**Topic Brief: Regenerative Medicine for Musculoskeletal Conditions**

**Date:** 1/4/2021  
**Nomination Numbers:** 0935, 0945

**Purpose:** This document summarizes the information addressing a nomination submitted on July 17, 2020 through the Effective Health Care Website. This information was used to inform the Evidence-based Practice Center (EPC) Program decisions about whether to produce an evidence report on the topic, and if so, what type of evidence report would be most suitable.

**Issue:** Regenerative medicine, including stem cell therapy and platelet-rich plasma (PRP) therapy, is used to treat numerous musculoskeletal conditions; however, little guidance exists regarding its efficacy and indications for use. The nominator would like an evidence report addressing these issues to be formulated and used by medical professionals to encourage evidence-based use of regenerative medicine therapies.

**Program Decision:** The scope of this topic met all EHC Program selection criteria and was considered for a systematic review. However, it was not selected.

**Key Findings**
- This nomination met all assessment criteria.
- We found 4 systematic reviews of knee (3 reviews) and hip (1 review) osteoarthritis (OA) that evaluate platelet-rich-plasma (PRP). Together, the reviews address part of the nomination.
- For the remainder of the nomination, we found 27 studies addressing the comparative effectiveness of regenerative treatments for OA and 12 studies addressing the comparative effectiveness of regenerative treatments for soft-tissue injuries.

**Background**

Musculoskeletal disorders, or injuries or disorders of the muscles, nerves, tendons, joints, cartilage, or spinal discs, are prevalent in the United States. In 2016, such disorders impacted approximately one in two (or 126.6 million) Americans and cost society $213 billion for treatment, care, and lost wages.\(^1\) Osteoarthritis (OA), a musculoskeletal condition in which the cartilage protecting the joint degenerates, affects over 32.5 million American adults\(^2\) and totaled an estimated $486.4 billion in direct and indirect costs between 2008 and 2014.\(^3\)

The American College of Rheumatology/Arthritis Foundation’s 2019 guideline recommends palliative treatments for OA such as exercise, weight loss, cane use, tai chi, bracing, nonsteroidal anti-inflammatory drugs, glucocorticoid injections, acupuncture, and steroid injections.\(^4\) However, regenerative medicine interventions which are proposed to repair, regenerate, or replace dysfunctional cells or tissues using allogeneic or autologous cells, may
Regenerative medicine interventions for musculoskeletal conditions include stem cell and platelet-rich plasma (PRP) therapies and may decrease pain and improve function. The nominator for this topic is interested in the relative effectiveness of regenerative treatments compared to one another, and to other interventions for OA of the joints and injuries to joint soft tissues (e.g., tendinitis, tendinopathy, enthesopathy, tendonitis, and bursitis).

**Nomination Summary**
The questions and PICOS were developed with input from the initial nominator, the American Academy of Physical Medicine and Rehabilitation. A second nomination was received from a non-profit organization for education/standards and guidelines in regenerative medicine for orthopedic condition while this assessment was in-process, and their input did not alter the scope. Both organizations intend to disseminate findings from the proposed report to inform practice but they do not have plans to develop clinical guidance.

**Scope**

1. What is the comparative effectiveness and harms of available regenerative medicine treatments compared to other treatments for osteoarthritis (OA) shoulder, elbow, wrist, knee, hip, or ankle?
   a. How do outcomes vary by patient characteristics?
   b. How do outcomes vary by intervention delivery characteristics?
2. What is the comparative effectiveness and harms of regenerative medicine treatments compared to other treatments for soft tissue injuries of the shoulder, elbow, wrist, knee, hip, or ankle?
   a. How do outcomes vary by patient characteristics?
   b. How do outcomes vary by intervention delivery characteristics?

**Contextual Questions**

1. What is the comparative mechanism of action of each of the three regenerative medicine therapies for the various joints and soft tissue injuries? (answered in background evidence, contextual)
2. Who are the stakeholders interested in using/administering regenerative medicine products for knee and other specified soft tissue injuries? (contextual background or based on the authors and participants of the studies?)

**Table 1. Questions and PICOS**

<table>
<thead>
<tr>
<th>Questions</th>
<th>1. Regenerative medicine for joint OA</th>
<th>2. Regenerative medicine for soft-tissue joint injuries</th>
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</thead>
<tbody>
<tr>
<td><strong>Population</strong></td>
<td>Ambulatory adults with OA of the wrist, shoulder, hip, knee, ankle, or elbow</td>
<td>Ambulatory adults with soft tissue injuries (e.g., tendinopathy; enthesopathy; tendonitis; bursitis of the wrist, shoulder, hip, knee, ankle, or elbow)</td>
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<td></td>
<td>Consider patient characteristics (e.g., sex, age, race, education level, health literacy, comorbidities, previous treatment, severity of condition)</td>
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<tr>
<td>Questions</td>
<td>1. Regenerative medicine for joint OA</td>
<td>2. Regenerative medicine for soft-tissue joint injuries</td>
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<td>Interventions</td>
<td>Regenerative treatments including PRP, bone marrow concentrate, harvested/donor stem cells and micronized fat transfer</td>
<td>Regenerative treatments including PRP, bone marrow concentrate, harvested/donor stem cells and micronized fat transfer</td>
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<td>Consider practitioner experience factors: (number of procedures), use of imaging to place the treatment, time working with the products, type of provider, years in practice, post procedural instructions</td>
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<td>Consider PRP factors: specific vendors, specific preparation procedures</td>
<td>Consider PRP factors: specific vendors, specific preparation procedures</td>
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<tr>
<td>Comparators</td>
<td>• Physical therapy, exercise, braces, orthotics, acupuncture, weight loss</td>
<td>• Physical therapy, exercise, braces, orthotics, acupuncture, weight loss</td>
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<td>• Steroid, hyaluronic acid (e.g., Synvisc, Hyalgan), other injections or ESWT</td>
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<td>• Other dosing regimens of a regenerative treatment</td>
<td>• Other dosing regimens of a regenerative treatment</td>
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<td>• Pharmacologic treatments (e.g., acetaminophen, non-steroidal medicines, glucosamine chondroitin, duloxetine)</td>
<td>• Pharmacologic treatments (e.g., acetaminophen, non-steroidal medicines, glucosamine chondroitin, duloxetine)</td>
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<td>• Bariatric procedures, orthopedic surgical procedures</td>
<td>Bariatric procedures, orthopedic surgical procedures</td>
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<td>Outcomes</td>
<td>Benefits: Functional/pain status (examples): PROMIS; DASH; KOOS; TUG; WOMAC Patient Quality of Life: SF-36; EQ5D Patient Satisfaction: GPE, VAS Pain; NRS Pain; SF-36 BPS</td>
<td>Benefits: Functional/pain status (examples): PROMIS; DASH; KOOS; TUG; WOMAC Patient Quality of Life: SF-36; EQ5D Patient Satisfaction: GPE, VAS Pain; NRS Pain; SF-36 BPS</td>
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<td>Harms: Healthcare outcomes:</td>
<td>Harms: Healthcare outcomes:</td>
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<td>• Adverse events (e.g., infections, aseptic reactions, other reactions)</td>
<td>• Adverse events (e.g., infections, aseptic reactions, other reactions)</td>
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<td>• Emergency room care/adverse events, severe vs. minor</td>
<td>• Emergency room care/adverse events, severe vs. minor</td>
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<td>• Hospitalization/adverse events, severe vs. minor</td>
<td>• Hospitalization/adverse events, severe vs. minor</td>
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<td></td>
<td>• Mortality</td>
<td>• Mortality</td>
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<td></td>
<td>Utilization</td>
<td>Utilization</td>
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<tr>
<td></td>
<td>• Costs of treatment</td>
<td>• Costs of treatment</td>
</tr>
<tr>
<td></td>
<td>• Number and costs of visits, hospital admission, ED visits</td>
<td>• Number and costs of visits, hospital admission, ED visits</td>
</tr>
<tr>
<td>Setting</td>
<td>Outpatient</td>
<td>Outpatient</td>
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</tbody>
</table>

Abbreviations: DASH=disabilities of the arm, shoulder, and hand; ED=emergency department; EQ-5D=EuroQol-5D; ESWT= extracorporeal shock wave therapy; GPE=global perceived effect scale; KOOS=knee injury and osteoarthritis outcome score; NRS Pain=numeric rating scale for pain; OA=osteoarthritis; PICOS= population, intervention, comparator, outcome, setting; PROMIS= patient-reported outcomes measurement information system; PRP=platelet-rich plasma; SF-36(BPS)=36-item short form survey (bodily pain scale); TUG=timed up & go test; WOMAC= Western Ontario McMaster arthritis index; VAS Pain=visual analog scale for pain.

**Assessment Methods**

See Appendix A.
Summary of Literature Findings

We found four systematic reviews to address part of the nomination. We also found an adequate number of primary studies to address key questions (KQs) 1 and 2 for the remainder of the nomination, as part of a new systematic review.

For KQ1, we found four systematic reviews, all involving PRP interventions. Three of these were in knee OA patients: one compared PRP to hyaluronic acid (HA);9 one compared single administrations of PRP to multiple administrations of PRP,10 and; one compared PRP plus HA to HA alone.11 We also found one systematic review of hip OA patients, comparing PRP to HA.12

We also found primary studies addressing parts of KQ1 not addressed by the systematic reviews. All but one study evaluated patients with knee OA. There was also one study in patients with ankle OA.13 In most KQ1 studies, the regenerative intervention was stem cell treatment compared to another treatment.13-33 There were also two studies that compared bone marrow interventions to other treatments.34, 35 An additional four studies compared PRP to a comparator intervention other than that in the included systematic reviews, such as corticosteroids or acetaminophen. 36-39

Studies addressing KQ2 included patients with soft-tissue joint conditions such as epicondylitis, capsulitis, and tendinopathy. Interventions were predominately PRP compared to another treatment.40-50 Additionally, one study compared stem cell treatment to another treatment.51

Additionally, we found seven upcoming and/or in-process studies (via ClinicalTrials.gov) that addressed KQ1; six of these studies addressed knee OA (Study 1 Link; Study 2 Link; Study 3 Link; Study 4 Link; Study 5 Link; Study 6 Link) and one addressed a variety of joint OA conditions (Study 7 Link). We also found one in-process study that applies to both KQ1 and 2, as the stem cell interventions included target both OA and soft-tissue injuries (tendinopathy and tendinosis) (Study 8 Link).

Table 2. Literature identified for each KQ

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<tbody>
<tr>
<td>Question 1: Regenerative medicine for joint OA</td>
<td>Total: 4 (non-AHRQ/Cochrane)</td>
<td>Total: 27</td>
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<tr>
<td></td>
<td></td>
<td>• RCT: 18</td>
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<td></td>
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<td>• Non-RCTs with comparator group(s): 9</td>
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<tr>
<td></td>
<td></td>
<td>Clinicaltrials.gov: 8</td>
</tr>
<tr>
<td>Question 2: Regenerative medicine for joint soft-tissue injuries</td>
<td>Total: 0</td>
<td>Total: 12</td>
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<tr>
<td></td>
<td></td>
<td>• RCT: 8</td>
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<tr>
<td></td>
<td></td>
<td>• Non-RCTs with comparator group(s): 4</td>
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<td></td>
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<td>Clinicaltrials.gov: 1</td>
</tr>
</tbody>
</table>

Abbreviations: KQ=key question; OA=osteoarthritis; RCT=randomized controlled trial.

See Appendix B for detailed assessments of all EPC selection criteria.

Summary of Selection Criteria Assessment
We found four systematic reviews addressing parts of KQ1, the comparative effectiveness of regenerative therapies for osteoarthritis of joints, and 27 studies addressing parts of KQ1 not addressed by the systematic reviews. We also found 12 studies addressing soft-tissue joint
injuries (KQ2). The nominators plan to disseminate a new systematic review to their foundation members, but there are no plans to develop practice guidelines with a new review.

Please see Appendix B for detailed assessments of individual EPC Program selection criteria.

**Related Resources**

We identified additional information in the course of our assessment that might be useful. Specifically, we found a protocol for an upcoming systematic review entitled *Interventional Treatments for Acute and Chronic Pain: Systematic Review*, which includes intradiscal and facet joint PRP and intradiscal stem cell interventions for back pain. While treatments for back pain are outside of the scope of this nomination, we present this information as it may be of interest to the nominator.

**References**


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Conflict of Interest: None of the investigators have any affiliations or financial involvement that conflicts with the material presented in this report.

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Christine Chang

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Appendix A: Methods

We assessed nomination for priority for a systematic review or other AHRQ Effective Health Care report with a hierarchical process using established selection criteria. Assessment of each criteria determined the need to evaluate the next one. See Appendix B for detailed description of the criteria.

Appropriateness and Importance
We assessed the nomination for appropriateness and importance.

Desirability of New Review/Absence of Duplication
We searched for high-quality, completed or in-process evidence reviews published in the last three years November 13, 2017 - November 13, 2020 on the questions of the nomination from these sources:

- AHRQ: Evidence reports and technology assessments
  - EHC Program https://effectivehealthcare.ahrq.gov/
  - AHRQ Technology Assessment Program https://www.ahrq.gov/research/findings/ta/index.html
- US Department of Veterans Affairs Products publications
  - Evidence Synthesis Program https://www.hsrd.research.va.gov/publications/esp/
  - VA/Department of Defense Evidence-Based Clinical Practice Guideline Program https://www.healthquality.va.gov/
- Cochrane Systematic Reviews https://www.cochranelibrary.com/
- PROSPERO Database (international prospective register of systematic reviews and protocols) http://www.crd.york.ac.uk/prospero/

Impact of a New Evidence Review
The impact of a new evidence review was qualitatively assessed by analyzing the current standard of care, the existence of potential knowledge gaps, and practice variation. We considered whether it was possible for this review to influence the current state of practice through various dissemination pathways (practice recommendation, clinical guidelines, etc.).

Feasibility of New Evidence Review
We conducted a limited literature search in PubMed from the last five years November 13, 2015 - November 13, 2020 on parts of the nomination scope not addressed by earlier identified systematic reviews. We reviewed all identified titles and abstracts for inclusion and classified identified studies by question and study design to estimate the size and scope of a potential evidence review.

Search strategy
"English"[Language]
KQ1: "osteoarthritis"[MeSH Terms] AND ("Arm"[Title/Abstract] OR "Shoulder"[Title/Abstract]
OR "Wrist"[Title/Abstract] OR "Knee"[Title/Abstract] OR "Hip"[Title/Abstract] OR
"Ankle"[Title/Abstract])
KQ2: ("soft tissue injuries"[MeSH Terms] OR "tendinopathy"[MeSH Terms] OR
"enthesopathy"[MeSH Terms] OR "bursitis"[MeSH Terms]) AND ("Arm"[Title/Abstract] OR
"Shoulder"[Title/Abstract] OR "Wrist"[Title/Abstract] OR "Knee"[Title/Abstract] OR
"Hip"[Title/Abstract] OR "Ankle"[Title/Abstract])

ClinicalTrials.gov link

Value
We assessed the nomination for value. We considered whether or not the clinical, consumer, or
policymaking context had the potential to respond with evidence-based change; and if a partner
organization would use this evidence review to influence practice.
### Appendix B. Selection Criteria Assessment

<table>
<thead>
<tr>
<th>Selection Criteria</th>
<th>Assessment</th>
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<tbody>
<tr>
<td>1. Appropriateness</td>
<td>1a. Yes</td>
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<tr>
<td>2. Importance</td>
<td>2a. Yes (Musculoskeletal disorders, or injuries or disorders of the muscles, nerves, tendons, joints, cartilage, or spinal discs, are prevalent, affecting roughly one in two (126.6 million) Americans and amounting to approximately $213 billion in treatment, care, and lost wage costs in 2016. OA, a musculoskeletal condition in which the cartilage protecting the joint wears down, affects over 32.5 million American adults and cost $486.4 billion in direct and indirect costs between 2008 and 2014.)</td>
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<td>2b. Yes (Musculoskeletal disorders, or injuries or disorders of the muscles, nerves, tendons, joints, cartilage, or spinal discs, are prevalent, affecting roughly one in two (126.6 million) Americans and amounting to approximately $213 billion in treatment, care, and lost wage costs in 2016. OA, a musculoskeletal condition in which the cartilage protecting the joint wears down, affects over 32.5 million American adults and cost $486.4 billion in direct and indirect costs between 2008 and 2014.)</td>
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<td>2c. Yes</td>
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<td>2d. Yes (Musculoskeletal disorders, or injuries or disorders of the muscles, nerves, tendons, joints, cartilage, or spinal discs, are prevalent, affecting roughly one in two (126.6 million) Americans and amounting to approximately $213 billion in treatment, care, and lost wage costs in 2016. OA, a musculoskeletal condition in which the cartilage protecting the joint wears down, affects over 32.5 million American adults and cost $486.4 billion in direct and indirect costs between 2008 and 2014.)</td>
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<tr>
<td>3. Desirability of a New Evidence Review/Absence of Duplication</td>
<td>3. Yes. We found four systematic reviews that covered part of KQ1.</td>
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<tr>
<td>4. Impact of a New Evidence Review</td>
<td>4a. Yes (Current consensus guidance on regenerative medicine is limited, reflecting limited evidence on the treatment.)</td>
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<tr>
<td>Selection Criteria</td>
<td>Assessment</td>
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<tr>
<td>4b. Is there practice variation (guideline inconsistent with current practice, indicating a potential implementation gap and not best addressed by a new evidence review)?</td>
<td>Yes. The current standard of practice does not include regenerative medicine interventions, but regenerative treatments for musculoskeletal conditions exist.</td>
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<tr>
<td><strong>5. Primary Research</strong></td>
<td></td>
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<tr>
<td>5. Effectively utilizes existing research and knowledge by considering:</td>
<td>Size/scope of review: We found 27 studies addressing KQ1 and 12 studies addressing KQ2, and estimate that a new review would be small in size.</td>
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<tr>
<td>- Adequacy (type and volume) of research for conducting a systematic review</td>
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<td>- Newly available evidence (particularly for updates or new technologies)</td>
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<td><strong>6. Value</strong></td>
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<tr>
<td>6a. The proposed topic exists within a clinical, consumer, or policy-making context that is amenable to evidence-based change</td>
<td>Yes. A current review of the evidence could influence the use of regenerative medicine interventions in musculoskeletal conditions.</td>
</tr>
<tr>
<td>6b. Identified partner who will use the systematic review to influence practice (such as a guideline or recommendation)</td>
<td>The nominators represent the AAPMR plan to disseminate a new systematic review to their members. There are no plans at this time for the development of a new guideline.</td>
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<td>A second nomination on regenerative medicine in orthopedics was received from a non-profit organization for education/standards and guidelines in regenerative medicine for orthopedic conditions, Interventional Orthobiologics Foundation. They are currently completing a white paper on the safety and efficacy of regenerative treatments, but have no plans to develop guidelines.</td>
</tr>
</tbody>
</table>

Abbreviations: AAPMR = American Academy of Physical Medicine and Rehabilitation; AHRQ = Agency for Health Research & Quality; KQ = key question; OA = osteoarthritis.