is a medical subspecialty that seeks to recruit and enhance the body's own inherent healing armamentarium in the treatment of patient pathology. This therapy's intention is to assist in the repair, and to potentially replace or restore damaged tissue through the use of autologous or allogenic biologics. This field is rising like a Phoenix from the ashes of underperforming conventional therapy amidst the hopes and high expectations of patients and medical personnel alike. But, because this is a relatively new area of medicine that has yet to substantiate its outcomes, care must be taken in its public presentation and promises as well as in its use.

Objective: To provide guidance for the responsible, safe, and effective use of biologic therapy in the lumbar spine. To present a template on which to build standardized therapies using biologics. To ground potential administrators of biologics in the knowledge of the current outcome statistics and to stimulate those interested in providing biologic therapy to participate in high quality research that will ultimately promote and further advance this area of medicine.

Methods: The methodology used has included the development of objectives and key questions. A panel of experts from various medical specialties and subspecialties as well as differing regions collaborated in the formation of these guidelines and submitted (if any) their appropriate disclosures of conflicts of interest. Trustworthy standards were employed in the creation of these guidelines. The literature pertaining to regenerative medicine, its effectiveness, and adverse consequences was thoroughly reviewed using a best evidence synthesis of the available literature. The grading for recommendation was provided as described by the Agency for Healthcare Research and Quality (AHRQ).

Summary of Evidence:

Lumbar Disc Injections:

Based on the available evidence regarding the use of platelet-rich plasma (PRP), including one high-quality randomized controlled trial (RCT), multiple moderate-quality observational studies, a single-arm meta-analysis and evidence from a systematic review, the qualitative evidence has been assessed as Level III (on a scale of Level I through V) using a qualitative modified approach to the grading of evidence based on best-evidence synthesis.

Based on the available evidence regarding the use of medicinal signaling/ mesenchymal stem cell (MSCs) with a high-quality RCT, multiple moderate-quality observational studies, a single-arm meta-analysis, and 2 systematic reviews, the qualitative evidence has been assessed as Level III (on a scale of Level I through V) using a qualitative modified approach to the grading of evidence based

on best evidence synthesis.

Lumbar Epidural Injections

Based on one high-quality RCT, multiple relevant moderate-quality observational studies and a single-arm meta-analysis, the qualitative evidence has been assessed as Level IV (on a scale of Level I through V) using a qualitative modified approach to the grading of evidence based on best evidence synthesis.

Lumbar Facet Joint Injections

Based on one high-quality RCT and 2 moderate-quality observational studies, the qualitative evidence for facet joint injections with PRP has been assessed as Level IV (on a scale of Level I through V) using a qualitative modified approach to the grading of evidence based on best evidence synthesis.

Sacroiliac Joint Injection

Based on one high-quality RCT, one moderate-quality observational study, and one low-quality case report, the qualitative evidence has been assessed as Level IV (on a scale of Level I through V) using a qualitative modified approach to the grading of evidence based on best evidence synthesis.

Conclusion: Based on the evidence synthesis summarized above, there is Level III evidence for intradiscal injections of PRP and MSCs, whereas the evidence is considered Level IV for lumbar facet joint, lumbar epidural, and sacroiliac joint injections of PRP, (on a scale of Level I through V) using a qualitative modified approach to the grading of evidence based on best evidence synthesis.

Regenerative therapy should be provided to patients following diagnostic evidence of a need for biologic therapy, following a thorough discussion of the patient's needs and expectations, after properly educating the patient on the use and administration of biologics and in full light of the patient's medical history. Regenerative therapy may be provided independently or in conjunction with other modalities of treatment including a structured exercise program, physical therapy, behavioral therapy, and along with the appropriate conventional medical therapy as necessary. Appropriate precautions should be taken into consideration and followed prior to performing biologic therapy. Multiple guidelines from the Food and Drug Administration (FDA), potential limitations in the use of biologic therapy and the appropriate requirements for compliance with the FDA have been detailed in these guidelines.

Key words: Regenerative medicine, platelet-rich plasma, medicinal signaling cells, mesenchymal stem cells, stromal vascular fraction, bone marrow concentrate, chronic low back pain, discogenic pain, facet joint pain, Food and Drug Administration, minimal manipulation, evidence synthesis

Disclaimer: These guidelines are based on the best available evidence and do not constitute inflexible treatment recommendations. Due to the changing body of evidence, this document is not intended to be a "standard of care." These guidelines are meant to provide a basis for the understanding behind the role of biologics in healing, to provide a source of appropriate indications for the use of biologics, to facilitate and help standardize biologic therapy, and to encourage the performance of high-quality studies in effort to document outcomes and advance this field.

1.0 INTRODUCTION

The field of Regenerative Medicine is expanding exponentially, creating new frontiers for the treatment of musculoskeletal and spinal pathology. Musculoskeletal and spinal complaints are 2 of the major reasons for seeking medical advice. Dieleman et al (1,2) and Conway (3) in an analysis of United States (U.S.) spending on personal health care, public health, and increases of health care costs from 1996 to 2013 showed an estimated spending of \$87.6 billion in managing low back and neck pain, and \$95.9 billion for managing musculoskeletal pain, accounting for the third and fourth highest health care costs among disease categories. Numerous therapeutic techniques have been developed for the management of chronic spinal pain, including over-the-counter medications, complex surgical fusions, and a variety of image-guided interventional techniques (4-9). Despite these advances,

treatment complications, poor outcomes, and persisting disabilities are contributing to the rise in health care costs and human suffering (1-3,10,11).

Among the 30 leading diseases and injuries contributing to years lived with disability in 1990, 2010, and 2016 in the U.S., low back pain and major depression ranked numbers 1 and 2 respectively, with other musculoskeletal disorders ranking number 4 and neck pain ranking number 6.

The management of spinal pain and other musculoskeletal disorders requires the appropriate diagnoses and the use of effective therapeutic modalities, under the auspices of evidence-based medicine, in a cost effective manner. Given the continued zeal for health care reform, including decreased health care costs (1-4, 8,9,12-16), government officials have produced legislation including the Affordable Care Act (ACA), along with a massive number of regulations, with mixed and often devastating results. Consequently, health care providers

have turned to natural and holistic therapies. The success of such therapies in professional athletes has thrust regenerative medicine into the forefront (17).

Regenerative medicine is based on the process of replacing, engineering or regenerating human cells, tissues or organs to restore or establish normal function (17-30). Stimulating the body's inherent repair mechanism and supplementing this process with homologous or autologous biologics when the body cannot heal itself is the foundation of regenerative medicine. Regenerative medicine incorporates biomedical, biochemical, and biomechanical technologies to improve cellular migration, replication, and modelling. Biomedical approaches include the injection of mesenchymal stromal/stem cells (medicinal signaling cells) or progenitor cells called cell therapy, the induction of regeneration by biologically active molecules administered alone or as a complex of infused cells referred to as immunomodulation therapy, and transplantation of in vitro grown organs and tissues that fall under the umbrella of tissue engineering (17,30-32).

Despite its appeal, there are just concerns regarding the ethical use of regenerative medicine. Both the medical literature and the general media have presented regenerative medicine as a "cure-all" for many disease processes, praying upon the hopes of desperate patients, without appropriate evidence reflecting both safety and reliable, consistent efficacy over the long term (17,21,30,32-43). Guidelines are pathways to gain evidence needed to justify the use of regenerative medicine, thereby negating these controversies. Although there are a large number of guidelines used in the management of spinal pain, including those of interventional pain management and surgical intervention, there are no guidelines addressing the use of regenerative medicine for the musculoskeletal system, and specifically for the spine.

The American Society of Interventional Pain Physicians (ASIPP) has been at the forefront of guideline development for the use of both interventional techniques and opioids (8,9). Consequently, these guidelines have been developed to foster the responsible, safe, and effective use of biologics in the musculoskeletal system. These guidelines include an overview of current literature applicable to the use of platelet-rich plasma (PRP) and medicinal signaling/ mesenchymal stem cell (MSC) injections as applied to the lumbar spine, including discs, facet joints, sacroiliac joints, as well as paraspinal muscles, ligaments, and tendons. These guidelines also incorporate various aspects of

the current national and international regulatory and bioethical recommendations. Finally, these guidelines provide an overview of clinical policies and procedures necessary to offer this therapy in a safe and professional environment.

2.0 METHODS

2.1 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 (44). 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 (45).

Chronic spinal pain is a complex and multifactorial disease process, of which low back pain is the most common. The high prevalence of chronic 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. Lumbar intervertebral discs, facet joints, sacroiliac joints, ligaments, fascia, muscles, and nerve root dura are all pain generators of low back and lower extremity pain (8). Interventional pain physicians are familiar with various image-guided interventional techniques for the management of low back and extremity pain, and regenerative medicine techniques are well-suited additions to their armamentarium following appropriate training under the enclosed guidelines.

2.2 Objectives

The objectives of these guidelines are to provide a rational and systematic approach to the application of regenerative medicine techniques based upon the available evidence concerning comparative effectiveness, safety, and avoidance of adverse effects in the treatment of low back and extremity pain

2.2.1 Key Questions

These guidelines focus on the following key questions regarding low back and extremity pain:

1. What is the impact of chronic low back and extremity pain on health care resources?
2. What are the statistics regarding the trends in utilization of treatment modalities?
3. What is the pathophysiologic and structural basis of low back pain?
4. What are the available regenerative medicine therapies?
5. How do regenerative medicine therapies work in the treatment of low back and extremity pain?
6. Are regenerative medicine therapies effective in managing chronic low back pain?
7. What are current guidelines for biologics?
8. What are the adverse consequences/harms of regenerative therapies?
9. What are the best preventive and therapeutic strategies to improve outcomes when performing regenerative therapies?
10. What comprises responsible performance of regenerative injection therapy?

2.3 Adherence to Trustworthy Standards

In preparation of these guidelines for regenerative medicine therapies, the standards from the Institute of Medicine (IOM) and the National Guideline Clearinghouse Extent Adherence to Trustworthy Standards (NEATS) were followed (46-48). The NEATS instrument was developed and tested as a tool to be used by the trained staff at the Agency for Healthcare Research and Quality (AHRQ) National Guideline Clearinghouse to provide assessment focused on adherence.

2.3.1 Disclosure of Guideline Funding Source

Responsible, safe, and effective guidelines for regenerative medicine therapies in managing low back pain were commissioned, prepared, edited, and endorsed by ASIPP without external funding sought or obtained.

2.3.2 Disclosure and Management of Financial Conflicts of Interests

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 experience, practice patterns, academic interests, and promotions. Participants with previously established

conflicts are considered those with opinions not being in line with 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.

2.3.3 Composition of Guideline Development Group

A panel of experts in regenerative medicine from various medical fields, convened by ASIPP, reviewed the evidence and formulated recommendations for regenerative medicine therapies as applied to low back pain. The panel was instructed to assess the evidence pertaining to important aspects of regenerative therapies. However, due to the emerging nature of regenerative medicine techniques in managing low back pain, the number of available participants for guideline preparation was limited compared to other guideline panels (8,9). Even with this limitation, the panel provided a broad representation of academic and non-academic clinical practitioners with interest and expertise in regenerative injection therapies and in the management of patients with chronic low back pain.

2.4 Evidence Review

These guidelines were developed utilizing consensus among the panel members after they had reviewed all published literature concerning the use and safety of regenerative injection therapy in patients with chronic non-cancer low back and lower extremity pain. The recommendations have been developed using principles of best evidence synthesis developed by the Cochrane Review, incorporating multiple guidelines modified by ASIPP (49).

2.4.1 Grading or Rating the Quality or Strength of Evidence

The grading of evidence is based on randomized controlled trials (RCTs), observational studies, and other clinical reports. In addition, systematic reviews and meta-analyses were utilized. The grading of evidence based on ASIPP guidelines is shown in Table 1.

This grading system specifies levels of scientific evidence and offers an approach to grading the quality of evidence and secondarily the strength of recommendations. AHRQ has recommended a similar approach to the strength of a recommendation (47,48).

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.

Modified from: Manchikanti et al. A modified approach to grading of evidence. *Pain Physician* 2014; 17:E319-E325 (49).

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 (47).

2.4.2 Assessment and Recommendations of Benefits and Harms

These guidelines clearly describe the potential benefits and harms for the interventions and explicitly link the information to specific recommendations.

2.4.3 Evidence Summary of Recommendations

Guideline-supporting documents summarize the relevant supporting evidence and link this information to the recommendations.

2.4.4 Rating or Grading the Strength of Recommendations

IOM standards demand that for each recommendation, a rating of the strength of the recommendation related to benefits and harms, available evidence, and the confidence in the underlying evidence should be provided. To meet appropriate standards, the rating schemes recommended by NEATS were utilized as shown in Table 2 (47).

2.4.5 Specificity of Recommendations

Guideline recommendations are specific and un-

ambiguous, providing guidance on what regenerative therapies should be utilized on a given disease process, and under what, if any, restrictions.

2.5 External Review

Guidelines have been subjected to external peer review as per the policies of the publishing journal, *Pain Physician*.

2.6 Updating Guidelines

The regenerative injection therapy guidelines will be updated within 5 years or less, based on significant changes in the scientific evidence, public policy, or adverse events occurring before January 2024.

3.0 IMPACT OF LOW BACK PAIN ON HEALTH CARE

Key Question 1. What is the impact of chronic low back and extremity pain on health care resources?

As illustrated in multiple worldwide reports, the impact of chronic pain is enormous (1-3,8-11,50-64). The annual U.S. expenditures alone (including direct medical costs and lost wages) may be higher than those

for cancer, heart disease, and diabetes combined. Even with these high expenditures, the treatments are marginally effective. The IOM report of 2011 concludes that the epidemic of chronic pain demands public health approaches with public education to counter myths, stereotypes, and stigma that hinder better care (50).

Figure 1 shows back pain to be more common than

neck pain or osteoarthritis of the knee relative to years lived with disability. Figures 2 and 3 show expenditures related to back and neck pain relative to other conditions. (10)

Chronic pain is defined by the International Association for the Study of Pain (IASP) as “pain that exists beyond an expected time frame for healing” (65).

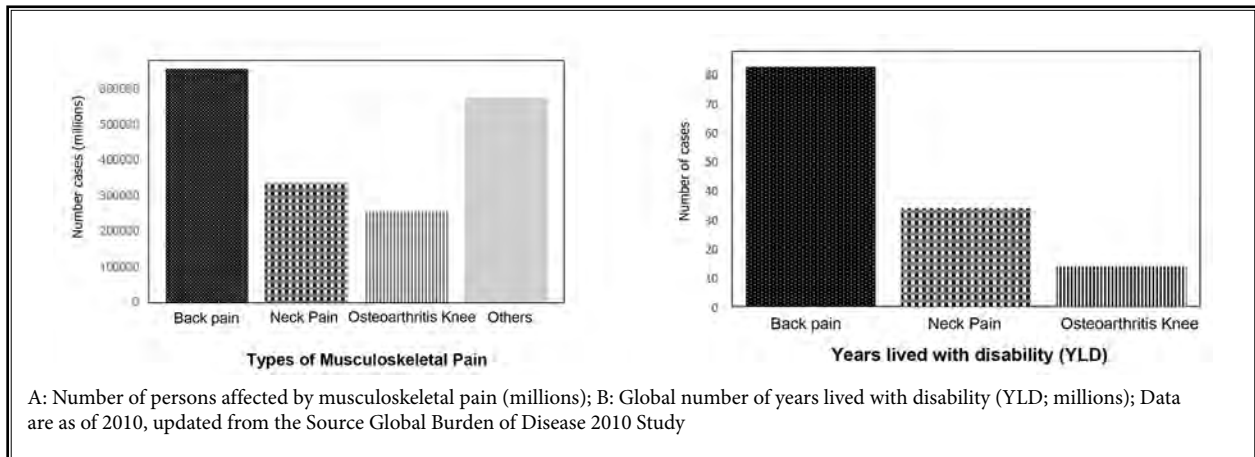


Fig. 1. Prevalence of musculoskeletal pain and years lived with disability (YLD).

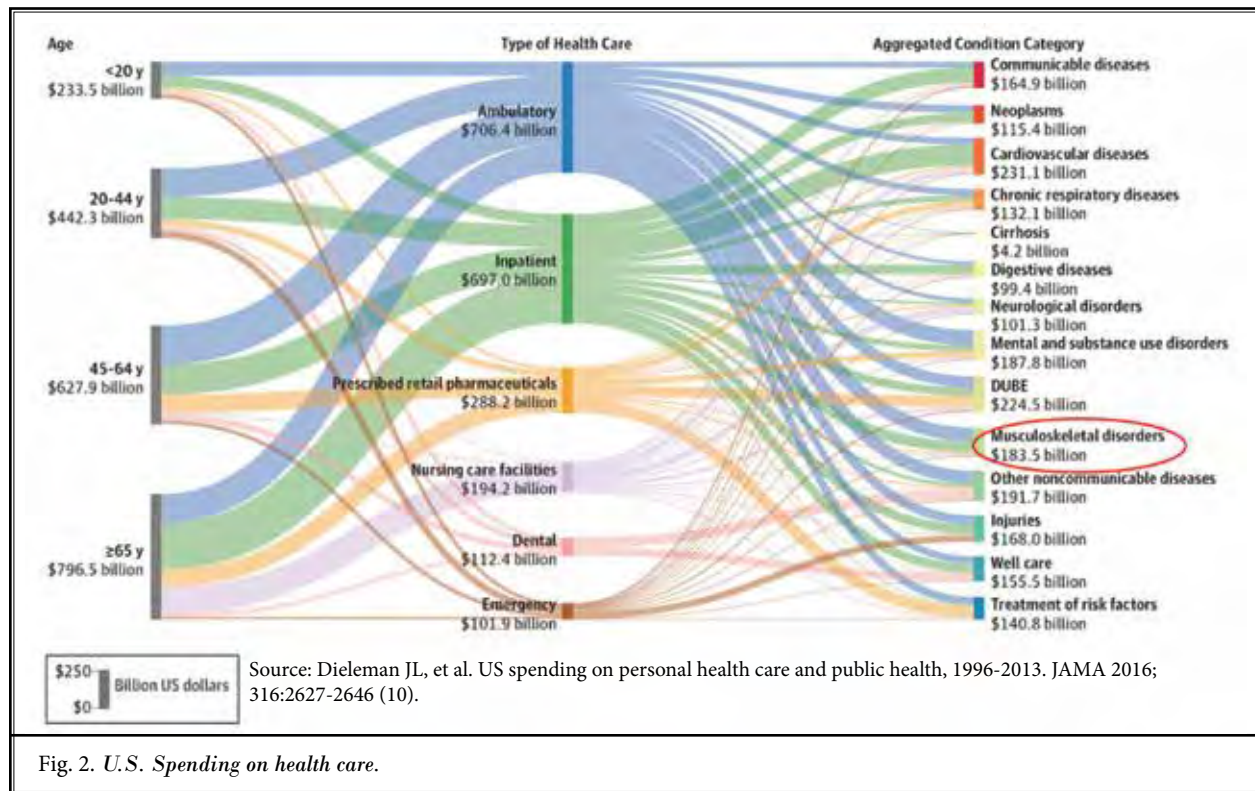
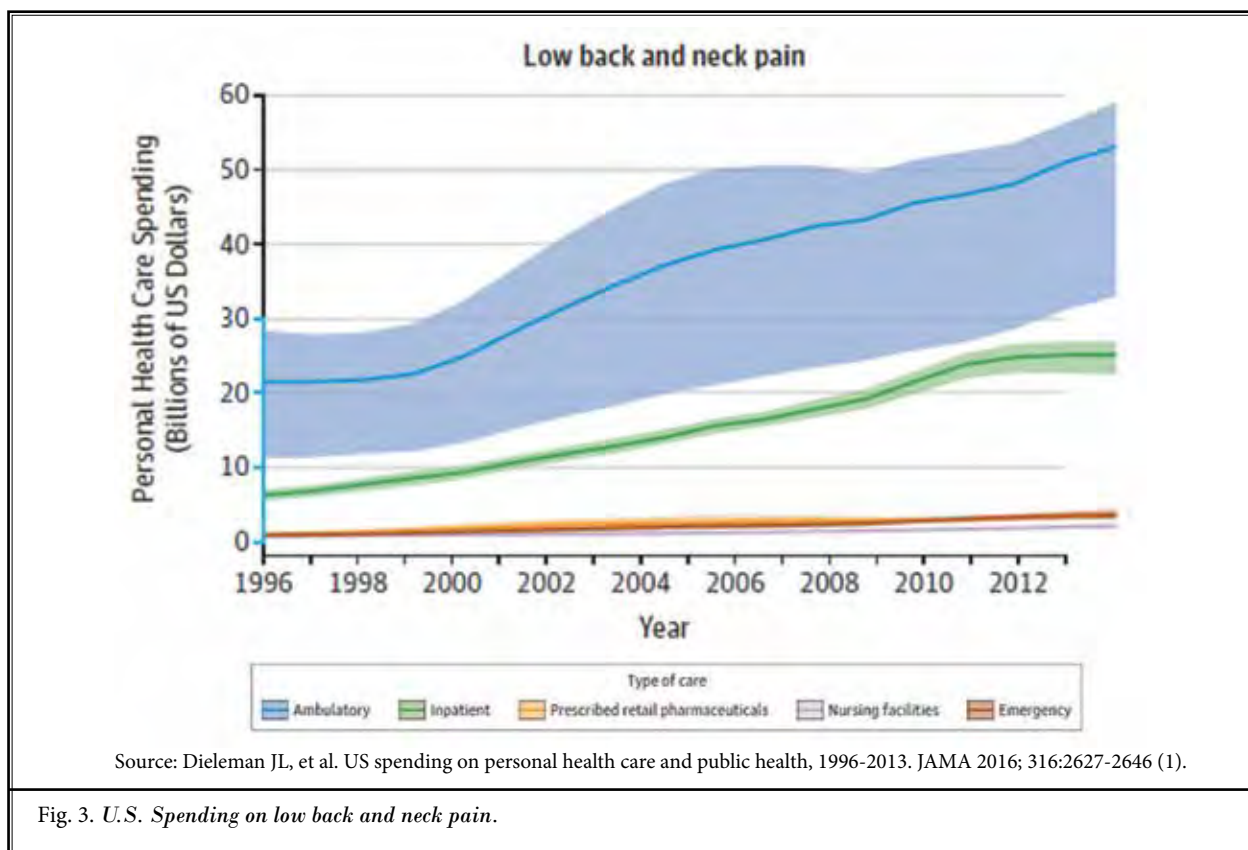


Fig. 2. U.S. Spending on health care.



However, others have defined chronic pain in more descriptive and functional terms. ASIPP has defined chronic pain as “pain that persists 6 months after an injury and beyond the usual course of an acute disease or a reasonable time for a comparable injury to heal, that is associated with chronic pathologic processes that cause continuous or intermittent pain for months or years, that may continue in the presence or absence of demonstrable pathologies; may not be amenable to routine pain control methods; and healing may never occur” (8).

A recent study of the state of the U.S. health between 1990 and 2010 describing the burden of diseases, injuries, and risk factors (10) showed that, with increasing life expectancy, morbidity, and chronic disability now account for nearly half of the U.S. health burden, despite substantial progress and improvement in health. The estimates of regional spine pain vary, with the highest prevalence in the low back of 43%, followed by the neck at 32%, with the lowest in the thoracic spine (63). Among the 30 leading diseases and injuries contributing to years lived with disability in the

U.S. between 1990 and 2010, low back pain, other musculoskeletal disorders, and neck pain ranked numbers 1, 3, and 4 respectively, while major depression and anxiety disorders ranked numbers 2 and 5 respectively (10). More recent analysis of the state of U.S. health from 1990 to 2016 (11) showed similar results with low back pain, other musculoskeletal disorders, and neck pain ranked numbers 1, 4, and 6, respectively. Major depressive disorders, migraine, and anxiety disorders ranked numbers 2, 5, and 7, respectively. In addition, this analysis also showed opioid disorders changed from number 7 between 1990 and 2010 to number 8 between 1990 and 2016. These results were echoed in multiple other manuscripts (56,57). Consequently, the top 5 conditions are consistently primary sources of or significantly related to chronic pain. Studies on the global burden of disability have determined the point prevalence of low back pain as 9.4%, with 17% of these individuals suffering from severe chronic low back pain while 25% of them suffer from severe chronic low back pain accompanied with leg pain (57). Chronic persistent spinal pain is reported to last at least one year in 25%

to 60% of patients, and even longer than one year in many patients. These findings contradict the usual belief that pain is always of limited duration (8,55,66). In fact, a recent study of long-term outcomes in a large, prospective observational cohort of older adults with back pain showed that over 80% of the individuals reported back pain or back pain-related disability at 2 years following their initial visits (66). This study also showed that these patients experienced 30% to 50% improvement in back pain and disability, respectively, 2 years after their initial visits. However, only 16% had complete resolution of their back pain and disability at 2 years despite multiple spinal interventions.

4.0 PREVALENCE OF USAGE OF HEALTH CARE MODALITIES IN MANAGING LOW BACK PAIN

Key Question 2. What are the statistics regarding the trends in utilization of treatment modalities?

Exploding health care costs are major U.S. and world issues which have led to the implementation of various health care reform measures, regulations, and to the imposition of guidelines which have often been based on public policy priorities to reduce health care costs. These governmental actions have often resulted from feigned evidence-based medicine and comparative effectiveness research muddled with conflicts and controversies (1-15). Dieleman et al (1) showed an estimated spending of \$87.6 billion in managing low back and neck pain, accounting for the third highest amount in their study. Martin et al (53) also demonstrated expenditures of \$86 billion in costs for managing back and neck problems. There has been escalating growth of various modalities for the treatment of musculoskeletal/spinal pain, including physical therapy, drug therapy, interventional techniques, and surgical interventions (1-12,55,66-94).

While the utilization of interventional techniques and surgical interventions are the focus of current debate, other conservative modalities have also been utilized extensively. Unfortunately, despite diagnostic and therapeutic advances, the prevalence of low back pain, secondary disability, and their adverse economic impact, continue to escalate.

4.1 Surgery

National trends in surgical interventions have been well described (5-7,67,69-72,83-85). Best et al (67) assessed the national surgical trends for intervertebral disc disorders and spinal stenosis between 1994 and 2006.

The number of procedures increased from 6.1 to 34.2 for intervertebral disc disorders, and from 0.38 to 3.46 for spinal stenosis per 100,000 population. Yoshihara et al (85) in an assessment of national surgical trends for lumbar degenerative disc disease in the U.S. from 2000 to 2009 showed a 2.4-fold population-adjusted increase. Bae et al (6) showed that from 2004 to 2009 there was an increase of spinal fusions for lumbar spinal stenosis from 21.5% to 31.2%, even though the rate of decompressions decreased from 58.5% to 49.2%.

Reoperation rates for disc herniation and spinal stenosis have been shown to vary from 10 to 23% (70). Overall, 40% of postoperative develop post-surgery syndrome or failed back surgery syndrome, requiring further treatment. Unfortunately, the numbers of pre- and post-operative patients with disabilities requiring surgical interventions including complex fusions, those patients being treated for failed back surgery syndrome, and patients with refractory chronic low back pain continue to increase (8,9,76,86-93,95-99).

4.2 Interventional Techniques

The use of interventional techniques for the treatment of spinal pain and musculoskeletal disorders continued to increase with recent declines (4,8,19,87-89). There was a minimal increase in transforaminal epidural injections and a significant increase in radiofrequency neurotomy as shown in Figs. 4 to 6 from 2009 to 2016 (4,89,90). Despite these increases, there has been a significant reduction in epidural injections and lumbar facet joint nerve blocks. In addition to the modest declines in epidural and lumbar facet joint injections, there have been extensive declines in adhesiolysis, as shown in Fig. 7 from 2009 to 2016 (86).

A recent analysis of the utilization of interventional techniques for managing chronic pain in the Medicare population after the institution of the ACA showed a decrease (4,90-93). The analysis of the fee-for-service (FFS) Medicare data from 2000 to 2009 demonstrated an increase of 11.8% per year per 100,000 population, whereas the data between 2009 and 2016 showed an overall decrease in utilization of interventional techniques by 0.6% per year.

The utilization of interventional techniques have been criticized for their lack of evidence-based medicine (95-100). However, there have been a multitude of studies based upon randomized controlled trials (RCTs) and evidence synthesis demonstrating significant effectiveness of interventional techniques when appropriately performed (8,97,101-121). Further, apart from

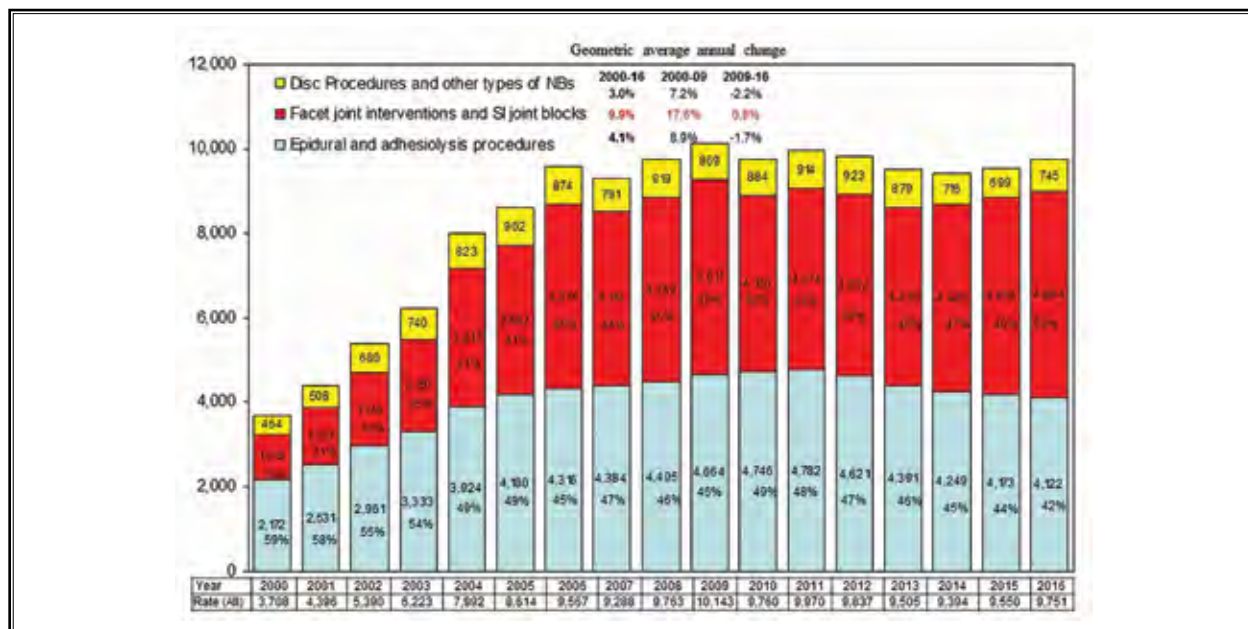


Fig. 4. Distribution of procedural characteristics (rates) by type of procedures from 2000 to 2016 (4).

their clinical effectiveness, the cost effectiveness of multiple interventional techniques has been demonstrated (122-127).

4.3 Opioid Usage

Opioids have been used extensively for the treatment of chronic pain, in addition to numerous other drugs, including nonsteroidal anti-inflammatory agents (NSAIDs) and anti-epileptic drugs (9,128). Opioid misuse increased approximately 4,700% from 1996 to 2011 (128). In a prospective evaluation of psychotherapeutic and illicit drugs used by patients presenting with chronic pain at the time of their initial evaluation, Manchikanti et al (129) showed that 94% of the patients were on long-term opioids, with 30% of these patients taking a combination of opioids and benzodiazepines. A significant proportion of these patients were on high dose opioids. Manchikanti et al (9) calculated

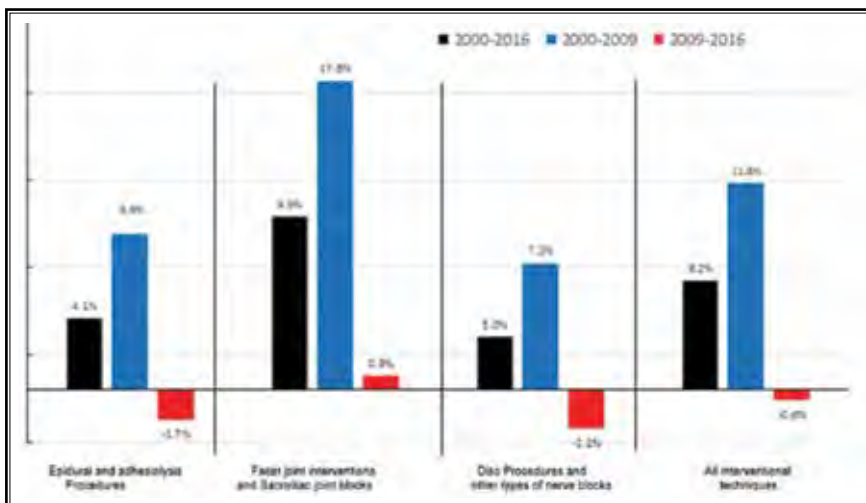


Fig 5. Comparative analysis of epidural and adhesiolysis procedures, facet joint interventions and sacroiliac joint blocks, disc procedures and other types of nerve blocks, and all interventional techniques (4).

global opioid consumption in kg from 2000 to 2014, showing a total increase of 210% from 69,092 kg in 2000 to 214,490 kg in 2014. They also showed that opioid consumption in the U.S. increased from 46,946 kg in 2000 to 148,316 kg in 2014, representing an increase of 178.4%. Proportionate use of opioids in the U.S. compared to global consumption ranged from 67.9% to 75%, with the U.S. population under 4.8% of the world's population. The data also showed that the majority of the opioid prescriptions were coming from non-pain management professionals (9). There is extensive literature available on the growing epidemic of the medical

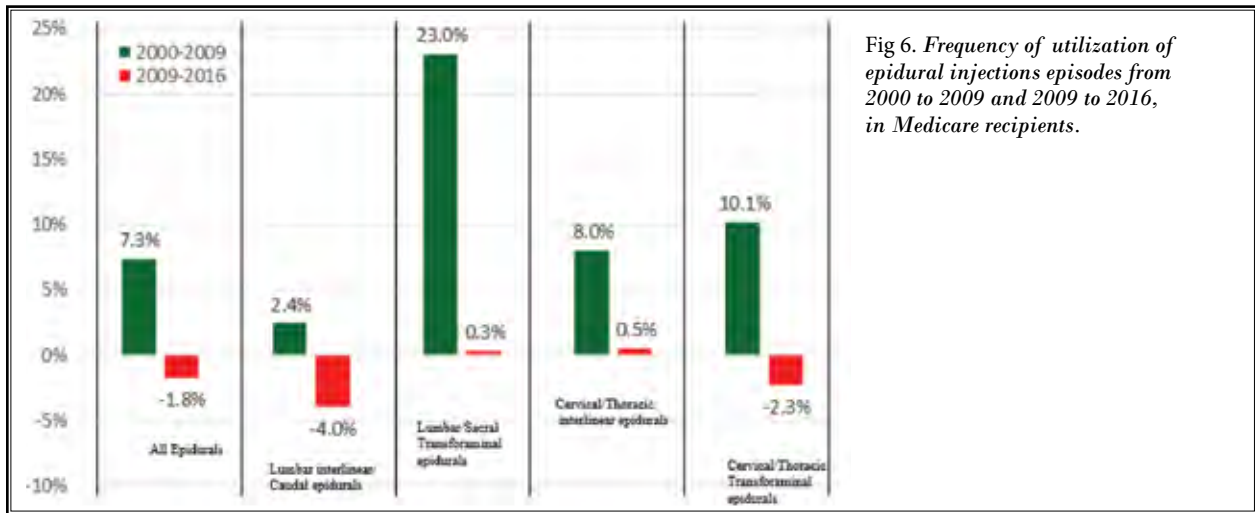


Fig 6. Frequency of utilization of epidural injections episodes from 2000 to 2009 and 2009 to 2016, in Medicare recipients.

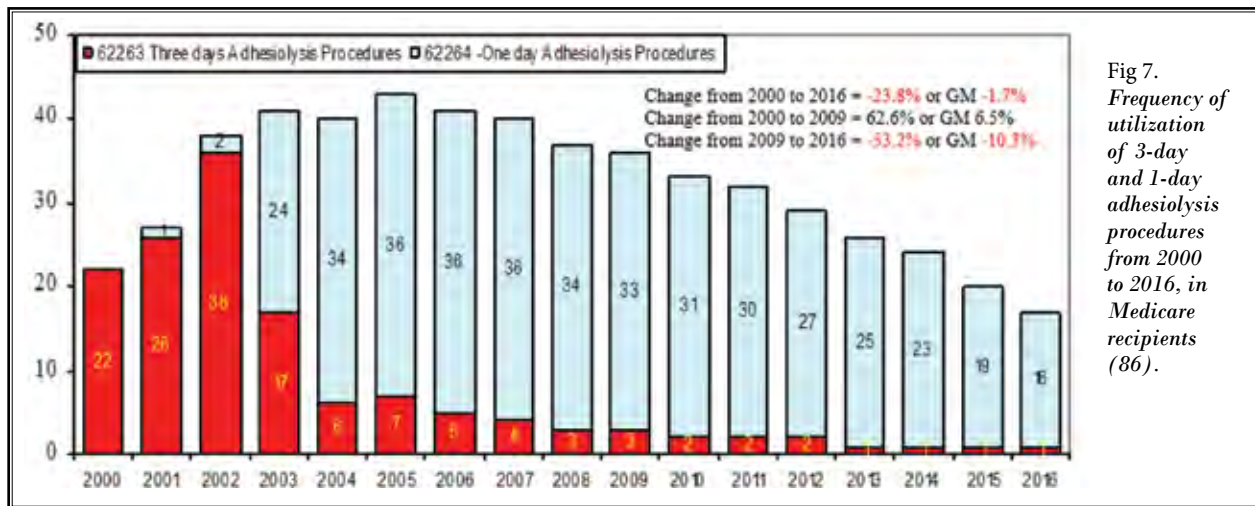


Fig 7. Frequency of utilization of 3-day and 1-day adhesion lysis procedures from 2000 to 2016, in Medicare recipients (86).

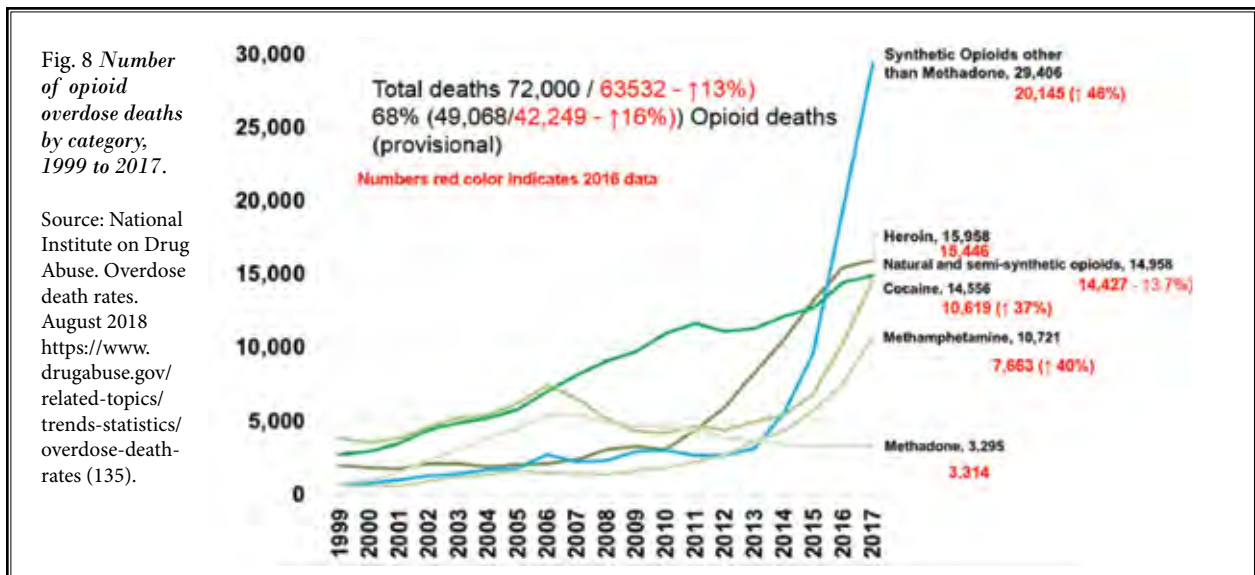


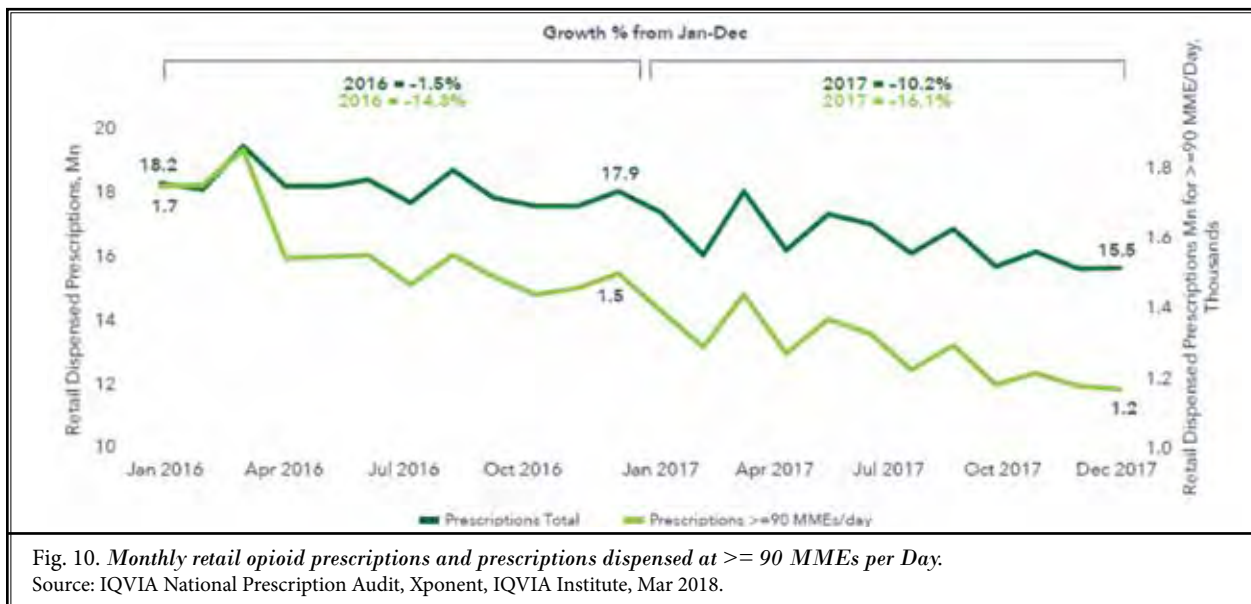
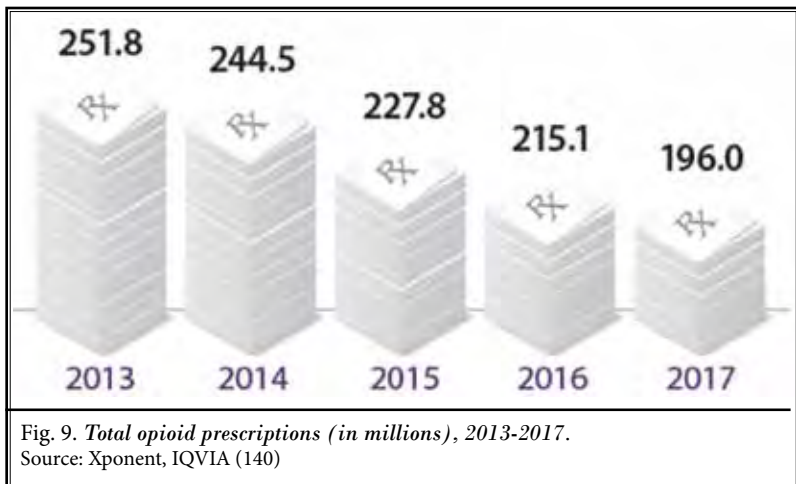
Fig. 8 Number of opioid overdose deaths by category, 1999 to 2017.

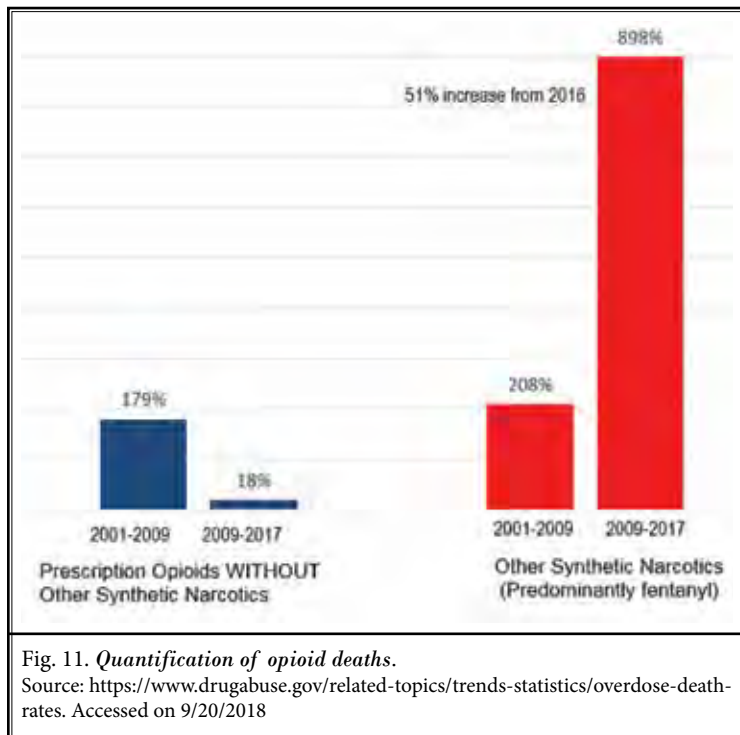
Source: National Institute on Drug Abuse. Overdose death rates. August 2018 <https://www.drugabuse.gov/related-topics/trends-statistics/overdose-death-rates> (135).

use and abuse of opioid analgesics and other controlled substances, which is closely associated with an economic burden and increased fatalities in the U.S. and many developed countries (9). Data shows that in 2016, more than 11 million Americans misused prescription opioids. Overdose deaths continue to be a major concern for the U.S., accounting for over 64,000 deaths in 2016 (9,130,131), increasing to 72,000 deaths in 2017, of which 49,068 were due to licit and illicit opioids (130-135).

Synthetic opioids other than methadone were responsible for 29,406 deaths, heroin for 15,958 deaths, natural and semi-synthetic opioids or prescription opioids for 14,958 deaths, cocaine for 14,556 deaths, methamphetamine for 10,721 deaths, and methadone for 3,295 deaths as shown in Fig. 8 (130-135). However, the evidence demonstrates that illicit fentanyl contributed to almost 60% of the deaths, whereas overall prescription opioid deaths without fentanyl or heroin, but including other illicit drugs, may have contributed to less than 8,000 deaths in 2017.

The Drug Enforcement Administration's (DEA) mandated reduction in the production of opioids of 25% in 2017 and 20% in 2018 and other measures showed a decline in total prescriptions and overall dosages, from a high of 252 million opioid prescriptions in 2013 to 196 million in 2017, as shown in Fig. 9 (133-140). In fact, a decreasing rate of prescriptions of over 9% annually from 2013 to 2017 was evident. In addition, data from 2017 showed that 23.3 billion fewer morphine milligram equivalents (MME) were dispensed to patients on a volume basis, with dispensed prescriptions decreasing 12.2%, while patients receiving high doses (greater than 90 MMEs per day) declined by 16.1% (140). Despite the decrease in opioid prescriptions, the opioid abuse and death rates are not decreasing (Fig. 10) (140) because of the availability of illicit narcotics.





The opioid epidemic is taking a great toll on the health and economy of the U.S. and the rest of the world. In an analysis of deaths and years of life lost with percentage change of the 25 leading causes of death in the U.S., from 1990 to 2016, opioid use disorders ranked number 52 in 1990, moving up to number 15 in 2010, and remaining at 15th in 2016 (10,11). In contrast, years lived with disability for the 25 leading causes of disability and injury, opioid use disorders ranked number 7 in 1990 and 2010, but moved to 8th in 2016, showing very little improvement over the years (10,11).

Deaths caused by illicit/synthetic fentanyl and heroin have been counted as prescription opioid deaths due to the inability to separate fentanyl formulations and the metabolites of heroin, as shown in Fig. 11 (135,139). Overall, deaths from synthetic narcotics, primarily fentanyl, increased 898% from 2009 to 2017 (130-135,139). Deaths attributed to illicitly manufactured fentanyl doubled from 10,000 to over 20,000 between 2015 and 2016 (132). The quantification of prescription and synthetic opioid deaths yields startling results as demonstrated in Fig. 11. Prescription opioid deaths increased 18% between 2009 and 2016, compared to the marked increase of 179% from 2001 to 2009 (139). Thus, beginning in 2009, the public-at-large and both governmental and medical authorities appropriately focused on the obvious opioid epidemic. Despite the reduction in prescription opioid deaths as of 2016, the problem persists. Consequently, the appropriate management of painful conditions using long-term

treatment alternatives to narcotics is essential for their management to increase the quality of life. Governmental and medical authorities continue to work on the enormous problem of illicit narcotics.

4.4 Cost Utility

Health care costs and utilization continue to escalate, despite minor reductions since 2009 following the enactment of the ACA (12-16). Clinical and cost effectiveness have become cornerstones in health care policies dealing with all forms of medical interventions (122-127,141-150). Two well-publicized studies of the cost effectiveness of surgical as opposed to nonoperative treatment for lumbar disc herniation and spinal stenosis with and without degenerative spondylolisthesis showed \$69,403 gained per quality-adjusted life year (QALY) in the surgical management of lumbar disc herniation, \$77,600 for spinal stenosis without degenerative spondylolisthesis, and \$115,600 for spinal stenosis with degenerative spondylolisthesis (143,144). Taylor et al (123) showed the cost effectiveness of spinal cord stimulation versus surgery and other interventions at £5,624 (\$7,058 USD) per QALY. Cost utility analysis was performed for interventional techniques compared to alternative treatments utilizing RCTs by Manchikanti et al (124-127), showing the cost utility of caudal epidural injections at \$3,628, percutaneous adhesiolysis at \$4,426, lumbar interlaminar epidural injections at \$3,301 (126,127), therapeutic lumbar facet joint nerve blocks at \$4,432 (124), and therapeutic cervical facet joint nerve blocks at \$4,261 (125). Multiple therapies including an exercise program, education using cognitive and behavioral therapy (CBT), and physical therapy were shown to be associated with significantly higher costs than interventional techniques (146-150). A combination of an exercise program and CBT education were found to be superior to education alone in patients with low back pain for more than 3 months, resulting in a QALY of \$8,650 (148). Fritz et al (149) performed a cost effectiveness study of primary care management for

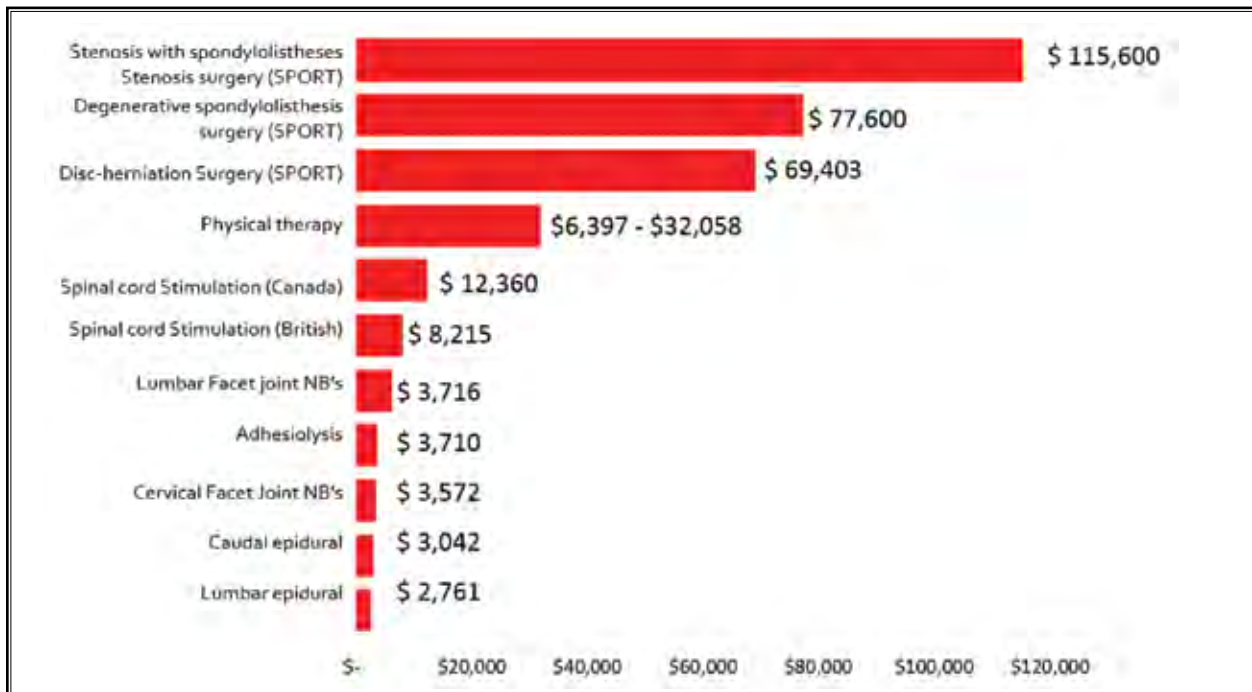


Fig. 12. Cost effectiveness per quality-adjusted life year (QALY)

acute low back pain, showing that early physical therapy resulted in a better quality of life with an incremental cost effectiveness ratio of \$32,058 per QALY. Kepler et al (146) performed a systematic review of various interventional modalities used in spine treatment showing that only 45% of the 33 analyzed studies had a cost less than \$100,000 per QALY, whereas around 23% had costs greater than \$100,000 per QALY. Indrakanti et al (147) showed that nonoperative treatments demonstrated greater value than surgery. Figure 12 shows comparative cost utility analysis of various modalities of treatments in managing chronic pain.

5.0 PATHOPHYSIOLOGIC AND STRUCTURAL BASIS OF LOW BACK PAIN

Key Question 3: What is the pathophysiologic and structural basis of low back pain?

Low back pain is the most common of all spinal and even chronic pain problems. Based on the available evidence, lumbar intervertebral discs, facet joints, sacroiliac joints, ligaments, fascia, muscles, the nerve root and its dorsal ganglion, and the dural sleeve have been shown to be capable of transmitting pain in the lumbar spine with resulting symptoms of low back pain and lower extremity pain (101,103-105,112,151-154).

5.1 Disc Related Pathology

Chronic persistent low back and radicular pain may be secondary to disc degeneration, disc herniation, spinal stenosis, or the post lumbar surgery syndrome resulting in disc-related pain with or without radiculopathy (8,18,112). Discogenic pain with or without disc herniation has been described since 1934 (112,151-157). Lumbar disc disorders may present as internal disc disruption (degeneration with an intact annulus fibrosus), nuclear herniation (protrusion, extrusion, or free fragment) via an annular fissure, or simply discogenic pain (leakage of disc fluid through an annular fissure). The prevalence of symptomatic herniated lumbar disc is about 1% to 5%, and the prevalence of lumbar radiculopathy or sciatica is 9.8 per 1,000 cases (1%) (112,156,158). While lumbar radiculopathy secondary to disc herniation resolves spontaneously in 23% to 48% of the patients, 30% to 70% will still have pronounced symptoms after one year, with 5% to 15% of patients undergoing surgery (145,159). The intervertebral disc has been described as a source of low back and lower extremity pain based on decades of pre-clinical, clinical, and epidemiological research, though the precise mechanisms still continue to be debated (8,18,112,151,154,160-164). Controlled evaluations of patients with proven lumbar disc disease

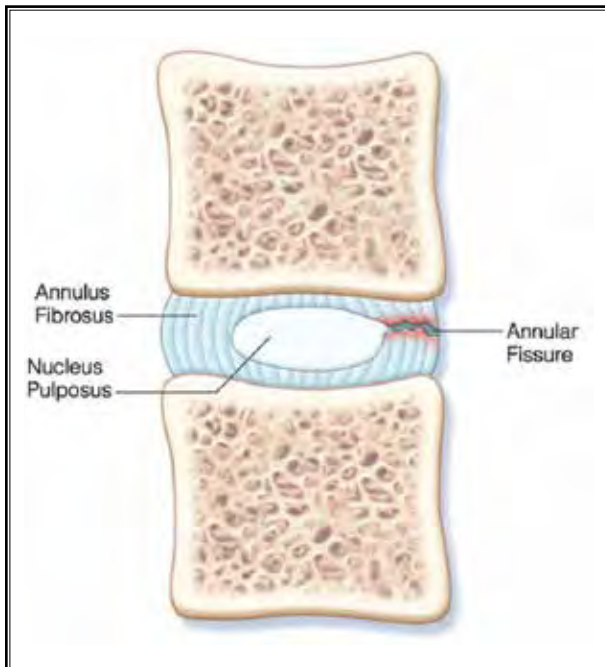


Fig. 13. Schematic sagittal anatomic section showing annular fissure.

Source: Manchikanti L, Albers SL, Hirsh JA, Boswell, MV. Lumbar Disk Herniation. In: Kaye AD, ed. Scientific American Pain Management. Hamilton: Decker; September 2017. DOI: 10.2310/7900.15047. www.DeckerIP.com (156)

showed a prevalence of internal disc disruption in 39% of a cohort of young patients following injury (164), and 42% in a heterogenous population comprised of all age groups and types of low back pain (165).

Disc pathology begins with nuclear and/or inner annular degeneration, potentially followed by annular disruption, which may permit nuclear herniation. Ongoing degeneration can lead not only to disc herniation, but can also contribute to central canal and foraminal stenoses, segmental instability, and degenerative scoliosis. The initial pathology in disc degeneration is the decrease in water content of the nucleus, followed by fissuring of the inner annulus, which allows the disc to bulge. The resulting changes in disc morphology lead to altered spinal biomechanics and also irritation of nerve roots by chemical irritation via an outer annular fissure near a nerve root, displacement or direct compression by disc material, or vascular compromise with canal or vascular stenoses. Discogenic pain may occur without internal disc disruption, such as by chemical leakage through an outer annular fissure, irritating the annulus, epidural soft tissues, and dura (8,18,151,154,160-165). Disc degeneration and herniation alter the disc integrity and predisposes the disc to additional pathology over time (156). Figures 13-15 show the pathophysiology of discogenic pain with disc herniation. Figure 16 shows a normal lumbar disc, whereas Fig. 17 shows disc bulging

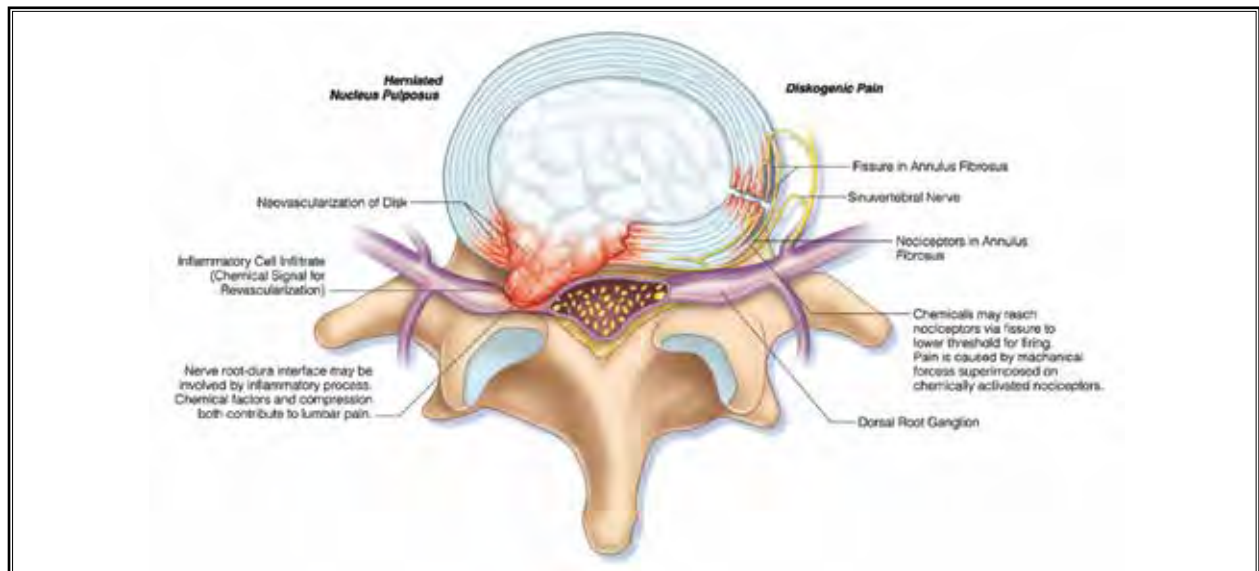


Fig. 14. Pathophysiology of disk-related pain.

Source: Manchikanti L, Albers SL, Hirsh JA, Boswell, MV. Lumbar Disk Herniation. In: Kaye AD, ed. Scientific American Pain Management. Hamilton: Decker; September 2017. DOI: 10.2310/7900.15047. www.DeckerIP.com (156)

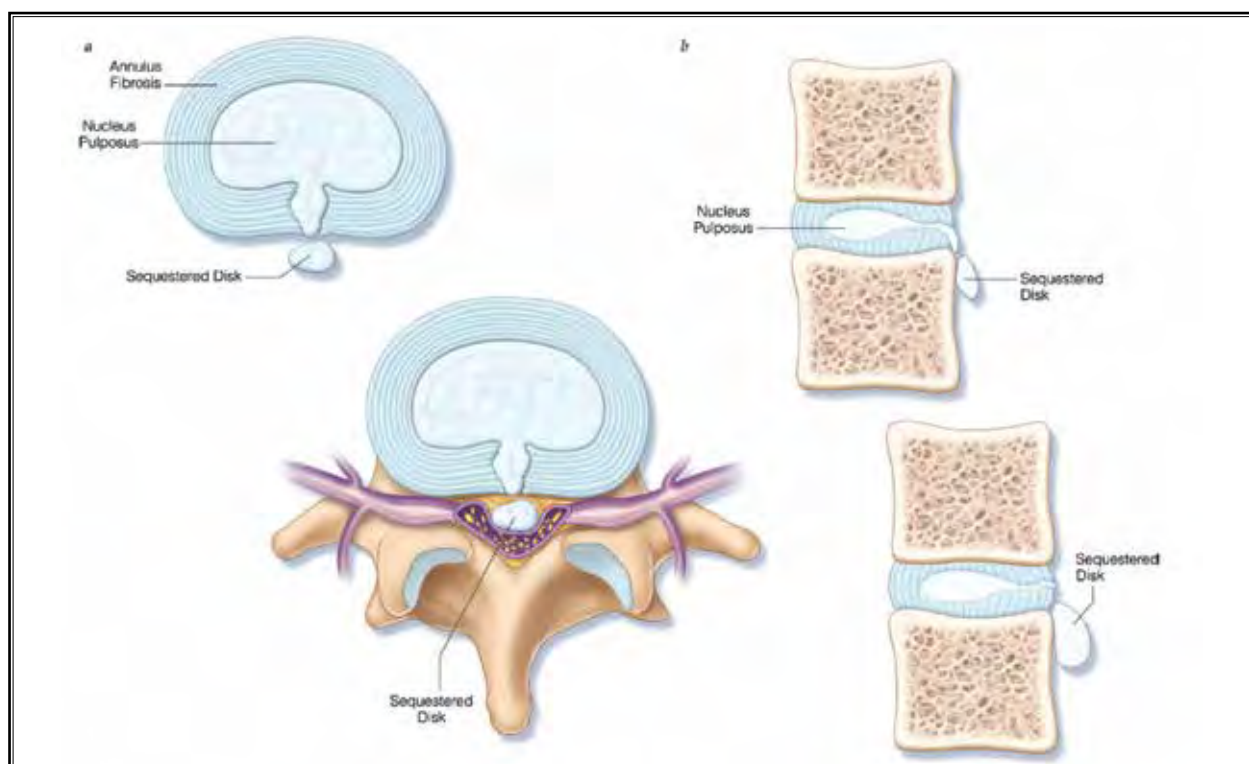


Fig. 15. Schematic illustration of disk sequestration. (a) Axial and (b) sagittal views.

Source: Manchikanti L, Albers SL, Hirsh JA, Boswell, MV. Lumbar Disk Herniation. In: Kaye AD, ed. Scientific American Pain Management. Hamilton: Decker; September 2017. DOI: 10.2310/7900.15047. www.DeckerIP.com (156)

and mild protrusion. Figure 18 shows a disc extrusion. Figure 19 shows chronic endplate changes (Modic Type I) and moderate central spinal canal stenosis.

5.2 Spinal Stenosis

Spinal stenosis is defined as narrowing of the spinal canal, resulting in symptoms and signs caused by entrapment and compression of the intraspinal neural and vascular structures. Varying degrees of stenosis have been shown to be present in 27.2% of the elderly population (166-168).

Congenital or acquired spinal stenosis may be central, foraminal, or a combination of both. Disc bulging, protrusion, and extrusion combined with osteophytes and arthritic changes of the facet joints and hypertrophy of the ligamenta flava can cause narrowing of the spinal canal and encroachment and/or compression on the contents of the dural sac. Foraminal stenosis is largely secondary to degenerative facet disease, with the possible addition of a significant disc component, producing compression or distortion of the exiting

nerve root. Symptoms of central spinal stenosis is secondary to direct compression of the cauda equina, altered arterial flow to the cauda equina, venous congestion producing increased epidural pressure, and nerve root excitation by local inflammation (8,166-168). Because spinal stenosis is a multifactorial disorder, the clinical presentation can be variable, ranging from focal radiculopathy to neurogenic claudication manifested by pain in the buttocks or legs when walking which disappears with sitting or lumbar flexion. Foraminal stenosis presents with radicular pain. A combination of central and foraminal stenoses generally presents with neurogenic claudication as well as radicular pain. In addition to congenital and acquired stenoses, acute trauma may also produce central and/or foraminal stenoses secondary to retropulsion of the vertebral body middle column into the spinal canal, with or without a significant epidural hematoma, along with distortion of the neural foramina.

Anterolisthesis of one vertebral body on another can be secondary to degenerative facet disease or, less

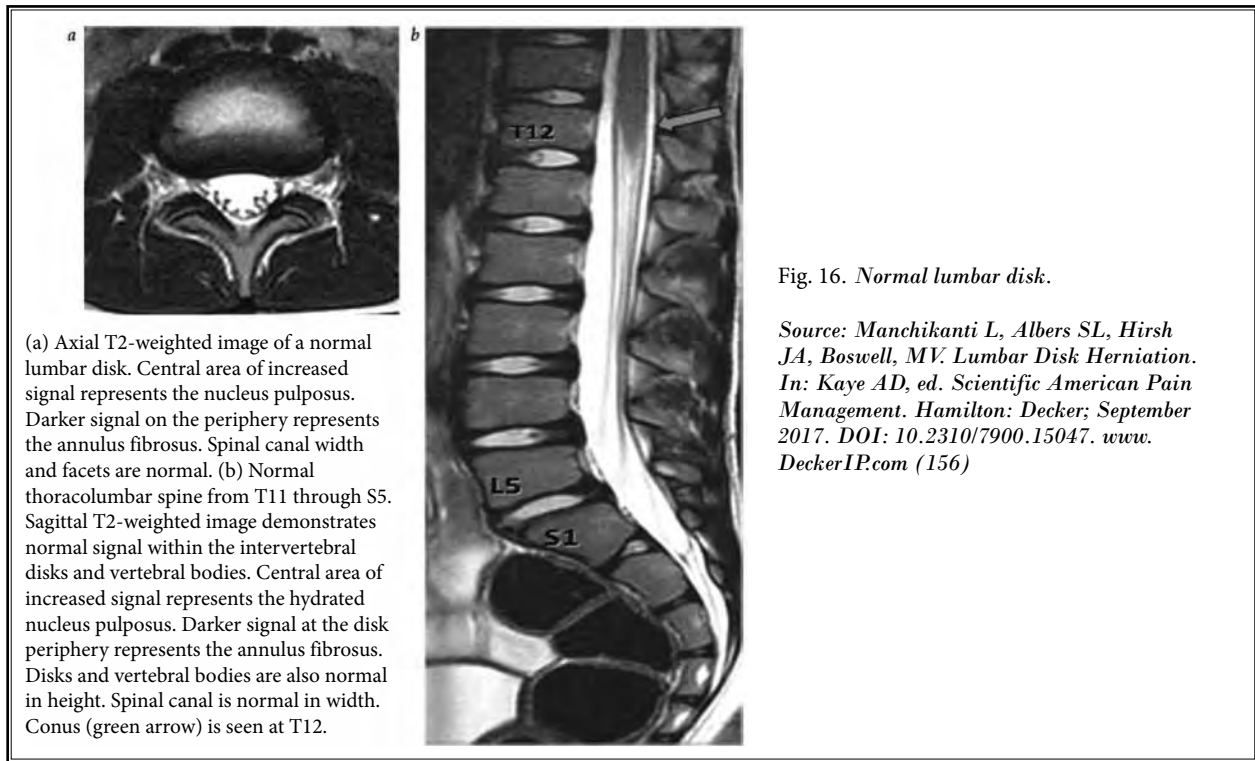
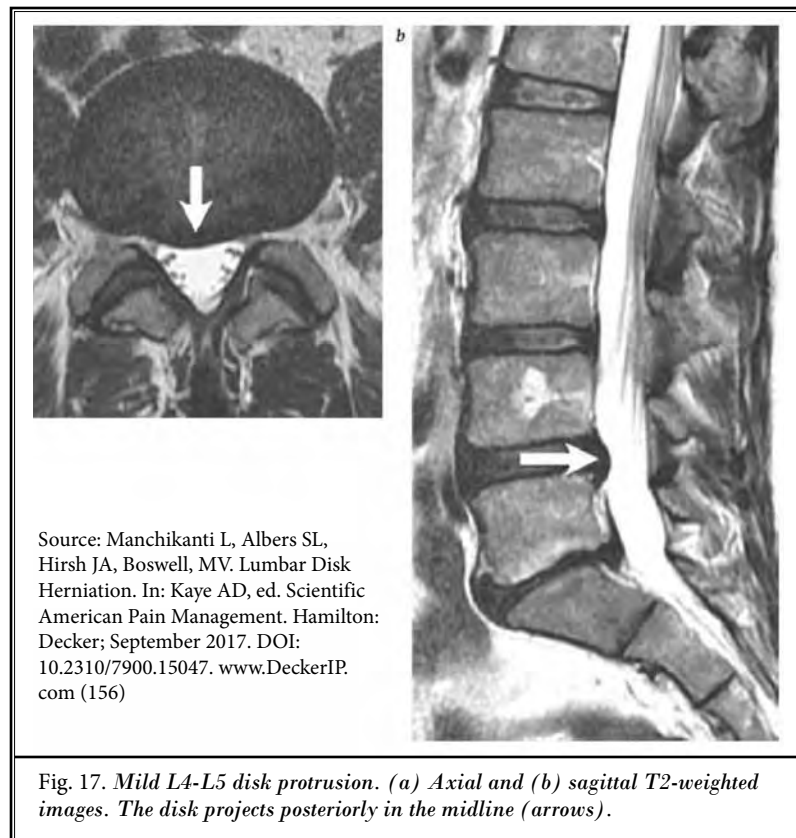


Fig. 16. Normal lumbar disk.

Source: Manchikanti L, Albers SL, Hirsh JA, Boswell, MV. Lumbar Disk Herniation. In: Kaye AD, ed. *Scientific American Pain Management*. Hamilton: Decker; September 2017. DOI: 10.2310/7900.15047. www.DeckerIP.com (156)



commonly, a defect in the pars interarticularis (spondylolysis), and can be an important component of both central and foraminal stenoses. It is vital to recognize increased slippage (instability when moving from a supine to a standing position or occurring with flexion), since this will influence treatment options.

Figure 20 shows a schematic illustration of spinal stenosis, whereas Figs. 21 to 23 show a radiographic presentation of lumbar spinal stenosis.

5.3 Post Surgery Syndrome

Low back and lower extremity pain occurs following lumbar spine surgery in a large proportion of cases, estimated to be as high as 40% (8,76). The incidence of the failed back surgery syndrome may be as high as 80,000 cases per year (76). Based on increasing surgical interventions, this number may be much higher. Even though post lumbar laminectomy syndrome

Fig. 18. Disk extrusion with recent inferior migration and right L4 root posterior displacement.



(a) The axial view demonstrates a component extending into the right lateral recess at the disk space level, posteriorly displacing the right L4 nerve root (white arrow). (b) Sagittal view. Part of this extrusion has an increased signal most consistent with a higher water content (black arrow), indicating its recent herniation.



Source: Manchikanti L, Albers SL, Hirsh JA, Boswell, MV. Lumbar Disk Herniation. In: Kaye AD, ed. Scientific American Pain Management. Hamilton: Decker; September 2017. DOI: 10.2310/7900.15047. www.DeckerIP.com (156)

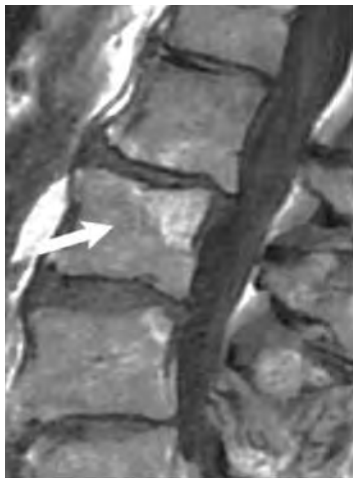
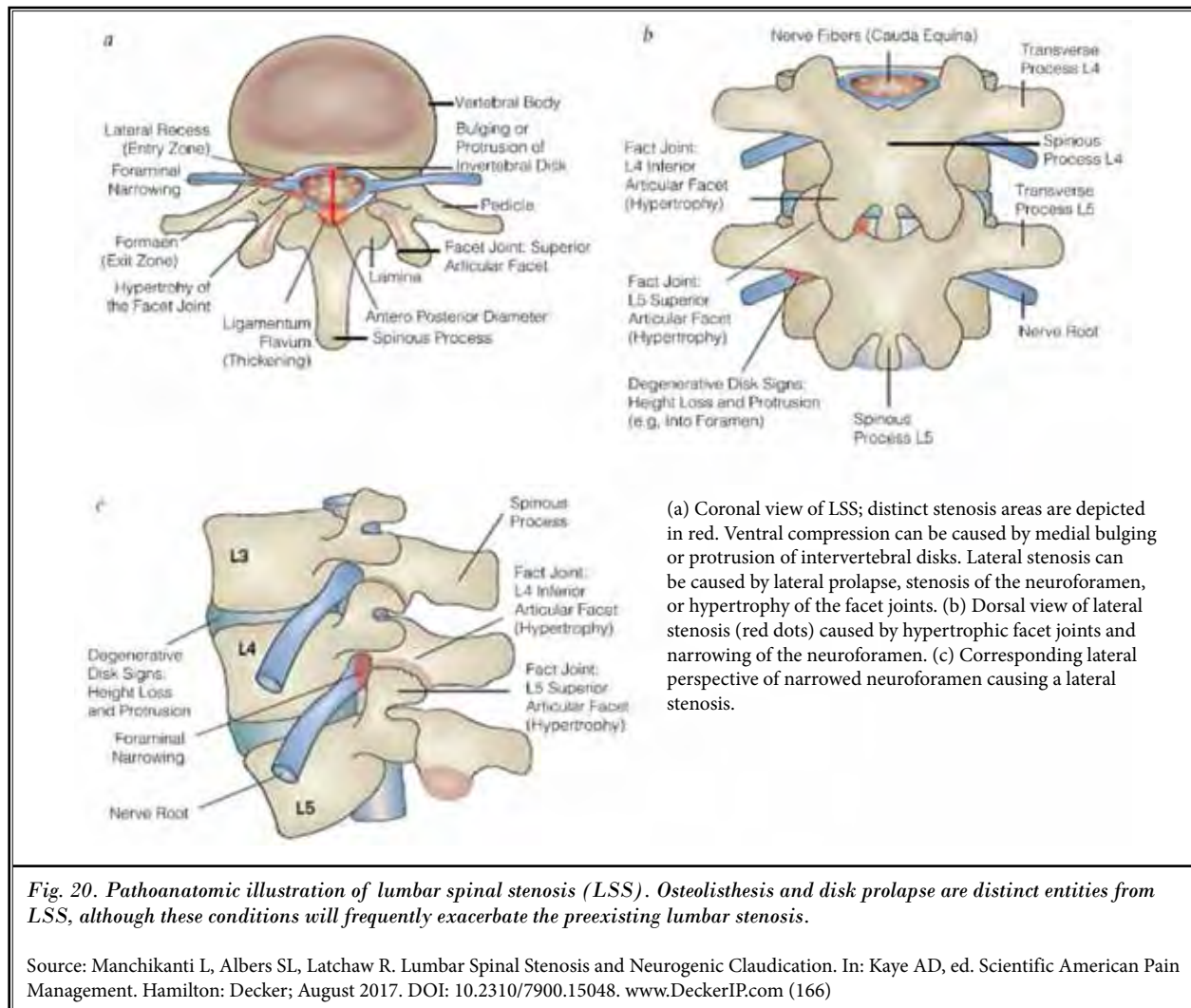


Fig. 19. Chronic end-plate changes (Modic type I) and moderate central spinal canal stenosis.

Source: Manchikanti L, Albers SL, Hirsh JA, Boswell, MV. Lumbar Disk Herniation. In: Kaye AD, ed. Scientific American Pain Management. Hamilton: Decker; September 2017. DOI: 10.2310/7900.15047. www.DeckerIP.com (156)



(a) A sagittal T1-weighted magnetic resonance image shows hyperintense changes (arrow) within both the L2 and L3 vertebral bodies on either side of a narrowed, bulging, degenerated disk. (b) A short tau inversion recovery image nulls the fat signal and excludes the presence of edema, which would be typical of acute Modic type I changes (arrow). (c) An axial T2-weighted image shows a bulging disk with an annular fissure and moderate facet hypertrophy, producing a mild degree of central canal spinal stenosis.

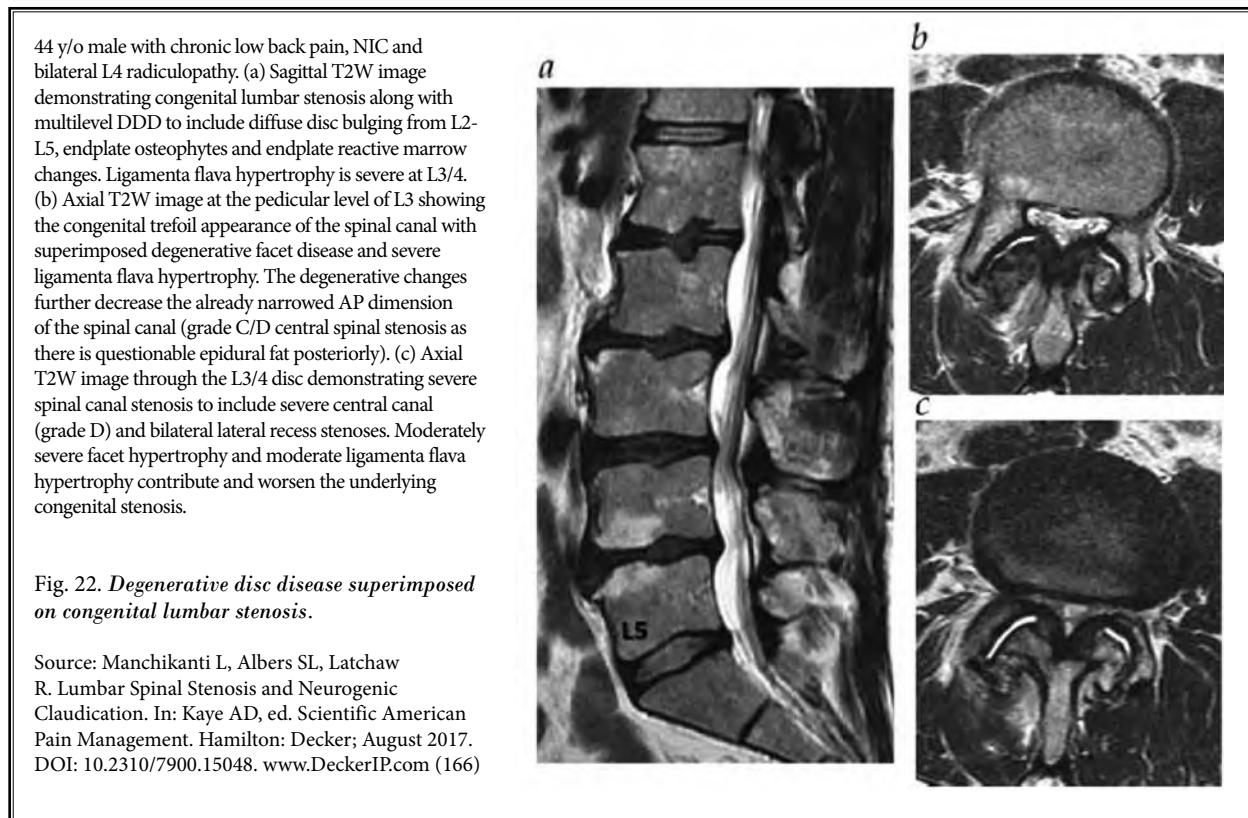
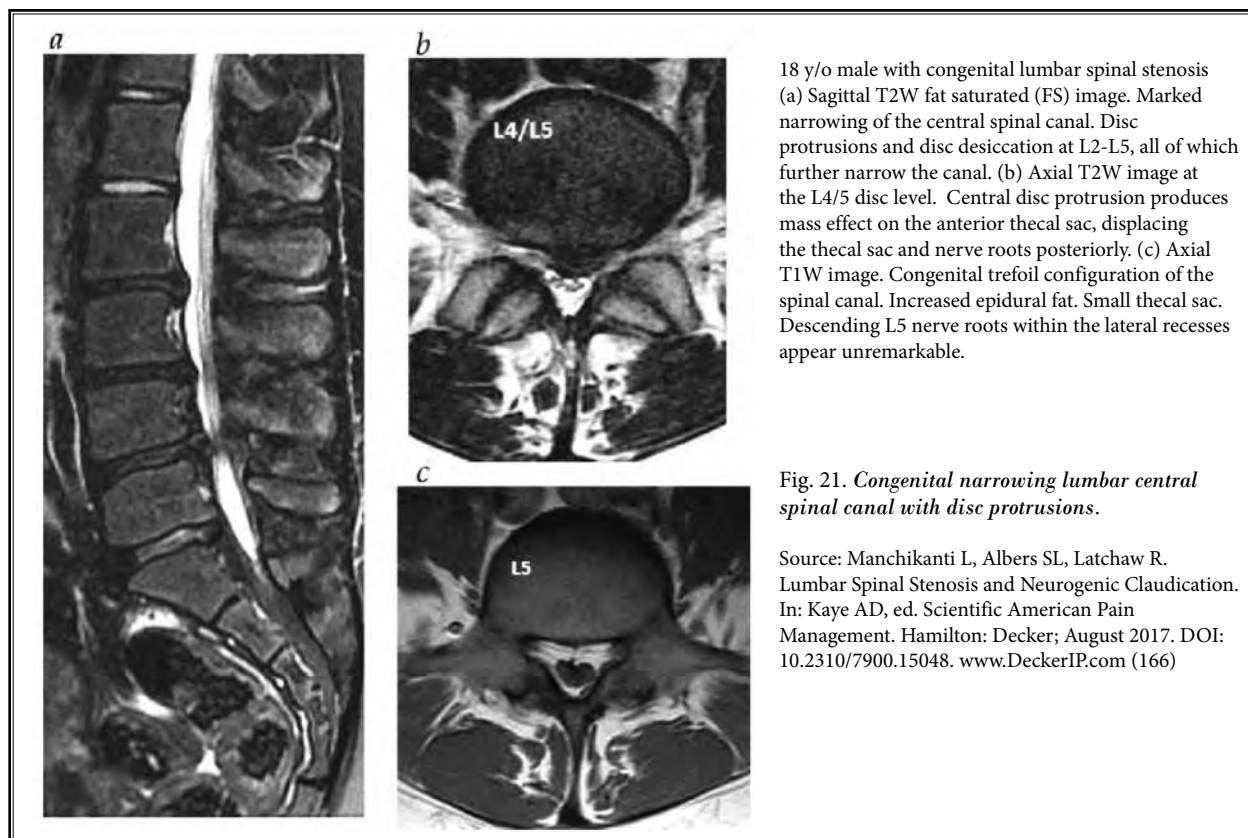


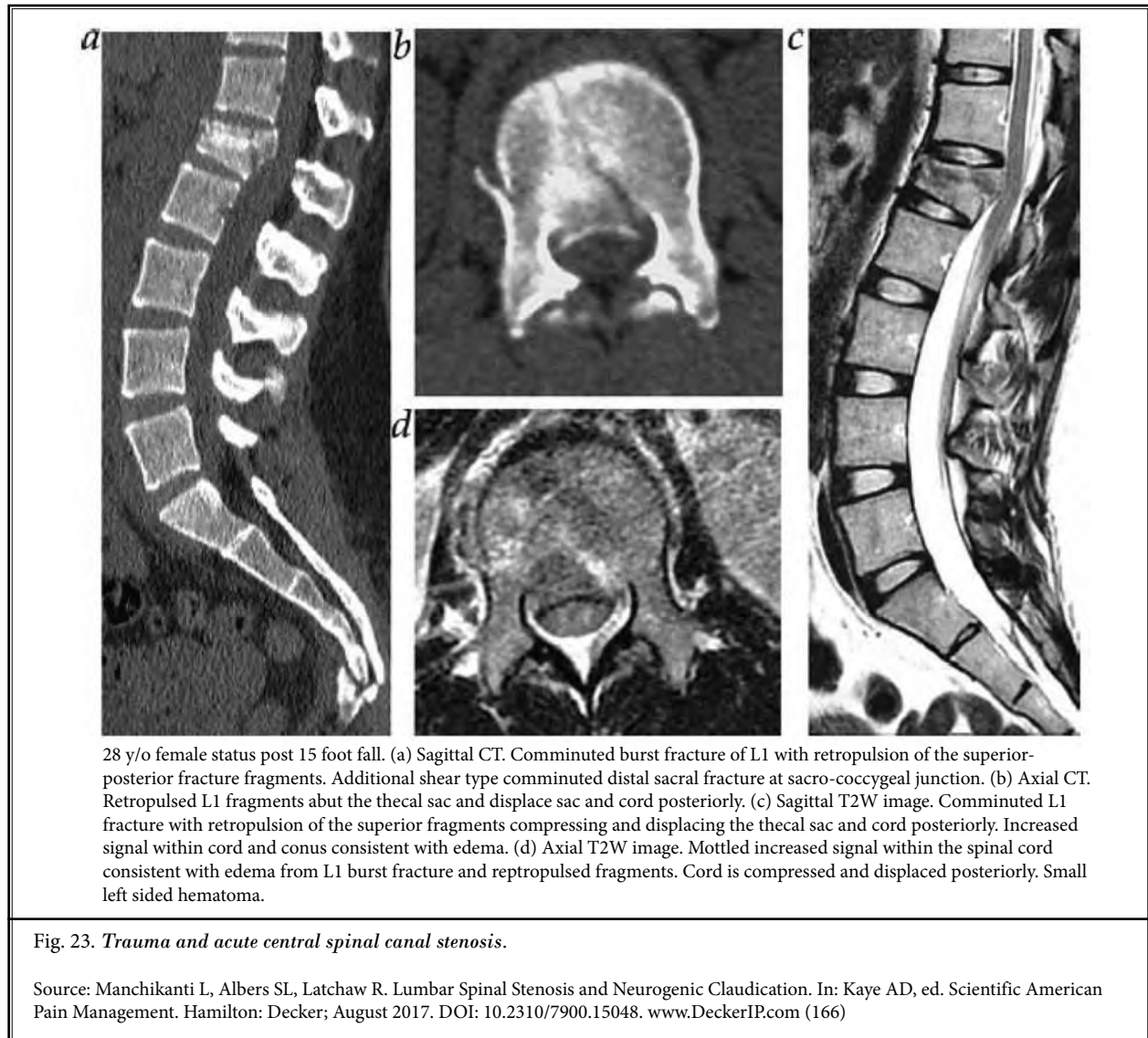
or failed back surgery syndrome denotes a failure of treatment, the nomenclature itself is inaccurate since it can be seen following any type of surgical intervention. Consequently, a more appropriate term would be the postsurgery syndrome. Furthermore, this term does not necessarily indicate a failed surgical procedure. Rather this may indicate a technically successful operation that has not been able to produce a satisfactory long-term clinical outcome. Pain and disability in the low back and lower extremity following lumbar spine surgery may be secondary to epidural fibrosis, sacroiliac joint pain, disc herniation, discogenic pain, spinal stenosis, arachnoiditis, facet joint pain, acquired spondylolisthesis, and/or myofascial pain, along with inappropriate surgery. A relatively common medium to long-term sequela is adjacent level degeneration. In addition, changes in

posture and body dynamics may challenge muscle and ligamentous structures with the eventuation of secondary pain generators such as the piriformis muscle.

5.4 Facet-related Pathology

Facet joints are pairs of joints that stabilize and guide motion in the spine (8). Lumbar facet joints are a well-recognized source of low back and referred pain into the lower extremities in patients with chronic low back pain, and controlled studies have established them as potential sources of chronic pain (8,101,102,104,154). In addition, the degenerated facets contribute to the cycle of discogenic pain because of their altered morphology and angulation, allowing for spondylolisthesis. Ultimately, they are major factors in the development of spinal stenosis. Facet joints are well





innervated by the medial branches of the dorsal rami. Neuroanatomic, neurophysiologic, and biomechanical studies have demonstrated free and encapsulated nerve endings in lumbar facet joints, as well as nerves containing substance P and calcitonin gene-related peptide (8,101,102,104,154). Multiple factors including mechanical injury, inflammation, and degeneration of the facet joints have been shown to produce persistent pain in animal models, as well as in humans (169-172). Prostaglandin E2 (PGE2) has been identified as a key mediator of inflammation-induced behavioral sensitivity and increased neuronal excitability (152,173). Overall, the diagnosis established by controlled diagnostic blocks in chronic low back pain patients has shown a

prevalence of facet joint pain ranging from 16% to 41% (8,101,102,104).

5.5 Sacroiliac Joint Pain

The sacroiliac joint is accepted as a potential source of low back and/or buttock pain with or without lower extremity pain (8,103). The sacroiliac joint receives innervation from the lumbosacral nerve roots. Neurophysiological studies have demonstrated both nociceptive and proprioceptive afferent units in the sacroiliac joint. Pain referral patterns based on sacroiliac joint provocation and analgesic response to local anesthetic in asymptomatic volunteers and patients with pain have been studied. The relatively accurate diagnosis of

sacroiliac joint pain is made by controlled local anesthetic blocks. These studies have shown the prevalence of sacroiliac joint pain in chronic low back and lower extremity pain to be between 10% to 25%. The literature suffers with a paucity of studies assessing the role of multiple available treatments.

5.6 Ligaments, Fascia, and Muscles

A significant prevalence of chronic low back pain may be related to muscles and ligaments in the low back, pelvis, and lower extremities (8). However, the available controlled diagnostic techniques are not amenable for an accurate diagnosis of these conditions or their prevalence.

6.0 REGENERATIVE MEDICINE

Key Question 4. What are the available regenerative medicine therapies?

Biological therapies assist the healing of tissues damaged acutely or chronically, including ligaments, menisci, articular cartilage, tendons, discs, and joints. While there are a variety of biologics utilized in regenerative therapy of the spine and other musculoskeletal disorders, PRP and MSCs are the current mainstays of regenerative medicine treatment.

6.1 Platelet-Rich Plasma (PRP)

PRP is a concentrate of whole blood that is cen-

trifuged to obtain plasma rich in platelets and hence growth factors. In the U.S., PRP is approved by the FDA for use with ligament grafting and the approximation of bony matrices during reconstructive procedures. Benefits occur by the increased concentration of growth factors that are secreted by platelets in an inflammatory environment, i.e., platelet-derived growth factors. These growth factors are essential to the healing process, as they increase fibroblast and/or osteoblast metabolic activity while reducing cell apoptosis; promoting angiogenesis, thereby increasing blood flow and circulation to the new-forming tissues; and increasing the expression of the pro-collagen gene and collagen-derived growth factors, which increase the tensile strength of the new tissue (17-19,23,174-180). Components of PRP include platelets, leukocytes, and red blood cells. However, platelets are central to mediating the anabolic effects of PRP by virtue of releasing growth factors stored in their alpha granules (178). Notable growth factors released from platelets that are involved in the healing process are shown in Table 3 (181-184).

Proteins present in PRP that stimulate proliferation include endothelial growth factor, platelet-derived growth factor, vascular endothelial growth factor, and basic fibroblast growth factor (b-FGF). Inhibitory proteins such as b-FGF2 are equally important in mediating overproliferation (180), although the exact balance between

Table 3. *Function of growth factors stored in platelet-rich plasma.*

Growth Factor	Function
PDGF	Stimulates cell proliferation, chemotaxis, and differentiation Stimulates angiogenesis
TGF- β	Stimulates production of collagen type I and type III, angiogenesis, re-epithelialization, and synthesis of protease inhibitors to inhibit collagen breakdown
VEGF	Stimulates angiogenesis by regulating endothelial cell proliferation and migration
EGF	Influences cell proliferation and cytoprotection Accelerates re-epithelialization Increases tensile strength in wounds Facilitates organization of granulation tissue
bFGF	Stimulates angiogenesis Promotes stem cell differentiation and cell proliferation Promotes collagen production and tissue repair
IGF-1	Regulates cell proliferation and differentiation Influences matrix secretion from osteoblasts and production of proteoglycan, collagen, and other noncollagen proteins

Abbreviations: PDGF = platelet-derived growth factor; TGF-b = transforming growth factor-b; VEGF = vascular endothelial growth factor; EGF = epidermal growth factor; bFGF = basic fibroblast growth factor; IGF-1 = insulin-like growth factor.

Adapted and Modified from: Refs. (181-184)

Table 4. *Consensus statements on platelet-rich plasma.*

1	Nomenclature and classification system that encompasses autologous blood/plasma products and categorizes preparations in sufficient detail to facilitate comparison across studies is not available. • A widespread system must be developed with involvement of academics, clinicians, and industry representatives
2	Quality assessment with influence of donor variance and processing and delivery factors on the composition of PRP must be established.
3	A validated assay of the efficacy of PRP should be established for each clinical application. • Specific formulations of PRP should be matched with specific pathologic indications. • Methods for establishing proof of safety and efficacy of PRP should be determined. This process may require evidence of phenotype stability or viability for each indication.
4	The relationship between PRP composition and efficacy must be established. • Minimum standards of reporting for all studies (preclinical and clinical) evaluating PRP must be established to facilitate communication and the interpretation and synthesis of scientific investigations. These standards must include measured characteristics of the PRP, factors relating to the donor, processing, and delivery of the PRP and outcome parameters.

PRP = platelet-rich plasma

Adapted from: LaPrade RF, Dragoo JL, Koh JL, et al. AAOS Research Symposium Updates and Consensus: Biologic Treatment of Orthopaedic Injuries. *J Am Acad Orthop Surg* 2016; 24:e62-e78 (188).

these proteins is not known. Because each person expresses unique proportional quantities of these proteins, it is uncertain if concentrating an individual's autologous proteins is ideal for their body's healing needs. Since the therapy is dependent on the function of the host's platelets, the therapeutic concentration of PRP injectate is recommended to be at least 2.5 times greater than the peripheral plasma concentration. Lesser concentrations are probably sub-therapeutic, and greater concentrations reduce osteoclastic activity (174).

PRP has been developed with a multitude of formulations (179). A meta-analysis reported 14 different indications for treatment and 9 different preparation systems used in clinical studies (185). Consequently, multiple authors have proposed classification systems for the various types of PRP based on its content including platelets, white blood cells, fibrin network, and exogenous activators. Dohan Ehrenfest et al (186) described a classification system based on cell content, primarily the amount of white blood cells, and the fibrin architecture. Based on these parameters, they grouped PRP into 4 different types.

- Pure PRP (PPRP), which does not contain leukocytes and has a low-density fibrin network.
- Leukocyte-rich PRP (L-PRP) has an increased concentration of white blood cells in addition to a high concentration of platelets, but also has a low-density fibrin network.
- Pure platelet-rich fibrin (P-PRF) is free of leukocytes, but has a high-density fibrin network.
- Leukocyte- and platelet-rich fibrin (L-PRF) has an increased concentration of leukocytes and a high-density fibrin network.

The preparations with a low-density fibrin network allow for injectable applications, which are more commonly used for musculoskeletal conditions. Consequently, the first 2 preparations are commonly utilized. The third and fourth preparations with high-density fibrin networks allow for a clot with growth factor present in the matrix architecture (186).

DeLong et al (187) proposed a classification known as the PAW (Platelets, Activation, White Blood Cells) classification of PRP based on platelet concentration, activators, and the presence of white blood cells, placing them into multiple categories based on their contents. Even though PRP nomenclature remains variable and no single classification system is consistently used, it is critical for clinicians to know what is in the milieu of PRP that is being injected (52). The American Academy of Orthopaedic Surgeons (AAOS) (188) identified several obstacles to the advancement of PRP therapies and made recommendations on how future research efforts should be directed to overcome the challenges. The consensus statement of PRP preparation and use from the AAOS is shown in Table 4 (188). The multiple variables that may influence the growth factor profile of PRP related to donor, processing, and delivery are shown in Table 5.

DEPA (Dose of injected platelets, Efficiency of production, Purity of the PRP, Activation of the PRP) classification has been proposed to extend the characterization of the injected PRP preparation. A classification system based on the platelet concentration and the presence or absence of white blood cells in the PRP. Lana et al (30) described a new classification called MARSPELL: M: Method; A: activation, R: red blood cells,

S: spin, P: platelets, I: image guidance, L: leukocytes, L: light activation.

The platelet poor fraction of blood is also known to have substances that may be of use for regenerative approaches including fibrinogen, alpha 2 macroglobulin and exosomes. A discussion about these factors is beyond the purview of the present review.

6.2 Medicinal Signaling Cells or Mesenchymal Stem Cells (MSCs)

Stem cells are essentially the base-model versions of each kind of cell, and have the potential to become one or more specific kind of cell. Fetal stem cells have the potential to not only differentiate into any kind of cell, but also to self-renew. Adult stem cells are located throughout adult tissue and are primed to become the cells in and for that particular tissue, as stimulated by the surrounding environment (17,189-195). The adult stem cells described by Caplan (189) have become well recognized but are now called “medicinal signaling cells (MSCs)” (189-195). These adult MSCs have a narrower range of potentials, but are sufficient for use in many current and emerging musculoskeletal and spine therapies.

A major benefit from of MSCs is their inherent lack of significant histocompatibility complex (MHC) class II surface proteins. This not only allows them to conform to a variety of different cell types, but also decreases the risk of rejection when transferred between hosts (allogeneic transfer) (187,196). MSCs that have clasped on to the vascular tree as pericytes are also able to migrate to a site of injury and then differentiate into the cell required for healing, such as osteoclasts, to directly contribute to the remodeling process (187,196).

An important area of research regarding the potential mechanism of action of MSCs is that of a paracrine influence” affecting the efficacy in differentiation of the cells. The concentration of the surrounding catabolic cytokines from acute inflammation favors osteoclastic activity, and the balance must shift away from inflammation in order for the anabolic effects of MSCs to take place. Two examples supporting this premise are the following: 1) there is evidence that concentrating MSCs in an area to artificially favor the balance towards osteoblastic activity is feasible, and has been a successful technique in preventing graft vs. host disease; 2). MSCs are most effective in degenerative diseases where there is little active inflammation (197).

Over the years, multiple researchers have attempted to standardize the nomenclature used in MSC re-

Table 5. Variables that may influence the growth factor profile of platelet-rich plasma.

<ul style="list-style-type: none"> • Donor <ul style="list-style-type: none"> • Age • Gender • Comorbidities • Concurrent medications (including anti-inflammatories) • Nutritional status
<ul style="list-style-type: none"> • Processing <ul style="list-style-type: none"> • Blood collection and storage conditions • Spin protocol (speed, time) • Activation protocol (agent, concentration, timing) • Storage
<ul style="list-style-type: none"> • Delivery <ul style="list-style-type: none"> • Form of delivery (gel, solution) • Timing of delivery in relation to isolation • Timing of delivery in relation to activation • Host factors (similar to donor factors) • Injury chronicity

Adapted from: LaPrade RF, Dragoo JL, Koh JL, et al. AAOS Research Symposium Updates and Consensus: Biologic Treatment of Orthopaedic Injuries. *J Am Acad Orthop Surg* 2016; 24:e62-e78 (188).

search (17). However, such standardization efforts have been unsuccessful because of variations and methods of isolation, culture, and assay resulting in complicated and, at times, misleading nomenclature. In 2006, the International Society for Cellular Therapy (ISCT) produced a position statement suggesting the minimum criteria required to define MSCs (198).

The first report of stem cells described those unique cells derived from bone marrow. They remain the most commonly utilized type of adult stem cells, and have the approval and recommendations of the FDA (17). Since that time, MSCs have been isolated from multiple organs and tissues with variable advantages and disadvantages depending upon the source. Apart from the intersource variation, MSCs originating in different anatomic locations having the same tissue may vary in yield and characteristics (188). Consequently, the equivalency of MSC populations derived from distinct anatomic origins continues to be debated and remains contentious. MSC populations from multiple sources have shown differences with respect to the immunophenotype, secreted cytokine profile, and results of proteome analysis (199-201). Further, it also has been shown that cloned human MSCs isolated from fat default to adipogenic potential, whereas those isolated from bone marrow default to osteogenic potential, indicating the importance of origin which ultimately influences the characteristics of MSCs and potentially the eventual outcomes (199). Thus, 4 key pathways that

Table 6. *Consensus statements on stem cell therapy.*

1	It is essential to identify the factors contributing to tissue development, regeneration, and healing in each specific tissue. <ul style="list-style-type: none"> The mechanisms regulating these contributions must be characterized.
2	The optimum preparation of stem cells for each indication must be established in a systematic fashion. <ul style="list-style-type: none"> Considerations should include cell number, concomitant use of growth factors, predifferentiation, and vehicle. Mesenchymal stem cells isolated from different tissues must be compared to identify the most appropriate cell source for each specific indication.
3	The mechanism responsible for therapeutic effects observed in applications and appropriate outcome parameters must be established. <ul style="list-style-type: none"> A standardized assay of stem cell efficacy is needed. Methods for establishing proof of safety of stem cell therapy should be determined in collaboration with industry and regulatory agencies. This process may require evidence of phenotype stability or viability. The most appropriate control for clinical studies evaluating stem cell therapy in each indication must be identified. The most appropriate, replicable outcomes must be established.

Adapted from: LaPrade RF, Dragoo JL, Koh JL, et al. AAOS Research Symposium Updates and Consensus: Biologic Treatment of Orthopaedic Injuries. *J Am Acad Orthop Surg* 2016; 24:e62-e78 (188).

have been identified in tissue regeneration, namely osteogenesis, adipogenesis, chondrogenesis (200-203), and fibrinogenesis (204,205) are derived with differing potential from MSCs that come from bone marrow compared to adipose tissue.

Adipose MSCs also have the noted characteristic of pro-angiogenic properties, which makes them a very promising therapy for both ischemic/vascular therapies and for commonly injured hypo- to avascular regions such as the avascular zone of the knee meniscus. Bone marrow-derived MSCs have the same progenitor potential as the adipose derived MSCs, but also home to the site of injury through a series of chemoattractants, integrating into the host marrow, bone, and cartilage (197).

True adult stem cells, in general, are relatively scarce; they can be difficult to isolate; they grow slowly; and they do not differentiate well without the appropriate peripheral cytokines. It can be difficult to isolate sufficient therapeutic quantities of these cells. These disadvantages may be partially overcome by selection of stem cells from an appropriate source such as bone marrow from a source containing red marrow such as the iliac crest where extraction yields 95-100% viable cells (187).

Due to the scarcity of stem cells, laboratory culture has been used to enrich and expand MSC populations (206), taking advantage of the rapid expansion of MSCs in laboratory conditions. However, laboratory cultures are not approved by the FDA (17,38-40). Consequently, within the confines of the FDA regulations requiring minimal manipulation, the stromal vascular fraction (SVF) which is derived from chemically manipulated adipose tissue is not recommended, and laboratory cultures are not approved by the FDA. The AAOS (188) has

provided a consensus statement on stem cell therapy, as shown in Table 6.

Although the absolute number of stem cells found in bone marrow concentrate may be relatively low, those growth factors that are derived in the bone aspirate process may confer additional therapeutic value to this process.

It is also important to consider that adult stem cells may contain the mutations of the host cell obtained at meiosis, and these mutations may be expressed regardless of the cell type into which they differentiate (187). Gene therapy is being actively studied to ensure the safety and efficacy of this biologic therapy.

6.3 Other Commercially Available Biologic Preparations

A simple web-based search can yield a multitude of kits and biologic products for office use. The Center for Biologic Evaluation and Research provides an 8 page listing of all commercially available biologic products byproduct name, date of licensure, and the date (if applicable) that it was withdrawn from the market (207).

A biologic of significant interest in regenerative medicine is the exosome or microvesicle (208). Similar to MSCs, exosomes are secretory products that home and travel via local diffusion, delivering proteins, micro RNA, and messenger RNA. However, unlike MSCs, extracellular vesicles or exosomes demonstrate a number of advantages distinct from their parent cells. They can travel systemically without the risk of clumping and they do not demonstrate a first pass effect into the lungs when administered intravascularly. They can also easily cross the blood-brain barrier without the utilization of mannitol. Exosomes are important in autocrine signaling (locally between the same cells), paracrine

signaling (locally between cells of different types) and endocrine signaling (between distant cells). Key immune and growth factors present in exosomes are similar to those found in MSCs. Exosomes have been utilized in a multitude of disorders similar to the use of MSCs (208).

Alpha 2 Macroglobulin (A2M) has known to be associated with degeneration of the discs serving as a dual regulator for both anabolism and catabolism in the cartilaginous endplate of intervertebral disc. Its expression has been shown to be more in nucleus pulposus compared to annulus fibrosus and recently, been shown to protect against the progression of IVD degeneration by inhibiting effects of pro-inflammatory cytokines. Similarly, intradiscal tocilizumab therapy has been studied in patients with discogenic low back pain.

7.0 PATHOPHYSIOLOGIC BASIS OF BIOLOGIC THERAPIES

Key Question 5. How do regenerative medicine therapies work in the treatment of low back and extremity pain?

The components of a 3-joint theory of spinal degeneration include intervertebral disc degeneration, facet loading, and degeneration, which can lead to spinal deformity, nerve root compression and possibly central canal and/or foraminal stenoses (17,18,112,209,210). Regenerative treatments for low back pain conditions have emerged over the years because of the suboptimal outcomes from conventional treatments and the population's demand for more natural and holistic medical approaches (17,18,25,209-222). Both PRP and stem cells represent 2 promising regenerative therapies that are currently being used in managing low back pain and radiculopathy.

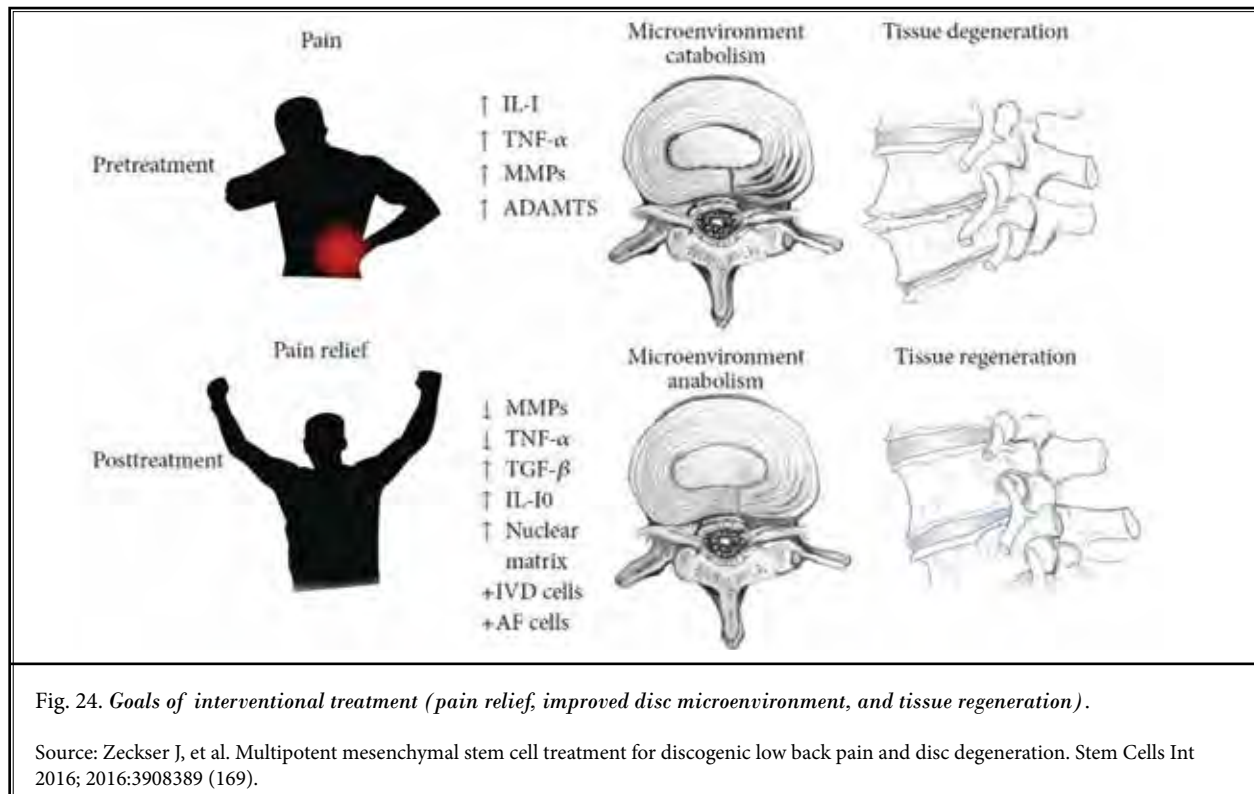
7.1 Intervertebral Disc

The disc is composed of the nucleus pulposus, the annulus fibrosis, and the fibrous attachments to the vertebral endplates (Sharpey's fibers). The intervertebral disc is a dynamic structure, with the disc microenvironment relying on a harmonious balance between anabolic and catabolic factors important for normal disc cell turnover (169). Growth factors including transforming growth factor- α (TGF- α), bone morphologic proteins (BMP), growth and differentiation factor 5 (GDF5), and insulin-like growth factor (IL-GF) are examples of important anabolic factors. Conversely, catabolic metabolism is achieved by catabolic enzymes, inflammatory cytokines, proteinases, and aggrecanases, which include interleukin-1 (IL-1), tumor necrosis

factor- α (TNF- α), a disintegrin and metalloproteinase with thrombospondin motifs (ADAMTS), and matrix metalloproteinase (MMPs). Degenerated discs contain cell clusters producing matrix-degrading enzymes, including MMPs (220). Unfortunately, the disc is relatively avascular, creating a difficult microenvironment with low oxygen tension, and a paucity of nutrients for intervertebral disc cells. Thus, analogous to other cartilaginous structures, limited vascular support is a significant contributor to the poor natural regenerative capacity of intervertebral discs when metabolic homeostasis is disrupted (18,213,223-233)

Degenerative disc disease is defined as a diffuse, progressive, and age-related phenomenon characterized by nuclear dehydration and fibrosis with resultant disc space narrowing of approximately 3-4% height loss per year (223). The pathophysiological mechanisms of degeneration include mechanical, biochemical, nutritional, and genetic factors contributing to a shift towards catabolic metabolism within the disc microenvironment. Hallmarks of degenerative disc disease include increased MMP activation, decreased intervertebral disc cell viability, and decreased proteoglycan production (219). The degeneration of the disc includes the development of focal fissures extending outward from the nucleus into the annulus (radial fissures) or along annular lamellae described as circumferential fissures (18,156,223,225). Further disc space narrowing leads to a redistribution of axial mechanical forces on the disc and on nearby structures including the vertebral body endplates and facet joints. With progressive degeneration, the disc loses its ability to act as a shock absorber and begins to bulge, pulling on Sharpey's fibers, which leads to the development of endplate osteophytes, (156,223,224). Further degenerative disc disease may or may not result in discogenic low back pain (156,219,224).

Annular fissures have been described as providing a conduit for inflammatory chemical mediators to trigger nociceptive nerve endings in the outer annulus fibrosis (156,223,225). In addition, nerve ingrowth proliferates along fissure sites with increasing exposure to nociceptive and mechanical stimuli. Discogenic pain develops with internal disc disruption when annular pain fibers are directly stimulated by inflammatory mediators; these fibers may also be indirectly stimulated by increased mechanical loading pressure (18,156,223,225). Internal disc disruption has been shown to be present in approximately 36% to 39% of the patients (164,165), whereas, discogenic pain secondary to degenerative



disc disease has been shown to be present in 26% of the patients (162).

Disc herniation is displacement of nuclear disc material beyond the normal confines of the nucleus, extending into and beyond the annulus to a variable degree (156,223). As described earlier and as shown in Figs. 13-15, multiple stages include disc protrusion, extrusion, and sequestration. Disc herniation has been described to be the most common etiology of radicular leg pain through either mechanical compression of nerve roots or chemical radiculitis (156). In addition, disc herniation may contribute to focal low back pain as a result of the inflammation of the dural sleeve of the nerve root described as somatic referred pain, or from activation of outer annular pain fibers within the disc (156,223). An alteration of the annulus may contribute to decreased disc integrity and acceleration of the degenerative disc disease (169).

Despite obvious tissue deterioration, viable cells isolated from degenerated discs have shown an ability to proliferate and differentiate in vitro, even though regeneration potential is limited (226). In fact, progenitor cells have been isolated from human degenerated discs (227), potentially derived from specific niche re-

gions located near the cartilaginous endplates (228) that migrate into the disc (229). While degenerated discs exhibit necrosis, cell senescence, and apoptosis, viable cells have been identified (220). Zeckser et al (169) have stated that all interventional therapies should optimally strive to fulfill a trio of treatment objectives including the decline and/or resolution of primary nociceptive disc pain with functional improvement, slowing and/or reversal of the catabolic metabolism and associated degradation within the disc environment, and partial or complete restoration of disc tissue, as shown in Fig. 24 (169). Even though the majority of therapies in managing disc related pain have shown variable degrees of patient improvement, they still produce suboptimal outcomes because they do not fulfill the 3 criteria of Zeckser et al (169). It is hoped that regenerative techniques will lead to better outcomes by fulfilling these criteria than epidural injections with or without steroids (8,97,106,107,111-118), intradiscal therapies (18,111,230), surgical interventions with or without fusion (213,232).

Percutaneously delivered multipotential MSCs have recently gained attention for their potential to revolutionize the treatment of discogenic low back pain. MSC

therapy may provide the necessary cellular support for regeneration. Current research suggests that these treatments may have the ability to uniquely accomplish the 3 stated objectives for treating disc pathology as shown in Fig. 25. However, the intervertebral disc is avascular, presenting a potential impediment to the viability of intradiscal cell implantation (26,233,234). Fortunately, several authors have demonstrated that regenerative techniques can lead to positive effects on intervertebral disc cell proliferation (26,235-282).

Stem cell therapy may address the underlying sources of disc degeneration by mitigating inflammation within the nucleus pulposus, rehydrating the nucleus, by remodeling the tissues or recruiting peripheral cells and nutrients, and/or by restoring the disc height to remove pressure on the adjacent nerves (206,213,221,222). These effects are achieved by decelerating or reversing the degenerative process by promoting synthesis of proteoglycans and Type II collagen (213). Stem cell therapy in animal models has consistently led to increased disc height, improved magnetic resonance imaging (MRI) T2 signal intensity, decreased grade of histologic disc degeneration, and increased expression of Type II collagen (212,221). Ghosh et al (237) reported that the injection of mesenchymal precursor cells (MPCs) in a bovine model produced increased disc height, higher T2 MRI signal, improved histological grading scores, and restoration of the extracellular matrix or ECM. An *in vitro* pilot study (238) assessing autogenous MSCs from the vertebral body showed enhancement of intervertebral disc generation via paracrine interaction. Some authors have speculated that implanting MSCs into a degenerated intervertebral disc may both stimulate MSC differentiation into a nucleus pulposus or annulus fibrosus-like phenotype and stimulate the biological activation of residual viable cells within the degenerated disc for self-repair (238). Others have investigated the effect of the proinflammatory-degenerative intervertebral disc microenvironment on the regenerative and immunomodulatory behavior of mesenchymal stem-stromal cells *in vivo* and *in vitro* (239-242) and have shown viability of MSCs, active cell migration, and an increase of multiple growth factors.

A systematic review of 53 manuscripts (25) of MSC use in the treatment of spinal cord injury, intervertebral disc repair, and spinal fusion demonstrated regeneration in both mice and rats following the injections of MSCs. A significant deceleration in disc degeneration was reported beginning 2 weeks following MSC injection (243). Although equally effective, MSCs derived

from bone marrow or adipose tissue survived only for 2 weeks. Another study demonstrated regeneration following bone marrow MSCs implanted into the tail discs of rodents (244), which resulted in proliferation of nucleus pulposus cells, an increase in disc height, and a decreased concentration of MSCs 4 weeks post injection. It was also shown that MSCs derived from umbilical cords were safely transplanted into patients, resulting in decreased pain and improved lumbar function (245). The comparative effects of MSCs and nucleus pulposus cells were also assessed (246). This study did not find conclusive evidence indicating MSCs were better than nucleus pulposus cells for transplantation. In contrast, multiple other studies have suggested that MSCs might work better when co-cultured (247). Further, co-transplantation of bone marrow-MSCs (BM-MSCs) and annulus fibrosus cells significantly increased Type II collagen and glycosaminoglycan expression (248). In addition, a telocollagen gel as a carrier in various studies has allowed BM-MSCs to survive up to 48 weeks while restoring disc height and water content (249). However, another carrier, hyaluronan gel, was found to have possible cytotoxic effect on MSCs and resulted in a decrease in injected cell numbers during the first 7 days, indicating hyaluronan failed to retain MSCs at the site of injection.

Regarding MSCs, Wang et al (250) demonstrated that MSCs derived from 4 origins (nucleus pulposus, annulus fibrosus, cartilage end plate, and bone marrow) showed similar capabilities to differentiate into the appropriate cell required for intervertebral disc regeneration. They suggested that any of these cell lines can be used for therapy, with convenience and quantity of extraction guiding the selection. Long-term studies of MSC intradiscal therapy are being conducted, but at this time the greatest duration of study length is 24 months.

Review of MSC use for intradiscal pathology by Valadà et al (251) describes the efficacy of intervertebral disc regeneration using stems cells from all origins (bone marrow, adipose, synovial fluid, muscle-derived stem cells, olfactory neural stem cells, induced pluripotent stem cells, hematopoietic stem cells, disc stem cells, embryonic stem cells) and tissue engineering approaches (hydrogel, viscoelastic scaffolds, and hyaluronic-based scaffolds). They conclude that patients could expect benefit from stem cell mediated therapy for mild-moderate grade intervertebral disc disease, as long as the structural integrity of the disc is preserved. There was no commentary on chronicity (251). Noriega

et al (283) demonstrated that the injection of 25×10^{10} allogeneic cells per disc segment achieved faster and more significant improvement than controls, and that allogeneic MSCs should be considered for patient comfort, procedural convenience, and in cases of stem cell deficiency. Pettine et al (253) showed that of 26 surgical candidates for spinal fusion or disc replacement surgery, 24 (92%) were able to avoid surgery for 12 months, and 21 patients (81%) were able to avoid surgery by 2 years following intradiscal bone marrow mesenchymal cell implantation. While no patient worsened, some improved on the MRI-based Pfirrmann grading system.

PRP may also be used for intervertebral disc degeneration, facet joint arthritis, and sacroiliac joint arthritis. While MSCs are used more commonly for intervertebral disc degeneration than PRP, inhibition of matrix degrading enzymes may occur with PRP (17-19,23,174-180,211). PRP contains amplified levels of growth factors and cytokines, which stimulate tissue healing. Over the years, clinicians have hypothesized that placing a high concentration of growth factors directly at the site of collagen injury promotes their function as humeral mediators to induce the natural healing cascade (211,254). An in vitro study of PRP-infused human intervertebral disc cultures supported this hypothesis and exhibited nucleus pulposus proliferation and differentiation, as well as the up regulation of proteoglycan synthesis (255). In animal models of experimentally injured intervertebral discs, treatments with intradiscal PRP have produced restoration of normal cellular architecture and disc height (256,257). PRP has been postulated to have an anti-inflammatory effect. In fact, an in vitro study found that the cytokines TNF- α and IL-1), induced proinflammatory degrading enzymes and their mediators were suppressed with the addition of PRP into the collagen matrix of human nucleus pulposus cells (258). PRP-impregnated gelatin hydrogel injected into the degenerated intervertebral discs of a rabbit model resulted in significantly higher water content as demonstrated by MRI, which corresponded with increased intradiscal proteoglycan content, up regulated micro RNA precursors for Type II collagen, and the significant reduction in apoptotic nucleus pulposus cells (259). Additionally, in a percutaneous annulus puncture induced degenerated disc rat model, discs treated with PRP had fewer inflammatory cells, higher preservation of normal morphology, and higher fluid content on T2 MRI compared with a sham injection after 4 weeks (256).

7.2 Facet Joints

PRP is the biologic most commonly used in the treatment of lumbar facet joints. The platelet-derived growth factors concentrated within PRP are essential to the healing process. These growth factors increase fibroblast and/or osteoblast metabolic activity while reducing cell apoptosis; promote angiogenesis, thereby increasing blood flow and circulation to the new-forming tissue; and increase the expression of the pro-collagen gene and collagen-derived growth factor, which increases the tensile strength of the new tissue (175,176). Proliferative proteins present in PRP include the endothelial growth factor, platelet-derived growth factor, vascular endothelial growth factor, and B-FGF (152).

Kristjánsson and colleagues (260) showed that the MSCs harvested from facet joints and interspinous ligaments had the trilineage potential to differentiate into osteogenic, adipogenic, and chondrogenic cells under the appropriate conditions. They concluded that facet joints and interspinous ligaments could provide an alternative source of MSCs for tissue engineering applications.

At present there is very little literature regarding the application of stem cells in the treatment of facet joint and sacroiliac joint pain. There is extensive literature discussing the application of MSCs for articular cartilage regeneration. The intra-articular use of autologous MSCs represents the current state-of-the-art treatment for cartilage regeneration (261).

7.3 Sacroiliac Joint

There is extensive literature discussing the use and effectiveness of biologicals in the management of peripheral joint pain. These same principles may be applied to sacroiliac joint injections and sacroiliac joint ligamentous infiltration (21,174).

8.0 EFFECTIVENESS OF BIOLOGIC THERAPY IN CHRONIC LOW BACK PAIN

Key Question 6. Are regenerative medicine therapies effective in managing chronic low back pain?

The methodology incorporated into the preparation of these guidelines includes the utilization of IOM standards for systematic review of comparative effectiveness research (262) as well as the use of additional publications relevant to systematic reviews and guideline preparation (8,9,46,47,49,262-265). These guidelines focus on the effectiveness of regenerative treatment modalities in managing low back and lower

extremity pain having a variety of etiologies. [Appendix Table 1](#) shows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria and [Appendix Table 2](#) shows A Measurement Tool to Assess Systematic Reviews (AMSTAR) criteria.

8.1. Data Sources

The literature search was strategized based on multiple available sources including PubMed, the Cochrane library, Google searches, the FDA, the CDC, and controlled clinical trials. The search was conducted over a time frame spanning from January 2000 to June 2018.

8.2 Search Criteria

Search criteria extensively covered chronic low back pain of various origins and injectable biologics including PRP and MSCs.

The search criteria was as follows: (((((((((((chronic low back pain) OR chronic mild back OR upper back pain) OR disc herniation) OR discogenic pain) OR herniated lumbar discs) OR nerve root compression) OR lumbosciatic pain) OR postlaminectomy) OR lumbar surgery syndrome) OR radicular pain) OR radiculitis) OR sciatica) OR spinal fibrosis) OR spinal stenosis) AND (((((((((((epidural injection) OR platelet rich plasma injection or stem cell injection) OR epidural perineural injection) OR interlaminar epidural) OR intraarticular platelet rich plasma OR stem cells) OR nerve root blocks) OR periradicular infiltration) OR transforaminal injection) OR platelet rich plasma OR stem cells) OR intradiscal injections or PRP or stem cells or sacroiliac joint or ligament injections or PRP or stem cells))) AND ((meta-analysis [pt] OR randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized controlled trials [mh] OR random allocation [mh] OR double-blind method [mh] OR single-blind method [mh] OR clinical trial [pt] OR clinical trials [mh] OR (“clinical trial” [tw]) OR ((singl* [tw] OR doubl* [tw] OR trebl* [tw] OR tripl* [tw])) AND (mask* [tw] OR blind* [tw]))) OR (placebos [mh] OR placebo* [tw] OR random* [tw] OR research design [mh:noexp]) NOT (animals [mh] NOT human [mh]))))

8.3 Study Selection

Study selection was based on predefined inclusion criteria where studies reported at least 3 months of outcomes assessment and included all types of studies having an appropriate description. We included intradiscal injections, all types of epidural injections, intraarticular injections of facet joints, nerve blocks,

sacroiliac joint injections, and sacroiliac joint ligamentous injections.

8.4 Data Extraction and Methodological Quality Assessment

Data extraction and methodologic quality assessment was performed by at least 2 of the review authors independently, in an unblinded standardized manner. The quality assessment of each individual article used in this analysis was performed utilizing the Cochrane review criteria ([Appendix Table 3](#)) (266), Interventional Pain Management techniques Quality Appraisal of Reliability and Risk of Bias Assessment (IPM-QRB) criteria ([Appendix Table 4](#)) (267) for randomized controlled trials (RCTs) was used, as was the Interventional Pain Management Techniques – Quality Appraisal of Reliability and Risk of Bias Assessment for Nonrandomized Studies (IPM-QRBNR) ([Appendix Table 5](#)) (268). Utilizing the Cochrane review criteria (266) or the IPM-QRB criteria (267), or the IPM-QRBNR (268), studies that met the inclusion criteria with a score of at least 9 to 13 for the Cochrane review criteria or 32 to 48 for the IPM-QRB and the IPM-QRBNR criteria were considered high quality and scores of 5 to 8 or 16 to 31 (respectively) were considered moderate quality, whereas those sources with scores of less than 5 or 16 (respectively) were considered low quality. Due to the scarcity of the literature, all studies were included in data synthesis or analysis.

All systematic reviews and studies were reviewed by 2 authors. Any disagreements between the reviewers were resolved by a third author and consensus. If there were any conflicts of interest with a manuscript (i.e. authorship), the review authors were recused from assessment and analysis.

8.5 Outcome of the Studies

For the present analysis, either 50% relief from the baseline pain score or a change of at least 3 points on an 11-point pain scale of 0 to 10 or 3-point or 30-point change on Visual Analog Scale (VAS) of 10 cm or 100 mm was considered clinically significant. For functional status improvement, a change of 30% or more on disability scores or 50% improvement from baseline was considered clinically significant.

A study was judged to be positive if the relevance and effectiveness of the regenerative injection therapy of interest was demonstrated with either a control group or upon comparison from baseline to follow-up. A negative study was defined as one where no differ-

ence was seen between the treatments or where no improvement from baseline could be measured. Reference point measurements were considered at 3 months, 6 months, and 1 year.

8.6 Analysis of Evidence

The analysis of the evidence was performed based on best-evidence synthesis and was modified and collated using multiple available criteria, including the Cochrane Review criteria and the United States Preventive Task Force (USPSTF) criteria as illustrated in Table 1 (49). The analysis was conducted using 5 levels of evidence ranging from strong to opinion- or consensus-based. The results of best evidence as per grading were utilized. At least 2 of the review authors independently, in an unblinded, standardized manner, analyzed the evidence. Any disagreements between reviewers were resolved by a third author and consensus was attained. If there were any conflicts of interest (e.g., authorship), these reviewers were recused from assessment and analysis.

8.7 Meta-analysis

The meta-analysis was performed using the Comprehensive Meta-analysis version 3.0 (Biostat Inc., Englewood, NJ). For pain and functional status improvement data, the studies were reported as standardized mean differences (SMD) with 95% confidence intervals (CI). Data were plotted with forest plots to evaluate treatment effects. Heterogeneity was interpreted through I^2 statistic.

Random-effects model (single-arm) meta-analysis was planned to assess net changes in the same outcome variable (28,29). Heterogeneity among the effect sizes of individual studies was assessed using the I^2 index and Q statistic. Heterogeneity analyzed with the I^2 statistic was defined as low (25%–50%), moderate (50%–75%), or high (> 75%) (269). Subgroup analyses were conducted based on follow-up periods (6 vs. 12 months or more) and the injected biologic solution type (MCSs vs. PRP). We conducted meta-regression analysis to identify factors related to a decrease in the pain score following therapy.

All analyses were based on each modality of treatment and the solution injected. Short-term improvement was defined as any improvement lasting for at least 3 months, and long-term improvement was described as that lasting for 6 months or longer. Meta-analysis was performed only when at least 3 studies were available and included an appropriate sample size of at least 10 for nonrandomized studies.

9.0 RESULTS

Our search strategy utilizing the PRISMA flow diagram as shown in [Appendix Fig. 1](#), illustrated published literature evaluating regenerative medicine therapies identifying 5 systematic reviews (25-29) and 26 individual manuscripts which met the criteria for inclusion (247,253,270-293). All of the individual studies were included in the recent systematic review by Sanapati et al (29) since the appropriate methodologic quality, bias assessment and utilization in qualitative and quantitative evidence synthesis of those manuscripts met the inclusion criteria.

9.1 Systematic Reviews

The search criteria identified 5 systematic reviews (25-29). Of these, only 1 systematic review studied MSCs in spinal cord injury, intervertebral disc repair, and spinal fusion (25). This review identified almost 2,600 manuscripts; however, only 53 met eligibility criteria. Of these, there were 28 studies on intervertebral disc repair, 6 were on spinal cord injury, and 9 were on spinal fusion. This systematic review found that MSCs were a very good source for treatment of spinal conditions. They also concluded that, despite the source of cells which has varied within the publications, the overall majority of studies used BM-MSCs. Bone marrow has been described as the gold standard of MSC origin.

The systematic review by Wang et al (27) assessed the efficacy of intervertebral disc regeneration with stem cells using a meta-analysis of animal control studies. Consequently, this study was not included in the evidence synthesis.

The 3 remaining systematic reviews (26,27,29) were assessed for methodologic quality assessment by PRISMA and AMSTAR. They showed variable quality. Two systematic reviews included a single arm meta-analysis (28,29) and both were of high quality by AMSTAR and PRISMA criteria. The results of the assessment are shown in [Appendix Tables 6 and 7](#).

9.1.1 Analysis of Systematic Reviews

Wu et al (28) included 6 studies which were eligible for the review. From baseline to follow-up, they reported 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 (ODI) with no adverse effects. In view of the improved pain relief and disability scores, they concluded that cell-based therapy is an option for patients who have discogenic low back pain.

However, they recommended that stringently designed, randomized, double blind clinical trials with appropriately determined sample sizes will be needed to confirm the clinical efficacy and safety of cell-based therapy.

In their analysis, Wu et al (28) reported that 3 studies (253,270,271) used stem cells, 3 studies used chondrocytes (247,272,273), 5 studies used expanded cells (247,270-273) and 1 study used unexpanded cells (253) that were injected into the lumbar disc with a cell dose range from 1 to 23 ± 5 million cells. The mean follow-up time among the 6 trials (247,253,270-273) was 22 months. In 5 of these studies, the post-treatment clinical outcomes were assessed with the Numeric Rating Scale (NRS) and the Visual Analog Scale (VAS) (253,270,271,273).

Wu et al (28) also conducted a subgroup analysis to explore the source of heterogeneity in pain scores with respect to the follow-up periods (6 months vs. ≥ 12 months), the injected cell type (stem cell vs. chondrocyte), and the cell preprocessing conditions (expanded vs. non-expanded). Their analysis demonstrated no difference in the decreased pain score among these variables (28). Subsequent meta-regression analysis to determine factors that were related to the decrease in pain scores following stem cell therapy showed that the pain score decrease was related to cell type (stem cells vs. chondrocytes), with stem cells being more effective than chondrocytes in reducing pain.

In this same systematic review, Wu et al (28) also reviewed the MRI examinations. Four trials had reviewed the post-treatment MRIs for identification of any interval changes (247,271-273). One study found improvements in the post-treatment disc contour or height (272). Another study assessed the ratio of fluid content in affected discs compared to healthy discs and found that this ratio was low at the beginning of the treatment, was unchanged at 6 months, but showed an increase by 12 months (271). One study found a substantially higher normalization of disc fluid content (41%) in the autologous cultured disc derived chondrocyte treated group when compared with the control group (25%) (273). Another study (247) identified stability in the post-treatment MRI findings that extended over 3 years.

In a systematic review of regenerative therapies for intervertebral disc degeneration by Basso et al (26), identified 3 manuscripts that involved the use of PRP, and 4 manuscripts that involved the use of stem cells. Of the 7 manuscripts, 3 (247,271,281) manuscripts were included in the systematic review by Wu et al (28). The

number of patients included in these studies varied from 8 to 86. Five of the studies had very small sample sizes. Only 2 studies had larger sample sizes, 47 and 86. Timing of the follow-up examination was variable, extending from 8 weeks to 2 years. All of the studies reported that the intradiscal injection of PRP was safe and effective in relieving pain and increasing function. It should be kept in mind that the majority of these studies were small, observational reports or case series and, therefore, provide limited evidence for PRP injection therapy in the management of discogenic pain. The results of the various studies by Basso et al (26), are included in our tables which summarize the literature for PRP use in the treatment of intervertebral disc degeneration.

Sanapati et al (29) identified 26 manuscripts, of which 23 met the criteria for inclusion (247,253,270-293) (253,271-281,283-293) following the removal of duplicate publications (253,281). Three studies using stem cell therapy were excluded due to a sample size of fewer than 10 participants (247,270,282). Of the remaining 20 studies, 1 utilized 3 modalities of treatment (278). Results indicated Level III evidence for disc injections of PRP and MSCs, and Level IV evidence for epidural injections, lumbar facet joint injections, and sacroiliac joint injections. However, single arm meta-analysis was performed only for disc injections and epidural injections.

9.2 Analysis of Individual Studies

All the initial 26 manuscripts available for inclusion (247,253,270-293) were considered by Sanapati et al (29) with rigorous assessment for the inclusion criteria, methodologic quality, and risk of bias assessment and for inclusion in qualitative and quantitative analyses incorporating best evidence synthesis using a single arm meta-analysis. Consequently, no additional analysis was performed.

Based on the recent systematic review by Sanapati et al (29), including all the available manuscripts, and due to lack of any other manuscripts, no analysis of individual studies was conducted and the data from Sanapati et al was adapted.

9.3 Evidence Analysis and Synthesis

Evidence analysis and synthesis was performed for lumbar discogenic pain, lumbar facet joint pain, and sacroiliac joint pain. This evidence was adapted from the systematic reviews of Sanapati et al (29), Wu et al (28), and Basso et al (26). There was no additional evidence for inclusion. Summary characteristics of the

Table 7. Characteristics and outcomes of studies of PRP in intervertebral disc degeneration.

Study Details	Chronicity of Injury and Biologic Used	Follow-up Period	Conclusions
Tuakli-Wosornu et al, 2016 (277) Lumbar discogenic pain Prospective, double-blind, randomized controlled study, n=47	Chronic PRP injections	One year	Intradiscal injections of PRP x1 showed significant improvement at 8-week follow-up, with maintained improvement compared to controls at 1-year follow-up.
Monfett et al, 2016 (276) Lumbar discogenic pain, lumbar disc degeneration Prospective trial, n=29	Chronic PRP injections	2 years	Intradiscal PRP injections show continued safety and improvements in pain and function at 2 years post-procedure
Navani et al, 2018 (274) Lumbar discogenic pain Prospective case series n=20	Chronic PRP, single injection, 2mL injected up to 3 disc levels	18 months	At 18 months, 15 patients remained for survey compared to 18 patients surveyed at 6 months: >50% relief in VAS in 93% of patients at 18 months (n=14/15) and in 94% of patients (n=17/18) at 6 months (2). Improvement in SF-36 scores in 93% of patients at 18 months (n=14/15) compared to 100% (n=18/18) at 6 months.
Akeda et al, 2017 (279) Lumbar discogenic pain Preliminary clinical trial, n=14	Chronic PRP injections	12 months	Intradiscal injection of autologous PRP releasate in patients with low back pain was safe with no adverse events observed during follow-up The results showed reduction in mean pain scores at one month, sustained throughout the observation periods of 6 months and 12 months.
Levi et al, 2016 (275) Lumbar discogenic pain Prospective trial, n=8	Chronic PRP, single injection	6 months	Single or multiple levels (up to 5) of discogenic pain injected with PRP showed encouraging improvement, with more patients developing improvement over time. Cohort up to 6 months.
Kirchner and Anitua, 2016 (278) Lumbar disc degeneration Observational retrospective pilot study, n=86	Chronic PRGF-Endoret	6 months	Fluoroscopy-guided infiltrations of intervertebral discs and facet joints with PRGF in patients with chronic low back pain resulted in significant pain reduction assessed by VAS. The results showed reduction of the VAS over time. The study ended at 6 months with 91% of the patients showing an excellent score, 8.1% showing moderate improvement, and 1.2% showing lack of response.

PRP=platelet-rich plasma; PRGF = plasma rich in growth factors; VAS = Visual Analog Scale; SF-36= 36-item Short Form Survey

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; in press (29).

included studies are described in Tables 7-11. Methodologic quality assessment of all the manuscripts are shown in Tables 12-14.

9.3.1 Lumbar Disc Injections

9.3.1.1 Platelet-Rich Plasma

Both the methodologic quality assessment and the

risk of bias assessment have shown that the RCT (277) was of high quality based on the Cochrane review criteria and the IPM-QRB criteria as demonstrated in Tables 12 and 13 (29). All of the observational studies were of moderate quality (274-276,278,279) as assessed by the IPM-QRBNR criteria and as depicted in Table 14 (29).

Study characteristics are described in Table 7. Since there was only 1 RCT meeting the criteria (277), a 2-arm

Table 8. The characteristics and outcomes of the included studies of stem cell therapy in disc degeneration.

Study Details	Population	Cell/Solution Type	Cell or Solution Dose and Delivery Pathway	Outcome Parameters	Results	Conclusion
Noriega et al, 2017 (283) Sample size = 24 Follow-up = 12 months RCT	24 patients with chronic low back pain with lumbar disc degeneration and unresponsive to conservative treatments were randomized into 2 groups. Patient age (yrs) mean age \pm SE = 38 \pm 2 s	Allogeneic bone marrow MSCs by intradiscal injection or a sham infiltration of paravertebral musculature with anesthetic	The intervention group received allogeneic bone marrow MSCs by intradiscal injection of 25 X 10 ⁶ cells per segment under local anesthesia	VAS, ODI, MRI, SF-12	<ul style="list-style-type: none"> MSC-treated patients displayed a quick and significant improvement in all functional indices versus the controls. Both lumbar pain and disability were significantly reduced at 3 months and improvement was maintained at 6 and 12 months. <p>Overall there was an average 28% improvement in pain and disability one-year after the intervention.</p> <ul style="list-style-type: none"> Only 5 of the 12 outcomes in patients (40%) receiving MSCs were described as perfect treatment with 100% improvement. 	<ul style="list-style-type: none"> 28% improvement in all patients 40% of patients perfect result Positive result
Pettine et al, 2015, 2016, 2017 (253,280,281) Sample size = 26 Follow-up = 3 years Prospective, open-label, non-randomized, 2-arm study	26 patients presented with symptomatic moderate to severe discogenic low back pain Patient age (yrs) = 18–61 years (median 40)	Autologous bone marrow concentration (nonexpanded)	2–3 mL of bone marrow concentrate was injected in lumbar disc (1.66_106/ mL)	ODI, VAS, and MRI	<ul style="list-style-type: none"> The average ODI and VAS scores were reduced to 22.8 and 24.4 at 3 months. After 36 months, 6 patients proceeded to surgery. After 36 months, 20 of the 26 patients reported average ODI and VAS improvement to 17.5 \pm 3.2 and 21.9 \pm 4.4 respectively. One year MRI indicated 40% of patients improved one modified Pfirrmann Grade and no patient worsened radiographically. 	<ul style="list-style-type: none"> At 36-month follow-up, 6 of 26 patients progressed to surgery. The remaining 20 patients (77%) reported significant ODI and VAS improvements. Authors concluded that there were no adverse effects and the study provided evidence of safety and feasibility of intradiscal BMC therapy.
Coric et al, 2013 (272) Sample size = 15 Follow-up = 1 year Prospective cohort	15 patients with single-level, symptomatic lumbar DDD from L-3 to S-1 and medically refractory low back pain Patient age (yrs) = 19–47 years (median 40)	Expanded allogeneic juvenile chondrocyte cells	Mean 1.3 mL (1–2 mL, 107/mL) cells solution was injected in the center of the disc space	ODI and NRS scores, 36-item Short Form Health Survey and MRI	<ul style="list-style-type: none"> The mean ODI, NRS, and Short-form-36 physical component summary scores all improved significantly from baseline Ten (77%) of these 13 patients exhibited improvements on MRI. Of these, the HIZ was either absent or improved in 8 patients (89%) by 6 months Of the 10 patients who exhibited radiological improvement at 6 months, findings continued to improve or were sustained in 8 patients at the 12-month follow-up Only 3 patients (20%) underwent total disc replacement by the 12-month follow-up due to persistent, but not worse than baseline, LBP 	<ul style="list-style-type: none"> The results of this prospective cohort are promising with 77% of patients improving Positive result

Table 8 con't. The characteristics and outcomes of the included studies of stem cell therapy in disc degeneration.

Study Details	Population	Cell/Solution Type	Cell or Solution Dose and Delivery Pathway	Outcome Parameters	Results	Conclusion
Orozco et al, 2011 (271) Sample size = 10 Follow-up=1 year Pilot phase 1 trial	10 patients with degenerative disc disease and persistent low-back pain (>6 months; decrease of disc height >50%); Patient age (yrs)= 35_7 (mean_SD)	Autologous expanded bone marrow-derived mesenchymal stem cells	23±5X106 autologous expanded BMSCs was injected into the nucleus pulposus area	ODI and VAS scores and MRI	<ul style="list-style-type: none"> Patients exhibited rapid improvement of pain and disability (85% of maximum in 3 months) that approached 71% of optimal efficacy This study confirmed feasibility and safety with identification of strong indications of clinical efficacy 	<ul style="list-style-type: none"> Authors concluded that MSC therapy may be a valid alternative treatment for chronic back pain caused by degenerative disc disease. They also concluded that advantages over current gold standards include simpler and more conservative intervention without surgery, preservation of normal biomechanics, and same or better pain relief
Kumar et al, 2017 (284) Sample size = 10 Follow-up = 1 year Phase 1 study	10 patients with chronic low back pain lasting for more than 3 months with a minimum intensity of 4/10 on a visual analog scale and disability level ≥ 30% on the Oswestry Disability Index. Patient age (yrs)=between 19 & 70	Combined hyaluronic acid derivative and AT-MSCs	A single intradiscal injection at a dose of 2 X 107 cells/disc (N=5) or 4 X 107 cells/disc (N=5)	VAS, ODI, Short-form 36, lumbar spine x-ray, MRI	<ul style="list-style-type: none"> VAS, ODI, and SF-36 scores significantly improved in both groups receiving both low and high cell doses, and did not differ significantly between the 2 groups At 12-month follow-up 7 patients reported 50% or greater improvement in VAS 6 patients achieved treatment success with pain reduction of 50% or greater and improvement on disability scores on ODI Among 6 patients who achieved significant improvement in VAS, ODI, and SF-36, 3 patients were determined to have increased water content based on an increased apparent diffusion coefficient on diffusion MRI 	<ul style="list-style-type: none"> 60% significant improvement with no adverse effect Authors concluded that combined implantation of AT-MSCs and hyaluronic acid derivative in chronic discogenic low back pain is safe and tolerable Positive result
Mochida et al (247) Sample size =9 Follow-up=3 years Prospective clinical study	9 patients with Pfirrmann grade III disc degeneration and posterior lumbar intervertebral fusion. Patient age (yrs)=20-29 years	Autologous cultured nucleus pulposus chondrocytes that cocultured with MSCs	One million activated autologous NP cells were injected into the degenerated disc 7 d after fusion surgery	JOA scoring and MRI	<ul style="list-style-type: none"> Clinical outcomes based on Japanese Orthopedic Association (JOA) scoring system for low back pain showed significant improvement from 14.2 ± 4.8 points preoperatively to 27.2 ± 1.6 points at 3 years after transplantation of the activated NP cells (maximum possible score of 29 points) The JOA scoring system also showed improvement in low back pain subscale from 1.2 ± 0.5 points preoperatively to 2.7 ± 0.2 points at 3 years after the transplantation with maximum possible score of 3 points for no pain No adverse effects were observed during the 3-year follow-up period 	<ul style="list-style-type: none"> Significant improvement in function and pain scores was reported This study confirmed the safety of activated NP cell transplantation, and the findings suggest the minimal efficacy of this treatment to slow the further degeneration of human intervertebral discs

Table 8 con't. The characteristics and outcomes of the included studies of stem cell therapy in disc degeneration.

Study Details	Population	Cell/Solution Type	Cell or Solution Dose and Delivery Pathway	Outcome Parameters	Results	Conclusion
Meisel et al, 2006 (273) Sample size = 12 Follow-up=2 years	Patients with discogenic pain after repeat discograms. Patients were treated with cell therapy at least 3 months post the endoscopic. Patient age (yrs)= 18-75 years	Autologous cultured disc-derived chondrocytes (from surgical treatment of their disc prolapse)	Cells are injected into disc approximately 12 weeks following discectomy. The cell dose was not mentioned	ODI and VAS scores and MRI	<ul style="list-style-type: none"> The median total Oswestry Score was 2 in the autologous disc chondrocyte transplantation (ADCT) group compared with 6 in the control group. Decreases in the Disability index in autologous disc chondrocyte transplantation (ADCT)-treated patients correlated with the reduction of low back pain Decreases in disc height over time were only found in the control group, and of potential significance, intervertebral discs in adjacent segments appeared to retain hydration when compared to those adjacent to levels that had undergone discectomy without cell intervention 	<ul style="list-style-type: none"> Significant improvement Positive result

RCT = randomized controlled trial; BMSCs= Bone marrow derived stem cells; MSCs=medicinal signaling cells or mesenchymal stem cells; JOA = Japanese Orthopedic Association; MRI = magnetic resonance imaging; NP = nucleus pulposus; DDD=degenerative disc disease; BMC = bone marrow concentrate; LBP=low back pain; NRS = Numerical Rating Scale; ODI = Oswestry Disability Index; VAS = Visual Analog Scale; SD=standard deviation; SF-12=12-item short-form survey; HIZ-high intensity zone; adipose-tissue derived mesenchymal stem cells (AT-MSCs)

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; in press (29).

meta-analysis was not feasible (29). Thus, a single-arm meta-analysis was performed which included all of the studies. Since the study details of the RCT were only available through 8 weeks, the data from the RCT was not included in the long-term assessment. Figure 26 shows the single-arm meta-analysis from the decreased pain score data obtained after the 6-month follow-up evaluation. With a pooled sample size of 171, 5 of the studies demonstrated a decrease in the pain scores following treatment (274-276,278,279). The pooled mean difference in pain scores from baseline to 6-month follow-up was 40.29 ± 13.76 points (95% CI: -67.25 to -13.33, *P* < 0.001, *I*² 93.3%). Heterogeneity across the studies was high (*I*² = 98%).

Figure 26 shows the pain relief data obtained from the 12-month follow-up evaluation. Three studies with a pooled sample size of 63, were included and demonstrated a decrease in post-treatment pain scores (274,276,279). The pooled mean difference in pain scores from baseline to 12-month follow-up was 34.405 ± 6.879 points (95% CI: -47.88 to -20.92, *P* < 0.013, *I*² 77.2%). Heterogeneity across the studies was high (*I*² = 77%). The authors of the 3 studies utilized different tools for functional improvement, and detailed data from their findings was not available. As a result, a meta-analysis of functional improvement data was not feasible.

9.3.1.2 Medicinal Signaling Cells or Mesenchymal Stem Cells

A total of 9 manuscripts studying MSCs as cell-based therapies for lumbar discogenic low back pain (247,253,270-273,280-284) were identified (29). Of these, there was one RCT (283). Three manuscripts reported data from only a single study (253,280,281), 2 studies had a small sample size of only 2 patients each (270,282), and 1 study had a sample size of 9 patients (247). Consequently, only 6 studies met the inclusion criteria (271-273,280,283,284). The methodologic quality and risk of bias assessment of these studies showed high quality evidence for the RCT (283) based on both the Cochrane review and the IPM-QRB criteria as shown in Tables 12 and 13 (29). Five of the observational studies that met inclusion criteria showed moderate quality (271-273,280,284) utilizing the IPM-QRBNR criteria as shown in Table 14 (29).

Table 8 breaks down the characteristics and outcomes of these MCS therapy for lumbar discogenic pain studies (29).

Because Sanapati's et al's (29) systematic review contained data from only a single RCT (283), a 2-arm

Table 9. Summary of lumbar epidural injection PRP studies published to date.

Study Details	Population	Cell/Solution Type	Call or Solution Dose and Delivery Pathway	Outcome Parameters	Results	Conclusion
Becker et al, 2007 (293) Sample size=84 Follow-up = 6 months Randomized controlled trial	84 patients with chronic lumbar radicular pain Patient age (yrs)=29-81 (mean 53.9)	IL-1 RA-enriched autologous conditioned serum (Orthokine; ACS)	Transforaminal or perineural injection of ACS once per week for 3 consecutive weeks. Perineural space was approached through interlaminar space with injection of 1 mL of local anesthetic and autologous serum in Group 3. Group 1 received 1 mL of local anesthetic plus 2 mg of triamcinolone or 5 mg of triamcinolone	VAS, ODI	<ul style="list-style-type: none"> Patients in all 3 groups improved comparably. Results were significant within each treatment group from week 12 to the final evaluation at week 26. injections with ACS showed a consistent pattern of superiority over both triamcinolone groups with VAS, with no significant difference for ODI among the groups 	<ul style="list-style-type: none"> ACS showed similar response to triamcinolone injection with local anesthetic initially; however, with significant improvement at 26 weeks with pain relief, but not with function. Results similar to local anesthetic and steroid injections One of the limitations in this trial is that of multiple injections
Centeno et al, 2017 (291) Sample size=470 Follow-up=2 years Prospective registry	Patients suffering with lumbar radicular pain and MRI findings that were consistent with symptoms.	Platelet lysate	<ul style="list-style-type: none"> Transforaminal or interlaminar epidural injection under fluoroscopic guidance. The final injectate consisted of plasma lysate 50% by volume, 4% lidocaine at 25% by volume, and compounded preservative free 100 to 200 nanograms per mL of hydrocortisone at 25% by volume For transforaminal and interlaminar epidural injections, 3 to 5 cm³ volume was injected 	NPS, Modified SANE rating, FRI	<ul style="list-style-type: none"> Patients treated with platelet lysate epidurals reported significantly lower NPS and FRI change scores at all time points compared to baseline Posttreatment FRI change score means exceeded the minimal clinically important difference beyond one month Average modified SANE rating showed 49.7% improvement at 24 months posttreatment 29 or 6.3% patients reported mild adverse events related to treatment. 	<ul style="list-style-type: none"> Positive results with registry presenting real world data. A large proportion of patients withdrawn 36% of the patients failed to provide baseline NPS data Information on number of procedures is unknown 26% of the patients failed to show any significant improvement
Kumar et al, 2015 (292) Sample size=20 patients Follow-up= 6 months Prospective evaluation	20 patients with unilateral lumbar radiculopathy	ACS	<ul style="list-style-type: none"> Interlaminar injection with 2 mL of contrast followed by 2 mL of ACS A maximum of 3 injections at 7 days interval were given based on the clinical response 20 patients received number of injections ranging from 1 to 3 	VAS, ODI	<ul style="list-style-type: none"> There was significant improvement in pain relief and function with VAS improving from 6.95 to 2.0 and ODI improving from 27.9 to 8.5. 5 patients (20%) had complications which were immediate and systematic rather than local and were of short duration lasting less than 30 minutes 	<ul style="list-style-type: none"> Positive results with injection of ACS with disease modifying course with reduction of pain and disability Small sample size with injection of contrast, which may diminish the effect of ACS
Kirchner and Anitua, 2016 (278) Sample size=86 patients Follow-up = 6 months Observational retrospective pilot study	86 patients 47 females: age range 22 to 81, median age 58 39 males: age range 29 to 79 years, median age 55	86 patients each received one intradiscal, one intraarticular facet and one transforaminal epidural injection of plasma rich in growth factors	Transforaminal injection of 2 mL of activated PRGF after intradiscal injection of 4 mL of PRGF and facet joint infiltration	VAS	<ul style="list-style-type: none"> At the end of the study (6 months), 90.7% of the patients showed an excellent score, 8.1% showed a moderate VAS score, and 1.2% of patients were included in the ineffective score group There were no major adverse events 	<ul style="list-style-type: none"> Approximately 90% of the patients improved after 6 months Positive study Results are unreliable because of observational study and multiple injections into the disc, facet joint and with transforaminal application Number of injections are unknown

Table 9 con't. Summary of lumbar epidural injection PRP studies published to date.

Study Details	Population	Cell/Solution Type	Cell or Solution Dose and Delivery Pathway	Outcome Parameters	Results	Conclusion
Bhatia & Chopra, 2016 (290) Sample size=10 patients Follow-up=3 months Prospective evaluation	10 patients with findings of lumbar disc herniation/prolapse in MRI, or either sex with age less than 65 years	Platelet-rich plasma	Interlaminar epidural injection with 2 mL of PRP	VAS and ODI	Patients who had received epidural injections of autologous PRP showed improvements in their scores of evaluation tools. Improvement was sustained during the 3 month study period and was not associated with any complications.	Autologous PRP can be considered as a good alternative to epidural steroids and surgery in management of patients with chronic prolapsed intervertebral disc.

ODI = Oswestry Disability Index; VAS = Visual Analog Scale; PRGF=platelet-rich growth factor; PRP=platelet-rich plasma; ACS=Autologous conditioned serum; NPS=Numeric Pain Score; SANE=Single Assessment Numeric Evaluation, FRI=Functional Rating Index

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; in press (29).

meta-analysis was not feasible. They performed a single-arm meta-analysis utilizing the 6 available studies in addition to the single RCT (271-273,280,283,284). Inclusion of these 6 studies revealed a pooled sample size of 71 (271-273,281,283,284).

Based on a single arm meta-analysis, Fig. 27 plots the changes in the pain scores (271-273,281,283,284). The pooled mean difference in the decreased pain scores from baseline to the 12 month follow-up was 36.943 points (95% CI: -49.855 to -24.030, $P < 0.001$). Heterogeneity across the studies was high ($I^2 = 86\%$).

Figure 28 shows the functional scores. Six studies reported an ODI assessment (271-273,281,283,292). This data was available over 12 months. 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 ($I^2 = 55\%$).

9.3.2 Epidural Injections

Multiple biologics have been administered epidurally in the management of radicular pain (278,290-293). However, only preliminary data is available for these studies. There has been only 1 randomized, double blind, reference-controlled study that has evaluated epidurally administered biologics for the treatment of radicular pain (293). The others have been prospective or retrospective observational studies (278,290-292). The only systematic review assessing epidural biologic injections was performed by Sanapati et al (29). Methodologic quality and risk of bias assessment of their included studies (29) showed that one RCT was of high quality (293) based on the Cochrane review and the IPM-QRB criteria as shown in Tables 12 and 13. The assessment of observational studies by the IPM-QRBNR demonstrated moderate quality for each of these studies as shown in Table 14 (278,290-292).

Since there was only 1 randomized, double-blind, controlled trial (293), a 2-arm systematic review was not feasible (29). Consequently, a single-arm systematic review and meta-analysis was performed (Fig. 29) (29).

Table 9 shows summary characteristics of lumbar epidural injections of PRP studies.

9.3.3 Lumbar Facet Intraarticular Injections

The literature search by Sanapati et al (29) regarding the use of regenerative therapies for lumbar facet joint pain yielded 3 studies that assessed the role of PRP in lumbar facet joint injections (278,285,286). Of these 3 studies, only 1 study was randomized in its comparison of

Table 10. Summary of lumbar facet joint PRP studies published to date.

Study Details	Methods	Results	Conclusion
Wu et al, 2017 (286) Sample size=46 Follow-up=6 months Prospective randomized trial Chronic facet joint pain	46 patients with lumbar facet syndrome were randomized to intra-articular injections of PRP versus local anesthetic/corticosteroid Outcomes were assessed with VAS, ODI, and RMDQ	<ul style="list-style-type: none"> • Back pain improved in both groups immediately and at one month follow-up • At 3 months, back pain relief was superior in PRP injection group compared to steroid group • Functional status improvement was observed in both groups; however, at 3 months, there was significant improvement in PRP group compared to steroid group • Highest objective success rate with over 50% pain relief in 81% was found at 3 and 6 months after treatment, whereas highest success rate in 85% of the patients in the steroid group dissipated after one month 	<ul style="list-style-type: none"> • There was significant improvement in both groups in short-term. However, improvement was long lasting for 6 months in PRP group • Positive study • Limited with a small number of patients
Wu et al, 2016 (285) Sample size=19 Follow-up=3 months Prospective clinical evaluation Chronic facet joint pain	19 patients with lumbar facet syndrome given intra-articular injections of PRP Outcomes were assessed with VAS, ODI, and RMDQ	<ul style="list-style-type: none"> • 79% of the patients reported satisfactory improvement with good or excellent at 3 month follow-up after injection of PRP • ODI and RMDQ were also significantly improved. There were no adverse events. A positive small study of intraarticular injection of autologous PRP 	Positive results in a study with a small number of patients and relatively short follow-up of 3 months
Kirchner and Anitua, 2016 (278) Sample size=86 Follow-up = 6 months Observational retrospective pilot study, n=86 humans Facet Joint Syndrome	One intradiscal, one intra-articular facet, and one transforaminal epidural injection of PRGF under fluoroscopic guidance-control were carried out in 86 patients with chronic LBP.	VAS showed a statistically significant drop at 1, 3, and 6 months after the treatment ($P < 0.0001$) except for the pain reduction between the 3rd and 6th month whose significance was lower ($P < 0.05$).	<ul style="list-style-type: none"> • Positive study with multiple drawbacks with multiple injections in each setting with injection into disc, facet joint, and epidural space • Extremely high positive results in a low quality observational study

VAS=visual analog scale; ODI=Oswestry Disability Index; RMDQ=Roland Morris Disability Questionnaire; PRP=platelet-rich plasma; PRGF=platelet-rich growth factor; LBP=low back pain

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; in press (29).

PRP to a local anesthetic combined with a corticosteroid (286). The methodologic quality assessment of lumbar facet intraarticular injections demonstrated that the single RCT (286) was of high quality by the Cochrane review quality and the IPM-QRB criteria as shown in Tables 12 and 13. The remaining 2 studies (278,285) demonstrated moderate quality based on the IPM-QRBNR criteria as shown in Table 14. Of the 3 studies, 2 were performed by the same group of authors and had sample sizes of 19 (285) and 46 (286). The third study performed by Kirchner and Anitua (278) was a complicated study using multiple injections (intradiscal, facet joint, as well as transforaminal) and reported excellent results. Because of the limitations of these 3 studies, a meta-analysis could not be performed. The summary characteristics of these studies are listed in Table 10.

9.3.4 Sacroiliac Joint Injection

The effectiveness of biologicals, specifically PRP, has been evaluated by 1 RCT (287) and 2 observational studies (288,289). The methodologic quality and risk of bias assessment of sacroiliac joint injections showed that the RCT (287) was of high quality based on the Cochrane review criteria and was of moderate quality based on the IPM-QRB criteria as shown in Tables 12 and 13. Of the 2 observational studies (288,289), 1 study was of moderate quality (288) while the second study one was of low quality (289) as shown in Table 14.

Because of the minimal number of studies with only 1 study performed as an RCT (287-289), a meta-analysis could not be performed. Table 11 describes a summary of the studies of sacroiliac joint PRP injections.

Table 11. Summary of sacroiliac joint injection PRP studies published to date.

Study Details	Methods	Results	Conclusion
Singla et al, 2017 (287) Sample size=40 Follow-up=3 months Prospective, randomized open blinded endpoint study Chronic low back pain with sacroiliac joint pathology	Patients were randomized into 2 groups with one group receiving 1.5 mL of methylprednisolone 40 mg/mL and 1.5 mL of 2% lidocaine with 0.5 mL of saline, whereas, PRP group receiving 3 mL of leukocyte free PRP with 0.5 mL of calcium chloride with ultrasound guided sacroiliac joint injection Outcomes were assessed with VAS scores, ODI, and SF-12	<ul style="list-style-type: none"> At 3-month follow-up, 90% of the patients reported satisfactory relief with PRP; whereas, satisfactory relief was observed in 25% of the patients receiving steroids. A strong association was observed in patients receiving PRP and showing a reduction of VAS of greater than 50% from baseline 	<ul style="list-style-type: none"> Positive first prospective, randomized study Small number of patients
Navani & Gupta, 2015 (288) Sample size=10 (4 males, 6 females) with sacroiliac joint pain of greater than 6 months duration Age Distribution=5 patients below 40 and 5 patients over 40 Sacroiliac joint pain	Sacroiliac joint injection under fluoroscopic guidance with PRP	<ul style="list-style-type: none"> All patients improved 3 months post injection and maintained low pain levels not requiring any additional treatment up to 6 months post injection SF-36 demonstrated improvement in both physical component summary scores and mental component summary scores in all patients No adverse events 	A positive case series of 10 patients
Ko et al, 2017 (289) Sample size=4 Follow-up=2 yrs. Case series	Sacroiliac joint injection with PRP under ultrasound Outcomes were assessed with Short form, McGill Pain Questionnaire, NRS, and ODI	<ul style="list-style-type: none"> At 12-month follow-up there was marked improvement in joint stability, a statistically significant reduction in pain, and improvement in quality of life The clinical benefits of PRP were still significant at 4 years post treatment 	PRP showed long lasting positive results in this short case series of 4

PRP=platelet-rich plasma; SF-36=36-item short form health survey; VAS=Visual Analog Scale; ODI=Oswestry Disability Index; SF-12=12-item short form health survey; NRS=Numeric Rating Scale

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; in press (29).

Table 12. Methodological quality assessment of randomized trials utilizing Cochrane review criteria.

	Tuakli-Wosornu et al (277)	Becker et al (293)	Wu et al (286)	Singla et al (287)	Noriega et al (283)
Randomization adequate	Y	Y	Y	Y	Y
Concealed treatment allocation	Y	Y	Y	Y	Y
Patient blinded	Y	Y	Y	Y	Y
Care provider blinded	Y	N	Y	N	N
Outcome assessor blinded	Y	Y	Y	Y	Y
Drop-out rate described	Y	Y	Y	Y	Y
All randomized participants analyzed in the group	Y	Y	Y	Y	Y
Reports of the study free of suggestion of selective outcome reporting	Y	Y	Y	Y	Y
Groups similar at baseline regarding most important prognostic indicators	Y	Y	Y	Y	Y
Co-interventions avoided or similar	Y	Y	Y	Y	Y
Compliance acceptable in all group	Y	Y	Y	Y	Y
Time of outcome assessment in all groups similar	Y	Y	Y	Y	Y
Are other sources of potential bias likely	Y	Y	Y	Y	Y
Score	13/13	12/13	13/13	12/13	12/13

Y = Yes; N = No; U = Unclear

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; in press (29).

Table 13. Methodologic quality assessment of randomized trials utilizing IPM – QRB.

		Tuakli- Wosornu et al (277)	Becker et al (293)	Wu et al (286)	Singla et al (287)	Noriega et al (283)
I.	TRIAL DESIGN AND GUIDANCE REPORTING					
1.	CONSORT or SPIRIT	0	0	0	0	0
II.	DESIGN FACTORS					
2.	Type and Design of Trial	3	2	2	2	3
3.	Setting/Physician	3	2	3	3	1
4.	Imaging	3	3	3	1	3
5.	Sample Size	2	2	2	1	0
6.	Statistical Methodology	1	2	1	1	1
III.	PATIENT FACTORS					
7.	Inclusiveness of Population	2	2	2	2	2
8.	Duration of Pain	2	2	2	2	2
9.	Previous Treatments	2	2	2	2	2
10.	Duration of Follow-up with Appropriate Interventions	2	2	1	0	2
IV.	OUTCOMES					
11.	Outcomes Assessment Criteria for Significant Improvement	2	2	4	1	4
12.	Analysis of all Randomized Participants in the Groups	2	2	2	2	2
13.	Description of Drop Out Rate	1	1	1	1	1
14.	Similarity of Groups at Baseline for Important Prognostic Indicators	2	2	2	2	2
15.	Role of Co-Interventions	1	1	1	1	1
V.	RANDOMIZATION					
16.	Method of Randomization	2	2	2	2	2
VI.	ALLOCATION CONCEALMENT					
17.	Concealed Treatment Allocation	2	2	2	2	2
VII.	BLINDING					
18.	Patient Blinding	1	2	1	1	1
19.	Care Provider Blinding	1	0	0	0	0
20.	Outcome Assessor Blinding	1	2	1	1	0
VIII.	CONFLICTS OF INTEREST					
21.	Funding and Sponsorship	0	2	0	0	3
22.	Conflicts of Interest	2	2	2	2	0
TOTAL		37	39	36	29	34

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; in press (29).

9.4 Assessment of Evidence

Evidence was assessed for intradiscal, epidural, lumbar facet, and sacroiliac joint injections.

9.4.1 Intradiscal Injections

Evidence for intradiscal injections was based on the use of 2 injected biologicals, either PRP or MSCs.

9.4.1.1 Platelet-Rich Plasma

Based on the available evidence, including 1 high-quality RCT (90), multiple moderate-quality observational studies (274-276,278,279), a single-arm meta-analysis, and evidence from a systematic review (26), the qualitative evidence has been assessed as Level III (on a scale of Level I through V) using a qualitative

Table 14. IPM checklist for assessment of nonrandomized or observational studies meeting inclusion criteria utilizing IPM - QRBNR.

	Pettine et al (253,280,281)	Navani et al (274)	Levi et al (275)	Coric et al (272)	Orozco et al (271)	Meisel et al (273)	Kumar et al (284)	Monfett et al (276)
I. STUDY DESIGN AND GUIDANCE REPORTING								
1. STROBE or TREND GUIDANCE	3	1	3	1	2	1	2	1
II. DESIGN FACTORS								
2. Study Design and Type	2	1	1	1	1	1	2	1
3. Setting/Physician	2	3	2	2	2	2	2	2
4. Imaging	3	3	3	3	3	3	3	3
5. Sample Size	0	0	0	0	0	0	0	0
6. Statistical Methodology	2	0	0	0	0	0	0	0
III. PATIENT FACTORS								
7. Inclusiveness of Population	4	4	4	4	4	4	4	4
8. Duration of Pain	2	2	2	2	2	2	2	2
9. Previous Treatments	2	2	2	2	2	2	2	2
10. Duration of Follow-up with Appropriate Interventions	4	2	2	3	3	4	3	4
IV. OUTCOMES								
11. Outcomes Assessment Criteria for Significant Improvement	2	2	2	0	0	0	2	0
12. Description of Drop Out Rate	2	2	2	2	2	2	2	2
13. Similarity of Groups at Baseline for Important Prognostic Indicators	0	0	0	0	0	0	0	0
14. Role of Co-Interventions	2	2	2	2	2	2	2	2
V. ASSIGNMENT								
15. Method of Assignment of Participants	0	0	0	0	0	0	0	0
VI. CONFLICTS OF INTEREST								
16. Funding and Sponsorship	1	2	1	1	1	1	1	0
TOTAL	31	26	26	23	24	24	27	23

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; in press (29).

Table 14 (cont.). IPM checklist for assessment of nonrandomized or observational studies of IPM techniques utilizing IPM - QRBNR.

	Akeda et al (279)	Kirchner & Anitua (278)	Wu et al (285)	Navani & Gupta (288)	Ko et al (289)	Bhatia & Chopra (290)	Centeno et al (291)	Kumar et al (292)
I. STUDY DESIGN AND GUIDANCE REPORTING								
1. STROBE or TREND GUIDANCE	1	2	2	1	0	2	1	2
II. DESIGN FACTORS								
2. Study Design and Type	1	1	2	1	0	2	2	1
3. Setting/Physician	2	2	2	3	1	3	3	2
4. Imaging	3	3	3	3	1	3	3	3
5. Sample Size	0	0	0	0	0	0	0	0
6. Statistical Methodology	2	2	2	0	0	0	2	2
III. PATIENT FACTORS								
7. Inclusiveness of Population	2	4	4	4	1	0	2	2
8. Duration of Pain	1	2	2	2	2	2	2	2
9. Previous Treatments	2	2	2	2	2	2	2	2
10. Duration of Follow-up with Appropriate Interventions	2	3	1	2	0	0	0	2
IV. OUTCOMES								
11. Outcomes Assessment Criteria for Significant Improvement	0	2	2	2	2	0	1	1
12. Description of Drop Out Rate	2	2	2	2	2	2	2	2
13. Similarity of Groups at Baseline for Important Prognostic Indicators	0	0	0	0	0	0	0	0
14. Role of Co-Interventions	2	2	2	2	2	2	2	2
V. ASSIGNMENT								
15. Method of Assignment of Participants	0	0	0	0	0	0	0	0
VI. CONFLICTS OF INTEREST								
16. Funding and Sponsorship	2	2	2	2	2	2	2	2
TOTAL	22	29	28	26	15	20	24	26

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; in press (29).

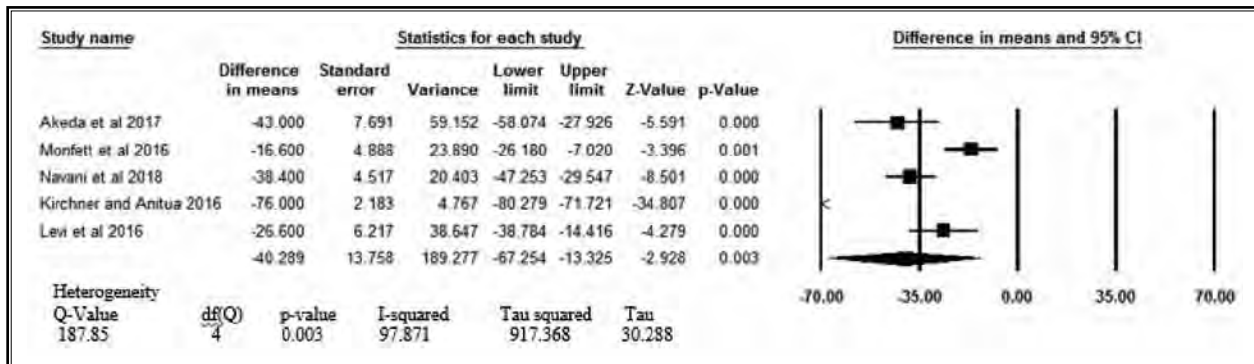


Fig. 25. Decreased pain score (numerical rating scale or visual analog scale, 0-100) after treatment (6-month follow-up data) of lumbar disc injections of PRP.

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 (29).

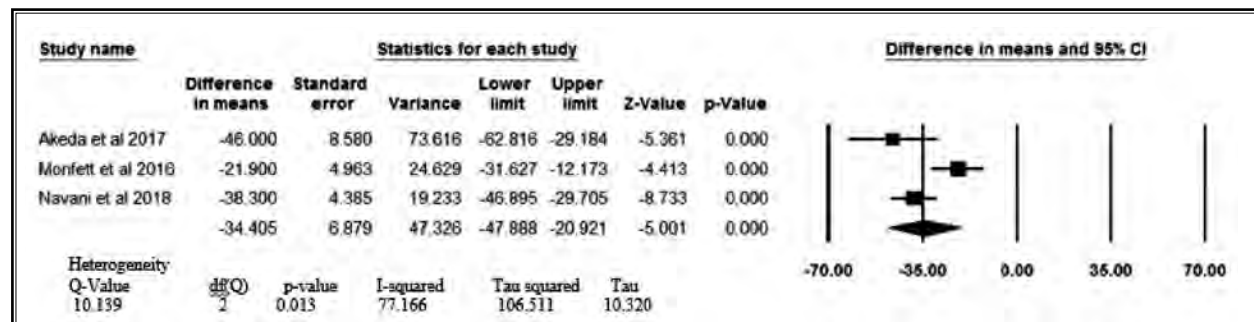


Fig 26. Pain scores (numerical rating scale or visual analog scale, 0-100) after treatment (12-month follow-up data) with lumbar disc PRP injections.

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 (29).

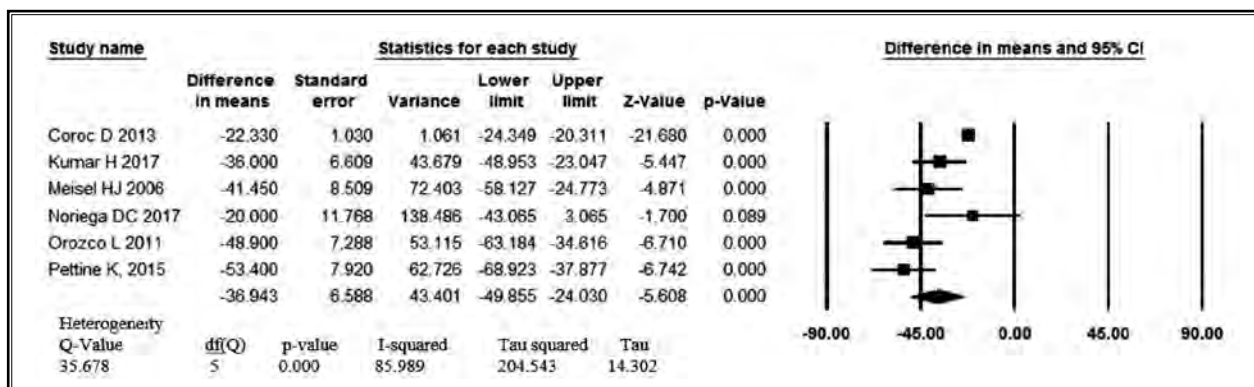


Fig 27. Changes in pain score (numerical rating scale or visual analog scale, 0-100) after treatment (12 months follow data) of cell therapy of lumbar disc.

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 (29).

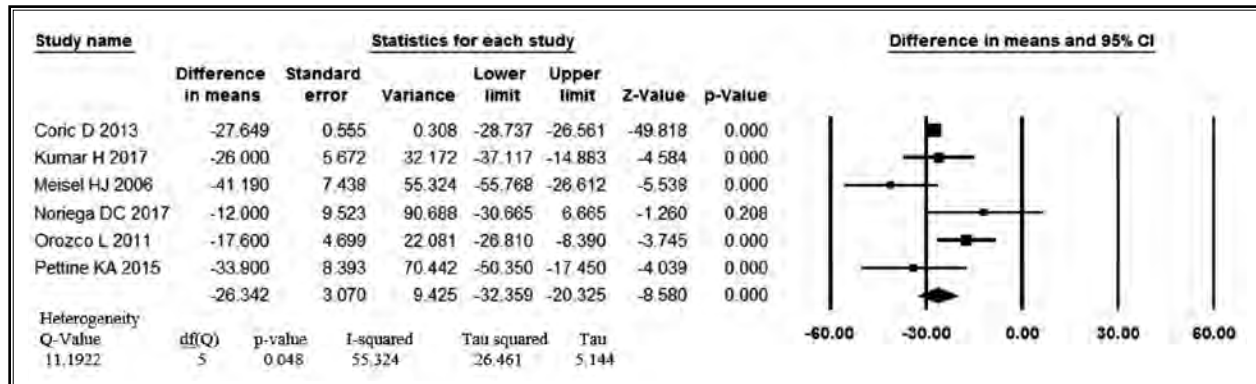


Fig 28. Changes in Oswestry Disability Index (ODI) after treatment (12 months follow data) of cell therapy of lumbar disc.

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 (29).

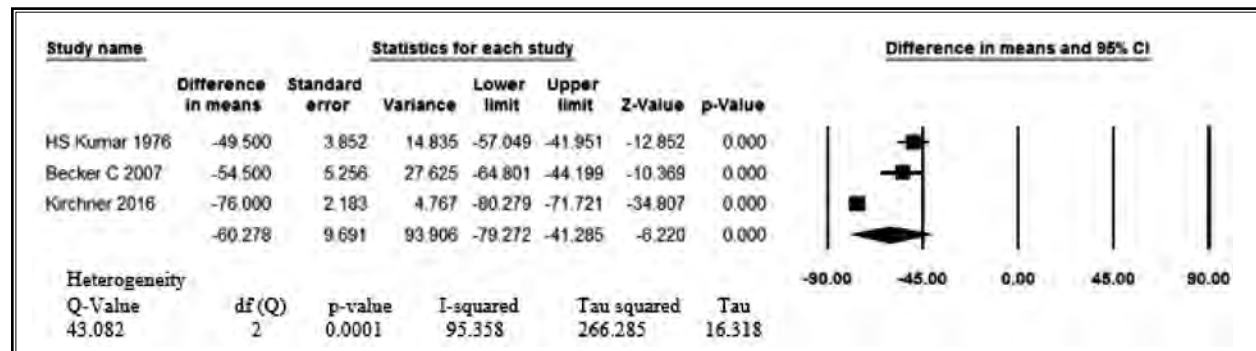


Fig 29. Changes in pain scores (0-100) after treatment (6 months follow data) of epidural PRP injections.

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 (29).

modified approach to the grading of evidence based on best-evidence synthesis.

9.4.1.2 Medicinal Signaling Cells or Mesenchymal Stem Cells

Based on the available evidence with a high-quality RCT (283), multiple moderate-quality observational studies (271-273,280,284), a single-arm meta-analysis, and 2 systematic reviews (26,28), the qualitative evidence has been assessed as Level III (on a scale of Level I through V) using a qualitative modified approach to the grading of evidence based on best evidence synthesis.

9.4.2 Epidural Injections

Based on 1 high-quality RCT (293), multiple rele-

vant moderate-quality observational studies (278,290-293) and a single-arm meta-analysis, the qualitative evidence has been assessed as Level IV (on a scale of Level I through V) using a qualitative modified approach to the grading of evidence based on best evidence synthesis.

9.4.3 Lumbar Facet Joint Injections

Based on 1 high-quality RCT (286) and 2 moderate-quality observational studies (278,285), the qualitative evidence for facet joint injections with PRP has been assessed as Level IV (on a scale of Level I through V) using a qualitative modified approach to the grading of evidence based on best evidence synthesis.

9.4.4 Sacroiliac Joint Injection

Based on 1 high-quality RCT (287), 1 moderate-quality observational study (288), and 1 low-quality case report (289), the qualitative evidence has been assessed as Level IV (on a scale of Level I through V) using a qualitative modified approach to the grading of evidence based on best evidence synthesis.

9.5 Summary of Evidence

Based on systematic reviews and individual studies, the summary of evidence is as follows:

1. Utilizing best evidence synthesis principles based on 3 systematic reviews (26,28,29) and 6 individual studies of PRP (274-276,278,279) and MSCs (271-273,280,284), the evidence for biologic management of lumbar discogenic pain has been assessed as Level III of V for PRP and MSC therapy.
2. Utilizing best evidence synthesis principles based on a single systematic review (29) and 3 individual studies (278,285,286), the evidence for management of lumbar facet joint disorders has been assessed as Level IV of V for PRP.
3. Utilizing best evidence synthesis principles based on a single systematic review (29), and 5 individual studies (278,290-293), the evidence for management of low back and lower extremity pain with epidural biologic injections has been assessed as Level IV of V for PRP.
4. Utilizing best evidence synthesis principles based on one systematic review (29), and 3 individual studies (287-289), the evidence for biologic management of sacroiliac joint pain has been assessed as Level IV of V for PRP.

10.0 CURRENT GUIDELINES FOR BIOLOGICS IN INDUSTRY AND REGULATORY AGENCIES

Key Question 7. What are the current guidelines for the use of biologics?

10.1 FDA/WHO as Regulatory Agency for Biologic Therapies

A multitude of regulatory and ethical challenges exist in the application of regenerative medicine therapies for the treatment of various chronic pain conditions (33,34,35,37,38,294-316). Of the 3 commonly used biologics, PRP and MCSs from bone marrow aspirate appear to be the least controversial, whereas adipose-derived MCSs appear to be the most controversial.

The World Health Organization (WHO) serves as the directing and coordinating authority for health

within the United Nations system. The World Health Assembly initiated the preparation of the first WHO Guiding Principles on Transplantation, which were endorsed by the Assembly in 1991, and which were most recently updated in 2010. These guidelines target appropriateness for use, human ethics, trafficking, availability of organs/obtainment, and discrepancy in costs among countries (294). They also encourage the registry of all providers and users of biologic products to collect global information regarding safety and adverse reactions (295).

Taylor-Weiner and Graff Zivin (299) described the unlicensed stem cell clinics in the United States as medicine's "Wild West". They reported that regardless of whether or not stem-cell therapy holds great potential, the field is less advanced than the public has been led to believe. They also point out that the majority of therapies offered by these stem cell clinics use adipose-derived stem cells packaged as a product called stromal vascular fraction (SVF) and that procedures using SVF have become increasingly popular because of the relative ease of acquiring the cells. They reveal that in the production of SVF, clinics collect liposuction aspirate from a patient, chemically separate the stem cells from the surrounding fat tissue, and administer the isolated cells back to the patient intravenously or by injection into the tissue to be treated. They also state that although it is easy to obtain SVF, the treatments are unproven and these stem cell clinics have been operating without regulation because of ambiguous FDA guidelines. In multiple manuscripts, the FDA (33,38,297) has warned that the current excitement over the potential for stem cell therapy to improve patient outcomes or even cure diseases must be accompanied by the understanding of its risks and benefits with the development of therapeutic approaches being based strictly on sound scientific evidence. The FDA continues to express concerns regarding stem cell therapy due to the lack of scientific evidence. Turner also described multiple issues related to the use of adipose-derived autologous stem cell interventions (37).

At the center of these contentious arguments is the fact that the FDA has not approved any adipose-derived stem cell medical products for the U.S. marketplace to date. Providers performing adipose-derived stem cell interventions claim that they are engaged in the practice of medicine, and that the FDA does not directly regulate the practice of medicine (33,35,37,38,297,303-305,309,310). Turner (37) believes that these procedures do not fall under the same surgical procedure exception

Table 15. *Categories of human cells, tissues, or cellular and tissue-based products (HCT/Ps).*

HCT/P
Cardiovascular tissue
Cell-derived therapeutic products (e.g., pancreatic islets, mesenchymal stem or stromal cells, fibroblasts)
Dura mater
Hematopoietic progenitor cells derived from peripheral or cord blood (including hematopoietic stem cells)
Musculoskeletal tissue (include adipose-derived stem cells)
Ocular tissue
Placenta or amnion
Reproductive cells and tissues
Skin
Not HCT/P
Blood vessels that are a part of an organ intended for transplantation
Human collagen
Human milk
In vitro diagnostic products
Minimally manipulated bone marrow for homologous use and not combined with another article (with a few exceptions described in the tissue regulations)
Nonhuman cells, tissues, or organs
Vascular composite allografts
Vascularized human organs for transplantation
Whole blood or blood components, including platelet-rich plasma

Source: Marks P, Gottlieb S. Balancing safety and innovation for cell-based regenerative medicine. *N Engl J Med* 2018 378:954-959 (297).

identified in 21 CFR 1271; however, many practitioners disagree with Turner (310). Guidance for the industry, issued by the FDA, currently addresses what actions clinicians and manufacturers can perform while remaining within the scope of the exception (297,303,304).

10.2 Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps)

Marks and Gottlieb (297) described the regulatory context for regenerative medicine. To implement comprehensive policy framework, the FDA's statutory authority in this area is based in part on the Public Health Service (PHS) Act. Section 351 of this Act provides the FDA with authority surrounding the licensure of biologic products, and Section 361 mandates that the agency will issue and enforce regulations necessary to prevent the introduction, transmission, or spread of infectious disease. That regulatory framework is risk-based and is divided into human cells, tissues, cellular, and tissue-based products (HCT/Ps) (297).

The products that are regulated under both Sections 351 and 361 of the Act are biologic products and must be studied under the provisions set forth for in-

vestigational new drugs (303). Furthermore, the manufacturers of such products are required to submit a biologics license application to the FDA for approval of their products before marketing. This creates a discrepancy since the products that are regulated solely under Section 361 and under the implementing regulations do not need premarket approval. Instead of premarket approval, these products require registration and listing with the FDA prior to marketing. However, these products still must be produced in compliance with the appropriate provisions in order to prevent the transmission of infectious diseases (297).

The decision pertaining to the regulatory pathway to be followed for a given product rests in part on whether the product meets or does not meet the criteria of the regulations promulgated under the Code of Federal Regulations part 1271 of Title 21 of 2005. Under this section, products that are regulated solely under Section 361 generally are those that do not undergo substantial processing (requiring only minimal manipulation), are used in a manner for the recipient that is similar to that of the donor (homologous use), are not combined with another drug or biologic prod-

ucts, and do not have a systematic effect unless they are designed for autologous transplantation, first- or second-degree-related allogeneic transplantation, or have been designed for reproductive use as shown in Table 15 (297). Thus, any HCT/P products other than tissue such as corneas and heart valves, are regulated as drugs, biologics, or devices and require the appropriate regulatory submissions for the conduct of clinical trials and marketing (297). Figure 30 illustrates in a flow chart how manufacturers and health care providers should apply the criteria outlined in 21 CFR 1271 to determine if a product meets the definition of an HCT/P (303).

In summary, an HCT/P product is regulated solely under Section 361 of the PHS Act and 21 CFR Part 1271 if it meets all of the following criteria (297,303,304):

- 1) The HCT/P is minimally manipulated;
- 2) The HCT/P is intended for homologous use only, as reflected by the labeling, advertising, or other indications of the manufacturer's objective intent;
- 3) The manufacture of the HCT/P does not involve the combination of the cells or tissues with another article, except for water, crystalloids, or a sterilizing, preserving, or storage agent, provided that the

addition of water, crystalloids, or the sterilizing, preserving, or storage agent does not raise new clinical safety concerns with respect to the HCT/P; and

- 4) Either:
 - i) The HCT/P does not have a systemic effect and is not dependent upon the metabolic activity of living cells for its primary function; or
 - ii) The HCT/P has a systemic effect or is dependent upon the metabolic activity of living cells for its primary function, and:
 - a) Is for autologous use;
 - b) Is for allogeneic use in a first-degree or second-degree blood relative; or
 - c) Is for reproductive use.

If an HCT/P does not meet the criteria set out in 21 CFR 1271.10(a), and if the establishment that manufactures the HCT/P does not qualify for any of the exceptions in 21 CFR 1271.15, the HCT/P will be regulated as a drug, device, and/or biological product under the FD&C Act, and/or section 351 of the PHS Act (42 U.S.C. 262), and applicable regulations, including 21 CFR Part 1271, and premarket review of the product will be required.

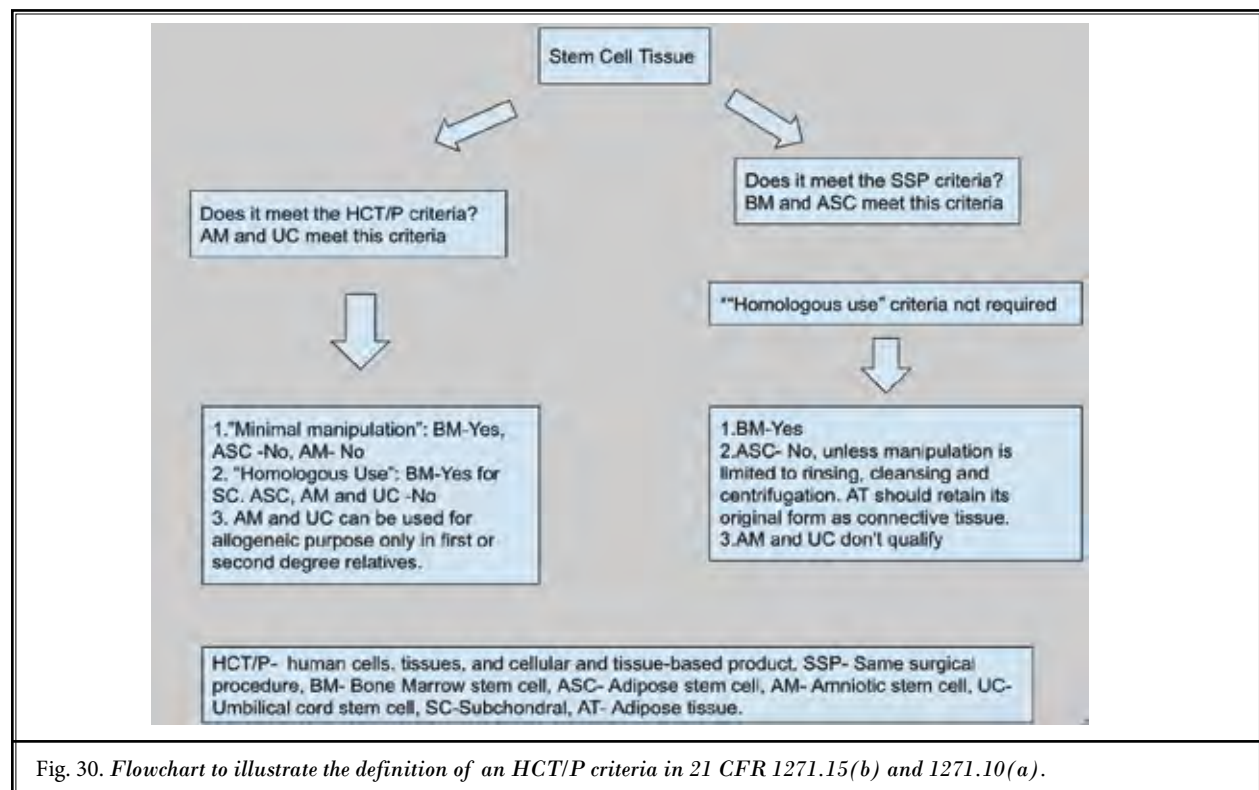


Fig. 30. Flowchart to illustrate the definition of an HCT/P criteria in 21 CFR 1271.15(b) and 1271.10(a).

10.3 Minimal Manipulation

Section 1271.10(a)(1) (21 CFR 1271.10(a)(1)) provides that one of the criteria for an HCT/P to be regulated solely under section 361 of the PHS Act and the regulations in Part 1271 is that the HCT/P is minimally manipulated (297,303,304). As defined in 21 CFR 1271.3(f), minimal manipulation means:

- 1) For structural tissue, processing that does not alter the original relevant characteristics of the tissue relating to the tissue's utility for reconstruction, repair, or replacement;
- 2) For cells or nonstructural tissues, processing that does not alter the relevant biological characteristics of cells or tissues.

The FDA noted that if information does not exist to show that the processing meets the definition of minimal manipulation, the FDA considers the processing of an HCT/P to be "more than minimal manipulation" and cannot qualify for regulation solely under section 361 of the PHS Act and 21 CFR Part 1271 (297,303,304).

Section 1271.3(f) provides two definitions of minimal manipulation, one that applies to structural tissue and one that applies to cells or nonstructural tissues. For structural tissue, minimal manipulation means that the processing of the HCT/P does not alter the original relevant characteristics of the tissue relating to the tissue's utility for reconstruction, repair, or replacement (21 CFR 1271.3(f)(1)). For cells or nonstructural tissues, minimal manipulation means that the processing of the HCT/P does not alter the relevant biological characteristics of cells or tissues (21 CFR 1271.3(f)(2)).

Original relevant characteristics of structural tissues generally include the properties of that tissue while in the donor that contribute to the tissue's function or functions. Similarly, relevant biological characteristics of cells or nonstructural tissues generally include the properties of the cells or nonstructural tissues within the donor that contribute to the cell's or tissue's function(s). Processing that alters the original characteristics of the HCT/P, raises increased safety and effectiveness concerns for the HCT/P because there would be less basis on which to predict the product's function after transplantation (303). Thus, the determination of whether an HCT/P is minimally manipulated is based on the effect that manufacturing has on the original relevant characteristics of the HCT/P as the HCT/P exists within the donor, and is not based on the intended use of the HCT/P in the recipient.

Processing is defined as any activity performed on an HCT/P, other than recovery, donor screening, donor testing, storage, labeling, packaging, or distribution, such as testing for microorganisms, preparation, sterilization, steps to inactivate or remove adventitious agents, preservation for storage, and removal from storage (21 CFR 1271.3(ff)). Processing also includes cutting, grinding, shaping, culturing, enzymatic digestion, and decellularization (303).

Tissues that physically support or serve as a barrier or conduit, or connect, cover, or cushion in the donor are generally considered structural tissues for the purposes of determining the applicable regulatory definition (i.e., bone, skin).

Adipose tissue is considered a structural tissue for the purpose of applying the HCT/P regulatory framework. Adipose tissue is typically defined as a connective tissue composed of clusters of cells (adipocytes) surrounded by a reticular fiber network and interspersed small blood vessels, divided into lobes and lobules by connective tissue septa (313). Additionally, adipose tissue contains other cells, including preadipocytes, fibroblasts, vascular endothelial cells, and macrophages (317,318). Adipose tissue provides cushioning and support for other tissues, including the skin and internal organs, stores energy in the form of lipids, and insulates the body, among other functions. While adipose tissue has multiple functions, because it is predominantly composed of adipocytes and surrounding connective tissues that provide cushioning and support to the body, the FDA considers adipose tissue to be a structural tissue for the purpose of applying the HCT/P regulatory framework.

To evaluate whether processing of adipose tissue would meet the regulatory definition of minimal manipulation, one should consider whether the processing alters the original relevant characteristics of the adipose tissue relating to its utility to provide cushioning and support (Fig. 31). An opposition view may consider the presence of stem cells within adipose tissue as an indication that this tissue also functions as a repository for regenerative factors.

10.4 Homologous Use

Section 1271.10(a)(2) (21 CFR 1271.10(a)(2)) provides that one of the criteria for an HCT/P to be regulated solely under section 361 of the PHS Act and the regulations in Part 1271 is that the "HCT/P is intended for homologous use only, as reflected by the labeling, advertising, or other indications of the manufacturer's objective intent."

As defined in 21 CFR 1271.3(c), homologous use means 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. This criterion reflects the FDA's conclusion that there would be increased safety and effectiveness concerns for HCT/Ps that are intended for a non-homologous use, because there is less basis on which to predict the product's behavior, whereas HCT/Ps for homologous use can reasonably be expected to function appropriately (assuming all of the other criteria are also met) (303,304).

In applying the homologous use criterion, the FDA will determine what the intended use of the HCT/P is, as reflected by the labeling, advertising, and other indications of a manufacturer's objective intent, and will then apply the homologous use definition.

Homologous use means 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 1271.3(c)), including when such cells or tissues are for autologous use:

- Recipient cells or tissues that are identical (e.g., skin for skin) to the donor cells or tissues, and perform one or more of the same basic functions in the recipient as the cells or tissues performed in the donor; or,
- Recipient cells or tissues that may not be identical to the donor's cells or tissues, but that perform one or more of the same basic functions in the recipient as the cells or tissues performed in the donor (319-321).

For the purpose of applying the HCT/P regulatory framework, the same basic function or functions of HCT/Ps are considered to be those basic functions that the HCT/P performs in the body of the donor, which, when transplanted, implanted, infused, or transferred, the HCT/P would then be expected to perform in the recipient. It is not necessary for the HCT/P in the recipient to perform all of the basic functions it performed in the donor in order to meet the definition of homologous use. However, to meet the definition of homologous use, any of the basic functions that the HCT/P is expected to perform in the recipient must be a basic function that the HCT/P performed in the donor.

The use of an HCT/P from adipose tissue for the repair, reconstruction, replacement, or supplementation of adipose tissue would be considered a homologous use. In these situations, the FDA would consider the HCT/P from adipose tissue to be performing the same basic function in the recipient as in the donor. In contrast, the use of an HCT/P from adipose tissue for the treatment of a degenerative, inflammatory, or demyelinating disorder would generally be considered a non-homologous use. Figure 31 illustrates how manufacturers and healthcare providers should apply the criteria outlined in 21 CFR 1271.15(b) and 1271.10(a) for HCT/Ps (303).

10.5 Regulatory Scope and Compliance Policy

This guidance only applies to products and establishments that are subject to FDA's regulations in 21 CFR Part 1271. Establishments that meet the same surgical procedure exception in 21 CFR 1271.15(b) are not subject to FDA's regulations in 21 CFR Part 1271.

This guidance also does not apply to products that fall outside the definition of HCT/P in 21 CFR 1271.3(d). For example, PRP (blood taken from an individual and given back to the same individual as PRP) is not an HCT/P under Part 1271 because it is a blood product. Accordingly, FDA does not apply the criteria in 21 CFR 1271.10(a) to PRP, and PRP is outside the scope of this guidance.

10.6 FDA's Comprehensive Framework for Regenerative Medicine

As per Marks and Gottlieb (297), the FDA recognizes the time and effort that go into the creation of regulatory submission and the effect that working through the regulatory process can have on timelines for the development of innovative products. Consequently, in November 2017, building on this policy and scientific opportunities, the FDA released a comprehensive framework for the oversight of regenerative medicine to help the field continue to advance. This regulatory framework is articulated in 2 final and 2 draft guidance documents as shown in Table 16 (297). The FDA's new policy framework is more clearly described for the developers of regenerative medicine to provide a distinction between therapies that require premarket authorization and those that do not. Consequently, the FDA provided appropriate criteria for minimal manipulation and homologous use. As part of the regulatory framework, the FDA also articulated a risk-based compliance and enforcement policy.

Table 16. *Four guidance documents describing the regenerative medicine framework.* *

Document	Summary	Example
Same Surgical Procedure Exception under 21 CFR 12.71.15(b): Questions and Answers Regarding the Scope of the Exception -- Final	Addresses the criteria required for the exception, the types of procedures generally considered to be the same surgical procedure, and what processing steps can be undertaken to still meet the exception. In essence, this guidance clarifies how the regulations apply in order to facilitate the optimal care of patients undergoing surgical procedures.	A situation in which this guidance would apply is when a piece of the skull is removed for decompression after traumatic head injury. The bone may be minimally processed, stored, and then returned to the patient a few weeks later when the acute event is over, without the need for regulatory interaction with FDA.
Regulatory Considerations for Human Cells, Tissues, and Cellular and Tissue-Based Products: Minimal Manipulation and Homologous Use – Final	Provides FDA's interpretation of the existing regulatory definitions of minimal manipulation and homologous use. The guidance clarifies that these are distinct concepts and notes how to determine whether an HCT/P has been minimally manipulated or is intended for homologous use. The guidance also describes the compliance and enforcement policy that the FDA will use for HCT/Ps. For the first 36 months after issuance of the final guidance in November 2017, the FDA intends to exercise enforcement discretion for certain products that pose a low risk to public health so that sponsors will be able to have a dialogue with the agency and file the appropriate regulatory documentation.	Adipose tissue is considered to be a structural tissue for the purpose of the regulatory framework. This is relevant to determining the appropriate regulatory pathway for stem cells derived from adipose tissue, which in many applications will be regulated under both Sections 351 and 361 of the Public Health Service Act.
Evaluation of Devices Used with Regenerative Medicine Advanced Therapies – Draft	Provides a comprehensive resource to developers of devices used with RMATs. Topics covered include how the FDA will simplify and streamline its application of regulatory requirements for devices and cell-tissue combination products.	Under certain circumstances, a device that is used with an RMAT might be classified as a class III device or be limited to a specific intended use with only one type of cell.
Expedited Programs for Regenerative Medicine Therapies for Serious Conditions -- Draft	Provides information about the expedited programs available to RMATs, including fast-track and breakthrough-therapy designations, and describes the FDA's considerations in implementing the new expedited program for RMATs. The guidance also describes an innovative program using cooperative development open to regenerative medicine products.	Multiple sites that manufacture a product using a common process may collaborate on clinical trials as part of a development program, which ultimately results in biologics licenses for each of the individual sites.

*The listed guidance documents can be accessed at www.fda.gov/BiologicsBloodVaccines/CellularGeneTherapyProducts/ucm58218.thm RMAT denotes regenerative medicine advanced therapy.

Source: Marks P, Gottlieb S. Balancing safety and innovation for cell-based regenerative medicine. *N Engl J Med* 2018 378:954-959 (297).

10.6.1 Expediting the Development of New Therapies

The FDA has developed a process of expediting the development of new therapies. The FDA traditionally has focused on insuring the quality, safety, and efficacy of medical products. However, its mandate has expanded to encompass a role in expediting the developments of new therapies, particularly those aimed at serious or life-threatening conditions. Consequently, the expedited programs including:

- Fast track designation
- Priority review
- Accelerated approval
- Designation as a breakthrough therapy

The FDA reports that these programs have been successful in accomplishing the goal of expediting the development of new therapies (322). Furthermore, the FDA also described its role in facilitating innovation while upholding the agency's approval standards, especially when it comes to areas of unmet medical need and new technologies as expressed in the legislative initiative contained in the 21st Century Cures Act, which was enacted on December 13, 2016 (323). To facilitate therapeutic advances from stem cell therapies, along with other HCT/Ps, the 21st Century Cures Act introduced an additional expedited program in which a product is designated as a regenerative advanced therapy, or regenerative medicine advanced therapy (RMAT). This designation provides sponsors of a quali-

fied regenerative medicine product that is intended for the treatment of serious or life-threatening conditions with advantages similar to those of breakthrough therapy designation; provided that preliminary clinical evidence indicates that the therapy addresses unmet medical needs. The requirement for preliminary clinical evidence of efficacy distinguishes RMAT from the breakthrough designation, which requires preliminary clinical evidence of a substantial improvement over existing therapies. Further, RMAT-designated products that receive accelerated approval may be eligible to use an expanded range of options to fulfill their postapproval commitments. Such options include the use of traditional studies, as well as the submission of patient registries or other sources of real world evidence (324,325). Multiple requests have been submitted for RMAT designation with the FDA approving at least one-third of them.

10.6.2 Implementation of Comprehensive Framework

The FDA described that it strove to take a modern approach to the existing regulations and statutes, balancing the objective of fostering expedient development of innovation products for patients who have medical needs with the need to ensure that such therapies are both safe and effective. In addition, as part of the regulatory framework, the FDA also articulated a risk-based compliance and enforcement policy. This policy essentially allows developers of lower risk products up to 36 months from November 16, 2017, to determine whether they need to submit an application for an investigational new drug or a marketing application in light of the recently published guidance documents and, if such an application is needed, to prepare the new drug or marketing application. However, the FDA intends to take additional enforcement actions in cases in which it believes unproven products may put patients at risk.

Finally, working within the existing regulatory framework, the FDA will make use of all available regulatory pathways and will adopt the use of some new principles that will make the appropriate premarket evaluation of stem cell-based therapies more efficient. On a large scale, the FDA will be incorporating some new concepts for how small investigators and firms can see and meet approval standard for products through efficient and expedited pathways. To achieve this goal, the FDA will provide tools to encourage individual or small groups of physicians to collaborate in support of the development of a stem cell

or other regenerative medicine product, which will ultimately lead to the receipt of a biologics license by each of the physicians or groups (Fig. 31).

10.7 State Medical Board Regulations/ Guidelines

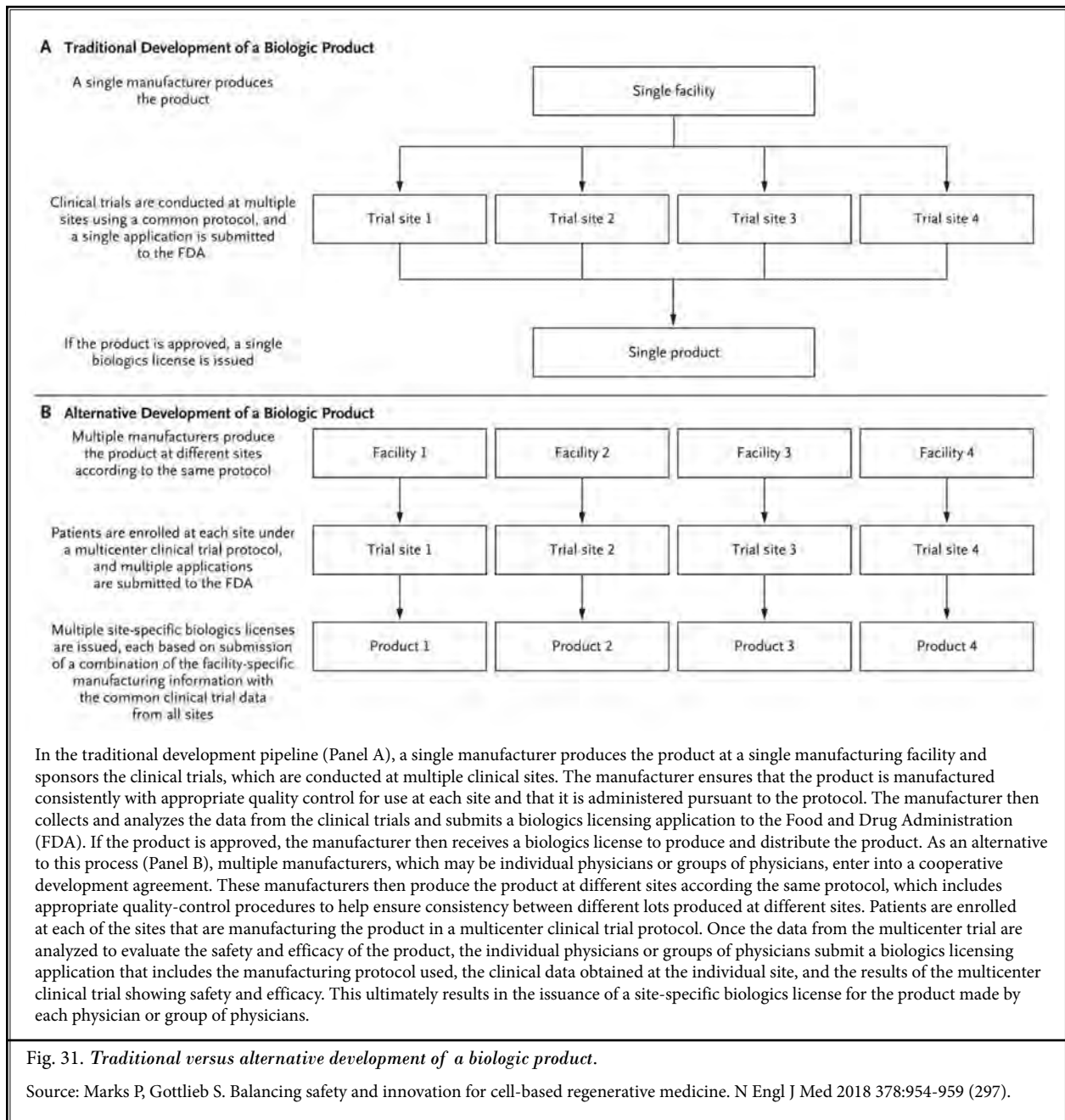
On April 21, 2017, Senator Lamar Alexander requested the Federation of State Medical Boards (FSMB) (326) to respond to multiple questions including:

1. How do state medical boards investigate complaints against stem cell clinics?
2. How are the existing false claims best practices enforced or used by state medical boards?
3. Are there standards or best practices regarding the use and communication of novel technology, such as adult stem cells?
4. Are there standards for education that are necessary before implementing novel technology, such as adult stem cell procedures?

Consequently, the FSMB formed a working group to develop a report on stem cells and regenerative medicine including the problem of direct-to-consumer clinics (41). The working group expressed concern over the landscape of stem cell clinics in the United States. They expressed that stem cell clinics market the presence of multiple elements including affiliations with a professional society or network, partnerships with academic institutions, FDA approval or explicit mention of exemption from FDA oversight, mention of official endorsement from a local or other authority or professional accreditation, listing of patents granted, and the statement that clinical trials of investigational stem cells based on interventions are being conducted (327). Table 17 shows co-opted tokens of scientific legitimacy as described by Sipp et al (328).

The working group expressed concern that the lack of a formal mechanism for reporting outcomes of unproven stem cells interventions, both positive and negative, adds to the difficulty involved in generating data on the effectiveness of such interventions, as does the fact that there is neither a requirement, nor a mechanism, for reporting adverse events related to interventions administered outside of the clinical trials and investigations. The working group emphasized existing regulations and made 10 recommendations in their draft report as shown in Table 18.

These recommendations as shown in Table 18 are as follows (41):



1. State Medical Boards raise awareness among licensee of applicable federal and state legislation and guidelines regarding regenerative and stem cell therapies, including “right to try” legislation existing or pending at the state and federal levels. State medical boards should also keep their licensees and the public apprised of new developments and regulations in the field of regenerative and

stem cell therapies including educational sources, guidance documents, and appropriate industry and stakeholder information on a state medical board’s website. State medical boards should further provide information as to reporting procedures of adverse actions related to stem cell interventions.

2. State medical boards should examine their policies and rules addressing informed consent and con-

Table 17. *Co-opted tokens of scientific legitimacy.*

Accreditations and awards	Asserting certification of products or practices by international standards organizations or claiming training certification
Boards and advisers	Convening scientific or medical advisory boards featuring prominent business leaders and academic faculty members
Clinical study registration	Registering trials whose apparent purpose is solely to attract patients willing to pay to participate in them
Ethics review	Using the imprimatur of “ethics review” to convey a sense of legitimacy to their products or procedures
Location	Renting of laboratory or business space within a legitimate scientific or government institution
Membership	Joining established academic or professional societies to suggest legitimacy by association
Outcome registries	Publication of open ended voluntary monitoring data sets rather than undertaking controlled clinical trials
Patenting	Suggesting that patent applications or grants indicate clinical utility rather than initiation of an application process or recognition of novelty and inventiveness
Publication	Publishing research and commentary in journals with limited anonymous peer review
Rationales	Citing preclinical and other research findings to justify clinical application without sufficient efficacy testing in humans
Self regulation	Forming organizations to self regulate in ways that support premature commercialization
Technical language	Using scientific sounding words that imply academic rigor Testimonials and endorsements
Testimonials and endorsements	Providing expert opinions or celebrity comments on unsupported clinical uses or standing of the provider

Source: Sipp D, Caulfield T, Kaye J, et al. Marketing of unproven stem cell based interventions: A call to action. *Sci Transl Med* 2017; 9(397) (328).

sider expanding these to include a shared decision making framework that includes the following general elements at a minimum:

- An explanation, discussion, and comparison of treatment options with the patient
 - An assessment of the patient’s values and preferences
 - Arrival at a decision in partnership with the patient
 - An evaluation of the patient’s decision in partnership with the patient
3. State medical boards should review professional marketing materials and claims, including any office/clinic and/or doctor websites, and information publicly available about an office/clinic or licensee on online blogs or social media, as information sources in the investigation of complaints made against physicians.
 4. State medical boards should proactively monitor warning letters sent to licensees that are made publicly available on the FDA website in order to ascertain information, and consider opening an investigation, about licensees who may be engaged in other unscrupulous or unprofessional practices related to the provision of regenerative and stem cell therapy. State medical boards should investigate such practices, when appropriate, in conjunction with applicable state laws, policies, and procedures (329).

Table 18. *Draft FSMB stem cell recommendations.*

1. Med Boards should raise awareness amongst licensees &
2. Examine rules on consent, potentially update &
3. Review clinic claims and marketing materials &
4. Follow-up on FDA warnings
5. Physicians should know patients well, stay in area of training &
6. Use caution in areas w/o evidence, exhaust standards of care 1st &
7. Avoid deceptive claims, raising expectations &
8. Don't use gag orders, disclaimers to avoid liability &
9. Support claims w/evidence including peer reviewed papers &
10. Avoid excessive fees

Source: Draft report of the FSMB Workgroup to study regenerative and stem cell therapy practices, December 2017 (41).

5. Physicians must only offer treatments to patients for which they have a bona fide physician patient relationship. Physicians must have received adequate and appropriate training, and be able to perform any proposed interventions safely and competently (330).
6. Where evidence is unavailable for a particular treatment in the form of clinical trials or case studies, physicians must only proceed with an appropriate rationale for the proposed treatment, and justification of its use, in relation to the patient’s symptoms or condition. Novel, experimental, and

Table 19. *Regulations applicable to stem cell based products adapted from regulatory focus.org Nov 2012 (351).*

Treatment product	Guidance and Legislation	Regulatory Law
Human stem cell, tissue, or cellular-based products (HCT/P)	Section 361, Public Health Service Act, Infectious disease	21 CFR 12711.3(d)
Biologics	Section 361, Public Health Service Act, Premarket approval, safety and effectiveness	21 CFR 600
Drugs	Food, Drug, and Cosmetic Act	21 CFR 200
Cell therapy and gene therapy when genetic material is transferred to cells ex vivo	Application of Current Statutory Authorities to Human Somatic Cell Therapy Product and Gene Therapy Products, 14 Oct 1993	
Xenotransplantation	US Public Health Service. Guideline on Infectious Disease Issues in Xenotransplantation, FDA 28 January 1997	
Medical devices		21 CFR 800

unproven interventions should only be proposed when traditional or accepted proven treatment modalities have been exhausted. In such instances, there must still be a basis in theory or peer reviewed acknowledged practice (331).

7. Physicians should employ a “shared decision-making” process when discussing treatment options with patients. Physicians must avoid any claims that may be deceptive or are intentionally or knowingly false or misleading, especially in terms of making promises about uncertain or unrealistic outcomes.
8. Physicians should not use gag orders (rulings that a case must not be discussed publicly) or disclaimers as a way to circumvent liability.
9. Physicians should be prepared to support any claims made about benefits of treatments or devices with documented evidence, for example with studies published in peer reviewed publications.
10. Physicians should refrain from charging excessive fees for treatments provided. Further, physicians should not recommend, provide, or charge for unnecessary medical services, nor should they make intentional misrepresentations to increase the level of payment they receive.

11.0 CLINICAL GUIDELINES

Key questions 8, 9, and 10

8. What are the adverse consequences/harms of regenerative injection therapy?
9. What are the best preventive and therapeutic strategies to improve outcomes when performing regenerative injection therapy?
10. What comprises responsible performance of regenerative injection therapy?

Beyond the general indications discussed above, the guidelines presented below for the most appropriate treatment will offer recommendation based on the

area of treatment, chronicity, and the type of injection. These recommendations will also consider the use of biologic therapy in an algorithm of treatment (first-line or other); obtaining a diagnosis necessary to initiate therapy; having knowledge of the number of treatments suggested to improve subjective pain and objective functional improvement scores; as well as employing evidence-based research in the use of regenerative therapies for a given condition.

11.1 Safety, Efficacy, and Informed Decision

To enhance safety, the patient should be considered a partner and should consider this therapy as an investment as a consumer. Consumers are encouraged to become empowered with as much reliable and independently verified information as possible. Individuals should ask whether the treatment is routine, if there is any scientific data to predict an expected response, and should ask about any benefits or adverse effects of the treatment. Consumers also should be instructed to learn about how the therapy works and understand how the treatment will be performed. They should also be committed to any follow-up visits and treatments that are necessary.

It cannot be emphasized enough, that before all interventional procedures, a consent form should be discussed with the patient and signed by both the provider and the patient. Risks and benefits of the procedure must be discussed, as well as giving a verbal review of the inclusion and exclusion criteria; this will prevent any future incidental errors or miscommunication in patient assumptions that the provider is fully aware of every medical problem they may have.

Factors a patient may want to consider before undergoing a cell therapy procedure include the following:

1. **Physician Selection:** Consumers must ensure that the physician who performs the treatment holds a

medical license and is board certified in the specific field of medicine or treating specialty for the condition being addressed. Consumers also must ensure that the physician performing the treatments is appropriately trained and, if necessary, holds at least a competency certification in regenerative medicine, if available, from an organization widely accepted, with rigorous testing of their fund of knowledge, and clinical and technical competency, such as the American Board of Interventional Pain Physicians (ABIPP) (www.abipp.org).

2. **Location Selection:** The consumer also should assess the facility where the treatment will be given and determine whether the personnel at that facility are knowledgeable, trained in the particular area, and know what to do in an emergency situation. Informed decision making also includes understanding the regulatory oversight, certification, and accreditation process.
3. **Medical Claims:** Claims such as “miracle cure” or claims to cure serious conditions often are not credible and may pose a significant risk to public health and safety. All claims made by clinics and/or physicians should be based on accepted and acknowledged scientific evidence and medical experience. Claims of safety should be based upon the collection of data through an established and accepted grading scale, such as the Adverse Event Reporting system used by the U.S. Department of Health and Human Services Office of Human Research Protections.
4. **Travel for Therapies:** Consumers considering stem cell transplantation in the U.S. should ask their physicians if the necessary Food and Drug Administration, or FDA, approval has been obtained, or if the procedure will be part of an FDA-regulated clinical study.
5. **Shared Decision-Making:** Shared decision-making has been described as one of the fundamental approaches to improving the quality of US health care (332). The Institute of Medicine (IOM), now the National Academy of Sciences, defined patient-centered care as “care that is respectful of and responsive to individual patient preferences, needs, and values,” and that ensures “that patient values guide all clinical decisions (333).” As the definition implies, the most important attribute of patient-centered care is the active engagement of patients when fateful health care decisions must be made – when an individual patient arrives at a

crossroads of medical options, where the diverging paths have different and important consequences with lasting implications (332). Usual examples described are major surgeries, medications that must be taken for the rest of one’s life, and screening and diagnostic tests that can trigger cascades of serious and stressful interventions. To add to these complex medical issues is decision-making related to regenerative therapies, which also incorporates financial implications as most insurers do not cover these procedures, multiple ethical issues including false advertising, and lackluster evidence – though evidence is evolving rapidly in favor of regenerative therapy. Through shared decision-making, apart from avoiding over diagnosis and over treatment, clinicians can help patients understand the importance of their values and preferences in making the decisions that are best for them (334). The present evidence shows that when patients know they have options for the best treatment, most of them will want to participate with their clinicians in making the choice. Consequently, clinicians need to relinquish their role as the single paternalistic authority and train to become more effective coaches or partners focusing on what matters to the patients and considering their wishes. Thus, shared decision-making is crucial in regenerative therapy.

6. **Informed Consent:** Informed consent to medical treatment is fundamental to both ethics and law. Patients have the right to receive information and ask questions about recommended treatments so that they can make well-considered decisions about care. Successful communication in the patient-physician relationship fosters trust and supports shared decision-making as described above.

In obtaining informed consent, physicians should assess the patients ability to understand the relevant medical information and the implications of the treatment alternatives and to make an independent, voluntary decision. The physician should include information about the diagnosis, the nature and purpose of recommended interventions, the burdens, risks, and expected benefits of all options, including foregoing treatment.

It is crucial to obtain informed consent in regenerative therapy considering the various issues described throughout this manuscript specifically due to the lack of an appropriate wealth of evidence, widespread guidelines except the present ones, highly prevalent fraud and abuse, and the expenses of the treatment.

There must be personal reflection, research, and due diligence practiced in all areas of the procedure in order to deliver safe and effective therapy. It is encouraged that providers not only personally research available publications, but also personally cooperate with the manufacturers of their chosen extraction kits; attend continuing medical education sessions regarding injection techniques including those with ultrasound guidance; and personally, review his or her equipment to ensure high-quality industry standards.

11.2 Office Set-Up

The environment in which a stem cell injection occurs must be a highly aseptic environment with comprehensive controls of both raw materials and handlers. To reach affordability and mass scale, the production process should be highly reproducible and validated both on a small scale for a single patient and on a large scale of a multitude of patients. The physicians performing the procedures need to be properly trained and comfortable in performing the interventional techniques. They must be ready and available to handle any resulting complications at all times, and be available on-call for emergencies that may ensue from the procedure.

11.3 Contraindications

Multiple contraindications described in the literature include:

- Hematologic blood dyscrasias
- Platelet dysfunction
- Septicemia or fever
- Cutaneous infections in the area to be injected
- Anemia (hemoglobin less than 10 g/dl)
- Malignancy, particularly with hematologic or bony involvement
- Allergy to bovine products if bovine thrombus is to be used
- Severe psychiatric impairment or unrealistic expectation

For an autologous therapy procedure, cell harvesting from the patient will be aimed at collecting healthy cells whenever this is possible. This is an especially important consideration for patients with inherited diseases. A disease with 100% mosaicism would be a contraindication for autologous biologic therapy, as every cell would carry the undesirable mutation. However, lesser degrees of mosaicism become a relative

contraindication. For example, mosaicism in hemophilia is found in only 30% of cases, thus leaving 70% of such patients with the potential to benefit from MSC or PRP therapy. Thus, consultation with a genetic specialist should be considered. There should be some awareness that abnormal proteins including those related to Parkinson's and Alzheimer's disease may be found in tissues throughout the body and may constitute a source of inadvertent spread of a prion-like effect.

11.4 Pre, Intra, and Post Procedural Considerations

The following recommendations are generally acceptable guidelines followed by practitioners for pre-injection management of the patient:

1. The patient candidacy requirements, as emphasized above, are met. Imaging modalities must also demonstrate the pathology, and can include MRI, computed tomography (CT) scan, ultrasound, or x-ray as appropriate for viewing a specific pathology.
2. The patient should avoid the use of any corticosteroids two or three weeks before the procedure. Also, NSAIDs are avoided within one week of the procedure; any necessary anticoagulation precautions should be taken before the procedure as recommended by consensus guidelines from ASIPP and American Society of Regional Anesthesia and Pain Medicine (335,336).
3. Before and during the procedure, anti-anxiety medications and mild sedation may be required for certain patients. However, deep sedation should be avoided ensuring that the patients are arousable and alert at all times.

Considerations for pre-injection management of biologic materials include:

1. To be clinically effective, it is agreed that platelet concentration in an injectate should be at least 2.5 times greater than the baseline plasma concentration (174).
2. The biologics follow the FDA recommended "minimal manipulation" and "homologous use" draft guidelines in clinical practice.
3. Cell viability is comparable between fresh extraction, 24 hours, and 72 hours, though proliferation may be enhanced at 24 hours. It is recommended to use the cells within 24 hours of thawing from a frozen medium (337) if so used.
4. The tri-lineage capabilities, differentiation, and

viability of MSCs are not affected by the gauge (G) of the needle used to extract them (when 19G, 21G, and 23G needles were compared), although it has been found that a 19G needle reduced the incidence of apoptosis (337).

5. A 2 mL syringe is recommended to avoid over-inflation. The majority of available studies are also performed with this value (337).

We recommend the following considerations for intra-injection management (337):

1. Cell material, patient, joint location and effected side should be verified before injection.
2. Materials should be injected under direct visualization with image guidance such as with ultrasound, fluoroscopic, CT, MRI or arthroscopic/endoscopic guidance.

The following recommendations are crucial for post-injection management:

1. Patients should be instructed to rest and partially immobilize the injected body part for a few days to 2 weeks.
2. The patient should avoid anti-inflammatory medications for at least a few weeks postoperatively, as the therapy is grounded in the benefit of the patient's inflammatory cascade. The risks and benefits for Aspirin should be reviewed in conjunction with the patient and the clinician prescribing it.
3. Post-operative instructions should be verbally discussed with the patient and the person driving the patient home. Red flags and appropriate pain control measures should also be reviewed. A written copy of the instructions should be given to the patient or the patient's driver prior to discharge.
4. Close follow-up should be scheduled every 2-4 weeks post-procedure. Follow-ups can extend to 1 or 2 times per year once there has been a demonstration of significant subjective and objective report of improvement in pain and function and is based on the discretion of the clinic thereafter.

The following course of action is recommended for continued therapy:

1. Repeat injections may be required, depending on the patient's response. This in turn may depend on several factors including the nature and extent of the pathology, the type and quality of the biologic

used, the baseline health status of an individual, and the injection technique. These factors are important and should be taken into account when considering regenerative medicine treatments for patients. Pain and functional improvements are the most likely effected outcomes as opposed to any structural improvement given the limitations of the currently available biologics.

2. Frequent repeat imaging is not recommended unless there has been a change in patient symptoms or pathology. However, obtaining an x-ray to determine improvement in a joint space or as an indirect assessment of cartilage interval while treating osteoarthritis or obtaining an MRI scan to identify changes in soft tissue structures including articular cartilage, may be considered necessary.

11.5 Antithrombotic Implications

11.5.1 Risks in Regenerative Medicine

Bone marrow aspiration and intra-articular/soft tissue injections have low risks of bleeding, while central nervous system/meningeal related injections have a higher risk of bleeding. A comprehensive review with literary search was conducted by ASIPP (336) analyzing various guidelines which produced recommendations specific to interventional techniques and the associated risk of bleeding. These recommendations are dependent on multiple factors including the patient's risk factors and the managing physician's opinion (8,335-342). While bleeding risk is present with any interventional procedure, thromboembolic events must be considered equally and must be clinically correlated in relation to a patient's past medical history, social history, and risk of each relative to these factors.

With respect to NSAIDs and aspirin when used in interventional techniques, there is little to no risk of bleeding at low doses. High doses of these medications should be evaluated and altered if the clinician correlates their medication status with previous episodes of heavy bleeding (8,335,336,341). Many patients may be taking additional medications that increase their risk of bleeding or supplements such as selective serotonin reuptake inhibitors (SSRIs), fish oil, garlic, and many others. Phosphodiesterase inhibitors also do not significantly increase the risk of bleeding in interventional techniques; however, they may or may not be discontinued in accordance with patient history (8,335,336,341). It has been suggested that platelet aggregation inhibitors such as ticlopidine, clopidogrel, and prasugrel

should be discontinued 7 to 10 days before an interventional technique is performed. While some studies indicate that 3 days is effective, the American Society of Regional Anesthesia and Pain Medicine (ASRA) consensus is at least 7 days is needed before a central nervous system related injection (8,335,336,341).

Warfarin is more complicated in regards to discontinuation, as much of the clinical decision-making depends on a patient's international normalized ratio (INR) achieved during therapy and trends associated with INR over the past few months. For high-risk interventional techniques such as interlaminar epidural injections, warfarin may need to be discontinued until an INR of 1.4 or less is achieved. For lower risk procedures, an INR of 2 is an appropriate level to achieve before undergoing these techniques (8,335,336,341). There is limited evidence to suggest that unfractionated or low molecular weight heparins should be discontinued prior to interventional techniques, but the current suggestion is 12 hours of discontinuation before central nervous system-related injections.

Similar to INR values in Warfarin, renal function values significantly alter clinical decision-making in relation to dabigatran (Pradaxa). In procedures with a high risk of bleeding, creatinine clearance greater than 50 mL per minute in patients allows a 2- to 4-day period of discontinuation. However, in those with 50 mL per minute or less, a period of 4 to 5 days is currently suggested before central nervous system-related interventional techniques.

11.5.2 Effects of Antithrombotic Therapy on PRP and Stem Cell Efficacy

The biochemical pathways of the coagulation cascade are key in that the disruption of platelet surfaces or prematurely activated platelets may cause the limited efficacy of the clinical procedure (342). Furthermore, with the recent advent of MSC technology in regenerative medicine, it is important to consider the viability of these cells in the context of antithrombotic therapy. To that end, the effects of heparin on ex vivo MSCs recovered from bone marrow showed that supplementation of even low doses of heparin could adversely impact the growth and differentiation potential of this pleiotropic cell type (343). Therefore, it is important to evaluate bone marrow tissue in patients receiving heparin treatment particularly if ex vivo expansion hMSCs is to occur.

The use of PRP is increasing due to its ligament and tendon healing potential. It is also considered to be a

natural alternative to surgery. However, anticoagulants and antiplatelet drugs are commonly used in patients who are candidates for receipt of PRP. Alternatively, the use of an anticoagulant, while not taken systemically, is required to process PRP to prevent automatic activation. Since antithrombotic agents influence the stability of platelets, they are, therefore, likely to exert an effect on PRP efficacy as well and should be ceased at a suitable timeframe preceding injection therapy (344). PRP has been shown to significantly improve the proliferation of differentiated cells, enhance synthesis of collagen, and prompt angiogenesis and revascularization, all of which aid regeneration. The study by Sutherland and colleagues (344) in 2005 eloquently demonstrated the utility of autologous MSCs in regenerative medicine using sheep through reconstruction of stem cell tissue-engineered heart valves.

The healing influence of the dispensation of PRP depends on the bioactive amalgams such as cytokines and growth factors that are being released (via activation and aggregation) precisely to the location of the injury. The characteristic of the platelets confined in autologous PRP (mainly exhibited by the potential of activation and aggregation of platelets) may be essential (345).

NSAIDs are depicted to have negative influences on platelets such as inhibition of activation, a decrease in storage of alpha granules, and aggregation of platelets. The negative impact of these medications on platelet activation and aggregation may be significant since a substandard quality of autologous PRP is emitted post-NSAID therapy. The coherent substantial inhibition of platelet function such as aggregation acquired post stimulation using arachidonic acid within the NSAID designated study group was found, regardless of NSAID duration, type of ingestion, and the blood compendium technique used for PRP formulation (345). Without NSAIDs intake, such effects could not be observed in the healthy control group. NSAID's impede cyclo-oxygenase-mediated oxygen utilization and therefore prevent platelet activation and aggregation (345). Moreover, bioactive compounds such as TGF- α , growth factors, and platelet factor 4 stored in the alpha granules, cannot be released adequately if NSAIDs bar this pathway, and platelet function is drastically compromised. Thus, such stipulations validate the hypothesis that autologous PRP generated after NSAID intake is of inferior attribute, and therefore, may negatively influence the healing outcomes.

NSAIDs are essential to control pain in the post-traumatic setting. While NSAIDs can interfere with bone

healing, some contradict these findings (346). Although NSAID analgesic potency is well documented, clinicians continue to question the associated safety issues. A 2012 study of the effects of NSAIDs on bone healing in animals reveal very mixed results (346). However, the authors' conclusion correctly notes that the "lack of evidence does not constitute the absence of an effect" and further cautions that the clinician should [continue to] treat NSAIDs as a risk factor for bone healing impairment and should be avoided in high-risk patients" (346).

Ramsook and Danesh (342) described issues related to PRP injections and antithrombotic therapy. They discussed the importance of understanding the intrinsic and extensive pathways of the coagulation cascade and that any disruption of this mechanism may result in prematurely activated platelets and therefore limited efficacy. They also made clear that antithrombotic agents affect platelet stability and will have an effect on PRP efficacy and must be discontinued at an appropriate time frame prior to injection therapy. Overall, the general rules appear to be the same for antithrombotic and anticoagulant agents similar to utilization in interventional techniques as described above.

However, there is a significant paucity of literature in regards to the safety, efficacy, and timing of PRP injections in patients with concomitant antithrombotic therapy. The importance of an intact platelet surface membrane allows for the appropriate release of the healing bioproteins and growth factors granting PRP therapy its efficacy. Antithrombotic agents that affect the stability of platelets will have an effect on PRP efficacy and must be discontinued at an appropriate time frame prior to injection therapy. With future research, appropriate guidelines may be established not only for PRP, but also for stem cell therapy.

11.5.3 Safe and Efficient Administration of Regenerative Medicine

If it is deemed advisable that antithrombotic therapy should be halted (even temporarily), then thromboembolic risk determines if bridging is necessary. "Heparin bridging" involves discontinuing warfarin 4-5 days prior to a procedure while using subcutaneous low molecular weight heparin (LMWH) to maintain anticoagulation until the day prior to the procedure. This mitigates thromboembolic risk during the time the patient is off warfarin by effectively shortening the amount of time the patient is not anticoagulated. LMWH has a shorter half-life than warfarin and can be discontinued the day prior to the procedure.

Bridging with subcutaneous LMWH is appropriate and reliable. For patients who have chronic kidney disease, the LMWH should be decreased in dose or substituted by intravenous unfractionated heparin. For atrial fibrillation patients, the American Heart Association (AHA) advocates a once-daily therapeutic dose of LMWH, with half the dose to be taken at dawn of the day before the procedure (347). Moreover, therapeutic LMWH should be taken up again 24 to 72 hours post procedure, dependent on the bleeding risk of the technique. Warfarin therapy ought to be resumed when viable. It is vital to consider that bridging could lead to unexpected post-op bleeding after anticoagulants are resumed.

International guidelines reflect the differing views on the safe interval between cessation of antithrombotic therapies and implementation of neuraxial and peripheral procedures, and for the re-introduction of the therapeutic drug regimen.

While 2 to 3 half-life intervals might be adequate in patients who are at excessive threat of venous thromboembolism (VTE) or stroke, an interval of 4 to 6 half-lives amid the cessation of the drug and neuraxial injection is reliable in the majority of patients at a low-level risk of thrombosis (348). However, in patients with kidney disease, the interval should be calculated on creatinine clearance. In particular instances, laboratory monitoring of the antithrombotic effect is applicable, and reversal agents may be suitable when a hemostatic function requires rapid restoration.

11.6 Adverse Reactions and Complications

Health care consumers must be informed of all aspects of potential therapies, risks, benefits, and indications. Risks may include, but are not limited to, infection, tissue rejection and changes in the characteristics of the cells in the product that may alter how they respond. PRP therapies derive their benefit from localized inflammation, and can thus cause worsening pain and sensations of pressure before healing demonstrates increased functionality. Generalized rest and restraining from the use of NSAID medications are important to optimize therapy.

A final concern for the use of biologic therapies is the induction of neoplasms from undifferentiated cells in high volume. A multicenter analysis of over 2,300 patients treated with MSCs (bone marrow and adipose included) for musculoskeletal conditions demonstrated that after nine years, only seven patients developed a neoplasm. This is lower than the rate of neoplasm development in the general population, MSC therapy is therefore not

considered causative (349). The review also noted that the majority of postoperative complications were very few, but included pain post-procedure (3.9%), and pain due to continued degeneration of the joint (3.8%) (349).

12.0 GUIDANCE FOR RESPONSIBLE, SAFE, AND EFFECTIVE USE OF BIOLOGICS

The current body of evidence on the use of biologics for the spine is limited. Previous systematic literature reviews, such as the 2015 review by Nourissat et al (350) reiterate the lack of many well-designed RCTs regarding PRP use in the most common tendinopathies⁷ and suggest that while PRP treatment for acute or chronic tendinopathy is more beneficial than standard non-intervention techniques of NSAIDs and rest, it should be considered after failure of ultrasound-guided corticosteroid injection into the specific tendon.

The variation of follow-up for the studies has ranged from 6 weeks to 3 years before conclusions were drawn. Of the studies reviewed, there has been a demonstration of benefit with the initial injection/injection series that can last from 6 months to 24 months. Studies requiring a repeat of the injection series after 24 months should be conducted to determine the maximum duration of time that can remain between series.

The lack of standardization of methodology and analysis is a handicap to the ability to reproduce the same models or make declarative recommendations. Since the factors at play in healing and regeneration are still unknown, clinicians continue to test new combinations, contributing to the heterogeneity in composition, techniques and outcomes (350-353).

In regard to cost, corticosteroid injections are cheaper than PRP and are the current standard of care for chronic conditions of joint degeneration. For this reason and in consistency with current guidelines from musculoskeletal interventional pain management, and national guidelines as listed in Table 19 (351), PRP is considered in patients after corticosteroids fail, or are deemed no longer appropriate for corticosteroid use. This may however, change depending on availability of more robust data on safety and long-term effectiveness of biologics when compared to corticosteroids.

13.0 CONCLUSION

Both PRP and MSCs are used autogenously to supplement the healing process. Their natural properties are being discovered, including functional strengths and limitations. The guidelines presented have reviewed studies that both confirm and refute current uses of

these biologics. In general, PRP is a concentration of inflammatory mediators and growth factors that complement healing in injured tissues. Biologics are considered by many to be a more economic and expedited healing approach and are becoming a reasonable alternative to patients that fail standard of care treatments. Based on the available literature, treatments for lumbar discs, facet and sacroiliac joints are performed in conjunction with a definitive diagnosis, and after the patient has tried and failed conservative therapy. The published studies have reported the results of single injection biologic use on chronic pathology which has provided short-term relief. PRP has been the most commonly utilized biologic within the lumbar spine.

The survival of the clinical use of biologics depends on the standardization of their use, the consistency of outcomes, and on the documentation of an overall decrease in healthcare costs. This can be achieved by the publication of high-quality studies which will increase the predictability in the use of biologic therapy. These efforts, on behalf of our patients and to ensure the future of Regenerative Medicine, will require dedication on the part of all stakeholders to move the science and technology of biologic therapy forward.

ACKNOWLEDGMENTS

The authors wish to thank Tonie M. Hatton and Diane E. Neihoff, transcriptionists, for their assistance in preparation of this manuscript. We would like to thank the editorial board of *Pain Physician* for review and criticism in improving the manuscript.

Disclosures

Funding: There was no external funding in the preparation of this manuscript.

Author Affiliations

¹Dr. Navani is Medical Director, Comprehensive Spine & Sports Center, Campbell, CA, and Adjunct Clinical Associate Professor, Stanford University School of Medicine, Stanford, CA.

²Dr. Manchikanti is Medical Director of the Pain Management Center of Paducah, Paducah, KY, and Clinical Professor, Anesthesiology and Perioperative Medicine, University of Louisville, Louisville, KY.

³Dr. Albers is Director of Research, Radiology Research and Consultation, Sacramento, CA.

⁴Dr. Latchaw is a Professor of Radiology, Department of Radiology, UC-Davis Medical Center, Sacramento,

CA.

- ⁵Dr. Sanapati, Pre-Intern, University Pain Medicine and Rehabilitation Center, Department of Physical Medicine and Rehabilitation, Rutgers New Jersey Medical School
- ⁶Dr. Kaye is Professor, Program Director, and Chairman, Department of Anesthesiology, Louisiana State University Health Science Center, New Orleans, LA.
- ⁷Dr. Atluri is Medical Director, Tri-State Spine Care Institute, Cincinnati, OH
- ⁸Dr. Jordan is a neurologist at Neurological Associates of West Los Angeles, Santa Monica, CA
- ⁹Dr. Gupta is Associate Director of Research at Millennium Pain Center, Bloomington, IL; Chief Science Officer at South Texas Orthopaedic Research Institute, Laredo, TX; and Adjunct Researcher at Illinois Wesleyan University, Bloomington, IL
- ¹⁰Dr. Cedeno, Millennium Pain Center, Department of Psychology, Illinois Wesleyan University, and Stimgenics LLC, Bloomington, IL
- ¹¹Mr. Vallejo, Millennium Pain Center, Bloomington, IL
- ¹²Bert Fellows is Director Emeritus of Psychological Services at the Pain Management Center of Paducah, Paducah, KY.
- ¹³Dr. Knezevic is Vice Chair for Research and Education, Advocate Illinois Masonic Medical Center, and Clinical Associate Professor of Anesthesiology and Surgery, University of Illinois, Chicago, IL.
- ¹⁴Dr. Pappolla is Medical Director, St. Michael's Pain and Spine Clinics, Houston, TX, and Professor of Neurology, University of Texas Medical Branch, Galveston, TX.
- ¹⁵Dr. Diwan is President, Park Avenue Spine and Pain, New York, NY
- ¹⁶Dr. Trescot is the Director, The Pain & Headache Center, Eagle River, AK.
- ¹⁷Dr. Soin is Medical Director, Ohio Pain Clinic, Centerville, OH and Clinical Assistant Professor of Surgery at Wright State University, Dayton, OH.
- ¹⁸Dr. A. M. Kaye is Clinical Professor of Pharmacy, Thomas J. Long School of Pharmacy and Health Sciences, University of the Pacific, Stockton, CA.
- ¹⁹Dr. Aydin is Chief of PMR & Interventional Pain Management, Kayal Orthopaedic Center, PC, Franklin Lakes, NJ, and Clinical Assistant Professor of PMR, Northwell Health-Hofstra School of Medicine, New York, NY.
- ²⁰Dr. Calodney is Director of Clinical Research, Precision Spine Care, Baylor Scott and White Texas Spine and Joint Hospital, Tyler, TX.
- ²¹Dr. Candido is Chairman, Department of Anesthesiology, Advocate Illinois Masonic Medical Center, Professor

of Clinical Anesthesiology, and Clinical Professor of Surgery, University of Illinois College of Medicine, Chicago, IL.

- ²²Dr. Bakshi is an interventional pain physician at Lenox Hill Hospital, New York, NY.
- ²³Dr. Benyamin is Medical Director, Millennium Pain Center, Bloomington, IL, Clinical Assistant Professor of Surgery, College of Medicine, University of Illinois, Urbana-Champaign, IL, Department of Psychology, Illinois Wesleyan University, and Stimgenics LLC, Bloomington IL
- ²⁴Dr. Vallejo is Director of Research, Millennium Pain Center, Adjunct Research Professor, Illinois Wesleyan University, Bloomington, IL, and Stimgenics LLC, Bloomington, IL
- ²⁵Dr. Watanabe is an Interventional Pain Physician, Mt. Baker Pain Center, Bellingham, WA.
- ²⁶Dr. Beall is Chief of Radiology Services, Clinical Radiology of Oklahoma, Oklahoma City, OK
- ²⁷Dr. Stitik is Director, Musculoskeletal/Occupational Medicine, Associate Professor, Department of Physical Medicine & Rehabilitation, Rutgers-New Jersey Medical School, Newark, NJ
- ²⁸Dr. Foye is Professor Clinical Chair, Department of Physical Medicine & Rehabilitation, Co-Director, Musculoskeletal Medicine, PM&R, Director, Coccyx Pain Center (Tailbone Pain Center), PM&R, Newark, NJ
- ²⁹Dr. Helander, Assistant Professor, Department of Anesthesiology, Louisiana State University Health Sciences Center, New Orleans, LA
- ³⁰Dr. Hirsch is Vice Chief of Interventional Care, Quality and Safety; Service Line Chief of Interventional Radiology; Division Chief: Interventional Neuroradiology Chief: NeuroInterventional Spine Service, Massachusetts General Hospital; Harvard Medical School, Boston, MA.

Conflicts of Interest

- Dr. Manchikanti has provided limited consulting services to Semnur Pharmaceuticals, Incorporated, which is developing nonparticulate steroids.
- Dr. Kaye is a speaker for Depomed and Merck, Inc.
- Dr. Gupta is a Scientific Advisory Board Member for Dumanis Medical and KLSMC Stem Cells Inc.
- Dr. Calodney is a consultant for Medtronic, SI-Bone, Stryker, Nevro, and APEX Biologix.
- Dr. Benyamin is a consultant for Medtronic Inc., Vertiflex Inc., Vertos Medical Inc.
- Dr. Vallejo is a consultant for Medtronic Inc. and Avanos Medical Inc.
- Dr. Hirsch is a consultant for Medtronic.

APPENDIX

[*Appendix Figure 1*](#)

[*Appendix Table 1*](#)

[*Appendix Table 2*](#)

[*Appendix Table 3*](#)

[*Appendix Table 4*](#)

[*Appendix Table 5*](#)

[*Appendix Table 6*](#)

[*Appendix Table 7*](#)

To view pdf with Appendix links active, visit
Pain Physician journal website
to access manuscript pdf.

REFERENCES

- Dieleman JL, Baral R, Birger M, Bui AL, Bulchis A, Chapin A, Hamavid H, Horst C, Johnson EK, Joseph J, Lavado R, Lomsadze L, Reynolds A, Squires E, Campbell M, DeCenso B, Dicker D, Flaxman AD, Gabert R, Highfill T, Naghavi M, Nightingale N, Templin T, Tobias MI, Vos T, Murray CJ. US spending on personal health care and public health, 1996-2013. *JAMA* 2016; 316:2627-2646.
- Dieleman JL, Squires E, Bui AL, Campbell M, Chapin A, Hamavid H, Horst C, Li Z, Matyas T, Reynolds A, Sadat N, Schneider MT, Murray CJL. Factors associated with increase in US health care spending, 1996-2013. *JAMA* 2017; 318:1668-1678.
- Conway PH. Editorial: Factors associated with increased US health care spending. Implications for controlling health care costs. *JAMA* 2017; 318:1657-1658.
- Manchikanti L, Sooin A, Mann DP, Bakshi S, Pampati V, Hirsch JA. Reversal of growth of utilization of interventional techniques in managing chronic pain in Medicare population post Affordable Care Act. *Pain Physician* 2017; 20:551-567.
- Rajae SS, Bae HW, Kanim LE, Delamarter RB. Spinal fusion in the United States: Analysis of trends from 1998 to 2008. *Spine (Phila Pa 1976)* 2012; 37:67-76.
- Bae HW, Rajae SS, Kanim LE. Nationwide trends in the surgical management of lumbar spinal stenosis. *Spine (Phila Pa 1976)* 2013;38:916-926.
- Kim CH, Chung CK, Park CS, Choi B, Kim MJ, Park BJ. Reoperation rate after surgery for lumbar herniated intervertebral disc disease: nationwide cohort study. *Spine (Phila Pa 1976)* 2013; 38:581-590.
- Manchikanti L, Abdi S, Atluri S, Benjamin RM, Boswell MV, Buenaventura RM, Bryce DA, Burks PA, Caraway DL, Calodney AK, Cash KA, Christo PJ, Cohen SP, Colson J, Conn A, Cordner HJ, Coubarous S, Datta S, Deer TR, Diwan SA, Falco FJE, Fellows B, Geffert SC, Grider JS, Gupta S, Hameed H, Hameed M, Hansen H, Helm II S, Janata JW, Justiz R, Kaye AD, Lee M, Manchikanti KN, McManus CD, Onyewu O, Parr AT, Patel VB, Racz GB, Sehgal N, Sharma M, Simopoulos TT, Singh V, Smith HS, Snook LT, Swicegood J, Vallejo R, Ward SP, Wargo BW, Zhu J, Hirsch JA. An update of comprehensive evidence-based guidelines for interventional techniques of chronic spinal pain: Part II: Guidance and recommendations. *Pain Physician* 2013; 16:S49-S283.
- Manchikanti L, Kaye AM, Knezevic NN, McAnally H, Trescot AM, Blank S, Pampati V, Abdi S, Grider JS, Kaye AD, Manchikanti KN, Cordner HJ, Gharibo CG, Harned ME, Albers SL, Atluri S, Aydin SM, Bakshi S, Barkin R, Benjamin RM, Boswell MV, Buenaventura RM, Calodney AK, Cedeno DL, Datta S, Deer TR, Fellows B, Galan V, Grami V, Hansen H, Helm S 2nd, Justiz R, Koyyalagunta D, Malla Y, Navani A, Nouri K, Pasupuleti R, Sehgal N, Silverman SM, Simopoulos TT, Singh V, Slavin KV, Solanki DR, Staats PS, Vallejo R, Wargo BW, Watanabe A, Hirsch JA. Responsible, safe, and effective prescription of opioids for chronic non-cancer pain: American Society of Interventional Pain Physicians (ASIPP) guidelines. *Pain Physician* 2017; 20:25S-33-592.
- U.S. Burden of Disease Collaborators. The state of US health, 1990 – 2010: Burden of diseases, injuries, and risk factors. *JAMA* 2013; 310:591-608.
- US Burden of Disease Collaborators, Mokdad AH, Ballestros K, Echko M, Glenn S, Olsen HE, Mullany E, Lee A, Khan AR, Ahmadi A, Ferrari AJ, Kasaieian A, Werdecker A, Carter A, Zipkin B, Sartorius B, Serdar B, Sykes BL, Troeger C, Fitzmaurice C, Rehm CD, Santomauro D, Kim D, Colombara D, Schwebel DC, Tsoi D, Kolte D, Nsoesie E, Nichols E, Oren E, Charlson FJ, Patton GC, Roth GA, Hosgood HD, Whiteford HA, Kyu H, Erskine HE, Huang H, Martopullo I, Singh JA, Nachega JB, Sanabria JR, Abbas K, Ong K, Tabb K, Krohn KJ, Cornaby L, Degenhardt L, Moses M, Farvid M, Griswold M, Criqui M, Bell M, Nguyen M, Wallin M, Mirarefin M, Qorbani M, Younis M, Fullman N, Liu P, Briant P, Gona P, Havmoller R, Leung R, Kimokoti R, Bazargan-Hejazi S, Hay SI, Yadgir S, Biryukov S, Vollset SE, Alam T, Frank T, Farid T, Miller T, Vos T, Bärnighausen T, Gebrehiwot TT, Yano Y, Al-Aly Z, Mehari A, Handal A, Kandel A, Anderson B, Biroscak B, Mozaffarian D, Dorsey ER, Ding EL, Park EK, Wagner G, Hu G, Chen H, Sunshine JE, Khubchandani J, Leasher J, Leung J, Salomon J, Unutzer J, Cahill L, Cooper L, Horino M, Brauer M, Breitborde N, Hotez P, Topor-Madry R, Soneji S, Stranges S, James S, Amrock S, Jayaraman S, Patel T, Akinyemiju T, Skirbekk V, Kinfu Y, Bhutta Z, Jonas JB, Murray CJL. The State of US Health, 1990-2016: Burden of Diseases, Injuries, and Risk Factors Among US States. *JAMA* 2018; 319:1444-1472.
- Manchikanti L, Helm S 2nd, Benjamin RM, Hirsch JA. A critical analysis of Obamacare: Affordable care or insurance for many and coverage for few? *Pain Physician* 2017; 20:111-138.
- Manchikanti L, Hirsch JA. Repeat and replace of affordable care: A complex, but not an impossible task. *Pain Physician* 2016; 19:E1109-E1113.
- Hirsch JA, Rosenkrantz AB, Nicola GN, Harvey HB, Duszak R Jr, Silva E 3rd, Barr RM, Klucznik RP, Brook AL, Manchikanti L. Contextualizing the first-round failure of the AHCA: Down but not out. *J Neurointerv Surg* 2017; 9:595-600.
- Hirsch JA, Leslie-Mazwi TM, Barr RM, McGinty G, Nicola GN, Patel AB, Manchikanti L. The Burwell roadmap. *J Neurointerv Surg* 2016; 8:544-546.
- Cannon MF. Is Obamacare harming quality? (Part 1). *Health Affairs*, January 4, 2018. <https://www.healthaffairs.org/doi/10.1377/hblog20180103.261091/full/>
- Manchikanti L, Navani A. Evolution of regenerative medicine in managing chronic pain. In: Manchikanti L, Navani A, Atluri S (eds). *Essentials of Regenerative Medicine in Interventional Pain Management*. ASIPP Publishing, Paducah, KY 2019, IN PRESS.
- Manchikanti L, Navani A, Singh V, Falco FJE, Hirsch JA. Intradiscal injection of biologics. In: Manchikanti L, Navani A, Atluri S (eds). *Essentials of Regenerative Medicine in Interventional Pain Management*. ASIPP Publishing, Paducah, KY 2019, IN PRESS.
- Manchikanti L, Navani A. Lumbar epidural administration of PRP and stem cells. In: Manchikanti L, Navani A, Atluri S (eds). *Essentials of Regenerative Medicine in Interventional Pain Management*. ASIPP Publishing, Paducah, KY 2019, IN PRESS.
- Navani A, Manchikanti L. Lumbar facet joints and regenerative medicine. In: Manchikanti L, Navani A, Atluri S (eds). *Essentials of Regenerative Medicine in Interventional Pain Management*. ASIPP Publishing, Paducah, KY 2019, IN PRESS.
- Cabaret J, Manchikanti L, Calodney AK. Regenerative medicine for sacroiliac joint dysfunction. In: Manchikanti L, Navani A, Atluri S (eds). *Essentials of Regenerative Medicine in Interventional Pain Management*. ASIPP Publishing,

- Paducah, KY 2019, IN PRESS.
22. Rodeback DG, Navani A. Sacroiliac ligaments. In: Manchikanti L, Navani A, Atluri S (eds). *Essentials of Regenerative Medicine in Interventional Pain Management*. ASIPP Publishing, Paducah, KY 2019, IN PRESS.
 23. Bodor M, Dregalla R, Uribe Y. Platelet rich plasma. In: Manchikanti L, Navani A, Atluri S (eds). *Essentials of Regenerative Medicine in Interventional Pain Management*. ASIPP Publishing, Paducah, KY 2019, IN PRESS.
 24. Valeri CR, Zaroulis CG. Rejuvenation and freezing of outdated stored human red cells. *N Engl J Med* 1972; 287:1307-1313.
 25. Khan S, Mafi P, Mafi R, Khan W. A systematic review of mesenchymal stem cells in spinal cord injury, intervertebral disc repair and spinal fusion. *Curr Stem Cell Res Ther* 2018; 13:316-323.
 26. Basso M, Cavagnaro L, Zanirato A, Divano S, Formica C, Formica M, Felli L. What is the clinical evidence on regenerative medicine in intervertebral disc degeneration? *Musculoskelet Surg* 2017; 101:93-104.
 27. Wang Z, Perez-Terzic CM, Smith J, Mauck WD, Shelerud RA, Maus TP, Yang TH, Murad MH, Gou S, Terry MJ, Dauffenbach JP, Pingree MJ, Eldrige JS, Mohammed K, Benkhadra K, van Wijnen AJ, Qu W. Efficacy of intervertebral disc regeneration with stem cells—A systematic review and meta-analysis of animal controlled trials. *Gene* 2015; 564:1-8.
 28. Wu T, Song HX, Dong Y, Li J. Cell-based therapies for lumbar discogenic low back pain: Systematic review and single-arm meta-analysis. *Spine (Phila Pa 1976)* 2018; 43:49-57.
 29. Sanapati J, Manchikanti L, Atluri S, Jordan S, Albers SL, Pappolla MA, Kaye AD, Candido KD, Pampati V, Hirsch JA. Do regenerative medicine therapies provide long-term relief in chronic low back pain: A systematic review and metaanalysis. *Pain Physician* 2018; 21:515-540.
 30. Lana JF, Purita J, Silva Rava CA, Nicholls MA, Parada CA, Forti AP, Ventura Vierira IF, Madureira Junior JL, Fortis Gusmão PD, de Camargo LS, Caliarí-Oliveira C. Bone marrow concentrate. In: Manchikanti L, Navani A, Atluri S (eds). *Essentials of Regenerative Medicine in Interventional Pain Management*. ASIPP Publishing, Paducah, KY 2019, IN PRESS.
 31. Riazi AM, Kwon SY, Stanford WL. Stem cell sources for regenerative medicine. *Methods Mol Biol* 2009; 482:55-90.
 32. Muneoka K, Allan CH, Yang X, Lee J; Han M. Mammalian regeneration and regenerative medicine. *Birth Defects Res C Embryo Today* 2008; 84:265-280.
 33. Marks PW, Witten CM, Califf CM. Clarifying stem-cell therapy's benefits and risks. *N Engl J Med* 2016; 376:1007-1009.
 34. Knoepfler PS. From bench to FDA to bedside: US regulatory trends for new stem cell therapies. *Adv Drug Deliv Rev* 2015; 82-83:192-196.
 35. FDA News Release. FDA acts to remove unproven, potentially harmful treatment used in 'stem cell' centers targeting vulnerable patients. Vaccinia Virus Vaccine (Live) seized after being used inappropriately in vulnerable cancer patients. August 28, 2017. www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm573427.htm
 36. Turner LG. Federal regulatory oversight of US clinics marketing adipose-derived autologous stem cell interventions: Insights from 3 new FDA draft guidance documents. *Mayo Clin Proc* 2015; 90:567-571.
 37. Turner L. US stem cell clinics, patient safety, and the FDA. *Trends Mol Med* 2015; 21:271-273.
 38. Charo A, Sipp D. Rejuvenating regenerative medicine regulation. *N Engl J Med* 2018; 378:504-505.
 39. U.S. Food and Drug Administration. FDA New Release: FDA announces comprehensive regenerative medicine policy framework. November 16, 2017. www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm585345.htm
 40. U.S. Food and Drug Administration. Regulation Considerations for Human Cells, Tissues, and Cellular and Tissue-Based Products: Minimal Manipulation and Homologous Use. Guidance for Industry and Food and Drug Administration Staff. www.fda.gov/downloads/Biologics-BloodVaccines/GuidanceCompliance-RegulatoryInformation/Guidances/CellularandGeneTherapy/UCM585403.pdf
 41. Draft report of the FSMB Workgroup to study regenerative and stem cell therapy practices, December 2017.
 42. Manchikanti L, Boswell MV, Hirsch JA. Innovations in interventional pain management of chronic spinal pain. *Expert Rev Neurother* 2016; 16:1033-1042.
 43. Knezevic NN, Candido KD, Desai R, Kaye AD. Is platelet-rich plasma a future therapy in pain management? *Med Clin North Am* 2016; 100:199-217.
 44. The National Uniform Claims Committee. Specialty Designation for Interventional Pain Management- 09. www.cms.hhs.gov/transmittals/Downloads/r1779b3.pdf
 45. Medicare Payment Advisory Commission. Report to the Congress: Paying for interventional pain services in ambulatory settings. Washington, DC: MedPAC. December. 2001. <http://www.medpac.gov/documents/reports/december-2001-report-to-the-congress-paying-for-interventional-pain-services-in-ambulatory-settings.pdf?sfvrsn=0>
 46. Graham R, Mancher M, Wolman DM, Greenfield S, Steinberg E (eds); Committee on Standards for Developing Trustworthy Clinical Practice Guidelines; Institute of Medicine. *Clinical Practice Guidelines We Can Trust*. The National Academies Press, Washington, DC, 2011.
 47. National Guideline Clearinghouse Extent Adherence to Trustworthy Standards (NEATS) instrument. www.ncbi.nlm.nih.gov/pubmedhealth/PMH0079458/.
 48. Harris RP, Helfand M, Woolf SH, Lohr KN, Mulrow CD, Teutsch SM, Atkins D; Methods Work Group, Third US Preventive Services Task Force. Current methods of the US Preventive Services Task Force. *Am J Prevent Med* 2001; 20:21-35.
 49. Manchikanti L, Falco FJE, Benjamin R M, Kaye AD, Boswell MV, Hirsch JA. A modified approach to grading of evidence. *Pain Physician* 2014; 17:E319-E325.
 50. Institute of Medicine (IOM). *Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research*. The National Academies Press, Washington, DC, June 29, 2011. www.iom.edu/~media/Files/Report%20Files/2011/Relieving-Pain-in-America-A-Blueprint-for-Transforming-Prevention-Care-Education-Research/Pain%20Research%202011%20Report%20Brief.pdf
 51. Gaskin DJ, Richard P. The economic costs of pain in the United States. *J Pain* 2012; 13:715-724.
 52. Manchikanti L, Atluri S, Candido KD, Boswell MV, Simopoulos TT, Grider JS, Falco FJE, Hirsch JA. Zohydro™ approval by Food and Drug Administration: Controversial or frightening? *Pain Physician* 2014; 17:E437-E450.

53. Martin BI, Turner JA, Mirza SK, Lee MJ, Comstock BA, Deyo RA. Trends in health care expenditures, utilization, and health status among US adults with spine problems, 1997-2006. *Spine (Phila Pa 1976)* 2009; 34:2077-2084.
54. Freburger JK, Holmes GM, Agans RP, Jackman AM, Darter JD, Wallace AS, Castel LD, Kalsbeek WD, Carey TS. The rising prevalence of chronic low back pain. *Arch Intern Med* 2009; 169:251-258.
55. Manchikanti L, Singh V, Falco FJE, Benyamin RM, Hirsch JA. Epidemiology of low back pain in adults. *Neuromodulation* 2014; 17:3-10.
56. Hoy DG, Bain C, Williams G, March L, Brooks P, Blyth F, Woolf A, Vos T, Buchbinder R. A systematic review of the global prevalence of low back pain. *Arthritis Rheum* 2012; 64:2028-2037.
57. Hoy D, March L, Brooks P, Blyth F, Woolf A, Bain C, Williams G, Smith E, Vos T, Barendregt J, Murray C, Burstein R, Buchbinder R. The global burden of low back pain: Estimates from the Global Burden of Disease 2010 study. *Ann Rheum Dis* 2014; 73:968-974.
58. Labusca L, Zugun-Eloae F, Mashayekhi K. Stem cells for the treatment of musculoskeletal pain. *World J Stem Cells* 2015; 7:96-105.
59. Sjøgren P, Ekholm O, Peuckmann V, Grønbaek M. Epidemiology of chronic pain in Denmark: An update. *Eur J Pain* 2009; 13:287-292.
60. Blyth FM, Rochat S, Cumming RG, Creasey H, Handelsman DJ, Le Couteur DG, Naganathan V, Sambrook PN, Seibel MJ, Waite LM. Pain, frailty and comorbidity on older men: The CHAMP study. *Pain* 2008; 140:224-230.
61. Cassidy JD, Carroll LJ, Côté P. The Saskatchewan Health and Back Pain Survey. The prevalence of low back pain and related disability in Saskatchewan adults. *Spine (Phila Pa 1976)* 1998; 23:1860-1867.
62. Côté P, Cassidy JD, Carroll L. The Saskatchewan Health and Back Pain Survey. The prevalence of neck pain and related disability in Saskatchewan adults. *Spine (Phila Pa 1976)* 1998; 23:1689-1698.
63. Leboeuf-Yde C, Nielsen J, Kyvik KO, Fejer R, Hartvigsen J. Pain in the lumbar, thoracic or cervical regions: Do age or gender matter? A population-based study of 34,902 Danish twins 20-71 years of age. *BMC Musculoskelet Disord* 2009; 10:39.
64. Waterman RS, Morgenweck J, Nosaman BD, Scandurro AE, Scandurro SA, Betancourt AM. Anti-inflammatory mesenchymal stem cells (MSC2) attenuate symptoms of painful diabetic peripheral neuropathy. *Stem Cells Transl Med* 2012; 1:557-565.
65. Merskey H, Bogduk N. Task Force on Taxonomy of the International Association for the Study of Pain. *Classification of Chronic Pain: Descriptions of Chronic Pain Syndromes and Definition of Pain Terms*. 2nd ed. IASP Press, Seattle, WA, 1994.
66. Jarvik JG, Gold LS, Tan K, Friedly JL, Nedejkovic SS, Comstock BA, Deyo RA, Turner JA, Bresnahan BW, Rundell SD, James KT, Nerenz DR, Avins AL, Bauer Z, Kessler L, Heagerty PJ. Long-term outcomes of a large, prospective observational cohort of older adults with back pain. *Spine J* 2018; 18:1540-1551.
67. Best MJ, Buller LT, Eismont FJ. National trends in ambulatory surgery for intervertebral disc disorders and spinal stenosis: A 12-year analysis of the national surveys of ambulatory surgery. *Spine (Phila Pa 1976)* 2015; 40:1703-1711.
68. Deyo RA, Mirza SK, Turner JA, Martin BI. Overtreating chronic back pain: Time to back off? *J Am Board Fam Med* 2009; 22:62-68.
69. Ragab A, Deshazo RD. Management of back pain in patients with previous back surgery. *Am J Med* 2008; 121:272-278.
70. Lad SP, Babu R, Ugiliweneza B, Patil CG, Boakye M. Surgery for spinal stenosis: Long-term reoperation rates, health care cost, and impact of instrumentation. *Spine (Phila Pa 1976)* 2014; 39:978-987.
71. Singh K, Nandyala SV, Marquez-Lara A, Fineberg SJ. Epidemiological trends in the utilization of bone morphogenetic protein in spinal fusions from 2002 to 2011. *Spine (Phila Pa 1976)* 2014; 39:491-496.
72. Rajaei SS, Kanim LE, Bae HW. National trends in revision spinal fusion in the USA: Patient characteristics and complications. *Bone Joint J* 2014; 96-B:807-816.
73. O'Gara T, Kemper KJ, Birkedal J, Curl W, Miller N, Abadie B. Survey of conventional and complementary and alternative therapy in patients with low back pain. *J Surg Orthop Adv* 2016; 25:27-33.
74. Karvelas DA, Rundell SD, Friedly JL, Gellhorn AC, Gold LS, Comstock BA, Heagerty PJ, Bresnahan BW, Nerenz DR, Jarvik JG. Subsequent health-care utilization associated with early physical therapy for new episodes of low back pain in older adults. *Spine J* 2017; 17:380-389.
75. Sclafani JA, Constantini A, Ho PS, Akuthota V, Chan L. Descriptive analysis of spinal neuroaxial injections, surgical interventions, and physical therapy utilization for degenerative lumbar spondylosis within Medicare beneficiaries from 2000 to 2011. *Spine (Phila Pa 1976)* 2017; 42:240-246.
76. Amirdelfan K, Webster L, Poree L, Sukul V, McRoberts P. Treatment options for failed back surgery syndrome patients with refractory chronic pain: An evidence based approach. *Spine (Phila Pa 1976)* 2017; 42:S41-S52.
77. Dagenais S, Caro J, Haldeman S. A systematic review of low back pain cost of illness studies in the United States and internationally. *Spine J* 2008; 8:8-20.
78. Becker A, Held H, Redaelli M, Strauch K, Chenot JF, Leonhardt C, Keller S, Baum E, Pflingsten M, Hildebrandt J, Basler HD, Kochen MM, Donner-Banzhoff N. Low back pain in primary care: Costs of care and prediction of future health care utilization. *Spine (Phila Pa 1976)* 2010; 35:1714-1720.
79. Bressler HB, Keyes WJ, Rochon PA, Badley E. The prevalence of low back pain in the elderly. A systematic review of the literature. *Spine (Phila Pa 1976)* 1999; 24:1813-1819.
80. Ritzwoller DP, Crouse L, Shetterly S, Rublee D. The association of comorbidities, utilization and costs for patients identified with low back pain. *BMC Musculoskelet Disord* 2006; 7:72.
81. Leavitt SB. NSAID dangers may limit pain-relief options. *Pain-Topics News/Research UPDATES*, March 14, 2010. <http://updates.pain-topics.org/2010/03/nsaid-dangers-may-limit-pain-relief.html>.
82. Moore A, Wiffen P, Kalso E. Antiepileptic drugs for neuropathic pain and fibromyalgia. *JAMA* 2014; 312:182-183.
83. Pannell WC, Savin DD, Scott TP, Wang JC, Daubs MD. Trends in the surgical treatment of lumbar spine disease in the United States. *Spine J* 2015; 15:1719-1727.
84. Gaudin D, Krafcik BM, Mansour TR, Alnemari A. Considerations in spinal fusion surgery for chronic lumbar pain: psychosocial factors, rating scales, and perioperative patient education-a review of the literature. *World Neurosurg* 2017; 98:21-27.
85. Yoshihara H, Yoneoka D. National trends in the surgical treatment for lumbar degenerative disc disease: United States, 2000 to 2009. *Spine J* 2015; 15:265-271.
86. Manchikanti L, Pampati V, Benyamin

- RM, Hirsch JA. Declining utilization of percutaneous epidural adhesiolysis in Medicare population: Evidence-based or over-regulated? *IPM Reports* 2018; 2:9-18.
87. Manchikanti L, Pampati V, Hirsch JA. Utilization of interventional techniques in managing chronic pain in Medicare population from 2000 to 2014: An analysis of patterns of utilization. *Pain Physician* 2016; 19:E531-E546.
 88. Manchikanti L, Hirsch JA, Pampati V, Boswell MV. Utilization of facet joint and sacroiliac joint interventions in Medicare population from 2000 to 2014: Explosive growth continues! *Curr Pain Headache Rep* 2016; 20:58.
 89. Manchikanti L, Pampati V, Hirsch JA. Retrospective cohort study of usage patterns of epidural injections for spinal pain in the US fee-for-service Medicare population from 2000 to 2014. *BMJ Open* 2016; 6:e013042.
 90. Manchikanti L, Sooin A, Mann DP, Bakshi S, Pampati V, Hirsch JA. Comparative analysis of utilization of epidural procedures in managing chronic pain in the Medicare population: Pre and the Post Affordable Care Act. *Spine (Phila Pa 1976)* 2018; Jul 12. [Epub ahead of print].
 91. Manchikanti L, Sooin A, Mann DP, Bakshi S, Pampati V, Hirsch JA. Utilization patterns of facet joint interventions in managing spinal pain: A retrospective cohort study in the U.S. fee-for-service Medicare population. *BMJ Open* 2018; in press.
 92. Manchikanti MV, Manchikanti L, Kaye AD, Pampati V, Hirsch JA. Usage patterns of sacroiliac joint injections - a comparative evaluation of pre and post Affordable Care Act in Medicare population. *IPM Reports* 2018; 2:157-166.
 93. Hirsch JA, Chandra RV, Pampati V, Barr JD, Brook AL, Manchikanti L. Analysis of vertebral augmentation practice patterns: A 2016 update. *J Neurointer Surg* 2016; 8:1299-1304.
 94. Graves JM, Fulton-Kehoe D, Jarvik JG, Franklin GM. Health care utilization and costs associated with adherence to clinical practice guidelines for early magnetic resonance imaging among workers with acute occupational low back pain. *Health Serv Res* 2014; 49:645-665.
 95. Chou R, Hashimoto R, Friedly J, Fu R, Dana T, Sullivan S, Bougatsos C, Jarvik J. Pain Management Injection Therapies for Low Back Pain. Technology Assessment Report ESIBo813. (Prepared by the Pacific Northwest Evidence-based Practice Center under Contract No. HHS 290-2012-00014-1.) Rockville, MD: Agency for Healthcare Research and Quality; July 10, 2015.
 96. Chou R, Hashimoto R, Friedly J, Fu R, Bougatsos C, Dana T, Sullivan SD, Jarvik J. Epidural corticosteroid injections for radiculopathy and spinal stenosis: A systematic review and meta-analysis. *Ann Intern Med* 2015; 163:373-381.
 97. Manchikanti L, Knezevic NN, Boswell MV, Kaye AD, Hirsch JA. Epidural injections for lumbar radiculopathy and spinal stenosis: A comparative systematic review and meta-analysis. *Pain Physician* 2016; E365-E410.
 98. Boswell MV, Manchikanti L. Appropriate design and methodologic quality assessment, clinically relevant outcomes are essential to determine the role of epidural corticosteroid injections. Commentary RE: Chou R, Hashimoto R, Friedly J, Fu R, Bougatsos C, Dana T, Sullivan SD, Jarvik J. Epidural corticosteroid injections for radiculopathy and spinal stenosis: A systematic review and meta-analysis. *Ann Intern Med* 2015; 163:373-381. *Evid Based Med* 2016; 21:89.
 99. Friedly JL, Comstock BA, Turner JA, Heagerty PJ, Deyo RA, Sullivan SD, Bauer Z, Bresnahan BW, Avins AL, Nedeljkovic SS, Nerenz DR, Standaert C, Kessler L, Akuthota V, Annaswamy T, Chen A, Diehn F, Firtch W, Gerges FJ, Gilligan C, Goldberg H, Kennedy DJ, Mandel S, Tyburski M, Sanders W, Sibell D, Smuck M, Wasan A, Won L, Jarvik JG. A randomized trial of epidural glucocorticoid injections for spinal stenosis. *N Engl J Med* 2014; 371:11-21.
 100. Manchikanti L, Candido KD, Kaye AD, Boswell MV, Benjamin RM, Falco FJE, Gharibo CG, Hirsch JA. Randomized trial of epidural injections for spinal stenosis published in the New England Journal of Medicine: Further confusion without clarification. *Pain Physician* 2014; 17:E475-E488.
 101. Boswell MV, Manchikanti L, Kaye AD, Bakshi S, Gharibo CG, Gupta S, Jha S, Nampiarampil DE, Simopoulos TT, Hirsch JA. A best-evidence systematic appraisal of the diagnostic accuracy and utility of facet (zygapophysial) joint injections in chronic spinal pain. *Pain Physician* 2015; 18:E497-E533.
 102. Manchikanti L, Kaye AD, Boswell MV, Bakshi S, Gharibo CG, Grami V, Grider JS, Gupta S, Jha S, Mann DP, Nampiarampil DE, Sharma ML, Shroyer LN, Singh V, Sooin A, Vallejo R, Wargo BW, Hirsch JA. A systematic review and best evidence synthesis of the effectiveness of therapeutic facet joint interventions in managing chronic spinal pain. *Pain Physician* 2015; 18:E535-E582.
 103. Simopoulos TT, Manchikanti L, Gupta S, Aydin SM, Kim CH, Solanki D, Nampiarampil DE, Singh V, Staats PS, Hirsch JA. Systematic review of the diagnostic accuracy and therapeutic effectiveness of sacroiliac joint interventions. *Pain Physician* 2015; 18:E713-E756.
 104. Manchikanti L, Hirsch JA, Falco FJ, Boswell MV. Management of lumbar zygapophysial (facet) joint pain. *World J Orthop* 2016; 7:315-337.
 105. Manchikanti L, Hirsch JA, Kaye AD, Boswell MV. Cervical zygapophysial (facet) joint pain: Effectiveness of interventional management strategies. *Postgrad Med* 2016; 128:54-68.
 106. Kaye AD, Manchikanti L, Abdi S, Atluri S, Bakshi S, Benjamin R, Boswell MV, Buenaventura R, Candido KD, Cordero HJ, Datta S, Doulatram G, Gharibo CG, Grami V, Gupta S, Jha S, Kaplan ED, Malla Y, Mann DP, Nampiarampil DE, Racz G, Raj P, Rana MV, Sharma ML, Singh V, Sooin A, Staats PS, Vallejo R, Wargo BW, Hirsch JA. Efficacy of epidural injections in managing chronic spinal pain: A best evidence synthesis. *Pain Physician* 2015; 18:E939-E1004.
 107. Manchikanti L, Kaye AD, Manchikanti KN, Boswell MV, Pampati V, Hirsch JA. Efficacy of epidural injections in the treatment of lumbar central spinal stenosis: A systematic review. *Anesth Pain Med* 2015; 5:e23139.
 108. Manchikanti L, Singh V, Cash KA, Pampati V, Datta S. A comparative effectiveness evaluation of percutaneous adhesiolysis and epidural steroid injections in managing lumbar post surgery syndrome: A randomized, equivalence controlled trial. *Pain Physician* 2009; 12:E355-E368.
 109. Helm II S, Racz GB, Gerdesmeyer L, Justiz L, Hayek SM, Kaplan ED, El Terany MA, Knezevic NN. Percutaneous and endoscopic adhesiolysis in managing low back and lower extremity pain: A systematic review and meta-analysis. *Pain Physician* 2016; 19:E245-E282.
 110. Grider JS, Manchikanti L, Carayanopoulos A, Sharma ML, Balog CC, Harned ME, Grami V, Justiz R, Nouri KH, Hayek SM, Vallejo R, Christo PJ. Effectiveness of spinal cord stimulation in chronic spinal pain: A systematic review. *Pain Physician* 2016; 19:E33-E54.

111. Manchikanti L, Staats PS, Nampiaparampil DE, Hirsch JA. What is the role of epidural injections in the treatment of lumbar discogenic pain: A systematic review of comparative analysis with fusion and disc arthroplasty. *Korean J Pain* 2015; 28:75-87.
112. Meng H, Fei Q, Wang B, Yang Y, Li D, Li J, Su N. Epidural injections with or without steroids in managing chronic low back pain secondary to lumbar spinal stenosis: a meta-analysis of 13 randomized controlled trials. *Drug Des Devel Ther* 2015; 9:4657-67.
113. Lee JH, Shin KS, Park SJ, Lee GJ, Lee CH, Kim DH, Kim DH, Yang HS. Comparison of clinical efficacy between transforaminal and interlaminar epidural injections in lumbosacral disc herniation: A systematic review and meta-analysis. *Pain Physician* 2018; 21:433-448.
114. Lee JH, Kim DH, Kim, DH, Shin KS, Park SJ, Lee GJ, Lee CH, Yang HS. Comparison of clinical efficacy of epidural injection with or without steroid in lumbosacral disc herniation: A systematic review and meta-analysis. *Pain Physician* 2018; 449-468.
115. Manchikanti L, Benyamin RM, Falco FJ, Kaye AD, Hirsch JA. Do epidural injections provide short- and long-term relief for lumbar disc herniation? A systematic review. *Clin Orthop Relat Res* 2015; 473:1940-1956.
116. Liu K, Liu P, Wu X, Cai M. Steroid for epidural injection in spinal stenosis: A systematic review and meta-analysis. *Drug Des Devel Ther* 2015; 9:707-716.
117. Zhai J, Zhang L, Li M, Tian Y, Zheng W, Chen J, Huang T, Li X, Tian Z. Epidural injection with or without steroid in managing chronic low back and lower extremity pain: A meta-analysis of ten randomized controlled trials. *Int J Clin Exp Med* 2015; 8:8304-8316.
118. Manchikanti L, Nampiaparampil DE, Manchikanti KN, Falco FJE, Singh V, Benyamin RM, Kaye AD, Sehgal N, Sooin A, Simopoulos TT, Bakshi S, Gharibo CG, Gilligan CJ, Hirsch JA. Comparison of the efficacy of saline, local anesthetics, and steroids in epidural and facet joint injections for the management of spinal pain: A systematic review of randomized controlled trials. *Surg Neurol Int* 2015; 6:S194-S235.
119. Hunter CW, Stovall B, Chen G, Carlson J, Levy R. Anatomy, pathophysiology and interventional therapies for chronic pelvic pain: A review. *Pain Physician* 2018; 21:147-167.
120. Shen J, Xu S, Xu S, Ye S, Hao J. Fusion or not for degenerative lumbar spinal stenosis: A meta-analysis and systematic review. *Pain Physician* 2018; 21:1-8.
121. Wu JJ, Chen HZ, Zheng C. Transforaminal percutaneous endoscopic discectomy and foraminoplasty after lumbar spinal fusion surgery. *Pain Physician* 2017; 20:E647-E651.
122. Kumar K, Rizvi S. Cost-effectiveness of spinal cord stimulation therapy in management of chronic pain. *Pain Med* 2013; 14:1631-1649.
123. Taylor RS, Ryan J, O'Donnell R, Eldabe S, Kumar K, North RB. The cost-effectiveness of spinal cord stimulation in the treatment of failed back surgery syndrome. *Clin J Pain* 2010; 26:463-469.
124. Manchikanti L, Pampati V, Kaye AD, Hirsch JA. Therapeutic lumbar facet joint nerve blocks in the treatment of chronic low back pain: Cost utility analysis based on a randomized controlled trial. *Korean J Pain* 2018; 31:27-38.
125. Manchikanti L, Pampati V, Kaye AD, Hirsch JA. Cost utility analysis of cervical therapeutic medial branch blocks in managing chronic neck pain. *Int J Med Sci* 2017; 14:1307-1316.
126. Manchikanti L, Falco FJE, Pampati V, Cash KA, Benyamin RM, Hirsch JA. Cost utility analysis of caudal epidural injections in the treatment of lumbar disc herniation, axial or discogenic low back pain, central spinal stenosis, and post lumbar surgery syndrome. *Pain Physician* 2013; 16:E129-E143.
127. Manchikanti L, Pampati V, Benyamin RM, Hirsch JA. Cost utility analysis of lumbar interlaminar epidural injections in the treatment of lumbar disc herniation, central spinal stenosis, and axial or discogenic low back pain. *Pain Physician* 2017; 20:219-228.
128. Atluri S, Sudarshan G, Manchikanti L. Assessment of the trends in medical use and misuse of opioid analgesics from 2004 to 2011. *Pain Physician* 2014; 17:E119-E128.
129. Manchikanti L, Cash KA, Malla Y, Pampati V, Fellows B. A prospective evaluation of psychotherapeutic and illicit drug use in patients presenting with chronic pain at the time of initial evaluation. *Pain Physician* 2013; 16:E1-E13.
130. Manchikanti L, Sanapati J, Benyamin RM, Atluri S, Kaye AD, Hirsch JA. Reframing the prevention strategies of the opioid crisis: Focusing on prescription opioids, fentanyl, and heroin epidemic. *Pain Physician* 2018; 21:309-326.
131. Guy Jr GP, Zhang K, Bohm MK, Losby J, Lewis B, Young R, Murphy LB, Dowell D. Vital Signs: Changes in opioid prescribing in the United States, 2006-2015. *MMWR Morb Mortal Wkly Rep* 2017; 66:697-704.
132. Dowell D, Noonan RK, Houry D. Underlying factors in drug overdose deaths. *JAMA* 2017; 318:2295-2296.
133. US Centers for Disease Control and Prevention. Provisional counts of drug overdose deaths as of August 6, 2017. https://www.cdc.gov/nchs/data/health_policy/monthly-drug-overdose-death-estimates.pdf
134. Singer JA. Stop calling it an opioid crisis – it's a heroin and fentanyl crisis. *Cato Institute*, January 9, 2018. <https://www.cato.org/blog/stop-calling-it-opioid-crisis-its-heroin-fentanyl-crisis>
135. National Institute on Drug Abuse. Overdose death rates. August 2018 <https://www.drugabuse.gov/related-topics/trends-statistics/overdose-death-rates>
136. United States Drug Enforcement Administration. DEA proposes reduction to amount of controlled substances to be manufactured in 2018. August 4, 2017. <https://www.dea.gov/divisions/hq/2017/hq080417.shtml>
137. Schuchat A, Houry D, Guy GP Jr. New data on opioid use and prescribing in the United States. *JAMA* 2017; 318:425-426.
138. Centers for Disease Control and Prevention. Annual Surveillance Report of Drug-Related Risks and Outcomes -- United States, 2017. Surveillance Special Report 1. Centers for Disease Control and Prevention, U.S. Department of Health and Human Services. August 31, 2017. <https://www.cdc.gov/drugoverdose/pdf/pubs/2017-cdc-drug-surveillance-report.pdf>
139. Seth P, Rudd RA, Noonan RK, Haegerich TM. Quantifying the epidemic of prescription opioid overdose deaths. *Am J Public Health* 2018; 108:500-502.
140. IQVIA Institute for Human Data Science Study. Medicine use and spending in the U.S. A review of 2017 and outlook for 2022. April 2018. https://www.iqvia.com/-/media/iqvia/pdfs/institute-reports/medicine-use-and-spending-in-the-us-a-review-of-2017-and-outlook-to-2022.pdf?_=1527706762033
141. Nwachukwu BU, Schairer WW, Shifflett

- GD, Kellner DB, Sama AA. Cost-utility analyses in spine care: a qualitative and systematic review. *Spine (Phila Pa 1976)* 2015; 40:31-40.
142. Al-Khouja LT, Baron EM, Johnson JP, Kim TT, Drazin D. Cost-effectiveness analysis in minimally invasive spine surgery. *Neurosurg Focus* 2014; 36:E4.
 143. Tosteson AN, Skinner JS, Tosteson TD, Lurie JD, Andersson GB, Berven S, Grove MR, Hanscom B, Blood EA, Weinstein JN. The cost effectiveness of surgical versus nonoperative treatment for lumbar disc herniation over two years: Evidence from the Spine Patient Outcomes Research Trial (SPORT). *Spine (Phila Pa 1976)* 2008; 33:2108-2115.
 144. Tosteson AN, Lurie JD, Tosteson TD, Skinner JS, Herkowitz H, Albert T, Boden SD, Bridwell K, Longley M, Andersson GB, Blood EA, Grove MR, Weinstein JN; SPORT Investigators. Surgical treatment of spinal stenosis with and without degenerative spondylolisthesis: Cost-effectiveness after 2 years. *Ann Intern Med* 2008; 149:845-853.
 145. Tosteson AN, Tosteson TD, Lurie JD, Abdu W, Herkowitz H, Andersson G, Albert T, Bridwell K, Zhao W, Grove MR, Weinstein MC, Weinstein JN. Comparative effectiveness evidence from the spine patient outcomes research trial: Surgical versus nonoperative care for spinal stenosis, degenerative spondylolisthesis, and intervertebral disc herniation. *Spine (Phila Pa 1976)* 2011; 36:2061-2068.
 146. Kepler CK, Wilkinson SM, Radcliff KE, Vaccaro AR, Anderson DG, Hilibrand AS, Albert TJ, Rihn JA. Cost-utility analysis in spine care: A systematic review. *Spine J* 2012; 22:676-690.
 147. Indrakanti SS, Weber MH, Takemoto SK, Hu SS, Polly D, Berven SH. Value-based care in the management of spinal disorders: A systematic review of cost-utility analysis. *Clin Orthop Relat Res* 2012; 470:1106-1123.
 148. Johnson RE, Jones GT, Wiles NJ, Chadock C, Potter RG, Roberts C, Symmons DP, Watson PJ, Torgerson DJ, Macfarlane GJ. Active exercise, education, and cognitive behavioral therapy for persistent disabling low back pain: A randomized controlled trial. *Spine (Phila Pa 1976)* 2007; 32:1578-1585.
 149. Fritz JM, Kim M, Magel JS, Asche CV. Cost-effectiveness of primary care management with or without early physical therapy for acute low back pain: Economic evaluation of a randomized clinical trial. *Spine (Phila Pa 1976)* 2017; 42:285-290.
 150. National Institute for Health and Clinical Excellence. *Guide to the Methods of Technology Appraisal*. NICE, London, 2008.
 151. Manchikanti L, Soin A, Benyamin RM, Singh V, Falco FJE, Calodney AK, Grami V, Hirsch JA. An update of the systematic appraisal of the accuracy and utility of discography in chronic spinal pain. *Pain Physician* 2018; 21:91-110.
 152. Manchikanti L, Navani A. Lumbar facet joints and regenerative medicine. In: Manchikanti L, Navani A, Atluri S (eds). *Essentials of Regenerative Medicine in Interventional Pain Management*. ASIPP Publishing, Paducah, KY 2018, pp ____.
 153. Fardon DF, Milette PC. Nomenclature and classification of lumbar disc pathology: Recommendations of the Combined Task Forces of the North American Spine Society, American Society of Spine Radiology, and American Society of Neuroradiology. *Spine (Phila Pa 1976)* 2001; 26:E93-E113.
 154. Manchikanti L, Hirsch JA, Datta S, Falco FJE. Low back and lumbar radicular pain. In: Manchikanti L, Christo PJ, Trescot AM, Falco FJE (eds). *Clinical Aspects of Pain Medicine and Interventional Pain Management: A Comprehensive Review*. ASIPP Publishing, Paducah, KY, 2011, pp 87-114.
 155. Mixer WJ, Barr JS. Rupture of the intervertebral disc with involvement of the spinal canal. *N Eng J Med* 1934; 211:210-215.
 156. Manchikanti L, Albers SL, Hirsh JA, Boswell, MV. Lumbar Disk Herniation. In: Kaye AD, ed. *Scientific American Pain Management*. Hamilton: Decker; September 2017. DOI: 10.2310/7900.15047. www.DeckerIP.com
 157. Postacchini F, Cinotti G. Etiopathogenesis. In: Postacchini F (ed). *Lumbar Disc Herniation*. Springer-Verlag, New York, 1999, pp 151-164.
 158. Savettieri G, Salemi G, Rocca WA, Meneghini F, D'Arpa A, Morgante L, Coraci MA, Reggio A, Grigoletto F, Di Perri R. Prevalence of lumbosacral radiculopathy in two Sicilian municipalities. Sicilian Neuro-Epidemiologic Study (SNES) Group. *Acta Neurol Scand* 1996; 93:464-469.
 159. Hahne AJ, Ford JJ, McMeeken JM. Conservative management of lumbar disc herniation with associated radiculopathy: A systematic review. *Spine (Phila Pa 1976)* 2010; 35:E488-E504.
 160. Peng B, Fu X, Pang X, Li D, Liu W, Gao C, Yang H. Prospective clinical study on natural history of discogenic low back pain at 4 years of follow-up. *Pain Physician* 2012; 15:523-532.
 161. Pang WW, Mok MS, Lin ML, Chang DP, Hwang MH. Application of spinal pain mapping in the diagnosis of low back pain—analysis of 104 cases. *Acta Anaesthesiol Sin* 1998; 36:71-74.
 162. Manchikanti L, Singh V, Pampati V, Damron K, Barnhill R, Beyer C, Cash K. Evaluation of the relative contributions of various structures in chronic low back pain. *Pain Physician* 2001; 4:308-316.
 163. Wolfer L, Derby R, Lee JE, Lee SH. Systematic review of lumbar provocation discography in asymptomatic subjects with a meta-analysis of false-positive rates. *Pain Physician* 2008; 11:513-538.
 164. Schwarzer AC, Aprill CN, Derby R, Fortin J, Kine G, Bogduk N. The prevalence and clinical features of internal disc disruption in patients with chronic low back pain. *Spine (Phila Pa 1976)* 1995; 20:1878-1883.
 165. DePalma MJ, Ketchum JM, Saullo T. What is the source of chronic low back pain and does age play a role? *Pain Med* 2011; 12:224-233.
 166. Manchikanti L, Albers SL, Latchaw R. Lumbar Spinal Stenosis and Neurogenic Claudication. In: Kaye AD, ed. *Scientific American Pain Management*. Hamilton: Decker; August 2017. DOI: 10.2310/7900.15048. www.DeckerIP.com
 167. Haig AJ, Tomkins CC. Diagnosis and management of lumbar spinal stenosis. *JAMA* 2010; 303:71-72.
 168. Kalichman L, Cole R, Kim DH, Li L, Suri P, Guermazi A, Hunter DJ. Spinal stenosis prevalence and association with symptoms: The Framingham Study. *Spine J* 2009; 9:545-550.
 169. Zeckser J, Wolff M, Tucker J, Goodwin J. Multipotent mesenchymal stem cell treatment for discogenic low back pain and disc degeneration. *Stem Cells Int* 2016; 2016:3908389.
 170. Dong L, Odeleye AO, Jordan-Sciutto KL, Winkelstein BA. Painful facet joint injury induces neuronal stress activation in the DRG: Implications for cellular mechanisms of pain. *Neurosci Lett* 2008; 443:90-94.
 171. Lee KE, Davis MB, Winkelstein BA. Capsular ligament involvement in the development of mechanical hyperalgesia after facet joint loading: Behavioral and inflammatory outcomes in a rodent model of pain. *J Neurotrauma* 2008; 25:1383-1393.
 172. Tachihara H, Kikuchi S, Konno S, Seki

- guchi M. Does facet joint inflammation induce radiculopathy?: An investigation using a rat model of lumbar facet joint inflammation. *Spine (Phila Pa 1976)* 2007; 32:406-412.
173. Vasquez E, Bär K, Ebersberger A, Klein B, Vanegas H, Schaible HG. Spinal prostaglandins are involved in the development but not the maintenance of inflammation-induced spinal hyperexcitability. *J Neurosci* 2001; 21:9001-9008.
174. Graziani F, Ivanovski S, Cei S, Ducci F, Tonetti M, Gabriele M. The in vitro effect of different PRP concentrations on osteoblasts and fibroblasts. *Clin Oral Implants Res* 2006; 17:212-219.
175. Yoshida R, Cheng M, Murray MM. Increasing platelet concentration in platelet-rich plasma inhibits anterior cruciate ligament cell function in three-dimensional culture. *J Orthop Res* 2014; 32:291-295.
176. Wasterlain AS, Braun HJ, Harris AH, Kim HJ, Dragoo JL. The systemic effects of platelet-rich plasma injection. *Am J Sports Med* 2013; 41:186-193.
177. Karli DC. PRP, BMC, and adipose mesenchymal stem cells: Hemo-analysis and quality control: What does it all mean? In: Manchikanti L, Navani A, Atluri S (eds). *Essentials of Regenerative Medicine in Interventional Pain Management*. ASIPP Publishing, Paducah, KY 2019, IN PRESS.
178. Wu PI, Diaz R, Borg-Stein J. Platelet-rich plasma. *Phys Med Rehabil Clin N Am* 2016; 27:825-853.
179. Lansdown DA, Fortier LA. Platelet-rich plasma: Formulations, preparations, constituents, and their effects. *Oper Tech Sports Med* 2017; 25:7-12.
180. Beitzel K, Allen D, Apostolakis J, Russell RP, McCarthy MB, Gallo GJ, Cote MP, Mazzocca AD. US Definitions, current use, and FDA stance on use of platelet-rich plasma in sports medicine. *J Knee Surg* 2015; 28:29-34.
181. Malanga GA, Goldin M. PRP: Review of the current evidence for musculoskeletal conditions. *Curr Phys Med Rehabil Rep* 2014; 2:1-5.
182. Davis VL, Abukabda AB, Radio NM, Witt-Enderby PA, Clafshenkel WP, Cairone JV, Rutkowski JL. Platelet-rich preparations to improve healing. Part I: Workable options for every size practice. *J Oral Implantol* 2014; 40:500-510.
183. Boswell SG, Cole BJ, Sundman EA, Karas V, Fortier LA. Platelet-rich plasma: A milieu of bioactive factors. *Arthroscopy* 2012; 28:429-439.
184. Blair P, Flaumenhaft R. Platelet alpha-granules: Basic biology and clinical correlates. *Blood Rev* 2009; 23:177-189.
185. Sheth U, Simunovic N, Klein G, Fu F, Einhorn TA, Schemitsch E, Ayeni OR, Bhandari M. Efficacy of autologous platelet-rich plasma use for orthopaedic indications: A meta-analysis. *J Bone Joint Surg* 2012; 94:298-307.
186. Dohan Ehrenfest DM, Rasmusson L, Albrektsson T. Classification of platelet concentrates: From pure platelet-rich plasma (P-PRP) to leucocyte- and platelet-rich fibrin (L-PRF). *Trends Biotechnol* 2009; 27:158-167.
187. DeLong JM, Russell RP, Mazzocca AD. Platelet-rich plasma: ThePAW classification system. *Arthroscopy* 2012; 28:998-1009.
188. LaPrade RF, Dragoo JL, Koh JL, Murray IR, Geeslin AG, Chu CR. AAOS Research Symposium Updates and Consensus: Biologic Treatment of Orthopaedic Injuries. *J Am Acad Orthop Surg* 2016; 24:e62-e78.
189. Caplan AI. Adult mesenchymal stem cells for tissue engineering versus regenerative medicine. *J Cell Physiol* 2007; 213:341-347.
190. Caplan AI. Cell delivery and tissue regeneration. *J Control Release* 1989; 11:157-165.
191. Caplan AI. Mesenchymal stem cells. *J Orthop Res* 1991; 9:641-650.
192. Caplan AI. Review: Mesenchymal stem cells: Cell-based reconstructive therapy in orthopedics. *Tissue Eng* 2005; 11:1198-1211.
193. Caplan AI. Mesenchymal stem cells: Time to change the name! *Stem Cells Transl Med* 2017; 6:1445-1451.
194. Sell S. *Stem Cells Handbook*. Springer Science & Business Media, New York, NY, 2013.
195. Kobolak J, Dinnyes A, Memic A, Khademhosseini A, Mobasheri A.. Mesenchymal stem cells: Identification, phenotypic characterization, biological properties and potential for regenerative medicine through biomaterial micro-engineering of their niche. *Methods* 2016; 99:62-68.
196. Rigotti G, Marchi A, Sbarbati A. Adipose-derived mesenchymal stem cells: Past, present, and future. *Aesthetic Plast Surg* 2009; 33:271-273.
197. Watson L, Elliman SJ, Coleman CM. From isolation to implantation: A concise review of mesenchymal stem cell therapy in bone fracture repair. *Stem Cell Res Ther* 2014; 5:51.
198. Murray IR, West CC, Hardy WR, James AW, Park TS, Nguyen A, Tawonsawatruk T, Lazzari L, Soo C, Péault B. Natural history of mesenchymal stem cells, from vessel walls to culture vessels. *Cell Mol Life Sci* 2014; 71:1353-1374.
199. Katz AJ, Tholpady A, Tholpady SS, Shang H, Ogle RC. Cell surface and transcriptional characterization of human adipose-derived adherent stromal (hADAS) cells. *Stem Cells* 2005; 23:412-423.
200. Mitchell JB, McIntosh K, Zvonick S, Garrett S, Floyd ZE, Kloster A, Di Halvorsen Y, Storms RW, Goh B, Kilroy G, Wu X, Gimble JM. Immunophenotype of human adipose derived cells: Temporal changes in stromal-associated and stem cell associated markers. *Stem Cells* 2006; 24:376-385.
201. Kilroy GE, Foster SJ, Wu X, Ruiz J, Sherwood S, Heifetz A, Ludlow JW, Stricker DM, Potiny S, Green P, Halvorsen YD, Cheatham B, Storms RW, Gimble JM. Cytokine profile of human adipose derived stem cells: Expression of angiogenic, hematopoietic, and proinflammatory factors. *J Cell Physiol* 2007; 212:702-709.
202. Day TF, Guo X, Garrett-Beal L, Yang Y. Wnt/beta-catenin signaling in mesenchymal progenitors controls osteoblast and chondrocyte differentiation during vertebrate skeletogenesis. *Dev Cell* 2005; 8:739-750.
203. Cawthorn WP, Bree AJ, Yao Y, Du B, Hemati N, Martinez-Santibañez G, MacDougall OA. Wnt6, Wnt10a and Wnt10b inhibit adipogenesis and stimulate osteoblastogenesis through a b-catenin-independent mechanism. *Bone* 2012; 50:477-489.
204. Li Y, Foster W, Deasy BM, Chan Y, Prisk V, Tang Y, Cummins J, Huard J. Transforming growth factor-beta1 induces the differentiation of myogenic cells into fibrotic cells in injured skeletal muscle: A key event in muscle fibrogenesis. *Am J Pathol* 2004; 164:1007-1019.
205. Serra R, Johnson M, Filvaroff EH, LaBorde J, Sheehan DM, Derynck R, Moses HL. Expression of a truncated, kinase defective TGF-beta type II receptor in mouse skeletal tissue promotes terminal chondrocyte differentiation and osteoarthritis. *J Cell Biol* 1997; 139:541-552.
206. Murphy MB, Moncivais K, Caplan AI. Mesenchymal stem cells: Environmentally responsive therapeutics for regenerative medicine. *Exp Mol Med* 2013; 45:e54.

207. Center for Biologic Evaluation and Research. List of Licensed Biological Products with (1) Reference Product Exclusivity and (2) Biosimilarity or Interchangeability Evaluations to Date. www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/UCM412398.pdf
208. Spiel D. The role of exosomes in regenerative medicine. In: Manchikanti L, Navani A, Atluri S (eds). *Essentials of Regenerative Medicine in Interventional Pain Management*. ASIPP Publishing, Paducah, KY 2019, IN PRESS.
209. Kirkaldy-Willis WH, Wedge JH, Yong-Hing K, Tchang S, de Korompay V, Shannon R. Lumbar spinal nerve lateral entrapment. *Clin Orthop Relat Res* 1982; 169:171-178.
210. Dowdell J, Erwin M, Choma T, Vaccaro A, Iatridis J, Cho SK. Intervertebral disk degeneration and repair. *Neurosurgery* 2017; 80:S46-S54.
211. Mascarinas A, Harrison J, Boachie-Adjei K, Lutz G. Regenerative treatments for spinal conditions. *Phys Med Rehabil Clin N Am* 2016; 27:1003-1017.
212. Kim KD. Stem cells and discogenic low back pain. *Spine (Phila Pa 1976)* 2016; 41:S11-S12.
213. Zhang J, Lu VM, van Wijnen AJ, Kerzoudis P, Yeap I, Cong L, Larson N, Qu W, Nassr A, Bydon M. Molecular factors in intervertebral disc degeneration. *J Am Acad Reg Med* 2017; 1:7203.
214. Bertolo A, Thiede T, Aebli N, Baur M, Ferguson SJ, Stoyanov JV. Human mesenchymal stem cell co-culture modulates the immunological properties of human intervertebral disc tissue fragments in vitro. *Eur Spine J* 2011; 20:592-603.
215. Priyadarshani P, Li Y, Yao L. Advances in biological therapy for nucleus pulposus regeneration. *Osteoarthritis Cartilage* 2016; 24:206-212.
216. Willems N, Tellegen AR, Bergknut N, Creemers LB, Wolfswinkel J, Freudigmann C, Benz K, Grinwis GC, Tryfonidou MA, Meij BP. Inflammatory profiles in canine intervertebral disc degeneration. *BMC Vet Res* 2016; 12:10.
217. Elabd C, Centeno CJ, Schultz JR, Lutz G, Ichim T, Silva FJ. Intra-discal injection of autologous, hypoxic cultured bone marrow-derived mesenchymal stem cells in five patients with chronic lower back pain: a long-term safety and feasibility study. *J Transl Med* 2016; 14:253.
218. Hunt CL, Her YF, Law LA, Bydon M, Nassr A, Smith J, Mauck WD, Eldrige JS, Malanga GA, Qu W. Five generations of cell preparation: A translational framework for categorizing regenerative stem cell therapies. *J Am Acad Regen Med* 2017; 1:7239.
219. Depalma M. Biologic treatments for discogenic low back pain. *SpineLine* 2012; 13:19-23.
220. Wei A, Shen B, Williams L, Diwan A. Mesenchymal stem cells: Potential application in intervertebral disc regeneration. *Transl Pediatr* 2014; 3:71-90.
221. Comella K, Silbert R, Parlo M. Effects of the intradiscal implantation of stromal vascular fraction plus platelet rich plasma in patients with degenerative disc disease. *J Transl Med* 2017; 15:12.
222. Buchanan RM, Blashki D, Murphy MB. Stem cell therapy for regenerative medicine. *Chem Eng Prog* 2014; 110:55-58.
223. Bogduk N. *Clinical and Radiological Anatomy of the Lumbar Spine*. 5th ed. Elsevier Churchill Livingstone, 2012.
224. Iatridis JC, Nicoll SB, Michalek AJ, Walter BA, Gupta MS. Role of biomechanics in intervertebral disc degeneration and regenerative therapies: what needs repairing in the disc and what are promising biomaterials for its repair? *Spine J* 2013; 13:243-262.
225. Bogduk N, Aprill C, Derby R. Lumbar discogenic pain: State-of-the-art review. *Pain Med* 2013; 14:813-836.
226. Hegewald AA, Endres M, Abbushi A, Cabraja M, Woiciechowsky C, Schmiender K, Kaps C, Thomé C. Adequacy of herniated disc tissue as a cell source for nucleus pulposus regeneration. *J Neurosurg Spine* 2011; 14:273-280.
227. Risbud MV, Guttapalli A, Tsai TT, Lee JY, Danielson KG, Vaccaro AR, Albert TJ, Gazit Z, Gazit D, Shapiro IM. Evidence for skeletal progenitor cells in the degenerate intervertebral disc. *Spine (Phila Pa 1976)* 2007; 32:2537-2544.
228. Brisby H, Papadimitriou N, Brantsing C, Bergh P, Lindahl A, Barreto Henriksson H. The presence of local mesenchymal progenitor cells in human degenerated intervertebral discs and possibilities to influence these in vitro: A descriptive study in humans. *Stem Cells Dev* 2013; 22:804-814.
229. Kim KW, Ha KY, Lee JS, Nam SW, Woo YK, Lim TH, An HS. Notochordal cells stimulate migration of cartilage end plate chondrocytes of the intervertebral disc in in vitro cell migration assays. *Spine J* 2009; 9:323-329.
230. Helm S 2nd, Simopoulos TT, Stojanovic MP, Abdi S, El Terany MA. Effectiveness of thermal annular procedures in treating discogenic low back pain. *Pain Physician* 2017; 20:447-470.
231. Lurie JD, Tosteson TD, Tosteson AN, Zhao W, Morgan TS, Abdu WA, Herkowitz H, Weinstein JN. Surgical versus nonoperative treatment for lumbar disc herniation: eight-year results for the spine patient outcomes research trial. *Spine (Phila Pa 1976)* 2014; 39:3-16.
232. Lurie JD, Tosteson TD, Tosteson A, Abdu WA, Zhao W, Morgan TS, Weinstein JN. Long-term outcomes of lumbar spinal stenosis: eight-year results of the Spine Patient Outcomes Research Trial (SPORT). *Spine (Phila Pa 1976)* 2015; 40:63-76.
233. Peng B, Wu W, Hou S, Li P, Zhang C, Yang Y. The pathogenesis of discogenic low back pain. *J Bone Joint Surg Br* 2005; 87:62-67.
234. Hiyama A, Mochida J, Iwashina T, Omi H, Watanabe T, Serigano K, Tamura F, Sakai D. Transplantation of mesenchymal stem cells in a canine disc degeneration model. *J Orthop Res* 2008; 26:589-600.
235. Zhang YG, Guo X, Xu P, Kang LL, Li J. Bone mesenchymal stem cells transplanted into rabbit intervertebral discs can increase proteoglycans. *Clin Orthop Relat Res* 2005; 430:219-226.
236. Yang H, Wu J, Liu J, Ebraheim M, Castillo S, Liu X, Tang T, Ebraheim NA. Transplanted mesenchymal stem cells with pure fibrinous gelatin-transforming growth factor-beta1 decrease rabbit intervertebral disc degeneration. *Spine J* 2010; 10:802-810.
237. Ghosh P, Moore R, Vernon-Roberts B, Goldschlager T, Pascoe D, Zannettino A, Gronthos S, Itescu S. Immunoselected STRO-3+ mesenchymal precursor cells and restoration of the extracellular matrix of degenerate intervertebral discs. *J Neurosurg Spine* 2012; 16:479-488.
238. Shim EK, Lee JS, Kim DE, Kim SK, Jung BJ, Choi EY, Kim CS. Autogenous mesenchymal stem cells from the vertebral body enhance intervertebral disc regeneration via paracrine interaction: An in vitro pilot study. *Cell Transplant* 2016; 25:1819-1832.
239. Teixeira GQ, Pereira CL, Ferreira JR, Maia AF, Gomez-Lazaro M, Barbosa MA, Neidlinger-Wilke C, Goncalves RM. Immunomodulation of human mesenchymal stem/stromal cells in intervertebral disc degeneration: Insights

- from a proinflammatory/degenerative ex vivo model. *Spine (Phila Pa 1976)* 2017; 43:E673-E682.
240. Le Maitre CL, Baird P, Freemont AJ, Hoyland JA. An in vitro study investigating the survival and phenotype of mesenchymal stem cells following injection into nucleus pulposus tissue. *Arthritis Res Ther* 2009; 11:R20.
 241. Pereira CL, Teixeira GQ, Ribeiro-Machado C, Caldeira J, Costa M, Figueiredo F, Fernandes R, Aguiar P, Grad S, Barbosa MA, Gonçalves RM. Mesenchymal stem/stromal cells seeded on cartilaginous endplates promote intervertebral disc regeneration through extracellular matrix remodeling. *Sci Rep* 2016; 6:33836.
 242. Jezierska-Wozniak K, Barczewska M, Habich A, Wojtacha P, Badowska W, Maksymowicz W, Wojtkiewicz J. The feasibility of the CD271+ and CD271- mesenchymal stromal cell enrichment toward nucleus pulposus-like cells. *Folia Histochem Cytobiol* 2017; 55:114-123.
 243. Jeong JH, Jin ES, Min JK, Jeon SR, Park CS, Kim HS, Choi KH. Human mesenchymal stem cells implantation into the degenerated coccygeal disc of the rat. *Cytotechnology* 2009; 59:55-64.
 244. Yang F, Leung VY, Luk KD, Chan D, Cheung KM. Mesenchymal stem cells arrest intervertebral disc degeneration through chondrocytic differentiation and stimulation of endogenous cells. *Mol Ther* 2009; 17:1959-1966.
 245. Fairbank JC, Pynsent PB. The Oswestry Disability Index. *Spine (Phila Pa 1976)* 2000; 25:2940-2952
 246. Feng G, Zhao X, Liu H, Zhang H, Chen X, Shi R, Liu X, Zhao X, Zhang W, Wang B. Transplantation of mesenchymal stem cells and nucleus pulposus cells in a degenerative disc model in rabbits: a comparison of 2 cell types as potential candidates for disc regeneration. *J Neurosurg Spine* 2011; 14:322-329.
 247. Mochida J, Sakai D, Nakamura Y, Watanabe T, Yamamoto Y, Kato S. Intervertebral disc repair with activated nucleus pulposus cell transplantation: a three-year, prospective clinical study of its safety. *Eur Cell Mater* 2015; 29:202-212.
 248. Wang YH, Yang B, Li WL, Li JM. Effect of the mixture of bone marrow mesenchymal stromal cells and annulus fibrosus cells in repairing the degenerative discs of rabbits. *Genet Mol Res* 2015; 14:2365-2373.
 249. Sakai D, Mochida J, Iwashina T, Hiyama A, Omi H, Imai M, Nakai T, Ando K, Hotta T. Regenerative effects of transplanting mesenchymal stem cells embedded in atelocollagen to the degenerated intervertebral disc. *Biomaterials* 2006; 27:335-345.
 250. Wang H, Zhou Y, Chu TW, Li CQ, Wang J, Zhang ZF, Huang B. Distinguishing characteristics of stem cells derived from different anatomical regions of human degenerated intervertebral discs. *Eur Spine J* 2016; 25:2691-2704.
 251. Vadalà G, Russo F, Ambrosio L, Loppini M, Denaro V. Stem cells sources for intervertebral disc regeneration. *World J Stem Cells* 2016; 8:185-201.
 252. Miguélez-Rivera L, Pérez-Castrillo S, González-Fernández ML, Prieto-Fernández JG, López-González ME, García-Cosamalón J, Villar-Suárez V. Immunomodulation of mesenchymal stem cells in discogenic pain. *Spine J* 2018; 18:330-342.
 253. Pettine K, Suzuki R, Sand T, Murphy M. Treatment of discogenic back pain with autologous bone marrow concentrate injection with minimum two year follow-up. *Int Orthop* 2016; 40:135-140.
 254. Foster TE, Puskas BL, Mandelbaum BR, Gerhardt MB, Rodeo SA. Platelet-rich plasma: from basic science to clinical applications. *Am J Sports Med* 2009; 37:2259-2272.
 255. Chen WH, Lo WC, Lee JJ, Su CH, Lin CT, Liu HY, Lin TW, Lin WC, Huang TY, Deng WP. Tissue-engineered intervertebral disc and chondrogenesis using human nucleus pulposus regulated through TGF-beta1 in platelet-rich plasma. *J Cell Physiol* 2006; 209:744-754.
 256. Gullung GB, Woodall JW, Tucci MA, James J, Black DA, McGuire RA. Platelet-rich plasma effects on degenerative disc disease: analysis of histology and imaging in an animal model. *Evid Based Spine Care J* 2011; 2:13-18.
 257. Obata S, Akeda K, Imanishi T, Masuda K, Bae W, Morimoto R, Asanuma Y, Kasai Y, Uchida A, Sudo A. Effect of autologous platelet-rich plasma-releasate on intervertebral disc degeneration in the rabbit anular puncture model: a preclinical study. *Arthritis Res Ther* 2012; 14:R241.
 258. Kim HJ, Yeom JS, Koh YG, Yeo JE, Kang KT, Kang YM, Chang BS, Lee CK. Anti-inflammatory effect of platelet-rich plasma on nucleus pulposus cells with response of TNF-a and IL-1. *J Orthop Res* 2014; 32:551-556.
 259. Sawamura K, Ikeda T, Nagae M, Okamoto S, Mikami Y, Hase H, Ikoma K, Yamada T, Sakamoto H, Matsuda K, Tabata Y, Kawata M, Kubo T. Characterization of in vivo effects of platelet-rich plasma and biodegradable gelatin hydrogel microspheres on degenerated intervertebral discs. *Tissue Eng Part A* 2009; 15:3719-3727.
 260. Kristjánsson B, Limthongkul W, Yingsakmongkol W, Thantiworasit P, Jirathanathornukul N, Honsawek S. Isolation and characterization of human mesenchymal stem cells from facet joints and interspinous ligaments. *Spine (Phila Pa 1976)* 2016; 41:E1-E7.
 261. Richardson SM, Kalamegam G, Pushparaj PN, Matta C, Memic A, Khademhosseini A, Mobasheri R, Poletti FL, Hoyland JA, Mobasheri A. Mesenchymal stem cells in regenerative medicine: Focus on articular cartilage and intervertebral disc regeneration. *Methods* 2016; 99:69-80.
 262. Eden J, Levit L, Berg A, Morton S (eds); Committee on Standards for Systematic Reviews of Comparative Effectiveness Research; Institute of Medicine. Finding What Works in Health Care. Standards for Systematic Reviews. The National Academies Press, Washington, DC, 2011.
www.nap.edu/catalog/13059/finding-what-works-in-health-carestandards-for-systematic-reviews
 263. Agency for Healthcare Research and Quality. Methods guide for effectiveness and comparative effectiveness reviews. AHRQ publication no. 10(13)-EHC063-EF. Rockville MD; 2014.
www.effectivehealthcare.ahrq.gov/ehc/products/60/318/CER-Methods-Guide-140109.pdf
 264. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. *PLoS Med* 2009; 6:e1000097.
 265. Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, Moher D, Tugwell P, Welch V, Kristjansson E, Henry DA. AMSTAR 2: A critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. *BMJ* 2017; 358:j4008.
 266. Furlan AD, Malmivaara A, Chou R, Maher CG, Deyo RA, Schoene M, Bronfort G, van Tulder MW; Editorial Board of the Cochrane Back, Neck Group. 2015 Updated Method Guideline for Systematic Reviews in the Cochrane Back and Neck Group. *Spine (Phila Pa 1976)* 2015; 40:1660-1673.

267. Manchikanti L, Hirsch JA, Cohen SP, Heavner JE, Falco FJE, Diwan S, Boswell MV, Candido KD, Onyewu CO, Zhu J, Sehgal N, Kaye AD, Benyamin RM, Helm S 2nd, Singh V, Datta S, Abdi S, Christo PJ, Hameed H, Hameed M, Vallejo R, Pampati V, Racz GB, Raj PP. Assessment of methodologic quality of randomized trials of interventional techniques: Development of an interventional pain management specific instrument. *Pain Physician* 2014; 17:E263-E290.
268. Manchikanti L, Hirsch JA, Heavner JE, Cohen SP, Benyamin RM, Sehgal N, Falco FJE, Vallejo R, Onyewu O, Zhu J, Kaye AD, Boswell MV, Helm II S, Candido KD, Diwan S, Simopoulos TT, Singh V, Pampati V, Racz GB, Raj PP. Development of an interventional pain management specific instrument for methodologic quality assessment of nonrandomized studies of interventional techniques. *Pain Physician* 2014; 17:E291-E317.
269. Huedo-Medina TB, Sánchez-Meca J, Marín-Martínez F, Botella J. Assessing heterogeneity in meta-analysis: Q statistic or I² index? *Psychol Methods* 2006; 11:193-206.
270. Pang X, Yang H, Peng B. Human umbilical cord mesenchymal stem cell transplantation for the treatment of chronic discogenic low back pain. *Pain Physician* 2014; 17:E525-E530.
271. Orozco L, Soler R, Morera C, Alberca M, Sánchez A, García-Sancho J. Intervertebral disc repair by autologous mesenchymal bone marrow cells: A pilot study. *Transplantation* 2011; 92:822-828.
272. Coric D, Pettine K, Sumich A, Boltes MO. Prospective study of disc repair with allogeneic chondrocytes presented at the 2012 Joint Spine Section Meeting. *J Neurosurg Spine* 2013; 18:85-95.
273. Meisel HJ, Ganey T, Hutton WC, Libera J, Minkus Y, Alasevic O. Clinical experience in cell based therapeutics: Intervention and outcome. *Eur Spine J* 2006; 15:S397-S405.
274. Navani A, Ambach MA, Navani R, Wei J. Biologics and lumbar discogenic pain: 18 month follow-up for safety and efficacy. *IPM Reports* 2018; *IPM Reports* 2018; 2:111-118.
275. Levi D, Horn S, Tyszko S, Levin J, Hecht-Leavitt C, Walko E. Intradiscal platelet-rich plasma injection for chronic discogenic low back pain: Preliminary results from a prospective trial. *Pain Med* 2016; 17:1010-1022.
276. Monfett M, Harrison J, Boachie-Adjei K, Lutz G. Intradiscal platelet-rich plasma (PRP) injections for discogenic low back pain: an update. *Int Orthop* 2016; 40:1321-1328.
277. Tuakli-Wosornu YA, Terry A, Boachie-Adjei K, Harrison JR, Gribbin CK, LaSalle EE, Nguyen JT, Solomon JL, Lutz GE. Lumbar intradiscal platelet-rich plasma (PRP) injections: A prospective, double-blind, randomized controlled study. *PM R* 2016; 8:1-10.
278. Kirchner F, Anitua E. Intradiscal and intra-articular facet infiltrations with plasma rich in growth factors reduce pain in patients with chronic low back pain. *J Craniovertebr Junction Spine* 2016; 7:250-256.
279. Akeda K, Ohishi K, Masuda K, Bae WC, Takegami N, Yamada J, Nakamura T, Sakakibara T, Kasai Y, Sudo A. Intradiscal injection of autologous platelet-rich plasma releasate to treat discogenic low back pain: A preliminary clinical trial. *Asian Spine J* 2017; 11:380-389.
280. Pettine KA, Suzuki RK, Sand TT, Murphy MB. Autologous bone marrow concentrate intradiscal injection for the treatment of degenerative disc disease with three-year follow-up. *Int Orthop* 2017; 41:2097-2103.
281. Pettine KA, Murphy MB, Suzuki RK, Sand TT. Percutaneous injection of autologous bone marrow concentrate cells significantly reduces lumbar discogenic pain through 12 months. *Stem Cells* 2015; 33:146-156.
282. Yoshikawa T, Ueda Y, Miyazaki K, Koizumi M, Takakura Y. Disc regeneration therapy using marrow mesenchymal cell transplantation: A report of two case studies. *Spine (Phila Pa 1976)* 2010; 35:E475-E480.
283. Noriega DC, Adura F, Hernández-Ramajo R, Martín-Ferrero MA, Sánchez-Lite I, Toribio B, Alberca M, García V, Moraleda JM, Sánchez A, García-Sancho J. Intervertebral disc repair by allogeneic mesenchymal bone marrow cells: A randomized controlled trial. *Transplantation* 2017; 101:1945-1951.
284. Kumar H, Ha DH, Lee EJ, Park JH, Shim JH, Ahn TK, Kim KT, Ropper AE, Sohn S, Kim CH, Thakor DK, Lee SH, Han IB. Safety and tolerability of intradiscal implantation of combined autologous adipose-derived mesenchymal stem cells and hyaluronic acid in patients with chronic discogenic low back pain: 1-year follow-up of a phase I study. *Stem Cell Res Ther* 2017; 8:262.
285. Wu J, Du Z, Lv Y, Zhang J, Xiong W, Wang R, Liu R, Zhang G, Liu Q. A new technique for the treatment of lumbar facet joint syndrome using intra-articular injection with autologous platelet rich plasma. *Pain Physician* 2016; 19:617-625.
286. Wu J, Zhou J, Liu C, Zhang J, Xiong W, Lv Y, Liu R, Wang R, Du Z, Zhang G, Liu Q. A prospective study comparing platelet-rich plasma and local anesthetic (LA)/corticosteroid in intra-articular injection for the treatment of lumbar facet joint syndrome. *Pain Pract* 2017; 17:914-924.
287. Singla V, Batra YK, Bharti N, Goni VG, Marwaha N. Steroid vs. platelet-rich plasma in ultrasound-guided sacroiliac joint injection for chronic low back pain. *Pain Pract* 2017; 17:782-791.
288. Navani A, Gupta D. Role of intra-articular platelet-rich plasma in sacroiliac joint pain. *Reg Anesth Pain Med* 2015; 19:54-59.
289. Ko GD, Mindra S, Lawson GE, Whitmore S, Arseneau L. Case series of ultrasound-guided platelet-rich plasma injections for sacroiliac joint dysfunction. *J Back Musculoskelet Rehabil* 2017; 30:363-370.
290. Bhatia R, Chopra G. Efficacy of platelet rich plasma via lumbar epidural route in chronic prolapsed intervertebral disc patients-A pilot study. *J Clin Diagn Res* 2016; 10:UC05-UC07.
291. Centeno C, Markle J, Dodson E, Stemper I, Hyzy M, Williams C, Freeman M. The use of lumbar epidural injection of platelet lysate for treatment of radicular pain. *J Exp Orthop* 2017; 4:38.
292. Kumar R, Goni VG, Batra YK. Autologous conditioned serum as a novel alternative option in the treatment of unilateral lumbar radiculopathy: A prospective study. *Asian Spine J* 2015; 9:916-922.
293. Becker C, Heidersdorf S, Drewlo S, de Rodriguez SZ, Krämer J, Willburger RE. Efficacy of epidural perineural injections with autologous conditioned serum for lumbar radicular compression: an investigator-initiated, prospective, double-blind, reference-controlled study. *Spine (Phila Pa 1976)* 2007; 32:1803-1808.
294. World Health Organization. Transplantation: Transplantation of human cells, tissues, and organs. www.who.int/transplantation/en/
295. World Health Organization. Transplantation: Human Cell and tissue transplantation. www.who.int/transplantation/cell_tissue/en/
296. CMC and GMP Guidelines. US Drug Administration, FDA. Accessed online 12 Dec 2016:

- <http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/General/ucm217665.htm>
297. Marks P, Gottlieb S. Balancing safety and innovation for cell-based regenerative medicine. *N Engl J Med* 2018; 378:954-959.
 298. Trounson A. Potential pitfall of pluripotent stem cells. *N Engl J Med* 2017; 377:490-491.
 299. Taylor-Weiner H, Graff Zivin J. Medicine's Wild West--unlicensed stem-cell clinics in the United States. *N Engl J Med* 2015; 373:985-987.
 300. Halme DG, Kessler DA. FDA regulation of stem-cell-based therapies. *N Engl J Med* 2006; 355:1730-1735.
 301. Okie S. Stem-cell politics. *N Engl J Med* 2006; 355:1633-1637.
 302. Daley GQ. Polar extremes in the clinical use of stem cells. *N Engl J Med* 2017; 376:1075-1077.
 303. Regulatory Considerations for Human Cell, Tissues, and Cellular and Tissue-Based Products: Minimal Manipulation and Homologous Use. Guidance for Industry and Food and Drug Administration Staff, November 2017. www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/UCM585403.pdf
 304. U.S. Department of Health and Human Services. Same Surgical Procedure Exception under 21 CFR 1271.15(b): Questions and Answers Regarding the Scope of the Exception. Guidance for Industry. November 2017. www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Tissue/UCM419926.pdf
 305. U.S. Food and Drug Administration. Regenerative medicine advanced therapy designation. March 13, 2017. www.fda.gov/BiologicsBloodVaccines/CellularGeneTherapyProducts/ucm537670.htm
 306. Shook JR, Giordano J. Ethical and policy issues in practices of regenerative medicine for the treatment of chronic pain. In: Manchikanti L, Navani A, Atluri S (eds). *Essentials of Regenerative Medicine in Interventional Pain Management*. ASIPP Publishing, Paducah, KY 2019, IN PRESS.
 307. Rosenthal RM, Murphy M. Regulatory aspects of regenerative therapy and stem cell therapy: Current perspectives. In: Manchikanti L, Navani A, Atluri S (eds). *Essentials of Regenerative Medicine in Interventional Pain Management*. ASIPP Publishing, Paducah, KY 2019, IN PRESS.
 308. Draft Guidance for Industry: Same Surgical Procedure Exception Under 21 CFR 1271.15(b): Questions and Answers Regarding the Scope of the Exception. www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Tissue/ucm419911.htm
 309. Aicher RH. Is the FDA regulating the practice of medicine? *Aesthet Surg J* 2013; 33:452-455.
 310. Berman M, Lander E. Regulatory issues with human cells: An alternate view. In: Manchikanti L, Navani A, Atluri S (eds). *Essentials of Regenerative Medicine in Interventional Pain Management*. ASIPP Publishing, Paducah, KY 2019, IN PRESS.
 311. Malarkey MA. Warning letter to Dr. Steven Victor, Chief Executive Officer, IntelliCell Biosciences Inc. Rockville, MD: Public Health Service, Food and Drug Administration; March 13, 2012. www.fda.gov/ICECI/EnforcementActions/WarningLetters/2012/ucm297245.htm.
 312. Mescher AL. Adipose Tissue. In: *Junqueira's Basic Histology: Text & Atlas*. 13th ed. McGraw-Hill, New York, 2013, pp 124-129.
 313. Malarkey MA. Warning letter to Thomas E. Young, MD, Owner and Medical Director, Young Medical Spa. Rockville, MD: Public Health Service, Food and Drug Administration; April 20, 2012. www.fda.gov/ICECI/EnforcementActions/WarningLetters/2012/ucm301620.htm
 314. Warning Letter to John S. Arnone, American CryoStem Corporation from Elizabeth Waltrip, Acting Program Division Director, Office of Biological Products Operations – Division 1, U.S. Food and Drug Administration. www.fda.gov/ICECI/EnforcementActions/WarningLetters/ucm591225.htm
 315. Associated Press. North Dakota stem cell clinic investigated after complaints. *The Seattle Times*, November 16, 2017. www.seattletimes.com/nation-world/bismarck-stem-cell-clinic-investigated-after-complaints/
 316. Kuriyan AE, Albini TA, Townsend JH, Rodriguez M, Pandya HK, Leonard RE 2nd, Parrott MB, Rosenfeld PJ, Flynn HW Jr, Goldberg JL. Vision loss after intravitreal injection of autologous "stem cells" for AMD. *N Engl J Med* 2017; 376:1047-1053.
 317. Malarkey MA. Warning letter to David G. Eller, Chief Executive Officer and President, Celltex Therapeutics Corporation. Rockville, MD: Public Health Service, Food and Drug Administration; September 24, 2012. www.fda.gov/ICECI/EnforcementActions/WarningLetters/2012/ucm323853.htm
 318. Brown SA, Levi B, Lequeux C, Wong VW, Mojallal A, Longaker MT. Basic science review on adipose tissue for clinicians. *Plast Reconstr Surg* 2010; 126:1936-1946.
 319. Department of Health and Human Services, Food and Drug Administration. 21 CFR Parts 207, 807, and 1271. Establishment Registration and Listing for Manufacturers of Human Cellular and Tissue-Based Products. Proposed Rule, May 14, 1998.
 320. Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps) From Adipose Tissue: Regulatory Considerations; Draft Guidance for Industry. Rockville, MD: Food and Drug Administration; December 2014. www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Tissue/ucm427795.htm
 321. Department of Health and Human Services, Food and Drug Administration. 21 CFR Parts 207, 807, and 1271. Human Cells, Tissues, and Cellular and Tissue-Based Products; Establishment Registration and Listing. Final Rule, January 19, 2001.
 322. Sherman RE, Li J, Shapley S, Robb M, Woodcock J. Expediting drug development — the FDA's new "breakthrough therapy" designation. *N Engl J Med* 2013; 369:1877-1880.
 323. H.R. 34 – 21st Century Cures Act. P.L. 114-255, December 13, 2016.
 324. Jarow JP, LaVange L, Woodcock J. Multidimensional evidence generation and FDA regulatory decision making: Defining and using "real-world" data. *JAMA* 2017; 318:703-704.
 325. Sherman RE, Anderson SA, Dal Pan GJ, Gray GW, Gross T, Hunter NL, LaVange L, Marinac-Dabic D, Marks PW, Robb MA, Shuren J, Temple R, Woodcock J, Yue LQ, Califf RM. Real-world evidence – What is it and what can it tell us? *N Engl J Med* 2016; 375:2293-2297.
 326. Letter to Gregory B. Snyder, MD, Federation of State Medical Boards from Senator Lamar Alexander RE: Stem cell

- therapy, April 21, 2017.
327. Berger I, Ahmad A, Bansal A, Kapoor T, Sipp D, Rasko JEJ. Global distribution of businesses marketing stem cell based interventions. *Cell Stem Cell* 2016; 19:158-162.
 328. Sipp D, Caulfield T, Kaye J, Barfoot J, Blackburn C, Chan S, De Luca M, Kent A, McCabe C, Munsie M, Sleeboom-Faulkner M, Sugarman J, van Zimmeren E, Zarzeczny A, Rasko JEJ. Marketing of unproven stem cell based interventions: A call to action. *Sci Transl Med* 2017; 9(397).
 329. FDA's warning letters: www.fda.gov/ICECI/EnforcementActions/WarningLetters/default.htm
 330. Federation of State Medical Boards. Model Policy for the Appropriate Use of Telemedicine Technologies in the Practice of Medicine, 2014.
 331. White BD, Gelinas LC. Balancing the surgeon's responsibility to individuals and society. In: Stain SC et al (eds). *The SAGES Manual Ethics of Surgical Innovation*. Springer International Publishing, Switzerland, 2016, pp 191-211.
 332. Barry MJ, Edgman-Levitan S. Shared decision making--pinnacle of patient-centered care. *N Engl J Med* 2012; 366:780-781.
 333. National Research Council. Crossing the quality chasm: a new health system for the 21st century. Washington, DC: National Academies Press, 2001.
 334. Stacey D, Légaré F, Lewis K, Barry MJ, Bennett CL, Eden KB, Holmes-Rovner M, Llewellyn-Thomas H, Lyddiatt A, Thomson R, Trevena L. Decision aids for people facing health treatment or screening decisions. *Cochrane Database Syst Rev* 2011; 4:CD001431.
 335. Narouze S, Benzon HT, Provenzano D, Buvanendran A, De Andres J, Deer T, Rauck R, Huntoon MA. Interventional spine and pain procedures in patients on antiplatelet and anticoagulant medications (Second Edition): Guidelines from the American Society of Regional Anesthesia and Pain Medicine, the European Society of Regional Anaesthesia and Pain Therapy, the American Academy of Pain Medicine, the International Neuromodulation Society, the North American Neuromodulation Society, and the World Institute of Pain. *Reg Anesth Pain Med* 2018; 43:225-262.
 336. Manchikanti L, Falco FJE, Benyamin RM, Caraway DL, Kaye AD, Helm II S, Wargo BW, Hansen H, Parr AT, Singh V, Swicegood JR, Smith HS, Schultz DM, Malla Y, Hirsch JA. Assessment of bleeding risk of interventional techniques: A best evidence synthesis of practice patterns and perioperative management of anticoagulant and antithrombotic therapy. *Pain Physician* 2013; 16:SE261-SE318.
 337. Garvican ER, Cree S, Bull L, Smith RK, Dudhia J. Viability of equine mesenchymal stem cells during transport and implantation. *Stem Cell Res Ther* 2014; 5:94.
 338. Breivik H, Bang U, Jalonen J, Vigfússon G, Alahuhta S, Lagerkranser M. Nordic guidelines for neuraxial blocks in disturbed haemostasis from the Scandinavian Society of Anaesthesiology and Intensive Care Medicine. *Acta Anaesthesiol Scand* 2010; 54:16-41.
 339. Gogarten W, Vandermeulen E, Van Aken H, Kozek S, Llau JV, Samama CM; European Society of Anaesthesiology. Regional anaesthesia and antithrombotic agents: Recommendations of the European Society of Anaesthesiology. *Eur J Anaesthesiol* 2010; 27:999-1015.
 340. Vandermeulen E. Regional anaesthesia and anticoagulation. *Best Pract Res Clin Anaesthesiol* 2010; 24:121-131.
 341. Horlocker TT, Wedel DJ, Rowlingson JC, Enneking FK, Kopp SL, Benzon HT, Brown DL, Heit JA, Mulroy MF, Rosenquist RW, Tryba M, Yuan CS. Regional anesthesia in the patient receiving antithrombotic or thrombolytic therapy: American Society of Regional Anesthesia and Pain Medicine Evidence-Based Guidelines (Third Edition). *Reg Anesth Pain Med* 2010; 35:64-101.
 342. Ramsook RR, Danesh H. Timing of platelet rich plasma injections during antithrombotic therapy. *Pain Physician* 2016; 19:E1055-E1061.
 343. Ling L, Camilleri ET, Helledie T, Samsonraj RM, Titmarsh DM, Chua RJ, Dreesen O, Dombrowski C, Rider DA, Galindo M, Lee I, Hong W, Hui JH, Nurcombe V, van Wijnen AJ, Cool SM. Effect of heparin on the biological properties and molecular signature of human mesenchymal stem cells. *Gene* 2016; 576:292-303.
 344. Sutherland FW, Perry TE, Yu Y, Sherwood MC, Rabkin E, Masuda Y, Garcia GA, McLellan DL, Engelmayr GC Jr, Sacks MS, Schoen FJ, Mayer JE Jr. From stem cells to viable autologous semilunar heart valve. *Circulation* 2005; 111:2783-2791.
 345. Schippinger G, Prüller F, Divjak M, Mahla E, Fankhauser F, Rackemann S, Raggam RB. Autologous platelet-rich plasma preparations. *Orthop J Sport Med* 2015; 3:232596711558889.
 346. Pountos I, Georgouli T, Calori GM, Giannoudis PV. Do nonsteroidal anti-inflammatory drugs affect bone healing? A critical analysis. *Sci World J* 2012; 2012:1-14.
 347. Ortel TL. Perioperative management of patients on chronic antithrombotic therapy. *Hematol Am Soc Hematol Educ Progr* 2012; 2012:529-535.
 348. Benzon HT, Avram MJ, Green D, Bonow RO. New oral anticoagulants and regional anaesthesia. *Br J Anaesth* 2013; 111:i96-i113.
 349. Centeno CJ, Al-Sayegh H, Freeman MD, Smith J, Murrell WD, Bubnov R. A multicenter analysis of adverse events among two thousand, three hundred and seventy two adult patients undergoing adult autologous stem cell therapy for orthopaedic conditions. *Int Orthop* 2016; 40:1755-1765.
 350. Nourissat G, Ornetti P, Berenbaum F, Sellam J, Richette P, Chevalier X. Does platelet-rich plasma deserve a role in the treatment of tendinopathy? *Joint Bone Spine* 2015; 82:230-234.
 351. Slabiak T. Stem cell-based therapies and FDA regulations. *Regulatory Focus*, November 2012.
 352. Navani A, Li G, Chrystal J. Platelet-rich plasma in musculoskeletal pathology: A necessary rescue it a lost cause? *Pain Physician* 2017; 20:E345-E356.
 353. Hakimi O, Murphy R, Stachewicz U, Hislop S, Carr AJ. An electrospun polydioxanone patch for the localisation of biological therapies during tendon repair. *Eur Cell Mater* 2012; 24:344-357.