Prior Authorization Review Panel
MCO Policy Submission

A separate copy of this form must accompany each policy submitted for review.
Policies submitted without this form will not be considered for review.

Plan: AmeriHealth Caritas Pennsylvania & Keystone First	Submission Date: 3/1/2025
Policy Number: ccp.1217	Effective Date: 4/2016 Revision Date: 2/2025
Policy Name: Prolotherapy	

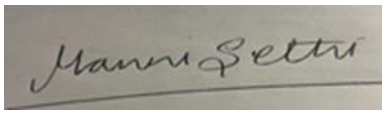
Type of Submission:

☐ New Policy	☒ Prior Authorization Policy
☒ Revised Policy*	☐ Base Policy
☐ Annual Review- no revisions	☐ Experimental/Investigational Policy
	☐ Statewide PDL
	☐ Other:

*All revisions to the policy must be highlighted using track changes throughout the document.

Please provide any clarifying information for the policy below:

Please see tracked changes below.

Name of Authorized Individual (Please type or print): Manni Sethi, MD, MBA, CHCQM	Signature of Authorized Individual: 

Keystone First
Family of Health Plans

Prolotherapy

Clinical Policy ID: CCP.1217

Recent review date: 2/2025

Next review date: 6/2026

Policy contains: Musculoskeletal pain; prolotherapy; regenerative injection therapy.

Keystone First has developed clinical policies to assist with making coverage determinations. Keystone First's clinical policies are based on guidelines from established industry sources, such as the Centers for Medicare & Medicaid Services (CMS), state regulatory agencies, the American Medical Association (AMA), medical specialty professional societies, and peer-reviewed professional literature. These clinical policies along with other sources, such as plan benefits and state and federal laws and regulatory requirements, including any state- or plan-specific definition of "medically necessary," and the specific facts of the particular situation are considered by Keystone First, on a case by case basis, when making coverage determinations. In the event of conflict between this clinical policy and plan benefits and/or state or federal laws and/or regulatory requirements, the plan benefits and/or state and federal laws and/or regulatory requirements shall control. Keystone First's clinical policies are for informational purposes only and not intended as medical advice or to direct treatment. Physicians and other health care providers are solely responsible for the treatment decisions for their patients. Keystone First's clinical policies are reflective of evidence-based medicine at the time of review. As medical science evolves, Keystone First will update its clinical policies as necessary. Keystone First's clinical policies are not guarantees of payment.

Coverage policy

Prolotherapy for musculoskeletal conditions is investigational/not clinically proven, and therefore, not medically necessary.

Limitations

No limitations were identified during the writing of this policy.

Alternative covered services

Surgical treatment.

Non-surgical approaches, including anti-inflammatory medications; physical or occupational therapy; immobilization; using heat or cold; reducing workload and increasing rest, relaxation, and biofeedback techniques; strengthening and conditioning exercises; stretching exercises; and therapeutic massage.

Background

Musculoskeletal conditions are among the most disabling and costly conditions suffered by Americans of all ages. Causes of musculoskeletal pain include the wear and tear of daily activities or trauma to an area, postural strain, repetitive movements, overuse, and prolonged immobilization. Changes in posture or poor body mechanics may bring about spinal alignment problems and muscle shortening, causing other muscles to be misused and become painful. Trauma, back pain, and arthritis are the most common musculoskeletal conditions in the United States (Orthopaedic Research Society, 2022).

Musculoskeletal pain is best treated by addressing its cause. Non-surgical approaches include anti-inflammatory medications; physical or occupational therapy; immobilization; using heat or cold; reducing workload and increasing rest, relaxation, and biofeedback techniques; strengthening and conditioning exercises; stretching

exercises; and therapeutic massage. Integrative therapies such as chiropractic care, acupuncture, or acupressure may be used (National Academies of Sciences, Engineering, and Medicine, 2020).

When conservative treatments fail to alleviate the pain, injection therapies in or around the painful sites may be used. Prolotherapy, also known as regenerative injection therapy, involves injecting an irritant into an injured joint, ligament, or tendon to relieve pain (American Osteopathic Association of Prolotherapy Regenerative Medicine, 2020). Used since the 1930s, prolotherapy (termed from proliferant therapy) has emerged as a treatment option for chronic musculoskeletal injuries. Its mechanism of action has not been clearly established but is hypothesized to stimulate growth factors in the inflammatory healing cascade and promote growth of new ligament or tendon fibers by producing new collagen tissue.

Injection agents may include ingredients such as dextrose, morrhuate sodium, saline, sarapin, procaine, or lidocaine. In recent years, platelet-rich plasma and autologous adult stem cell sources typically taken from bone marrow or adipose (fat) tissue have emerged. Prolotherapy techniques and injected solutions vary by condition, clinical severity, and practitioner preferences and commonly consist of several injection sessions delivered every three to six weeks over several months (American Osteopathic Association of Prolotherapy Regenerative Medicine, 2020).

The U.S. Food and Drug Administration has approved the most commonly used agents, such as dextrose and lidocaine, for injection, but these substances are not specifically approved for prolotherapy for joint and ligamentous injections, making such use off-label. Morrhuate sodium is not currently listed as an approved sclerosing agent (U.S. Food and Drug Administration, 2025).

Findings

Guidelines

Few professional guidelines address prolotherapy. A guideline on low back pain from the Institute for Health Economics determined that prolotherapy was not recommended as a sole treatment, but could be used as an adjunctive therapy. The most commonly reported adverse events were temporary increases in back pain and stiffness following injections, and some patients had severe headaches suggestive of lumbar puncture, but no serious or permanent adverse events were reported (Institute for Health Economics, 2017). The North American Spine Society (2020) did not issue a recommendation for or against prolotherapy for treatment of low back pain.

The American College of Occupational and Environmental Medicine did not recommend for or against prolotherapy for treatment of lateral epicondylitis (Hegmann, 2013). The American College of Rheumatology/Arthritis Foundation issued a conditional recommendation against using prolotherapy in patients with knee or hip osteoarthritis, but issued no recommendation for or against for patients with hand osteoarthritis (Kolasinski, 2020)

Evidence review

The best available evidence consists of systematic reviews and meta-analyses of randomized controlled trials. The most commonly studied indications for prolotherapy were knee osteoarthritis and tendinopathies such as lateral epicondylitis, rotator cuff tendinopathies, plantar fasciitis, Osgood-Schlatter disease, and Achilles tendinosis. Hypertonic dextrose solution was the most commonly applied proliferant.

The results suggest hypertonic dextrose prolotherapy is safe with no serious adverse effects reported. It may be an efficacious alternative to other non-invasive treatments for the above indications, when the expected benefits in pain control or function have not been achieved by conservative care. It should not be used with other irritants, and it typically requires multiple injections and multi-session regimens to maximize its effectiveness. However, the quality of the evidence is low with moderate-to-high risk of bias, and evidence of comparative effectiveness

to other non-invasive or injectable treatments is conflicting. All authors recommended studies of higher quality to confirm these findings and validate long-term efficacy.

Osteoarthritis

A systematic review of 14 randomized controlled trials (n = 936) examined the safety and effectiveness of hypertonic dextrose prolotherapy for treating osteoarthritis: 11 studies were of the knee, two of the hand, and one of the hip. Prolotherapy was compared to saline (five studies), exercise (three), intra-articular injections of hyaluronic acid (three), platelet-rich plasma (two), ozone prolotherapy (one), erythropoietin (one), pulsed radiofrequency (one), and local corticosteroid (one). All studies were classified as a high risk of bias due to insufficient blinding of participants and investigators and inadequate documentation of missing data and drop-outs (Waluyo, 2023).

For pain reduction, ten of 14 studies reported that prolotherapy was more effective than the other interventions. In 12 studies, prolotherapy was at least as effective in improving function outcomes as other interventions. In five studies, prolotherapy significantly improved pain intensity and function (Western and Ontario McMaster Osteoarthritis Index scores) compared with saline, but injections with a biological agent as the active substance were superior to prolotherapy. Although prolotherapy using hypertonic dextrose confers potential benefits for pain and functional outcome in osteoarthritis, its therapeutic benefit could not be quantified due to variation in study protocols and intervention choices and a high risk of bias across studies. Differences in the injection concentration, time intervals of injection, sites of injection, and type and severity of osteoarthritis are factors in achieving pain relief and functional recovery (Waluyo, 2023).

For patients with knee osteoarthritis who are unsuitable for surgery or have mild-to-moderate disease severity, non-surgical interventions are considered. A network meta-analysis of 71 studies (n = 5,414) demonstrated the superiority of exercise combined with pharmacological treatment over monotherapeutic approaches. Exercise therapy (primarily resistance training programs) combined with intraarticular injections of mesenchymal stem cells, dextrose, platelet rich plasma, platelet rich in growth factor, or botulinum toxin A were the most efficacious for pain reduction and physical function restoration with moderate-to-high certainty (Cheng, 2024).

Tendinopathies

As a treatment for sports-related tendinopathies, lateral epicondylitis, rotator cuff, and plantar fasciitis tendinopathies were the most studied conditions (17 studies), while Achilles tendinosis and Osgood-Schlatter disease were the least studied (three studies). Nineteen of 20 studies used dextrose solutions. In 85% of studies, prolotherapy was effective in treating tendinopathy. Prolotherapy was superior to control in all outcomes in 25% of the studies, comparable or superior to control in specific outcomes (e.g., pain and function scores) in 60% of the studies, and inferior to control in 15% of the studies. While studies appear to be of higher quality, high heterogeneity between studies persists particularly with respect to dextrose solution, control groups (e.g., hyaluronic acid, steroids, or saline), and injection technique limit the certainty of the findings (Capotosto, 2024).

Goh (2021) analyzed the effectiveness of prolotherapy in 87 randomized controlled trials (n = 5,859) involving upper limb (74%), lower limb (23%), and truncal/hip (3%) chronic soft tissue injuries. Study quality was mixed, ranging from low to moderate. At all time points, prolotherapy had no statistically significant pain benefits over other therapies. Compared to placebo, the effect size for prolotherapy was marginally better for elbow injuries in the medium term (four to eight months) and for shoulder injuries in the short term (less than four months) and long term (more than eight months).

A systematic review of ten studies (three randomized) of prolotherapy used in participants with chronic patellar tendinopathy showed a decrease in pain with no serious adverse events, leading authors to conclude that prolotherapy may be an effective treatment option to treat pain and improve function (Morath, 2020).

Other conditions

A systematic review/meta-analysis of three randomized controlled trials of persons with temporomandibular joint syndrome found a significant reduction in maximum mouth opening after dextrose prolotherapy (*P* = .0008). Prolotherapy was also found to reduce pain significantly compared with placebo (*P* = .0007) (Nagori, 2018). Zhou (2024) reached similar findings based on the results of eight randomized controlled trials, along with low-quality evidence suggesting minimal difference in outcomes between dextrose prolotherapy, autologous blood injection, and botulinum toxin injection.

In 2022, we updated the references and made no policy changes.

In 2023, we updated the references and made no policy changes.

In 2024, we updated the references and made no policy changes.

In 2025, we updated the references and deleted several older references, resulting in no policy changes.

References

On January 7, 2025, we searched PubMed and the databases of the Cochrane Library, the U.K. National Health Services Centre for Reviews and Dissemination, the Agency for Healthcare Research and Quality, and the Centers for Medicare & Medicaid Services. Search terms were ("prolotherapy" (MeSH), "pain management" (MeSH), "musculoskeletal pain," "prolotherapy," and "regenerative injection therapy." We included the best available evidence according to established evidence hierarchies (typically systematic reviews, meta-analyses, and full economic analyses, where available) and professional guidelines based on such evidence and clinical expertise.

American Osteopathic Association of Prolotherapy Regenerative Medicine. What is prolotherapy? http://prolotherapycollege.org/what-is-prolotherapy/. Published 2020.

Capotosto S, Nazemi AK, Komatsu DE, Penna J. Prolotherapy in the treatment of sports-related tendinopathies: A systematic review of randomized controlled trials. *Orthop J Sports Med*. 2024;12(11):23259671241275087. Doi: 10.1177/23259671241275087.

Cheng HY, Liang CW, Lee YH, Vitoonpong T, Liao CD, Huang SW. Effects of the combination of various pharmacological treatments and exercise on knee osteoarthritis: A systematic review and network meta-analysis. *EFORT Open Rev*. 2024;9(7):668-675. Doi: 10.1530/eor-23-0136.

Goh SL, Jaafar Z, Gan YN, et al. Efficacy of prolotherapy in comparison to other therapies for chronic soft tissue injuries: A systematic review and network meta-analysis. *PLoS One.* 2021;16(5):e0252204. Doi: 10.1371/journal.pone.0252204.

Hegmann KT, Hoffman HE, Belcourt RM, et al. ACOEM practice guidelines: Elbow disorders. *J Occup Environ Med*. 2013;55(11):1365-1374. Doi: 10.1097/JOM.0b013e3182a0d7ec.

Institute for Health Economics. Toward Optimized Practice (TOP) Low Back Pain Working Group. 2015 December. Evidence-informed primary care management of low back pain: Clinical practice guideline. Edmonton, AB. https://actt.albertadoctors.org/CPGs/Lists/CPGDocumentList/LBP-guideline.pdf. Last revised 2017.

Kolasinski SL, Neogi T, Hochberg MC, et al. 2019 American College of Rheumatology/Arthritis Foundation guideline for the management of osteoarthritis of the hand, hip, and knee. *Arthritis Rheumatol*. 2020;72(2):220-233. Doi: 10.1002/art.41142.

Morath O, Beck M, Taevmans J, Hirschmuller A. Sclerotherapy and prolotherapy for chronic patellar tendinopathies – a promising therapy with limited available evidence, a systematic review. *J Exp Orthop*. 2020;7(1):89. Doi: 10.1186/s40634-020-00303-0.

Nagori SA, Jose A, Gopalakrishnan V, Roy ID, Chattopadhyay PK, Roychoudhury A. The efficacy of dextrose prolotherapy over placebo for temporomandibular joint hypermobility: A systematic review and meta-analysis. *J Oral Rehabil*. 2018;45(12):998-1006. Doi: 10.1111/joor.12698.

National Academies of Sciences, Engineering, and Medicine; Health and Medicine Division; Board on Health Care Services; Committee on Identifying Disabling Medical Conditions Likely to Improve with Treatment. Selected health conditions and likelihood of improvement with treatment: Musculoskeletal disorders. https://www.ncbi.nlm.nih.gov/books/NBK559512/. Published April 21, 2020.

North American Spine Society. Evidence-based clinical guidelines for multidisciplinary spine care: North American Spine Society (NASS) clinical guideline for the diagnosis and treatment of low back pain. https://painmed.wpengine.com/wp-content/uploads/2020/12/LowBackPain.pdf. Published 2020.

Orthopaedic Research Society. The burden of musculoskeletal disease. https://www.ors.org/burden-of-disease/. Published 2022.

U.S. Food and Drug Administration. Orange book: Approved drug products with therapeutic equivalence evaluations. https://www.accessdata.fda.gov/scripts/cder/ob/. Current through January 2025.

Waluyo Y, Artika SR, Insani Nanda Wahyuni, Gunawan AMAK, Zainal ATF. Efficacy of prolotherapy for osteoarthritis: A systematic review. *J Rehabil Med*. 2023;55:jrm00372. Doi: 10.2340/jrm.v55.2572.

Zhou G, Hu Y, Wang S. Efficacy of dextrose prolotherapy for temporomandibular joint hypermobility: A systematic review and meta-analysis. *Cranio*. 2024:1-10. Doi: 10.1080/08869634.2024.2419845.

Policy updates

1/2016: initial review date and clinical policy effective date: 4/2016

1/2017: Policy references updated.

1/2018: Policy references updated.

1/2019: Policy references updated. Policy ID changed to CCP.1217.

2/2020: Policy references updated.

2/2021: Policy references updated.

2/2022: Policy references updated.

2/2023: Policy references updated.

2/2024: Policy references updated.

2/2025: Policy references updated.