Health Evidence Review Commission (HERC)

Coverage Guidance: Newer Interventions for Osteoarthritis of the Knee

Approved 3/14/2019

HERC Coverage Guidance

Whole body vibration

Whole body vibration is not recommended for coverage (*strong recommendation*).

TENS

TENS is not recommended for coverage (*strong recommendation*).

Glucosamine-chondroitin

Glucosamine-chondroitin is not recommended for coverage (*weak recommendation*).

Glucosamine alone is not recommended for coverage (*strong recommendation*).

Chondroitin alone is not recommended for coverage (*weak recommendation*).

Platelet-rich plasma

Platelet-rich plasma is not recommended for coverage (*weak recommendation*)

Note: Definitions for strength of recommendation are in Appendix A. *GRADE Table Element Descriptions*.

Rationales for each recommendation appear below in the GRADE table.

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Rationale for development of coverage guidances and multisector intervention reports

Coverage guidances are developed to inform coverage recommendations for public and private health plans in Oregon as plan administrators seek to improve patients' experience of care, population health, and the cost-effectiveness of health care. In the era of public and private sector health system transformation, reaching these goals requires a focus on maximizing the benefits and minimizing the harms and costs of health interventions.

HERC uses the following principles in selecting topics for its reports to guide public and private payers:

- Represents a significant burden of disease or health problem
- Represents important uncertainty with regard to effectiveness or harms
- Represents important variation or controversy in implementation or practice
- Represents high costs or significant economic impact
- Topic is of high public interest

HERC bases its reports on a review of the best available research applicable to the intervention(s) in question. For coverage guidances, which focus on diagnostic and clinical interventions, evidence is evaluated using an adaptation of the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) methodology. For more information on coverage guidance methodology, see Appendix A.

Multisector interventions can be effective ways to prevent, treat, or manage disease at a population level. In some cases, HERC has reviewed evidence and identified effective interventions, but has not made formal coverage recommendations when these policies are implemented in settings other than traditional health care delivery systems because effectiveness could depend on the environment in which the intervention is implemented.

GRADE Table

HERC develops recommendations by using the concepts of the GRADE system. GRADE is a transparent and structured process for developing and presenting evidence and for performing the steps involved in developing recommendations. The table below lists the elements that determine the strength of a recommendation. HERC reviews the evidence and assesses each element, which in turn is used to develop the recommendations presented in the coverage guidance box. Estimates of effect are derived from the evidence presented in this document. Assessments of confidence are from the published systematic reviews and meta-analyses, where available and judged to be reliable.

In some cases, no systematic reviews or meta-analyses encompass the most current literature. In those cases, HERC may describe the additional evidence or alter the assessments of confidence in light of all available information. Such assessments are informed by clinical epidemiologists from the Center for Evidence-based Policy. Unless otherwise noted, statements regarding resource allocation, values and preferences and other considerations are the assessments of HERC, as informed by the evidence reviewed, public testimony, and subcommittee discussion.

Recommendations for coverage are based on the balance of benefit and harms, resource allocation, values and preferences, and other considerations. See Appendix A for more details about the factors that constitute the GRADE table.

GRADE Table

Should whole body vibration be recommended for coverage for osteoarthritis of the knee?

Outcomes	Estimate of Effect for Outcome/ *Confidence in Estimate*	Resource Allocation	Values and Preferences	Other Considerations
Long-term pain *(Critical outcome)*	Insufficient evidence	The machines for home use range from $100 to $250 to thousands of dollars. Clinic-based treatments would be low to moderate expense depending on what is charged and the frequency of treatments.	Patients would likely prefer noninvasive interventions. Whole body vibration appears to be popular based on its widespread availability for home purchase, but the physical experience of doing this intervention might not be universally appealing (e.g., for older adults who are unsteady on their feet). We would expect moderate variability in values and preferences.	The improvement in intermediate-term function did not meet the threshold of minimal clinically important difference.
Long-term function *(Critical outcome)*	Insufficient evidence			
Intermediate-term pain *(Important outcome)*	No significant difference between exercise programs with whole body vibration and exercise and strength-training programs alone SMD -0.20 (95% CI -1.12 to 0.71) ●●○○ *(Low confidence, based on 4 RCTs, n = 180)*			
Intermediate-term function *(Important outcome)*	Improved in exercise programs with whole body vibration compared to exercise and strength-training programs alone SMD -0.26 (95% CI -0.45 to -0.06) ●●○○ *(Low confidence, based on 4 RCTs, n = 180)*			
Harms *(Important outcome)*	Adverse events were rare and did not differ significantly between active and control groups ●●○○ *(Low confidence, based on 4 studies, n = 180)*			

Balance of benefits and harms: We have low confidence that whole body vibration improves intermediate-term function but not to a clinically significant degree, and it is similar to exercise and strength-training programs in terms of pain. There appear to be few adverse events.
Rationale: We recommend against coverage because of the low evidence for a lack of clinically significant improvement in outcomes, moderate cost, and moderate variability in values and preferences. It is a strong recommendation because there is no evidence of clinically significant improvement, and there are alternative treatments for this condition. Because of the prevalence of this condition and the ease of studying this intervention, we would require at least moderate-quality evidence of benefit in order to recommend coverage.

Recommendation: Whole body vibration is not recommended for coverage (*strong recommendation*).

Should transcutaneous electrical nerve stimulation (TENS) be recommended for coverage for osteoarthritis of the knee?

Outcomes	Estimate of Effect for Outcome/ *Confidence in Estimate*	Resource Allocation	Values and Preferences	Other Considerations
Long-term pain *(Critical outcome)*	Insufficient evidence	TENS is generally an inexpensive intervention (although very expensive models are available). If it were effective, its low price would make it very appealing.	Patients would prefer simple, inexpensive, noninvasive treatments for knee osteoarthritis that improve pain and function. Some patients have preferences for or against nonallopathic treatments, which leads to moderate variability in values and preferences.	
Long-term function *(Critical outcome)*	Insufficient evidence			
Intermediate-term pain *(Important outcome)*	No significant difference between TENS and sham control Pooled estimates not provided ●●○○ *(Low confidence, based on 2 RCTs, n = 650)*			
Intermediate-term function *(Important outcome)*	No significant difference between TENS and sham control Pooled estimates not provided ●●○○ *(Low confidence, based on 2 RCTs, n = 650)*			
Harms *(Important outcome)*	Adverse events were rare and did not differ significantly between active and sham control groups ●●○○ *(Low confidence, based on 2 studies, n = 650*			

Balance of benefits and harms: We have low confidence that TENS appears to have no benefits in terms of intermediate-term pain and function, has no harms, and insufficient evidence for long-term outcomes.

Rationale: Given that there is evidence that TENS is ineffective, even though it is inexpensive and patients may be willing to try it, coverage is not recommended. It is a strong recommendation because available evidence supports inefficacy rather than clinical benefit. Because of the prevalence of this condition and the ease of studying this intervention, we would require at least moderate-quality evidence of benefit in order to recommend coverage.

Recommendation: TENS is not recommended for coverage for osteoarthritis of the knee (*strong recommendation*).

Should glucosamine-chondroitin be recommended for coverage for osteoarthritis of the knee?

Outcomes	Estimate of Effect for Outcome/ *Confidence in Estimate*	Resource Allocation	Values and Preferences	Other Considerations
Long-term pain *(Critical outcome)*	No significant difference between glucosamine-chondroitin and placebo control SMD -0.73 (95% CI -4.03 to 2.57) ●●●○ *(Moderate confidence, based on 3 RCTs, n = 466)*	Glucosamine-chondroitin is an inexpensive daily supplement. Its low cost would increase its favorability.	Patients would prefer simple, inexpensive, noninvasive treatments for knee osteoarthritis that improve pain and function. A daily supplement would likely be acceptable to many patients, so we would expect low variability of values and preferences.	A separate systematic review with serious limitations raised questions about whether the individual components were more effective than the combination. Individual patient data meta-analysis showed that glucosamine alone has no effect. Because this is an over-the-counter supplement, product quality may vary significantly.
Long-term function *(Critical outcome)*	No significant difference between glucosamine-chondroitin and placebo control SMD -0.45 (95% CI -2.75 to 1.84) ●●●○ *(Moderate confidence, based on 3 RCTs, n = 466)*			
Intermediate-term pain *(Important outcome)*	Improved with glucosamine-chondroitin compared to placebo control Pooled estimates not provided ●●○○ *(Low confidence, based on 3 RCTs, n = 881)*			
Intermediate-term function *(Important outcome)*	Improved with glucosamine-chondroitin compared to placebo control Pooled estimates not provided ●●○○ *(Low confidence, based on 3 RCTs, n = 881)*			
Harms *(Important outcome)*	Adverse effects were rare and did not differ significantly between active and control groups ●●●○ *(Moderate confidence, based on 6 studies, n = 4,195)*			

Balance of benefits and harms: We have moderate confidence that glucosamine-chondroitin has no effect on long-term pain or function, but have low confidence that it improves intermediate-term pain and function (although the estimates include mixed effect sizes with regards to clinical significance). There appear to be no harms.

Rationale: We recommend against coverage because of moderate-quality evidence of no benefit in long-term pain and function, and it is unclear that the intermediate-term benefit is clinically significant given the mixed effect sizes. The low cost and low variability in patient preferences temper the recommendation against, and the combination of these factors and the possible clinically significant intermediate effect lead to a weak recommendation against coverage. Because of the prevalence of this condition and the ease of studying this intervention, we would require at least moderate-quality evidence of benefit in order to recommend coverage.
Recommendation: Glucosamine-chondroitin is not recommended for coverage (*weak recommendation*).

Should glucosamine alone be recommended for coverage for osteoarthritis of the knee?

Outcomes	Estimate of Effect for Outcome/ *Confidence in Estimate*	Resource Allocation	Values and Preferences	Other Considerations
Long-term pain *(Critical outcome)*	No significant difference between glucosamine and placebo control SMD -0.05 (95% CI -0.22 to 0.12) ●●●○ *(Moderate confidence, based on 3 RCTs, n = 1,007)*	Glucosamine alone is a very inexpensive daily supplement. Its low cost would increase its favorability.	Patients would prefer simple, inexpensive, noninvasive treatments for knee osteoarthritis that improve pain and function. A daily supplement would likely be acceptable to many patients, so we would expect low variability of values and preferences.	Because this is an over-the-counter supplement, product quality may vary significantly.
Long-term function *(Critical outcome)*	No significant difference between glucosamine and placebo control Pooled estimates not provided ●●○○ *(Low confidence, based on 3 RCTs, n = 1,007)*			
Intermediate-term pain *(Important outcome)*	Insufficient evidence			
Intermediate-term function *(Important outcome)*	Insufficient evidence			
Harms *(Important outcome)*	Adverse effects were rare and did not differ significantly between active and placebo control groups ●●●○ *(Moderate confidence, based on 6 studies, n = 4,195)*			

Balance of benefits and harms: We have low to moderate confidence that glucosamine alone is ineffective for long-term pain and function; there is insufficient evidence for other outcomes. There appear to be no significant adverse effects.
Rationale: Despite patients' willingness to take a supplement and the supplement being low cost and not harmful, the available evidence suggests glucosamine alone is an ineffective intervention. Therefore, we make a strong recommendation against coverage. Because of the prevalence of this condition and the ease of studying this intervention, we would require at least moderate-quality evidence of benefit in order to recommend coverage.
Recommendation: Glucosamine alone is not recommended for coverage (*strong recommendation*).

Should chondroitin alone be recommended for coverage for osteoarthritis of the knee?

Outcomes	Estimate of Effect for Outcome/ *Confidence in Estimate*	Resource Allocation	Values and Preferences	Other Considerations
Long-term pain *(Critical outcome)*	No significant difference between chondroitin and control Pooled estimates not provided ●●●○ *(Moderate confidence, based on 3 RCTs, n = 1,889)*	Chondroitin alone is a very inexpensive daily supplement. Its low cost would increase its favorability.	Patients would prefer simple, inexpensive, noninvasive treatments for knee osteoarthritis that improve pain and function. A daily supplement would likely be acceptable to many patients, so we would expect low variability of values and preferences.	Because this is an over-the-counter supplement, product quality may vary significantly.
Long-term function *(Critical outcome)*	No significant difference between chondroitin and control Pooled estimates not provided ●●○○ *(Low confidence, based on 2 RCTs, n = 1,267)*			
Intermediate-term pain *(Important outcome)*	Improved with chondroitin compared to control Pooled estimates not provided ●●○○ *(Low confidence, based on 2 RCTs, n = 974)*			
Intermediate-term function *(Important outcome)*	Insufficient evidence			
Harms *(Important outcome)*	Adverse effects were rare and did not differ significantly between active and control groups ●●●○ *(Moderate confidence, based on 6 studies, n = 4,195)*			

Balance of benefits and harms: Chondroitin alone has no benefit for long-term pain or function, but we have low confidence that it improves intermediate-term pain. There do not appear to be significant adverse effects.
Rationale: This is a low-cost, apparently safe, and acceptable intervention that improves intermediate-term pain but has no long-term impact. There is less evidence to support it than glucosamine and chondroitin in combination. Therefore, we make a recommendation against coverage; it is a weak recommendation because further evidence could support intermediate-term improvements in pain and function. Because of the prevalence of this condition and the ease of studying this intervention, we would require at least moderate-quality evidence of benefit in order to recommend coverage.
Recommendation: Chondroitin alone is not recommended for coverage (*weak recommendation*).

Should platelet-rich plasma be recommended for coverage for osteoarthritis of the knee?

Outcomes	Estimate of Effect for Outcome/ *Confidence in Estimate*	Resource Allocation	Values and Preferences	Other Considerations
Long-term pain *(Critical outcome)*	Improved with platelet-rich plasma compared to control MD 6.0 on WOMAC pain score (95% CI not provided, p < 0.05) ●●○○ *(Low confidence, based on 1 RCT, n = 30)*	Platelet-rich plasma injections are relatively expensive, ranging from hundreds to thousands of dollars.	Patients would generally prefer noninvasive interventions. However, a single minimally invasive intervention would likely be appealing if it offered long-term relief and had few risks. We would expect low variability in patient preferences.	The one study evaluating long-term pain and function was industry-funded but well designed.
Long-term function *(Critical outcome)*	Improved with platelet-rich plasma compared to control MD 24.0 on WOMAC function score (95% CI not provided, p < 0.05) ●●○○ *(Low confidence, based on 1 RCT, n = 30)*			
Intermediate-term pain *(Important outcome)*	Improved with platelet-rich plasma compared to controls Pooled estimates not provided ●●○○ *(Low confidence, based on 5 RCTs, n = 439)*			
Intermediate-term function *(Important outcome)*	Insufficient evidence			

Should platelet-rich plasma be recommended for coverage for osteoarthritis of the knee?

Outcomes	Estimate of Effect for Outcome/ *Confidence in Estimate*	Resource Allocation	Values and Preferences	Other Considerations
Harms *(Important outcome)*	Adverse events were rare and did not differ significantly between active and control groups ●●○○ *(Low confidence, based on 3 studies, n = 215)*			

Balance of benefits and harms: There is low confidence that platelet-rich plasma injections yield improvements in intermediate-term pain and long-term pain and function with no increased risk of adverse effects.
Rationale: We do not recommend coverage for platelet-rich plasma for osteoarthritis of the knee because the data supporting long-term efficacy are based on a single, small, industry-funded trial and there is low confidence in intermediate-term improvements on pain (however, this assessment appears to be based on studies with mixed results), and also moderate resource allocation. For such a common condition, which is relatively straightforward to research, further research is necessary to support use of platelet-rich plasma prior to covering it. The recommendation is weak because there would likely be low variability in patient values and preferences and further evidence could change the recommendation. Because of the prevalence of this condition and the ease of studying this intervention, we would require at least moderate-quality evidence of benefit in order to recommend coverage.
Recommendation: Platelet-rich plasma is not recommended for coverage (*weak recommendation*)

Note: GRADE table elements are described in Appendix A. A GRADE Evidence Profile is in Appendix B.

Background

Osteoarthritis is a common cause of pain in the limbs, and it frequently occurs in the knees; the risk of osteoarthritis increases with age (Centers for Disease Control and Prevention, 2017). Knee osteoarthritis is the progressive destruction of the cartilage that lines the knee joints, the subchondral bone surfaces, and synovium, which can cause pain, immobility, muscle weakness, and reduction in function (Newberry et al., 2017). Osteoarthritis is usually the result of progressive joint cartilage destruction over time, but can also be caused by trauma, inactivity, excess weight, or disease processes such as rheumatoid arthritis (Newberry et al., 2017). The aging of the population and the increasing prevalence of obesity have led to an increase in the incidence of knee osteoarthritis (Newberry et al., 2017).

Osteoarthritis is usually treated with a combination of therapies, including physical activity, weight loss, medications (prescription drugs and over-the-counter pain relievers), physical therapy, alternative therapies (e.g., massage, acupuncture), corticosteroid injections, and surgery (National Institute of Arthritis and Musculoskeletal and Skin Disease, 2014). Treatments for osteoarthritis aim to reduce symptoms and improve function, and most treatments do not modify the natural history or progression of the disease (Newberry et al., 2017).

The visual analog scale (VAS) is a common way to measure pain, consisting of a straight line with the endpoints defining extreme limits such as "no pain at all" and "pain as bad as it could be." The patient is asked to indicate the pain intensity on the line between the two endpoints. The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) is one of the most commonly used measures to evaluate patients with lower limb osteoarthritis (Walker et al, 2018). WOMAC is a composite measure that includes pain, stiffness, and functional limitations, with scores ranging from zero to 68. Appendix E shows the minimal clinically important difference (MCID) for these scales as defined by a representative sample of studies in a review by Newberry et al. (2017) for the Agency for Healthcare Research and Quality (AHRQ).

Indications

The clinical diagnosis of knee osteoarthritis is usually based on presentation, including gradual onset of weight-bearing knee pain that is exacerbated by use of the joint and tends to worsen over the course of the day (Newberry et al., 2017). Radiographs may be used to diagnose osteoarthritis, but radiographic osteoarthritis scales do not correlate well with symptoms (Newberry et al., 2017).

Technology Description

This coverage guidance reviews four treatments for knee osteoarthritis: whole body vibration, TENS, glucosamine and/or chondroitin, and platelet-rich plasma. Whole body vibration involves placing a person on a vibrating platform (Wang et al., 2016). TENS is the application of electrical current through electrodes placed on the skin for pain control, applied with varying frequencies, from low (< 10 Hz) to high (> 50 Hz) (DeSantana et al., 2008).

Glucosamine is one of the most abundant monosaccharides in the human body and is an amino sugar precursor in the synthesis of glycosylated proteins and lipids. The proposed mechanism of action for glucosamine is based on its supposed anti-inflammatory activity, stimulation of proteoglycan synthesis, and inhibition of proteolytic enzyme synthesis (Simental-Mendia et al., 2018).

In the past decade, there has been growing interest in the use of autologous growth factors for the treatment of knee osteoarthritis, such as intra-articular injections of platelet-rich plasma. To prepare platelet-rich plasma, autologous blood is put through a centrifuge, yielding a higher concentration of platelets than baseline values. The regenerative effect and anti-inflammatory potential of platelet-rich plasma in the tissue healing process have led to investigation of platelet-rich plasma as a treatment for musculoskeletal indications, including osteoarthritis (Shen et al., 2018).

Evidence Review

Whole Body Vibration

Newberry et al., 2017

This is a good-quality systematic review and health technology assessment of selected nonsurgical treatments of osteoarthritis of the knee conducted for the AHRQ. The interventions included in this report are glucosamine and chondroitin, cell-based therapies, exercise therapies, balneotherapy, electrical stimulation, whole body vibration, heat, ultrasound, orthoses, weight loss diets, and home-based or self-management programs. The report updates earlier systematic reviews of the included interventions that had previously been conducted for AHRQ. The authors used standard AHRQ methods for conducting this updated review, and the final searches were conducted in September 2016. For efficacy outcomes, only randomized controlled trials (RCTs) were eligible for inclusion, with the exception that prospective cohort studies of weight loss could also be included. Because of the large amount of data available for glucosamine-chondroitin, small trials (those with fewer than 50 participants per arm) were excluded. For outcomes related to adverse events, prospective observational studies and case reports were included. The report analyzed outcomes of pain, function, and quality of life in the short term (4-12 weeks), medium term (12-26 weeks), and long term (> 26 weeks). Studies with less than four weeks of follow-up were excluded. The authors applied an adapted GRADE methodology to rate the strength of evidence.

The authors identified four RCTs (n = 180) assessing the effects of whole body vibration on medium-term pain and function. Treatment was provided three to five times per week in a 30-minute session. A random effects meta-analysis of these studies found no statistically significant difference in medium-term WOMAC pain scores between whole body vibration and controls (exercise and strength-training programs) (SMD -0.20, 95% CI -1.12 to 0.71, I^2 = 74.2%), and a small but statistically significant improvement in medium-term WOMAC function with whole body vibration (SMD -0.26, 95% CI -0.45 to -0.06, I^2 = 0%). This improvement did not meet the threshold for a minimal clinically important difference (defined as a SMD of -0.37). With regard to adverse effects, the authors observed that there were no significant differences in adverse events between whole body vibration and control groups, although one patient who received whole body vibration reported minor back pain. Overall, the authors concluded that there was low strength of evidence of no effect of whole body vibration on medium-term pain, but low strength of evidence that whole body vibration resulted in small but statistically significant improvements in medium-term function.

Transcutaneous Electrical Nerve Stimulation

Newberry et al., 2017

This review is described above. The authors identified two RCTs (n = 650) that reported on medium-term pain and function. One of the studies compared TENS to sham TENS, and the second study compared TENS plus exercise to sham TENS plus exercise or exercise alone. With respect to medium-term pain and function, neither study showed significant between-group differences for TENS and sham TENS at six months. The latter study showed no statistically significant difference for any outcome between the TENS plus exercise and exercise-alone groups. With regard to adverse events, there was no significant difference between TENS and control groups in adverse events. Overall, the authors concluded that although there was moderate strength of evidence that TENS produced small improvements in short-term pain, there was low-strength evidence of no effect of TENS on short-term function, medium-term pain, and medium-term function.

Glucosamine and Chondroitin

Newberry et al., 2017

This review is described above. For the combination of glucosamine and chondroitin, the authors identified three RCTs (n = 881) that addressed medium-term pain and function. One study comparing glucosamine-chondroitin to celecoxib showed similar clinically significant reductions in pain. The WOMAC function score showed similar clinically significant declines in function in both groups in a six-month period (45.5% for glucosamine chondroitin and 46.4% for celecoxib, RR 1.02, 95% CI 0.86 to 1.21). The second RCT, an open-label study that compared glucosamine-chondroitin plus a low-calorie weight loss diet to diet alone found that the glucosamine-chondroitin group had greater improvement in WOMAC pain scores (MD -1.59, 95% CI -2.31 to -0.87) and VAS pain scores (MD -2.08, 95% CI -2.40 to -1.76). The glucosamine-chondroitin group also had significant improvements in WOMAC function compared to diet alone (MD -3.86, 95% CI -6.16 to -1.56). A third trial comparing glucosamine-chondroitin to a placebo found greater improvement in pain scores in the placebo arm, and no difference in WOMAC function between the two arms.

For the combination of glucosamine and chondroitin, the authors identified three RCTs (n = 466) that addressed long-term pain and function. A random effects meta-analysis of these studies found no statistically significant difference in long-term WOMAC pain scores between glucosamine-chondroitin and controls (SMD -0.73, 95% CI -4.03 to 2.57, I^2 = 96.8%). Similarly, a random effects meta-analysis of these studies found no statistically significant difference in long-term WOMAC function scores between glucosamine-chondroitin and controls (SMD -0.45, 95% CI -2.75 to 1.84, I^2 = 94.5%).

Overall, the authors concluded that there was low strength of evidence that glucosamine-chondroitin improved medium-term pain and function, and moderate strength of evidence that glucosamine-chondroitin had no effect on long-term pain and function.

For glucosamine alone, the authors identified three studies (two RCTs and one post-hoc analysis of two additional RCTs) (n = 1,007) assessing long-term pain. A random effects meta-analysis of these studies found no statistically significant difference in long-term WOMAC pain scores between glucosamine and controls (SMD -0.05, 95% CI -0.22 to 0.12, I^2 = 0%). In two of the three trials, there were no significant differences between glucosamine and placebos in long-term WOMAC function, whereas the third study

found that glucosamine improved function compared to a placebo in a three-year period as measured by the Lequesne index. A pooled analysis of long-term functional outcomes was not performed.

Overall, the authors concluded that there was moderate strength of evidence that glucosamine alone had no effect on long-term pain and low strength of evidence of no effect on long-term function.

For chondroitin alone, two RCTs (n = 974) assessed medium-term pain and function. In the first RCT, both chondroitin dosing regimens (1,200 mg once daily or 400 mg thrice daily), performed better than a placebo with respect to VAS pain scores (MD -7.70, 95% CI -14.43 to -0.97 for once daily dosing and MD -8.30, 95% CI -15.20 to -1.40 for thrice daily dosing). This trial also found improved medium-term function in the chondroitin arm compared to a placebo as measured by the Lequesne index (MD -2.2, 95% CI -3.37 to -1.03 for once daily dosing and MD -1.90, 95% CI -3.11 to -0.69 for thrice daily dosing). The second RCT compared chondroitin to a placebo and reported three categorical pain response outcomes: 40 mm and 60 mm decreases in VAS were achieved more often in the chondroitin group (RR 0.68, 95% CI 0.51 to 0.91 and RR 0.44, 95% CI 0.23 to 0.85, respectively), but there was no statistically significant difference in the achievement of a 40% reduction in WOMAC pain score (RR 0.83, 95% CI 0.68 to 1.02). In this study, there was no difference between chondroitin and a placebo in WOMAC function scores at six months.

For chondroitin alone, three RCTs (n = 1,889) assessed long-term pain and two RCTs (n = 1,267) assessed long-term function. Among the three RCTs assessing WOMAC pain scores at one to two years, none found statistically significant differences between chondroitin and a placebo. Similarly, the two RCTs reporting on WOMAC function scores at one to two years found no statistically significant differences between chondroitin and placebo.

Overall, the authors concluded that there was low strength of evidence that chondroitin alone improved medium-term pain, but insufficient evidence on medium-term function. There was moderate strength evidence of no effect on long-term pain and low strength of evidence of no effect on long-term function.

With regard to adverse effects, the authors observed that serious adverse events were rare in all studies. In particular, glucosamine and chondroitin did not appear to result in greater rates of gastrointestinal side effects or hyperglycemia compared to placebos. However, in one study comparing chondroitin to a placebo, there was a higher rate of withdrawal due to adverse effects in the chondroitin group, but the specific effects were not described.

Simental-Mendia et al., 2018

This is a fair-quality systematic review and meta-analysis of randomized placebo-controlled trials of glucosamine, chondroitin, or their combination for treatment of osteoarthritis of the knee. Studies were eligible for inclusion if they were designed as parallel arm or crossover placebo-controlled randomized trials with a treatment duration of at least one month and that reported on VAS or WOMAC pain scores. Overall, the authors identified 29 trials with a total of 6,120 participants. Compared to the AHRQ review, many of the trials included in this review were older, reported only short-term outcomes, and had fewer than 50 participants in each arm. Additionally, many of the studies had methodological limitations: six failed to report random sequence generation, 13 trials failed to report adequate methods of allocation concealment, and 16 trials had insufficient information about blinding. The meta-analytic results were not stratified by follow-up period and sensitivity analyses were not performed. A random-effects model was used for meta-analysis.

On the basis of six studies with 1,168 patients, glucosamine alone resulted in a small but statistically significant reduction in VAS pain score compared to a placebo (weighted mean difference [WMD] -7.41, 95% CI -14.31 to -0.51, I^2 = 78%). Based on 10 studies with 1,967 patients, glucosamine alone did not result in statistically significant improvement in the WOMAC pain score (WMD -0.76, 95% CI -1.93 to 0.40, I^2 = 91%), or in the WOMAC function score (WMD -1.57, 95% CI -3.81 to 0.68, I^2 = 78%).

On the basis of 16 studies with 3,462 patients, chondroitin alone resulted in a small but statistically significant reduction in VAS pain score compared to a placebo (WMD -8.35, 95% CI -11.84 to -4.85, I^2 = 80%). Based on two studies with 933 patients, chondroitin alone did not result in statistically significant improvement in the WOMAC pain score (WMD -0.13, 95% CI -0.65 to 0.40, I^2 = 0%). Based on one study with 631 patients, chondroitin alone did not result in statistically significant improvement in the WOMAC function score (WMD 0.30, 95% CI -0.02 to 0.62).

On the basis of three studies with 1,051 patients, glucosamine-chondroitin did not result in a statistically significant reduction in VAS pain score compared to a placebo (WMD -0.28, 95% CI -8.87 to 8.32, I^2 = 94%). Based on five studies with 1,236 patients, glucosamine-chondroitin did not result in statistically significant improvement in the WOMAC pain score (WMD 0.84, 95% CI -2.51 to 4.18, I^2 = 99%), or in the WOMAC function score (WMD -0.98, 95% CI -3.61 to 1.65, I^2 = 89%).

Overall, the authors concluded that glucosamine alone or chondroitin alone improved knee pain on the VAS, but did not result in statistically significant improvements in the WOMAC pain or function score. The combination of glucosamine and chondroitin did not result in statistically significant improvements in VAS pain score or the WOMAC pain or function scores. There was a moderate-to-high degree of heterogeneity in most of the analyses.

Runhaar et al., 2017

This is a good-quality individual patient data meta-analysis and subgroup analysis of the effectiveness of glucosamine alone for knee and hip osteoarthritis. The authors identified 21 eligible randomized placebo-controlled studies, but only six shared their data with the authors of this review. None of the six studies that shared data were industry funded. There were 1,625 patients in the included studies, which represented 55% of the total number of participants in the eligible placebo-controlled trials. Overall, two trials contributed to the estimate of short-term effects for knee osteoarthritis, two trials contributed to the estimates of long-term effects for knee osteoarthritis, and one trial contributed estimates of short- and long-term effects for hip osteoarthritis. In the overall meta-analysis, there were no differences in short-term WOMAC pain (SMD -0.03, 95% CI -0.15 to 0.09, I^2 = 0%), or long-term WOMAC pain (SMD -0.04, 95% CI -0.18 to 0.10, I^2 = 14%).

The use of individual patient data meta-analysis allows for subgroup analyses that are not generally possible with a traditional meta-analysis. For this review, the authors examined subgroups defined by baseline pain, body mass index, sex, radiographic arthritis grade, and evidence of inflammation. When considering only the four studies of knee osteoarthritis, there were no statistically significant treatment-subgroup interactions for any reported outcome (short- and long-term pain or function).

Overall, the body of evidence synthesis on the topic of glucosamine-chondroitin has found mixed results with generally high levels of heterogeneity. However, in the analyses that focus on summarizing large placebo-controlled trials and that report outcomes stratified by follow-up period, there may be a small benefit in medium-term pain and function, but no difference in long-term outcomes.

Platelet-Rich Plasma

Newberry et al., 2017

This review is described above. The authors identified five RCTs (n = 439) that assessed the effects of platelet-rich plasma on medium-term pain and two RCTs that assessed medium-term function.

In the first trial, participants were randomized to receive one platelet-rich plasma injection, two platelet-rich plasma injections, or a saline placebo injection. Both platelet-rich plasma groups showed significant reductions in VAS pain score at six months compared to the placebo (MD -2.45, 95% CI -2.92 to -1.98 for single injection and MD -2.07, 95% CI -2.59 to -1.55 for two injections). Similarly, at six months, WOMAC function scores were significantly better in the platelet-rich plasma groups than the placebo group (MD -19.38, 95% CI not reported for single injection and MD -17.06, 95% CI not reported for two injections).

In the second trial, participants were randomized to two injections of platelet-rich plasma separated by four weeks or to no treatment. At six months, there were no statistically significant differences in WOMAC pain scores between the groups (MD -0.96, 95% CI -2.88 to 0.96). Similarly, there was no significant difference between the groups with respect to WOMAC function score at six months.

In the third trial, participants were randomized to one platelet-rich plasma injection, three platelet-rich plasma injections, or saline placebo injection. Both platelet-rich plasma arms showed significant improvement over a placebo in EuroQol VAS pain scores at six months (MD -14.0, 95% CI -16.44 to -11.56 for one injection and MD -23.40, 95% CI -27.14 to -19.66 for three injections).

In the fourth trial, participants were randomized to two injections of platelet-rich plasma or to paracetamol (acetaminophen). At six months, the KOOS pain score was significantly lower in the platelet-rich plasma group than the paracetamol group (MD -6.90, 95% CI -18.29 to -4.49).

In the fifth trial, participants were randomized to three injections of platelet-rich plasma over six weeks or to acetaminophen. At six months, there were no significant differences between the groups with respect to VAS pain scores.

With regard to adverse events, the authors noted that one trial reported no serious adverse events, and the second trial reported that one participant had increased pain and stiffness after the platelet-rich plasma injection.

Overall, the authors concluded that there was low strength of evidence that platelet-rich plasma improved medium-term pain, and insufficient evidence to assess the effects of platelet-rich plasma on medium-term function.

Shen et al., 2017

This is a systematic review and meta-analysis of platelet-rich plasma injections. With the exception of one saline placebo-controlled study discussed separately below, the studies included in this review either used a variety of questionably effective active controls like hyaluronic acid or ozone injections, or were already included in the AHRQ review. In their meta-analysis, the authors did not separately consider studies using active and placebo controls. It is thus regarded as out of scope for this coverage guidance.

Smith, 2016

This is a small, single-center, but good-quality double-blind randomized placebo-controlled trial of autologous platelet-rich plasma injection for knee osteoarthritis. This study was not included in the Newberry review. In this study, 30 patients were randomized (1:1) to undergo three weekly injections with autologous platelet-rich plasma or with an equivalent amount of saline placebo control. Adequate allocation concealment and blinding measures are described. Participants were followed for 12 months with full retention of all study participants. However, the study likely did not enroll enough participants to attain optimal information size when assessing a continuous variable. The study author disclosed that he is a consultant for Arthrex Inc., which also funded the study (Arthrex Inc. makes a device to prepare autologous platelet-rich plasma for injection).

Eligible patients were between ages 30 and 80, had a documented diagnosis of osteoarthritis for at least six weeks, had Kellgren-Lawrence radiographic grade 2-3 knee osteoarthritis, and a WOMAC pain scale score of at least eight. There were multiple exclusions including clinically significant effusions, valgus or varus deformities, viscosupplementation or surgery on the target knee in the prior six months, anticoagulation, and the presence of osteoarthritis in the hips or contralateral knee. The groups were similar at baseline with respect to sex, BMI, and radiographic grade; the platelet-rich plasma group had a slightly older mean age than the saline control group.

At 12 months, the mean WOMAC pain score had improved from 10 to 2 (76% improvement) in the platelet-rich plasma group compared to 11 to 9 (19% improvement) in the saline control group. The mean WOMAC function score had improved from 32 to 7 (78% improvement) in the platelet-rich plasma group compared to 31 to 30 (3% improvement) in the control group. These between-group differences were statistically significant ($p < 0.05$). There were no serious adverse events in either group, although one patient in the placebo group reported increased pain in the target leg.

Evidence Summary

On the basis of a recently updated AHRQ review on selected nonsurgical interventions for osteoarthritis of the knee, there is low strength of evidence that glucosamine-chondroitin and platelet-rich plasma result in small improvements in medium-term pain and function. There was low strength of evidence that TENS has no significant effects on medium-term pain or function. Evidence for the long-term effectiveness of these interventions is generally lacking, although there is moderate strength of evidence that glucosamine-chondroitin has no significant long-term effects on pain or function. A small RCT of platelet-rich plasma that was not included in the AHRQ review concluded that there were statistically significant benefits for pain and function at 12 months; the AHRQ review itself only found low strength of evidence for improvement in medium-term pain. For all interventions, serious adverse events were rare and did not significantly differ between intervention and control groups.

Policy Landscape

Payer Coverage Policies

Medicaid

No Washington Medicaid policy was identified for whole body vibration, glucosamine, or chondroitin. A 2009 coverage decision for Washington Medicaid states that electrical neural stimulation, including

TENS, is a non-covered benefit. A 2016 coverage decision for Washington Medicaid states that autologous blood/platelet-rich plasma injections are not a covered benefit.

Medicare

No Medicare National Coverage Determination (NCD) or Local Coverage Determination (LCD) was identified for whole body vibration, glucosamine, chondroitin, or platelet-rich plasma for knee osteoarthritis.

An NCD for Assessing Patient's Suitability for Electrical Nerve Stimulation Therapy (effective: 6/19/2006) provides coverage for electrical nerve stimulation for assessing a patient's suitability for ongoing treatment with a transcutaneous or an implanted nerve stimulator. TENS is to be used on a trial basis while its effectiveness in modulating pain is monitored by a physician or physical therapist. In most cases, a determination of whether the patient is likely to derive a significant therapeutic benefit from continuous use of TENS can be made within a trial period of one month. LCD L34821 on Transcutaneous Electrical Joint Stimulation Devices (effective: 1/1/2017) does not provide coverage for TENS.

Private Payers

The Aetna policy on complementary and alternative medicine (last review: 6/15/2018) does not provide coverage for whole body vibration. Coverage policies for whole body vibration were not identified for Cigna, Moda, or Regence.

Aetna and Moda provide coverage for the use of TENS for knee osteoarthritis under certain conditions. The Cigna policy on electrical stimulation therapy (effective: 7/15/2017) covers TENS only for conventional postoperative pain management within 30 days of surgery. The Regence policy on electrical stimulation therapy (effective: 8/1/2018) does not provide coverage for electrical stimulation or electromagnetic therapy for the treatment of osteoarthritis or rheumatoid arthritis.

The Aetna policy on electrical stimulation for pain (last review: 3/12/2018) does not provide coverage for acute pain (less than 3 months duration) except for postoperative pain. Aetna considers TENS medically necessary durable medical equipment for certain types of chronic, intractable pain not adequately responsive to other methods of treatment including physical therapy and pharmacotherapy. Aetna considers use of TENS medically necessary initially for a trial period of one to two months. After this trial period, coverage depends on the treatment significantly alleviating pain.

The Moda policy on electrical stimulation therapy (last review: 10/25/2017) covers TENS for chronic pain other than low back pain when all of the following criteria are met:

- Pain must have been present for at least three months
- Other appropriate treatment modalities must have been tried and failed (e.g., physical therapy, pharmacotherapy)
- Patients must have an in-person examination with their provider for the condition prescribed

The Aetna policy on complementary and alternative medicine (last review: 6/15/2018) and the Cigna policy on complementary and alternative medicine (effective: 8/15/2018) do not provide coverage for glucosamine, and no policy on glucosamine was found for Moda or Regence. No policy on chondroitin was identified for any of the four private payers: Aetna, Cigna, Moda, or Regence.

Platelet-rich plasma is not covered in policies identified for Aetna (last review: 4/3/2018), Cigna (effective: 10/15/2017), Moda (effective: 12/6/2017), and Regence (effective: 11/1/2017).

Recommendations from Others

Five guidelines were identified that encompassed knee osteoarthritis or osteoarthritis more broadly:

- U.S. Department of Veterans Affairs (VA) and Department of Defense (DoD) guideline on nonsurgical management of hip and knee osteoarthritis (VA/DoD, 2014)
- American Academy of Orthopaedic Surgeons (AAOS) guideline on knee osteoarthritis (Jevsevar, 2013)
- American College of Rheumatology (ACR) recommendations for osteoarthritis of the hand, hip, and knee (Hochberg et al., 2012). Note: publication of an update to these guidelines is anticipated in 2018 (ACR, 2018)
- European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO) guidelines for knee osteoarthritis (Bruyere et al., 2014)
- Osteoarthritis Research Society International (OARSI) guidelines on nonsurgical management of knee osteoarthritis (McAlindon et al., 2014)

None of the identified guidelines included recommendations on whole body vibration.

ACR and ESCEO include TENS as a treatment option. ACR conditionally recommends TENS only when the patient has chronic moderate to severe pain and is a candidate for total knee arthroplasty, but is unwilling to undergo the procedure, has comorbid medical conditions, or is taking concomitant medications that lead to a relative or absolute contraindication to surgery or a decision by the surgeon not to recommend the procedure. AAOS is unable to recommend for or against TENS, and OARSI considers TENS a treatment of uncertain appropriateness. TENS is not mentioned in the VA/DoD guidelines.

Glucosamine and chondroitin sulfate are not recommended in the VA/DoD and AAOS guidelines. ACR conditionally recommends that patients should not use glucosamine and chondroitin sulfate, and OARSI considers glucosamine and chondroitin sulfate as treatments of uncertain appropriateness. ESCEO recommends the use of glucosamine and chondroitin and provides updated recommendations on their use in a 2016 consensus statement (Bruyere et al., 2016). ESCEO advocates the use of prescription patented crystalline glucosamine sulfate as a first-line symptomatic slow-acting drug for medium-to long-term control of knee osteoarthritis symptoms.

Of the five identified guidelines, only AAOS includes a recommendation on platelet-rich plasma, and these guidelines are unable to recommend for or against platelet-rich plasma for knee osteoarthritis. The National Institute for Health and Care Excellence (NICE) published an interventional procedures guidance, which states that the evidence on efficacy is inadequate in quality and that there is no evidence of major safety concerns. Therefore, the guidance concludes that platelet-rich plasma should only be used with special arrangements for clinical governance, consent, and audit or research (NICE, 2014).

Quality Measures

No quality measures were identified when searching the National Quality Measures Clearinghouse for whole body vibration, transcutaneous electrical nerve stimulation, glucosamine, chondroitin, or platelet-rich plasma for osteoarthritis.

References

Evidence Sources

Newberry, S. J., FitzGerald, J., SooHoo, N. F., Booth, M., Marks, J., Motala, A., . . . Shekelle, P. G. (2017). *AHRQ comparative effectiveness reviews treatment of osteoarthritis of the knee: An update review.* Rockville (MD): Agency for Healthcare Research and Quality (US). Retrieved from https://effectivehealthcare.ahrq.gov/sites/default/files/pdf/osteoarthritis-knee-update_research-2017.pdf

Runhaar, J., Rozendaal, R. M., van Middelkoop, M., Bijlsma, H. J. W., Doherty, M., Dziedzic, K. S., . . . Bierma Zeinstra, S. (2017). Subgroup analyses of the effectiveness of oral glucosamine for knee and hip osteoarthritis: A systematic review and individual patient data meta-analysis from the OA trial bank. *Annals of the Rheumatic Diseases, 76*(11), 1862-1869. doi: 10.1136/annrheumdis-2017-211149

Shen, L., Yuan, T., Chen, S., Xie, X., & Zhang, C. (2017). The temporal effect of platelet-rich plasma on pain and physical function in the treatment of knee osteoarthritis: Systematic review and meta-analysis of randomized controlled trials. *Journal of Orthopedic Surgery and Research, 12*(1), 16. doi: 10.1186/s13018-017-0521-3

Simental-Mendia, M., Sanchez-Garcia, A., Vilchez-Cavazos, F., Acosta-Olivo, C. A., Pena-Martinez, V. M., & Simental-Mendia, L. E. (2018). Effect of glucosamine and chondroitin sulfate in symptomatic knee osteoarthritis: A systematic review and meta-analysis of randomized placebo-controlled trials. *Rheumatology International*. doi: 10.1007/s00296-018-4077-2

Smith, P. A. (2016). Intra-articular autologous conditioned plasma injections provide safe and efficacious treatment for knee osteoarthritis: An FDA-sanctioned, randomized, double-blind, placebo-controlled clinical trial. *American Journal of Sports Medicine, 44*(4), 884-891. doi: 10.1177/0363546515624678

Other Citations

American College of Rheumatology. (2018). *Osteoarthritis*. Retrieved from https://www.rheumatology.org/Practice-Quality/Clinical-Support/Clinical-Practice-Guidelines/Osteoarthritis

Bruyere, O., Cooper, C., Pelletier, J. P., Branco, J., Luisa Brandi, M., Guillemin, F., . . . Reginster, J. Y. (2014). An algorithm recommendation for the management of knee osteoarthritis in Europe and internationally: A report from a task force of the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO). *Seminars in Arthritis and Rheumatism, 44*(3), 253-263. doi: 10.1016/j.semarthrit.2014.05.014

Bruyere, O., Cooper, C., Pelletier, J. P., Maheu, E., Rannou, F., Branco, J., . . . Reginster, J. Y. (2016). A consensus statement on the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO) algorithm for the management of knee osteoarthritis—From evidence-based medicine to the real-life setting. *Seminars in Arthritis and Rheumatism, 45*(4 Suppl), S3-11. doi: 10.1016/j.semarthrit.2015.11.010

Centers for Disease Control and Prevention. (2017). *Osteoarthritis (OA)*. Retrieved from https://www.cdc.gov/arthritis/basics/osteoarthritis.htm

Department of Veterans Affairs and Department of Defense. (2014). *VA/DoD clinical practice guideline for the non-surgical management of hip & knee osteoarthritis.* Retrieved from https://www.healthquality.va.gov/guidelines/CD/OA/VADoDOACPGFINAL090214.pdf

DeSantana, J. M., Walsh, D. M., Vance, C., Rakel, B. A., & Sluka, K. A. (2008). Effectiveness of transcutaneous electrical nerve stimulation for treatment of hyperalgesia and pain. *Current Rheumatology Reports, 10*(6), 492-499.

Hochberg, M. C., Altman, R. D., April, K. T., Benkhalti, M., Guyatt, G., McGowan, J., . . . Tugwell, P. (2012). American College of Rheumatology 2012 recommendations for the use of nonpharmacologic and pharmacologic therapies in osteoarthritis of the hand, hip, and knee. *Arthritis Care Research (Hoboken), 64*(4), 465-474.

Jevsevar, D. S. (2013). Treatment of osteoarthritis of the knee: Evidence-based guideline, 2nd edition. *Journal of the American Academy of Orthopaedic Surgeons, 21*(9), 571-576. doi: 10.5435/jaaos-21-09-571

McAlindon, T. E., Bannuru, R. R., Sullivan, M. C., Arden, N. K., Berenbaum, F., Bierma-Zeinstra, S. M., . . . Underwood, M. (2014). OARSI guidelines for the non-surgical management of knee osteoarthritis. *Osteoarthritis Cartilage, 22*(3), 363-388. doi: 10.1016/j.joca.2014.01.003

National Institute for Health and Care Excellence. (2014). *Platelet-rich plasma injections for osteoarthritis of the knee*. Retrieved from https://www.nice.org.uk/guidance/ipg491/resources/plateletrich-plasma-injections-for-osteoarthritis-of-the-knee-pdf-1899870047302597

National Institute of Arthritis and Musculoskeletal and Skin Disease. (2014). *What is osteoarthritis?* Retrieved from https://www.niams.nih.gov/sites/default/files/catalog/files/osteoarthritis_ff.pdf

Walker, L. C., Clement, N. D., & Deehan, D. J. (2018). Predicting the outcome of total knee arthroplasty using the WOMAC score: A review of the literature. *Journal of Knee Surgery*. doi: 10.1055/s-0038-1666866

Wang, P., Yang, L., Liu, C., Wei, X., Yang, X., Zhou, Y., . . . He, C. (2016). Effects of whole body vibration exercise associated with quadriceps resistance exercise on functioning and quality of life in patients with knee osteoarthritis: A randomized controlled trial. *Clinical Rehabilitation, 30*(11), 1074-1087. doi: 10.1177/0269215515607970

Coverage guidance is prepared by the Health Evidence Review Commission (HERC), HERC staff, and subcommittee members. The evidence summary is prepared by the Center for Evidence-based Policy at Oregon Health & Science University (the Center). This document is intended to guide public and private purchasers in Oregon in making informed decisions about health care services.

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Appendix A. GRADE Table Element Descriptions

Element	Description
Balance of benefits and harms	The larger the difference between the desirable and undesirable effects, the higher the likelihood that a strong recommendation is warranted. An estimate that is not statistically significant or has a confidence interval crossing a predetermined clinical decision threshold will be downgraded.
Quality of evidence	The higher the quality of evidence, the higher the likelihood that a strong recommendation is warranted
Resource allocation	The higher the costs of an intervention—that is, the greater the resources consumed in the absence of likely cost offsets—the lower the likelihood that a strong recommendation is warranted
Values and preferences	The more values and preferences vary, or the greater the uncertainty in values and preferences, the higher the likelihood that a weak recommendation is warranted
Other considerations	Other considerations include issues about the implementation and operationalization of the technology or intervention in health systems and practices within Oregon.

Strong recommendation

In Favor: The subcommittee concludes that the desirable effects of adherence to a recommendation outweigh the undesirable effects, considering the balance of benefits and harms, resource allocation, values and preferences and other factors.

Against: The subcommittee concludes that the undesirable effects of adherence to a recommendation outweigh the desirable effects, considering the balance of benefits and harms, resource allocation, values and preferences and other factors.

Weak recommendation

In Favor: The subcommittee concludes that the desirable effects of adherence to a recommendation probably outweigh the undesirable effects, considering the balance of benefits and harms, resource allocation, values and preferences and other factors., but further research or additional information could lead to a different conclusion.

Against: The subcommittee concludes that the undesirable effects of adherence to a recommendation probably outweigh the desirable effects, considering the balance of benefits and harms, cost and resource allocation, and values and preferences, but further research or additional information could lead to a different conclusion.

Confidence in estimate rating across studies for the intervention/outcome

Assessment of confidence in estimate includes factors such as risk of bias, precision, directness, consistency and publication bias.

High: The subcommittee is very confident that the true effect lies close to that of the estimate of the effect. Typical sets of studies are RCTs with few or no limitations and the estimate of effect is likely stable.

Moderate: The subcommittee is moderately confident in the estimate of effect: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Typical sets of studies are RCTs with some limitations or well-performed nonrandomized studies with additional strengths that guard against potential bias and have large estimates of effects.

Low: The subcommittee's confidence in the estimate of effect is limited: The true effect may be substantially different from the estimate of the effect. Typical sets of studies are RCTs with serious limitations or nonrandomized studies without special strengths.

Very low: The subcommittee has very little confidence in the estimate of effect: The true effect is likely to be substantially different from the estimate of effect. Typical sets of studies are nonrandomized studies with serious limitations or inconsistent results across studies.

Appendix B. GRADE Evidence Profile

Quality Assessment (Confidence in Estimate of Effect) for Whole Body Vibration							
No. of Studies	**Study Design(s)**	**Risk of Bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other Factors**	**Quality**
Long-term pain							
0							Insufficient
Long-term function							
0							Insufficient
Intermediate-term pain							
4	RCTs	2 Low 1 moderate 1 unclear	Serious	Not serious	Not serious		Low ●●○○
Intermediate-term function							
4	RCTs	2 Low 1 moderate 1 unclear	Serious	Not serious	Not serious		Low ●●○○
Harms							
4	RCTs	N/A	N/A	N/A	N/A		Low ●●○○

Quality Assessment (Confidence in Estimate of Effect) for Transcutaneous Electrical Nerve Stimulation							
No. of Studies	**Study Design(s)**	**Risk of Bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other Factors**	**Quality**
Long-term pain							
0							Insufficient
Long-term function							
0							Insufficient
Intermediate-term pain							
2	RCTs	2 Low	Not serious	Not serious	Not serious		Low ●●○○
Intermediate-term function							
2	RCTs	2 Low	Not serious	Not serious	Not serious		Low ●●○○
Harms							
2	RCTs	N/A	N/A	N/A	N/A		Low ●●○○

Quality Assessment (Confidence in Estimate of Effect) for Glucosamine alone							
No. of Studies	**Study Design(s)**	**Risk of Bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other Factors**	**Quality**
Long-term pain							
3	RCTs	2 low 1 high	Serious	Not serious	Not serious		Low ●●○○
Long-term function							
3	RCTs	2 low 1 high	Serious	Not serious	Not serious		Low ●●○○
Intermediate-term pain							
0							Insufficient
Intermediate-term function							
0							Insufficient
Harms							
6	Mixed	N/A	N/A	N/A	N/A		Moderate ●●●○

Quality Assessment (Confidence in Estimate of Effect) for Glucosamine-Chondroitin							
No. of Studies	**Study Design(s)**	**Risk of Bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other Factors**	**Quality**
Long-term pain							
3	RCTs	2 low 1 high	Serious	Not serious	Not serious		Moderate ●●●○
Long-term function							
3	RCTs	2 low 1 high	Serious	Not serious	Not serious		Moderate ●●●○
Intermediate-term pain							
3	RCTs	2 low 1 high	Serious	Not serious	Not serious		Low ●●○○
Intermediate-term function							
3	RCTs	2 low 1 moderate	Serious	Not serious	Not serious		Low ●●○○
Harms							
6	Mixed	N/A	N/A	N/A	N/A		Moderate ●●●○

Quality Assessment (Confidence in Estimate of Effect) for Chondroitin alone							
No. of Studies	**Study Design(s)**	**Risk of Bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other Factors**	**Quality**
Long-term pain							
3	RCTs	3 low	Not serious	Not serious	Not serious		Moderate ●●●○
Long-term function							
2	RCTs	2 low	Not serious	Not serious	Not serious		Low ●●○○
Intermediate-term pain							
2	RCTs	2 Low	Not serious	Not serious	Not serious		Low ●●○○
Intermediate-term function							
2	RCTs	2 Low	Serious	Not serious	Not serious		Insufficient
Harms							
6	Mixed	N/A	N/A	N/A	N/A		Moderate ●●●○

Quality Assessment (Confidence in Estimate of Effect) for Platelet-Rich Plasma							
No. of Studies	**Study Design(s)**	**Risk of Bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other Factors**	**Quality**
Long-term pain							
1	RCT	Low	Not serious	Not serious	Serious	Sparse data Industry involvement	Very Low ●○○○
Long-term function							
1	RCT	Low	Not serious	Not serious	Serious	Sparse data Industry involvement	Very Low ●○○○
Intermediate-term pain							
5	RCTs	2 Low 1 moderate 2 high	Not serious	Not serious	Not serious		Low ●●○○
Intermediate-term function							
2	RCTs	2 moderate	N/A	Not serious	Not reported		Insufficient
Harms							
3	RCTs	N/A	N/A	N/A	N/A		Low ●●○○

Quality Assessment (Confidence in Estimate of Effect) for Transcutaneous Electrical Nerve Stimulation							
No. of Studies	**Study Design(s)**	**Risk of Bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other Factors**	**Quality**
Long-term pain							
0							Insufficient
Long-term function							
0							Insufficient
Intermediate-term pain							
2	RCTs	2 Low	Not serious	Not serious	Not serious		Low ●●○○
Intermediate-term function							
2	RCTs	2 Low	Not serious	Not serious	Not serious		Low ●●○○
Harms							
2	RCTs	N/A	N/A	N/A	N/A		Low ●●○○

Appendix C. Methods

Scope Statement

Populations

Adults with osteoarthritis of the knee(s)

Population scoping notes: None

Interventions

Whole body vibration, transcutaneous electrical nerve stimulation, glucosamine-chondroitin, platelet-rich plasma

Intervention exclusions: None

Comparators

Effective nonsurgical care (e.g., oral analgesics, exercise therapy)

Outcomes

Critical: Long-term pain, long-term function

Important: Intermediate-term function, intermediate-term pain, harms

Considered but not selected for the GRADE table: None

Key Questions

KQ1: What is the comparative effectiveness of newer interventions for the treatment of osteoarthritis of the knees?

KQ2: Does the comparative effectiveness of newer interventions for the treatment of osteoarthritis of the knees vary by:

a. Patient characteristics (age, gender, socioeconomic status, baseline weight)
b. Baseline severity
c. Disease subtype
d. Comorbidities
e. Prior treatments

KQ3: What are the harms of newer interventions for the treatment of osteoarthritis of the knees?

Search Strategy

A full search of the core sources was conducted to identify systematic reviews, meta-analyses, and technology assessments that meet the criteria for the scope described above. Searches of core sources were limited to citations published after 2013.

The following core sources were searched:

Agency for Healthcare Research and Quality (AHRQ)

Canadian Agency for Drugs and Technologies in Health (CADTH)

Cochrane Library (Wiley Online Library)
Institute for Clinical and Economic Review (ICER)
Medicaid Evidence-based Decisions Project (MED)
National Institute for Health and Care Excellence (NICE)
Tufts Cost-effectiveness Analysis Registry
Veterans Administration Evidence-based Synthesis Program (ESP)
Washington State Health Technology Assessment Program

A MEDLINE® search was also conducted to identify systematic reviews, meta-analyses, and technology assessments, using the search terms knee osteoarthritis and (whole body vibration or transcutaneous electrical nerve stimulation or glucosamine or chondroitin or platelet-rich plasma). The search was limited to publications in English published since 2013. In addition, a MEDLINE® search was conducted for randomized controlled trials published after the search dates of the most recent systematic review selected for each indication.

Searches for clinical practice guidelines were limited to those published since 2013. A search for relevant clinical practice guidelines was also conducted using MEDLINE® and the following sources:

Australian Government National Health and Medical Research Council (NHMRC)
Canadian Agency for Drugs and Technologies in Health (CADTH)
Centers for Disease Control and Prevention (CDC), Community Preventive Services
National Guidelines Clearinghouse
National Institute for Health and Care Excellence (NICE)
Scottish Intercollegiate Guidelines Network (SIGN)
United States Preventive Services Task Force (USPSTF)
Veterans Administration/Department of Defense (VA/DoD) Clinical Practice Guidelines

Inclusion/Exclusion Criteria

Studies were excluded if they were not published in English; did not address the scope statement; or were study designs other than systematic reviews, meta-analyses, technology assessments, randomized controlled trials, or clinical practice guidelines.

Appendix D. Applicable Codes

CODES	DESCRIPTION	
CPT Codes		**Intervention**
0232T	Injection(s), platelet rich plasma, any site, including image guidance, harvesting and preparation when performed	Platelet rich plasma
97110	Therapeutic procedure, 1 or more areas, each 15 minutes; therapeutic exercises to develop strength and endurance, range of motion and flexibility	Whole body vibration (as physical therapy service)
97112	Therapeutic procedure, 1 or more areas, each 15 minutes; neuromuscular reeducation of movement, balance, coordination, kinesthetic sense, posture, and/or proprioception for sitting and/or standing activities	Whole body vibration (as physical therapy service)
97530	Therapeutic activities, direct (one-on-one) patient contact (use of dynamic activities to improve functional performance), each 15 minutes	Whole body vibration (as physical therapy service)
64550	Application of surface (transcutaneous) neurostimulator (eg, TENS unit)	TENS
97014	Application of a modality to 1 or more areas; electrical stimulation (unattended)	TENS
97032	Application of a modality to 1 or more areas; electrical stimulation (manual), each 15 minutes	TENS
HCPCS Level II Codes		
A9270	Non-covered item or service	Whole body vibration therapy machine
E0720	Transcutaneous electrical nerve stimulation (tens) device, two lead, localized stimulation	TENS
E0730	Transcutaneous electrical nerve stimulation (tens) device, four or more leads, for multiple nerve stimulation	TENS
E0731	Form fitting conductive garment for delivery of tens or nmes (with conductive fibers separated from the patient's skin by layers of fabric)	TENS

Note: Inclusion on this list does not guarantee coverage.

Appendix E. MCID cutoffs developed or used in a representative sample of articles from the AHRQ review (Newberry et al., 2017)

Author, Year	Condition/Intervention/ Follow-up	Cutoffs	Notes
Eberle, 1999 PMID: 10489324	Knee OA hyaluronic acid injection, 6 month follow-up	VAS pain: 8.4mm on a 0-100 mm scale; 0.7 points on Lequesne 24-point scale	Anchor question: complaints reduced
Angst, 2001 PMID:11501727	Knee or hip OA Rehabilitation, 3 month follow-up	WOMAC pain: 0.75 (0-10 scale) WOMAC function and total: 0.67 SF-36 physical function: 3.3 (0-100 scale)	Anchor question: current subjective health much better, slightly better, no change, slightly worse. Converted all 5 WOMAC pain item scores to a 0-10 scale and took the average) Separate values for worsening and improvement
Salaffi, 2004 PMID: 15207508	Chronic musculoskeletal pain (OA knee, OA hip, AS, rheumatoid arthritis, OA hand) Not described	Numeric rating scale: 15% or 1 point decrease for minimum improvement, 33% or 2 points for much better (which they regarded as clinical improvement)	Anchor: Patient global impression of change
Tubach, 2005 PMID:15208174	Knee or hip OA nonsteroidal anti-inflammatory drugs, 4 weeks	Knee: VAS pain: −19.9mm (−40.8%) WOMAC function: −9.1 (−26%)	WOMAC 17 items, 5-point Likert scale, total score normalized to 0-100 scale MCII Initial severity affected MCII but age, disease duration, and sex did not
Wandel, 2010 PMID: 20847017	Knee or hip OA Glucosamine-chondroitin vs. placebo network meta-analysis	MCID 0.37 SD units, corresponding to 0.9cm (0-10cm VAS scale)	Median pooled SD of 2.5cm used to back transform effect sizes to 10cm VAS scale

OMERACT-OARSI responder criteria Pham 2003 PMID: 12858473	Knee or hip OA	Clinical response was defined as either 1. improvement of at least 50% in pain or function and an absolute change of at least 20 points on a scale of 0-100 in the WOMAC pain or function subscores, or 2. at least 2 of the following criteria: improvement of at least 20% and an absolute change greater than 10 points on a scale of 0-100 in the WOMAC pain score, improvement of at least 20% and an absolute change greater than 10 points (on a 0-100 scale) in the WOMAC function score, or improvement of at least 20% in the patient Global Assessment score and an absolute change >10 points on a scale of 0-100	WOMAC pain and function scales converted to single 0-100 scores.

Abbreviations: OA: osteoarthritis; VAS: visual analog scale; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index