

PROLOTHERAPY FOR MUSCULOSKELETAL INDICATIONS

Guideline Number: MMG111.J

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[Instructions for Use](#) ⓘ

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Related Medical Management Guideline
<ul style="list-style-type: none"> Bone or Soft Tissue Healing and Fusion Enhancement Products

COVERAGE RATIONALE

Prolotherapy is unproven and not medically necessary due to insufficient evidence of efficacy.

APPLICABLE CODES

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this guideline does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies and Guidelines may apply.

CPT Code	Description
0232T	Injection(s), platelet rich plasma, any site, including image guidance, harvesting and preparation when performed
0481T	Injection(s), autologous white blood cell concentrate (autologous protein solution), any site, including image guidance, harvesting and preparation, when performed

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HCPCS Code	Description
M0076	Prolotherapy

DESCRIPTION OF SERVICES

Prolotherapy is an injection-based complementary and alternative medical therapy for chronic musculoskeletal pain. Its core principle is that a relatively small volume of an irritant or sclerosing solution is injected at sites on painful ligament and tendon insertions, and in adjacent joint space over the course of several treatment sessions. It has been assessed as a treatment for a wide variety of painful chronic musculoskeletal conditions which are refractory to "standard of care" therapies. The three most commonly used prolotherapy solutions are hypertonic dextrose, phenol-glycerine-glucose, and morrhuate sodium. Its precise mechanism of action is not known (Rabago et al., 2010).

Prolotherapy is considered to be contraindicated in individuals with metastatic cancer, non-musculoskeletal pain, spinal anatomical defects, systemic inflammation, morbid obesity, bleeding disorders, low pain threshold, inability to perform post treatment exercises, chemical dependency, or whole body pain. Because high doses of a prolotherapy solution containing dextrose 12.5%, glycerin 12.5%, phenol 1.0%, and lidocaine 0.25% may produce a temporary increase in hepatic enzymes, it may not be prudent to administer these solutions to patients with pre-existing hepatic conditions (Dagenais et al., 2008).

Osteoarthritis (OA)**Knee**

Sit et al. (2016) conducted a systematic review with meta-analysis to synthesize clinical evidence on the effect of prolotherapy for knee OA. Three randomized controlled trials (RCTs) with moderate risk of bias and 1 quasi-randomized trial met inclusion criteria with data from a total of 258 patients. The primary outcome of interest was change in the Western Ontario and McMaster Universities Osteoarthritis (WOMAC) score. In the meta-analysis of 2 eligible studies, prolotherapy was superior to exercise alone by a standardized mean difference of 0.81, 0.78 and 0.62 on the WOMAC composite scale and WOMAC function and pain subscale scores, respectively. Moderate heterogeneity existed in all cases. The authors concluded that prolotherapy demonstrated a positive and significant beneficial effect in the treatment of knee OA. Adequately powered, longer-term trials with uniform end-points are needed to better clarify its efficacy.

van Drumpt et al. (2016) conducted an open label, prospective trial (NCT01773226) assessing safety and efficacy of an injection therapy for individuals with early to moderate OA. Using an Autologous Protein Solution (APS) called nSTRIDE[®], 11 participants who had failed at least one other type of conservative therapy received the injection. Assessment for adverse events (AE) and clinical response outcomes occurred at 1 week, 2 weeks, 1 month, 3 months, and 6 months postinjection. Long-term follow up lasted an average of 18 months. Only mild AEs were reported. Postinjection pain scores were reduced by 83% and 90% at 3 and 6 months, respectively. At 18 months, mean WOMAC Index function scores reflected 61% improvement. The authors concluded that a single injection of APS for treatment of early to moderate knee OA had very positive outcomes and that well-controlled, randomized multicenter clinical studies to confirm efficacy are warranted. Study limitations include the lack of a control group and small sample size, although the study design was deemed adequate to determine feasibility.

Kon et al. (2017) conducted a multicenter, double-blind, RCT to investigate if 1 intra-articular injection of APS can reduce pain and improve function in patients affected by knee OA (NCT02138890). Forty-six patients with unilateral knee OA were randomized into the APS group, which received a single ultrasound-guided injection of APS, and the saline (control) group, which received a single saline injection. Patient-reported outcomes and AEs were collected at 2 weeks and at 1, 3, 6, and 12 months through a variety of assessment tools including the visual analog scale (VAS), WOMAC Index, and Knee injury and Osteoarthritis Outcome Score (KOOS). There were no significant differences in frequency and severity of AEs between groups. The improvement from baseline to 2 weeks and to 1, 3, and 6 months was similar between treatments as well. At 12 months, improvement in WOMAC pain score was 65% in the APS group and 41% in the saline group. There were no significant differences in VAS pain improvement between groups. Significant differences between groups were detected in changes from baseline to 12 months in bone marrow lesion size as assessed on magnetic resonance imaging (MRI) and osteophytes in the central zone of the lateral femoral condyle, both in favor of the APS group. There were no significant differences between the APS and control group in other measured secondary endpoints. The authors concluded that this study supports that a single injection of APS is safe and demonstrates clinical improvement at 1-year in patients affected by knee OA. Treatment with APS or a saline injection provided significant pain relief over the course of the study with differences becoming apparent at between 6 and 12 months after treatment. Study limitations include the need for longer follow up as well as small sample size.

O'Shaughnessey et al. (2014) conducted a multi-center controlled feasibility study (NCT01050894) to determine if blood from OA patients (N=105) could be mechanically processed to form an APS with preferentially increased concentrations of anti-inflammatory versus inflammatory cytokines. Through examination of whole blood taken from control donors and OA donors, it was identified that the APS device system does preferentially increase anti-inflammatory cytokines over inflammatory cytokines. The study also identified that results were no different when using blood from the control or from the OA donors. The authors concluded that these results, combined with findings in previous studies, provides strong support for further investigation of APS as a promising therapy for OA.

There are 3 active clinical trials involving the APS nStride[®] (Zimmer Biomet) for OA of the knee. For more information, go to www.clinicaltrials.gov. (Accessed February 27, 2019)

Rabago et al. assessed long-term effects of prolotherapy on knee pain, function and stiffness among adults with knee OA through a post clinical-trial, open-label follow-up study. Participants (N=65) received 3-5 monthly interventions and were assessed using the validated WOMAC index, 0-100 points), at baseline, 12, 26, 52 weeks, and 2.5 years. Progressive improvement in WOMAC scores were reported at all time intervals. The authors concluded that prolotherapy resulted in safe, significant, progressive improvement of knee pain, function and stiffness scores among most participants through a mean follow-up of 2.5 years and may be an appropriate therapy for patients with knee OA refractory to other conservative care (2015).

In an Evidence-based Practice Center Systematic Review Protocol for the Treatment of OA of the Knee, the Agency for Healthcare Review and Quality (AHRQ) does not address intra-articular injected agents such as prolotherapeutic substances (Newberry et al. 2017).

Fingers

Jahangiri et al. compared the advantages of prolotherapy in the treatment of first carpometacarpal OA with those of corticosteroid local injection in a double-blind RCT. Sixty participants (60 hands) with OA of the first carpometacarpal joint were assigned equally to 2 groups. For the corticosteroid group, after 2 monthly saline placebo injections, a single dose of 40 mg methylprednisolone acetate (0.5 ml) mixed with 0.5 ml of 2% lidocaine was injected. For the dextrose (DX) group, 0.5 ml of 20% DX was mixed with 0.5 ml of 2% lidocaine and the injection was repeated monthly for 3 months. Pain intensity, hand function and the strength of lateral pinch grip were measured at the baseline and at 1, 2, and 6 months post-treatment. The 2 groups were comparable at 2 months, but significantly different at 1 month (better results for corticosteroid), and at 6 months (more favorable outcome for DX). After 6 months of treatment, both groups increased functional level, but DX seemed to be more effective. The authors concluded that for the long term, DX seemed to be more advantageous, while the 2 treatments were comparable in the short term. Further research with a large sample size is needed to compare possible complications of corticosteroid/lidocaine vs DX/lidocaine injections in the management of OA. (2014).

Krstičević and colleagues conducted a systematic review on the efficacy and safety of proliferative injection therapy (prolotherapy) for treatment of knee and hand OA. Seven RCTs were included, with 393 participants aged 40-75 years having joint pain ranging from 3 months to 8 years. Dextrose was the most commonly used agent, with follow-up ranging from 12 weeks to 12 months. All studies concluded that prolotherapy was effective treatment for OA and no serious AEs were reported. The authors concluded that current data about prolotherapy for OA should be considered preliminary and that future high-quality trials are warranted since these low-quality studies did not provide reliable evidence (2017).

In a systematic review and meta-analysis, Hung and colleagues (2016) compared the effectiveness of dextrose prolotherapy versus control injections and exercise in the management of OA pain. Searching PubMed and Scopus from the earliest record until February 2016, 1 single-arm study and 5 RCTs were included (N = 326). The investigators estimated the effect sizes of pain reduction before and after serial dextrose injections and compared the values between dextrose prolotherapy, comparative regimens, and exercise 6 months after the initial injection. Regarding the treatment arm using dextrose prolotherapy, the effect sizes compared with baseline were 0.65, 0.84, 0.85, and 0.87 after the 1st, 2nd, 3rd, and 4th or more injections, respectively. The overall effect of dextrose was better than control injections, demonstrating superiority when compared with local anesthesia and exercise. There was an insignificant advantage of dextrose over corticosteroids which was only estimated from 1 study. The authors concluded that dextrose injections decreased pain in OA patients; but did not exhibit a positive dose-response relationship following serial injections. Dextrose prolotherapy was found to provide a better therapeutic effect than exercise, local anesthetics, and probably corticosteroids when patients were re-tested 6 months following the initial injection. The researchers also noted that the effect of prolotherapy did not differ between hand and knee OA. This study had several drawbacks, including but not limited to the minimal number of trials eligible for meta-analysis, as well as heterogeneity in the patient populations, injection protocols, comparative regimens, and outcome assessment.

Lateral Epicondylitis (LE)

Dong et al. (2015) conducted a systematic review and meta-analysis comparing many injection therapies (including prolotherapy) for LE. All of the injection treatments showed a trend towards better effects than placebo, and the study authors concluded prolotherapy's superiority would need to be confirmed by more research.

Sims et al. (2014) conducted a systematic review of RCTs examining 11 non-surgical treatments for LE which included prolotherapy. They concluded that the existing literature does not provide conclusive evidence that there is one preferred method of non-surgical treatment for this condition.

A pilot study was conducted assessing dextrose prolotherapy (PrT) for chronic LE. The study design was a three-arm RCT. Twenty-six adults (32 elbows) with chronic LE for 3 months or longer were randomized to ultrasound-guided PrT with dextrose solution, ultrasound-guided PrT with dextrose-morrhuate sodium solution, or watchful waiting ("wait and see"). The primary outcome was the Patient-Rated Tennis Elbow Evaluation (PRTEE) (100 points) at 4, 8, and 16 weeks (all groups) and at 32 weeks (PrT groups). The secondary outcomes included pain-free grip strength and MRI severity score. The participants in both PrT groups reported improved PRTEE composite and subscale scores at 4, 8, and/or 16 weeks compared with those in the wait-and-see group. At 16 wks, compared with baseline, the PrT with dextrose and PrT with dextrose-morrhuate groups reported improved composite PRTEE scores by a mean of 18.7 and 17.5 points, respectively. The grip strength of the participants receiving PrT with dextrose exceeded that of the other 2 groups at 8 and 16 weeks. There were no differences in MRI scores. Satisfaction was high and there were no AEs. PrT resulted in safe, significant improvement of elbow pain and function compared with baseline status and follow-up

data and the wait-and-see control group. This pilot study suggests the need for a definitive trial to validate these results across a larger population (Rabago et al., 2013).

There are several open clinical trials involving the use of prolotherapy in the treatment of LE. For more information, go to www.clinicaltrials.gov. (Accessed February 27, 2019)

Rotator Cuff (RC) Tendinopathies

Seven et al. (2017) evaluated the efficacy of prolotherapy in treating chronic refractory RC lesions through a randomized prospective comparative trial. Individuals with chronic RC lesions and symptoms that persisted for > 6 months were divided into 2 groups: the control group (N = 60), treated with exercise 3 times weekly for 12 weeks; and the prolotherapy group (N = 60), receiving 2 to 6 ultrasound-guided prolotherapy injection sessions in addition to the 3 times weekly home exercise program. A total of 101 patients out of 120 were included in the results. Clinical assessment of shoulder function was performed using a VAS for pain, Shoulder Pain and Disability Index (SPADI), Western Ontario Rotator Cuff (WORC) Index, patient satisfaction, and shoulder range of motion (ROM). Participants were examined at baseline, weeks 3, 6, and 12, and last follow-up (minimum of one year). At one year, 92.9% versus 56.8% of participants reported excellent or good outcomes overall in the prolotherapy and control groups, respectively. No AEs were reported. Limitations of this study included but were not limited to small sample size and lack of a placebo control. The investigators concluded that prolotherapy is an easily applicable and satisfying auxiliary method in the treatment of partial RC lesions, reducing pain and improving both shoulder function and patient satisfaction. Larger studies with longer follow-up times are needed.

Bertrand and colleagues (2016) compared the effect of dextrose prolotherapy on pain levels and degenerative changes in painful RC tendinopathy. In this blinded RCT, 72 participants who received 3 monthly injections of 0.1% lidocaine with dextrose prolotherapy (entheses dextrose [Enth-Dex group]) or one of two control injections (entheses saline injection without dextrose [Enth-Saline group] or superficial saline injection [Superfic-Saline group]) were included in the 9-month follow-up data. All participants received concurrent physical therapy. The primary outcome measure was achieving an improvement in maximal current shoulder pain ≥ 2.8 (twice the minimal clinically important difference for VAS pain score). At 9 months, the Enth-Dex group maintained a 2.9-point improvement in pain in comparison with 1.8 and 1.3 for the Enth-Saline and Superfic-Saline groups, respectively. The use of prolotherapy in the Enth-Dex group reported a significant improvement compared to the Superfic-Saline group (16 [59%] vs. 7 [27%]); however, the difference between the Enth-Dex group and the Enth-Saline group did not reach clinical significance. The authors concluded that prolotherapy may provide an effective and welcome addition to the management of patients with painful RC tendinopathy. Additional, larger clinical trials with more complete functional assessment tools are required to determine the clinical utility of this technology.

In a retrospective, case-control study, Lee and colleagues (2015) examined the effectiveness of prolotherapy for non-traumatic refractory RC disease in 151 patients who were unresponsive to 3 months of aggressive conservative treatment. Of the patients, 63 received prolotherapy with 16.5% dextrose 10-ml solution (treatment group), and 63 continued conservative treatment (control group). Main outcome measures included VAS score of the average shoulder pain level for the past 1 week, SPADI score, isometric strength of the shoulder abductor, active ROM of the shoulder, maximal tear size on ultrasonography, and number of analgesics required per day. Over 1-year follow-up, 57 patients in the treatment group and 53 in the control group were analyzed. There was no significant difference between the 2 groups in age, sex, shoulder dominance, duration of symptoms, and ultrasonographic findings at pre-treatment. The average number of injections in the treatment group was 4.8. Compared with the control group, outcome measures showed significant improvement in the treatment group. There were no AEs. The authors concluded that prolotherapy can be an option for patients with refractory chronic RC disease who showed no response to other treatments. They stated that prospective RCTs are needed to further demonstrate efficacy. The only limitation cited was the non-randomized retrospective study design.

Groin Pain

A case series by Topol and Reeves (2008) evaluated the use of prolotherapy in 75 athletes with chronic groin/abdominal pain. Participants received monthly injections of 12.5% dextrose in 0.5% lidocaine for 2 months. Average number of treatments received was 3 (range 1-6). Outcomes were measured using VAS and Nirschl pain phase scale (NPPS). Seventy two athletes completed the full treatment. Follow-up occurred at an average of 26 months (range 6-73). VAS and NPPS improved 82% and 79% respectively. Sixty-six of 72 athletes returned to full sport, and all but 2 of the 66 athletes returned to full sport pain free. The authors found that 81% of the athletes had improvement in pain with 92% returning to unrestricted sports. The study is limited by small sample size and study design. Additional studies are needed to validate these results across a larger and more diverse population.

Temporomandibular Joint (TMJ) Hypermobility

Cömert Kiliç et al. (2016) conducted a RCT involving 30 adult patients with bilateral TMJ hypermobility referred for treatment. They were divided randomly into 2 treatment groups using either saline (placebo group) or dextrose injections (study group). The solution was injected into 5 different TMJ areas in 3 sessions at monthly intervals. The

predictor variable was the treatment technique. The outcome variables were VAS evaluations and maximum inter-incisal opening (MIO). Outcome variables were recorded preoperatively and at 12 months postoperatively. The follow-up sample was comprised of 26 subjects, 12 in the placebo group and 14 in the study group. Masticatory efficiency increased and general pain complaints and joint sounds decreased significantly in both groups. MIO decreased significantly only in the study group. Insignificant changes in the other parameters were found for both groups. The authors concluded that after estimating differences between follow-up and baseline outcomes, the mean change in primary outcome variables showed no statistically significant difference between the 2 groups, suggesting that dextrose prolotherapy is no more effective than placebo for TMJ hypermobility.

Zhou and colleagues conducted a single center study with 45 patients, introducing a modified technique of prolotherapy using an injection of lignocaine and 50% dextrose at a single site in the posterior periarticular tissues. The criteria for inclusion in this study were open lock of the jaw > twice in the past 6 months, and no long-standing dislocation of the TMJ. Patients were followed for at least one year. There were appreciable improvements in the number of episodes of dislocation and clicking after the injection. The overall success rate, defined as the absence of any further dislocation or subluxation for more than 6 months, was 41/45 (91%). Of the 41 rehabilitated patients, 26 (63%) required a single injection, 11 (27%) had 2 treatments, and 4 (10%) needed a third injection. All patients tolerated the injections well. The authors concluded that the modified dextrose prolotherapy is simple, safe, and cost-effective for the treatment of recurrent dislocation of the TMJ. Study limitations include small study size and the lack of a control group (2014).

Refai, et al. (2011) conducted a prospective, randomized, double-blind clinical study with 12 patients to assess the efficacy of dextrose prolotherapy for the treatment of TMJ hypermobility. While therapeutic results were promising, the authors concluded that continued research into prolotherapy's effectiveness with large sample sizes and long-term follow-up is needed.

Lower Limb Tendonopathies

Because their efficacy and potential AEs are unclear, Morath et al. (2018) conducted a systematic review and meta-analysis of available published literature on sclerotherapy and prolotherapy for treating Achilles tendinopathy (AT) in athletes. While the initial search yielded 1104 entries, only 13 were human studies. Four RCTs were ranked as having a low risk of selection bias. Three of those reported a statistically significant drop in the VAS score. Positive results regarding pain relief and patient satisfaction were identified in 12 of the 13 studies. Meta-analysis was clearly in favor of the intervention. Only one serious AE and two minor AEs were reported in the entire body of literature. The researchers concluded that both sclerotherapy and prolotherapy are safe and may be effective treatment options for AT, however long-term studies and RCTs are still needed to support their recommendation.

A systematic review by Sanderson and Bryant (2015) evaluated the effectiveness and safety of prolotherapy injections for management of lower limb tendinopathy and fasciopathy. While no AEs following prolotherapy injections were reported in any study in this review, the authors found limited evidence that prolotherapy injections are a safe and effective treatment for AT, PF and Osgood-Schlatter disease. More robust research using large, methodologically-sound RCTs is required.

Low Back Pain (LBP)

A systematic review by Chou et al. (2009) included 174 articles of which 97 met criteria to assess the benefits and harms of nonsurgical interventional therapies for low back and radicular pain. Of the 97, only 5 addressed prolotherapy. Three of these studies found no difference between prolotherapy and either saline or local anesthetic control injections for short- or long-term (up to 24 months) pain or disability. One higher quality trial found prolotherapy associated with increased likelihood of short-term improvement in pain or disability versus control injection, but both treatment groups received a number of co-interventions including spinal manipulation, local injections, exercises, and walking. In the fifth trial, effects of prolotherapy could not be determined because the prolotherapy group received strong manipulation and the control injection group only light manipulation. The authors concluded that prolotherapy has not been found to be effective for the treatment of low back and radicular pain.

In a 2007 Cochrane Review on prolotherapy injections for chronic LBP, Dagenais et al. concluded that there is conflicting evidence regarding the efficacy of prolotherapy injections for these patients. When used alone, prolotherapy is not an effective treatment for this condition. When combined with spinal manipulation, exercise, and other co-interventions, prolotherapy may improve pain and disability. Conclusions are confounded by clinical heterogeneity amongst studies and by the presence of co-interventions.

Chronic Pain

A systematic review by Hauser et al. examined dextrose (d-glucose) prolotherapy efficacy in the treatment of chronic pain from a number of musculoskeletal indications, searching databases from 1990 to January 2016. Fourteen RCTs, 1 case-control study, and 18 case series studies met the inclusion criteria. Pain conditions were clustered into

tendinopathies, OA, spinal/pelvic, and myofascial pain. The RCTs were high quality and found that dextrose injection was superior to controls in Osgood–Schlatter disease, LE traumatic RC injury, knee OA, finger OA, and myofascial pain; in biomechanical but not subjective measures in TMJ conditions; and comparable in a short-term RCT but superior in a long-term RCT in LBP. Many observational studies were of high quality and reported consistent positive evidence in multiple studies of tendinopathies, knee OA, sacroiliac pain, and iliac crest pain that received RCT confirmation in separate studies. The reviewers concluded that overall, dextrose prolotherapy has been demonstrated to be efficacious and should be considered in patients who fail to respond to conservative therapies as a treatment for pain and dysfunction associated with chronic musculoskeletal conditions, particularly tendinopathies and OA. With inclusion limited to patients with pain > 3–6 months in the reviewed studies, the efficacy of prolotherapy for acute (< 3 months) musculoskeletal pain cannot be determined (2016).

U.S. FOOD AND DRUG ADMINISTRATION (FDA)

Prolotherapy is a procedure and, therefore, not subject to FDA regulation. However, any medical devices, drugs, biologics, or tests used as a part of this procedure may be subject to FDA regulation.

Two sclerosing agents have been approved by the FDA: sodium tetradecyl sulfate (Sotradecol®), and ethanolamine (Ethamolol®) for the treatment of varicose veins and esophageal varices. The agents used in the reviewed studies, such as dextrose and lidocaine, are approved for injection by the FDA but are not specifically approved for prolotherapy for joint and ligamentous injections, making such use off-label.

Another agent, sodium morrhuate (Scleromate®), is not currently listed as an approved sclerosing agent per the FDA.

NStride® (Zimmer Biomet), an autologous protein solution device, does not have FDA approval and is limited to investigational use.

Additional information, under active ingredient name sodium tetradecyl sulfate and ethanolamine, is available at: <https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=040541> and <https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=BasicSearch.process>. (Accessed April 29, 2019)

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GUIDELINE HISTORY/REVISION INFORMATION

Date	Action/Description
05/01/2019	<ul style="list-style-type: none">Updated supporting information to reflect the most current description of services, clinical evidence, and references; no change to coverage rationale or lists of applicable codesArchived previous policy version MMG111.I

INSTRUCTIONS FOR USE

This Medical Management Guideline provides assistance in interpreting UnitedHealthcare standard benefit plans. When deciding coverage, the member specific benefit plan document must be referenced as the terms of the member specific benefit plan may differ from the standard benefit plan. In the event of a conflict, the member specific benefit plan document governs. Before using this guideline, please check the member specific benefit plan document and any applicable federal or state mandates. UnitedHealthcare reserves the right to modify its Policies and Guidelines as necessary. This Medical Management Guideline is provided for informational purposes. It does not constitute medical advice.

UnitedHealthcare may also use tools developed by third parties, such as the MCG™ Care Guidelines, to assist us in administering health benefits. UnitedHealthcare West Medical Management Guidelines are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.

Member benefit coverage and limitations may vary based on the member's benefit plan Health Plan coverage provided by or through UnitedHealthcare of California, UnitedHealthcare Benefits Plan of California, UnitedHealthcare of Oklahoma, Inc., UnitedHealthcare of Oregon, Inc., UnitedHealthcare Benefits of Texas, Inc., or UnitedHealthcare of Washington, Inc.