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Medical Benefit		Effective Date: 10/01/15	Next Review Date: 07/21
Preauthorization	No	Review Dates: 07/15, 07/16, 07/17, 07/18, 05/20, 07/20	

This protocol considers this test or procedure investigational. If the physician feels this service is medically necessary, preauthorization is recommended.

The following protocol contains medical necessity criteria that apply for this service. The criteria are also applicable to services provided in the local Medicare Advantage operating area for those members, unless separate Medicare Advantage criteria are indicated. If the criteria are not met, reimbursement will be denied and the patient cannot be billed. Please note that payment for covered services is subject to eligibility and the limitations noted in the patient's contract at the time the services are rendered.

RELATED PROTOCOLS

Autografts and Allografts in the Treatment of Focal Articular Cartilage Lesions

Autologous Platelet-Derived Growth Factors for Wound Healing and Other Non-Orthopedic Conditions

Intra-articular Hyaluronan Injections for Osteoarthritis

Orthopedic Applications of Stem Cell Therapy (Including Allograft and Bone Substitute Products Used With Autologous Bone Marrow)

Prolotherapy

Populations	Interventions	Comparators	Outcomes
Individuals: • With tendinopathy	Interventions of interest are: • Platelet-rich plasma injections	Comparators of interest are: • Nonpharmacologic therapy (e.g., exercise, physical therapy) • Analgesics • Anti-inflammatory agents	Relevant outcomes include: • Symptoms • Functional outcomes • Health status measures • Quality of life • Treatment-related morbidity
Individuals: • With non-tendon soft tissue injury or inflammation (e.g., plantar fasciitis)	Interventions of interest are: • Platelet-rich plasma injections	Comparators of interest are: • Nonpharmacologic therapy (e.g., exercise, physical therapy) • Analgesics • Anti-inflammatory agents	Relevant outcomes include: • Symptoms • Functional outcomes • Health status measures • Quality of life • Treatment-related morbidity
Individuals: • With osteochondral lesions	Interventions of interest are: • Platelet-rich plasma injections	Comparators of interest are: • Nonpharmacologic therapy • Analgesics • Anti-inflammatory agents • Surgery	Relevant outcomes include: • Symptoms • Functional outcomes • Health status measures • Quality of life • Treatment-related morbidity

Populations	Interventions	Comparators	Outcomes
Individuals: <ul style="list-style-type: none"> • With knee or hip osteoarthritis 	Interventions of interest are: <ul style="list-style-type: none"> • Platelet-rich plasma injections 	Comparators of interest are: <ul style="list-style-type: none"> • Exercise • Weight loss (if appropriate) • Analgesics • Anti-inflammatory agents • Surgery 	Relevant outcomes include: <ul style="list-style-type: none"> • Symptoms • Functional outcomes • Health status measures • Quality of life • Treatment-related morbidity
Individuals: <ul style="list-style-type: none"> • With anterior cruciate ligament reconstruction 	Interventions of interest are: <ul style="list-style-type: none"> • Platelet-rich plasma injections plus orthopedic surgery 	Comparators of interest are: <ul style="list-style-type: none"> • Orthopedic surgery alone 	Relevant outcomes include: <ul style="list-style-type: none"> • Symptoms • Functional outcomes • Health status measures • Quality of life • Morbid events • Resource utilization • Treatment-related morbidity
Individuals: <ul style="list-style-type: none"> • With hip fracture 	Interventions of interest are: <ul style="list-style-type: none"> • Platelet-rich plasma injections plus orthopedic surgery 	Comparators of interest are: <ul style="list-style-type: none"> • Orthopedic surgery alone 	Relevant outcomes include: <ul style="list-style-type: none"> • Symptoms • Functional outcomes • Health status measures • Quality of life • Morbid events • Resource utilization • Treatment-related morbidity
Individuals: <ul style="list-style-type: none"> • With long bone nonunion 	Interventions of interest are: <ul style="list-style-type: none"> • Platelet-rich plasma injections plus orthopedic surgery 	Comparators of interest are: <ul style="list-style-type: none"> • Recombinant human bone morphogenetic protein-7 plus orthopedic surgery 	Relevant outcomes include: <ul style="list-style-type: none"> • Symptoms • Functional outcomes • Health status measures • Quality of life • Morbid events • Resource utilization • Treatment-related morbidity
Individuals: <ul style="list-style-type: none"> • With rotator cuff repair 	Interventions of interest are: <ul style="list-style-type: none"> • Platelet-rich plasma injections plus orthopedic surgery 	Comparators of interest are: <ul style="list-style-type: none"> • Orthopedic surgery alone 	Relevant outcomes include: <ul style="list-style-type: none"> • Symptoms • Functional outcomes • Health status measures • Quality of life • Morbid events • Resource utilization • Treatment-related morbidity
Individuals: <ul style="list-style-type: none"> • With spinal fusion 	Interventions of interest are: <ul style="list-style-type: none"> • Platelet-rich plasma injections plus orthopedic surgery 	Comparators of interest are: <ul style="list-style-type: none"> • Orthopedic surgery alone 	Relevant outcomes include: <ul style="list-style-type: none"> • Symptoms • Functional outcomes • Health status measures • Quality of life • Morbid events • Resource utilization • Treatment-related morbidity

Populations	Interventions	Comparators	Outcomes
Individuals: <ul style="list-style-type: none"> • With subacromial decompression surgery 	Interventions of interest are: <ul style="list-style-type: none"> • Platelet-rich plasma injections plus orthopedic surgery 	Comparators of interest are: <ul style="list-style-type: none"> • Orthopedic surgery alone 	Relevant outcomes include: <ul style="list-style-type: none"> • Symptoms • Functional outcomes • Health status measures • Quality of life • Morbid events • Resource utilization • Treatment-related morbidity
Individuals: <ul style="list-style-type: none"> • With total knee arthroplasty 	Interventions of interest are: <ul style="list-style-type: none"> • Platelet-rich plasma injections plus orthopedic surgery 	Comparators of interest are: <ul style="list-style-type: none"> • Orthopedic surgery alone 	Relevant outcomes include: <ul style="list-style-type: none"> • Symptoms • Functional outcomes • Health status measures • Quality of life • Morbid events • Resource utilization • Treatment-related morbidity

DESCRIPTION

The use of platelet-rich plasma has been proposed as a treatment for various musculoskeletal conditions and as an adjunctive procedure in orthopedic surgeries. The potential benefit of platelet-rich plasma has received considerable interest due to the appeal of a simple, safe, low-cost, and minimally invasive method of applying growth factors.

SUMMARY OF EVIDENCE

PRIMARY TREATMENT FOR TENDINOPATHIES

For individuals with tendinopathy who receive platelet-rich plasma injections, the evidence includes multiple randomized controlled trials (RCTs) and systematic reviews with meta-analyses. Relevant outcomes are symptoms, functional outcomes, health status measures, quality of life, and treatment-related morbidity. Findings from meta-analyses of RCTs have been mixed and have generally found that platelet-rich plasma did not have a statistically and/or clinically significant impact on symptoms (i.e., pain) or functional outcomes. Findings from subsequently published RCTs have also been mixed. In RCTs that have found significantly improved pain outcomes for platelet-rich plasma injections, important relevancy gaps and study conduct limitations preclude reaching strong conclusions based on their findings. The evidence is insufficient to determine the effects of the technology on health outcomes.

PRIMARY TREATMENT FOR NON-TENDON SOFT TISSUE INJURY OR INFLAMMATION

For individuals with non-tendon soft tissue injury or inflammation (e.g., plantar fasciitis) who receive platelet-rich plasma injections, the evidence includes six small RCTs, multiple prospective observational studies, and a systematic review. Relevant outcomes are symptoms, functional outcomes, health status measures, quality of life, and treatment-related morbidity. The systematic review, which identified three RCTs on platelet-rich plasma for plantar fasciitis, did not pool study findings. Results among the six RCTs were inconsistent. The largest RCT showed that treatment using platelet-rich plasma compared with corticosteroid injection resulted in statistically significant improvement in pain and disability, but not quality of life. Larger RCTs are still needed to address important uncertainties in efficacy and safety. The evidence is insufficient to determine the effects of the technology on health outcomes.

PRIMARY TREATMENT FOR OSTEOCHONDRAL LESIONS

For individuals with osteochondral lesions who receive platelet-rich plasma injections, the evidence includes an open-labeled quasi-randomized study. Relevant outcomes are symptoms, functional outcomes, health status measures, quality of life, and treatment-related morbidity. The quasi-randomized study found a statistically significant greater impact on outcomes in the platelet-rich plasma group than in the hyaluronic acid group. Limitations of the evidence base include lack of adequately randomized studies, lack of blinding, lack of sham controls, and comparison only to an intervention of uncertain efficacy. The evidence is insufficient to determine the effects of the technology on health outcomes.

PRIMARY TREATMENT FOR KNEE OR HIP OSTEOARTHRITIS

For individuals with knee or hip osteoarthritis who receive platelet-rich plasma injections, the evidence includes multiple RCTs and systematic reviews. Relevant outcomes are symptoms, functional outcomes, health status measures, quality of life, and treatment-related morbidity. Most trials have compared platelet-rich plasma with hyaluronic acid for knee osteoarthritis. Systematic reviews have generally found that platelet-rich plasma was more effective than placebo or hyaluronic acid in reducing pain and improving function. However, systematic review authors have noted that their findings should be interpreted with caution due to important limitations including significant residual statistical heterogeneity, questionable clinical significance, and high risk of bias in study conduct. RCTs with follow-up durations of at least 12 months published subsequent to the systematic reviews found statistically significantly greater 12 month reductions in the Western Ontario and McMaster Universities Osteoarthritis Index scores, but these findings were also limited by important study conduct flaws including potential inadequate control for selection bias and unclear blinding. Also, benefits were not maintained at five years. Also, using hyaluronic acid as a comparator is questionable, because the evidence demonstrating the benefit of hyaluronic acid treatment for osteoarthritis is not robust. The single RCT evaluating hip osteoarthritis reported statistically significant reductions in visual analog scale scores for pain, with no difference in functional scores. Additional studies comparing platelet-rich plasma with placebo and with alternatives other than hyaluronic acid are needed to determine the efficacy of platelet-rich plasma for knee and hip osteoarthritis. Studies are also needed to determine the optimal protocol for delivering platelet-rich plasma. The evidence is insufficient to determine the effects of the technology on health outcomes.

ADJUNCT TO SURGERY

For individuals with anterior cruciate ligament reconstruction who receive platelet-rich plasma injections plus orthopedic surgery, the evidence includes two systematic reviews of multiple RCTs and prospective studies. Relevant outcomes are symptoms, functional outcomes, health status measures, quality of life, morbid events, resource utilization, and treatment-related morbidity. Only one of the two systematic reviews conducted a meta-analysis; it showed that adjunctive platelet-rich plasma treatment did not result in a significant effect on International Knee Documentation Committee scores, a patient-reported, knee-specific outcome measure that assesses pain and functional activity. Individual trials have shown mixed results. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals with hip fracture who receive platelet-rich plasma injections plus orthopedic surgery, the evidence includes an open-labeled RCT. Relevant outcomes are symptoms, functional outcomes, health status measures, quality of life, morbid events, resource utilization, and treatment-related morbidity. The single open-labeled RCT failed to show a statistically significant reduction in the need for surgical revision with the addition of platelet-rich plasma treatment. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals with long bone nonunion who receive platelet-rich plasma injections plus orthopedic surgery, the evidence includes three RCTs. Relevant outcomes are symptoms, functional outcomes, health status measures, quality of life, morbid events, resource utilization, and treatment-related morbidity. One trial with a substantial

risk of bias failed to show significant differences in patient-reported or clinician-assessed functional outcome scores between those who received platelet-rich plasma plus allogenic bone graft and those who received only allogenic bone graft. While the trial showed a statistically significant increase in the proportion of bones that healed in patients receiving platelet-rich plasma in a modified intention-to-treat analysis, the results did not differ in the intention-to-treat analysis. The second RCT, which compared platelet-rich plasma with recombinant human bone morphogenetic protein-7, also failed to show any clinical or radiologic benefits of platelet-rich plasma over morphogenetic protein. The third RCT reported no difference in the number of unions or time to union in patients receiving platelet-rich plasma injections vs. no treatment. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals with rotator cuff repair who receive platelet-rich plasma injections plus orthopedic surgery, the evidence includes multiple RCTs and systematic reviews. Relevant outcomes are symptoms, functional outcomes, health status measures, quality of life, morbid events, resource utilization, and treatment-related morbidity. Although systematic reviews consistently found significant reductions in pain with platelet-rich plasma at 12 months, important study conduct and relevance weaknesses limit interpretation of these findings. Additionally, the pain reductions with platelet-rich plasma were not maintained in longer-term studies. Further, the systematic reviews and meta-analyses failed to show a statistically and/or clinically significant impact on other outcomes. Findings of subsequently published small, single-center RCTs were consistent with the systematic reviews. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals with spinal fusion who receive platelet-rich plasma injections plus orthopedic surgery, the evidence includes two controlled prospective studies. Relevant outcomes are symptoms, functional outcomes, health status measures, quality of life, morbid events, resource utilization, and treatment-related morbidity. The two studies failed to show any statistically significant differences in fusion rates between the platelet-rich plasma arm and the control arm. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals undergoing spinal fusion who receive platelet-rich plasma injections, the evidence includes a single small RCT and a few observational studies. Relevant outcomes include symptoms, functional outcomes, health status measures, quality of life, morbid events, resource utilization, and treatment-related morbidity. Studies have generally failed to show a statistically and/or clinically significant impact on symptoms (i.e., pain). The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals with subacromial decompression surgery who receive platelet-rich plasma injections plus orthopedic surgery, the evidence includes a small RCT. Relevant outcomes are symptoms, functional outcomes, health status measures, quality of life, morbid events, resource utilization, and treatment-related morbidity. A single small RCT failed to show a reduction in self-assessed or physician-assessed spinal instability scores with platelet-rich plasma injections. However, subjective pain, use of pain medications, and objective measures of range of motion showed clinically significant improvements with platelet-rich plasma. Larger trials are required to confirm these benefits. The evidence is insufficient to determine the effects of the technology on health outcomes.

For individuals with total knee arthroplasty who receive platelet-rich plasma injections plus orthopedic surgery, the evidence includes a small RCT. Relevant outcomes are symptoms, functional outcomes, health status measures, quality of life, morbid events, resource utilization, and treatment-related morbidity. The RCT showed no significant differences between the platelet-rich plasma and untreated control groups in bleeding, range of motion, swelling around the knee joint, muscle power recovery, pain, or Knee Society Score and Knee Injury and Osteoarthritis Outcome Score. The evidence is insufficient to determine the effects of the technology on health outcomes.

POLICY

Use of platelet-rich plasma is considered **investigational** for all orthopedic indications. This includes, but is not limited to, use in the following situations:

- Primary use (injection) for the following conditions:
 - Achilles tendinopathy
 - Lateral epicondylitis
 - Plantar fasciitis
 - Osteochondral lesions
 - Osteoarthritis
- Adjunctive use in the following surgical procedures:
 - Anterior cruciate ligament reconstruction
 - Hip fracture
 - Long-bone nonunion
 - Patellar tendon repair
 - Rotator cuff repair
 - Spinal fusion
 - Subacromial decompression surgery
 - Total knee arthroplasty

BACKGROUND

A variety of growth factors have been found to play a role in wound healing, including platelet-derived growth factors, epidermal growth factor, fibroblast growth factors, transforming growth factors, and insulin-like growth factors. Autologous platelets are a rich source of platelet-derived growth factor, transforming growth factors that function as a mitogen for fibroblasts, smooth muscle cells, osteoblasts, and vascular endothelial growth factors. Recombinant platelet-derived growth factor has also been extensively investigated for clinical use in wound healing (see the Autologous Platelet-Derived Growth Factors for Wound Healing and Other Non-Orthopedic Conditions Protocol).

Autologous platelet concentrate suspended in plasma, also known as platelet-rich plasma, can be prepared from samples of centrifuged autologous blood. Exposure to a solution of thrombin and calcium chloride degranulates platelets, releasing the various growth factors. The polymerization of fibrin from fibrinogen creates a platelet gel, which can then be used as an adjunct to surgery with the intent of promoting hemostasis and accelerating healing. In the operating room setting, platelet-rich plasma has been investigated as an adjunct to various periodontal, reconstructive, and orthopedic procedures. For example, bone morphogenetic proteins are a type of transforming growth factors, and thus platelet-rich plasma has been used in conjunction with bone-replacement grafting (using either autologous grafts or bovine-derived xenograft) in periodontal and maxillofacial surgeries. Alternatively, platelet-rich plasma may be injected directly into various tissues. Platelet-rich plasma injections have been proposed as a primary treatment of miscellaneous conditions, such as epicondylitis, plantar fasciitis, and Dupuytren contracture.

Injection of platelet-rich plasma for tendon and ligament pain is theoretically related to prolotherapy (see the Prolotherapy Protocol). However, prolotherapy differs in that it involves the injection of chemical irritants intended to stimulate inflammatory responses and induce the release of endogenous growth factors.

Platelet-rich plasma is distinguished from fibrin glues or sealants, which have been used as a surgical adjunct to promote local hemostasis at incision sites. Fibrin glue is created from platelet-poor plasma and consists primarily of fibrinogen. Commercial fibrin glues are created from pooled homologous human donors; Tisseel® (Baxter) and Hemaseel® (Haemacure Corp) are examples of commercially available fibrin sealants. Autologous fibrin sealants can be created from platelet-poor plasma. This evidence review does not address the use of fibrin sealants.

REGULATORY STATUS

The U.S. Food and Drug Administration (FDA) regulates human cells and tissues intended for implantation, transplantation, or infusion through the Center for Biologics Evaluation and Research, under Code of Federal Regulation, title 21, parts 1,270 and 1,271. Blood products such as platelet-rich plasma are included in these regulations. Under these regulations, certain products including blood products such as platelet-rich plasma are exempt and therefore do not follow the traditional FDA regulatory pathway. To date, the FDA has not attempted to regulate activated platelet-rich plasma.

A number of platelet-rich plasma preparation systems are available, many of which were cleared for marketing by the FDA through the 510(k) process for producing platelet-rich preparations intended to be mixed with bone graft materials to enhance the bone grafting properties in orthopedic practices. The use of platelet-rich plasma outside of this setting (e.g., an office injection) would be considered off-label. The Aurix System™ (previously called AutoloGel™; Cytomedix) and SafeBlood® (SafeBlood Technologies) are two related but distinct autologous blood-derived preparations that can be used at the bedside for immediate application. Both AutoloGel™ and SafeBlood® have been specifically marketed for wound healing. Other devices may be used during surgery (e.g., Medtronic Electromedics, Elmd-500 Autotransfusion system, the Plasma Saver device, the SmartPReP [Harvest Technologies] device). The Magellan™ Autologous Platelet Separator System (Medtronic Sofamor Danek) includes a disposable kit for use with the Magellan™ Autologous Platelet Separator portable tabletop centrifuge. GPS®II (BioMet Biologics), a gravitational platelet separation system, was cleared for marketing by the FDA through the 510(k) process for use as disposable separation tube for centrifugation and a dual cannula tip to mix the platelets and thrombin at the surgical site. Filtration or plasmapheresis may also be used to produce platelet-rich concentrates. The use of different devices and procedures can lead to variable concentrations of activated platelets and associated proteins, increasing variability between studies of clinical efficacy.

Services that are the subject of a clinical trial do not meet our Technology Assessment and Medically Necessary Services Protocol criteria and are considered investigational. *For explanation of experimental and investigational, please refer to the Technology Assessment and Medically Necessary Services Protocol.*

It is expected that only appropriate and medically necessary services will be rendered. We reserve the right to conduct prepayment and postpayment reviews to assess the medical appropriateness of the above-referenced procedures. **Some of this protocol may not pertain to the patients you provide care to, as it may relate to products that are not available in your geographic area.**

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We are not responsible for the continuing viability of web site addresses that may be listed in any references below.

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