

<b>2.01.26</b>	<b>Prolotherapy</b>		
<b>Original Policy Date:</b>	November 15, 1970	<b>Effective Date:</b>	January 1, 2022
<b>Section:</b>	2.0 Medicine	<b>Page:</b>	Page 1 of 16

## Policy Statement

Prolotherapy is considered **investigational** as a treatment of musculoskeletal pain.

**NOTE:** Refer to [Appendix A](#) to see the policy statement changes (if any) from the previous version.

## Policy Guidelines

### Coding

The following HCPCS code is specific to prolotherapy:

- **M0076:** Prolotherapy

However, providers may be using one of the following nonspecific CPT codes:

- **20550:** Injection(s); single tendon sheath, or ligament, aponeurosis (e.g., plantar "fascia")
- **20551:** Injection(s); single tendon origin/insertion
- **20552:** Injection(s); single or multiple trigger point(s), 1 or 2 muscle(s)
- **20999:** Unlisted procedure, musculoskeletal system, general
- **27096:** Injection procedure for sacroiliac joint, anesthetic/steroid, with image guidance (fluoroscopy or CT) including arthrography when performed
- **64490:** Injection(s), diagnostic or therapeutic agent, paravertebral facet (zygapophyseal) joint (or nerves innervating that joint) with image guidance (fluoroscopy or CT), cervical or thoracic; single level
- **64491:** Injection(s), diagnostic or therapeutic agent, paravertebral facet (zygapophyseal) joint (or nerves innervating that joint) with image guidance (fluoroscopy or CT), cervical or thoracic; second level (List separately in addition to code for primary procedure)
- **64492:** Injection(s), diagnostic or therapeutic agent, paravertebral facet (zygapophyseal) joint (or nerves innervating that joint) with image guidance (fluoroscopy or CT), cervical or thoracic; third and any additional level(s) (List separately in addition to code for primary procedure)
- **64493:** Injection(s), diagnostic or therapeutic agent, paravertebral facet (zygapophyseal) joint (or nerves innervating that joint) with image guidance (fluoroscopy or CT), lumbar or sacral; single level
- **64494:** Injection(s), diagnostic or therapeutic agent, paravertebral facet (zygapophyseal) joint (or nerves innervating that joint) with image guidance (fluoroscopy or CT), lumbar or sacral; second level (List separately in addition to code for primary procedure)
- **64495:** Injection(s), diagnostic or therapeutic agent, paravertebral facet (zygapophyseal) joint (or nerves innervating that joint) with image guidance (fluoroscopy or CT), lumbar or sacral; third and any additional level(s) (List separately in addition to code for primary procedure)

## Description

Prolotherapy describes a procedure intended for healing and strengthening ligaments and tendons by injecting an agent that induces inflammation and stimulates endogenous repair mechanisms. Prolotherapy may also be referred to as proliferant injection, prolo, joint sclerotherapy, regenerative injection therapy, growth factor stimulation injection, or nonsurgical tendon, ligament, and joint reconstruction.

## Related Policies

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

## Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

## Regulatory Status

Sclerosing agents have been approved by the U.S. Food and Drug Administration for use in treating spider and varicose veins. These sclerosing agents include Asclera® (polidocanol), Varithena® (an injectable polidocanol foam), Sotradecol® (sodium tetradecyl sulfate), Ethamolin® (ethanolamine oleate), and Scleromate® (sodium morrhuate). These agents are not currently approved as joint and ligamentous sclerosing agents.

## Rationale

### Background

The goal of prolotherapy is to promote tissue repair or growth by prompting the release of growth factors, such as cytokines, or by increasing the effectiveness of existing circulating growth factors. The mechanism of action is not well understood but may involve local irritation and/or cell lysis. Agents used with prolotherapy have included zinc sulfate, psyllium seed oil, combinations of dextrose, glycerin, and phenol, or dextrose alone, often combined with a local anesthetic. Polidocanol, sodium morrhuate, and vascular sclerosants have also been used to sclerose areas of high intratendinous blood flow associated with tendinopathies. Prolotherapy typically involves multiple injections per session conducted over a series of treatment sessions.

A similar approach involves the injection of autologous platelet-rich plasma, which contains a high concentration of platelet-derived growth factors. Treatment of musculoskeletal pain conditions (e.g., tendinopathies) with platelet-rich plasma is discussed in Blue Shield of California Medical Policy: Autologous Platelet-Derived Growth Factors for Wound Healing and Other Non-Orthopedic Conditions.

### Literature Review

Evidence reviews assess the clinical evidence to determine whether the use of technology improves the net health outcome. Broadly defined, health outcomes are the length of life, quality of life, and ability to function-including benefits and harms. Every clinical condition has specific outcomes that are important to patients and managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of technology, 2 domains are examined: the relevance, and quality and credibility. To be relevant, studies must represent 1 or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. Randomized controlled trials are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

Prolotherapy has been investigated as a treatment of various etiologies of musculoskeletal pain, including arthritis, degenerative disc disease, fibromyalgia, tendinitis, and plantar fasciitis. As with any therapy for pain, a placebo effect is anticipated, and thus randomized placebo-controlled trials are necessary.

### **Prolotherapy**

#### **Clinical Context and Therapy Purpose**

The purpose of prolotherapy in patients who have musculoskeletal pain, osteoarthritic pain, or tendinopathies of the upper or lower limbs is to provide a treatment option that is an alternative to or an improvement on existing therapies.

The question addressed in this evidence review is: Does the use of prolotherapy improve the net health outcome in those with musculoskeletal pain, osteoarthritic pain, or tendinopathies of the upper or lower limbs?

The following PICO was used to select literature to inform this review.

#### **Populations**

The relevant population of interest is individuals with musculoskeletal pain, osteoarthritic pain, or upper- or lower-limb tendinopathies.

#### **Interventions**

The therapy being considered is prolotherapy.

#### **Comparators**

The following therapies and practices are currently being used to treat musculoskeletal pain, osteoarthritic pain, and upper- or lower-limb tendinopathies: observation and other conservative therapies.

#### **Outcomes**

The general outcomes of interest are reductions in pain and medication use, improvements in function, and treatment-related adverse events (mostly mild but in rare instances, serious).

Varying by condition, injections are administered over a series of sessions, which can last from several weeks to months.

#### **Study Selection Criteria**

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs;
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies;

- To assess long-term outcomes and adverse effects, single-arm studies that capture longer periods of follow-up and/or larger populations were sought;
- Studies with duplicative or overlapping populations were excluded.

## Review of Evidence

### Chronic Neck and Back Pain

#### Systematic Reviews

A Cochrane review by Dagenais et al (2007) evaluated prolotherapy for chronic low back pain and concluded that "When used alone, prolotherapy is not an effective treatment for chronic low back pain."<sup>1</sup> Reviewers also concluded that, although confounded by cointerventions and heterogeneity of studies, "When combined with spinal manipulation, exercise, and other interventions, prolotherapy may improve chronic low-back pain and disability."

Another systematic review by Dagenais et al (2008) of the same 5 studies included in the Cochrane review and by 1 of the same authors concluded that despite its use for more than 50 years, there is no evidence of efficacy for prolotherapy injections alone for chronic low back pain.<sup>2</sup> The same evidence was evaluated in a systematic review conducted by Chou et al (2009) for the American Pain Society.<sup>3</sup> In this case, reviewers also concluded that prolotherapy was ineffective when used alone to manage chronic low back pain. This seems to be working fine.

#### Randomized Controlled Trials

Three randomized trials were identified that focused on the use of injections of dextrose, glycerin, and phenol as a treatment for low back pain. Yelland et al (2004) reported on a partially blinded RCT of prolotherapy injections, saline injections, and exercises for chronic low back pain in 110 subjects.<sup>4</sup> While decreases in pain and disability were noted in all study groups, there were no significant differences between treatment groups at 12 and 24 months. Therefore, the effects of prolotherapy did not significantly exceed placebo effects.

Klein et al (1993) reported on a trial that randomized 79 patients with low back pain to a series of 6 weekly injections using either saline or a proliferant solution of dextrose, glycerin, and phenol.<sup>5</sup> Thirty of the 39 patients assigned to the proliferant group achieved a 50% or greater diminution in pain compared with 21 of the 40 in the placebo group. While the incremental benefit of the treatment group was statistically significant ( $p=.04$ ), blinding of the treatment groups was not maintained because those assigned to the proliferant group experienced a clinically recognizable local inflammatory response.

Ongley et al (1987) reported on a trial of 81 patients with low back pain who were randomized to spinal manipulation plus prolotherapy or a control group that received less forceful spinal manipulation, less local anesthesia, and placebo injections of saline.<sup>6</sup> Although improved responses were reported for the treatment group, it was not possible to evaluate the contribution of prolotherapy compared with the impact of the different types of spinal manipulation.

#### Other Musculoskeletal Pain

##### Randomized Controlled Trials

A trial by Kim et al (2010) compared intra-articular prolotherapy with intra-articular corticosteroid injection for sacroiliac pain.<sup>7</sup> The double-blind, randomized study included 48 patients with sacroiliac joint pain lasting 3 months or more, confirmed by 50% or more improvement in response to the local anesthetic block. The injections were performed on a biweekly schedule (maximum of 3 injections) under fluoroscopic guidance with confirmation of the intra-articular location with an arthrogram. Pain and disability scores were assessed at baseline, 2 weeks, and monthly after completion of treatment. At 2 weeks after treatment, all patients met the primary outcome measure of 50% or more reduction in pain scores, and there was no significant difference between groups. The numeric rating scale score for pain was reduced from 6.3 to 1.4

in the prolotherapy group and from 6.7 to 1.9 in the steroid group. The Oswestry Disability Index score decreased from 33.9 to 11.1 in the prolotherapy group and from 35.7 to 15.5 in the steroid group. Kaplan-Meier survival analysis showed a significantly greater percentage of patients with sustained relief following prolotherapy. At 6 months after treatment, 63.6% of patients in the prolotherapy group reported 50% or more improvement from baseline compared with 27.2% of the steroid group. At 15 months after treatment, 58.7% of patients in the prolotherapy group reported 50% or more relief compared with 10.2% of the steroid group. Key differences between this and other studies on prolotherapy were the selection of patients using a diagnostic sacroiliac joint block and the use of an arthrogram to confirm the location of the injection. Additional trials are needed to confirm the safety and efficacy of this procedure.

### Prospective Studies

Reeves and Hassanein (2003) reported on a study of dextrose prolotherapy for anterior cruciate ligament laxity.<sup>8</sup> Of 16 evaluable patients, statistically significant improvements were found at 6, 12, and 36 months in anterior cruciate ligament laxity, pain, swelling, and knee range of motion. However, this was a small, nonrandomized trial and, as previously noted, without placebo control, the extent to which improvements with prolotherapy exceeded those associated with placebo could not be determined.

### Osteoarthritis

#### Systematic Reviews

Wee et al (2021) published a systematic review and meta-analysis involving 11 RCTs (N=837) that evaluated the use of dextrose prolotherapy in knee osteoarthritis.<sup>9</sup> The included studies compared dextrose prolotherapy to other injectates (active or placebo) or interventions in adults with a knee osteoarthritis diagnosis and included the 3 RCTs of prolotherapy in knee osteoarthritis summarized below [Sert et al (2020)<sup>10</sup>; Rabago et al (2013)<sup>11</sup>; Reeves and Hassanein (2000)<sup>12</sup>]. Study size ranged from 31 to 120 patients. Concentrations of dextrose intra-articular injections ranged from 10% to 25% while extra-articular dextrose injection concentrations ranged from 12.5% to 15%. The number of injections and the intervals between injections were heterogeneous across studies. Overall, the authors concluded that dextrose prolotherapy (as a single 25% intra-articular injection) may confer potential benefits in terms of pain and function for patients with knee osteoarthritis; however, the majority of included studies were at a high risk of bias. The high risk of bias in the included studies was due to deviations from intended interventions and missing outcome data. Many trials did not discuss how missing data or trial deviations were managed and drop-outs were not clearly defined. The blinding of outcome assessors was also not well documented. For the 2 studies that were of low risk, the authors concluded that dextrose prolotherapy may be considered a treatment option in knee osteoarthritis, particularly in patients with limited treatment alternatives; however, despite good study designs, the study interventions were heterogeneous across trials. The authors concluded that more high-quality RCTs are warranted to establish the benefits of this intervention.

#### Randomized Controlled Trials

Sert et al (2020) reported on an RCT of prolotherapy in symptomatic knee osteoarthritis refractory to conservative therapy.<sup>10</sup> A total of 66 patients between the ages of 40 to 70 years were randomized to dextrose prolotherapy, saline injection, or a control group. Injections were blinded and given at week 0, 3, and 6, while the control group was not blinded. All groups performed an at home exercise program. At 18 weeks, the primary outcome, the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain subscale score was significantly improved in all groups, with the change in the prolotherapy group (-7.2 points) showing a significant improvement compared to the saline (-3.5 points;  $p < .002$ ) and control groups (-3 points;  $p < .001$ ). The WOMAC Total Score and pain visual analogue scale (VAS) scores were also significantly improved in all treatment groups at 18 weeks, with a greater improvement in the prolotherapy group (WOMAC: -36 points and VAS: -6 points) compared to the saline group (WOMAC: -22.5 points,  $p < .001$ ; VAS: -2.8 points,  $p < .001$ ) and the control group (WOMAC: -9 points,  $p = .002$ ; VAS: -2.4 points,  $p < .001$ ). Rates of patients achieving a minimum clinically important difference (MCID) of a 12-point change in the WOMAC score were not reported.

There were no significant differences between the prolotherapy and saline groups on changes in Short Form 36 (SF-36) mental or physical component scores at 18 weeks. This study was limited by its small sample size and relatively short follow-up. The majority of the included population was composed of women (85.7% to 90.9% of groups) and adhered to the at home exercise regimen (85% to 87% of groups); both of these factors have been shown to increase benefit of prolotherapy limiting generalizability of the findings to all osteoarthritis patients.

Jahangiri et al (2014) reported on a double-blind, randomized trial that compared prolotherapy with corticosteroid for the treatment of osteoarthritis in the first carpometacarpal joint.<sup>13</sup> Sixty patients were randomized to 3 monthly prolotherapy injections or 2 monthly saline injections plus a corticosteroid injection in the third month. The groups were comparable at baseline, with a VAS score for pain on pressure of 6.7 in the prolotherapy group and 6.4 in the corticosteroid group. At the 6-month follow-up, the pain had decreased more (by »2 cm on the VAS; VAS final score, <2) in the prolotherapy group compared with the corticosteroid-treated group ( $p < .001$ ). Pain on movement and hand function had also improved to a greater extent in the prolotherapy group.

Rabago et al (2013) reported on an RCT of prolotherapy for knee osteoarthritis.<sup>11</sup> This trial was supported by the National Center for Complementary and Alternative Medicine. Ninety patients were randomized to blinded injections (3 to 5 treatments with dextrose prolotherapy or saline) or at-home exercise. All 3 groups showed improvements on the composite WOMAC, with significantly greater improvement in the prolotherapy group (15.3 points) than in the saline and exercise groups (7.6 and 8.2 points, respectively). At 52 weeks, 50% of prolotherapy patients achieved the MCID of a 12-point change in the WOMAC score, compared with 30% of saline-treated patients and 24% of exercise participants. Knee pain scores also improved more in the prolotherapy group. Rabago et al (2015) reported on a 2.5-year telephone follow-up from prolotherapy-treated patients in their randomized trial and from 2 uncontrolled open-label studies.<sup>14</sup> The 3 prolotherapy groups were comparable, having undergone similar treatment courses and showing similar improvements in the WOMAC score at 52 weeks (15.3, 12.4, 15.9 points, respectively). At a mean 2.5-year follow-up (range, 1.5 to 3.5 years), the 65 patients who agreed to participate in this follow-up study had a mean 20.9-point improvement in the WOMAC score. There is a risk of bias due to the open-label design and the relatively high proportion (10%) of prolotherapy-treated patients who declined to participate in the telephone interview.

Reeves and Hassanein (2000) reported on 2 trials that used dextrose to treat osteoarthritis of the knee.<sup>12</sup> The first trial randomized 68 patients with 111 osteoarthritic knees to either 3 bimonthly injections of dextrose or placebo. The patients were evaluated with a VAS for pain and swelling, frequency of leg buckling, goniometrically measured flexion, and radiographic measures of joint narrowing. As presented, the data suggested a significant improvement in both the placebo and the treatment groups, but it is difficult to determine the comparative magnitude of improvement between the groups. For example, for the various outcome measures of pain, it appears that there were probably no clinically significant incremental effects of prolotherapy compared with the placebo group. However, for other nonpain outcomes (i.e., swelling, buckling, flexion range), prolotherapy might have been associated with a significant incremental improvement. The various outcome measures were combined and assessed using a Hotelling multivariate analysis. With this statistical measurement, prolotherapy demonstrated a statistically superior overall effect ( $p = .015$ ) compared with the control group. It should be recognized that the statistical significance of this measure was most likely due to the improvements in the nonpain symptoms (i.e., swelling, buckling, flexion range). In summary, it is uncertain whether the incremental improvement in the non-pain-related outcomes of the prolotherapy group compared with the control group is clinically significant.

In a similarly designed study, Reeves and Hassanein (2000) also assessed the effectiveness of prolotherapy as a treatment of osteoarthritic thumb and finger joints.<sup>15</sup> Twenty-seven patients with 150 osteoarthritic joints were randomized to 3 bimonthly injections of dextrose or water.

Patients were evaluated with both VAS for pain and goniometric assessment of joint movement. Because patients had a variable number of joints injected (range, 1 to 22), the VAS score for every symptomatic joint in each patient was added together for a total and divided by the number of symptomatic joints to provide an average joint pain score for each patient. There were improvements in pain scores in both the placebo and the treatment groups, but the incremental improvement of the treatment group compared with the placebo group was not statistically significant. Regarding flexion, the treatment group reported statistically significant improvement ( $p=.043$ ), while the placebo group reported a greater, statistically significant decrease ( $p=.011$ ). Therefore, the statistically significant difference in flexion between the groups ( $p=.003$ ) was primarily related to the decrease in the control group, with a smaller contribution related to the positive response in the treatment group. In summary, the clinical significance of an isolated finding of improved flexion without a corresponding significant improvement in pain is uncertain.

## **Tendinopathies of the Upper and Lower Limbs**

### **Chronic Soft Tissue Injuries**

#### **Systematic Reviews**

Goh et al (2021) conducted a systematic review and network meta-analysis of the efficacy of prolotherapy in comparison to other treatments for patients with chronic soft tissue injuries (e.g., tendinopathies and enthesopathies) having a mean symptom duration lasting at least 6 weeks.<sup>16</sup> The review included 91 articles (87 RCTs with 5859 subjects) involving upper limb (74%), lower limb (23%), and truncal/hip (3%) injuries. The "other treatments" within the network meta-analysis were primarily injections such as blood derivatives, corticosteroid, hyaluronic acid, and botulinum toxin. The primary outcome of interest was pain, evaluated mainly at a measurement time point 6 months post-intervention. If a 6 month time point was not available then measurements of pain at other times were evaluated. Results revealed that prolotherapy had no statistically significant benefits over other therapies with regard to pain relief at all assessed time points. However, prolotherapy was associated with better pain improvement over placebo at selected time points and injuries, primarily shoulder (<4 and >8 months) and elbow (4 to 8 months) injuries. The authors noted that more than 50% of included studies had a high overall risk of bias and some comparisons were connected by a small number of RCTs.

Chung et al (2020) published a systematic review and meta-analysis involving 10 RCTs (N=358) that analyzed the effects of dextrose prolotherapy on tendinopathy, fasciopathy, and ligament injuries.<sup>17</sup> Included studies compared the effects of hypertonic dextrose prolotherapy to placebo, no prolotherapy, or corticosteroids and evaluated either pain or activity level at follow-up. Results revealed that there were no significant differences between dextrose prolotherapy and no treatment or placebo with regard to pain control for the majority of studies. Dextrose prolotherapy was effective in improving activity only at an immediate follow-up period of 0 to 1 month (standardized mean difference [SMD], 0.98; 95% CI, 0.40 to 1.50) and was superior to steroid injections only in pain reduction at short-term follow-up (1 to 3 months; SMD, 0.70; 95% CI, 0.14 to 1.27). The authors concluded there was insufficient evidence to support the clinical benefits of dextrose prolotherapy in managing dense fibrous tissue injuries.

#### **Lateral Epicondylitis**

##### **Systematic Reviews**

A systematic review by Rabago et al (2009) evaluated injection therapies for lateral epicondylitis (tennis elbow); 2 RCTs and a prospective case series on prolotherapy were included.<sup>18</sup> One of the randomized trials was referenced as a report from a 2006 conference on complementary and alternative medicine; no authors were listed in the reference, and the trial does not appear to be published in the peer-reviewed literature. The second double-blind, randomized placebo-controlled trial by Scarpone et al (2008) involved 20 patients who had elbow pain for at least 6 months and failure of conservative therapy (rest, physical therapy, nonsteroidal anti-inflammatory drugs, 2 corticosteroid injections) and who received 3 treatments (over 8 weeks) of prolotherapy or saline injection.<sup>19</sup> There was a significant reduction in pain with prolotherapy

injection (5.1 to 0.5 on a Likert scale) compared with saline injection (4.5 to 3.5). Isometric strength also improved (13 to 31lb vs. 10 to 11lb, respectively), but there was no difference in grip strength between both groups.

### Randomized Controlled Trials

Two RCTs were published in 2020 evaluating the efficacy of dextrose prolotherapy in the treatment of lateral epicondylopathy/epicondylalgia. Both of these trials were conducted in Turkey in small patient populations. Table 1 summarizes key study characteristics and Table 2 presents a summary of results. Akcay et al (2020) enrolled 60 subjects with chronic lateral epicondylopathy with randomization to dextrose 15% prolotherapy or normal saline injection.<sup>20</sup> Results revealed that there was no significant difference between groups in VAS scores at rest or in motion, Disabilities of the Arm, Shoulder, and Hand (DASH) score, and handgrip strength at any time points in terms of improvement ( $p > .05$ ). Dextrose prolotherapy was noted to outperform normal saline with regard to effect on the Patient Rated Tennis Elbow Evaluation (PRTEE). Additionally, a significant percentage of patients in both groups achieved an MCID for all outcome measurements at the end of 12 weeks with no significant difference among the groups in terms of MCID achievement ( $p > .05$  for VAS at rest and motion, DASH, and PRTEE). Apaydin et al (2020) compared the effects of dextrose prolotherapy to hyaluronic acid injection in 32 patients with lateral epicondylalgia.<sup>21</sup> Overall, dextrose prolotherapy was favored over hyaluronic acid for improvements in pain with activity, at night, and at rest from baseline to 12 weeks. Dextrose prolotherapy was also associated with a significant improvement in quick-DASH scores. No between-group improvement in grip pain was observed. Results of both studies were limited by a short follow-up time, small sample size, and non-US-based, single center design.

**Table 1. Summary of RCT Characteristics**

Study	Countries	Sites	Participants	Interventions	
				Active	Comparator
Akcay et al (2020) <sup>20</sup>	Turkey	1	Adults with chronic lateral epicondylopathy with pain at the lateral side of the elbow lasting a minimum of 3 months despite treatment (N=60)	Dextrose 15% prolotherapy (n=30) injection given at baseline and at the end of the 4th and 8th weeks	Normal saline (n=30) injection given at baseline and at the end of the 4th and 8th weeks
Apaydin et al (2020) <sup>21</sup>	Turkey	1	Adults with a clinical diagnosis of lateral epicondylalgia of at least 6 months duration, pain provoked by palpation and resisted wrist/middle finger extension or gripping, and a score of at least 30/100 on the VAS (N=32)	Dextrose 15% prolotherapy (n=16) injection at weeks 0, 3, and 6	Hyaluronic acid (n=16) injection administered as a single 30 mg dose at baseline

RCT: randomized controlled trial; VAS: visual analog scale

**Table 2. Summary of RCT Results**

Study	VAS (at rest)	VAS (in motion)	DASH	Pain-Free Grip Strength
Akcay et al (2020) <sup>20</sup>	12 week follow-up	12 week follow-up	12 week follow-up	12 week follow-up
Dextrose 15% prolotherapy [median (Q1-Q3)]	2.0 (1.0 to 4.0)	3.0 (1.0 to 6.0)	29.1 (5.0 to 55.0)	0.40 (0.30 to 0.42)
Normal saline [median (Q1-Q3)]	3.0 (1.0 to 4.0)	4.0 (3.0 to 6.0)	41.6 (13.0 to 42.5)	0.40 (0.30 to 0.51)
p value (between groups)	NS	NS	NS	NS



Study	VAS (at rest)	VAS (in motion)	DASH	Pain-Free Grip Strength
<b>Apaydin et al (2020)<sup>21</sup></b>	12 week follow-up	12 week follow-up	12 week follow-up	12 week follow-up
<b>Dextrose 15% prolotherapy (mean ± SD)</b>	2.7 ± 1.7	3.18 ± 2.3	28.4 ± 13.4	7.3 ± 6.4
<b>Hyaluronic acid (mean ± SD)</b>	3.8 ± 2.09	4.81 ± 1.2	43.5 ± 17.6	4.8 ± 3.2
<b>p value (between groups)</b>	.04	.04	.04	.38

DASH: Disabilities of the Arm, Shoulder, and Hand; NS: nonsignificant; RCT: randomized controlled trial; SD: standard deviation; VAS: visual analog scale.

A double-blind RCT reported by Bayat et al (2019) compared dextrose prolotherapy with corticosteroid injection for chronic lateral epicondylitis.<sup>22</sup> Patients (N=28) received a single injection during the treatment period. There was a significant improvement in VAS pain score at 1- and 3- month follow-up in both the prolotherapy group (mean difference: 1.9 and 4.4 points, respectively) and the corticosteroid group (mean difference: 1.5 and 1.9 points, respectively). No difference was observed between groups in VAS score at 1 month ( $p=.74$ ); however, prolotherapy resulted in significantly better scores at 3 months ( $p=.03$ ). At 1 month follow-up, no statistically significant difference was observed between the prolotherapy and corticosteroid groups in the quick-DASH score (24.3 vs. 34.8, respectively;  $p=.14$ ); however, quick-DASH score was significantly better with prolotherapy compared to corticosteroid at 3 months (score=14.7 vs. 34.6, respectively;  $p=.01$ ). Results of this study are limited by a short follow-up, use of a single injection regimen, small sample size, and a notable non-significant difference in baseline symptom duration and quick-DASH score.

Another small (17 subjects) double-blind, randomized trial comparing prolotherapy with corticosteroid injections for chronic lateral epicondylitis was reported by Carayannopoulos et al (2011).<sup>23</sup> Each subject received an injection at baseline followed by a second injection at 1 month. The VAS for pain, quadruple VAS, and DASH were measured at baseline and at 1, 3, and 6 months. Changes of 2 in VAS score and 12 in DASH score were considered clinically significant. Per protocol analysis showed a significant improvement in VAS and DASH scores at both 3 months (2.38 and 19.89) and 6 months (2.63 and 21.76), both respectively, for the prolotherapy group, while the corticosteroid group showed significant improvement for DASH scores at 3 months (13.33) and 6 months (15.56). The trial was underpowered to detect a significant difference between the prolotherapy and corticosteroid groups for change in VAS, quadruple VAS, or DASH scores.

### Achilles Tendonitis

Yelland et al (2011) reported a multicenter randomized trial of prolotherapy or exercises for Achilles tendonitis in 43 patients.<sup>24</sup> Inclusion criteria were a diagnosis of unilateral or bilateral mid-portion Achilles tendinosis with pain between 2 cm and 7 cm proximal to the calcaneal attachment in adults older than 18 years with activity-related pain for at least 6 weeks. The sample size was limited by the available resources and slow recruitment rate, resulting in 15 participants in the eccentric loading exercise group, 14 in the prolotherapy group, and 14 in the combined treatment group. Randomization was conducted by a central site and resulted in a lower median duration of pain in the combined treatment group (6 months) than in the exercise alone (21 months) or prolotherapy alone (24 months) groups. An average of 4.4 injections per treatment was directed at tender points in the subcutaneous tissues adjacent to the affected tendon, with 4 to 12 weekly treatments until participants attained pain-free activity or requested to cease treatment. Participants were instructed to perform eccentric loading exercises. Clinical reviews were performed at 3, 6, and 12 weeks to check technique and progress. Mean increases in the validated Victorian Institute of Sport Assessment-Achilles score were 23.7 for exercise alone, 27.5 for prolotherapy alone, and 41.1 for the combined treatment. At 6 weeks and 12 months, these increases were significantly greater for combined treatment (exercise and

prolotherapy) than for exercise alone. The predefined minimum clinically important increase of 20 points or more on the Victorian Institute of Sport Assessment-Achilles was obtained by 12 subjects in the combined treatment group and 11 each in the exercise alone and prolotherapy alone groups; the difference was not statistically significant. The percentage of patients achieving full recovery (Victorian Institute of Sport Assessment-Achilles score of  $\geq 90$  at 12 months) was 53% for exercise alone, 71% for prolotherapy alone, and 64% for the combined treatment group; but these differences were not significant. This trial was limited by the combination of a small number of subjects per group, unequal durations of pain in the treatment groups at baseline, and minimal differences in the number of patients showing recovery (11/14 vs. 12/15, respectively).

### Rotator Cuff Tendinopathy

Kazempour Mofrad et al (2021) compared periarticular (neurofascial) dextrose prolotherapy and physiotherapy for the short-term treatment of chronic rotator cuff tendinopathy in 66 patients with associated symptoms lasting  $>3$  months.<sup>25</sup> Patients were randomly assigned to physiotherapy, involving 20 minutes of superficial heat using a hot pack followed by transcutaneous electrical nerve stimulation as well as pulsed ultrasound and exercise ( $n=33$ ), or prolotherapy with hypertonic dextrose 12.5% and 40 mg of 2% lidocaine ( $n=33$ ). This mixture was injected twice over a 1 week interval around the shoulder joint and to tender joints along the suprascapular nerve. Study outcomes included change in shoulder pain and in a disability index. Overall, 23 patients (70%) in the physiotherapy group and 29 (91%) patients in the prolotherapy group experienced a decrease in pain of 2.8 or greater on a VAS at study end. The difference between the groups was not significant ( $p=.072$ ). Dextrose prolotherapy was more effective than physiotherapy at alleviating pain at 2 weeks ( $p<.001$ ) after the intervention; however, both treatments were found to alleviate pain similarly at 3 months ( $p=.055$ ). Regarding improvement in disability, dextrose prolotherapy was more effective than physiotherapy at 2 weeks and 3 months post-intervention (both  $p<.001$ ); however, the changes in the physiotherapy group were more sustained. The authors concluded that both treatments were beneficial for chronic rotator cuff tendinopathy, at least in the short term; long-term research is needed to effectively track the pattern of clinical benefits for prolotherapy.

Bertrand et al (2016) reported on an RCT of prolotherapy in rotator cuff tendinopathy with supraspinatus pathology.<sup>26</sup> A total of 73 participants were randomized to a blinded injection of dextrose prolotherapy ( $n=27$ ), entheses saline injection ( $n=20$ ), or superficial saline injection ( $n=27$ ), all of which were given at months 0, 1, and 2, along with physical therapy. The primary outcome was achieving at least a 2.8 point improvement on the Numeric Rating Scale (NRS), which was obtained by phone by a blinded evaluator. Because the NRS rates pain in only whole numbers, pain levels are typically rated higher than with the VAS. For this reason, the improvement threshold was set as twice the MCID for VAS change in rotator cuff tendinopathy. After 9 months, the primary outcome occurred in 59% of patients in the prolotherapy group, which was significantly higher than in the superficial saline group (27%;  $p=.017$ ) and similar to the entheses saline group (37%;  $p=.088$ ). Patient satisfaction at 9 months, assessed using a 10-point satisfaction scale (0=not satisfied, 10=completely satisfied), revealed highest satisfaction in the prolotherapy group (6.7 points), followed by entheses saline (4.7 points;  $p=.079$  compared to prolotherapy) and superficial saline (3.9 points;  $p=.003$  compared to prolotherapy). Scores from the Ultrasound Shoulder Pathology Rating Scale did not differ significantly between groups ( $p=.734$ ). Important limitations of this study are the single-center design, which may limit generalizability to all patients. Additionally, the entheses saline injection group was not sufficiently powered to find a difference from the prolotherapy group. Finally, the use of the NRS as an alternative to the VAS may have biased the measurement of pain improvement.

### Summary of Evidence

For individuals who have musculoskeletal pain (e.g., chronic neck, back pain), osteoarthritic pain, or tendinopathies of the upper or lower limbs who receive prolotherapy, the evidence includes small randomized trials with inconsistent results. Relevant outcomes are symptoms, functional outcomes, and quality of life. The strongest evidence evaluates the use of

prolotherapy for the treatment of osteoarthritis, but the clinical significance of the therapeutic results is uncertain. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

### Supplemental Information

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

### Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

#### American Association of Orthopedic Medicine

As of September 2020, the American Association of Orthopedic Medicine (AAOM) currently has a recommendation posted online for the use of prolotherapy for back pain, with an unknown original publication date.<sup>27</sup> The AAOM has indicated that "...prolotherapy should be considered a valid treatment option in a selected group of chronic low back pain patients."

#### American College of Rheumatology/Arthritis Foundation

The 2019 American College of Rheumatology/Arthritis Foundation guideline for osteoarthritis of the hand, hip, and knee conditionally recommends against the use of prolotherapy in patients with knee and/or hip osteoarthritis, given limited number of trials involving small sample sizes showing limited effect.<sup>28</sup> The guideline does not make any recommendation regarding hand osteoarthritis, given lack of trials.

#### U.S. Preventive Services Task Force Recommendations

Not applicable.

#### Medicare National Coverage

The Centers for Medicare & Medicaid currently do not cover prolotherapy, joint sclerotherapy, and ligamentous injections with sclerosing agents.<sup>29</sup>

#### Ongoing and Unpublished Clinical Trials

Some currently ongoing and unpublished trials that might influence this review are listed in Table 3.

**Table 3. Summary of Key Trials**

NCT No.	Trial Name	Planned Enrollment	Completion Date
<i>Ongoing</i>			
NCT01934868	A Comparison of the Long Term Outcomes of Prolotherapy Versus Interlaminar Epidural Steroid Injections (ESI) for Lumbar Pain Radiating to the Leg	110	Dec 2022
NCT03411811	Dextrose Prolotherapy in Chronic Ulnar Wrist Pain Resistant to Usual Care: Comparison to a Naive-to-Treatment Cohort Who Receive Usual Care	60	Jan 2023
<i>Unpublished</i>			
NCT01897259	Comparison of Conservative Methods for the Treatment of Lateral Epicondylitis: A Randomized, Prospective Study	200	Jun 2019 (unknown status)
NCT04805242	Effects of Dextrose Prolotherapy in Rotator Cuff Disease: A Randomized Controlled Study	60	Nov 2021

NCT: national clinical trial.

## References

1. Dagenais S, Yelland MJ, Del Mar C, et al. Prolotherapy injections for chronic low-back pain. *Cochrane Database Syst Rev*. Apr 18 2007; (2): CD004059. PMID 17443537
2. Dagenais S, Mayer J, Haldeman S, et al. Evidence-informed management of chronic low back pain with prolotherapy. *Spine J*. Jan-Feb 2008; 8(1): 203-12. PMID 18164468
3. Chou R, Atlas SJ, Stanos SP, et al. Nonsurgical interventional therapies for low back pain: a review of the evidence for an American Pain Society clinical practice guideline. *Spine (Phila Pa 1976)*. May 01 2009; 34(10): 1078-93. PMID 19363456
4. Yelland MJ, Glasziou PP, Bogduk N, et al. Prolotherapy injections, saline injections, and exercises for chronic low-back pain: a randomized trial. *Spine (Phila Pa 1976)*. Jan 01 2004; 29(1): 9-16; discussion 16. PMID 14699269
5. Klein RG, Eek BC, DeLong WB, et al. A randomized double-blind trial of dextrose-glycerine-phenol injections for chronic, low back pain. *J Spinal Disord*. Feb 1993; 6(1): 23-33. PMID 8439713
6. Ongley MJ, Klein RG, Dorman TA, et al. A new approach to the treatment of chronic low back pain. *Lancet*. Jul 18 1987; 2(8551): 143-6. PMID 2439856
7. Kim WM, Lee HG, Jeong CW, et al. A randomized controlled trial of intra-articular prolotherapy versus steroid injection for sacroiliac joint pain. *J Altern Complement Med*. Dec 2010; 16(12): 1285-90. PMID 21138388
8. Reeves KD, Hassanein KM. Long-term effects of dextrose prolotherapy for anterior cruciate ligament laxity. *Altern Ther Health Med*. May-Jun 2003; 9(3): 58-62. PMID 12776476
9. Wee TC, Neo EJR, Tan YL. Dextrose prolotherapy in knee osteoarthritis: A systematic review and meta-analysis. *J Clin Orthop Trauma*. Aug 2021; 19: 108-117. PMID 34046305
10. Sert AT, Sen EI, Esmailzadeh S, et al. The Effects of Dextrose Prolotherapy in Symptomatic Knee Osteoarthritis: A Randomized Controlled Study. *J Altern Complement Med*. May 2020; 26(5): 409-417. PMID 32223554
11. Rabago D, Patterson JJ, Mundt M, et al. Dextrose prolotherapy for knee osteoarthritis: a randomized controlled trial. *Ann Fam Med*. May-Jun 2013; 11(3): 229-37. PMID 23690322
12. Reeves KD, Hassanein K. Randomized prospective double-blind placebo-controlled study of dextrose prolotherapy for knee osteoarthritis with or without ACL laxity. *Altern Ther Health Med*. Mar 2000; 6(2): 68-74, 77-80. PMID 10710805
13. Jahangiri A, Moghaddam FR, Najafi S. Hypertonic dextrose versus corticosteroid local injection for the treatment of osteoarthritis in the first carpometacarpal joint: a double-blind randomized clinical trial. *J Orthop Sci*. Sep 2014; 19(5): 737-43. PMID 25158896
14. Rabago D, Mundt M, Zgierska A, et al. Hypertonic dextrose injection (prolotherapy) for knee osteoarthritis: Long term outcomes. *Complement Ther Med*. Jun 2015; 23(3): 388-95. PMID 26051574
15. Reeves KD, Hassanein K. Randomized, prospective, placebo-controlled double-blind study of dextrose prolotherapy for osteoarthritic thumb and finger (DIP, PIP, and trapeziometacarpal) joints: evidence of clinical efficacy. *J Altern Complement Med*. Aug 2000; 6(4): 311-20. PMID 10976977
16. 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. PMID 34038486
17. Chung MW, Hsu CY, Chung WK, et al. Effects of dextrose prolotherapy on tendinopathy, fasciopathy, and ligament injuries, fact or myth?: A systematic review and meta-analysis. *Medicine (Baltimore)*. Nov 13 2020; 99(46): e23201. PMID 33181700
18. Rabago D, Best TM, Zgierska AE, et al. A systematic review of four injection therapies for lateral epicondylitis: prolotherapy, polidocanol, whole blood and platelet-rich plasma. *Br J Sports Med*. Jul 2009; 43(7): 471-81. PMID 19028733
19. Scarpone M, Rabago DP, Zgierska A, et al. The efficacy of prolotherapy for lateral epicondylitis: a pilot study. *Clin J Sport Med*. May 2008; 18(3): 248-54. PMID 18469566

20. Akcay S, Gurel Kandemir N, Kaya T, et al. Dextrose Prolotherapy Versus Normal Saline Injection for the Treatment of Lateral Epicondylopathy: A Randomized Controlled Trial. *J Altern Complement Med*. Dec 2020; 26(12): 1159-1168. PMID 32990454
21. Apaydin H, Bazancir Z, Altay Z. Injection Therapy in Patients with Lateral Epicondylalgia: Hyaluronic Acid or Dextrose Prolotherapy? A Single-Blind, Randomized Clinical Trial. *J Altern Complement Med*. Dec 2020; 26(12): 1169-1175. PMID 32931308
22. Bayat M, Raeissadat SA, Mortazavian Babaki M, et al. Is Dextrose Prolotherapy Superior To Corticosteroid Injection In Patients With Chronic Lateral Epicondylitis?: A Randomized Clinical Trial. *Orthop Res Rev*. 2019; 11: 167-175. PMID 31819675
23. Carayannopoulos A, Borg-Stein J, Sokolof J, et al. Prolotherapy versus corticosteroid injections for the treatment of lateral epicondylitis: a randomized controlled trial. *PM R*. Aug 2011; 3(8): 706-15. PMID 21871414
24. Yelland MJ, Sweeting KR, Lyftogt JA, et al. Prolotherapy injections and eccentric loading exercises for painful Achilles tendinosis: a randomised trial. *Br J Sports Med*. Apr 2011; 45(5): 421-8. PMID 19549615
25. Kazempour Mofrad M, Rezasoltani Z, Dadarkhah A, et al. Periarticular Neurofascial Dextrose Prolotherapy Versus Physiotherapy for the Treatment of Chronic Rotator Cuff Tendinopathy: Randomized Clinical Trial. *J Clin Rheumatol*. Jun 01 2021; 27(4): 136-142. PMID 32975923
26. Bertrand H, Reeves KD, Bennett CJ, et al. Dextrose Prolotherapy Versus Control Injections in Painful Rotator Cuff Tendinopathy. *Arch Phys Med Rehabil*. Jan 2016; 97(1): 17-25. PMID 26301385
27. American Association of Orthopedic Medicine, Klein RG, Patterson J, et al. Prolotherapy for Back Pain Treatment. n.d.; <http://www.aaomed.org/prolotherapy-back-pain>. Accessed September 11, 2021.
28. 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*. Feb 2020; 72(2): 220-233. PMID 31908163
29. Centers for Medicare and Medicaid Services. National Coverage Determination (NCD) for PROLOThERAPY, Joint ScleroTherapy, and Ligamentous Injections with Sclerosing Agents (150.7). 1999; <https://www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?NCDId=15&ncdver=1&bc=AAAAQAAAAAAA&>. Accessed September 11, 2021
30. Blue Cross Blue Shield Association. Medical Policy Reference Manual, No. 2.01.26 (November 2021).

## Documentation for Clinical Review

- No records required

## Coding

*This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy.*

*The following codes are included below for informational purposes. Inclusion or exclusion of a code(s) does not constitute or imply member coverage or provider reimbursement policy. Policy Statements are intended to provide member coverage information and may include the use of some codes for clarity. The Policy Guidelines section may also provide additional information for how to interpret the Policy Statements and to provide coding guidance in some cases.*

Type	Code	Description
CPT®	20550	Injection(s); single tendon sheath, or ligament, aponeurosis (e.g., plantar "fascia")
	20551	Injection(s); single tendon origin/insertion
	20552	Injection(s); single or multiple trigger point(s), 1 or 2 muscle(s)
	20999	Unlisted procedure, musculoskeletal system, general
	27096	Injection procedure for sacroiliac joint, anesthetic/steroid, with image guidance (fluoroscopy or CT) including arthrography when performed
	64490	Injection(s), diagnostic or therapeutic agent, paravertebral facet (zygapophyseal) joint (or nerves innervating that joint) with image guidance (fluoroscopy or CT), cervical or thoracic; single level
	64491	Injection(s), diagnostic or therapeutic agent, paravertebral facet (zygapophyseal) joint (or nerves innervating that joint) with image guidance (fluoroscopy or CT), cervical or thoracic; second level (List separately in addition to code for primary procedure)
	64492	Injection(s), diagnostic or therapeutic agent, paravertebral facet (zygapophyseal) joint (or nerves innervating that joint) with image guidance (fluoroscopy or CT), cervical or thoracic; third and any additional level(s) (List separately in addition to code for primary procedure)
	64493	Injection(s), diagnostic or therapeutic agent, paravertebral facet (zygapophyseal) joint (or nerves innervating that joint) with image guidance (fluoroscopy or CT), lumbar or sacral; single level
	64494	Injection(s), diagnostic or therapeutic agent, paravertebral facet (zygapophyseal) joint (or nerves innervating that joint) with image guidance (fluoroscopy or CT), lumbar or sacral; second level (List separately in addition to code for primary procedure)
64495	Injection(s), diagnostic or therapeutic agent, paravertebral facet (zygapophyseal) joint (or nerves innervating that joint) with image guidance (fluoroscopy or CT), lumbar or sacral; third and any additional level(s) (List separately in addition to code for primary procedure)	
HCPCS	M0076	Prolotherapy

### Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

Effective Date	Action
11/15/1970	New Policy Adoption
10/10/1990	Policy Revision
03/25/1995	Policy Review
11/05/2002	Administrative Review
06/01/2004	Policy Revision
06/28/2007	BCBSA Medical Policy adoption
12/05/2008	Policy Revision
10/07/2011	Policy revision without position change
10/31/2014	Policy revision without position change
01/01/2017	Policy revision without position change
01/01/2019	Policy revision without position change
02/01/2020	Annual review. No change to policy statement. Literature review updated.
01/01/2021	Annual review. No change to policy statement. Literature review updated.

Effective Date	Action
01/01/2022	Annual review. No change to policy statement. Literature review updated.

## Definitions of Decision Determinations

**Medically Necessary:** Services that are Medically Necessary include only those which have been established as safe and effective, are furnished under generally accepted professional standards to treat illness, injury or medical condition, and which, as determined by Blue Shield, are: (a) consistent with Blue Shield medical policy; (b) consistent with the symptoms or diagnosis; (c) not furnished primarily for the convenience of the patient, the attending Physician or other provider; (d) furnished at the most appropriate level which can be provided safely and effectively to the patient; and (e) not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of the Member's illness, injury, or disease.

**Investigational/Experimental:** A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

**Split Evaluation:** Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

## Prior Authorization Requirements (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department at (800) 541-6652, or the Transplant Case Management Department at (800) 637-2066 ext. 3507708 or visit the provider portal at [www.blueshieldca.com/provider](http://www.blueshieldca.com/provider).

*Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.*

**Appendix A**

POLICY STATEMENT (No changes)	
BEFORE	AFTER
<p><b>Prolotherapy 2.01.26</b></p> <p><b>Policy Statement:</b> Prolotherapy is considered <b>investigational</b> as a treatment of musculoskeletal pain.</p>	<p><b>Prolotherapy 2.01.26</b></p> <p><b>Policy Statement:</b> Prolotherapy is considered <b>investigational</b> as a treatment of musculoskeletal pain.</p>