Analytical Review of Guidelines

Regenerative Therapies in the Management of Chronic Low Back Pain from Evidence to Practice: An Analytical Summary of the 2025 Comprehensive Evidence-Based Guidelines

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Background: Regenerative medicine is an evolving medical subspecialty dedicated to enhancing the body's natural healing mechanisms to repair or to replace damaged tissues. By using autologous or allogeneic biologics, it offers the potential to restore function where conventional therapies have shown limited success. While this field holds great promise and continues to generate enthusiasm among both patients and clinicians, it remains in early stages of clinical validation. Therefore, it must be approached with careful optimism and responsible application, ensuring that its presentation, promotion, and use in clinical settings are grounded in evidence and ethical standards. In 2025, the American Society of Interventional Pain Physicians (ASIPP) published updated comprehensive evidence-based guidelines.

Study Design: Summary and structured synthesis of a multidisciplinary, evidence-based clinical practice guideline developed by systematic literature review, dual-instrument methodologic quality appraisal, Grading of Recommendations Assessment, Development, and Evaluation (GRADE) certainty assessment, and modified Delphi consensus.

Objectives: The present investigation summarizes the 2025 updated comprehensive evidence-based guidelines for regenerative therapies in the management of chronic low back pain published by ASIPP. The critical and analytical summary is organized around these recommendations, presenting for each underlying evidence, the assigned evidence level, the consensus-based clinical recommendation, and the practical consequences for patient selection, product preparation and dosing, procedural technique, regulatory compliance, and informed consent.

Methods: A multidisciplinary panel convened by ASIPP defined key clinical questions, reviewed relevant literature, formulated evidence-based statements, and reached consensus through structured discussion and formal voting. Methodologic quality of randomized trials was assessed with Cochrane review criteria and the Interventional Pain Management Techniques – Quality Appraisal of Reliability and Risk of Bias (IPM-QRB) instrument; nonrandomized studies were assessed with the Risk of Bias in Non-Randomized Studies of Exposure (ROBINS-E) tool and IPM-QRBNR. Evidence was graded on the 5-level modified ASIPP scale and appraised for certainty under GRADE. Consensus required at least 80% agreement among eligible panelists without a primary conflict of interest.

Results: Thirty-five authors contributed and 33 participated in the formal consensus process. Nineteen recommendations were generated, all achieving 100% agreement. Effectiveness recommendations were graded by anatomical target: lumbar intradiscal injections of platelet-rich plasma (PRP) and of bone marrow aspirate concentrate (BMAC) each carry Level III, fair evidence with a moderate consensus-based recommendation; lumbar epidural PRP injections carry Level III, fair evidence with a moderate recommendation; facet joint PRP and mesenchymal stem cell (MSC) injections carry Level IV, limited evidence with a moderate recommendation; sacroiliac joint PRP injections carry Level IV, limited evidence with a low recommendation; and functional spine unit multitarget injections carry very low evidence with a low recommendation. The remaining recommendations address available therapies and regulatory status, the risks of unapproved stem

cell products, quality and standards for PRP and BMAC preparation, minimum quality control measures and platelet dosing, patient education, administration criteria, procedural risk stratification, and antithrombotic management.

Limitations: The scarcity of high-quality studies, with much available evidence derived from small or heterogeneous trials.

Conclusion: Regenerative therapies for chronic low back pain rely on fair evidence at the intervertebral disc and epidural space and limited evidence at evidence for facet and sacroiliac joints. The panel issued moderate consensus-based recommendations for all biologics in the lumbar spine, conditioned on definitive diagnosis, failure of conservative therapy, adherence to Food and Drug Administration (FDA) regulation, quantitative verification of the injectate, and transparent informed consent covering the experimental nature and out-of-pocket cost of these treatments.

Key words: Chronic low back pain, discogenic pain, facet joint pain, sacroiliac joint pain, regenerative medicine, platelet-rich plasma, mesenchymal stem cells, stromal vascular fraction, exosomes, bone marrow concentrate, intradiscal injections, functional spine unit, Food and Drug Administration, minimal manipulation

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Regenerative medicine is a science dedicated to the repair, restoration, and regeneration of diseased or injured cells, tissues, or organs to reestablish homeostasis and improve functionality. It spans tissue engineering and cellular biology, and has produced injectables, implants, and scaffolds designed to replicate normal tissue structure and function (1-29). In contemporary chronic pain practice the two principal components are platelet-rich plasma (PRP) and stem cell therapy, with exosomes representing an emerging application (1-23).

The field occupies an unusual position, and the guidelines summarized here reflect the total of present scientific literature. In this regard, the literature describes the good, the bad, and the ugly aspects of regenerative medicine. The good lies in potential to repair or replace damaged tissue, offering hope for conditions previously considered untreatable. The bad involves uncertain long-term outcomes, limited high-quality clinical data, and substantial cost. The ugly encompasses unethical practice, including exploitation of vulnerable patients through unproven stem cell interventions and the tumorigenicity risks attached to some products. PRP applications are relatively uncontroversial apart from cost; bone marrow concentrate is promising but technically demanding and expensive; and most of the controversy and regulatory scrutiny surrounds stem cell therapies (17).

The regulatory environment is active rather than settled. As of July 2025, enforcement actions remained in force against products derived from stromal vascular fraction, umbilical cord blood, and exosomes, and courts have upheld the authority of the Food and Drug Administration (FDA) to regulate these products as drugs or biologics subject to established safety and efficacy standards (14,30). The Federal Trade Commission has pursued clinics engaged in deceptive advertising of unproven cell-based therapies. Oversight of clinical trials has increased, with new studies halted where they involved exporting patients' cells to foreign laboratories for genetic modification and reinfusion, on grounds of data security and informed consent. The agency warns specifically against stem cell tourism, citing blindness, human immunodeficiency virus and hepatitis infection, tumor formation, neurological complications, and death. Approved regenerative treatments remain extremely limited, and stem cell products derived from stromal vascular fraction, umbilical cord blood, and exosomes are not approved for musculoskeletal indications (14).

Against this background, utilization has expanded widely while accurate data on prevalence and outcomes remain scarce. Numerous guidelines exist for spinal pain generally, encompassing interventional and surgical management, but few provide high-quality evidence-based recommendations specific to regenerative medicine in musculoskeletal disorders (3,5,31-38).

There present investigation, therefore, summarizes the resulting recommendations. Consistent with the purpose of a critical and analytical summary article, the emphasis falls on the recommendations. Each is presented in full, accompanied by a condensed account of the evidence from which it was derived, its assigned evidence level and consensus-based clinical recommendation, and a statement of what it means at the point of care. Readers requiring the complete evidence tables, individual study appraisals, and the full regulatory analysis are referred to the primary guideline document (1).

Methods

Rationale, Objective, and Scope

The objective is to provide updated, evidence-based recommendations for the role of regenerative therapies in managing moderate to severe chronic low back pain. The guidelines are intended to establish a basis for understanding the role of biologics in healing, to identify appropriate indications for their use, to facilitate and help standardize biologic therapy, and to encourage the performance of high-quality studies that document outcomes and advance the field. They are applicable across specialties but are directed principally at interventional pain physicians.

The panel states three conditions on application that recur throughout the document and that distinguish this guideline from those covering insurance-covered interventions. Regenerative therapies should be considered only after thorough diagnostic evaluation confirming clinical necessity. Treatment decisions must account for the patient's medical condition, preferences, and expectations. And patients must be fully informed about the nature, potential benefits, risks, and costs of these treatments, most of which are not covered by commercial insurance. Clinicians must follow all applicable FDA regulations.

Key Questions

Twelve key questions were prespecified and used to structure the evidence review. They are reproduced in Table 1.

Panel Composition, Conflicts, and Consensus

Thirty-five authors contributed to the development of the guidelines, of whom 33 participated in the formal consensus process. The panel was multidisciplinary, drawing on academic and non-academic practitioners together with methodologists experienced in systematic review. Potential conflicts of interest were evaluated before finalization, and members with conflicts were recused from the relevant discussion and preparation. The guidelines were commissioned, prepared, edited, and endorsed by American Society of Interventional Pain Physicians (ASIPP) without external funding; internal funding was limited to preparation of the publication.

A modified Delphi technique (e.g., multiple rounds of anonymous surveys to gather expert opinions and reach reliable group consensus) was used to reach consensus, minimizing bias arising from group interaction and preserving anonymity. Panelists without a primary conflict voted through an online survey and could propose edits to the wording or add clarifying comments on implementation. Inclusion required at least 80% agreement (39,40). All 19 recommendations achieved 100% agreement, though the panel records that disagreements occurred in some statements regarding the strength or direction of the recommendation before the final vote.

Evidence Grading and Quality Assessment

Two frameworks were applied in parallel. The

Table 1. *The 12 key questions addressed by the 2025 ASIPP regenerative medicine guidelines.*

No.	Key question
1	What is the spinal functional unit describing the pathophysiologic and structural basis of low back pain?
2	What are the available regenerative medicine therapies?
3	Are regenerative medicine therapies effective in treating low back and lower extremity pain?
4	What is the evidence of effectiveness for the use of intradiscal PRP or bone marrow aspirate concentrate (BMAC), and the consensus-based clinical recommendations?
5	What is the evidence of effectiveness for the use of epidural injections of PRP and derivatives, and the consensus-based clinical recommendations?
6	What is the evidence of effectiveness for using intraarticular facet joint injections of PRP, and the consensus-based clinical recommendations?
7	What is the evidence of effectiveness for the use of PRP in sacroiliac joint injections, and the consensus-based clinical recommendations?
8	What is the evidence of effectiveness for the functional spine unit approach, and the consensus-based clinical recommendations?
9	What are the current guidelines for biologics?
10	What are the adverse consequences and harms of regenerative therapies?
11	What are the precautions in perioperative management of patients receiving regenerative interventional techniques and antiplatelet and anticoagulant therapy?
12	What are the best preventive and therapeutic strategies to improve outcomes when performing regenerative therapies?

qualitative modified ASIPP approach assigns one of five levels, from Level I, strong, to Level V, consensus based, as reproduced in Table 2 (41). Grading of Recommendations Assessment, Development, and Evaluation (GRADE) was used to characterize the certainty of evidence as very low, low, moderate, or high (42,43). This dual use of vocabulary requires care in reading the recommendations and is discussed further below.

Methodologic quality of randomized controlled trials was assessed with Cochrane review criteria and with the Interventional Pain Management Techniques – Quality Appraisal of Reliability and Risk of Bias (IPM-QRB) instrument, under which scores of 32 to 48 denote high quality, 16 to 31 moderate quality, and below 16 low quality, with the last excluded (44). Nonrandomized studies were assessed with the Risk of Bias in Non-Randomized Studies of Exposure tool and with IPM-QRBNR, applying the same numeric thresholds (44,45). The use of Risk of Bias in Non-Randomized Studies of Exposure (ROBINS-E) for nonrandomized studies is a change from the Newcastle-Ottawa Scale employed in companion ASIPP guidelines and reflects the predominance of exposure-based observational designs in this literature.

Outcomes were considered clinically significant on the conventions applied across the ASIPP guideline program. Evidence was analyzed by qualitative synthesis, with quantitative synthesis undertaken where the available data permitted. The guidelines are scheduled for updating within 5 years, or sooner in response to material changes in scientific evidence, public policy, or reported adverse events, and in any event before January 2030.

Results

Overview of the Recommendations

Nineteen recommendations were generated, all achieving 100% agreement among the 33 panelists participating in the consensus process. Table 3 presents them in full with their assigned evidence level and consensus-based clinical recommendation, and Fig.1 shows the distribution of both.

Three features of that distribution deserve comment at the outset. First, the guideline uses two distinct grading vocabularies in parallel, as its companion documents do. The five effectiveness recommendations covering specific anatomical targets are graded on the

Table 2. *Modified ASIPP qualitative approach to grading the evidence of therapeutic effectiveness.*

Level	Descriptor	Definition
I	Strong	Evidence obtained from multiple relevant high-quality randomized controlled trials
II	Moderate	Evidence obtained from at least one relevant high-quality randomized controlled trial, or from multiple relevant moderate- or low-quality randomized controlled trials
III	Fair	Evidence obtained from at least one relevant moderate- or low-quality randomized trial, or from at least one relevant high-quality nonrandomized trial or observational study together with multiple moderate- or low-quality observational studies
IV	Limited	Evidence obtained from multiple moderate- or low-quality relevant observational studies
V	Consensus based	Opinion or consensus of a large group of clinicians and/or scientists

Table 3. *The 19 recommendations of the 2025 ASIPP regenerative medicine guidelines.*

No.	Recommendation (condensed)	Evidence level	Recommendation
1	Available regenerative medicine therapies in the United States include PRP and bone marrow concentrate when obtained with FDA-cleared devices.	High (GRADE)	High
2	Multiple therapies are unavailable in the United States because of FDA regulation but available elsewhere, including adipose stem cells and stromal vascular fraction, autologous, allogeneic or stored stem cells, umbilical cord–derived cells, and exosomes. There is no clear guidance on micronized fat.	High (GRADE)	High
3	Unapproved stem cell treatments carry rare but significant risks including blindness, infection (HIV, hepatitis, bacterial), thrombosis, tumor formation, neurological complications, and death.	Moderate (GRADE)	High
4	The functional spinal unit is the smallest physiological unit of the spine exhibiting the biomechanical properties of the whole, comprising two adjacent vertebrae, the intervertebral disc, facet joints, ligaments, and muscles. It is used in regenerative medicine in contrast to single-structure precision diagnosis and therapy; it may provide better results but there is no significant evidence at present.	Very low (GRADE)	Low

Table 3 cont. *The 19 recommendations of the 2025 ASIPP regenerative medicine guidelines.*

No.	Recommendation (condensed)	Evidence level	Recommendation
5	Regenerative therapies carry risk comparable to interventional techniques, though severe complications can occur including discitis, epidural hematoma and abscess, superficial infection, allergy, neurological complications, tumor formation, and death. The chondrotoxicity, genotoxicity, neurotoxicity, and systemic toxicities of steroid-based injections are absent with PRP and bone marrow concentrate.	High (GRADE)	High
6	PRP quality and standards: no universally accepted standard defines optimal concentration of cells and growth factors; different conditions may benefit from different formulations (leukocyte-rich versus leukocyte-poor). Quality assurance requires process validation, testing and monitoring, traceability, and device selection.	Low (GRADE)	Moderate
7	BMAC quality and standards: devices are expected to produce viable cells at approximately 90% viability; quality depends heavily on aspiration technique, volume, and site. No standardized protocols exist. Minimum requirements include qualifying mesenchymal and hematopoietic stem cells. Different processing devices and methods produce different results.	Low (GRADE)	Moderate
8	Minimum required quality control measures for clinical purposes include final volume, platelet count, white blood cell count, red blood cell count, and the concentration factor relative to whole blood.	Moderate (GRADE)	Moderate
9	A minimum of 4 billion and an optimum of 10 billion platelets per injection is needed for significant clinical effect in knee intraarticular injections; a cumulative dose of approximately 10 billion platelets into structures of a functional spine unit is recommended. Intradiscal PRP at greater than 10 times baseline platelet concentration produced greater improvement than concentrations below five times.	Low (GRADE)	Moderate
10	It is essential to understand PRP and BMAC with their multiple variations, and the effectiveness, technical considerations, and complications of spinal injections.	High (GRADE)	High
11	Patient education is a crucial aspect of the success of regenerative medicine injections.	High (GRADE)	High
12	Evidence of effectiveness and consensus-based clinical recommendation for intradiscal PRP therapy.	III, Fair (ASIPP)	Moderate
13	Evidence of effectiveness and consensus-based clinical recommendation for intradiscal BMAC therapy.	III, Fair (ASIPP)	Moderate
14	Evidence of effectiveness and consensus-based clinical recommendation for epidural PRP injections in managing low back and lower extremity pain due to degenerative disc pathology and other conditions.	III, Fair (ASIPP)	Moderate
15	Evidence of effectiveness and consensus-based clinical recommendation for facet joint intraarticular PRP and MSC injections in managing chronic low back pain.	IV, Limited (ASIPP)	Moderate
16	Evidence of effectiveness and consensus-based clinical recommendation for sacroiliac joint PRP injections.	IV, Limited (ASIPP)	Low
17	Guidelines for administration of biologics include failure of conservative modalities, understanding of risks and benefits, willingness to participate in a rehabilitation program, and appropriate consent with shared decision-making.	High (GRADE)	High
18	Risk stratification for regenerative medicine therapies: high risk for intradiscal therapy, moderate risk for epidural injections, low risk for facet joint injections, and low risk for sacroiliac joint injections.	Moderate (GRADE)	Moderate
19	Antiplatelet and anticoagulant therapy guidelines in continuation, discontinuation, and re-establishment are utilized per ASIPP guidelines for low- and high-risk procedures.	Moderate (GRADE)	Moderate

BMAC, bone marrow aspirate concentrate; FDA, Food and Drug Administration; GRADE, Grading of Recommendations Assessment, Development and Evaluation; HIV, human immunodeficiency virus; MSC, mesenchymal stem cell; PRP, platelet-rich plasma. Parenthetical scale identifiers have been added in this summary for clarity and do not appear in the source document. The column headed Recommendation reports the consensus-based clinical recommendation.

ASIPP scale, where the descriptors are Level III, fair and Level IV, limited. The remaining fourteen are graded on the GRADE certainty scale, where the descriptors are very low, low, moderate, and high. A reader comparing Recommendation 1, graded high, with Recommendation 12, graded Level III fair, should not conclude that the evidence for the availability of therapies is stronger than the evidence for intradiscal effectiveness; the

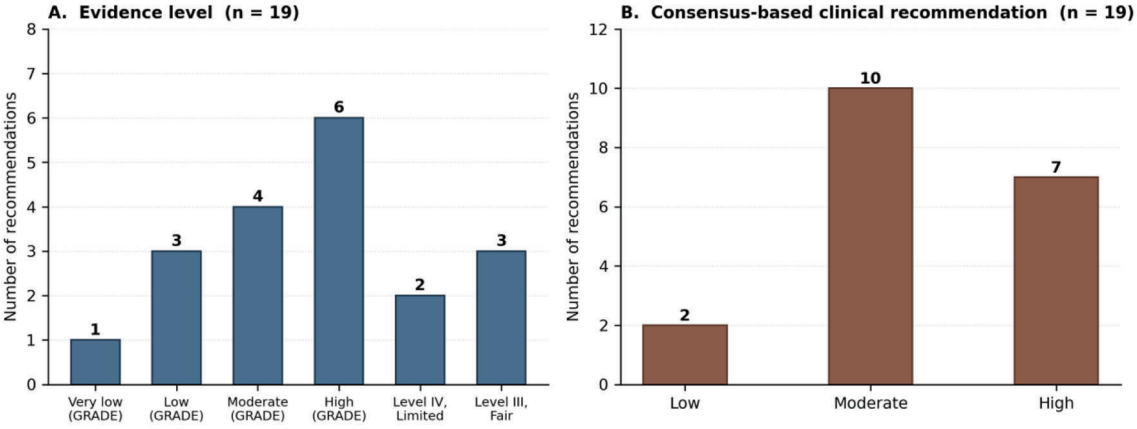


Fig. 1. *Distribution of the assigned evidence level (A) and consensus-based clinical recommendation (B) across the 19 recommendations. The evidence-level labels derive from two different scales: Level III (fair) and Level IV (limited) are descriptors of the modified ASIPP grading scheme, whereas very low, low, moderate, and high are GRADE certainty ratings. Every recommendation graded high on evidence describes availability, regulation, or risk rather than therapeutic effect.*

two are not on a common scale and measure different things. Table 3 has been annotated in this summary to identify which scale applies.

Second, the recommendations graded high on evidence are, without exception, statements of fact about what exists, what is regulated, and what is known to be hazardous, rather than statements about therapeutic effect. Recommendations 1 and 2 describe which therapies are available in the United States and which are not; Recommendation 5 describes the risk profile; Recommendation 10 concerns understanding the products; Recommendation 11 concerns patient education; and Recommendation 17 concerns the criteria for administration. None of these is a claim that a biologic works. Every recommendation that does make such a claim is graded Level III or IV, or very low.

Third, the gradient across anatomical targets is orderly and clinically meaningful. Evidence is strongest at the intervertebral disc and epidural space, weaker at the facet and sacroiliac joints, and weakest of all for the multitarget functional spine unit approach. Fig. 2 displays this gradient.

Available Therapies, Regulatory Status, and Risk (Recommendations 1 to 5)

What is available, and what is not

The first two recommendations are jurisdictional rather than therapeutic, and they carry the highest grading in the document precisely because the facts are not in dispute. In the United States, the available regenerative therapies are PRP and bone marrow concentrate obtained with devices cleared by the FDA. Multiple other modalities are unavailable under current regulation but are available in other countries, including adipose-derived stem cells and stromal vascular fraction, autologous, allogeneic, and stored stem cells, umbilical cord–derived cells, and exosomes. Many states, such as Floria (among others), have adopted laws that permit the use of stem cells and exosomes for a variety of pain interventions. Micronized fat occupies an ambiguous position, with no clear guidance, and is used by some practitioners.

This framing matters for a reason the guideline states plainly elsewhere: the gap between what is available domestically and what is marketed internationally is the mechanism of stem cell tourism, and Recommendation 3 attaches to precisely that gap. Unapproved stem cell treatments carry rare but significant risks including blindness, human immunodeficiency virus, hepatitis, and bacterial infection, thrombosis, tumor formation, neurological complications, and death. The evidence is graded moderate but the recommendation is graded high, a deliberate asymmetry: the events are rare enough that the evidence base is necessarily thin, yet their severity and the absence of any offsetting benefit make the guidance unambiguous.

Recommendation 1. Available regenerative medicine therapies in the United States

Available regenerative medicine therapies include PRP and BMC when obtained with FDA-cleared devices.

Evidence level: High | Strength of recommendation: High

Recommendation 2. Therapies available outside the United States

Multiple therapies are not currently available due to FDA regulations in the United States. In other countries, multiple therapies are available, including adipose stem cells including stromal vascular fraction (SVF), autologous, allogenic, or stored stem cells, stem cells derived from umbilical cord and exosomes. There is no clear guidance on micronized fat and it is used by some in the field.

Evidence level: High | Strength of recommendation: High

Recommendation 3. Risks of unapproved stem cell treatments

There are rare, but significant potential risks associated with unapproved stem cell treatments, including blindness, infections (like human immunodeficiency virus, hepatitis, or bacterial infections), thrombosis, tumor formation, neurological complications, and even death.

Evidence level: Moderate | Strength of recommendation: High

The functional spine unit

Recommendation 4 defines a concept that runs through the document and that distinguishes regenerative practice from conventional interventional pain management. A functional spinal unit, also called a spinal motion segment, is the smallest physiological unit of the spine exhibiting the same biomechanical properties as the whole. It is a three-joint complex comprising two adjacent vertebrae, the intervertebral disc, the facet joints, and the associated ligaments and muscles, responsible for coordinated movement, protection of neural structures, and provision of a stable base (3).

The clinical significance is that the functional spine unit is used in regenerative medicine as the treatment target, in contrast to the precision diagnosis and single-structure therapy that interventional pain management advocates. The rationale is biomechanical: understanding load distribution across spinal structures suggests that most patients with chronic low back pain have multiple pain generators rather than one. The panel observes that this approach appears appropriate given that regenerative therapies are not bound by local coverage determinations and medical policies, and may produce better results, but states directly that there is no significant evidence at present. The grading follows: very low evidence with a low recommendation, the weakest pairing in the document.

The tension here is worth naming because it will

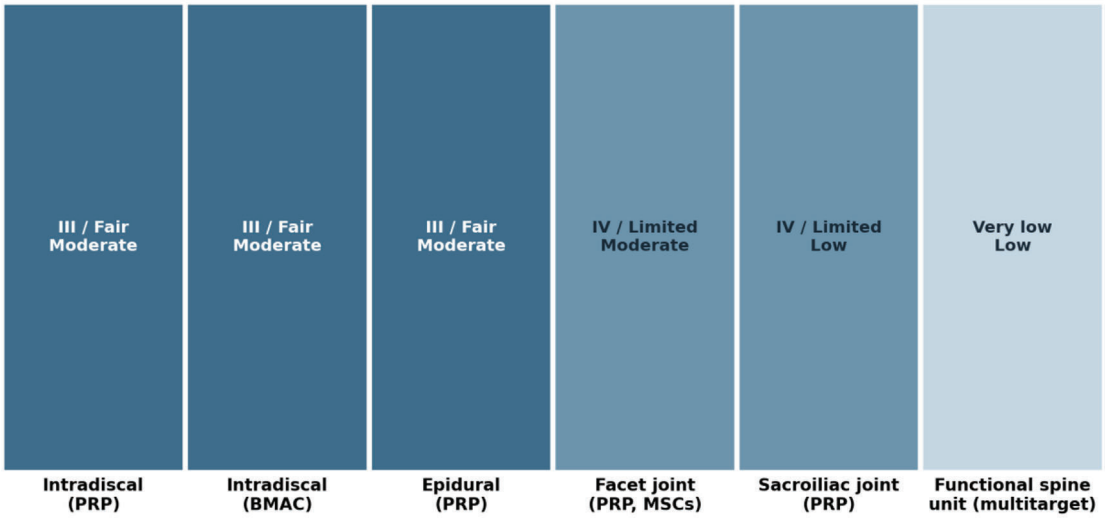


Fig. 2. *Evidence level and consensus-based clinical recommendation for regenerative therapy by anatomical target. Darker cells denote stronger evidence. Evidence is strongest at the intervertebral disc and epidural space, weaker at the facet and sacroiliac joints, and weakest for the multitarget functional spine unit approach.*
BMAC, bone marrow aspirate concentrate; MSCs, mesenchymal stem cells; PRP, platelet-rich plasma.

shape how the guideline is read. The same panel that recommends a precision-diagnosis pathway in its facet joint and epidural guidelines acknowledges a multitarget paradigm here, on the explicit ground that the constraint driving precision, coverage policy, does not apply. Whether the multitarget approach is biologically superior or merely unconstrained is exactly what the evidence cannot currently settle, and the grading says so.

Recommendation 4. Definition and role of the functional spine unit

A functional spinal unit (FSU), also known as spinal motion segment, is the smallest physiological unit of the spine that exhibits the same biomechanical properties of the entire spine. Each FSU is a 3-joint complex and is responsible for coordinated movement protecting neural structures and providing a stable base for the body. A FSU consists of 2 adjacent vertebrae, intervertebral disc, facet joints, ligaments, and muscles. Functional spine unit is utilized in managing back pain in regenerative medicine, in application of therapies in contrast to precision diagnosis and therapy with the single structure, as advocated in interventional pain management. While this approach appears to be appropriate considering that regenerative medicine therapies are not bound by LCDs and medical policies, functional spine unit may provide better results; however, there is no significant evidence at the present time.

Evidence level: Very low | Strength of recommendation: Low

Risk profile of regenerative therapies

Recommendation 5 makes a comparative claim that is easily misread. Regenerative therapies carry risk comparable to interventional techniques generally, which is to say low, though severe complications can occur: discitis in particular, together with epidural hematoma and abscess, superficial infection, allergy, neurological complications, tumor formation, and death. The second half of the recommendation is the substantive one. The overall risk of conventional interventional procedures has been considered by some to be higher because of the chondrotoxicity, genotoxicity, neurotoxicity, and systemic toxicities of steroid-based injections, and these toxicities are absent with PRP and BMAC.

This is an argument about comparative harm rather than comparative benefit, and it is the strongest argument the guideline makes for regenerative therapy. It does not assert that biologics work better than corticosteroid; the effectiveness recommendations, graded Level III and IV, make no such claim. It asserts that the harms differ in kind, and that a therapy with fair evidence and no chondrotoxicity may be preferable to one with better evidence and known tissue toxicity. Readers should note that this is a reasoned position rather than a demonstrated one; no trial in the evidence base compared long-term tissue outcomes between the two.

Recommendation 5. Identified risks of regenerative medicine therapies

Regenerative medicine therapies are similar to interventional techniques with low risk; however, severe complications can occur including infection, specifically, discitis, epidural hematoma, and abscess, superficial infections, allergies, neurological complications, tumor formation and death. Overall risk of interventional procedures has been considered by some as higher because of the steroid-based injections with chondrotoxicity, genotoxicity, neurotoxicity, and multiple systematic toxicities. These toxicities are absent with PRP and BMC.

Evidence level: High | Strength of recommendation: High

Product Quality, Standards, and Dosing (Recommendations 6 to 10)

Five recommendations address what is arguably the field's central methodological problem: that "PRP" and "BMAC" name preparation processes rather than defined products, and that two injections bearing the same name may differ by an order of magnitude in the quantity delivered.

Platelet-rich plasma

The panel identifies three problems: a lack of standardized protocols, variation in preparation technique, and regulatory limitation. Unlike pharmaceuticals, no universally accepted standard defines the optimal concentration of cells and growth factors, and different conditions may benefit from different formulations, with leukocyte-rich and leukocyte-poor preparations having distinct profiles. Quality assurance therefore rests on process validation, testing and monitoring, traceability, and device selection rather than on product specification. The evidence is graded low and the recommendation moderate.

Bone marrow aspirate concentrate

Devices are expected to produce viable cells at approximately 90% viability, but quality depends heavily on aspiration technique, with volume and site both important. As with PRP, no standardized protocols exist and preparation varies within regulatory constraints. Minimum requirements include qualifying mesenchymal and hematopoietic stem cells, and different processing devices and methods produce materially different results. The evidence is graded low and the recommendation moderate.

Quality control and dosing

Recommendation 8 specifies the minimum quality control measures for clinical purposes: final volume, platelet count, white blood cell count, red blood cell count, and the concentration factor relative to whole blood. The rationale appears in the clinical guidance section, where the panel states that a quantitative laboratory capable of providing cell counts is essential and often overlooked, and that without knowing cell counts, dosing accuracy cannot be confirmed and inadequate dosing can compromise outcomes.

Recommendation 9 supplies the numbers. Studies in knee intraarticular injections show that a minimum of 4 billion platelets are needed for significant clinical effect, with 10 billion as the optimum. Extrapolating to the spine, a cumulative dose of approximately 10 billion platelets into the structures of a functional spine unit is recommended. Direct spinal evidence exists and points the same way: intradiscal PRP at greater than ten times baseline platelet concentration produced greater improvement in pain scores and functional outcomes at long-term follow-up than concentrations below five times baseline. Elsewhere the guidance is more specific still, recommending PRP concentrations exceeding 5 billion platelets and bone marrow concentrate exceeding 100 million total nucleated cells in general practice, with double centrifugation producing more than 10 billion platelets described as yielding optimal results, and a total nucleated cell count above 1.5 billion as the goal after bone marrow concentration. Fig. 3 displays the risk stratification and the dosing thresholds together.

The dosing recommendation is graded low on evidence and moderate on recommendation, and the gap between those two gradings is where the practical significance lies. The panel is not confident that 10 billion is the correct number. It is confident that injecting an unmeasured quantity is indefensible. That distinction should govern how the recommendation is implemented: the requirement is to count, not to hit a particular figure.

Recommendation 6. Platelet-rich plasma: quality and standards

Key issues concerning quality and standards for PRP include a lack of standardized protocols, variations in preparation techniques, and regulatory limitations. Unlike pharmaceuticals, no universally accepted standard defines the optimal concentration of cells and growth factors. Different conditions may benefit

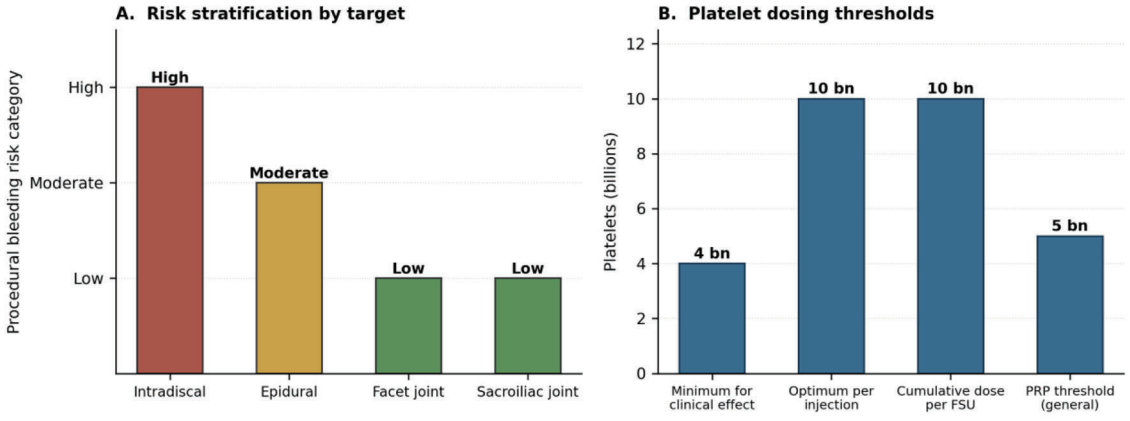


Fig. 3. *Procedural risk stratification by anatomical target (A) and platelet dosing thresholds (B). Risk categories determine the applicable antithrombotic schedule under Recommendation 18. Dosing thresholds are derived principally from knee intraarticular studies and extrapolated to the spine; the cumulative figure applies across the structures of a functional spine unit.* FSU, functional spine unit; PRP, platelet-rich plasma

from different formulations (leukocyte-rich versus leukocyte-poor). Quality assurance practices include process validation, testing and monitoring, traceability, and device selection.
Evidence level: Low | Strength of recommendation: Moderate

Recommendation 7. Bone marrow aspirate concentrate: quality and standards
BMAC devices are expected to produce viable cells with cell viability rates of approximately 90%. The quality of BMAC is heavily dependent on the aspiration technique. Volume and site are important. There are no established standardized protocols. Consequently, there are variations in preparation technique limited by regulatory standards. Minimum requirements for BMAC include qualifying mesenchymal stem cells (MSCs) and hematopoietic stem cells (HSCs). Different processing devices and methods produce different results. Quality assurance practices include process validation, testing and monitoring, traceability, and device selection.
Evidence level: Low | Strength of recommendation: Moderate

Recommendation 8. Minimum required quality control measures
The minimum required quality control measures for clinical purposes include final volume, platelet count, white blood cell (WBC) count, red blood cell (RBC) count, and the concentration factor relative to whole blood. Further, different processing devices and methods produce different results regarding final cell counts, viability, and volume.
Evidence level: Moderate | Strength of recommendation: Moderate

Recommendation 9. Minimum required platelets per injection
Studies show that a minimum of 4 billion and 10 billion as optimum count of platelets per injection is needed for a significant clinical effect in knee intraarticular injections. Even though limited, literature is available regarding spinal injections; based on other joints, a cumulative dose of around 10 billion platelets into structures of a FSU are recommended. There is literature showing intradiscal injections of PRP with greater than 10 times baseline platelet concentration resulted in greater improvements in pain scores and functional outcomes at long-term follow-up compared to lower concentration PRP less than five times.
Evidence level: Low | Strength of recommendation: Moderate

Recommendation 10. Understanding the products and their spinal application
It is essential to understand PRP and BMAC with multiple variations and the effectiveness, technical considerations, and complications with the spinal injections.
Evidence level: High | Strength of recommendation: High

Patient Education (Recommendation 11)

Patient education carries high evidence and a high recommendation, and in this field it bears a weight it does not bear elsewhere. Regenerative medicine is not covered by medical insurance, and at the time of writing no standardized protocols or treatments are governed by the Centers for Medicare and Medicaid Services (CMS). The panel states that because of this, the physician–patient partnership must be emphasized more strongly than in most other procedures.

The specific content the panel requires is unusually direct. Clinicians must be prepared to discuss the realistic potential of these procedures and manage expectations accordingly. A standard interventional consent form serves as a foundation, but additional language should explain the experimental nature of the treatment, since these therapies are not approved by the FDA for orthopedic conditions of the joints or spine. All treatment options must be reviewed and patient questions fully addressed before proceeding. The guidelines go further into practice conduct than is customary, advising clinicians to educate rather than sell and to avoid promotional tactics such as time-limited discounts. That a clinical practice guideline finds it necessary to say so is itself a comment on the state of the field.

Recommendation 11. Patient education
Based on the available evidence and all available guidance, patient education is a crucial aspect of the success of regenerative medicine injections.
Evidence level: High | Strength of recommendation: High

Effectiveness by Anatomical Target (Recommendations 12 to 16)

Five recommendations address effectiveness, and they are the reason the guideline exists. Evidence was derived from randomized and nonrandomized studies and synthesized on study quality, risk of bias, qualitative and quantitative analysis where available, and the GRADE framework. The resulting gradient is set out in Table 4 and Fig. 2.

Table 4. *Summary of evidence for regenerative therapy by anatomical target.*

Target and product	Evidence level	Consensus-based clinical recommendation
Intradiscal injection — PRP	Level III, Fair	Moderate
Intradiscal injection — BMAC	Level III, Fair	Moderate
Epidural injection — PRP	Level III, Fair	Moderate
Facet joint intraarticular injection — PRP and MSCs	Level IV, Limited	Moderate
Sacroiliac joint injection — PRP	Level IV, Limited	Low
Functional spine unit multitarget injection	Very low	Low

BMAC, bone marrow aspirate concentrate; MSCs, mesenchymal stem cells; PRP, platelet-rich plasma

Intradiscal injections

Intradiscal injection of PRP and of BMAC each carry Level III, fair evidence with a moderate consensus-based recommendation. This is the strongest effectiveness grading in the document, and the disc is where most published work on spinal orthobiologics has concentrated. It is also the highest-risk target: Recommendation 18 classifies intradiscal therapy as high risk, and the clinical guidance section requires intravenous antibiotics for intradiscal and intraosseous procedures. Discitis is named first among the severe complications in Recommendation 5.

The practical consequence is that the target with the best evidence is also the target demanding the most stringent precautions, and the two must be weighed together at the point of consent. The dose-response signal described earlier, in which concentrations above ten times baseline outperformed those below five times, derives from this literature and is the clearest demonstration in the guideline that preparation quality determines outcome.

Recommendation 12. Intradiscal PRP therapy
The evidence of effectiveness for PRP and consensus-based clinical recommendations for intradiscal therapy: Evidence Level III, Fair; Consensus-Based Clinical Recommendation: Moderate.
Evidence level: Level III, Fair | Strength of recommendation: Moderate

Recommendation 13. Intradiscal BMAC therapy
The evidence of effectiveness for BMAC and consensus-based clinical recommendations for intradiscal therapy: Evidence Level III, Fair; Consensus-Based Clinical Recommendation: Moderate.
Evidence level: Level III, Fair | Strength of recommendation: Moderate

Epidural injections

Epidural PRP injection for low back and lower extremity pain due to degenerative disc pathology and other conditions carries Level III, fair evidence with a moderate recommendation, the same grading as intradiscal therapy at a lower procedural risk category. Recommendation 18 classifies epidural injection as moderate risk, between intradiscal and the peripheral joints. For a patient in whom the epidural space is an anatomically plausible target, this pairing of equal evidence with lower risk is clinically material. Long term outcomes are unavailable and considering that PRP is known to induce collagen formation, we do not know what the risk is for epidural fibrosis.

Recommendation 14. Epidural PRP injections
The evidence of effectiveness and consensus-based clinical recommendations for epidural injections with PRP in managing low back and lower extremity pain due to degenerative disc pathology and other conditions: Evidence Level III, Fair; Consensus-Based Clinical Recommendation: Moderate.
Evidence level: Level III, Fair | Strength of recommendation: Moderate

Facet and sacroiliac joint injections

Facet joint intraarticular injection with PRP or mesenchymal stem cells (MSCs) carries Level IV, limited evidence with a moderate recommendation. Sacroiliac joint PRP injection carries the same Level IV, limited evidence but a low recommendation. The divergence between two recommendations resting on the same evidence level is the single most informative grading decision in this section, and it is not explained in the source text. The most plausible reading is that the panel found the facet literature more consistent in direction, or the benefit-to-harm ratio more favorable, than the sacroiliac literature. Readers should treat the sacroiliac recommendation as the weakest effectiveness statement in the document that concerns a single named structure.

Both are classified as low risk under Recommen-

dation 18, which places them alongside conventional facet and sacroiliac interventions in the antithrombotic framework and means that antithrombotic therapy may generally be continued for bleeding-risk purposes. The efficacy caveat described in Section 3.7 nonetheless applies and points the other way.

Recommendation 15. Facet joint intraarticular PRP and MSC injections

The evidence of effectiveness and consensus-based clinical recommendations for facet joint intraarticular PRP and MSC injections in managing chronic low back pain: Evidence Level IV, Limited; Consensus-Based Clinical Recommendation: Moderate.

Evidence level: Level IV, Limited | Strength of recommendation: Moderate

Recommendation 16. Sacroiliac joint PRP injections

The evidence of effectiveness and consensus-based clinical recommendations for sacroiliac joint PRP injections: Evidence Level IV, Limited; Consensus-Based Clinical Recommendation: Low.

Evidence level: Level IV, Limited | Strength of recommendation: Low

Functional spine unit injections

Multitarget injection addressing the functional spine unit carries very low evidence with a low recommendation, and no separately numbered recommendation is issued for its effectiveness; the grading appears in the evidence synthesis and in the definitional Recommendation 4. The supporting literature is thin: the guideline cites a case series of 14 patients with neck pain treated with autologous concentrated platelet product and prolotherapy under a functional spine unit protocol, targeting the cervical facet capsule, the supraspinous and interspinous ligaments, and the cervical epidural space, with clinically significant improvement in pain and function at 24 months (46). That study is in the cervical spine, is uncontrolled, and enrolled 14 patients; the guideline is explicit that it supports the paradigm rather than establishing it.

The panel's conclusion nonetheless notes that recent advances have shifted focus toward a comprehensive model addressing the entire functional spine unit as a disease-modifying approach, and that emerging literature demonstrates multiple-structure injection reflecting increasingly common clinical practice. The honest summary is that practice has moved ahead of evidence here, and the guideline records both facts without reconciling them.

Administration Criteria and Regulatory Compliance (Recommendation 17)

Recommendation 17 states the conditions for administering biologics: failure of conservative modalities, understanding of the risks and benefits, willingness to participate in a rehabilitation program, and appropriate consent with shared decision-making. It carries high evidence and a high recommendation. The inclusion of willingness to participate in rehabilitation as a precondition rather than an adjunct is notable and is reinforced in the clinical guidance, where inability to participate in a proper rehabilitation program appears among the relative contraindications.

The regulatory framework within which these criteria operate is set out at length in the source document. Human cells, tissues, and cellular and tissue-based products are regulated under a risk-based approach with two tiers. Products under Section 361 of the Public Health Service Act receive less stringent oversight, require no premarket approval, and must meet Good Tissue Practices; they must be minimally manipulated and used in homologous environment. Products under Section 351 require a Biologics License Application, premarket approval, clinical trial phases, current Good Manufacturing Practice, and extensive post-market surveillance. Minimal manipulation means, for structural tissue, processing that does not alter the original relevant characteristics relating to utility for reconstruction, repair, or replacement, and for cells or nonstructural tissue, processing that does not alter the relevant biological characteristics. Where information does not exist to show that processing meets this definition, the agency treats the processing as more than minimal manipulation, and the product becomes ineligible for regulation solely under Section 361 (30). Homologous use requires that the product serves a purpose consistent with its natural role (47). Table 5 summarizes the framework.

Recommendation 17. Guidelines for administration of biologics

The guidelines for administration of biologics include failure of conservative modalities, understanding of the risks and benefits, willingness to participate in rehabilitation program and appropriate consent with shared decision making.

Evidence level: High | Strength of recommendation: High

Risk Stratification and Antithrombotic Management (Recommendations 18 and 19)

Recommendations 18 and 19 operate together and import the framework of the companion 2024 ASIPP antithrombotic guidelines. Regenerative procedures are stratified by anatomical target: intradiscal therapy is high risk, epidural injection moderate risk, and facet joint and sacroiliac joint injection low risk. The antithrombotic schedule for the assigned category then applies, governing continuation, discontinuation, and re-establishment of therapy (37,38). Both recommendations carry moderate evidence and a moderate recommendation. Table 6 sets out the schedule (48,49).

A consideration arises here that has no counterpart in the antithrombotic guidelines and that clinicians should not overlook. In conventional interventional practice, the only reason to interrupt antithrombotic therapy is bleeding risk. In regenerative practice there

Table 5. *Regulatory framework for human cells, tissues, and cellular and tissue-based products.*

Element	Section 361 HCT/Ps	Section 351 HCT/Ps
Regulatory burden	Minimally regulated	Subject to more stringent regulation
Premarket approval	Not required	Biologics License Application required
Manufacturing standard	Good Tissue Practices (GTP)	Current Good Manufacturing Practice (cGMP)
Manipulation	Must be minimally manipulated	More than minimal manipulation permitted
Use	Must be homologous to natural function	Not restricted to homologous use
Clinical trials	Not required	Required, with post-market surveillance
Representative products	Skin, bone, and corneal grafts; PRP used homologously; amniotic tissue–derived products used homologously	Cell therapies with expansion or differentiation in culture; gene therapies; some tissue-engineered products
Expedited pathway	—	Regenerative Medicine Advanced Therapy (RMAT) designation, introduced 2017

HCT/Ps, human cells, tissues, and cellular and tissue-based products; PRP, platelet-rich plasma. Regulated under 21 CFR Part 1271.

Table 6. *Antithrombotic management for regenerative procedures by risk category.*

Medication	Low risk (facet, sacroiliac)	Moderate risk (epidural)	High risk (intradiscal)	Restart
NSAIDs	Stop 7–10 days before and 2 weeks after for efficacy, irrespective of bleeding risk	Stop 7–10 days before and 2 weeks after	Stop 7–10 days before and 2 weeks after	2 weeks
Low- and high-dose aspirin	Continue, or may stop 3 days	Continue, or may stop 3 days	Stop 6 days	24 h
Dipyridamole; cilostazol	May continue	May continue	May continue, or stop 2 days	12 h
Aggrenox	May continue	May continue	Stop 6 days	24 h
Clopidogrel	May continue	May continue, or stop 5 days	Stop 6 days	12 h
Prasugrel	May continue	May continue, or stop 5 days	Stop 6 days	24 h
Ticagrelor	May continue	May continue, or stop 3 days	Stop 5 days	24 h
Warfarin	May continue, or stop 1–2 days; INR ≤ 3.0	May continue, or stop 2–3 days; INR ≤ 2.0	Stop 3–5 days; INR ≤ 1.5	12–24 h
Dabigatran	May continue, or stop 1 day	Stop 2 days	Stop 2 days	24 h
Dabigatran (CrCl ≤ 50 mL/min)	May continue, or stop 1 day	Stop 3–4 days	Stop 3–4 days	24 h
Apixaban; rivaroxaban; edoxaban	May continue, or stop 1 day	Stop 1 day	Stop 2 days	24 h
Heparin, intravenous	Discontinue 4 h	Discontinue 4 h	Discontinue 4 h	24 h
Heparin, subcutaneous	Discontinue 6 h	Discontinue 6 h	Discontinue 24 h	24 h
Low molecular weight heparin	Discontinue 24 h	Discontinue 24 h	Discontinue 24 h	24 h

CrCl, creatinine clearance; INR, international normalized ratio; NSAIDs, nonsteroidal anti-inflammatory drugs. Schedule adapted from the 2024 ASIPP antithrombotic guidelines. The NSAID row reflects the efficacy-driven interval recommended in the clinical guidance section, which is longer than the bleeding-risk schedule would require.

is a second reason, and it points in the same direction for a different cause: antithrombotic agents may reduce the efficacy of the injectate itself. The coagulation cascade is central to platelet function, and disruption of platelet surfaces or premature activation may reduce clinical efficacy (50). Nonsteroidal anti-inflammatory drugs (NSAIDs) inhibit platelet activation, reduce alpha granule storage, and impair aggregation, and studies have shown that exposure significantly inhibits platelet function regardless of drug type, duration, or blood processing method, yielding lower-quality autologous PRP (51). Cyclooxygenase inhibition impedes release of growth factors including transforming growth factor alpha and platelet factor 4. For MSCs the concern is analogous: even low-dose heparin can negatively affect ex vivo growth and differentiation potential (52,53).

The clinical guidance section translates this into a specific instruction that sits alongside the antithrombotic schedule rather than within it: discontinuation of NSAIDs and immunotherapy 7 to 10 days before and for 2 weeks after the procedure is advised to optimize results. This interval is longer than any bleeding-risk schedule would require for a low-risk procedure, and it is recommended for efficacy rather than safety. Antiplatelet therapy including NSAIDs also appears among the relative contraindications. The panel notes that literature on the safety, efficacy, and timing of injection in patients on antithrombotic therapy remains limited (54,55).

Recommendation 18. Risk stratification for regenerative medicine therapies

Risk stratification for regenerative medicine therapies, based on ASIPP guidelines: high risk for intradiscal therapy, moderate risk for epidural injections, low risk for facet joint injections, and low risk for sacroiliac joint injections.

Evidence level: Moderate | ***Strength of recommendation: Moderate***

Recommendation 19. Antiplatelet and anticoagulant therapy

Antiplatelet and anticoagulant therapy guidelines in continuation, discontinuation, and re-establishment are utilized per ASIPP guidelines for low- and high-risk procedures.

Evidence level: Moderate | ***Strength of recommendation: Moderate***

The Care Pathway: Contraindications, Technique, and Rehabilitation

The clinical guidance section assembles the recommendations into an operational pathway, presented in Fig. 4. Absolute contraindications are active cancer, active infection, hemodynamic instability or other disorder meeting hospitalization criteria, and abnormally high baseline cell counts that could represent undiagnosed cancer or active infection and require work-up before injection. Relative contraindications comprise low baseline platelet counts of 50 to 100 thousand per microliter, antiplatelet therapy including NSAIDs, disease-modifying antirheumatic drugs and immunotherapy, low PRP or bone marrow concentrate counts on post-processing analysis, advanced degeneration with lower baseline substrate, bony growths such as osteophytes, significant loss of range of motion, systemic compromise such as metabolic syndrome or organ failure or home oxygen use, and inability to participate in rehabilitation. Table 7 reproduces these.

Procedural technique is specified in more detail than in the companion guidelines. For PRP, venous blood should be drawn with a large-bore 18- to 20-gauge needle to minimize cellular damage, and double centrifugation producing more than 10 billion platelets yields optimal results. Bone marrow aspiration is typically performed at the posterior superior iliac spine, with a total nucleated cell count above 1.5 billion as the goal after concentration. Needle approach must account for anatomical variation and adjacent neurovascular structures, and image guidance by ultrasound or fluoroscopy is required. Intravenous antibiotics are recommended for intradiscal and intraosseous procedures. Vital signs are monitored throughout according to American Society of Anesthesiologists (ASA) guidance.

Post-procedural management diverges from conventional practice in one respect that patients must be warned about. Symptoms often intensify during the first 7 to 10 days after injection because of the inflammatory healing response, before returning to baseline within a few weeks. NSAIDs are avoided, with gabapentinoids, acetaminophen, muscle relaxants, and opioids as acceptable alternatives. Cryotherapy is applied for the first 24 hours and heat thereafter. Rehabilitation follows the four overlapping phases of tissue healing summarized in Table 8 (56-58), with a home program from weeks 4 to 6 at approximately 50% intensity using isometric exercise, most restrictions lifted after 6 weeks, noticeable improvement typically between weeks 4 and 6, and formal review at 3 months.

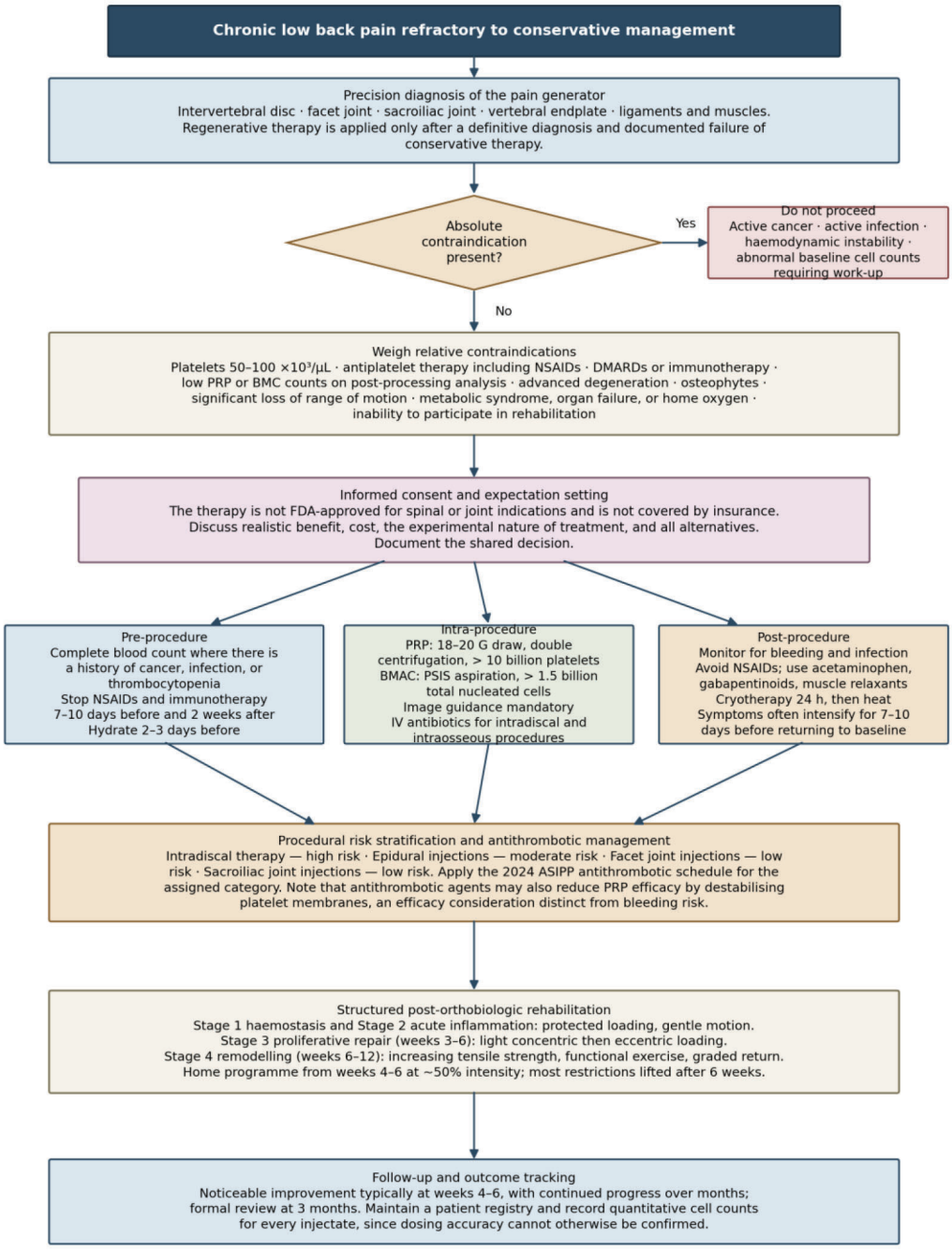


Fig. 4. *Care pathway for regenerative therapy in chronic low back pain, assembling precision diagnosis, contraindication screening, informed consent, pre-, intra-, and post-procedural management, risk stratification and antithrombotic considerations, structured rehabilitation, and outcome tracking.*
BMAC, bone marrow aspirate concentrate; BMC, bone marrow concentrate; DMARDs, disease-modifying antirheumatic drugs; FDA, Food and Drug Administration; NSAIDs, nonsteroidal anti-inflammatory drugs; PRP, platelet-rich plasma; PSIS, posterior superior iliac spine

Table 7. *Contraindications to regenerative therapy.*

Category	Criteria
Absolute	Active cancer
	Active infection
	Hemodynamic instability or other disorder meeting hospitalization criteria
	Abnormally high baseline cell counts, which could represent undiagnosed cancer or active infection and require work-up before reinjection
Relative	Low baseline platelet count (50–100 $\times 10^3/\mu L$)
	Antiplatelet therapy, including NSAIDs
	Immunotherapy or disease-modifying antirheumatic drugs (DMARDs)
	Low PRP or BMC counts on post-processing cell analysis, since injecting a suboptimal dose is less likely to be effective
	Advanced conditions, which carry a lower probability of efficacy owing to lower baseline substrate
	Bony growths such as osteophytes, as sources of pain or tear
	Significant loss of range of motion causing functional limitation, since range of motion tends not to improve with treatment
	Systemic compromise such as metabolic syndrome, organ failure, or home oxygen use, with reduced regenerative capacity
	Inability to participate in a proper rehabilitation program after the procedure

BMC, bone marrow concentrate; DMARDs, disease-modifying antirheumatic drugs; NSAIDs, nonsteroidal anti-inflammatory drugs; PRP, platelet-rich plasma

Table 8. *Phases of tissue healing and corresponding loading after orthobiologic injection.*

Stage	Phase	Timing	Loading and rehabilitation
1	Hemostasis	Immediate	Limited or protected weight-bearing to facilitate cross-link formation; gentle motion to prevent stiffness
2	Acute inflammatory	First 7–10 days	Symptoms often intensify; protected loading continues; range of motion and daily activities encouraged
3	Proliferative or repair	Weeks 3–6	Pain typically decreases; light concentric and later eccentric loading; adjunctive soft tissue mobilization and extracorporeal shockwave therapy may help; home program at ~50% intensity from weeks 4–6
4	Remodeling	Weeks 6–12	Increasing tensile strength as type 3 collagen is replaced by organized matrix; functional exercise and graded return to full activity; most restrictions lifted after 6 weeks

Individual variation of 4 to 8 weeks is common, depending on pathology, comorbidity, biomechanics, activity level, and tissue quality

Discussion

What the Recommendations Establish

The 19 recommendations make three claims and decline to make a fourth.

The first is that regenerative therapy for chronic low back pain has fair evidence at the intervertebral disc and the epidural space, and limited evidence at the facet and sacroiliac joints. No target reaches Level II, and none approaches Level I. The consensus-based recommendations are moderate throughout except at the sacroiliac joint, where they are low.

The second is that product quality is not incidental to effect but constitutive of it. Neither PRP nor BMAC is a defined product; both preparation processes whose outputs vary by device, technique, and operator. The requirement to count what is injected, and the specific dosing thresholds attached to that requirement, are the guideline's most actionable contribution.

The third is that the regulatory boundary is not negotiable. PRP and BMAC obtained with cleared devices are available; stromal vascular fraction, umbilical cord products, and exosomes are not approved for musculoskeletal use, and the risks of obtaining them elsewhere are enumerated with a high strength of recommendation on moderate evidence.

What the recommendations decline to claim is that regenerative therapy outperforms conventional intervention. Recommendation 5 argues that the harms differ, since the chondrotoxicity, genotoxicity, and neu-

rotoxicity of corticosteroid are absent from biologics, but no recommendation asserts superior efficacy, and none compares biologic against corticosteroid head-to-head. A reader looking for permission to substitute one for the other will not find it here.

Two Grading Vocabularies, and Why the High Gradings Are Not About Efficacy

As in the companion peripheral nerve stimulation guidelines, this document runs two grading scales in parallel without signaling the distinction. Six effectiveness recommendations use ASIPP Levels III and IV; thirteen use GRADE certainty descriptors from very low to high. The scales measure different constructs and are not comparable.

The consequence is more consequential here than elsewhere, because the distribution is systematically skewed. Every recommendation graded high on evidence is a statement about what exists, what is regulated, what is hazardous, or what the clinician should do procedurally. Not one is a claim that a biologic relieves pain. A reader who scans Fig. 1 and sees six recommendations at high evidence may reasonably but wrongly infer that the field rests on strong foundations. It does not. Every efficacy claim in the document sits at Level III, Level IV, or very low. This summary has annotated Table 3 accordingly, and a future revision of the source would be improved by reporting both scales for every recommendation or by separating descriptive from therapeutic statements.

The Tension Between Precision Diagnosis and the Functional Spine Unit

The most interesting internal tension in the document concerns the functional spine unit. ASIPP guidelines for facet joint and epidural interventions are built on precision diagnosis: identify the pain generator by controlled blockade, then treat that structure. The regenerative guidelines describe a paradigm in which multiple structures within a motion segment are injected together, on the biomechanical rationale that most patients with chronic low back pain have multiple pain generators.

The panel is candid about why this is possible: regenerative therapies are not bound by local coverage determinations and medical policies. That is an accurate observation about the regulatory environment, but it is not a scientific argument, and the guideline does not present it as one. The evidence grading, very low with a low recommendation, and the single supporting case series of 14 cervical patients, place the multitarget approach firmly in the category of plausible but unestablished. Practice has moved ahead of evidence, the guideline records both, and the honest position is that the absence of a coverage constraint has permitted a paradigm that the evidence has not yet been tested.

Antithrombotic Therapy: Two Reasons to Interrupt, Pointing the Same Way

A distinctive feature of this guideline, absent from every companion document, is that antithrombotic therapy is discussed as an efficacy problem as well as a bleeding problem. In conventional interventional practice the only question is whether continuing therapy raises bleeding risk enough to warrant interruption, and for low-risk procedures the answer is usually no. Here a second consideration arises: NSAIDs and antiplatelet agents degrade the injectate itself by inhibiting platelet activation, reducing alpha granule storage, and impairing aggregation, and even low-dose heparin impairs MSC growth and differentiation ex vivo.

The two considerations point the same way but on different timescales, and the efficacy interval is the longer of the two. A facet joint injection is low risk, so bleeding considerations would permit continuation of antiplatelet therapy; the efficacy consideration nonetheless calls for discontinuation of NSAIDs drugs 7 to 10 days before and 2 weeks after. Clinicians who apply the antithrombotic schedule alone will under-treat this. The evidence base is acknowledged to be limited, and the panel notes that future research may provide clearer guidance.

Implications for Practice

For the interventionalist the recommendations reduce to a sequence. Establish a definitive diagnosis of the pain generator and document failure of conservative therapy. Screen for the four absolute contraindications and weigh the nine relative ones. Obtain consent that states plainly that the therapy is not approved for spinal indications, is not covered by insurance, and carries uncertain long-term outcomes. Stop NSAIDs and immunotherapy 7 to 10 days beforehand for efficacy and apply the antithrombotic schedule for the procedural risk category. Prepare the injectate with a large bore draw and double centrifugation, and measure it: final volume, platelet count, white and red cell counts, and concentration factor. Target roughly 10 billion platelets cumulatively across the treated structures. Inject under fluoroscopic or ultrasound guidance, with intravenous

antibiotics for intradiscal and intraosseous work. Warn the patient that symptoms usually worsen for 7 to 10 days. Enroll the patient in structured rehabilitation and review at 3 months. Record the outcome in a registry.

For the patient, the accurate summary is more restrained than the field's marketing conveys. The evidence supporting benefit is fair at best and limited at the peripheral joints. Published studies of single-injection biologics for chronic pathology demonstrate primarily short-term relief. The treatment is expensive, is paid out of pocket, and is not approved for this indication. Against that, the procedure is among the safer orthopedic interventions, the injectate is autologous, and the tissue toxicities associated with repeated corticosteroid exposure are absent. That is a defensible basis for an informed patient to proceed, and an indefensible basis for promotional claims of regeneration or cure.

Research Priorities

The guideline states its own principal limitation as the scarcity of high-quality studies, with much evidence derived from small or heterogeneous trials, and identifies where effort should go.

First, and most tractably, the field needs standardized reporting of the injectate. Because preparation determines the product, a trial that does not report final volume, platelet count, cell counts, and concentration factor cannot be interpreted or replicated. Adopting Recommendation 8 at a minimum as a reporting standard would cost nothing and would immediately improve the comparability of the literature.

Second, dose-response requires direct study. The 10 billion platelet target is extrapolated from knee intraarticular work, and the one spinal signal, favoring concentrations above ten times baseline over those below five times, is suggestive rather than definitive. Randomized comparison of defined doses at a single spinal target would settle it.

Third, the functional spine unit paradigm should be tested against single-structure therapy in a randomized trial. It is currently supported by one uncontrolled case series of 14 patients in a different spinal region. Fourth, biologic should be compared against corticosteroid directly, with long-term structural as well as symptomatic endpoints, since the comparative-harm argument of Recommendation 5 is reasoned rather than demonstrated. Fifth, the interaction between antithrombotic therapy and injectate efficacy needs quantification, so that the 7- to 10-day interval rests on measurement rather than inference. Sixth, and underlying all of these, large-scale randomized controlled trials are required to determine whether orthobiologic therapies provide consistent, durable results for low back pain and to identify the conditions under which they are most effective (26,59-64).

Limitations

First, and as the guideline states, the primary limitation is the scarcity of high-quality studies, with much of the available evidence derived from small or heterogeneous trials. No anatomical target reaches Level II evidence.

Second, heterogeneity is not merely statistical but definitional. Variation in the extent and duration of pathology, in the biologic products used, in procedural technique, and in outcome measures makes it difficult to draw firm conclusions, and the lack of standardization in methodology and analysis hinders reproduction of study models. Clinicians continue to experiment with new combinations, further increasing heterogeneity.

Third, the predictability of structural repair remains inconsistent across studies, even where symptomatic benefit is reported. Published studies of single-injection biologics for chronic pathology demonstrate primarily short-term relief.

Fourth, the guideline uses two grading vocabularies without signaling the distinction, with the effect described in Section 4.2.

Fifth, unanimity was achieved on all 19 recommendations, which is unusual in guideline development, though the panel records that disagreements arose on some statements before the final vote. The panel was convened by a professional society whose members perform these procedures, in a field that is entirely out-of-pocket and therefore directly revenue-generating for the practitioner. The conflict procedures are documented and the guidelines were developed without industry support, and the document is notably candid about commercial pressures, including its instruction to educate rather than sell. Readers should nonetheless weigh the structural incentive.

Sixth, the functional spine unit paradigm is described and its clinical adoption noted, while the evidence supporting it is graded very low. Practice and evidence are not aligned here.

Seventh, this article is a summary. Individual study appraisals, the full evidence tables, the complete regulatory analysis, and the detailed office-setup and rehabilitation guidance are not reproduced. Where

a clinical decision turns on the details of a particular study, the primary guideline document should be consulted (1).

Conclusion

PRP and MSCs are used autologously to support and enhance healing, and their functional strengths and limitations continue to be investigated. The 2025 ASIPP guidelines summarized here provide a graded framework for their application in chronic low back pain, developed by a 35-member panel with 33 participating in formal consensus and all 19 recommendations achieving unanimous agreement.

The evidence gradient is orderly. Lumbar intradiscal injection of PRP and of bone marrow aspirate concentrate, and lumbar epidural PRP injection, each rest on Level III, fair evidence with a moderate consensus-based recommendation. Facet joint injection of PRP or MSCs rests on Level IV, limited evidence with a moderate recommendation, and sacroiliac joint PRP on Level IV evidence with a low recommendation. The multitarget functional spine unit approach rests on very low evidence. Treatment is indicated only after definitive diagnosis and failure of conservative therapy, and requires adherence to Food and Drug Administration regulation, quantitative verification of the injectate, structured rehabilitation, and consent that states the experimental nature and out-of-pocket cost of the treatment plainly.

The document's principal strength is its refusal to overstate. A panel of practitioners in a cash-pay field graded every one of its own efficacy claims at Level III or below, recorded that the multitarget paradigm its members increasingly use has no significant supporting evidence, and found it necessary to instruct colleagues to educate rather than sell. Its principal contribution to practice is the insistence that the injectate be measured, since a therapy whose active ingredient varies tenfold between clinics cannot generate an interpretable literature. Continued clinical success will depend on standardizing use, achieving consistent outcomes, and demonstrating reductions in overall health care cost, which in turn depends on the publication of high-quality studies that make biologic therapy predictable.

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All authors contributed to the conception of the summary, the extraction and verification of the recommendations and supporting evidence, drafting and critical revision of the article, and approval of the final version.

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64. Shapiro SA, Master Z, Arthurs JR, Mautner K. Tiered approach to considering orthobiologics for patients with musculoskeletal conditions. *Br J Sports Med* 2023; 57:179-180. Appendix Table 1. Sources of risk of bias and Cochrane Review collaboration. Bias Domain Source of Bias Possible Answers Selection (1) Was the method of randomization adequate? A random (unpredictable) assign.